2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Cholesterol Guideline Data Supplements

(Section numbers correspond to the full-text guideline)

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Methodology and Evidence Review

The recommendations listed in this guideline are, whenever possible, evidence based. An extensive evidence review was conducted from May 1980 through July 2017. Other selected references published through August 2018 were incorporated by the writing committee. Literature included was derived from research involving human subjects, published in English, and indexed in PubMed and other selected databases relevant to this guideline. Key search words included but were not limited to the following: hyperlipidemia, cholesterol, LDL-C, HDL-C, ezetimibe, bile acid sequestrants, PCSK9 inhibitors, lifestyle, diet, exercise, medications, child, adolescent, screening, primary prevention, secondary prevention, cardiovascular disease, coronary artery calcium, familial hypercholesterolemia. ASCVD risk enhancing factors, statin therapy, diabetes, women, adherence, Hispanic/Latino, South Asian, African American. Terms may have been used alone or in combination.

Abbreviations 1° indicates primary; 2°, secondary; ACC, American College of Cardiology; ACE, angiotensin-converting-enzyme; ACR, albumin-to-creatinine ratio; AHA, American Heart Association; ALT, alanine aminotransferase; AMI, acute myocardial infarction; ARB, angiotensin-receptor blocker; ART; antiretroviral therapy; AS, ankylosing spondylitis; ASCOT-LLA, Anglo-Scandinavian Cardiac Outcomes Trial—lipid-lowering arm; ASPEN, the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in non-insulin-dependent diabetes mellitus; Atorva, atorvastatin; AURORA, A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis; BMI, body mass index; BP, blood pressure; CAC, coronary artery calcium; CARDS, Collaborative Atorvastatin Diabetes Study; CHD, coronary heart disease; chol, cholesterol; CI, confidence interval; CIMT, carotid intima-media thickness; CK, Creatine kinase; CKD, chronic kidney disease; cPB, carotid plaque burden score; CPK, creatine phosphokinase; CRP, C-reactive protein; CVD, cardiovascular disease; DM, diabetes mellitus; DR, diabetic retinopathy; EC, extended care; eGFR, estimated glomerular filtration rate; ERD, electronic reminder device; f/u, follow up; FDC, fixed-dose combination; FET, Fisher's exact test; FOCUS, Fixed Dose Combination Drug [Polypill] for Secondary Cardiovascular Prevention; GFR, glomerular filtration rate; h/o, history of; HbA1c, hemoglobin A1c; HCV, Hepatitis C viral; HF, heart failure; HPS, Heart Protection Study; HPS2-THRIVE, Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events; HR, hazard ratio; ICD, International Classification of Disease; IQR, Inter Quartile range; ITT, intention to treat; JART, Justification for Atherosclerosis Regression Treatment; KDIGO, kidney international guidelines; LDL-C, low density lipoprotein cholesterol; LFT, liver function test; LVH, left ventricular hypertrophy; MACE, Major adverse cardiovascular events; MAQ, Morisky Green questionnaire; MEMS, medication event monitoring system; MESA, Multi-Ethnic Study of Atherosclerosis; MI, myocardial infarction; N/A, not applicable; NHANES, National Health And Nutrition Education Survey; NNT, number needed to treat; NODM, new onset diabetes mellitus; NP, nurse practitioner; NR, not reported; NRI, net reclassification index; NYHA, New York Heart Association; OR, odds ratio; P01, first co-primary outcome; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; P02, second co-primary outcome; PCP, primary care provider; PI, pharmacist-delivered intervention; PN, Peripheral neuropathy; pts, patients; RA, rheumatoid arthritis; RAS, renin angiotensin system; revasc, revascularization; RC, routine care; RCT, randomized controlled trial; rhabdo, rhabdomyolysis; rosuva; rosuvastatin; RUTHERFORD, Reduction of LDL-C with PCSK9 Inhibition in Heterozygous Familial Hypercholesterolemia Disorder; RR, relative risk; RRF, reduced renal function; RRR, relative risk reduction; SBP, systolic blood pressure; SCr, serum creatinine; SD, standard deviation; SE, standard error; SHARP, Study of Heart and Renal Protection; Simva; simvastatin; SLE, systemic lupus erythematosus; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; TC, total cholesterol; UC, usual care; UL, upper limit; ULN, Upper limit of normal; UMPIRE, Use of a Multidrug Pill In Reducing Cardiovascular Events; UK, United Kingdom; US, United States; vs., versus; WOSCOPS, West of Scotland Coronary Prevention Study; y, years; yr, year.

Data Supplement 1. Nonrandomized Trials, Observational Studies, and/or Registries of Q3: Evidence regarding the difference in lipid levels measured in fasting and non-fasting individuals, and associations with outcomes (Section 2.2)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Di Angelantonio E, et al., 2009 (1) 19622820	**Study type:** Individual patient data meta-analysis of prospective cohort studies **Size:** 302,430 individuals	**Inclusion criteria:** • Studies with information on total cholesterol, HDL-C, triglycerides and other CVD risk factors at a baseline examination. **Exclusion criteria:** • Participants with missing data.	**1° endpoint:** Incident myocardial infarction or fatal CHD. **Results:** • 8857 nonfatal MIs, 3928 CHD deaths. • Adjusted HRs per 1 SD higher lipid measures: **HDL-C** Fasting participants HR: 0.79; 95% CI: 0.74-0.84. Nonfasting participants HR: 0.75; 95% CI: 0.68-0.83. **Triglycerides** Fasting participants HR: 1.02; 95% CI: 0.95-1.09. Nonfasting participants HR: 0.92; 95% CI: 0.82-1.03.	• Hazard ratios for HDL-C and incident CHD were at least as strong for those who were not fasting as for those who fasted. • After adjustment for HDL-C, non-HDL-C, and other standard CVD risk factors, triglycerides were not independently associated with CHD risk overall, in women and under nonfasting conditions.
Doran B, et al., 2014 (2) 25015340	**Study type:** Nested matched prospective cohort **Size:** 16,161 individuals (8,598 individuals after propensity matching: 4299 fasting; 4299 nonfasting)	**Inclusion criteria:** • ≥18 y of age • Noninstitutionalized US adults examined between 1988-1994 as part of NHANES III • Fasting defined as ≥8 H for main analyses **Exclusion criteria:** • Missing lipid values or fasting information. • TG ≥400 mg/dL	**1° endpoint:** All-cause mortality; mean follow up of 14.0 y. Secondary outcome: CVD mortality. **Results:** • Mean LDL-C 118.55 mg/dL among fasting and 118.33 among nonfasting matched participants. • 3788 total deaths; 1454 CVD deaths. • HRs adjusted for potential confounders. **All-cause mortality** **Fasting:** LDL-C tertile 1: HR: 1.0 (referent).	• Similar prognostic value for fasting and non-fasting LDL-C levels in association with all-cause and CVD mortality over 14 y. • Similar prognostic value also observed for fasting and nonfasting total cholesterol and triglyceride levels. • Results question the value of fasting for prognostic information from lipid panel. • Large sample representative of broad US population. • Fasting and nonfasting samples from different individuals; propensity score used to match fasting and nonfasting participants; content of last meal unknown.

			LDL-C tertile 2: HR: 1.61; 95% CI: 1.25-2.08. LDL-C tertile 3: HR: 2.10; 95% CI: 1.70-2.61. C statistic: 0.59; 95% CI: 0.56-0.61. **Nonfasting:** LDL-C tertile 1: HR: 1.0 (referent). LDL-C tertile 2: HR: 1.21; 95% CI: 0.92-1.60. LDL-C tertile 3: HR: 2.23; 95% CI: 1.76-2.83. C statistic: 0.58; 95% CI: 0.56-0.60 (p=0.73 compared with C statistic for fasting). $P_{interaction}$ for fasting status x LDL-C=0.11. C statistics for triglyceride levels for fasting (0.60; 95% CI: 0.59-0.62) vs. nonfasting (0.61; 95% CI: 0.59-0.62) participants were not different (p=0.96). C statistics for total cholesterol levels for fasting (0.60; 95% CI: 0.59-0.62) vs. nonfasting (0.59; 95% CI: 0.57-0.61) participants were not different (p=0.31). Sensitivity analyses: Pattern of results similar for unmatched participants, participants with triglycerides ≥400 mg/dL, and for different definitions of fasting (4 H or 12 H). • **Cardiovascular mortality** **Fasting:** LDL-C tertile 1: HR: 1.0 (referent) LDL-C tertile 2: HR: 1.68; 95% CI: 1.13-2.51. LDL-C tertile 3: HR: 3.04; 95% CI: 2.00-4.62. C statistic: 0.62; 95% CI: 0.60-0.66.	

			Nonfasting: LDL-C tertile 1: HR: 1.0 (referent). LDL-C tertile 2: HR 1.59; 95% CI: 0.97-2.61. LDL-C tertile 3: HR: 4.00; 95% CI: 2.58-6.19. C statistic: 0.62; 95% CI: 0.60-0.66 (p=0.73 compared with C statistic for fasting). $P_{interaction}$ for fasting status x LDL-C=0.34. C statistics for triglyceride levels for fasting (0.62; 95% CI: 0.60-0.64) vs. nonfasting (0.61; 95% CI: 0.59-0.64) participants were not different (p=0.81). C statistics for total cholesterol levels for fasting (0.64; 95% CI: 0.62-0.66) vs. nonfasting (0.63; 95% CI: 0.60-0.65) participants were not different (p=0.49). Sensitivity analyses: Pattern of results similar for unmatched participants, participants with triglycerides ≥400 mg/dL, and for different definitions of fasting (4 H or 12 H).	
Langsted A, et al., 2008 – Part 1 (3) 18955664	**Study type:** Cross-sectional cohort (Copenhagen General Population Study, 2003-2006 and Copenhagen City Heart Study, 2001-2003) **Size:** 33,391 individuals	**Inclusion criteria:** • All adults ages 20-95 y • Fasting (≥8 H) or nonfasting (<8 H) **Exclusion criteria:** • Outliers with lipid levels beyond ±3 SD from the mean	**1° endpoint:** Lipid levels stratified by time since last reported meal **Results:** • Compared with levels in participants fasting >8 H, total cholesterol, LDL-C and HDL-C were minimally but statistically significantly lower for 3-5 H after the last reported meal; triglyceride levels were significantly higher for up to 6 H after the last meal. Adjustment for effects related to hemodilution altered some of these differences slightly.	• Lipid levels differed minimally across time after normal food intake. • Limitations: fasting and nonfasting samples from different individuals; exclusively northern European Caucasian sample; content of last meal unknown.

			• Levels of non-HDL-C, apo A1, apo B, total/HDL-C and apo B/apo A1 did not differ by time from last meal in response to normal food intake. • Patterns of results did not differ substantially by time of day of blood sampling, although total cholesterol and LDL-C were somewhat lower for 5 H after a meal when blood was drawn in the evening. • After normal food intake, maximum mean differences in levels were observed for: Total cholesterol: -0.2 mmol/L at 0-2 H LDL-C: -0.2 mmol/L at 0-2 H HDL-C: -0.1 mmol/L at 0-5 H Triglycerides: +0.3 mmol/L at 1-4 H • Results were similar after excluding participants on lipid lowering therapy (5% of sample).	
Langsted A, et al., 2008 – Part 2 (3) 18955664	**Study type:** Prospective cohort (Copenhagen City Heart Study, 1991-1994) **Size:** 9,319 individuals	**Inclusion criteria:** • Adults ages 20-95 y and free of ischemic CVD • Nonfasting **Exclusion criteria:** • Missing lipid levels	**1° endpoint:** Fatal and nonfatal myocardial infarction and ischemic stroke; Mean follow up 14.0 y. **Results:** • 1,166 primary endpoint events. • Adjusted HRs for nonfasting lipids: Total cholesterol Men Tertile 1: HR: 1.0 (referent) Tertile 2: HR: 1.1; 95% CI: 0.7-1.6 Tertile 3: HR :1.7; 95% CI: 1.1-2.5 Women Tertile 1: HR: 1.0 (referent) Tertile 2: HR: 1.4; 95% CI: 0.9-2.3 Tertile 3: HR: 1.9; 95% CI: 1.2-3.1 LDL-C Men Tertile 1: HR: 1.0 (referent) Tertile 2: HR: 1.3; 95% CI: 0.8-2.0 Tertile 3: HR: 1.8; 95% CI: 1.2-2.7	• Nonfasting lipid levels are associated with ASCVD events. • Limitations: exclusively northern European Caucasian sample; content of last meal unknown.

			Women Tertile 1: HR: 1.0 (referent) Tertile 2: HR: 1.6; 95% CI: 1.0-2.4 Tertile 3: HR: 2.2; 95% CI: 1.5-3.5 • Patterns of results by tertile were overall similar for other nonfasting lipid measures (non-HDL-C, HDL-C, Apo A1, Apo B, triglycerides, total/HDL-C, and Apo B/Apo A1.	
Langsted A, et al., 2011 (4) 21189274	**Study type:** Cross-sectional cohort (Copenhagen General Population Study, 2003-2009) **Size:** 58,434 individuals	**Inclusion criteria:** • All adults ages 20-95 y • Fasting (≥8 H) or nonfasting (<8 H) **Exclusion criteria:** N/A	**1° endpoint:** Lipid levels stratified by time since last reported meal, in participants with and without diabetes. **Results:** • 2270 participants with and 56,164 without diabetes. • 52% of participants with and 8% of those without diabetes taking statins • Lipid levels were lower in participants with vs. without diabetes. • Overall patterns of lipid levels as a function of time since last meal were similar between participants with and without diabetes. • Compared with levels in participants fasting >8 H, total cholesterol and LDL-C were modestly lower for 3-5 H after the last reported meal; triglyceride levels were somewhat higher for up to 6 H after the last meal. Differences tended to be statistically significant among people without diabetes and nonsignificant among people with diabetes (smaller N). • After normal food intake, maximum mean differences in levels were observed for: **People without diabetes** Total cholesterol: -0.3 mmol/L at 0-1 H LDL-C: -0.3 mmol/L at 0-2 H HDL-C: 0.0 mmol/L at 0-8 H Triglycerides: +0.2 mmol/L at 0-5 H	• Cholesterol and triglyceride levels differed minimally, and similarly, across time after normal food intake in individuals with and without diabetes. • Limitations: fasting and nonfasting samples from different individuals; exclusively northern European Caucasian sample; content of last meal unknown; smaller number of participants with diabetes limits statistical power to detect differences.

			People with diabetes Total cholesterol: -0.4 mmol/L at 0-2 H LDL-C: -0.6 mmol/L at 1-2 H HDL-C: 0.0 mmol/L at 0-8 H Triglycerides: +0.2 mmol/L at 0-4 H • Adjustment for effects related to hemodilution attenuated these differences.	
Mora S, et al., 2008 (5) 18711012	**Study type:** Prospective cohort **Size:** 26,330 women	**Inclusion criteria:** • Women aged ≥45 y • Asymptomatic from CVD or cancer • Fasting (≥8 H) or nonfasting (<8 H) **Exclusion criteria:** • Missing data on time since last meal	**1° endpoints:** Lipid concentrations in fasting vs. nonfasting women; Composite end point of incident CVD (nonfatal myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, nonfatal stroke, or cardiovascular death). Median follow up 11.4 y. **Results:** • 19,983 fasting; 6,347 nonfasting • Median (IQR) lipid concentrations, fasting vs. nonfasting women Total cholesterol: 209 (185-236) mg/dL vs. 206 (181-234) mg/dL, p<0.001 LDL-C: 123 (102-146) mg/dL vs. 117 (97-140) mg/dL, p<0.001 HDL-C: 52 (43-62) mg/dL vs. 52 (43-62) mg/dL, p=0.25 Triglycerides: 115 (81-169) mg/dL vs. 133 (93-196) mg/dL, p<0.001 • There were no substantial differences in the distributions of lipid and apolipoprotein concentrations as a function of time since the last meal, with the exception of triglycerides. Triglycerides were at their maximum in women 4-5 H after the last reported meal. • 961 CVD events • Adjusted HRs for CVD events per 1 SD:	• Lipid levels differed minimally in fasting compared with nonfasting women, with the exception of triglycerides. • Associations of fasting total cholesterol, LDL-C and non-HDL-C with incident CVD were stronger than associations of nonfasting levels with incident CVD. Associations with incident CVD were similar for fasting and nonfasting levels of HDL-C and total/HDL-C. • Results suggest that nonfasting blood draws may be useful when limited to HDL cholesterol, total/HDL cholesterol ratio, and triglycerides. • Results also suggest that a fasting sample is preferred if risk assessment is based on total cholesterol, LDL cholesterol, or non-HDL cholesterol alone. • Limitations: women only; fasting and nonfasting samples from different individuals; largely Caucasian sample, higher SES; content of last meal unknown; smaller number of participants with diabetes limits statistical power to detect differences.

			Total cholesterol Nonfasting: HR: 1.07; 95% CI: 0.93-1.21 Fasting: HR: 1.22; 95% CI: 1.14-1.30 $P_{interaction}$=0.10 **LDL-C** Nonfasting: HR: 1.00; 95% CI: 0.87-1.15 Fasting: HR: 1.21; 95% CI: 1.13-1.29 $P_{interaction}$=0.03 • After adjustment for total and HDL-C, nonfasting triglycerides remained associated with incident CVD events, whereas fasting triglyceride levels did not. • Results were generally similar for women using vs. not using hormone replacement therapy • For total cholesterol, LDL-C, and non-HDL-C, significant associations with CVD were noted only after at least 10 H postprandially. The strongest associations for the other lipids and apolipoproteins were noted 6 to 8 H postprandially.	
Mora S, et al., 2009 (6) 19395440	**Study type:** Prospective cohort **Size:** 27,331 women	**Inclusion criteria:** • Women aged ≥45 y • Asymptomatic from CVD or cancer • Fasting (≥8 H) or nonfasting (<8 H) **Exclusion criteria:** • Missing data on time since last meal	**1° endpoints:** LDL-C measured by Friedewald calculation or direct LDL-C measurement in fasting vs. nonfasting women; Composite end point of incident CVD (nonfatal myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, nonfatal stroke, or cardiovascular death); Mean follow up 11.4 y **Results:** • Correlation between fasting Friedewald calculated LDL-C and fasting direct LDL-C, r=0.976, p<0.001; mean difference (direct minus Friedewald) was -0.146 (95% CI: -0.149, -0.143) mmol/L for fasting samples and -0.125 (95% CI: -	• Direct LDL-C measurements were lower by 0.13-0.26 mmol/L (5-10 mg/dL) compared with Friedewald fasting measurements. • Lower LDL-C measured by direct methods may lead to misclassification of some individuals when LDL-C strata are applied. • Associations of Friedewald and direct LDL-C were nearly identical for fasting samples. • No association of nonfasting direct LDL-C with incident CVD, calling into question the utility of a direct assay for prognosis in nonfasting samples. • Limitations: women only; fasting and nonfasting samples from different individuals; largely Caucasian sample, higher SES; content of last meal unknown.

			0.131, -0.120) mmol/L for nonfasting samples. • LDL-C values Friedewald, fasting mean 3.40 ± 0.90 mmol/L (median 3.33; IQR: 2.78-3.94) Direct, fasting mean 3.26 ± 0.88 mmol/L (median 3.19; IQR: 2.65-3.78) Direct, nonfasting mean 3.11 ± 0.86 mmol/L (median 3.03; IQR: 2.51- 3.62) p<0.001 for comparisons of fasting Friedewald vs. fasting direct and for fasting Friedewald vs. nonfasting direct. • Overall distributions of Friedewald or direct LDL-C did not differ substantially by time since last meal. • 945 incident CVD events. • Adjusted HRs for incident CVD per 1 SD higher LDL-C: • Friedewald, fasting HR: 1.22; 95% CI: 1.14-1.30 Direct, fasting HR: 1.23; 95% CI: 1.15-1.32 Direct, nonfasting HR: 1.03; 95% CI: 0.89-1.18	
Sidhu D, et al., 2012 (7) 23147400	**Study type:** Cross-sectional cohort (Calgary Laboratory Services) **Size:** 209,180 individuals	**Inclusion criteria:** • All individuals with at least 1 lipid profile **Exclusion criteria:** • Missing fasting time data • LDL-C data missing when triglycerides ≥400 mg/dL	**1° endpoint:** Lipid levels stratified by time (1-16 H) since last reported meal, in men and women. **Results:** • Compared with those who fasted >8 H, adjusted mean levels of lipid subclasses varied minimally in 1-7 H as a function time from last meal for total cholesterol and HDL-C, and somewhat more for LDL-C and triglycerides: Mean total cholesterol varied by <2% lower (NS for men; p<0.05 for H 1-2 in women)	• Fasting time since last meal showed minimal associations with total cholesterol and HDL-C, and modest associations with LDL-C (lower after meal by up to 10%) and triglycerides (higher after meal by up to 20%). • Large population-based sample of those receiving testing. • Limitations: content of last meal unknown; unknown status with regard to lipid lowering drugs.

			Mean HDL-C varied by <2% lower (NS for men and women) Mean LDL-C varied by <10% (p<0.05 for H 1-5 in men; p<0.05 for H 1-4 in women) Mean triglycerides varied by <20% (p<0.05 for H 1-6 in men; p<0.05 for H 1-5 in women).	

Abbreviations: 1° indicated primary; CI, confidence interval; HR, hazard ratio; N/A, not available; OR, odds ratio; RCT, randomized controlled trial; and RR, relative risk. NHANES
Search Terms and Date of Search: Author to provide

Data Supplement 2. RCTs of Statin Therapy for Primary Prevention of ASCVD Among Patients with the Metabolic Syndrome or its Subcomponents (Section 3.1.2)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
MEGA Matshushima T, et al., 2012 (8) 22573644	**Aim:** To evaluate the effectiveness of pravastatin for preventing ASCVD events among individuals with the metabolic syndrome **Study type:** RCT (post-hoc subgroup analysis) **Size:** 8,214 pts (subgroup of 2,636 with metabolic syndrome)	**Inclusion criteria:** Men and post-menopausal women aged 40-70 with total cholesterol 220-270 mg/dl **Exclusion criteria:** History of CVD, familial hypercholesterolemia, secondary hyperlipidemia or current malignancy	**Intervention:** Pravastatin 10-20 mg **Comparator:** Placebo	**1° endpoint:** CHD, defined as composite of fatal and nonfatal MI, cardiac and sudden death, coronary revascularization procedure and angina (Among those with metabolic syndrome: Pravastatin 5.3 vs. Placebo 6.9, events per 1000 person-y; HR: 0.78 [95% CI: 0.49-1.24]) **Safety endpoint (if relevant):** N/A	• Stroke (Pravastatin 2.6 vs. Placebo 5.7, events per 1000 person-y; HR: 0.45 [95% CI: 0.25-0.83]) •Total CVD events, defined as CHD, stroke, transient ischemic attack [TIA], and arteriosclerosis obliterans (Pravastatin 8.6 vs. Placebo 13.6, events per 1000 person-y; HR: 0.64 [95% CI: 0.45-0.90]) •Total Mortality (Pravastatin 2.5 vs. Placebo 5.2, events per 1000 person-y; HR: 0.50 [95% CI: 0.27-0.92]) Limitation: Post-hoc subgroup analysis among individuals with the metabolic syndrome

					5 y follow-up data utilized
AFCAPS/TEXCAPS Clearfield M, et al., (9) 16360356	**Aim:** To determine the effectiveness of lovastatin for the primary prevention of ASCVD events among several clinical subgroups, including individuals with the metabolic syndrome **Study type:** RCT (post-hoc subgroup analysis) **Size:** 6,605 pts (48% of trial population with metabolic syndrome)	**Inclusion criteria:** Men aged 45-73 and women aged 55-73, with LDL cholesterol 130-190 mg/dl and triglycerides < 400 mg/dl **Exclusion criteria:** Previous Hx of MI/CHD, stroke/TIA or PAD; uncontrolled hypertension, secondary hyperlipidemia, type 1 or type 2 diabetes mellitus that either managed with insulin or associated with a Hemoglobin A1C level of at least 10%, or body weight > 50% greater than desirable weight for height	**Intervention:** Lovastatin 20-40 mg **Comparator:** Placebo	**1° endpoint:** 10-y incidence of MI, CHD Mortality or Unstable Angina (Among those with metabolic syndrome: Lovastatin 7.7% vs. Placebo 13.0%; RR: 0.59; p<0.05) **Safety endpoint:** N/A	• Limitation: Post-hoc subgroup analysis among individuals with the metabolic syndrome. 10-y follow-up data utilized
WOSCOPS Sattar N, et al., 2003 (10) 12860911	**Aim:** To evaluate the risk for CHD associated with metabolic syndrome and risk reduction from pravastatin in those with and without metabolic syndrome **Study type:** RCT (post-hoc subgroup analysis) **Size:** 6,447 pts (1,691 with metabolic syndrome)	**Inclusion criteria:** Men with LDL cholesterol from 174-232 mg/dl and triglycerides < 530 mg/dl **Exclusion criteria:** History of myocardial infarction, angina requiring hospitalization; arrhythmias; severe hypertension (>180/110); congestive heart failure; congenital heart disease; rheumatic heart disease; baseline diabetes	**Intervention:** Pravastatin 40 mg **Comparator:** Placebo	**1° endpoint:** CHD, defined as nonfatal CHD or CHD death (Among those with metabolic syndrome: Pravsatatin 7.7% vs. Placebo 10.4%, event rate; HR: 0.73; 95% CI: 0.53-1.01) **Safety endpoint:** N/A	• Limitation: Post-hoc subgroup analysis among individuals with the metabolic syndrome Average 4.9 y follow-up

JUPITER Ridker PM, et al., 2008 (11) 18997196	**Aim:** To evaluate whether rosuvastatin decreases the rate of first major cardiovascular events among individuals with elevated high sensitivity CRP and LDLC < 130 mg/dl **Study type:** RCT **Size:** 17,802 pts (7,375 with metabolic syndrome)	**Inclusion criteria:** LDL-C less than 130 mg/dl, triglycerides < 500 mg/dl and high sensitivity CRP ≥ 2 mg/dl **Exclusion criteria:** A history of CVD; current use of lipid lowering therapy; elevated CK (3x normal), ALT (2x normal) or creatinine (> 2 mg/dl); uncontrolled HTN; history of systemic inflammatory condition	**Intervention:** Rosuvastatin 20 mg **Comparator:** Placebo	**1° endpoint:** First major cardiovascular event, defined as nonfatal MI, nonfatal stroke, hospitalization for unstable angina, arterial revascularization procedure or death from cardiovascular causes (Rosuvastatin 0.77 vs. Placebo 1.36, rate per 100 person-y; HR: 0.56; 95% CI: 0.46-0.69) **Safety endpoint:** Any serious event (Rosuvastatin 15.2% vs. Placebo 15.5%; p=0.60); notable statistically significant findings: newly diagnosed diabetes (Rosuvastatin 3.0% vs. Placebo 2.4%, p=0.01); death from cancer (Rosuvastatin 0.4% vs. Placebo 0.7%; p=0.02); median GFR at 12 mo (Rosuvastatin 66.8 vs. Placebo 66.6, in ml/min/1.73 m^2; p= 0.02)	• All-cause mortality (Rosuvastatin 1.00 vs. Placebo 1.25, rate per 100 person-y; HR: 0.80; 95% CI: 0.67-0.97) • In subgroup analyses, rosuvastatin was associated with a reduction in the primary endpoint among individuals with and without the metabolic syndrome, with no evidence of statistical interaction (p=0.14)
HOPE-3 Yusuf S, et al., 2016 (12) 27040132	**Aim:** To evaluate the effects of rosuvastatin on preventing cardiovascular events among intermediate risk persons without baseline cardiovascular disease **Study type:** RCT **Size:** 12,705 pts	**Inclusion criteria:** Men ≥ 55 y and Women ≥ 65 y with at least one of the following risk factors: elevated waist-hip ratio; low HDL-C; dysglycemia; current or recent smoking; mild renal dysfunction; or a family history of premature CAD. Women ≥ 60 y with at least two of the above risk factors **Exclusion criteria:** Known cardiovascular disease; an existing indication for or contraindication to statin therapy	**Intervention:** Rosuvastatin 10 mg **Comparator:** Placebo	**1° endpoint:** 1st co-primary outcome: composite of death from cardiovascular causes, nonfatal MI and nonfatal stroke (Rosuvastatin 3.7% vs. Placebo 4.8%, event rates; HR: 0.76; 95% CI: 0.64-0.91) 2nd co-primary outcome: composite of death from cardiovascular causes, nonfatal MI, nonfatal stroke, resuscitated cardiac arrest, heart failure and revascularization (Rosuvastatin 4.4% vs. Placebo 5.7%, event rates; HR: 0.75; 95% CI: 0.64-0.88) **Safety endpoint:** New onset diabetes	• Composite of death from cardiovascular causes, nonfatal MI, nonfatal stroke, resuscitated cardiac arrest, heart failure, revascularization and angina with evidence of ischemia (Rosuvastatin 4.8% vs. Placebo 6.2%, event rates; HR: 0.77; 95% CI: 0.66-0.89) • Death from any cause (Rosuvastatin 5.3% vs. Placebo 5.6%, event rates; HR: 0.93; 95% CI: 0.80-1.08) • Limitation: Metabolic syndrome components part of the inclusion criteria, but only a subset met diagnostic criteria for the metabolic syndrome

				Cognitive decline	Median follow-up of 5.6 y

Abbreviations: 1° indicated primary; CI, confidence interval; HR, hazard ratio; N/A, not available; OR, odds ratio; RCT, randomized controlled trial; and RR, relative risk.
Search Terms and Date of Search: Author to provide

Data Supplement 3. Meta-analyses comparing statins versus placebo or various intensities of statin therapy (Section 3.2)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
Baigent C, et al., 2010 (13) 21067804	**Aim:** To evaluate safety and efficacy of more intensive lowering of LDL cholesterol **Study type:** Individual patient-level meta-analysis of 26 randomized trials of statin therapy **Size:** 170000 participants from 26 randomized trials of statin therapy	**Inclusion criteria:** All eligible statin trials published by the end of 2009, main intervention to lower LDL-C using statin therapy, at least 1000 participants recruited with at least 2 y of scheduled duration. **Exclusion criteria:** Trials where other risk factor modification (except LDL-C reduction via statins) were excluded. -5 trials of more versus less intense statin therapy included 100% patients with CHD. -Proportion of patients with CHD in the remaining 21 trials varied from <1% (AFCAPS/TexCAPS, ASCOT LLA, CARDS, MEGA, JUPITER) to 100%	**Intervention/Comparator:** 1. Statin (n= 64744)/ placebo (n= 64782) [21 trials] 2. More (high) [n=19829] /less intense statin therapy (n=19783) [5 trials] **Definition of Outcomes:** 1. Major vascular events (first occurrence of any major coronary event, coronary revascularization, or stroke) 2. Major coronary event (coronary death or non-fatal MI) 3. Coronary revascularization (angioplasty or bypass grafting) 4. Stroke (any, ischemic, hemorrhagic, unknown)	**Endpoints:** **Statin (S) / Placebo (P):** Average LDL-C difference between statin and placebo = 1.07 mmol/L* 1. Major vascular events: S= 2.8% per annum, P = 3.6% per annum (RR: 0.78; 95% CI: 0.76-0.81). 2. Major coronary event: S= 1.3% per annum, P = 1.7% per annum (RR: 0.73; 95% CI: 0.70-0.77). 3. Coronary revascularization: S = 1.2% per annum, P = 1.6% per annum (RR: 0.75; 95% CI: 0.72-0.79) 4. Stroke: S = 0.7% per annum, P = per annum (RR: 0.85; 95% CI: 0.80-0.91). **More statin (MS) / less statin (LS):** Average LDL-C difference between MS and LS = 0.51 mmol/L 1. Major vascular events; MS = 4.5% per annum, LS = 5.3% per annum (RR: 0.85; 95% CI: 0.82-0.89).	• No heterogeneity of effect for major vascular events among those with previous vascular disease versus those without any previous vascular disease (p for heterogeneity = 0.3) -History of prior CHD: Statin/MS (4.5% per annum) versus P/LS (5.6% per annum) - RR: 0.79; 95% CI: 0.76-0.82. - History of non-CHD vascular disease: Statin/MS (3.1% per annum) versus P/LS (3.7% per annum)- RR: 0.81; 95% CI: 0.71-0.92. -No history of prior vascular disease: Statin/MS (1.4% per annum) versus P/LS (1.8% per annum)- RR: 0.75; 95% CI: 0.69-0.82. • No significant reduction in CHD death when comparing MS versus LS (RR: 0.93; 95% CI: 0.81-1.07). Significant reduction in non-fatal MI (RR: 0.85; 95% CI: 0.76- 0.94), coronary revascularization (RR: 0.81; 95% CI: 0.76-0.85), ischemic

		(SSSS, CARE, Post-CABG, LIPID, GISSI-P, LIPS, ALLIANCE). -Overall, 52% of the patients had prior CHD -15% had other vascular disease (history of intracerebral bleed, transient ischemic attack, ischemic stroke, unknown stroke, peripheral artery disease, or heart failure) -41% with no prior vascular disease (no known history of CHD or other vascular disease).	5. First cancer after randomization 6. Mortality (overall, vascular, non-vascular, unknown) [described for all 26 trials combined] - Median follow-up = 4.8 y in statin/placebo trials -Median follow-up 5.1 y in more versus less statin trials.	2. Major coronary events: MS = 1.9% per annum, LS = 2.2% per annum (RR: 0.87; 95% CI: 0.81-0.93). 3. Coronary revascularization; MS 2.6% per annum, LS 3.2% per annum (RR: 0.81; 95% CI: 0.76-0.85) 4. Stroke; MS 0.6% per annum, LS 0.7% per annum (RR: 0.86; 95% CI: 0.77-0.96). **For all 26 trials combined (Described per mmol/L reduction in LDL-C):** -Mortality: Statin/MS (2.1% per annum) versus P/LS (2.3% per annum)- RR: 0.90; 95% CI: 0.87-0.93. -Vascular mortality: Statin/MS (1.2% per annum) versus P/LS (1.3% per annum)- RR: 0.86; 95% CI: 0.82-0.90. -Any non-vascular mortality: Statin/MS (0.8% per annum) versus P/LS (0.8% per annum)- RR: 0.97; 95% CI: 0.92-1.03. -Unknown cause of mortality: Statin/MS (0.1% per annum) versus P/LS (0.1% per annum)- RR: 0.87; 95% CI: 0.73-1.03. -Although mortality data not provided for separately for statin versus placebo and more versus less statin, the authors state that "the proportional reduction in risk per 1.0 mmol/L LDL cholesterol reduction did not differ between the two types of trial comparisons (all heterogeneity p values >0.1).	stroke (RR: 0.84; 95% CI: 0.74-0.99) when comparing MS versus LS. • Although major vascular events reduced non-significantly when comparing patients with CHD aged >75 y receiving MS versus LS (RR: 0.78, 99% CI: 0.52-1.18); heterogeneity; p=0.8 when comparing MS versus LS across groups of CHD patients aged ≤65 y, >65 y to ≤75 y, and >75 y. • For major vascular events, RR: 0.71 (99% CI: 0.63-0.80) for males and RR 0.75 (99% CI: 0.58-0.97) for females when comparing MS versus LS among males/ females (p for heterogeneity = 0.6). •RR: 0.85 (99% CI: 0.73-0.99) for major vascular events in those aged >75 y comparing S versus P (p for heterogeneity = 0.4 when comparing S versus P among those aged ≤65 y, >65 y to ≤75 y, and >75 y). •Among comparison of 5 trials of MS versus LS, large absolute reduction in LDL cholesterol were associated with larger proportional risk reduction (p for trend = 0.0004). After adjustment for LDL cholesterol differences, there was little residual variation (p for trend = 0.05). **Limitations:** 1. Individual patient-level data on 3 trials (CORONA, SPARCL,

				Safety endpoint (if relevant): -Cancer: S = 1.4% per annum, P = 1.4% per annum (RR: 1.00, 95% CI: 0.95-1.04). -Cancer: MS = 1.6% per annum, LS = 1.6% per annum (RR: 1.00, 95% CI: 0.93-1.07). - Rhabdomyolysis: Observed excess of rhabdomyolysis = 1 (SE 1) per 10,000 in 21 trials of S versus P (14 vs. 9 cases) 4 (SE 2) per 10,000 in 5 trials of MS versus LS (14 vs. 6 cases) [All excess cases occurred in SEARCH and A to Z study (simvastatin 80 mg po daily)]. -Hemorrhagic Stroke: S= 0.1% per annum, P = 0.1% per annum, RR: 1.15 (99% CI: 0.87-1.51) MS = 0.1% per annum, LS = 0.1% per annum, RR: 1.21, 99% CI: 0.76-1.91).	GREACE) not available and therefore, not included.

Abbreviations: 1° indicated primary; CI, confidence interval; HR, hazard ratio; N/A, not available; OR, odds ratio; RCT, randomized controlled trial; RR, relative risk; LDL-C, low-density lipoprotein cholesterol; S, statin; P, placebo; LS, less statin; MS, more statin; CHD, coronary heart disease
* 1 mmol/L LDL-C = 38.67 mg/dL of LDL-C

Data Supplement 4. Risk stratification among patients with ASCVD to identify those most likely to benefit from non-statin therapy (Section 3.2.2)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)

Bohula EA, et al., 2017 (14) 28231942	**Aim:** To test the hypothesis that atherothrombotic risk stratification may be useful to identify post-ACS patients who have the greatest potential for benefit from the addition of ezetimibe to statin therapy. **Study type:** Post-hoc analyses from an RCT (IMPROVE-IT). **Size:** 17,717 patients post ACS	**Inclusion criteria:** Patients at least 50 y of age with hospitalization for ACS within the preceding 10 ds, including MI with or without ST-segment elevation or high-risk unstable angina **Exclusion criteria:** Incomplete baseline characteristics, baseline ezetimibe use in combination with a statin, creatinine clearance of <30 ml/min., statin therapy with a potency >40 mg simvastatin, hemodynamic instability, or revascularization by CABG for the index event.	**1° endpoint:** Composite of CV death, MI, or ischemic stroke. **Results:** 9 clinical risk factors used to define a score. These included CHF, HTN, age ≥75 y, DM, prior stroke, prior CABG, PAD, eGFR <60ml/min./1.73 m^2, and current smoking. -Each of the 9 clinical variables in the model were independent predictors of 1^0 endpoint in the control (simvastatin +placebo) group. - Mean number of risk indicators for each patient was 1.8 ± 1.2 in both treatment arms. -The use of this risk stratification tool showed a graded relationship with the primary outcome (8.6% for patients with 0 risk indicators to 68.4% for those with ≥5 risk indicators, p for trend <0.0001). -Goodness-of-fit was 4.5 (p=0.48) indicating adequate calibration. -The c-statistic for the 9-component clinical model was 0.67 (95% CI: 0.65-0.68). -Risk categories, defined as low (0 to 1 risk indicators), intermediate (2 indicators), and high (≥3 indicators) represented 45% (n = 8,032), 30% (n = 5,292), and 25% (n = 4,393) of the overall population, respectively. - 7-y event rates with HR (95% CI) associated with the addition of ezetimibe, ARR (95% CI) in ezetimibe +simvastatin group (eze+simva) compared with simvastatin + placebo (simva) group:	• This risk score identified patients with ACS at high risk of recurrent CV events who derive the greatest benefit from the addition of ezetimibe to statin therapy. • Of note, this risk score was initially developed in a population of patients with MI within 2 wk to one year of randomization to a thrombin receptor agonist. The results of the current study validated the utility of this score in post-ACS population of IMPROVE-IT (Circulation. 2016 Jul 26;134(4):304-13) (36)

			• 0-1 risk indicators: 14% (eze+simva), 13.1% (simva), HR: 1.05; 95% CI: 0.92-1.19; ARR: -0.9%; 95% CI: -2.5, 0.7. •2 risk indicators: 19.3% (eze+simva), 21.5% (simva), HR: 0.89 (95% CI: 0.78-1.01), ARR: 2.2%; 95% CI: -0.3, 4.6. •3 or more risk indicators: 40.2% (eze+simva), 33.9% (simva), HR: 0.81 (95% CI: 0.73, 0.90), ARR: 6.3%; 95% CI: 2.9-9.7). -Number-needed-to-treat for 7 y to prevent one primary event = 16 among those with 3 or more risk indicators. -Similar results were obtained for IMPROVE-IT pre-specified primary and secondary trial endpoints as well as most of the individual, nonfatal endpoints. -No significant reduction in CV death or all-cause mortality. -The median achieved LDL-C values at 1 y were similar across risk categories by treatment.	

Abbreviations: 1° indicated primary; CI, confidence interval; HR, hazard ratio; RCT, randomized controlled trial; IMPROVE-IT, Improved Reduction of Outcomes: Vytorin Efficacy International Trial; ACS, acute coronary syndrome; MI, myocardial infarction; CV, cardiovascular; CHF, congestive heart failure; HTN, hypertension; DM, diabetes; CABG, coronary artery bypass grafting; PAD, peripheral artery disease; GFR, glomerular filtration rate; ARR, absolute risk reduction; LDL-C, low-density lipoprotein cholesterol

Data Supplement 5. RCTs of Non-Statin or Combination Lipid Lowering Therapy for Primary Prevention of ASCVD Among Patients with the Metabolic Syndrome or its Subcomponents (Section 3.2.3)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
HHS: Helsinki Heart Study Frick et al., 1987 (15) 3313041	**Aim:** To test the efficacy of gemfibrozil for lowering CHD risk among asymptomatic men with high Non-HDL-C **Study type:** RCT **Size:** 4,081 pts	**Inclusion criteria:** Men 40-55 y of age with Non-HDL-C greater than or equal to 200 mg/dl in two consecutive pretreatment assessments **Exclusion criteria:** Clinical or ECG evidence of baseline CHD; congestive heart failure; other comorbidities that "could have an influence on the study outcome"	**Intervention:** Gemfibrozil 600 mg twice a day **Comparator:** Placebo	**1° endpoint:** Composite of fatal and nonfatal MI and cardiac death (Gemfibrozil 27.3 vs. Placebo 41.4, cumulative events per 1000 over 5 y; relative risk reduction of 34% [95% CI: 8.2-52.6]) **Safety endpoint (if relevant):** Moderate to severe upper gastrointestinal symptoms - in 1st year: Gemfibrozil 11.3% vs. Placebo 7.0% (p<0.001); in subsequent years: Gemfibrozil 2.4% vs. Placebo 1.2% (p<0.05)	• Nonfatal MI (Gemfibrozil 21.9 vs. Placebo 35.0, cumulative events per 1000 over 5 y; p<0.02; relative risk reduction of 37%) • Gallstone operations (Gemfibrozil 18 vs. Placebo 12; p value nonsignificant [>0.05]) • All gastrointestinal operations, including hemorrhoidectomies (Gemfibrozil 81 vs. Placebo 53; p<0.02) • 5 y of follow-up
Tenkanen L, et al., 1995 (16) 7671361	**Aim:** To evaluate the effectiveness of gemfibrozil for CHD prevention among overweight subjects with metabolic risk factors **Study type:** RCT subgroup analysis **Size:** 4,081 pts	**Inclusion criteria:** Men 40-55 y of age with Non-HDL-C greater than or equal to 200 mg/dl in two consecutive pretreatment assessments **Exclusion criteria:** Clinical or ECG evidence of baseline CHD; congestive heart failure; other comorbidities that "could have an influence on the study outcome"	**Intervention:** Gemfibrozil 600 mg twice a day **Comparator:** Placebo	**1° endpoint:** Composite of fatal and nonfatal MI and cardiac death Among those with BMI greater than 26 kg/m^2, high triglycerides (greater than or equal to 200 mg/dl) and low HDL-C (less than 42 mg/dl): Gemfibrozil 4 vs. Placebo 17, events per 1000 person-y; relative risk reduction of 78% [p=0.002]) Among those with BMI greater than 26 kg/m^2, and 3-4 of the following: hypertension (greater than or equal to 140/90), glucose greater than 80 mg/dl, sedentary lifestyle and smoking (Gemfibrozil 8 vs. Placebo 27, events per 1000 person-y;	• Post-hoc subgroup analysis • 5 y of follow-up

				relative risk reduction of 68% [p=0.03]) **Safety endpoint:** N/A	
FIELD Keech A, et al., 2005 (17) 16310551	**Aim:** To assess the effect of fenofibrate on CVD events among patients with type 2 diabetes **Study type:** RCT **Size:** 9.795 pts (80% meeting criteria for metabolic syndrome)	**Inclusion criteria:** **Exclusion criteria:**	**Intervention:** N/A **Comparator:** N/A	**1° endpoint:** Nonfatal MI or CHD Death **Safety endpoint:** N/A	• Total CVD events, including nonfatal MI, CHD death, stroke, coronary and carotid revascularization • Nonfatal MI • CHD mortality
ACCORD Lipid Trial Ginsberg HN, et al., 1998 (18) 20228404	**Aim:** To assess whether combination therapy with fenofibrate plus simvastatin lowers the rate of incident CVD events more than simvastatin alone among high risk patients with type 2 diabetes **Study type:** RCT **Size:** 5,518 pts	**Inclusion criteria:** Men and women aged 40-79 y (55-79 y if subclinical CVD or 2 additional risk factors) with type 3 DM with hemoglobin A1C greater than or equal to 7.5%; an LDL-C level of 60-180 mg/dl; HDL less than 55 mg/dl for women and blacks and less than 50 mg/dl for others; and triglycerides less than 750 mg/dl (or 400 mg/dl on lipid therapy). Included subjects with (36.5%) and without a previous cardiovascular event (primary and secondary prevention trial) **Exclusion criteria:** taking any medication known to interact with statins or fibrates; history of pancreatitis, gallbladder	**Intervention:** Combination of Fenofibrate (160 mg, with adjustment as needed to eGFR) plus open label Simvastatin (20-40 mg) **Comparator:** Placebo + open label Simvastatin (20-40 mg)	**1° endpoint:** Composite of nonfatal MI, nonfatal stroke and death from cardiovascular causes (Fenofibrate 2.2% vs. Placebo 2.4%, annual event rate; HR: 0.92 [95% CI: 0.79-1.08; p=0.32]) **Safety endpoint:** Elevations of CK more than 10 times the upper limit of normal (Fenofibrate 0.4% vs. Placebo 0.3%; cumulative rate during trial; p=0.83) Any unexplained myalgias with CK greater than 5 times the upper limit of normal (Fenofibrate 0.3% vs. Placebo 0.3%; cumulative rate during trial; p=0.79) Serum creatinine elevation – for women (ever greater than 1.3 mg/dl; Fenofibrate 27.9% vs. Placebo 18.7%; cumulative rate during trial; p<0.001)	• Prespecified subgroup analyses: Triglycerides greater than or equal to 204 mg/dl and HDL-C less than or equal to 34 mg/dl (Fenofibrate 12.4 vs. Placebo 17.3, overall % of events in group; p=0.032). Others without high triglycerides and low HDL-C (Fenofibrate 10.1 vs. Placebo 10.1, overall % of events in group; p=0.032). p for interaction 0.06 Women (Fenofibrate 9.1 vs. Placebo 6.6, overall % of events in group). Men (Fenofibrate 11.2 vs. Placebo 13.3, overall % of events in group). p for interaction 0.01 No interaction seen with prior CVD (p=0.45) Mean duration of follow-up 4.7 y for primary outcome

		disease or myositis/myopathy		– for men (ever greater than 1.5 mg/dl; Fenofibrate 36.7% vs. Placebo 18.5%; cumulative rate during trial; p<0.001) ALT greater than 5 times the upper limit of normal (Fenofibrate 0.6% vs. Placebo 0.2%; cumulative rate during trial; p=0.03)	

Abbreviations: 1° indicated primary; CI, confidence interval; HR, hazard ratio; N/A, not available; OR, odds ratio; RCT, randomized controlled trial; and RR, relative risk.
Search Terms and Date of Search: Author to provide

Data Supplement 6. Evidence Tables for Statin initiation in patients with heart failure meta-analysis of CORONA and GISSI HF trials (Section 4.1)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
CORONA Kjekshus et al., 2007 (19) 17984166	**Aim:** To assess beneficial effects and harms of initiation of rosuvastatin therapy in patients with chronic, symptomatic, ischemic heart failure. **Study type:** RCT **Size:** 5011 patients (2497 in placebo, 2514 in rosuvastatin arm) **Median follow-up**: 32.8 mo 371 sites in 19 European countries,	**Inclusion criteria:** Patients who were at least 60 y of age and who had chronic New York Heart Association (NYHA) class II, III, or IV heart failure of ischemic cause (as reported by investigators) and an ejection fraction of no more than 40% (no more than 35% in patients in NYHA class II) were eligible, if the investigator thought they did not need treatment with a cholesterol-lowering drug. **Exclusion criteria:** Previous statin-induced myopathy or hypersensitivity reaction; decompensated heart failure or a need for inotropic therapy; myocardial infarction	**Intervention:** G1: Rosuvastatin 10 mg QD (n=2514) **Comparator:** G2: Placebo (n = 2497) **End points:** **1° endpoint:** Composite of: death from cardiovascular causes, nonfatal myocardial infarction, and nonfatal stroke, **Secondary**: Death from any cause, any coronary event (defined as sudden death, fatal or nonfatal myocardial infarction, the performance of PCI or CABG, ventricular defibrillation by an	G1: LDL-C 137 to 76 mg/dL G2: LDL-C 136 to 138 mg/dL Absolute LDL-C difference of 45% between groups (p<0.001) **1° endpoint:** G1: 692 (11.4 per 100 patient-y of follow-up) G2: 732 (12.3 per 100 patient-y of follow-up) HR: 0.92; 95% CI: 0.83-1.02 p 0.12 No heterogeneity of effect across subgroups **Secondary Outcomes** (per 100 patient-y of follow-up): Death from any cause: G1: 728 (11.6 per 100 patient-y of follow-up)	• Mean age 73 y, 41% participants were at least 75 y old. •Nonfatal MI and stroke relatively uncommon. • Composite of Fatal or nonfatal MI, or stroke: GI: 227; G2: 264 HR: 0.84; 95% CI: 0.7-1.00; p=0.05 • Adverse events: -Study drug discontinuation: G1 490, G2 546 HR: 0.88; 95% CI: 0.78-0.99 -ALT >3 x ULN (at least one episode): G1: 25; G2: 24 -Muscle adverse events: G1: 170; G2: 155 -CK >10 x ULN: G1: 1; G2: 3 -CK >10 x ULN with muscle symptoms: G1: 0, G2: 1

	Russia and South Africa	within the past 6 mo; unstable angina or stroke within the past 3 mo; percutaneous coronary intervention (PCI), coronary-artery bypass grafting (CABG), or the implantation of a cardioverter–defibrillator or biventricular pacemaker within the past 3 mo or a planned implantation of such a device; previous or planned heart transplantation; clinically significant, uncorrected primary valvular heart disease or a malfunctioning prosthetic valve; hypertrophic cardiomyopathy; acute endomyocarditis or myocarditis, pericardial disease, or systemic disease (e.g., amyloidosis); acute or chronic liver disease; levels of alanine aminotransferase or thyrotropin of more than 2 times the upper limit of the normal range; a serum creatinine level of more than 2.5 mg per deciliter (221 μmol per liter); chronic muscle disease or an unexplained creatine kinase level of more than 2.5 times the upper limit of the normal range; previous treatment with cyclosporine; any other condition that would substantially reduce	implantable cardioverter–defibrillator, resuscitation after cardiac arrest, or hospitalization for unstable angina); death from cardiovascular causes (with an additional analysis of cause-specific death from a cardiovascular cause); and the number of hospitalizations for cardiovascular causes, unstable angina, or worsening heart failure.	G2: 759 (12.2 per 100 patient-y of follow-up) HR: 0.95; 95% CI: 0.86- 1.05 p=0.31 Any coronary event: G1: 554 (9.3 per 100 patient-y of follow-up) G2: 588 (10 per 100 patient-y of follow-up) HR: 0.92; 95% CI: 0.82-1.04 p=0.18 **Other outcomes** (per 100 patient-y of follow-up): Death from Cardiovascular causes: G1: 9.3 G2: 9.6 HR: 0.97; 95% CI: 0.87-1.09 Death from noncadiovascular cause: G1: 2.2 G2: 2.6 Nonfatal MI: GI 1.9, G2 2.4 Nonfatal Stroke: G1 1.5, G2 1.7 Hospitalization (total number of hospitalizations): -For any cause: G1 3694, G2 4074, p 0.007 -For a cardiovascular cause: G1 2193, G2 2564, p<0.001	

		life expectancy or limit compliance with the protocol; or the receipt of less than 80% of dispensed placebo tablets during the run-in period.		-For worsening heart failure: G1 1109, G2 1299, p=0.01 - For unstable angina: G1 74, G2 90, p 0.30 -For a non-cardiovascular cause: G1 1501, G2 1510, p 0.82	

Abbreviations: 1° indicated primary; CI, confidence interval; HR, hazard ratio; N/A, not available; OR, odds ratio; RCT, randomized controlled trial; RR, relative risk; MI, myocardial infarction; ULN, upper limits of normal; LDL-C, low-density lipoprotein cholesterol.

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
GISSI HF Tavazzi L, et al., 2008 (20) 18757089	**Aim:** To investigate the safety and efficacy of rosuvastatin in patients with heart failure **Study type:** RCT **Size:** 4631 randomized **Median follow-up**: 3.9 y -326 cardiology and 31 internal medicine centers in Italy	**Inclusion criteria:** Men and women with symptomatic heart failure (NYHA Class II-IV). Both ischemic and non-ischemic etiologies of HF included. Those with LV EF >40% had to have at least hospital admission for CHF in the preceding year. **Exclusion criteria:** Known hypersensitivity to study treatment; presence of any noncardiac comorbidity (e.g., cancer) that was unlikely to be compatible with a sufficiently long follow-up; treatment with any investigational agent within 1 month before randomization; acute coronary syndrome or a revascularization procedure within 1 month before	**Intervention:** G1: Rosuvastatin 10 mg QD (n=2285) **Comparator:** G2: placebo (n= 2289) **Endpoints**: **Co-primary**: Time to death, and time to death or admission to hospital for cardiovascular reasons. **Secondary**: Cardiovascular mortality, cardiovascular mortality or admission for any reason, sudden cardiac death, admission for any reason, admission for cardiovascular reasons, admission for heart failure, myocardial infarction, and stroke	G1: LDL-C 3.16 mmol/L* to 2.31 mmol/L after 3 y G2: LDL-C 3.13 mmol/L to 3.06 mmol/L after 3 y. **1° endpoint:** Death from any cause: G1: 657 (29%), G2: 644 (28%) HR: 1.03; 95% CI: 0.91-1.14 Death from any cause or admission to hospital for cardiovascular reasons: G1: 1305 (57%), G2:1283 (56%) HR: 1.02; 95% CI: 0.92-1.13 No heterogeneity of effect across various subgroups. **Secondary Outcomes** -Cardiovascular mortality: G1: 478 (20.9%), G2:488 (21.3%) HR: 0.98; 95% CI: 0.87-1.12	• Mean age 68 y, 44% older than 70 y. 23.8% women in G1, 21.4% women in G2 • Etiology of HF: Ischemic (40%), primary dilated (35%), hypertensive (18%) • Mean EF: 33.4% G1, 33.1% G2 • 10.3% in G1 and 9.8% in G2 with LV EF >40% • Per protocol analysis: Death from any cause: G1 29%, G2: 27% (HR: 1.12; 95%: CI: 0.97-1.29). • Adverse events -Permanent discontinuation of study treatment: G1: 790 (34.6%), G2: 831 (36.3%), p=0.22 -Permanent discontinuation due to adverse drug reaction: G1: 104 (4.6%), G2: 91 (4.0%), p=0.36 -Permanent discontinuation due to muscle-related symptoms: G1: 23, G2: 21. -CK >5x ULN: G1: 9, G2: 2 -CK >10x ULN: G1: 1, G2: 1

		randomization; planned cardiac surgery, expected to be done within 3 mo after randomization; significant liver disease; serum creatinine concentration greater than 221 µmol/L; alanine and aspartate transaminase concentrations more than 1.5 times the upper normal limit; creatine phosphokinase concentrations above the upper normal limit; and pregnant or lactating women or women of childbearing potential who were not adequately protected against becoming pregnant.		-Cardiovascular mortality or admission for any reason: G1: 1417 (62%), G2:1385 (60.5%) HR: 1.03; 95% CI: 0.96-1.11 -Sudden Cardiac death: G1: 220 (9.6%), G2:196 (8.6%) HR: 1.13; 95% CI: 0.93-1.37 -Patients admitted: G1: 1278 (55.9%), G2:1286 (56.1%) HR: 1.00; 95% CI: 0.93-1.08 -Admission for cardiovascular reason: G1: 1033 (45.2%), G2:1060 (46.3%) HR: 0.98; 95% CI: 0.90-1.07 - Admission for HF: G1: 629 (27.5%), G2:634 (27.7%) HR: 1.00; 95% CI: 0.90-1.12 -Fatal and non-fatal MI: G1: 61 (2.7%), G2:70 (3.1%) HR: 0.88; 95% CI: 0.63-1.24 -Fatal and non-fatal stroke: G1: 82 (3.6%), G2:66 (2.9%) HR: 1.25; 95% CI: 0.91-1.73	

Abbreviations: 1° indicated primary; CI, confidence interval; HR, hazard ratio; N/A, not available; OR, odds ratio; RCT, randomized controlled trial; RR, relative risk; LDL-C, low-density lipoprotein cholesterol; ULN, upper limit of normal.
*1 mmol/L LDL-C=38.67 mg/dL LDL-C

Data Supplement 7. Meta-analysis of CORONA and GISSI HF trials (Section 4.1)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
Pooled individual-level reanalysis of CORONA and GISSI-HF Feinstein MJ, et al., 2015 (21) 25684642	**Aim:** Using pooled data from CORONA and GISSI HF trials, to assess whether HF patients randomized to rosuvastatin 10 mg daily vs. placebo had statistically significant differences in atherothrombotic events after accounting for competing causes of death. **Study type:** Individual trial participant-level reanalysis. **Size:** CORONA (n= 5011), GISSI HF (n = 4574) **Median follow-up**: 32.8 mo in CORONA, 46.9 mo in GISSI HF	**Inclusion criteria:** Inclusion criteria for CORONA and GISSI HF trials as discussed above. **Exclusion criteria:** Exclusion criteria for CORONA and GISSI HF trials as discussed above.	**Intervention:** G1: Rosuvastatin 10 mg QD (n = 4799) **Comparator:** G2: placebo (n = 4786) **End points**: A competing Cox regression model was used to analyze the joint and simultaneous risks for the following outcomes: -MI (fatal and non-fatal) -Stroke (fatal and non-fatal) -Other cardiovascular death -Death from non-cardiovascular causes Data presented here are for (a) CORONA and GISSI-HF pooled (b) CORONA and GISSI HF pooled for those with ischemic etiology of HF.	**CORONA and GISSI-HF pooled (all participants):** MI (fatal and non-fatal): G1 186, G2 223, HR: 0.83; 95% CI: 0.68-1.00; p=0.055 Stroke (fatal and non-fatal): G1 186, G2 169, HR: 1.07; 95% CI: 0.87-1.32; p=0.50 Other cardiovascular death: G1 877, G2 890, HR: 0.98; 95% CI: 0.90-1.08; p=0.74 Death from non-cardiovascular causes: G1 305, G2 288, HR: 1.06; 95% CI: 0.90-1.25; p=0.48 **CORONA and GISSI HF pooled for those with ischemic etiology of heart failure:** MI (fatal and non-fatal): G1 171, G2 208, HR: 0.81; 95% CI: 0.66-0.99; p=0.049 Stroke (fatal and non-fatal): G1 145, G2 140, HR: 1.08; 95% CI: 0.86-1.37; p 0.50 Other cardiovascular death: G1 687, G2 695, HR: 0.99; 95% CI: 0.89-1.10; p 0.88	• NNT to prevent one MI = 94 • Relatively few MIs in both the trials compared to other outcomes. • Traditional Cox regression analyses (without accounting for competing risk) yielded largely similar results. CORONA and GISSI HF pooled for those with ischemic etiology of heart failure (using traditional Cox regression): -MI (fatal and non-fatal): HR: 0.82; 95% CI: 0.67-1.00. -Stroke (fatal and non-fatal): HR: 0.87; 95% CI: 0.67-1.14. -Other cardiovascular death: HR: 0.97; 95% CI: 0.88-1.07. -Non-cardiovascular death: HR: 1.02; 95% CI: 0.85-1.22.

				Death from non-cardiovascular causes: G1 227, G2 214, HR: 1.07; 95% CI: 0.89-1.29; p 0.49.	

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SPARCL Amarenco P, et al., 2006 (22) 16899775	**Aim:** To assess whether atorvastatin 80 mg daily (compared to placebo) reduces the incidence of stroke in patients with a recent stroke or transient ischemic stroke (TIA) **Study type:** RCT **Size:** 4731 patients **Follow-up**: Median = 4.9 y 205 participating centers.	**Inclusion criteria:** Men and women over 18 y of age with no known CHD who had had an ischemic or hemorrhagic stroke or a TIA (diagnosed by a neurologist within 30 d after the event) 1 to 6 mo before randomization. Patients with hemorrhagic stroke were included if they were deemed by the investigator to be at risk for ischemic stroke or coronary heart disease. **Exclusion criteria:** Presence of atrial fibrillation, other causes of embolism, subarachnoid hemorrhage. • Mean Time since index event to entry in the trial = 87.1 d in the atorvastatin group and 84.3 d in the placebo group.	**Intervention:** GI: Atorvastatin 80 mg po daily (n= 2365). **Comparator:** G2: Placebo (n= 2366). **End Points:** -Analyses adjusted for geographic region, entry event (stroke or TIA), time since entry event, sex, and baseline age. This was pre-specified. **Primary:** Time from randomization to a first nonfatal or fatal stroke. **Secondary**: 1. Stroke or TIA 2. Major coronary event (death from cardiac causes, nonfatal myocardial infarction, or resuscitation after cardiac arrest). 3. Major cardiovascular event (stroke plus any major coronary event).	**LDL-C:** G1: 132.7 mg/dL at baseline versus mean of 72.9 mg/dL during the trial. G2: 133.7 mg/dL at baseline versus mean of 128.5 mg/dL during the trial. **1° endpoint:** G1: 265 (11.2%), G2 311 (13.1%) Adjusted HR: 0.84; 95% CI: 0.71-0.99. **Secondary and other relevant endpoints:** 1. Stroke or TIA: G1: 375 (15.9%), G2 476 (20.1%) Adjusted HR: 0.77; 95% CI: 0.67-0.88. 2. Major coronary event: G1: 81 (3.4%), G2 120 (5.1%) Adjusted HR: 0.65; 95% CI: 0.49-0.87. 3. Major cardiovascular event: G1: 334 (14.1%), G2 407 (17.2%) Adjusted HR: 0.80; 95% CI: 0.69-0.92. 4. Acute coronary event: G1: 101 (4.3%), G2 151 (6.4%)	• More patients in the placebo group than in the atorvastatin group permanently discontinued treatment (20.2% vs. 15.4%) •After randomization, open-label statin therapy use (25.4% in the placebo group versus 11.4% percent in the atorvastatin group) •The net difference in statin use between groups was 78.1%. • All-cause death: G1: 216 (9.1%), G2 211 (8.9%) Adjusted HR: 1.00; 95% CI: 0.82-1.21. -Death from cardiovascular disease: G1: 78 (3.3%), G2 98 (4.1%) Adjusted HR: 0.78; 95% CI: 0.58-1.06. -Death from Cancer: G1: 57 (2.4%), G2 53 (2.2%) Adjusted HR: 1.05; 95% CI: 0.72-1.53. • **Post-hoc analyses:** - 492 ischemic strokes: 218 atorvastatin, 274 placebos.

			4. Acute coronary event (major coronary event or unstable angina). 5.Any coronary event (acute coronary event plus a coronary revascularization procedure, unstable angina, or angina or ischemia requiring emergency hospitalization) 6. Revascularization procedure (coronary, carotid, or peripheral). 7. Any cardiovascular event (any of the former plus clinically significant peripheral vascular disease).	Adjusted HR: 0.65; 95% CI: 0.50-0.84. 5. Any coronary event: G1: 123 (5.2%), G2 204 (8.6%) Adjusted HR: 0.58; 95% CI: 0.46-0.73. 6. Revascularization: G1: 94 (4.0%), G2 163 (6.9%) Adjusted HR: 0.55; 95% CI: 0.43-0.72. 7. Any cardiovascular event: G1: 530 (22.4%), G2 687 (29.0%) Adjusted HR: 0.74; 95% CI: 0.66-0.83. **<u>Safety endpoint (if relevant)</u>:** -Any adverse event: G1 2199 (93%), G2 2156 (91.1%) -Any serious adverse event: G1 998 (41.8%), G2 975 (41.2%) -Any adverse event resulting in discontinuation of study treatment: G1 415 (17.5%), G2 342 (14.5%) -Myalgias: G1 129 (5.5%), G2 141 (6.0%) -Rhabdomyolysis: G1 2 (0.1%), G2 3(0.1%) -AST or ALT >3 x ULN at 2 consecutive measurements: G1 51 (2.2%), G2 11(0.5%) -CK >10 x ULN at 2 consecutive measurements: G1 2 (0.1%), G2 0	HR: 0.78; 95% CI: 0.66-0.94. - 88 hemorrhagic strokes: 55 atorvastatin, 33 placebo. HR: 1.66; 95% CI: 1.08-2.55. -19 unclassified strokes: 7 atorvastatin, 12 placebo. HR: 0.55; 95% CI: 0.21-1.40. -Incidence of fatal hemorrhagic stroke did not differ: 17 in the atorvastatin group, 18 in the placebo group.

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
GREACE Athyros VG, et al., 2002 (23) 12201623	**Aim:** To assess the effect of atorvastatin on morbidity and mortality (total and coronary) of patients with established coronary heart disease (CHD), **Study type:** Randomized (please see last column) **Size:** 1600 patients **Follow-up**: 3 y	**Inclusion criteria:** Patients with established CHD: history of prior MI or >70% stenosis of at least one coronary artery on a coronary angiogram. Age< 75 y, LDL-C >100 mg/dL, triglycerides <400 mg/dL. **Exclusion criteria:** Recent acute coronary syndrome, renal or liver dysfunction, prior hypolipidemic treatment, childbearing potential, any significant disease likely to limit life to less than the study duration (e.g. NYHA Class III or IV heart failure, malignancies), and patients scheduled for coronary revascularization.	**Intervention (G1):** Atorvastatin dose titration (from 10-80 mg daily) to get LDL-C below 100 mg/dL (n=800) performed in the university clinic. **Comparator (usual care) [G2]:** Lifestyle changes such as hypolipidemic diet, weight loss, exercise plus all necessary drug treatment (e.g. lipid lowering treatment) [n=800].	**Lipids/Lipid lowering medications:** -Intervention group (G1): 100% received atorvastatin, mean dose = 24 mg/d. -Usual care group (G2): 211 (26%) of the patients received hypolipidemia drug treatment. 98(12%) of these discontinued their treatment at 6-8 mo. Overall, 14% (n =113) of the patients in the usual care continued hypolipidemic treatment throughout the study (12% statins, 2% fibrates). -Mean LDL-C: G1 180 mg/dL (baseline), 97 mg/dL (on-treatment) G2: 179 mg/dL (baseline), 169 mg/dL (on-treatment). -Mean Non-HDL-C: G1 218 mg/dL (baseline), 123 mg/dL (on-treatment) G2: 218 mg/dL (baseline), 204 mg/dL (on-treatment). G1: 95% achieved LDL-C <100 mg/dL and 97% achieved non-HDL-C <130 mg/dL. G2: 3% achieved LDL-C <100 mg/dL and none achieved non-HDL-C <130 mg/dL. **1° endpoints (No OR or HR provided):**	•No placebo •No blinding •Adjudicators likely not blinded to the identity of the study group of the participants. •Active treatment (atorvastatin) versus usual care in different settings. •Two separate adjudication committees (one for each group). • Cost per quality-adjusted life year gained with atorvastatin = $US 8350.

				-Total mortality: G1 23 (2.9%), G2 40 (5%), p=0.0021. -Coronary mortality: G1 20 (2.5%), G2 38 (4.8%), p=0.0017. -Non-fatal MI: G1 21 (2.6%), G2 51 (6.4%), p=0.0001 -Unstable angina: G1 10 (1.2%), G2 21 (2.6%), p=0.0032. -PTCA/CABG: G1 22 (2.7%), G2 45 (5.6%), p=0.0011. -CHF: G1 11 (1.3%), G2 22 (2.7%), p=0.021. -Stroke: G1 9 (1.1%), G2 17 (2.1%), p=0.034. **Safety endpoint (if relevant):** Intervention group: 9 (1.1%) had side effects; 7 with liver enzyme increase >3 x ULN (specific liver enzymes i.e. AST or ALT not mentioned), 2 with persistent epigastric discomfort. No cases of myopathy. 6 patients withdrawn from the study due to side-effects attributed to atorvastatin. Usual care: Withdrawal from the study in 3 patients with liver enzyme elevation >3x ULN (0.4%) [p non-significant vs. atorvastatin).	

relative risk; NYHA, new York Heart Association; HF, heart failure; MI, myocardial infarction; LV, left ventricular; EF, ejection fraction; CK, creatine kinase; ULN, upper limits of normal; NNT = numbers needed to treat; LDL-C, low-density lipoprotein cholesterol; ULN, upper limit of normal; Non-HDL-C, non-high-density lipoprotein cholesterol; NYHA, New York Heart Association; PTCA, percutaneous transluminal coronary angioplasty; CHF, congestive heart failure; CABG, coronary artery bypass grafting; ULN, upper limit of normal

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events

REAL-CAD Taguchi I, et al., 2018 (24) 29735587	**Aim:** To determine whether higher-dose of pitavastatin (4 mg) would be beneficial and safe compared to lower-dose (pitavastatin 1 mg) in Japanese patients with stable CAD. **Study type:** Prospective, multicenter, randomized, open-label, blinded end point, physician-initiated superiority trial **Size:** 13,054 total. **Follow-up**: median follow-up = 3.9 years.	**Inclusion criteria:** Men and women 20 to 80 y of age with stable CAD as defined by a history of acute coronary syndrome or coronary revascularization >3 mo ago or a clinical diagnosis of CAD with angiographically documented coronary artery stenosis of at least 75% diameter narrowing. **Exclusion criteria:** Patient with LDL-C <100 mg/dL without statin therapy. Other major exclusions included coronary revascularization scheduled but not yet completed, active malignancy, history of hypersensitivity to any of the ingredients of pitavastatin, serious liver disorder or bile duct obstruction, currently under treatment with cyclosporin, women who are pregnant, potentially pregnant, or lactating, serious heart failure (left ventricular ejection fraction <30% or NYHA classification class III or above), receiving dialysis, familial hypercholesterolemia, participating in another clinical study, under treatment with a prohibited	**Intervention (G1):**. Pitavastatin 4mg (n= 6526) **Comparator (G2):** Pitavastatin 1mg (n= 6528)	**Lipids/ Lipid lowering medications:** -Intervention group (G1): Mean baseline LDL-C (after run-in period) = 87.7 mg/dL 6 mo LDL-C = 73.7 mg/dL. -Comparator group (G2): Mean baseline LDL-C (after run-in period) = 88.1 mg/dl 6 mo LDL-C = 89.4 mg/dL. - LDL-C difference = 14.7 mg/dL between G1 and G2. **1° endpoints** (composite of cardiovascular death, nonfatal myocardial infarction, nonfatal ischemic stroke, or unstable angina requiring emergency hospitalization): -4.3% in G1 versus 5.4% in G2 (HR: 0.81; 95% confidence interval, 0.69–0.95; p=0.01) **Secondary and other relevant endpoints** (composite of the primary end point event and clinically indicated coronary revascularization, excluding target-lesion revascularization for lesions treated at prior percutaneous coronary intervention): -7.9% In G1 versus 9.7% in G2 (HR: 0.83; 95% CI: 0.73–0.93; p=0.002) -Death from any cause: 3.3% in G1 versus 4.2% in G2 (HR: 0.81; 95% CI, 0.68-0.98)	• Open label • Run in period with pitavastatin 1 mg po daily for at least 1 month. • The actual event rate was lower than anticipated. However, the steering committee decided not to extend the study further despite the original event-driven trial design because a substantial number of centers were reluctant to extend the study further. • Final follow-up completed in 83.4% in G1 and 83.2% in G2. • The rate of adherence to the study drug was high in both groups, although it was slightly but significantly lower in G1 than in G2 (97.1% and 98.7% at 6 mo, 74.8% and 76.8% at 4 y; p=0.02) • Study drug discontinuation was slightly but significantly more frequent in G1 than G2 (9.8% and 8.1%; p<0.001).

		concomitant drug that cannot be discontinued, not a suitable candidate for study participation for some other reasons, in the opinion of the investigator or subinvestigator.		- Myocardial Infarction: 0.6% in G1 versus 1.2% in G2 (HR: 0.57; 95% CI: 0.38-0.83) -Coronary revascularization (all): 8.5% in G1 versus 10.1% in G2 (HR: 0.86; 95% CI: 0.76-0.96) - Coronary revascularization (nontarget-lesion): 4.5% in G1 versus 5.7% in G2 (HR: 0.79; 95% CI: 0.68-0.92) -No significant difference in the risk of cardiovascular death, cardiac death, ischemic stroke, hemorrhagic stroke, unstable angina requiring emergency hospitalization, target lesion coronary revascularization. **Safety endpoint (if relevant):** -Muscle complaints: 1.9% in G1 versus 0.7% in G2, p<0.001 -No significant difference in rhabdomyolysis, gallbladder-related events, new onset diabetes mellitus, psychiatric disorders, elevation of alanine aminotransferase, aspartate aminotransferase, or both ≥3 upper limit of normal range, elevation of creatine kinase ≥5 upper limit of normal range	

Abbreviations: 1° indicated primary; CI, confidence interval; HR, hazard ratio; N/A, not available; OR, odds ratio; RCT, randomized controlled trial; RR, relative risk; LDL-C, low-density lipoprotein cholesterol; CAD, coronary artery disease; NYHA, New York Heart Association

Data Supplement 8. Evidence Tables for Secondary Prevention (Section 4.1)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)

Virani SS et al, 2017(25) 28465286	**Study type:** Observational Study evaluating what proportion of patients with ASCVD seeking care in the VA health care system would qualify for evolocumab based on FOURIER trial criteria. The authors also evaluated how eligibility for PCSK9 inhibitor therapy would change if high-intensity statins, ezetimibe, or the combination of both agents were used. **Size**: 631, 855 patients with ASCVD receiving care in the VA health care system between October 2013 and September 2014	**Inclusion criteria:** Same as FOURIER trial inclusion criteria **Exclusion criteria:** Same as FOURIER trial exclusion criteria	**1° endpoint:** Proportion of patients with ASCVD meeting FOURIER trial criteria **Results:** -154,823 patients (24.5%) with ASCVD met FOURIER criteria based on LDL-C and non-HDL-C cutoffs. - 49.9% of the ASCVD patients who qualified were on high-intensity statins, 47.5% were on moderate intensity statins, and 2.6% were on a statin/ezetimibe combination -Titration to a high-intensity statin would be expected to reduce LDL-C to <70 mg/dL in an additional 28,930 FOURIER-eligible patients (18.7%) with a mean achieved LDL-C of 63 mg/dL. -Initiation of ezetimibe would lead to LDL-C <70 mg/dL in an additional 78,507 patients (50.7%) with a mean achieved LDL-C of 60 mg/dL. -Combination of high-intensity statin plus ezetimibe would lead to LDL-C <70 mg/dL in 92,538 patients (59.8%) with a mean achieved LDL-C of 58 mg/dL. -Estimated costs associated with treating the 154,823 patients eligible for FOURIER with evolocumab would be $2.08 billion/year. Restricting evolocumab use in patients with LDL ≥70 mg/dL, after accounting for cost associated with titration to high-intensity statin plus ezetimibe, would be expected to result in an annual net cost savings of $1.13 billion.	-Healthcare systems have considerable opportunity to increase the use of evidence-based high-intensity statins and ezetimibe, which may reduce the need for additional PCSK9 inhibitor therapy.

Cannon et al, 2017 (26) 28768335	**Study type:** Observational study using a large database of medical and pharmacy claims (MarketScan). The study aimed to estimate the percentage of patients with ASCVD who would require a PCSK9 Inhibitor (alirocumab) when oral lipid-lowering therapy is intensified first. **Size:** Cohort of 105269 patients with ASCVD who met inclusion criteria (database cohort). Patients were sampled with replacement (bootstrapping) to match the US epidemiologic distribution and entered into a Monte Carlo simulation (simulation cohort) that applied stepwise treatment intensification algorithms in those with LDL-C levels of at least 70mg/dL. The simulation cohort included 1 million patients (bootstrapping allowing for multiple replications per individual).	**Inclusion criteria:** Patients 21 years or older; LDL-C level measured from January1, 2012, through December 31, 2013; 2 years of continuous enrollment before the index date; and ASCVD defined as (1) recent acute coronary syndrome, (2) other coronary heart disease, (3) ischemic cerebrovascular disease, and (4) peripheral arterial disease.	**1° endpoint:** Use of lipid lowering therapy in the ASCVD patients and distributions of LDL-C levels under various treatment intensification scenarios **Results:** -53.2% ASCVD patients were receiving statins at baseline and 15.3% were receiving a high-intensity statin. -25.2% achieved LDL-C levels of less than 70mg/dL. -When a 20-mg dose of atorvastatin was added for patients not receiving a statin, 49.1% of the overall cohort achieved an LDL-C level of less than 70mg/dL. Of the remaining 50.9% patients, 9.1% were already receiving high-intensity statins and 41.8% would undergo uptitration to atorvastatin, 80mg. The uptitration resulted in an additional 20.2% achieving an LDL-C level of less than 70mg/dL (overall cohort with LDL-C level <70 mg/dL, 69.3% at this stage). - Of the remaining 30.7% not at the LDL-C goal, 0.9% were already taking concomitant ezetimibe; therefore, ezetimibe was added in the remaining 29.8% of the cohort receiving high intensity statins and not at the LDL-C level goal. After this step in intensification, an additional 16.7% were able to achieve the LDL-C goal (total at LDL-C goal, 86%) and 14% of the original cohort required additional treatment with alirocumab.	- 69.3% of ASCVD patients could achieve LDL-C levels of less than 70mg/dL with statin initiation and/or uptitration only, and add-on ezetimibe could increase this percentage to 86%. Adding a PCSK9 inhibitor to therapy for the remaining14% still above the LDL-C threshold could result in more than 99% of the population with ASCVD having LDL-C levels of less than 70mg/dL. -In a model that assumes no lipid lowering therapy intolerance and full adherence, intensification of oral lipid lowering therapy could achieve an LDL-C level of less than 70mg/dL in most patients, with only a modest percentage requiring a PCSK9 inhibitor

			- Addition of a 75-mg dose of alirocumab for patients not at the LDL-C goal resulted in an incremental 12% achieving an LDL-C level of less than 70 mg/dL. The remaining 2% of the cohort received uptitration to alirocumab, 150mg. At this final step of the intensification, only 0.7% of the original cohort failed to achieve an LDL-C level goal of less than 70 mg/dL. -In summary, simulation of maximal lipid-lowering treatment intensification indicated that 99.3% could achieve LDL-C levels of less than 70mg/dL, including 86% receiving statins and ezetimibe and 14% with add-on PCSK9 inhibitors.	

Abbreviations: 1° indicated primary; CI, confidence interval; HR, hazard ratio; N/A, not available; OR, odds ratio; RR, relative risk; ASCVD, atherosclerotic cardiovascular disease; FOURIER, Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk; VA, Veterans Affairs; LDL-C, low-density lipoprotein cholesterol; non-HDL-C, non-high density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9.

Study	Sample Size Study Duration Adherence	Drug Tested Statin Used	Study Population	Primary and Secondary Outcomes*	Major Adverse Events
dal-OUTCOMES (Schwartz et al) (27) 23126252	15,871 Median 31 mo *Adherence* – Active 79% – Placebo 81% – Based on % of participants who continued taking study drug throughout the study – 89% of participants in each group had	Dalcetrapib 600 mg daily 97% on a statin Intensity or dose not reported	*Inclusion* – Prior hospitalization for ACS, MI with PCI – Target baseline LDL <100 mg/dL, preferably 70 mg/dL, but not excluded if higher *Exclusion (cardiovascular)* – TG >400 mg/dL Mean age 60.3±9.1 y 20% women 12% nonwhite	ERC primary outcome Not reported ERC secondary outcome Not reported Study primary outcome Death from coronary heart disease, nonfatal MI, ischemic stroke, unstable angina, or cardiac arrest with resuscitation) – HR: 1.04 (0.93–1.16) – Event rates 9.2% vs. 9.1%, *p*=0.52	– Mean SBP remained approximately 0.6 mm Hg higher with dalcetrapib vs. placebo (*p*<0.001) – Greater incidence of hypertension with dalcetrapib (7.3% vs. 6.5%) but smaller difference in report of hypertension as a serious event (0.6% vs. 0.3%) – Greater incidence of diarrhea 6.8 vs. 4.3

	at least 80% adherence to study drug				
FOURIER (Sabatine et al) (28) 28304224	27,564 Median follow-up 2.2 y *Adherence* – Active 88% – Placebo 87% – Based on number taking study drug; specifics of adherence not reported	Evolocumab either 140 mg every 2 wk or 420 mg monthly – High-intensity statin 69.5% – Moderate-intensity statin 30.2%	*Inclusion* – Age 40–85 y – Clinically evident ASCVD (prior MI, nonhemorrhagic stroke, or symptomatic PAD) – Most recent fasting LDL-C ≥70 mg/dL or non-HDL-C ≥100 mg/dL after ≥2 weeks of stable lipid-lowering therapy – Fasting TG <400 mg/dL – PLUS • *At least 1 major risk factor* (DM, age >65 y, prior MI or nonhemorrhagic stroke in the last 6 mo, current daily smoking, prior MI, stroke, symptomatic PAD) • Or *2 minor risk factors* (prior non–MI-related revascularization, residual >40% stenosis in ≥2 large vessels, most recent HDL-C <40 mg/dL for men and <50 mg/dL for women, most recent hsCRP >2.0 mg/L, most recent LDL-C ≥130 mg/dL or non-HDL-C ≥160 mg/dL, metabolic syndrome) *Exclusion (cardiovascular)* – MI or stroke within 4 weeks	ERC primary outcome – HR: 0.80 (95% CI: 0.73–0.88) – Event rates (5.9% vs. 7.4%), $p<0.001$ – ARR: 1.5% – NNT: 67 ERC secondary outcome – HR: 0.85 (95% CI: 0.79–0.92) – Event rates (9.8% vs. 11.3), $p<0.001$ – ARR: 1.5% – NNT: 67	Injection site reactions more frequent with evolocumab (2.1% vs. 1.6%), 90% were considered mild, 0.1% in each group stopped treatment because of a reaction

			– NYHA class III or IV or last ejection fraction <30% – Any prior hemorrhagic stroke – Uncontrolled BP – Uncontrolled or recurrent ventricular tachycardia Mean age 62.5±9.1 y 25% women 15% nonwhite		
ODYSSEY Outcomes (Schwartz et al,) (29) PMID-IN PRESS	18,924 Median follow-up 2.8 y *Adherence* – Active 96.4 % – Placebo 96.6 % – Based on study discontinuation rates	Alirocumab 75–150 mg every 2 wk Drug was titrated to goal LDL 25–50 mg/dL; switched to placebo if LDL<15 mg/dL High-intensity statin in 88.6% Low-moderate intensity in 8.8%	*Inclusion* – Age >40 y – ACS within past 1–12 mo – LDL ≥70 mg/dL or non-HDL ≥100 mg/dL or ApoB ≥80 mg/dL – High-intensity statin ≥2 weeks *Exclusion (cardiovascular)* – Uncontrolled hypertension – NYHA class III or IV heart failure – Ejection fraction <25% – TG >400 mg/dL Mean age 58 y 25% women Nonwhite participation not reported	ERC primary outcome – HR: 0.85 (95% CI: 0.78, 0.93) – Event rates 9.5% vs. 11.1, *p*<0.001 – ARR: 1.6% – NNT: 63 ERC secondary outcome‡ – HR: 0.87 (95% CI: 0.81, 0.94) – Event rates 13.7% vs. 15.6%, *p*<0.001 – ARR: 1.9% – NNT: 53	Injection site reaction 3.8% vs. 2.1%, HR: 1.82 (95% CI: 1.54–2.17)

ACC indicates American College of Cardiology; ACS, acute coronary syndrome(s); ALT, alanine aminotransferase; apoB, apolipoprotein B; ARR, absolute risk reduction; ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CABG, coronary artery bypass graft; CAD, coronary artery disease; CI, confidence interval; CKD, chronic kidney disease; CRP, C-reactive protein; CV, cardiovascular; CVD, cardiovascular disease; DBP, diastolic blood pressure; DM, diabetes mellitus; ERC, evidence review committee; FDA, U.S. Food and Drug Administration; FH, familial hypercholesterolemia; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; hsCRP, high-sensitivity C-reactive protein; IV, intravenous; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; NNT, number needed to treat; NYHA, New York Heart Association; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; TG, triglycerides; and ULN, upper limit of normal.

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†Outcomes only included coronary death, not CVD death.

‡Includes only coronary heart disease death, not CVD death.

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Giugliano RP et al 2017 (30) 28813214	**Study type/Design:** Substudy of the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial that evaluated ASCVD outcomes in those on statin therapy assigned to evolocumab or placebo Double-blind randomization was performed with the use of a central, 24-hour, interactive, computerized response system, with stratification according to region and final screening LDL cholesterol level (<85 mg per deciliter [2.2 mmol per liter] or ≥85 mg per deciliter). Evaluated cognition using the Cambridge Neuropsychological Test Automated Battery (CANTAB, www.cambridgecognition.com) **Study Size:** A total of 2442 patients in the FOURIER trial were screened for eligibility for the	**Inclusion criteria:** Enrolled before administration of first dose of study drug or placebo -40 and 85 years of age, -clinically evident atherosclerosis -LDL cholesterol level of 70 mg per deciliter (1.8 mmol per liter) or higher or a non–high-density lipoprotein level of 100 mg per deciliter (2.6 mmol per liter) or higher, -receiving moderate-intensity or high-intensity statin therapy. **Excusion criteria:** Current or past diagnosis of dementia or mild cognitive impairment or any condition or situation, including other mental or neurologic disorders, that, in the investigator's opinion, could confound the study results or considerably interfere with the	**1° endpoint:** The score on the spatial working memory strategy index of executive function, a principal component of CANTAB; CANTAB was performed at screening (training session), at baseline, at 24 weeks, yearly, and at the end of the trial. **Results:** Primary endpoint: Evolocumab: -0.21±2.62 Placebo group: 0.29±2.81 P<0.001 for noninferiority; P=0.85 for superiority) Secondary endpoints: No significant between-group differences in scores for working memory (change in raw score Evolocumab: -0.52 Placebo group: -0.93) For episodic memory (change in raw score, Evolocumab: -1.53 Placebo group: -1.53) For psychomotor speed (change in raw score, Evolocumab: 5.2 msec	**Conclusions:** In a randomized trial involving patients who received either evolocumab or placebo in addition to statin therapy, no significant between-group difference in cognitive function was observed over a median of 19 months **Strengths: Done in the context of a randomized controlled clinical trial of large size** **CANTAB tool has been validated as a research tool** **There was absence of sef reported clinical change in cognition to parallel these results** **Limitations:** Followup period short Patients with mid cognitive impairment or known dementia were not included CANTAB tool not a standard in clinical practice

	EBBINGHAUS study, and 1974 were enrolled (full-analysis population).	patient's participation in the trial.	Placebo group: 0.9 msec) In an exploratory analysis, there were no associations between LDL cholesterol levels and cognitive changes	

Data Supplement 9. RCTs comparing evidence on Severe Hypercholesterolemia (Section 4.2)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
ENHANCE Kastelein JJ, et al., 2008 (31) 18376000	To assess the effect of ezetimibe on progression of carotid intima-media thickness in patients with HeFH **Study design**: Double blind placebo-controlled RCT multicenter study **Size**: N=720 patients	**Inclusion criteria:** Men and women age 30-75 with clinical HeFH defined by WHO criteria. LDL-C ≥ 210 mg/dL untreated; if on treatment LDL-C ≥ 210 mg/dL after placebo run-in. **Exclusion criteria:** high-grade stenosis or occlusion of the carotid artery, a history of carotid endarterectomy or carotid stenting, homozygous FH, New York Heart Association class III or IV congestive heart failure, cardiac arrhythmia, angina pectoris, or recent cardiovascular events.	**Intervention/Comparator:** Simvastatin 80 mg daily plus placebo (360) vs. simvastatin 80 mg daily plus ezetimibe 10 mg (360) daily over 24 mo.	**Primary endpoint:** Change from baseline in the average of the means of the far-wall intima–media thickness of the right and left common carotid arteries, carotid bulbs, and internal carotid arteries in the two study groups. **Results:** There was no significant difference in the change in CIMT in the simvastatin monotherapy group versus with simvastatin-ezetimibe group Fasting blood samples were obtained for analysis of lipid measures, as well as laboratory measures of liver aminotransferase levels, renal function, and hematologic values. **Results:** There was a statistically significant difference in the fall in LDL-C and apo B between the simvastatin monotherapy group (317.8±66.1 mg/dl to 192.7±60.3	**Secondary endpoint:** Proportion of patients with regression in carotid- artery intima–media thickness from baseline, the proportion of patients with new carotid-artery plaques of more than 1.3 mm, the change from baseline in the maximal carotid-artery intima–media thickness and the change from baseline in the average intima–media thickness of the carotid and common femoral arteries. Results: No difference between the simvastatin monotherapy and simvastatin-ezetimibe group in any secondary endpoint Adverse events: Adverse events and safety profile were similar in the two groups **Study limitations:** 1. Statin pre-treatment resulting in plaque lipid depletion and normal baseline CIMT may have biased the results.

				mg/dL for LDL-C and 254.1±49.3 to 168.8±44.3 for apo B) and the simvastatin-ezetimibe group (319.0±65.0 mg/dL to 141.3±52.6 mg/dL for LDL-C and 253.9±47.6 to134.6±39.1 for apo B), p<0.01 for both.	
IMPROVE-IT Cannon C, et al., 2015 (32) 26039521	**Aim:** To determine whether the addition of ezetimibe to a statin reduces the incidence of cardiovascular events as compared to statin monotherapy. **Study design:** Double blind placebo-controlled RCT multicenter study **Size:** N= 18,144	**Inclusion criteria:** 1. Men and women 50 y of age or older who had been hospitalized with the preceding 10 d for an acute coronary syndrome 2. Patients required to have LDL-C ≥ 50 mg/dL 3. For those not on lipid-lowering therapy at baseline, LDL-C ≤ 125 mg/dL. 4. For those on lipid-lowering therapy, LDL-C ≤ 100 mg/dL. **Exclusion criteria:** 1. Planned coronary bypass surgery for the acute coronary event 2. Creatinine clearance <30 ml/min. 3. Active liver disease 4. Use of statin therapy that had potency greater than simvastatin 40 mg daily.	**Intervention/Comparator:** Simvastatin 40 mg daily (9072) plus placebo versus simvastatin 40 mg daily plus ezetimibe 10 mg daily (9072) over a median follow-up of 6 y.	**1º endpoint:** 1. Composite of cardiovascular death, nonfatal myocardial infarction, unstable angina requiring re-hospitalization, coronary revascularization (≥30 d after randomization), or nonfatal stroke. **Results:** 1. Median time- weighted average LDL-C for placebo patients was 69.5 mg/dl vs. 53.7 for those taking ezetimibe. 2. Kaplan Meier event rate for the primary endpoint was 34.7% in those receiving placebos vs.32.7% in those on ezetimibe (absolute risk reduction 2%, hazard ratio: 0.936; 95% CI: 0.89-0.99; p=0.016.	1. Ezetimibe added to moderate-intensity statin therapy lowered LDL-C and reduced the incidence of cardiovascular events. 2. Ezetimibe therapy was safe and well-tolerated. **Limitations:** 1. 42% of the patients stopped the study medicine prematurely.
Silverman MG, et al., 2016 (33) 27673306	**Aim:** To evaluate association between LDL cholesterol lowering and relative cardiovascular risk reduction employing statin and non-statin therapies	**Inclusion criteria:** 49 RCT's of 9 different approaches to LDL-C reduction with reported ASCVD outcomes that included myocardial infarction	**Intervention/comparator:** Drug vs. placebo	**1ºendpoint:** Relative risk of major vascular events (a composite of cardiovascular death, acute MI or other acute coronary syndrome, coronary revascularization, or stroke) associated with the absolute reduction in LDL-C level; 5-y rate of	**Limitations:** PCSK9 inhibitor outcome trial results were not available to be included in the results of this study

	Study type: Meta-analysis of RCT's **Size:** N=312,175	**Exclusion criteria:** RCT's of <6 mo duration or with fewer than 50 clinical events		major coronary events (coronary death or MI) associated with achieved LDL-C level. 1. Relative risk for major vascular events per 38.7 mg/dL reduction in LDL-C was 0.77 (95% CI: 0.71-0.84), p<0.001) and was 0.75 for non-statin interventions that work primarily by up-regulation of LDL-receptor expression, including diet, bile acid sequestrants, ileal bypass and ezetimibe (between-group significance, p=0.72). Combined therapies were associated with a relative risk reduction of 0.77 (95% CI: 0.75-0.79, p<0.001). 2. Achieved absolute LDL-C level was associated with the absolute rate of major coronary events (11,301 coronary deaths or myocardial infarctions for primary prevention trials (1.5% lower event rate [95% CI: 0.5-2.6%] per each 38.7 mg/dL lower LDL-C level; p=0.008) and secondary prevention trials (4.6% lower event rate [95% CI: 2.9-6.4%] for each 38.7 mg/dL lower LDL-C; p<0.001). 3. Interventions (in aggregate) that lower LDL-C via other mechanisms did not demonstrate ASCVD risk reduction.	
Shepherd J, et al., 1995 (34) 7566020	**Aim:** To assess the effect of pravastatin therapy on the incidence of non-fatal MI and coronary heart disease death in hypercholesterolemic Scottish men	**Inclusion criteria:** Men 45-64 y of age with no history of MI with LDL-C ≥ 155 mg/dL during and at least one value 174-232 mg/dL during pre-randomization visits. Patients with a history of	**Intervention/comparator:** Pravastatin 40 mg daily vs. placebo over a mean follow-up period of 4.9 y	**1º endpoint:** 1. Combined occurrence of nonfatal MI or death from coronary heart disease as a first event. 2. Occurrence of death from coronary heart disease and nonfatal MI.	**2º endpoint:** Death from cardiovascular causes, death from any cause, and the frequency of coronary revascularization procedures. Results: In the pravastatin group there was a 32% relative risk reduction in risk of death from all cardiovascular causes (95% CI: 3-

	Study Design: Double blind placebo controlled RCT **Size:** N= 6595	stable angina could be enrolled if no hospitalization in the preceding 12 mo **Exclusion criteria:** 1. No history or ECG evidence of MI 2. No atrial fibrillation, flutter, frequent premature ventricular beats, high grade atrioventricular block 3. Blood pressure >180/110 mm Hg 4. History of rheumatic, congenital or pulmonary heart disease 5. Cardiomegaly, congestive heart failure or significant valvular heart disease 6. Psychiatric illness 7. Current lipid lowering therapy 8. Excluding laboratory values, including triglycerides >534 mg/dL		**Results:** 1. In the pravastatin group there was a 31% relative risk reduction (95% CI: 17-43%, p<0.001) in the combined endpoint of definite non-fatal MI and coronary heart disease death (absolute risk reduction 2.4%)	53%, p=0.0333) and a 37% reduction in revascularization procedures (95% CI: 11-56%; p=0.009) Adverse events were similar in pravastatin and placebo groups. **Limitations:** Men only
RUTHER-FORD Raal FJ, et al., 2015 (35) 25282519	**Aim:** To investigate the effect of PCSK9 inhibition with evolocumab on LDL-C in patients with heterozygous FH **Study Type**: Randomized double-blind placebo-controlled multicenter trial **Size**: N=331 patients	**Inclusion criteria:** Men and women age 18-80 with clinical FH using Simon-Broome criteria on stable dose of statin ± ezetimibe, resins, stanols or niacin; LDL-C ≥ 100 mg/dL; mutations causative of FH were recorded in 211 of 264 patients (80%) who consented to genetic analysis. **Exclusion criteria**: Fibrate therapy. Apheresis within the past 4 mo. HoFH.	**Intervention/comparator:** Patients randomly allocated in a 2:2:1:1 ratio to receive SQ evolocumab 140 mg Q2 wk (N=111), 420 mg Q month (N=110), placebo Q2 wk (n=55) or placebo Q month (n=55) for 12 wk	**1ºendpoint**: Compared with placebo: Evolocumab Q 2 wk: reduced LDL-C by 59% (95% CI: 4-65.1, p<0.0001) Q 4 wk: reduced LDL-C 61.3% (95% CI: 53.6-69, p<0.0001). >60% treated with evo at either dose achieved LDL-C < 70 mg/dL Reduction in Lp(a) ranged from 19-45%. Post hoc analysis showed LDL-C reduction in those with no genetically defined mutation was similar to that in those with genetically confirmed FH	**Adverse events**: Rates of adverse events with evolocumab similar to placebo. Limitations: 1. Analysis of response based on genotype was post hoc. 2. Short study duration (12 wk)

ODYSSEY FH 1 and 2 Kastelein JJP, et al., 2015 (36) 26330422	**Aim:** To assess LDL-C lowering efficacy and safety of long-term (78 wk) alirocumab treatment in patients with HeFH **Study type**: Combined results of two randomized double-blind placebo-controlled multicenter trials **Size:** N=735 patients	**Inclusion criteria:** Men and women age ≥18 y with HeFH with no history of CV events; and those who had a history of a myocardial infarction or ischemic stroke, if their LDL-C levels were ≥ 100 mg/dL for primary or ≥ 70 mg/dL for secondary prevention, respectively. HeFH was diagnosed with a score >8 points. Patients had to be on stable dose of statin for ≥4 wk and/or fenofibrate ≥6 wk prior to screening visit and from screening visit to randomization. **Exclusion criteria:** Known HoFH or fasting TG >400 mg/dL	**Intervention/comparator:** Patients were randomized 2: 1 to receive either alirocumab 75 mg every 2 wk or placebo. Randomization stratified by history of MI or ischemic stroke, statin treatment (atorvastatin 40–80 mg or rosuvastatin 20–40 mg daily vs. simvastatin in any dose, atorvastatin <40 mg daily, or rosuvastatin <20 mg daily), and geographic region (FH I only). Dose of alirocumab was increased in a blinded fashion to 150 mg Q2W at Wk 12 if the patient's LDL-C level at wk 8 was 70 mg/dL. Comparator: Placebo	**1º endpoint:** % change in calculated LDL-C from baseline to Wk 24. using an intention-to-treat (ITT)approach, including values obtained after stopping treatment in patients who discontinued therapy: **Results:** Mean LDL-C decreased from 145 mg/dL at baseline to 71 mg/dL (-57.9% vs. placebo) at wk 24 in patients randomized to alirocumab in FH 1 and from 135 mg/dL to 68 mg/dL in FH 2 (p<0.0001).	**Secondary endpoints:** % change in LDL-C in an on-treatment analysis and the proportion of patients reaching LDL-C <100 mg/dL (for those without prior CV events) and <70 mg/dL regardless of prior CV events; the proportion achieving LDL-C <70 regardless of CV events. All achieved significant reductions. The reductions were maintained through wk 78. LDL-C <70 mg/dL, regardless of CV risk was achieved at wk 24 by 59.8 and 68% of alirocumb-treated patients in FH1 and FH2 respectively. **Safety endpoints:** The percentage of patients experiencing treatment-emergent adverse events were similar between treatment groups in the individual studies. Anti-drug antibodies were observed in 17 (5.5%) of alirocumab and one (0.6%) placebo-treated patient in FH I and 14 (8.6%) alirocumab and one (1.3%) placebo
Ross S, et al., 2015 (37) 26043746	**Aim:** To assess the effect of bile acid sequestrants on the incidence of coronary artery disease events **Study type**: Meta-analysis of RCT N=7,021	**Inclusion criteria:** 19 RCT's employing therapy with cholestyramine or coselsevelam was performed as part of a study using Mendelian randomization to assess the effect of bile acid sequestrants on CAD: 6 of	**Intervention/comparator:** Bile acid sequestrant vs. placebo, or bile acid sequestrant vs. additional lipid lowering drug or bile	**1ºendpoint:** Studies evaluating: 1. Cardiovascular mortality 2. Incidence of myocardial infarction 3. Baseline and mean endpoint values or the absolute difference in the intervention and placebo arms for change in LDL-C	**2ºendpoints:** Baseline and endpoint mean values or the absolute treatment difference in the intervention and placebo arms for the change in HDL-C, total cholesterol, triglycerides, apolipoprotein A1 and apolipoprotein B

		cholestyramine, 3 of colestipol and 10 of colesevelam. **Exclusion criteria:** 1.The 3 studies on colestipol were excluded because of lack of reported data and differences in the study dose 2. Only the Lipid Research Clinics Coronary Primary Prevention Trial was used for cholestyramine because of the heterogeneity in the pooled estimates of the lipid results from the cholestyramine studies	acid sequestrant + additional lipid-lowering drug	**Results:** 1. Cholestyramine therapy 24 grams daily reduced LDL-C by 23.5 mg/dL (95% CI: -26.8 to -20.2; N=3,806 and exhibited a trend toward reduced coronary artery disease risk (odds ratio: 0.81; 95% CI: 0.70-1.02; p=0.07; N=3806) 2. Colesevelam 3.75 grams daily reduced LDL-C by 22.7 mg/dL (95% CI: -28.3, -17.2; N=759) 3. There ae no adequately powered trials of bile acid sequestrants to determine their effect on coronary artery disease endpoints.	
Huijgen R, 2010 (38) 20435231	**Aim:** Assess efficacy ad tolerability of colesevelam added to maximally tolerated, stable dose combination treatment with a statin plus ezetimibe in patients with heterozygous FH. **Study type**: Randomized double-blind placebo controlled multicenter trial **Study size:** N=86 patients (45 colesevelam and 41 placebo)	**Inclusion criteria**: Men and women age 18-75 y with history of a documented LDL receptor mutation or an untreated LDL-C >95th percentile for sex and age in combination with at least one of the following: (1) typical tendon xanthomas in the patient or in a first-degree relative; (2) an LDL-C > 95th percentile in a first-degree relative; and (3) coronary artery disease in the patient or in a first-degree relative aged <60 y. Additional eligibility criteria were refractory FH, defined as an LDL-C concentration >95 mg/dL despite combination treatment with a maximally tolerated and stable regimen of a	**Intervention:** Colesevelam 625 mg 6 tablets daily with a meal or beverage taken either as 6 tablets one daily or 3 tablets twice daily **Comparator:** Placebo	**1º endpoint:** difference in the percentage change from baseline to wk 6 in LDL-C between colesevelam and placebo. Tolerability was assessed based on prevalence and severity of adverse events or on laboratory analysis of hematology and blood chemistry, including CK, liver and kidney function tests, and discontinuation due to AEs at the end of 12 wk. **Results:** The between-group difference in change from baseline LDL-C was significant at wk 6, with an LSM change of –18.5% (95% CI: –25.3 to –11.8) p<0.001 Apo A1/apo B ratio fell by 14% (p=0.003). No change in hs-CRP	**2º endpoint:** Various lipid parameters, HgbA1C and hs-CRP Adverse events: Frequency of treatment-emergent adverse events over the 12-wk study period was not significantly different between the colesevelam and placebo groups. The most commonly reported TEAEs were gastrointestinal (12/45 [27%] and 7/40 [18%], respectively; p=NS). **Limitations:** 1. Small number of patients 2. Short duration 3. DM and high TG were exclusion criteria

		combination of a statin + ezetimibe for ≥12 consecutive wks preceding the screening visit.			
Cholesterol Treatment Trialists Collaborators, 2010 (13) 21067804	**Aim:** Assess the safety and efficacy of more intensive statin therapy Meta-analysis of individual participant data from statin RCT with ASCVD outcomes **Size:** N=169,138	Major statin primary and secondary prevention trials with at least 1000 participants with a minimum follow-up of 2 y, including trials of more versus less intensive statin regimens (five trials; 39, 612 subjects; median follow-up 5.1 y) and statin versus control (21 trials; 129 526 subjects; median follow-up 4.8 y). **Exclusion criteria:** For acute coronary syndrome subjects, revascularization not related to recurrent ischemia or occurring <30 d from the time of randomization	**Intervention/Comparator:** Statin versus control More intense versus less intense statin	**1º endpoint:** Cause-specific mortality, major coronary event defined as coronary death or non-fatal MI percutaneous coronary intervention or bypass grafting), stroke (subdivided by type), and new cancer diagnosis (subdivided by site). **Results:** 1. More intensive versus less intensive regimens produced a 15% (95% CI: 11-18; p<0.0001) further reduction in major vascular events, including a 13% (95% CI: 7-19; p<0.0001) further reduction in coronary death or non-fatal MI, a 19% (95% CI: 15-24; p<0.0001) reduction in coronary revascularization, and a 16% (95% CI: 5-26, p=0.005) in ischemic stroke. 2. For every 39 mg/dL reduction in LDL-C, there was a 22% (rate ratio 0.78; 95% CI: 0.76-0.80; p<0.0001) reduction in the relative risk of major vascular events. 3. All-cause mortality was reduced by 10% for every 39 mg/dL LDL-C reduction (rate ratio 0.9; 95% CI: 0.87-0.93; p<0.0001) primarily due to reduction in coronary heart disease death (risk ratio: 0.8; 99% CI: 0.74-0.87; p<0.0001) and other cardiac causes (risk ratio: 0.89: 99% CI: 0.89-0.98; p=0.002).	N/A

				3. No effect on death due to stroke or other vascular causes and no effect on death due to cancer, death from non-vascular causes or on cancer incidence.	

Data Supplement 10. Non-randomized Trials, Observational Studies and/or Registries for Severe Hypercholesterolemia (Section 4.2)

Study Acronym: Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Perak, AM, et al., 2016 (39) 27358432	**Study Type:** Pooled cohort analysis from 6 large US epidemiological cohorts **Size:** 68565 baseline person-examination	**Inclusion criteria:** Men and women stratified by LDL-C at ages 20-79 y with at least 1 baseline examination with direct measurement of serum lipids, physiological and anthropometric variables. Primary analysis defined FH phenotype as LDL-C ≥ 190 mg/dL and referent <130 mg/dL **Exclusion criteria:** N/A	**1ºendpoint:** long term CHD and total ASCVD risks in UD adults with an FH phenotype. **Results:** After co-variate adjustment, FH phenotype was associated with HR: up to 5.0 (95% CI: 1.1-21.7). CHD risk was accelerated by 10-20 y in men and 20-30 y in women. Total ASCVD risk was associated with HR: up to 4.1 (95% CI: 1.2-13.4)	**Summary:** FH phenotype is associated with increased risk for ASCVD and accelerates risk in both men and women. **Limitations:** 1. Phenotypic rather than genotypic diagnosis of FH. 2. Single measurement of LDL-C for inclusion 3. Secondary hypercholesterolemia was not excluded. 4. Limited family data available
Khera AV, et al., 2016 (40) 27050191	**Study Type**: Pooled cohort analysis of 7 CAD case control cohorts and 5 prospective cohort studies **Size:** 20,485 subjects	**Inclusion criteria:** 1386 subjects were identified with LDL-C ≥ 190 mg/dL. Whole exome gene sequencing was done on those with LDL-C ≥ 190 mg/dL comparing risk for CAD in those with vs. without FH-causing mutations. **Exclusion criteria:** N/A	**1ºendpoint:** Prevalence of an FH mutation among those with severe hypercholesterolemia and determination of whether CAD risk varies according to mutation status beyond the observed LDL-C level. **Results:** 1. Those with LDL-C ≥190 mg/dL and no FH mutation had a 6-fold higher risk for CAD (odds ratio: 6.0; 95% CI: 5.2-6.9) than those with LDL-C <130 mg/dl and no mutation. Those with both LDL-C ≥190 mg/dl and an FH mutation had a 22-fold increased risk (odds ratio: 22.3; 95% CI: 10.7-53.2).	**Summary:** CAD risk is higher in those with LDL-C ≥ 190 mg/dL than in those with LDL-C <130 mg/dL and the risk is more than tripled in those with LDL-C ≥190 mg/dL and a concomitant FH causing mutation 3. These findings may be mediated via a higher cumulative exposure to LDL-C. **Study limitations:** 1. Study participants could not be stratified by family history or physical examination 2. Assumption of 30% LDL-C lowering in those treated with statin therapy may not be accurate 3. Those with LDL mutations may have had survivorship bias

			2. Cumulative exposure to high LDL-C was assessed using a cohort from of 5,727 Atherosclerosis Risk in Communities Study cohort participants and 2,714 Framingham Heart Study participants and in those with serial lipid measurements over many y. Among these subjects 25 participants with an FH mutation and LDL cholesterol ≥130 mg/dL were identified Compared with matched non-carriers with similar LDL-C levels participants with an FH mutation had a 17 mg/dl (95% CI: 5-29 mg/dl; p=0.007) higher average LDL cholesterol exposure in the y preceding the last visit.	
Nanchen D, et al., (41) 27462068	**Study type:** Multicenter prospective cohort study **Size:** 4534 patients	**Inclusion criteria:** 1. Patients ≥ age 18 y with a primary diagnosis of ST elevation MI, non-ST elevation MI or unstable angina, hospitalized with acute coronary syndrome in Switzerland between 2009 and 2013 and who were individually screened for clinical FH using the definitions of the American Heart Association, Simon Broome, and the Dutch Lipid Clinic criteria. 2. Patients with complete baseline and follow-up lipid measurements and family history information. **Exclusion criteria:** Those with missing lipid or family history information.	**1º endpoint:** 1-y risk of first recurrent coronary death or myocardial infarction after multivariable adjustment, assessed by telephone monitoring and by a follow-up clinic visit 1 y after the acute event. **Results:** The risk of recurrent coronary events was greater in patients with FH than in those without, with an adjusted hazard ratio of 2.46 (95% confidence interval: 1.07–5.65; p=0.034) for the American Heart Association definition, 2.73 (95% confidence interval: 1.46–5.11; p=0.002) for the Simon Broome definition, and 3.53 (95% confidence interval: 1.26–9.94; p=0.017) for the Dutch Lipid Clinic definition. Depending on which clinical definition of FH was used, between 94.5% and 99.1% of patients with FH were discharged on statins and between 74.0% and 82.3% on high-intensity statins	**Summary:** Recurrent coronary events are more likely in those with FH than in those without despite high-dose statins **Limitations:** 1. Possible selection bias of MI patients with vs. without FH presenting with recurrent ACS 2. No genetic testing was performed, so the presence of polygenic hypercholesterolemia could not be excluded. 3. No data were collected on family history or physical findings related to possible FH 4. Lower LDL-C values on blood collected 12-24 H after ACS may have resulted in underestimation of prevalence of FH.
Versmissen J, et al., 2008 (42) 19001495	**Study Type:** Retrospective cohort study of 27 outpatient	**Inclusion criteria:** Patients with phenotypic familial hypercholesterolemia identified in a Dutch cohort from 1/1/90 to 2002.	**1ºendpoint**: Relative risk of myocardial infarction in statin treated patients and in those who were delayed in starting statin treatment compared with a Cox	**Summary:** Statin therapy reduces incident myocardial infarction risk in subjects with familial hypercholesterolemia

	lipid clinics in the Netherlands. **Size:** 2146 patients	Enrollees had to have no documented coronary heart disease prior to 1/1/90. **Exclusion criteria:** Those with established coronary heart disease prior to 1/1/90.	regression model in which statin use was a time dependent variable. Results: In January 1990, 413 (21%) of the patients had been started on a statin, and during follow-up 1294 patients (66%) started after a mean delay of 4.3 y (SD 3.3 y). During a mean follow-up of 8.5 y (SD 3.1 y) there was a reduction in myocardial infarction risk reduction of 76% (hazard ratio: 0.24; CI: 0.18-0.30), p<0.001) in those initially started on a statin as compared to those in whom statin administration had been delayed. After additional reduction for baseline characteristics, there was an 82% risk reduction (HR: 0.18; 95% CI: 0.13-0.25; p<0.001).	**Limitations**: 1. Possible selection bias favoring earlier treatment of patients with perceived higher risk. 2. Lack of placebo control 3. Intention to treat analysis was not employed
Besseling J, et al., 2016 (43) 27417002	**Study Type** Retrospective cohort study of the database of the national FH cascade screening program in the Netherlands and a patient-centric data network of multiple health care databases **Size:** 1559 patients	**Inclusion criteria**: Patients' age ≥18 y with genetically determined deleterious mutations associated with FH and free of clinical CAD at entry into the study. **Exclusion criteria:** Patients with homozygous, compound heterozygous or double heterozygous FH or carriers of a non-deleterious mutation.	**1ºendpoint:** Relative risk reduction for CAD (myocardial infarction, angina pectoris, or other forms of atherosclerotic or ischemic heart disease or coronary artery bypass graft or PCI), and all-cause mortality by statins in heterozygous FH patients. **Results:** Patients treated with statins (n = 1,041) (most often simvastatin 40 mg daily] [23.1%] or atorvastatin 40 mg daily [22.8%]) had 89 CAD events and 17 deaths during 11,674 person-y of follow-up versus those never treated with statins (n = 518), who had 22 CAD events and 9 deaths during 4,892 person-y (combined rates 8.8 vs. 5.3 per 1,000 person-y, respectively; p<0.001). After applying IPTW and adjusting for other medications, the hazard ratio of statin use for CAD and all-cause mortality was	**Summary:** In patients with heterozygous FH, moderate- to high-intensity statin therapy lowered the risk for CAD and all-cause mortality by 44%. **Limitations:** 1. Because of the observational nature of the study, indication bias could have been present. 2. Time lag between the first observation in the database and the first visit in the screening program may have affected results 3. Cause of death was not specified.

			0.56 (95% confidence interval: 0.33 to 0.96).	
Perez de Isla, 2017 (44) 28275165	**Study Type:** Prospective cohort study from multiple medical centers in Spain employing the SAFEHEART registry **Size**: 2404 patients	**Inclusion criteria:** Age ≥ 18 y with molecularly defined heterozygous FH, with or without previous ASCVD Assessment of fasting lipids; Lp(a); ASCVD risk factors; whole blood molecular analysis of DNA; assessment of previous and incident ASCVD **Exclusion criteria: N/A**	**1º endpoint:** Identification of key risk factors for prediction of ASCVD in patients with familial hypercholesterolemia using the SAFEHEART registry. **Results:** 1. Over a mean period of 5.5 y, 12 (0.5%) had fatal and 122 (5.1%) non-fatal ASCVD incidents. 2. Age male gender, history of pervious ASCVD, high blood pressure, increased waist circumference, active smoking, LDL-C and Lp(a) were independent predictors of incident ASCVD See table 3 from article below 3. Molecular diagnosis: Two hundred and nine different functional mutations in LDL receptor (LDLR) (97.0%) and APO-B (3.0%) genes were identified. In the cohort 856 (35.6%) patients had LDLR null mutations, 1092 (45.4%) defective-mutations and 384 (16.0%) unclassified mutations. 4. A risk equation was derived from these results with Harrell's C index of 0.85 5. Individual risk was estimated for each person without established ASCVD before enrollment using SAFEHEART risk equation, modified Framingham risk Scoring and ACC/AHA Pooled cohort Risk Equations. SAFEHEART-RE outperformed the other two models.	**Summary:** 1. Several easily obtained clinical and laboratory studies were independent predictors of incident ASCVD. 2. A SAFEHEART risk equation, derived from the ASCVD outcomes of this cohort, was shown to be a useful tool to predict ASCVD risk in these patients with molecularly defined FH. **Limitations**: 1. No data from children or adolescents 2. Not all patients had pre-treatment lipid values 3. No external validation cohort available 4. Relatively short mean follow-up period of 5.5 y
Perez de Isla et al., 2017 (44) 28275165	**Study Type:** Prospective cohort study from multiple medical centers in Spain	**Inclusion criteria:** Age ≥ 18 y with molecularly defined heterozygous FH, with or without previous ASCVD	**1º endpoint**: Identification of key risk factors for prediction of ASCVD in patients with familial hypercholesterolemia using the SAFEHEART registry.	**Summary:** 1. Several easily obtained clinical and laboratory studies were independent predictors of incident ASCVD.

	employing the SAFEHEART registry **Size:** 2404 patients	Assessment of fasting lipids; Lp(a); ASCVD risk factors; whole blood molecular analysis of DNA; assessment of previous and incident ASCVD **Exclusion criteria : N/A**	1. Over a mean period of 5.5 y, 12 (0.5%) had fatal and 122 (5.1%) non-fatal ASCVD incidents. 2. Age male gender, history of pervious ASCVD, high blood pressure, increased waist circumference, active smoking, LDL-C and Lp(a) were independent predictors of incident ASCVD See table 3 from article below 3. Molecular diagnosis: Two hundred and nine different functional mutations in LDL receptor (LDLR) (97.0%) and APO-B (3.0%) genes were identified. In the cohort 856 (35.6%) patients had LDLR null mutations, 1092 (45.4%) defective-mutations and 384 (16.0%) unclassified mutations. 4. A risk equation was derived from these results with Harrell's C index of 0.85 5. Individual risk was estimated for each person without established ASCVD before enrollment using SAFEHEART risk equation, modified Framingham risk Scoring and ACC/AHA Pooled cohort Risk Equations. SAFEHEART-RE outperformed the other two models.	2. A SAFEHEART risk equation, derived from the ASCVD outcomes of this cohort, was shown to be a useful tool to predict ASCVD risk in these patients with molecularly defined FH. **Limitations:** 1. No data from children or adolescents 2. Not all patients had pre-treatment lipid values 3. No external validation cohort available 4. Relatively short mean follow-up period of 5.5 y

Data Supplement 11. Nonrandomized Trials, Observational Studies, and/or Registries of Diabetes Mellitus 40-75 Years (Section 4.3)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Wong ND, et al., 2012 (45) 22377485	**Study type**: Cross sectional cohort analysis **Design**: Assessment of distribution of 10 y CVD risk in a representative US sample of subjects with diabetes (NHANES 2003-6) using the Framingham score which divides 10 y CVD risk into low (<10%), intermediate (10-20%) and high risk (>20%) categories. **Size**: n=1,114, representing 18.2 million	**Inclusion criteria**: adults 30-74 y with DM **Exclusion criteria**: N/A	**1° endpoint**: 10 y total CVD events estimated by the Framingham algorithm. **Results:** r• Among those without pre-existing CVD 27% had <10%, 23% had 10-20% and 50% had >20% 10 y risk. • Age subgroups: ○ 40-49 y, low risk 47%; high risk 15% ○ 50-59 y, low risk 17%; high risk 33% ○ 60-69 y, low risk 6%, high risk 42% • 49.3% of subjects with T1DM, 10.3% with type 2 and 17.5% with previously undiagnosed DM were at low risk. • Low risk subgroups (% low risk): Sex; Female/Male: 26.8%/18.6% Race/Ethnicity; Black/Hispanic/Caucasian: 30.6%/32.4%/16.8% • 59% of low risk subjects had metabolic syndrome and 7% had CKD.	**Summary:** • 75% of subjects without CVD were at intermediate or high risk. • A minority of adults with T2DM and about half of those with T1DM are at <10% 10y CVD risk using the Framingham score, especially those <50 y, females>males, minorities>Caucasians. • Half the cohort were at high risk (>20% 10 y CVD risk). • Low risk subjects frequently have comorbidities that increase their long-term. **Limitations:** • Though representative of the US population, the study group is relatively small. • The Framingham score may underestimate risk and its validity in subjects with diabetes has been questioned.
Rana JS, et al., 2016 (46) 26666660	**Study type**: Prospective population-based cohort case-control study **Design:** Comparison of risk of incident CHD events over 10 y (2002-2011) among members of Kaiser Permanente with or without diabetes or CHD **Size**: 1,586,061 adults of whom 138,507 had diabetes (ICD code diagnosis)	**Inclusion criteria**: • continuously enrolled • 30-90 y **Exclusion criteria**: N/A	**1° endpoint**: Age-adjusted rate of new fatal or non-fatal CHD or revascularization; n/1,000 pt.-y (95%CI) **Results:** • With CHD only; Overall; 22.5 (22.0–22.98) • With DM only (n=118,952); Overall; 12.2 (95% CI: 12.02–12.49) HR: 3.7 (95% CI: 3.6–3.8) vs. no DM/CHD men; 15.2 (95% CI: 14.8–15.53) women 8.8 (95% CI: 8.58–9.14) • By age subgroups; - 40-49 y (n=19,746); men 9.0,	**Summary:** • Overall incident CHD rates were 15.2% in men and 8.8% in women. By age subgroup rates rose from 5% or less for those 30-39 y old and rose incrementally with age reaching 15-25% for age 60-69 y. -There was a modest increase of incident CHD in those with duration of diabetes <5 y (compared to those without DM) and event rates increased with duration until it was not different from those with prior CVD and no diabetes in those with duration >10 y. • Overall the risk for a CHD event in a large cohort with diabetes but no CVD is about half that in subjects without diabetes but with CHD

			women 6.6 • Rates for other subgroups are taken from a figure and are therefore not exact, but because their importance are shown • 30-39y; men~5%; women<5% • 50-59 y; men~18%; women~10% • 60-69 y; men~25%; women~15% • By DM duration: risk increased by duration with no tabulated data provided but data from a figure were taken because of their importance and are shown as HRs by duration compared to the group without diabetes and CVD • <5 y ~1.4 • 5-9 y~1.8 • >10 y~2.5 (not different from the group with prior CHD but no DM)	**Limitations:** • All diagnoses were based on electronic records only, including CHD ascertainment • All subjects were insured and therefore results may not be generalizable to other segments of the population
MESA Malik S, et al., 2011 (47) 21844289	**Study type**: Prospective observational multiethnic cohort study **Design**: Comparisons of CAC and CIMT in subjects free of CVD with metabolic syndrome, DM or neither in prediction of incident CVD. **Size**: 6,603 people in the MESA including 881 subjects with T2DM and 1,686 with metabolic syndrome.	**Inclusion criteria**: Persons living within 6 defined geographic boundaries between 45 and 84 y who are African-American, Chinese-American, Caucasian or Hispanic **Exclusion criteria:** • People with clinical CVD • 6,603 had CAC and CIMT measurements and were followed for a median of 6.4 y for incident CVD Mean (SD) age (DM, metabolic syndrome, no DM/metabolic syndrome) y; 65 (9.6), 64 (10), 62(10)	**1° endpoint**: CVD events **Results**: • Mean (SD) CAC score (DM, metabolic syndrome, no DM/metabolic syndrome): ○ 255 (596), 157 (417), 119 (365) ○ CAC 0%; 38, 45, 55 • Annual CVD events (%) ○ CAC 0; 0.8, 0.4, 0.2 ○ CAC 1-99; 2.2, 1.2, 0.7 ○ CAC 100-399; 2.9, 2.4, 1.7 ○ CAC 400+; 5.1, 4.6, 2.6 ○ CVD events in CAC 1-99 vs. CAC 0 ○ HR: 2.0; 95% CI: 1.1–3.7; p<0.05 ○ In a model adjusted for the Framingham risk score CAC still predicted CVD events in D; HR: 2.0; 95% CI: 1.5–2.6.	• Although mean CAC was higher in DM vs. metabolic syndrome vs. no DM/metabolic syndrome, 38% of DM had CAC 0. • CAC 0 in DM was associated with a 0.8% annual rate risk of CVD. • CAC 1-99 doubled the rate • CAC >100 more than tripled the rate • CAC screening in diabetes predicts risk independent of the Framingham risk score • CIMT showed the same trends as CAC but was not as good a predictor of CVD.
Mulnier HE, et al., 2008 (48) 18581091	**Study type**: Prospective case- control observational cohort study **Design**:	Inclusion criteria: • Men and women aged 35-89 y • Free of CHD **Baseline characteristics:**	**1° endpoint:** 7 y Incident MI **Results:** Incident MI: rate/1000 pt. y (95% CI) over mean follow-up of 7 y	• The primary objective of this study, to compare incident MI rates in DM versus no DM, demonstrated overall more than a 2-fold excess risk

	• Comparison of adjudicated MI over time in patients with and without DM and no prior MI in the very large General Practice Research Database representing ~5% of the UK population • This permitted estimates of incident MI by age, specifically those >75 y **Size**: 40,727 subjects with and 194,913 without DM	• Average baseline age in DM group; men 65 y, women 68.5 y • n>75 y of age; men 4,952, women 6,746 • MI diagnosed by diagnostic codes **Exclusion criteria**: N/A	• DM 18.03 (95% CI: 17.41–18.69) • No DM 7.00 (95% CI: 6.82–7.18) • RR (adjusted) 2.47 (95% CI: 2.36–2.59) • MI events (n) and rates/1,000 pt. y (95% CI) by attained age in group with DM; • Men ○ 35-54 y: 119, 8.64 (95% CI: 7.22–10.34) ○ 55-64 y: 328, 14.03 (95% CI: 12.59–15.64) ○ 65-74 y: 655, 19.40 (95% CI: 18.27–20.6) ○ 75-84 y: 517, 25.61 (24.1–27.22) ○ >85 y: 120, 27.91 (24.88–31.32) • Women ○ 35-54 y: 40, 4.32 (3.17–5.88) ○ 55-64 y: 177, 10.30 (8.89–11.94) ○ 65-74 y: 405, 15.88 (14.41–17.51) ○ 75-84 y: 517, 23.24 (21.32–25.34) ○ >85 y: 170, 25.32 (21.78–29.42)	• The study also demonstrated that MI rates in the DM cohort increase with age and are greater in those >75 y than those <75 y in both men and women • The excess risk for MI in subjects with vs. without DM persisted in those >75 y of age (~2-fold) • The limitation is that incident MI was diagnosed by diagnostic codes
Soedamah-Muthu SS, et al., 2006 (49) 16567818	**Study type**: Prospective case- control observational cohort study **Design**: • To estimate absolute and relative CVD risk in subjects with type 1 DM in the very large General Practice Research Database representing ~6% of the UK population • Incident major CVD events between 1992-1999 from computerized database records checked against medical charts **Size**: 7,479 subjects with and 38,116 without Type 1 DM	**Inclusion criteria:** • Men and women aged <35 - >75 y with type 1 DM (defined as being treated with insulin + diagnosed <35 years of age) • 5 randomly selected age and sex-matched controls for each 1 subject with type 1 DM **Baseline characteristics:** • Baseline age (mean±SD) 33±14.5 y; 55% men, type 1 DM prevalence 2.15/1000; average DM duration 15 y • Baseline CVD prevalence; 3% in type 1 DM, 1% in controls, RR 3.0 [95% CI 2.5–3.5] **Exclusion criteria**: N/A	**Results:** **First major CVD event** • DM vs non-DM: 219 vs 289 events (cumulative incidence 3% vs 0.76%) • DM vs non-DM HR (95% CI); 4.5 (3.8-5.4) • Men [absolute risk/1000 person-y (95%CI); HR (95%CI); ○ Overall: 7.3 (6.1–8.6); 5.5 (4.4–6.8) ○ <35 y: 0.8 (0.4–1.6); 11.3 (2.9–43.8) ○ 35-44y: 4.8 (3.2–7.1); 4.4 (2.5–7.6) ○ 45-54 y: 10.6 (7.3–15.2); 3.0 (1.9–4.8) ○ 55-64 y: 39.4 (29.5–52.6); 4.1 (2.8–6.0) ○ 65-74 y: 35.2 (21.6–57.5); 2.3 (1.3–4.1) ○ >75 y: 122.2 (69.4–215.2); 3.5 (1.6–7.3) • Women ○ Overall: 5.5 (4.4–6.8); 7.7 (5.5–10.7) ○ <35 y: 0.5 (0.2–1.3); 9.8 (1.8–53.6) ○ 35-44 y: 3.5 (2.1–6.1); 15.4 (5.0–47.3) ○ 45-54 y: 10.2 (6.7–15.5); 10.1 (5.0–20.4) ○ 55-64 y: 22.8 (15.0–34.7); 5.7 (3.2–10.4) ○ 65-74 y: 38.7 (24.1–62.3); 8.3 (4.0–17.2) ○ >75 y: 87.3 (39.2–194.3); 4.0 (1.4–11.2)	• The study demonstrated an age-dependent increase in absolute event rates in type 1 DM; rates increasing by each decade in both men and women beginning at age <35 y and increasing through age>75 y • The HR for fatal CVD was much greater in type 1 DM than controls especially in women (men 5.8, women 11.6). • The HR for each secondary endpoint in those with type 1 DM was increased and varied from 3.0-5.8 in men and 4.8-16.8 in women • The absolute risk of a first major CVD event in men with type 1 DM aged 45-55 y was equivalent to men 10-15 y older without DM; the risk in women with type 1 DM aged 45-55 y was equivalent to women >20 y older without DM **Limitations:** • The diagnosis of type 1 DM was not confirmed by antibody testing so the cohort

		1° endpoint: First major CVD event defined as fatal or non-fatal MI or stroke, fatal CHD or coronary revascularization **2° endpoints:** Acute coronary event, coronary revascularization, stroke, major CHD, fatal CVD, major CVD	**Fatal CVD:** fatal MI, stroke and CHD [absolute risk/1000 person-y (95%CI); HR (95%CI); • Men: 2.8 (2.1–3.7); 5.8 (3.9–8.6) • Women: 2.5 (1.9–3.5); 11.6 (6.7–20.1)	may have included subjects with type 2 DM diagnosed <35 years and requiring insulin • The data were collected over 20 years ago
Huo X, et al., 2016 (50) 26704379	**Study type**: Retrospective cohort analysis **Design**: • Comparison of rates of non-fatal CVD identified from records of patients attending 603 medical centers with early onset (<40 y) versus late onset T2DM taken from the China National HbA1c Surveillance System. • This provides information of CVD prevalence in patients with DM who are 40-50 y of age and by 5 y increments to >70 y **Size**: 222,773 subjects	**Inclusion criteria**: Being an outpatient with T2DM 18 y or older **Exclusion criteria:** • T1DM • secondary diabetes	**1° endpoint:** Non-fatal CVD **Results**: • Mean (SD) age at assessment; ○ Early onset; 40.9 (7.9) y ○ Late onset; 60.7 (9.6) y • Mean age at diagnosis; ○ Early onset; 34·5 (5·0) y ○ Late onset; 55·3 (8·9) y • Risk of non-fatal CVD in Early onset vs. Late onset diabetes ○ OR: 1.91; 95% CI: 1.81–2.02 ○ (p<0.0001) which was attenuated when adjusted for diabetes duration (OR: 1.13; 95% CI: 1.06–1.20. • Prevalence of CVD by age in Early onset: ○ 30-34 y; 1.9% ○ 35-39 y; 3.3% ○ 40-44 y; 5.8% ○ 45-49 y; 8.8% ○ 50-54 y; 13.9% ○ 55-59 y; 21.3% ○ 60-64 y; 29.6% ○ 65-69 y; 28.4% ○ >70 y; 42.7%	• This is one of two studies that provides information on rates of CVD in a cohort with T2DM diagnosed <40 y of age. • Although prevalence of CVD is relatively low in 30-44 y old subjects (1.9-5.8%) diagnosed <40 y, it increases rapidly with age in both men and women. • The principal finding was that Early onset T2DM has a higher lifetime risk for CVD than Late onset, which occurs at an earlier stage of life in Early onset, but in regression analysis was more strongly related to duration of diabetes rather than lower age of DM onset.

Constantino MI, et al., 2013 (51) 23846814	**Study type**: 25-y retrospective review of hospital records **Design:** Comparison of diabetic complications and mortality in T1DM and T2DM cohorts with age of onset between 15 and 30 y of age Size: 354 patients with T2DM and 470 patients with T1DM	**Inclusion criteria**: • Records of all patients with diabetes aged 15-30 y in the Royal Prince Alfred Hospital diabetes database in Sydney Australia during the period 1986-2011. **Baseline characteristics:** • Mean current age (SD) y; • T2DM: 40.4 (12.5) • T1DM: 38.9 (10.9) • Median diabetes duration (IQR) y • T2DM: 11.6 (4.5–22.6) • T1DM: 14.7 (8.2–23.6) **Exclusion criteria:** N/A	**1° endpoint**: Mortality **Results:** • Other outcomes: Macrovascular disease • Mortality T2DM vs. T1DM (%) • Total: 11% vs. 6.8% • Median duration of DM until death (IQR) y: • T2DM; 26.9 [18.1–36.0] • T1DM; 36.5 [24.4– 45.4], p=0.01 • Mean age at death (SD) y: • T2DM; 52.9 (14.7) • T1DM; 57.4 (12) • CVD death; • T2DM; 50.0% • T1DM; 30.3%, p=0.053 • Cumulative macrovascular disease T2DM vs. T1DM (%) • IHD: 12.6% vs. 2.5%, p<0.0001 • Stroke: 4.3% vs. 0.7%, p<0.0001 • Any: 14.4% vs. 5.7%, p<0.0001	• This study provides comparative, long-term data on complications and mortality in subjects with T1DM or T2DM, diagnosed between age 15 and 30 y of age. • The principal finding is that those with T2DM have a greater risk of macrovascular disease and mortality than those with T1DM. •The study also demonstrates that over a mean duration of diabetes of 11.6-14.7 y, 14.4% of T2DM and 5.7% of T1D diagnosed between 15 and 30 y develop CVD.
Svensson MK, et al., 2013 (52) 24002670	**Study type:** Observational cohort study **Design:** To evaluate the predictive value of reduced renal function and albuminuria on CVD events and all- cause mortality in diabetes **Size**: 66,065	**Inclusion criteria:** Subjects with T2DM aged 30-79 y (mean age 64 y) registered with the Swedish National Diabetes Register and followed for an average of 5.7 y 17% of the cohort had RRF, (eGFR<60 ml/min/1.73m2); 24% had albuminuria (>30mcg/mg creatinine). **Exclusion criteria**: N/A	**1° endpoint:** • Fatal/non-fatal CHD • Fatal/non-fatal CVD • All-cause mortality **Results:** • Fatal/non-fatal CVD events (n [%], fully adjusted HR [95%CI] vs. those without either albuminuria or RRF - No albuminuria/RRF: 3306 (7.7%), 1.0 -albuminuria: 1484 (12.5%), 1.27; 95% CI: 1.20–1.36. -RRF: 951 (12.7%), 1.21; 95% CI: 1.12–1.30. -albuminuria +RRF: 749 (19.3%), 1.41; 95% CI: 1.30–1.53. • All-cause mortality -No albuminuria /RRF: 2713 (6.3%) 1.0 -albuminuria: 1378 (11.6%), 1.43; 95% CI: 1.34–1.53.	•Albuminuria and reduced renal function are each independent risk factors for CVD and mortality in type 2 diabetes. •Albuminuria was predictive at all levels of renal function and additive to the effects of RRF. •In normoalbuminuric patients, reduced renal function is an important predictor of CVD events and mortality. •Limitations include the fact that subjects with more severe degrees of RRF were not included, that only 1 baseline measure of renal function was used, and effects of RAS inhibitors were not assessed.

			-RRF: 965 (12.9%), 1.30; 95% CI: 1.20–1.40. -albuminuria +RRF: 907 (23.4%), 1.82; 95% CI: 1.67–1.97.	
Guo VY, et al., 2016 (53) 27068777	**Study type:** Meta-analysis of cohort studies **Design:** To evaluate the association between any diabetic retinopathy (DR) and CVD in T1DM AND T2DM without prior CVD **Size**: 17,611 patients from 13 studies; 10,200 with T2DM (8 studies) and 7411 with T1DM (5 studies)	**Inclusion criteria:** • presented original data in prospective, observational studies; • evaluated the presence of DR in pts T2DM or with T1DM • reported all-cause mortality and/or fatal or nonfatal CV events • No prior CVD • T1DM studies (showing range of findings between individual studies). **Population characteristics** T1DM studies -Mean ages; 28-37 y -Mean durations of diabetes; 10-22 y -Mean f/us; 6-12 y -Prevalence of DR; T2DM studies -Mean ages; 53-62 y -Mean durations; mostly N/A -Mean f/us; 4.7-18 y -Prevalence of DR; N/A **Exclusion criteria**: N/A	**1° endpoint:** Risk ratio for first CVD event in DR vs. no DR **Results:** • Risk ratio (RR) range from studies - All T1D 1.63-6.66 - All T2D 1.30-2.55 • Mean RR (95%CI) - Overall; 2.42, (1.77-3.31) • Overall adjusted for risk factors; 2.01 (1.65-2.45) - T2DM; 1.81 (1.47-2.23) - T1DM; 3.59 (1.79-7.20) • RR for CHD -Overall, 1.83, (1.52-2.19)	• Overall DR is associated with an increased risk of CVD events in diabetes. • The risk associated with DR is greater in those with T1DM than those with T2DM, although the T1DM data were strongly. influenced by a single large study that only studied pts with advanced retinopathy. • The DR associated CVD risk is independent of other risk factors. • It was not possible in this meta-analysis to determine whether severity of DR was related to CVD risk, although the ACCORD study did show this.
Brownrigg JR, et al., 2014 (54) 25095826	**Study type**: Observational case- control cohort study **Design:** To compare incident first CVD events in a large group of patients with type 2 diabetes seen	**Inclusion criteria:** • >18 y of age • no prior CVD • type 2 diabetes • foot exam using a monofilament	**1° endpoint:** First CVD event, death **Results:** • CVD events, n (%) ○ PN; 65 (5.0%) ○ No PN; 334 (2.8%) • Crude mortality, n per 1000 pt. y	• PN is associated with increased risk for a first CVD event in people with diabetes after adjustment for conventional risk factors. • The presence of PN led to modest reclassification of individuals into different risk categories. • A limitation is the short follow-up period

	in primary care practice in the UK with or without peripheral neuropathy (55) Size: Data on 13,043 individuals from 122 primary care practices extracted using a national software program	**Baseline characteristics:** • mean age (SD); 63.8 y (12.8) • PN prevalence 9.9% (1296/13,043) • Mean follow-up was 30 mo **Exclusion criteria**: N/A	○ PN; 22.8 ○ No PN; 11.3, p<0.001 • Effect of PN vs. no PN on CVD; ○ Unadjusted HR: 1.78; (95% CI: 1.37–2.32); p<0.001 ○ Adjusted for risk factors; HR: 1.38; 95% CI: 1.05 to1.80; p=0.02 • Reclassification of risk categories based on the Framingham score: - • PN reclassified 6.9% into a higher or lower risk category.	• The diagnosis of PN is imprecise, which is a potential limitation.
Pang XH, et al., 2017 (56) 28607554	**Study type**: Cross-sectional case-control cohort study **Design:** Comparison of CVD risk estimated by the United Kingdom Prospective Diabetes Study risk engine in Chinese subjects with diabetes and with or without PAD and free of CVD. **Size:** 1,178 subjects with diabetes	**Inclusion criteria:** •All 1,178 patients with type 2 diabetes admitted to Zhejiang University Medical College Hospital between 2008 and 2013 •88 had asymptomatic PAD defined as an ABI <0.9 or >1.4 •Mean (SD) age y •No PAD; 57.2 (12.3) •PAD; 69.8 (11.8) **Exclusion criteria**: N/A	**1° endpoint:** 10 y % fatal/non-fatal CVD risk assessed by UKPDS risk engine. **Results:** • Mean [95%CI]% - No PAD; 20.5 [19.6–21.4] - PAD; 35.1 [30.7–39.5] p<0.001 • Multivariate logistic regression (OR [95%CI]) of PAD vs. non-PVD on CVD risk that included age and standard risk factors, - CHD: 3.6, (2.2–6.0); p<0.001 - Stroke: 6.9, (4.0–11.8); p<0.001	•An ABI<0.9>1.4 in a large Chinese cohort with type 2 diabetes free of CVD was associated with increased risk for future CVD as assessed by the UKPDS risk engine. •This increased risk was found to be independent of age and of standard risk factors. •A limitation is the use of a risk engine to assess CVD instead of incident events.

Data Supplement 12. RCTs Comparing Diabetes Mellitus 40-75 Years (Section 4.3)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
HPS Collins R, et al., 2003 (57) 12814710	**Aim:** • To evaluate whether (moderate intensity) statin therapy reduces CVD morbidity and mortality in subjects with diabetes and with or without CVD compared to placebo. • This report summarizes findings in the pre- specified subgroup of participants without ASCVD only. **Study type:** Randomized double-blind placebo- controlled clinical trial **Size:** 5,963 subjects with diabetes 615 of whom had T1DM; 3,051 subjects had ASCVD and 2,912 individuals did not.	**Inclusion criteria:** • Age 40-80 y • T1DM or T2DM • Non-fasting cholesterol >3.5 mmol/l (135 mg/dl) • treated hypertension (if also male and aged at least 65 y) **Exclusion criteria:** • No CVD for the pre-specified primary prevention subgroup • Subject's physician assessment that statins clearly indicated or contraindicated • liver disease • severe renal disease • cyclosporine, fibrates, niacin • Baseline LDL-C; mean (SD) 3·2 (0·82) mmol/l [125 (32) mg/dl]	**Intervention:** Simva 40 mg daily (n=1455) -average statin usage 83%, -average LDL-C 2.2 mmol/l (86 mg/dl) **Comparator:** Placebo (n=1457) -average statin usage 11% -average LDL-C 3.1 mmol/L (121 mg/dl) • LDL-C difference between simva and placebo 0.9 mmol (35 mg/dl) • Mean duration 4.8 y	**1° endpoint:** • Non-fatal MI, death from any coronary disease **Results:** • n (rate ratio %) Simva; 135 (9.3%) Placebo; 196 (13.5%) RRR 33% (95% CI: 17–46; p=0·0003) • Men: RRR [SE] 33% [10], p=0·002 • Women RRR 30% [19], p=0·1 • 40-64 y of age: RRR 33% [12], p=0·006 • 65-80 y of age: RRR 31% [14], p=0.03	• Adverse events: (full group with diabetes) • Liver enzymes >4X UL Simvastatin: n (%) 14 [0·47%] Placebo: 11 [0·37%]) • CK >10X UL Simva: 4 [0·13%] Placebo: 2 [0·07%]
CARDS Colhoun HM, et al., 2004 (58) 15325833	**Aim:** To test the effectiveness of atorvastatin 10 mg for primary prevention of major CVD events in patients with T2DM without high LDL-C	**Inclusion criteria:** • Men and women aged 40-75 • T2DM • At least one of hypertension, retinopathy, microalbuminuria and smoking	**Intervention:** Atorva 10 mg daily (n=1428) **Comparator:** • Placebo (n=1410) • 1 y LDL -C • Mean (SD) mmol/l/ mg/dl	**1° endpoint:** (first acute CHD event [MI including silent MI, unstable angina, CHD death, resuscitated cardiac arrest], coronary revascularization, or stroke) **Results:**	**2° Endpoint**: • Acute coronary events, n (%) Atorva: 51 (3.6) Placebo: 77 (5.5) • Acute coronary events, rate per 100 per y Atorva: 0.94 Placebo: 1.47 HR: 0.64; 95% CI: 0.45 - 0.91;

	Study type: Randomized double-blind placebo- controlled clinical trial **Size:** 2,838	**Exclusion criteria:** • Any CVD • LDL-C >160 mg/dl • triglyceride >160 mg/dl • plasma creatinine >150 mol/L • HbA1c >12% • <80% compliance • with placebo during the baseline phase • Baseline LDL-C: mean (SD) mmol/l/mg/dl Atorva: 3.04 (0.72)/118 (28) Placebo: 3.02 (0.70)/118 (27)	Atorva:1.86 (0.69)/ 70 (39) Placebo: 3.10 (0.80)/ 121 (31) • Mean change % Atorva: 38.8 Placebo; 2.65 Absolute change %, Atorva: -1.1/46 Placebo: 0.08/3 • Between-group Difference, 40%	• The trial was terminated 2 y earlier than expected (median duration 3.9 y) because efficacy had been met • Events n (%) Atorva: 83 (5.8) Placebo: 127 (9.0) • Rate per 100 pt-y Atorva: 1.54 Placebo: 2.46 HR: 0.63; 95% CI: 0.48 - 0.83; p=0.001 • Death from any cause HR: 0.73; 95% CI: 0.52 -1.01; p=0.059 • NNT is 37 major vascular events per 1000 over 4 y	p=NR • Any acute CVD event, n (%) Atorva: 134 (9.4) Placebo: 189 (13.4) HR: 0.68; 95% CI: 0.55 – 0.85; p=0.001 • Stroke, n (%) Atorva: 21 (1.7) Placebo: 39 (2.8) HR: 0.52; 95% CI: 0.31 – 0.89; p=NR • Coronary revascularization, n (%) Atorva: 24 (1.7) Placebo: 34 (2.4) HR: 0.69; 95% CI: 0.41 – 1.16; p=NR **Adverse events:** No excess of adverse events was noted in the atorvastatin group **Limitations:** 15% drop-in lipid lowering meds in placebo
ASCOT-LLA Sever PS, et al., 2005 (59) 15855581	**Aim:** • To establish the benefits of lowering cholesterol in patients with well-controlled hypertension and average/below-average cholesterol concentrations, but without established coronary disease. • This report focuses on the group with diabetes which was analyzed and reported separately	**Inclusion criteria:** • Men and women 40-80 y • Hypertension • Total chol <6.5mmol/l (253 mg/dl) • 3 of; T2DM, male sex, age >55 y, microalbuminuria or proteinuria, smoking, total/HDL-C >6, premature FH of CHD, LVH, specified ECG abnormalities, PAD, stroke or TIA **Exclusion criteria:** • MI current angina, cerebrovascular event in past 3 mo	**Intervention:** • Atorva 10 mg daily (n=1258) - Baseline LDL-C mean (SD) mmol.l/ mg/dl; 3.3 (0.7)/ 128 (27) -1 y LDL-C; 2.1 (0.66)/82 (26) **Comparator** • Placebo (n=1274) - Baseline LDL-C; 3.3 (0.8)/128 (31) -1 y LDL-C; 3.3 (0.8)/128 (31)	**1° endpoint:** • The trial was terminated earlier than expected (median duration 3.3 y) because efficacy for the primary endpoint for the full group had been met. However, this meant there was insufficient power in the subgroup with diabetes for the primary outcome, which was non-fatal MI + fatal CHD • Diabetes group results: n(%) [per 1000 pt. y] Atorva: 38(3.0) [9.6] Placebo: 46(3.6%) [11.4] HR: 0.84 (95% CI: 0.55-1.29); p=NR • Accordingly, the subgroup with diabetes was analyzed based on the	• 2° endpoint for the main study which became the primary endpoint for the diabetes cohort: ○ Total CVD events; CVD mortality, nonfatal MI, unstable angina, chronic stable angina, life-threatening arrhythmias, non-fatal heart failure, non-fatal stroke, PAD, retinal thrombosis, revascularization, TIA, and reversible ischemic neurological deficits. • Diabetes group results: ○ Total CVD events n(%) [per 1000 pt. y] ○ Atorva: 116(9.2%) [30.2]

	Study type: Randomized double-blind placebo controlled clinical trial **Size:** 10,305 subjects of whom 2532 had T2DM	• uncontrolled arrythmia • fasting trig >4.5 mmol/l (400 mg/dl) • clinically important laboratory abnormalities • no current statin/ fibrate **Baseline characteristics:** • Mean age 64 >60 y (66%) • 16% had previous cerebrovascular disease or PAD • Mean no. of risk factors including diabetes = 4	• Differences in LDL-C between treatment groups not provided for diabetes subgroup	study trial secondary outcome, namely total CVD events	○ Placebo: 151(11.9%) [39.1] ○ HR: 0.77; 95% CI: 0.61-0.98; p=0.036 ○ Excluding those with baseline CVD (12%); HR: 0.75; 95% CI: 0.57-0.99; p=0.038. ○ No difference in liver enzyme or other adverse events between atorva and placebo groups **Limitation:** There was insufficient power to test the efficacy of statin therapy on the primary outcome in the diabetes group
ASPEN Knopp RH, et al., 2006 (60) 16801565	**Aim:** • To evaluate whether (moderate intensity) statin therapy (atorvastatin 10 mg daily) reduces CVD morbidity and mortality in subjects with DM compared to placebo • This study was originally designed as a 4-y secondary prevention trial but after 2 y it became a primary prevention trial. This report focuses on the group without baseline ASCVD **Study type:** Randomized double-blind placebo controlled clinical trial	**Inclusion criteria:** • Men and women 40-75 y • T2DM • LDL cholesterol <160mg/dl • Triglyceride <600 mg/dl **Exclusion criteria:** • T1DM • CVD • HbA1c>10% • hepatic dysfunction • severe renal disease • BP >160/100 • BMI >35 • alcohol abuse • <80% placebo run-in compliance • Excluded medications **Baseline data:** • Atorva: ○ mean age 60.5 y	**Intervention:** • Atorva 10 mg daily (Primary prevention n=959) ○ Baseline LDL-C mg/dl; 114 (26) ○ End of treatment % change from baseline LDL-C • -30.5% **Comparator:** • Placebo (Primary prevention n=946) ○ Baseline LDL-C 114 (26) ○ End of treatment % change from baseline LDL-C • -0.5%	**1° endpoint:** • time to first CVD death, nonfatal or silent MI, nonfatal stroke, revascularization, resuscitated cardiac arrest, unstable angina • Duration; median duration was 4 y overall; mean duration for primary prevention group was 2.4 y (reflecting change in protocol) **1° endpoint results:** n (rate%) Atorva: 100 (10.4%) Placebo: 102 (10.8%) HR: (0.97; 95% CI: 0.74–1.28)	**Reasons proposed for lack of significant benefit:** • 26.9% drop-in lipid lowering in placebo group • relatively short duration of trial • lower number of risk factors • younger cohort than other trials • requirement that study medication be discontinued after end point reached • inclusion of hospitalization for angina in endpoint may have diluted statin effect **Adverse events:** • abnormal LFTs • Atorva 1.4% • Placebo 1.2% • myalgia • Atorva 3% • Placebo 1.6% • rhabdo • Atorva 1

	Size: 2,410 subjects with T2DM. 505 had CVD and 1,905 did not	○ >65 y n=332 (35%) ○ diabetes duration 8 y ○ hypertension; 55% • Placebo: • mean age 60.4 y • >65 y n=305 (32%) • DM duration 8 y • hypertension; 53%			• Placebo 1
de Vries FM, et al., 2012 (61) 23186103	**Aim:** To assess the efficacy of statins in the primary prevention of major ASCVD event in patients with diabetes **Study type:** Fixed effects meta- analysis of 4 high quality clinical trials comparing moderate statin to therapy to placebo in patients with diabetes for the primary prevention of major ASCVD **Size:** 10,187 subjects, 5100 on statins and 5087 on placebo	**Inclusion criteria:** • double-blinded, randomized study • separate data on primary prevention subjects • minimum of 500 participants • mean follow-up of >2 y • high quality – Jadad score >4 **Exclusion criteria:** •11 reports were retrieved for detailed evaluation and 7 were excluded; 2 not double-blinded, 2 too few subjects, 1 used surrogate endpoints, 1 had no separate results and 1 was in a specific population •Trials included were HPS, CARDS, ASPEN, ASCOT-LLA •Baseline data in the 4 trials: • Men; 77%, 62%, 68%, NR • Mean age; 60, 62, 64, NR • HTN%; 52, 84, 100, NR • Smokers; 20.4, 12, 23 NR • Mean LDL-C mmol/l 3.3, 2.9, 3.0, NR	**Intervention:** Statin; n=5100 (simva 40mg daily in 1 study, atorva 10mg in 3 studies **Comparator:** Placebo; n=5087 Mean(range) follow-up; 3.8 (2.4-4.8) y	**1° endpoint:** •Major cardiovascular and cerebrovascular events; •Results: n (%) Statin 434 (8.5%) Placebo 576 (11.3%) RR: 0.75; 95% CI: 0.67–0.85; 3/4 studies were significant •NNT/3.8 y; 35; (95% CI: 25–58)	**2° endpoints:** • -Fatal/non-fatal stroke events (n) (3 studies) • Statin 75 • Placebo 109 • RR 0.69 (0.51–0.92) • NNT 0.69 (0.51–0.92) • Fatal/non-fatal MI events (n) (3 studies) • Statin 99 • Placebo 141 • RR 0.70 (0.54–0.90) • NNT 86 (50–290) • All-cause mortality events (n) (2 studies) • Statin 105 • Placebo 123 • RR 0.84 (0.65–1.09) • NNT 130 **Limitations:** • differences between studies in endpoints although these were minor • included some subjects with CVD (~12% in ASCOT-LLA) • diagnostic criteria of diabetes differed • differences in baseline risk • in HPS and ASCOT-LLA subject with diabetes were a subgroup

					• Drop-in statin used in placebo groups.

JUPITER
Ridker PM, et al., 2008 (11)
18997196
	Aim: To investigate whether treatment with rosuvastatin, 20 mg daily vs. placebo, would decrease MACE in apparently healthy persons with levels of LDL-C below current treatment thresholds but with elevated high-sensitivity (hs) CRP
	
	Study type:
	Randomized double-blind placebo controlled clinical trial
	
	Size: 17,802 subjects
		Inclusion criteria:
		• Age: men >50 and women >60 y
		• LDL-C<130 mg/dl
		• hsCRP >2 mg/l
		• triglyceride<500 mg/dl
		
		Exclusion criteria:
		• history of CVD
		• diabetes
		• past or current lipid-lowering therapy
		• PMP hormone therapy
		• ALT>2X ULN
		• CPK>3X ULN
		• SCr ±2.0 mg/dl
		• uncontrolled HTN
		• cancer
		• inflammatory state
		• hypothyroidism
		• substance abuse
		
		Baseline characteristics:
		• mean [IQR] age;
		• 66 [60-71] y
		• females 38-39%
		• Metabolic syndrome (41-42%)
		• mean LDL-C 108 mg/dl
			Intervention:
			Rosuvastatin 20 mg daily
			-n=8901
			-median [IQR] 1 y LDL-C; 55 [44-72] mg/dl
			- 50% reduction vs. placebo
			
			Comparator: Matching placebo
			n=8901
			-median [IQR] 1 y LDL-C; 110 [94-125] mg/dl
				1° endpoint:
				•Median follow-up 1.9 y; the study ended early because efficacy had been met
				•Primary endpoint: first nonfatal MI, non-fatal stroke, hospitalization for unstable angina, revascularization, or CVD death.
				Results:
				• n (rate/100pt.yrs)
				Rosuva 142 (0.77)
				Placebo 251 (1.36)
				HR: 0.56 ; 95% CI: 0.46–0.69; p<0.0001
					2° Endpoint n (rate/100pt.yr):
					• MI
					  ○ Rosuva 31 (0.17)
					  ○ Placebo 68 (0.37)
					  ○ HR: 0.46;0.30–0.70; p=0.0002
					• Stroke
					  ○ Rosuva 33 (0.18)
					  ○ Placebo 64 (0.34)
					  ○ HR: 0.52; 95% CI: 0.34–0.79; p=0.002
					• Revascularization
					  ○ Rosuva 71 (0.38)
					  ○ Placebo 131 (0.71)
					  ○ HR: 0.54; 95% CI: 0.41–0.72; p<0.0001
					• Death
					  ○ Rosuva 198 (1.00)
					  ○ Placebo 247 (1.25)
					  ○ HR: 0.80; 95% CI: 0.67-0.97; p<0.02
					
					Adverse events n(%):
					• Muscle symptoms
					• Rosuva 1421 (16.0)
					• Placebo 1375 (15.4) p=0.34
					• ALT >3XULN
					• Rosuva 23 (0.3) 17
					• Placebo 17 (0.2) p=0.34
					• New diabetes
					• Rosuva 270 (3.0)
					• Placebo 216 (2.4) p<0.01
					
					Limitations:
					• Non-diabetic participants
					• age restricted to men >50 and women >60 y

Data Supplement 13. Nonrandomized Trials, Observational Studies, and/or Registries of ASCVD Risk Associated with the Metabolic Syndrome (Section 4.4.1)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Gami AS, et al., 2007 (62) 17258085	**Study type:** Systematic Review and Meta-Analysis **Size:** 43 cohorts and 172,573 pts	**Inclusion criteria:** Included only prospective studies, with assessment of metabolic syndrome and follow-up for CV events or death **Exclusion criteria:** see above	**1° endpoint:** Composite of cardiovascular events and death; also, individual endpoints of CV events and total mortality **Results:** Metabolic syndrome associated with RR of 1.78 (95% CI: 1.58-2.00) for the primary outcome; RR: 2.18 (95% CI: 1.63-2.93) for CV events; and RR: 1.60 (95% CI: 1.37-1.92) for total mortality	• Demonstrates clear association between metabolic syndrome and increased risk of CVD events and mortality • Trend towards stronger associations among women than men (RR: 2.63 vs. 1.98; p=0.09) • Stronger associations in lower (<10% ten y risk) than higher risk populations (RR: 1.96 vs. 1.43; p=0.04) • Persistent association after adjusting for traditional cardiovascular risk factors (RR: 1.54; 95% CI: 1.32-1.79)
Galassi A et al., (63) 17000207	**Study type:** Meta-analysis **Size:** 21 studies	**Inclusion criteria:** **Exclusion criteria:**	**1° endpoint:** CVD mortality, total mortality, incident CVD, incident CHD and incident stroke **Results:** Metabolic syndrome associated with increased risk for all outcomes: RR: 1.74 for CVD mortality (95% CI: 1.29-2.35); RR 1.35 for total mortality (95% CI: 1.17-1.56); RR: 1.53 for incident CVD (95% CI: 1.26-1.87); RR: 1.52 for incident CHD (95% CI: 1.37-1.69); and RR: 1.76 for incident stroke (95% CI: 1.37-2.25)	• Metabolic syndrome strongly associated with incident CVD, CVD mortality and all-cause mortality • Stronger risk associations seen among women (RR: 2.10; 95% CI: 1.79-2.45) than men (RR: 1.57; 95% CI: 1.41-1.75); no p for interaction reported

Data Supplement 14. Nonrandomized Trials, Observational Studies, and/or Registries of Q1: Performance of the Pooled Cohort Equations (PCE) when used for the prediction of first incident atherosclerotic cardiovascular disease (ASCVD) events in diverse populations (Section 4.4.1.2)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Framingham Heart Study Andersson C, et al., 2015 (64) 25888372	**Study type:** Prospective Observational Cohort study **Size:** 7234 participants in the U.S. Framingham Heart Study Offspring Cohort	**Inclusion criteria:** • Age 40 to 75 y at baseline • Absence of clinical ASCVD • Participants of Framingham Heart Study Offspring Cohort cycle 1 (1971– 1975), 3 (1983–1987), and/or 6 (1995–1998) **Exclusion criteria:** • Prevalent MI or stroke (recognized or silent) • Missing values of blood pressure, treatment for hypertension, cholesterol values, diabetes, and smoking • Lipid-lowering medication use at baseline	**1° endpoint:** New-onset ASCVD, defined as incident MI, nonfatal or fatal ischemic stroke (excluding transient ischemic attack), or death due to coronary artery disease; Median duration follow-up 10 y **Results:** • 284 incident ASCVD events (8.4%) in men and 112 events (3%) in women. • Hosmer–Lemeshow chi-square statistics were 16.3 in men (340 predicted versus 285 observed events) and 29.1 in women (166 predicted versus 112 observed events). • Overprediction predominantly occurred among women in the highest risk decile and among men in the ≥ 7th risk deciles, for which observed ASCVD event rates were ≥ 7.5%. • Assessed by PCE, 36% had estimated ASCVD risks ≥7.5% (or diabetes) and LDL-C ≥70 mg/dL and thus were eligible for statins. In contrast, only 24% were eligible according to ATP III guidelines, translating into a net overall 51% increase (59% increase in women and 47% increase in men for statin eligibility). • The discrepancy between statin-eligible participants in the new versus old guidelines increased in the higher age groups, exceeding 10% in men aged >50 y and in women aged >60 y. Discordance in statin eligibility between the 2 guidelines was greatest in women aged >65 y • Censored for initiation of lipid-lowering treatment, the calibration of the PCE was slightly improved, with chi-square values of 13.1 (340 predicted versus	• The PCE overpredicted ASCVD risk but did so mainly among high-risk participants who would be considered eligible for statin use anyway. • Limitations: sample was not a completely independent external validation sample of PCE because data from some of the participants were included in the PCE derivation (i.e., Offspring Cohort examination cycles 1 and 3); included whites only; somewhat low ASCVD event rate. OVERALL QUALITY: Moderate

			301 observed) among men and 22.8 (166 predicted versus 126 observed) among women.	
Chia YC, et al., 2014 (65) 25410585	**Study type:** Retrospective Cohort study **Size:** 922 patients in Asia (Malay, Chinese and Indian race)	**Inclusion criteria:** • Age 40 to 79 y • Absence of clinical ASCVD • Enrolled in an outpatient primary care clinic in Kuala Lumpur, Malaysia **Exclusion criteria:** • Age <40 or >79 y • Clinical ASCVD at baseline • Missing data for calculation of risk score (PCE or FRS) or data on ASCVD events	**1° endpoint:** Nonfatal MI, coronary heart disease death, and fatal/nonfatal stroke; 10 y follow up **Results:** • Mean age 57.5 ± 8.8 y; 66.7% female; 47% diabetic • Overall AUC=0.632 (95% CI: 0.557-0.70), p=0.003 - Malay race: 0.737 (95% CI: 0.641-0.834), p=0.011 - Chinese race: 0.625 (95% CI: 0.512-0.737), p=0.054 - Indian race: 0.576 (95% CI: 0.417-0.736), p=0.335 • Good calibration (Hosmer-Lemeshow test $\chi 2$ =12.6, p=0.12) • Net Reclassification Improvement (NRI) 0.031, p=0.001 compared to FRS • Notably, the number of patients receiving statin therapy increased from 9.7% (n = 90) to 63.7% (n = 587) over the 10-y period of follow up (1998-2007) and mean blood pressure, total cholesterol and HbA1c were lower at follow up • Observed/predicted events: 45 actual ASCVD events (4.9%) over 10-y: 22 (7.2%) in men and 23 (3.7%) in women vs. predicted 93 (10.1%) ASCVD events: 21.1% in men and 6.7% in women. Observed v. Predicted (%) All Adults Men Women < 7.5% 2.2 v. 3.8 0 v. 4.5 2.4 v. 3.6 7.5%-9.9% 7.0 v. 8.4 5.3 v. 8.2 7.5 v. 8.4 10-19.9% 5.3 v.13.9 6.5 v.14.3 4.4 v.13.5 >=20% 7.9 v.30.5 9.1 v.31.1 5.3 v.28.2	• The PCE had poor discrimination and fair calibration in an Asian population overall, with reasonable calibration at lower risk levels and more substantial overprediction at higher predicted risk levels (≥10%, and especially ≥20%) in men and women • Lower observed vs. predicted ASCVD events may be partially explained by the very high proportion of patients who initiated statin therapy, and observed improvements in risk factor control (e.g., lower blood pressure and lower HbA1c) over the 10-y study period, which likely resulted in a reduction in observed ASCVD events. • Limitations: recall bias potential, unclear if chart abstractors were blinded to ASCVD event outcome prior to calculating risk; significant missing data (36%) led to participant exclusion; very high predicted risk population overall with fewer persons in low-risk category and intensive treatment after assessment OVERALL QUALITY: Moderate
REGARDS Colantonio L, et al., 2017 (66) 28314800	**Study type:** Prospective Observational Cohort Study	**Inclusion criteria:** • Age 45 to 70 y • No history of ASCVD or DM	**1° endpoint:** Nonfatal/fatal stroke, MI, or coronary heart disease death, stratified by socioeconomic status; Median ~7 y follow-up	• The PCE had good discrimination and calibration overall, with overprediction among individuals at higher SES with higher risk, fairly accurate prediction

	Size: 9066 black and white participants from the U.S. REGARDS (REasons for Geographic And Racial Differences in Stroke) study	• Not taking statin at baseline • Fasting LDL-C 70-189 mg/dL or NHDL-C 100-219 mg/dL • Participants from the REGARDS (REasons for Geographic And Racial Differences in Stroke) study **Exclusion criteria:** • Prevalent ASCVD, diabetes mellitus, heart failure or Afib • Low-density lipoprotein cholesterol level <70 or >189 mg/dL or NHDL-C <100 or > 219 mg/dL • Statin use at baseline	**Results:** • 457 incident ASCVD events occurred during 59,648 person-y of follow-up • Social deprivation was defined as any of the following: 1) self-reported annual household income <$35,000, 2) < high school education or 3) living without a partner. • C statistics generally >0.70 and H-L X2 ≤15 for all groups. • Predicted and observed rates similar at lower predicted risks, with overprediction observed more in higher risk individuals and higher SES individuals, and modest underprediction in lower SES groups • Predicted and observed per 1000 per-y *By number of indicators of deprivation:* 0 indicators: 8.02 and 6.23 (95% CI: 5.31– 7.31), H-L12.43, p=0.01 1 indicator: 8.05 and 6.61 (95% CI: 5.29– 8.24), H-L 6.6, p=0.09 2 or 3 indicators: 9.83 and 11.40 (95% CI: 9.23–14.05), H-L 5.77, p=0.12 *Annual household income* ≥$50 000: 6.91 and 5.15 (95% CI?!: 4.21–6.29), H-L: 10.91, p=0.01 $25 000 to <$50 000: 9.16 and 7.48 (95% CI?!: 6.22–9.00), H-L8.09, p=0.04 <$25 000: 9.72 and 10.73 (95% CI?!: 8.88–12.95), h-l 4.74, p=0.19 *Education* College graduate+: 7.74 and 6.03 (95% CI?!:5.01–7.26), h-l 9.01, p=0.03 High school/some college: 8.33 and 7.18 (95% CI?!: 6.15–8.39), H-L 8.62, p=0.03 Less than high school: 11.87 and 14.56 (95% CI?!: 10.92–19.35), H-L 8.92, p=0.03 *Relationship status*	among individuals at intermediate SES, and modest underprediction among individuals at lower SES. • Adding information on social deprivation added a modest improvement in risk classification of the PCE. • Large, representative sample. • Limitations: 7-y observation period for ASCVD events OVERAL QUALITY: HIGH

			Living with a partner: 8.42 and 6.92 (6.02–7.96), H-L 11.45, p=0.01 Living without a partner: 8.23 and 7.79 (95% CI?!: 6.50–9.32, H-L 7.49, p=0.06) • Discrimination Harrell's C-index (95% CI) *indicators of deprivation:* 0: 0.72 (0.69– 0.75) 1: 0.73 (0.69– 0.78) 2 or 3: 0.70 (0.65– 0.75) *Annual household income* ≥$50 000: 0.724 (0.683–0.765) $25 000 to <$50 000: 0.711 (0.671–0.751) <$25 000: 0.703 (0.660–0.746) *Education* College graduate: 0.724 (0.685–0.763) High school/some college: 0.704 (0.671–0.737) Less than high school: 0.742 (0.676–0.808) *Relationship status* Living with a partner: 0.720 (0.692–0.749) Living without a partner: 0.722 (0.680–0.763 • The NRI after adding deprivation data to the PCE was modest (0.12; 95% CI: 0.03– 0.21); for annual household income: 0.16 (0.06–0.25); education: 0.07 (95% CI?!: 0.02 to 0.15), relationship status: 0.02 (95% CI?!: 0.07 to 0.11)	
Cook N, et al., 2014 (67) 25285455	**Study type:** Prospective Observational Cohort Study **Size:** 27,542 participants from the US Women's Health Study	**Inclusion criteria:** • Participants from the US Women's Health Study • Women ages 45 to 70 y • No clinical ASCVD at baseline • Complete ascertainment of plasma lipids and information on other risk factors	**1° endpoint:** ASCVD, defined as any myocardial infarction, any stroke, or death due to cardiovascular cause. **Results:** • The PCE average predicted risk was 3.6% over 10 y vs. actual observed risk in the WHS of 2.2%. • Ratios of predicted to observed rates were 1.90 or higher in the groups with 0 to less than 5.0% and 5.0%	• The PCE overpredicted risk in this study sample, with the largest absolute discrepancies at the highest predicted risks (>10%). Ratios of predicted to observed risks were greatest at lower predicted risk but absolute differences between predicted and observed rates were highest at high predicted risks (>10%).

		Exclusion criteria: • The WHS excluded women with angina at baseline	to less than 7.5% risk and were over 1.40 in the groups with 7.5% to less than 10.0% and 10.0% or higher risk • The ratios of predicted to observed remained 1.80 or higher in the lower 2 risk groups and over 1.30 in the higher risk groups after adjustment for hypothetical statin use, revascularization procedures and confounding by indication Observed vs. Predicted, % E/O. <5% 1.01 1.92 1.90 5-7.5% 3.20 6.13 1.91 7.5%-9.9% 6.04 8.62 1.43 >10% 10.79 15.60 1.45	• Statin use and revascularization during follow up explained only part of the discrepancy between observed rates of ASCVD in the WHS and those predicted by PCE. Other assumptions regarding effects of statin use might explain more, but not all, of the discrepancy. • Large, lower risk sample of women in clinical trial (half receiving aspirin by design) and at high SES • Limitations: cumulative incidence of ASCVD was estimated as of 8 y because women were followed for 8 y, and then extrapolated to 10 y using a converting equation. Statin use was not assessed at every exam in the WHS. Estimates of confounding by indication were hypothetical and not data-derived. No report of discrimination/calibration statistics. OVERALL QUALITY: Moderate
Crowson et al., 2017 (68) 28339992	**Study type:** Combined Observational Cohort (both prospective and retrospective) **Size:** 1796 patients with rheumatoid arthritis (RA) from UK, Norway, Netherlands, USA, South Africa, Canada, and Mexico	**Inclusion criteria:** • Seven RA cohorts from UK, Norway, Netherlands, USA, South Africa, Canada and Mexico were combined. • No prior CVD • Physician diagnosis of RA and/or fulfilment of 1987 or 2010 American College of Rheumatology criteria for RA **Exclusion criteria:** • Other RA cohorts without information on disease activity or CVD death • CVD prior to baseline	**1° endpoint:** CVD event, defined as MI, ischemic stroke or CVD death **Results:** • The Standardized Incidence Ratio (SIR) for PCE was 0.73, 95% CI: 0.60, 0.89 • There were no significant differences between predicted and observed risks by decile for the PCE • Discrimination was moderate (c-statistic: 0.72) • In sensitivity analysis including only patients aged 40-74 y at baseline, calibration of the PCE improved (SIR: 0.73-0.93), but discrimination decreased (c-statistic: 0.70) • Other risk calculators that include RA-specific risk factors (e.g., ERS-RA, QRISK2 and EULAR 1.5 multiplier) did not improve risk prediction for patients with RA compared with the PCE	• PCE had moderate discrimination and fair overall calibration among patients with RA, with modest underestimation of risk at lower predicted risk and modest overprediction at very high levels of predicted risk (>20%). • RA-specific risk calculators do not predict CVD risk in patients with RA more accurately than the general population risk calculators. • Limitations: lower than expected CVD event rate for RA patients, who were treated at specialty centers; combined prospective and retrospective studies so risk of ascertainment bias; CVD events were not adjudicated

				OVERALL QUALITY: Moderate
Dalton JE, et al., 2017 (69) 28847012	**Study type:** Retrospective Cohort study **Size:** 109,793 patients	**Inclusion criteria:** • Patients from the Cleveland Clinic Health System who had an outpatient lipid panel drawn between 2007 and 2010 • White or African-American • Age > 35 y • Resided in 1 of 21 northeastern Ohio counties **Exclusion criteria:** • History of MI, stroke, heart valve disorder, or pericarditis, endocarditis, myocarditis, or cardiomyopathy • Missing data	**1° endpoint:** Incident major ASCVD event, defined as first occurrence of MI, stroke or CVD death; Median follow up of 5 y **Results:** • 4933 incident events (1676 MI, 2605 strokes, 652 CVD deaths) • PCE model discrimination was poorer among patients from disadvantaged communities (C statistic 0.70; [95% CI: 0.67 to 0.74]) than the most affluent communities (0.80 [95% CI: 0.78 to 0.81]) • PCE systematically underpredicted risk across all predicted risk levels in individuals living in disadvantaged neighborhoods, who were more likely to be black and female. Underprediction was observed especially in the top quartile (least affluent) of neighborhood disadvantage index. • PCE had near perfect calibration among individuals living in more affluent communities (neighborhood disadvantage index below the median).	• PCE were well calibrated and discriminate well in more affluent communities • PCE underpredicted ASCVD risk substantially among patients from disadvantaged communities • Limitations: Patients from affluent communities were overrepresented. Socioeconomic position was assessed using a composite index and thus cannot determine which measures of neighborhood characteristics and SES actually contribute to the disparity; used EHR data and thus subject to ascertainment bias, particularly with regard to event outcomes, since persons with low SES were more likely to not follow up; may have missed some events occurring at facilities outside of CCHS system; use of administrative data may have led to overdiagnosis of some ASCVD events; 5 y follow up.

<table>
<tr><td></td><td></td><td></td><td></td><td>OVERALL QUALITY: Moderate</td></tr>
<tr><td>MESA
DeFilippis AP, et al., 2015 (70)
25686167</td><td><u>Study type</u>:
Prospective cohort

<u>Size</u>: 4227 participants from the U.S. Multi-Ethnic Study of Atherosclerosis (MESA) Cohort</td><td><u>Inclusion criteria</u>:
• Age 50 to 74 y
• Free of clinical ASCVD or diabetes at baseline
• MESA participants who identified as White, African American, Hispanic, or Chinese

<u>Exclusion criteria</u>:
• Diabetes at baseline
• Missing data (2.7%)</td><td><u>1° endpoint</u>: MI, death from CHD, and stroke

<u>Results:</u>
• Five prediction scores were calculated and compared: PCE, FRS-CHD, FRS-CVD, ATPIII-FRS, CHD, and RRS

<u>ALL P O C slope</u>
FRS-HD 9.42 6.22 .68 0.05
FRS-CVD 13.28 10.60 .71 0.09
ATPIII-FRS-CHD 6.83 3.17 .71 0.06
RRS 7.43 7.64 .72 0.07
PCE 9.16 5.16 .71 0.06

<u>MEN P O C slope</u>
FRS-HD 12.8 8.36 .69 0.05
FRS-CVD 18.29 13.31 .71 0.09
ATPIII-FRS-CHD 11.15 4.39 .71 0.05
RRS 10.89 9.99 .70 0.06
PCE 11.84 6.37 .71 0.06

<u>WOMEN P O C slope</u>
FRS-HD 6.47 4.37 .60 0.01
FRS-CVD 8.94 8.25 .70 0.05
ATPIII-FRS-CHD 3.10 2.12 .67 0.02
RRS 4.44 5.60 .72 0.05
PCE 6.84 4.10 .70. 0.05

• For those with PCE risk score of 7.5% to 10%, the actual event rate was 3% in men and 5.1% in women.
• C-statistic for PCE: overall, 0.71; men, 0.71; women 0.70
• Calibration results in clinically relevant predicted risk categories:
<u>PCE: MEN</u>
P O H-L
<5% 3.4 1.3 4.94
5-7.5% 6.2 2.5 7.45</td><td>• Four of the 5 risk scores, including the PCE, overestimated risk in a modern multiethnic cohort
• Absolute differences in predicted vs. observed risk were most notable at higher levels of predicted risk
• Women experienced less overestimation than men in all models, including PCE, and had underestimation by the RRS
• Attempts to adjust for aspirin, lipid-lowering or antihypertensive therapy during follow up and interim revascularization did not appear to explain the overestimation
• Limitations: multi-ethnic cohort, and PCE were derived only in whites and blacks; participants with diabetes excluded; participants received intensive, repeated screenings for subclinical CVD at baseline and during follow up, which may have influenced preventive approaches; may represent a healthier subset of the U.S. population; inadequate adjustment for follow up therapy

OVERALL QUALITY: Moderate</td></tr>
</table>

			7.5%-9.9% 8.7 3.0 10.56 >10% 17.6 10.3 36.32 PCE: WOMEN P O H-L <5% 2.4 1.7 2.64 5-7.5% 6.1 4.5 1.65 7.5%-9.9% 8.7 5.1 3.86 >10% 15.9 8.6 21.60	
MESA DeFilippis AP, et al., 2017 (71) 27436865	**Study type:** **Size:** 6441 participants from the U.S. Multi-Ethnic Study of Atherosclerosis (MESA) Cohort	**Inclusion criteria:** • Age 45-79 y • Free of known ASCVD at baseline **Exclusion criteria:** • Missing data for risk score calculation (<1%) or no follow-up data after baseline (<1%)	**1° endpoint:** Incident MI, death from CHD, and stroke **Results:** • Risk overestimation was similar for women (100%) and men (93%) as was discrimination: c-statistic: 0.74 for women and 0.71 for men • Overestimation was observed in all race/ethnicity groups and was highest among Chinese (252% for women and 314% for men), and lowest in White women (72%) and Hispanic men (67%). Modelling of the AHA-ACC- ASCVD risk score in MESA demonstrates a mean absolute risk overestimation of 5.5% (p=0.001) • C-statistics in women: overall, 0.74; white 0.70; black, 0.75; Hispanic, 0.79; Chinese, 0.83 • C-statistics in men: overall, 0.71; white 0.71, black 0.68; Hispanic, 0.75; Chinese, 0.63 • C-statistics in women not on lipid-lowering medications with baseline LDLC 70-189: overall, 0.77; white 0.70; black, 0.77; Hispanic, 0.84; Chinese (too few events) • C-statistics in men not on lipid-lowering medications with baseline LDLC 70-189: overall, 0.71; white 0.72, black 0.70; Hispanic, 0.74; Chinese (too few events) • Predicted risks were higher, and absolute differences between predicted and observed event rates were greater, for those who initiated preventive therapies or had revascularization during follow up.	• PCE overestimated ASCVD risk among men, women, and all four race/ethnic groups in a modern American primary prevention cohort • Overestimation was highest among Chinese men and lowest in Hispanic Men. • Suggested that overestimation could not be fully attributed to treatment effect, although it did explain some • Limitations: very few events in Chinese subgroup OVERALL QUALITY: Moderate

Feinstein et al., 2017 (72) 28002550	**Study type:** Retrospective analysis of previously collected multicenter clinical prospective cohort study data **Size:** 11,288 HIV-infected adults from the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) cohort	**Inclusion criteria:** • Adults age 18 y or older receiving HIV care at 1 of 5 centers for AIDS research clinics in the US with adjudicated MI as outcome • Free of MI at baseline **Exclusion criteria:** • MI prior to baseline	**1° endpoint:** Incident MI only; Median follow up of 4.1 y **Results:** • PCE adequately discriminated MI risk in the overall cohort (Harrell C statistic=0.75, 95% CI: 0.71-0.78) • Among those with baseline age >=40 y, C-statistic 0.70 (95% CI: 0.66,0.74) overall; white men 0.69 (95% CI: 0.64-0.75); black men 0.69 (95% CI: 0.63, 0.76); white women 0.65 (95% CI: 0.48, 0.82); black women 0.74 (95% CI: 0.66, 0.83) • PCE were moderately calibrated in the overall cohort (slope = 0.815; intercept = 0.0015; GND test statistic = 13.1; p=0.16), particularly for white men (slope = 0.857; intercept = 0.009; GND test statistic = 6.4; p=0.50)	• PCE, which predict ASCVD risk, adequately discriminated MI risk overall and in most race and sex combinations, and were moderately calibrated in a multicenter HIV cohort, with modest underestimation of MI risk at lower risk. This indicates substantial underestimation of risk for ASCVD since stroke events were not captured in the cohort. • PCE were not as well fitted for black men, black women or white women. • HIV-related factors did not appreciably increase the discrimination and actually worsened model fit compared to the PCE OVERALL QUALITY: High
MESA Flueckiger P, et al., 2017 (73) 27859433	**Study type:** Prospective Observational Cohort study **Size:** 5,002 participants from the U.S. Multi-Ethnic Study of Atherosclerosis (MESA) Cohort	**Inclusion criteria:** • Adults age 45 to 75 y • Free of CVD **Exclusion criteria:** • missing covariates for ASCVD risk prediction • taking statins at baseline • age > 75 y	**1° endpoint:** 10-y CVD events defined as fatal and nonfatal MI, CHD death, fatal and nonfatal stroke and sudden cardiac death and CAC categories (>0, >=100, >=300) **Results (for PCE):** • For incident ASCVD, sensitivity was 79.6%, specificity was 50.7%, NPV was 98.0%, PPV was 7.7%, Negative LR 1.61 (95% CI: 1.50-1.73), Positive LR 0.40 (95% CI: 0.31-0.52) • Overall, the PCE had higher sensitivity and NPV than the 2004 NCEP ATP III and 2016 ESC/EAS • For CAC >=300, sensitivity was 87.2%, specificity was 52.6%, NPV was 97.8%, PPV was 14.5%, Negative LR 0.24 (95% CI: 0.19-0.31), positive LR 1.84 (95% CI: 1.76-1.93) • For CAC >=100, sensitivity was 83.1%, specificity was 56.1%, NPV was 97.8%, PPV was 14.5%, Negative LR 0.30 (95% CI: 0.26-0.35), Positive LR 1.89 (95% CI: 1.81-1.98) • For CAC >0, sensitivity was 69.8%, specificity was 63.2%, NPV was 97.8%, PPV was 14.5%, Negative	• ACC/AHA approach (including use of PCE) appears to be an improved screening tool for the identification of asymptomatic individuals with future ASCVD events and current subclinical CAC compared with the 2004 NCEP ATP III and 2016 ESC/EAS class I indications for statins/lipid-lowering therapy • Limitations: overall low event rates, did not account for statin use over time (25% of population taking statins after baseline) OVERALL QUALITY: Moderate

			LR 0.47 (95% CI: 0.44-0.51), Positive LR 1.90 (95% CI: 1.80-2.01)	
Korean Heart Study Jung KJ, et al., 2015 (74) 26255683	**Study type:** Prospective Observational Cohort **Size:** 192,605 participants	**Inclusion criteria:** • Age 40-79 y • Korean adults in the Korean Heart Study who had a minimum 10 y follow-up by 2012 **Exclusion criteria:** • Stroke or CVD at baseline • use of lipid-lowering meds at baseline • Persons with missing values of blood pressure, total cholesterol, HDL cholesterol, fasting glucose, smoking status, or BMI	**1° endpoint:** ASCVD incidence; Minimum of 10 y of follow up; mean 12.8 y **Results:** • 12,237 ASCVD events overall (10,049 of which were nonfatal stroke) • Discrimination: ACC/AHA PCE for white or black men exhibited moderate discrimination (AUROC 0.727 and 0.725 respectively), and similarly for the white or black women PCE (AUROC 0.738 and 0.739, respectively) • Calibration: ACC/AHA PCEs overestimated event rates in KHS cohort for men. Absolute 10y risk overestimated by 56.5% from the white men model and 74.1% from the black men model. For women, risk was underestimated by 27.9% in the white model but overestimated by 29.1% in the black model. These patterns of inadequate calibration were consistent across risk deciles • A recalibrated model exhibited improved calibration; the largest differences between actual and predicted rates within a risk decile were 1.7% in the recalibrated model (compared with 8.75% in the original ACC/AHA models) • The Korean Risk Prediction Model (KRPM) exhibited somewhat better calibration than the PCEs; of note, it appears that the KRPM was derived from the same KHS cohort it was then validated in	• PCE exhibited moderate discrimination but inadequate calibration when applied to a large Korean prospective cohort • PCE had systematic mismatch for men whereby predicted risks consistently exceeded observed; this was not consistently the case for women • A simple recalibrated ACC/AHA model was better calibrated • A Korean-specific model was best calibrated, though this is expected given the derivation and validation cohorts appear to be the same • Limitations: The better calibrated nature of the KRPM is expected as these analyses were biased toward optimism because the derivation and validation cohort appear to have been the same; very different population than PCE derivation cohorts – far more strokes than CHD OVERALL QUALITY: Moderate
Kavousi M, et al., 2014 (75) 24681960	**Study type:** Prospective Observational Cohort study **Size:** 4854 participants	**Inclusion criteria:** • Age 55-75 y in Rotterdam, Netherlands **Exclusion criteria:** • Lipid-lowering medication use • Prevalent CVD or LDL-c >190	**1° endpoint:** Hard ASCVD: stroke, nonfatal MI, fatal CHD, fatal MI; Median follow up >10 y **Results:** • 343 ASCVD events • PCE: Predicted vs. observed ASCVD risk was 21.5% (95% CI: 20.9-22.1%) vs. 12.7% (95% CI: 11.1-14.5%) for men; and 11.6% (95% CI: 11.2-12.0%) vs. 7.9%	• All 3 risk models exhibited moderate discrimination and poor calibration with overestimation of risk in an older (55-75 y) population from the Netherlands • Calibration of PCE was better at lower (<10%) compared with higher (≥10%) predicted risks, especially in women, and overall in women compared with men.

			(95% CI: 6.7-9.2%) for women. The C-statistic of this model was 0.67 (95% CI: 0.63-0.71) for men and 0.68 (95% CI: 0.64-0.73) for women. Across predicted risk strata, absolute mismatch between PCE predicted and observed rates was moderate for men at <10% and substantial at ≥10% predicted risk; for women, absolute mismatch was small at <10% and moderate at ≥10% predicted risk. • ATP3: C-statistic 0.67 (95% CI: 0.62-0.72) for men and 0.69 (95% CI: 0.63-0.75) for women • ESC SCORE: C-statistic 0.76 (95% CI: 0.70-0.82) for men, 0.77 (95% CI: 0.71-0.83) for women	**Limitations:** Older age of the cohort, which included only persons age 55 and over at baseline; all white cohort. OVERALL QUALITY: Moderate
Khalili D, et al., 2015 (76) 25769004	**Study type:** Prospective Observational Cohort study **Size:** 6275 participants	**Inclusion criteria:** • Age 40-75 y • Iranian urban population in Tehran **Exclusion criteria:** • Lipid-lowering medication use • Hemodialysis • Missing data on LDL-c, DM, SBP, or current smoking at baseline • Missing follow-up data	**1° endpoint:** Incident CVD, defined as CHD and cerebrovascular events **Results:** • Among pts without prevalent CVD at baseline, mean calculated and observed 10-y ASCVD risks were 12.4% and 7.9% for men, respectively, and 4.9% and 3.3% for women • Discrimination was better for men (C-index 0.82; 95% CI: 0.78-0.86) than women (0.74; 95% CI: 0.71-0.78). This corresponded to consistent mismatch whereby ASCVD risks were 57% lower than predicted for men and 48% lower than predicted for women. H-L chi-square was 23.5 for men and 56.7 for women • Simple recalibrations improved the calibration, with H-L chi-square down to 14.7 for men and 12.9 for women • Moderate statin therapy: Net Benefit Fraction for non-diabetic Men with LDL-c 70-189 and no prior CVD with predicted 10y ASCVD risk of 5% to 7.4% is 0.46. For women, this was 0.11 (not significant). Among those with DM, these numbers were 0.72 for men and 0.39 for women. • Intensive statin therapy: Net Benefit Fraction for non-diabetic Men with LDL-c 70-189 and no prior CVD with predicted 10y ASCVD risk of ≥7.5% is 0.71. For	• Although there was consistent mismatch whereby risk predicted by PCEs exceeded observed ASCVD risk in this population, this overestimation had negligible effect on the validity and clinical usefulness of the PCEs and related guideline, as the net benefit fraction was positive for men with 5% or greater predicted risk and women with 7.5% or greater predicted risk • Limitations: Some of the analyses use the PCE inappropriately to estimate risk among persons with pre-existing CVD; the results included in this evidence synthesis thus focus on the analyses that evaluated the PCEs in persons with no prior CVD. OVERALL QUALITY: Moderate

			women, this was 0.96. Among those with DM, these numbers were 0.12 for men and 0.55 for women.	
Lee CH, et al., 2015 (77) 26350809	**Study type:** Prospective Observation Cohort study **Size:** 1753 participants	**Inclusion criteria:** • Chinese men and women in Hong Kong aged 25-75 y **Exclusion criteria:** • Lipid-lowering med use • Prevalent CVD or LDL-c >190	**1° endpoint:** Incident CVD event: First-recorded diagnosis of CV event based on administrative codes (ICD-9); hard ASCVD defined as MI, stroke, CHD, or stroke-related mortality; Total CVD defined as MI, coronary insufficiency, angina, stroke, TIA, PVD, HF, and CHD or stroke-related mortality; Median follow up of 10 y **Results:** • 122 persons had incident ASCVD, 138 with total CVD; 45 CHD events and 41 strokes in men, 32 CHD events and 20 strokes in women • PCE C statistic 0.714 (95% CI: 0.567-0.770) for men, 0.765 (95% CI: 0.69-0.84) for women. Calibration chi-square was 24.1 for men and 10.1 for women. • Framingham CV risk equation AUROC 0.773 (95% CI: 0.742-0.802) for men, 0.788 (95% CI: 0.724-0.852) for women. Chi-square was 20.1 for men and 12.1 for women • Recalibration not possible for PCE due to variable misclassification across predicted risk categories.	• PCE were poorly calibrated in Hong Kong Chinese population, especially in men • PCE and Framingham total CVD equations had moderate discrimination • Limitations: Events were not adjudicated; potential for misclassification; relatively few events. OVERALL QUALITY: Poor
NHANES Loprinzi PD, et al., 2016 (78) 27180122	**Study type:** Prospective cohort **Size:** 11,171	**Inclusion criteria:** • Noninstitutionalized US adults age 40-79 y without CVD, non-pregnant, and with complete BMI data • NHANES 1999-2010 samples **Exclusion criteria:** • Pregnant • Prevalent CVD • Lipid-lowering med use	**1° endpoint:** All-cause and CVD-specific mortality across different levels of predicted ASCVD risk; Median follow-up of 72 mo. **Results:** • 851 total deaths; 124 CVD deaths • Predicted 10y ASCVD risk was significantly associated with all-cause and CVD-specific mortality. • Each 1% higher predicted 10y ASCVD risk was associated with a 6% greater risk for all-cause and CVD mortality (HR: 1.06; 95% CI: 1.05-1.07 for both per 1% higher predicted risk by PCEs). Harrell's C-statistic for this was 0.74 for all-cause mortality and 0.79 for CVD mortality. • After adjustment for physical activity, obesity, age, sex and race/ethnicity, HR per 1% higher predicted risk	• Predicted 10y ASCVD risk levels were significantly associated with all-cause and CVD-specific mortality among those free of CVD • PCE can rank-order all-cause and CVD mortality risk • Strength of association was similar for all-cause and CVD-specific mortality. Limitations: Outcomes assessed do not include nonfatal ASCVD events OVERALL QUALITY: Moderate-to-poor.

			was 1.03 (95% CI: 1.02-1.04) for all-cause mortality and 1.03 (95% CI: 1.01-1.05) for CVD mortality.
			• Hazard ratios for total mortality by predicted 10y ASCVD risk:
			  • ≥7.5% vs. <7.5%: Unadjusted HR: 5.44; 95% CI: 4.34-6.77; HR adjusted for physical activity, obesity, age, sex and race/ethnicity: 1.77; 95% CI: 1.27-2.48
			  • ≥20% vs. <20%: HR: 5.57; 95% CI: 4.73-6.56; HR adjusted for physical activity, obesity, age, sex and race/ethnicity 1.47; 95% CI: 1.10-1.97
			• Hazard ratios for CVD-specific mortality by predicted 10y ASCVD risk
			  • ≥7.5% vs. <7.5%: HR: 7.21; 95% CI: 3.70-14.05; HR adjusted for physical activity, obesity, age, sex and race/ethnicity 3.16; 95% CI: 1.16-8.58
			  • ≥20% vs. <20%: HR: 5.24; 95% CI: 3.43-7.99; HR adjusted for physical activity, obesity, age, sex and race/ethnicity 1.36; 95% CI: 0.71-2.60.	

Mortensen MB, et al., 2015 (79)
26700832
	Study type:
	Prospective Observation Cohort study (Copenhagen General Population Study, 2003-2008)
	
	Size: 37,892 participants
		Inclusion criteria:
		• Adults age 40-75 y in Copenhagen, Denmark
		
		Exclusion criteria:
		• Diabetes
		• Lipid-lowering medication use
		• Prevalent ASCVD
			1° endpoint: Incident ASCVD;
			5 y follow up
			
			Results:
			• Compared statin eligibility of sample by ACC/AHA approach using PCE (42% eligible) vs. approach using trial eligibility criteria (56%) vs. hybrid approach (21%)
			• 834 ASCVD events (323 myocardial infarctions)
			• PCE well calibrated below 10% predicted 10 y risk, with predicted and observed event rates statistically similar for predicted risk strata <10%, and overprediction of observed risk at predicted risk ≥10%
			• Events (K-M adjusted) over 5 y stratified by 10y ASCVD predicted risk by PCE:
			  - <5% predicted risk: 1.0% observed events, 0.8% predicted, ratio P/O 0.8
			  - 5 to <7.5% predicted risk: 2.1% observed, 2.3% predicted, ratio P/O 1.1
			  - 7.5 to <10% predicted risk: 2.7% observed, 3.4% predicted, ratio P/O 1.2
				• In a contemporary Danish cohort, clinical performance of ACC/AHA risk-based approach (based on PCE) was superior to other approaches, suggesting this approach would prevent more ASCVD events and treat fewer people than the trial-based approach
				• PCE were well calibrated at predicted risks <10%
				
				Limitations: No formal calibration calculation used; white-only cohort; persons with diabetes excluded; 5-y predicted and observed event rates used given lack of 10 y of follow up
				
				OVERALL QUALITY: Moderate

			- 10%+ predicted risk: 5.7% observed, 8.2% predicted, ratio P/O 1.4 • C statistics: 0.676 for ACC/AHA PCEs (vs. 0.572 for trial-based approach and 0.613 for hybrid approach, p<0.0001 for both); for men this was 0.647 and for women this was 0.669 for the PCEs with poorer discrimination by trial-based and hybrid approaches • Net reclassification improvement for improving decision making for statin therapy compared with PCE: -0.21 for trial-based approach, -0.13 for hybrid approach (p<0.0001 for both), with similar NRI among men and women	
Mortensen MB, et al., 2017 (80) 28363217	**Study type:** Prospective Observational Cohort study (Copenhagen General Population Study, 2003-2009) **Size:** 44,889 participants	**Inclusion criteria:** • Adults age 40-75 y in Copenhagen, Denmark **Exclusion criteria:** • Diabetes • Lipid-lowering medication use • Prevalent ASCVD	**1° endpoint:** Incident ASCVD (for PCE) or incident CVD death (for European-SCORE equations); 5 y follow-up **Results:** • Compared statin eligibility of sample by ACC/AHA approach using PCE (42% eligible) vs. approach using ESC/EAS guidelines using European-SCORE approach (6%) • 1265 ASCVD events • PCE were well calibrated overall (overall predicted to observed ratio 1.2), especially below 10% predicted 10 y risk, with predicted and observed event rates statistically similar for predicted risk strata <10%. Overprediction of observed risk at predicted risk ≥10% was seen. • European-SCORE was not well calibrated at any level of predicted risk for CVD death (overall predicted to observed ratio 5.0, range 3.6 to 5.4 across all risk strata). • Events (K-M adjusted) over 5 y stratified by 10y ASCVD predicted risk by PCE: - <5% predicted risk: 235 observed events, 164 predicted, ratio P/O 0.7 - 5 to <7.5% predicted risk: 123 observed events, 125 predicted, ratio P/O 1.0	• In a contemporary Danish cohort, clinical performance of ACC/AHA risk-based approach (based on PCE) was superior to European-SCORE approach • PCE were well calibrated at predicted risks <10% Limitations: No formal calibration calculation used; white-only cohort; persons with diabetes excluded; 5-y predicted and observed event rates used given lack of 10 y of follow up OVERALL QUALITY: Moderate

			- 7.5 to <10% predicted risk: 115 observed events, 130 predicted, ratio P/O 1.1 - ≥10% predicted risk: 792 observed events, 1144 predicted, ratio P/O 1.4 • Overall C-statistic for PCEs 0.72 for ASCVD overall and 0.82 for fatal ASCVD; for men these numbers were 0.71 and 0.77, and for women they were 0.71 and 0.85. These were consistently superior to the European SCORE model. • Net reclassification improvement for improving decision making for statin therapy compared with European-SCORE: +0.27 for PCE for ASCVD overall (+0.21 in men, +0.28 in women, p<0.0001 for both).	
REGARDS Muntner P, et al., 2014 (81) 24682252	**Study type:** Prospective Observational Cohort study (REasons for Geographic And Racial Differences in Stroke [REGARDS] Study, 2003-2007) **Size:** 10,997 participants (subgroup analysis in 3333 Medicare beneficiaries)	**Inclusion criteria:** • Adults age 45-79 y in nationwide US cohort with LDL-C 70 to 189 mg/dl **Exclusion criteria:** • Lipid-lowering medication use • Prevalent ASCVD • Diabetes	**1° endpoint:** Incident ASCVD (CHD death, nonfatal MI, fatal or nonfatal stroke); Follow-up of 5 y **Results:** • 338 ASCVD events (192 CHD events, 146 strokes) • PCE were very well calibrated in lower predicted risk strata (<10% predicted 10-y risk), and overpredicted events in higher predicted risk strata (≥10% predicted 10-yr risk) • In the group for whom the PCE were intended, events over 5 y across 10y ASCVD predicted risk strata were: - <5% predicted risk: 1.9% observed events, 1.9% predicted - 5 to <7.5% predicted risk: 4.8% observed, 4.8% predicted - 7.5 to <10% predicted risk: 6.1% observed, 6.9% predicted - ≥10% predicted risk: 12.0% observed, 15.1% predicted - C-statistics for PCE: • Overall: 0.72, 95% CI: 0.70-0.75 • Women: 0.75, 95% CI: 0.71-0.79 • Men: 0.66, 95% CI: 0.62-0.70 • Blacks: 0.69, 95% CI: 0.65-0.74	• PCE exhibited moderate to good discrimination and were moderately well calibrated, especially at predicted risk levels <10%, in a large geographically diverse US cohort, and particularly when the cohort was restricted to persons without DM, not taking statins, LDL 70-189 mg/dl, and without pre-existing ASCVD, for whom the PCE were intended. PCE overpredicted risk somewhat at very high risk levels. • PCE were well calibrated across deciles of risk in Medicare population • Broad-based representative population sample • Limitations: 5 y of follow-up; use of administrative codes for additional events in Medicare subset may have led to some misclassification of events; did not assess effects of statin or other preventive therapy after baseline. QUALITY: MODERATE

			• Whites: 0.74, 95% CI: 0.71-0.77 • Discrimination (Hosmer-Lemeshow X2: • Overall: 19.9; p=0.01 • Women: 8.3; p=0.41 • Men: 16.5; p=0.04 • Blacks: 11.8; p=0.16 • Whites: 14.0; p=0.08 • PCE performed similarly in the stroke belt states (NC, SC, GA, AL, MS, LA, TN, AK) and in the remainder of the continental US • In the subgroup of Medicare beneficiaries (N=3333) without diabetes and not taking statins, with LDL-C 70-189 mg/dL, PCE tended to underpredict event rates somewhat. Events over 5 y across 10y ASCVD predicted risk strata were: - <7.5% predicted risk: 5.3% observed, 4.0% predicted - 7.5 to <10% predicted risk: 7.9% observed, 6.4% predicted - ≥10% predicted risk: 17.4% observed, 16.4% predicted - Overall C statistic 0.67, 95% CI: 0.64-0.71 - Hosmer-Lemeshow X^2 5.4, p=0.71.	
MESA Nasir K, et al., 2015 (82) 26449135	**Study type:** Prospective Observational Cohort study (MESA) **Size:** 4758	**Inclusion criteria:** • Adults age 45-75 y with complete data for risk factors used in PCE **Exclusion criteria:** • Lipid-lowering medication use • Prevalent ASCVD • LDL <70 mg/dl	**1° endpoint:** Incident ASCVD (CHD death, resuscitated cardiac arrest, myocardial infarction, and stroke); Median follow up of 10.3 y **Results:** • 247 ASCVD events; 155 hard CHD events • Event rates based on recommendation status for statins per 2013 ACC/AHA guidelines: - Recommended for statins based on PCE (10-y predicted risk ≥7.5% or LDL-C 190 mg/dL or diabetes): 9.1/1000 person-y, 95% CI: 7.9-10.5); - Considered for statins (10-y predicted risk 5% - <7.5%): 4.00/1000 person-y, 95% CI: 2.6-6.0;	• PCE rank-ordered ASCVD risk appropriately, but there was evidence for mis-calibration with overprediction of observed event rates in this cohort • Limitations: No formal discrimination /calibration assessment, as the purpose of this study was not as much to evaluate the PCE as it was to evaluate the additive value of CAC to the PCE OVERALL QUALITY: Moderate

			- Not statin candidates (10-y predicted risk <5%): 1.62/1000 person-y, 95% CI: 1.2-2.3.	
Rana JS, et al., 2016 (83) 27151343	**Study type:** Retrospective administrative cohort (integrated healthcare system, baseline 2008) **Size:** 307,591	**Inclusion criteria:** • Adults aged 40-75 y with LDL-c 70-189 mg/dl receiving care at Kaiser Permanente Northern California with blood pressure and cholesterol data **Exclusion criteria:** • Lipid-lowering medication use within 5 y before index date • Unknown race/ethnicity • Prior hospitalization for MI, stroke, CABG, PCI	**1° endpoint:** Incidence of ASCVD (MI, CHD death, stroke) based on administrative codes and hospital discharge plans; Follow-up of 5 y **Results:** • 2061 ASCVD events observed during 1,515,142 person-y • Consistent mismatch between predicted and observed event rates; PCE substantially overpredicted event rates in this sample and in all subgroups by sex and race and diabetes status • Event rates over 5 y by 5-y predicted risk strata in patients without diabetes (N=307,591): - <2.5%: observed rate 0.20%, predicted rate 1.04% - 2.5% to <3.75%: observed rate 0.65%, predicted rate 3.08% - 3.75% to <5.0%: observed rate 0.9%, predicted rate 4.34% - ≥5.0%: observed rate 1.85%, predicted rate 8.72% • Event rates over 5 y by 5-y predicted risk strata in patients with diabetes (N=4242): - <2.5%: observed rate 0.10%, predicted rate 1.36% - 2.5% to <3.75%: observed rate 2.55%, predicted rate 3.11% - 3.75% to <5.0%: observed rate 2.65%, predicted rate 4.37% - ≥5.0%: observed rate 5.50%, predicted rate 13.38% • Mis-calibration similar with substantial overprediction by PCE across all subgroups by sex, race, and diabetes status • Discrimination C statistics moderate to good: - Overall without diabetes: 0.74 - Women: 0.72	• Authors concluded that PCE should be recalibrated due to the substantial and consistent overestimation of ASCVD risk in their sample • Limitations: Approximately 90% of all covered individuals and >2/3 of original eligible population excluded, including those treated after baseline; as a result, very low prevalence of diabetes (1.4%) and other high-risk conditions, and there were very low event rates compared with other samples from the same population. Administrative data used to ascertain endpoints, which may have led to some misclassification; uncertain how scaling of 10-y to 5-y predicted risks was performed. QUALITY: Low

			- Men: 0.68 - Non-Hispanic White: 0.74 - African American: 0.70 - Asian-Pacific Islander: 0.72 - Hispanic: 0.74 - Overall with diabetes: 0.64	
Ungprasert et al., 2017 (84) 28705378	**Study type:** Retrospective Case-Cohort study from Olmsted County, MN, 1989-2013 **Size:** 358 patients with sarcoidosis and matched controls (N=203 total for persons for whom PCE were applied)	**Inclusion criteria (for analysis of PCE):** • Patients aged 40 to 74 y with incident sarcoidosis and randomly selected comparators from underlying population matched on age, sex and date of diagnosis of sarcoidosis in case **Exclusion criteria (for analysis of PCEs):** • Incomplete data on lipids and other variables needed for PCE • Prevalent CVD • Prevalent statin use	**1° endpoint:** Incident CHD or stroke (for analyses of PCE); Median follow up N/A **Results:** • In analysis of the PCE, the predicted number of ASCVD events among those with sarcoidosis was 4.6, and the observed number of events was 16, corresponding to a standardized incidence ratio (SIR) of 4.11, 95% CI: 2.62-6.44. Among comparators, the predicted number of events was 5.4 and the observed number was 6, for an SIR of 1.12, 95% CI: 0.50-2.49. • In analysis of Framingham general CVD equations, the predicted number of CVD events among those with sarcoidosis was 11.8, and the observed number of CVD events was 34, corresponding to a SIR of 2.88, 95% CI: 2.06-4.04. Among comparators, the predicted number of events was 11.0 and the observed number was 11, for an SIR of 1.00, 95% CI: 0.56-1.81. FRS consistently underpredicted risk across subgroups of age, sex and severity of sarcoidosis.	• PCE substantially underestimated the risk of CVD among patients with sarcoidosis • Limitations: Small sample size, retrospective study; unclear what the role of controls is here; non-parallel nature of ASCVD PCE and overall CVD endpoint QUALITY: Poor
Wolfson J, et al., 2017 (85) 28438733	**Study type:** Retrospective administrative cohort study, 2001-2011 **Size:** 84,116 patients	**Inclusion criteria:** • Adults aged 40-79 y without CVD, in a large combined medical care network and/or insurance plan in Minnesota • Two or more medical encounters with blood pressure measurement >30 ds but <1.5 y apart	**1° endpoint:** Incident CHD or stroke based on administrative codes; Median follow-up of 4.5 y **Results:** • PCE were well calibrated in lower-risk strata and overpredicted risk notably in higher risk strata (~>10% 10-y risk) • Kaplan-Meier event rates for strata of predicted 5-y risk by PCE were:	• PCE exhibited good calibration, except at higher risk levels (~>10% predicted 10-y risk), and moderate discrimination in this EHR-based cohort. Recalibrating the PCE did not improve calibration substantially. • Limitations: Retrospective cohort study; administrative data and non-adjudicated endpoints; 4.5 y of follow up; missing data handled by imputation rather than restricting analyses; no accounting of preventive therapy after baseline

		• Prescription drug benefit during the same period **Exclusion criteria:** • Prevalent CVD based on ICD codes	• 0%-2.5%: observed rate of 13/1000 person-y, predicted rate of 9/1000 person-y • 2.5%-5%: observed rate of 41/1000 person-y, predicted rate of 35/1000 person-y • 5% to 7.5%: observed rate of 56/1000 person-y, predicted rate of 61/1000 person-y • 7.5%-10%: observed rate of 74/1000 person-y, predicted rate of 86/1000 person-y • >10%: observed rate of 117/1000 person-y, predicted rate of 148/1000 person-y • Hosmer-Lemeshow-like calibration statistic of PCE overall was 43.7 ($p<0.001$) • Discrimination C-statistic of PCE was 0.747; 95% CI: 0.727-0.768 • Results were similar when restricted to non-statin users only, and whites and blacks only. PCE calibration was excellent for blacks when considered separately; calibration statistic 2.8, p=0.42 • PCE were well calibrated across all 5-y age groups from 40 to 75 y, and overpredicted risk among those 75 to 80 y old • Recalibration of PCE using locally derived coefficients and hazards only modestly improved calibration • Framingham risk score performed slightly better for its endpoint of total CVD	QUALITY: Moderate to poor
Yang X, et al., 2016 (86) 27682885	**Study type:** Prospective Observational Cohort study **Size:** 84,961 participants (combination of two external validation cohorts)	**Inclusion criteria:** • Adults aged 35-74 y at baseline **Exclusion criteria:** • Prevalent MI or stroke • Missing data	**1° endpoint:** Incident ASCVD (nonfatal MI or CHD death, stroke); Median follow up of 12 y **Results:** • PCE for white individuals tended to overestimate risk in men and underestimate risk in women • Using PCE for white participants, measures of utility were: - Kaplan-Meier-adjusted observed events 218.7, predicted events 336.9; C-statistic 0.768; 95% CI: 0.733-0.803; calibration X2 118.8 ($p<0.001$) in China MUCA men	• PCE exhibited good discrimination and poor calibration in two large Chinese cohorts, in both men and women. A separate Chinese-specific risk prediction model demonstrated better calibration than the PCE when applied in this cohort. • Limitations: PCE applied in race/ethnic population not included in the derivation of the PCE. OVERALL QUALITY: Moderate

			- Kaplan-Meier-adjusted observed events 166.4, predicted events 121.6; C-statistic 0.786; 95% CI: 0.752-0.820; X2 18.7 (p=0.03) in China MUCA women - Kaplan-Meier-adjusted observed events 746.7, predicted events 1249.3; C-statistic 0.793; 95% CI: 0.778-0.808; X2 81.3 (p<0.001) in CIMIC men - Kaplan-Meier-adjusted observed events 716.0, predicted events 646.3; C-statistic 0.785 (95% CI: 0.771-0.800); X2 65.9 (p<0.001) in CIMIC women • Recalibration improved discrimination and calibration of PCE	

Data Supplement 15. Nonrandomized Trials, Observational Studies, and/or Registries of Q2: Performance of coronary artery calcium screening to reclassify risk appropriately for atherosclerotic cardiovascular disease (ASCVD) events when used for the prediction of first incident ASCVD events in diverse populations, especially in the context of the Pooled Cohort Equations (Section 4.4.1.2)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
CARDIA Carr J, et al.(87) 2017 28196265	**Study type:** Prospective cohort (CARDIA study, exam years 15, 20 and 25) **Size:** 3036 participants	**Inclusion criteria:** • Black and white men and women attending Year 15 examination of the CARDIA Study and undergoing CAC measurement • Adults age 32-46 years **Exclusion criteria:** • Missing data • Pregnant • Prevalent CHD	**1° endpoint:** Incident clinical CHD, CVD, or all-cause mortality, considered separately; Median follow up of 12.5 years **Results:** • **Any CAC versus CAC=0** • All CHD (57 events/38,056 p-y) Any CAC: 30 events/3644 p-y CAC=0: 27 events/34,413 p-y Adjusted HR 5.0, 95% CI: 2.8-8.7 • CHD excluding coronary revascularization without acute events (46 events/38,125 p-y) Any CAC: 23 events/3693 p-y CAC=0: 23 events/34,432 p-y Adjusted HR 4.1, 95% CI: 2.2-7.7	• CAC>0 among adults age 32-46 years was associated with higher risk of fatal and nonfatal CHD; CAC>100 was associated with nearly four-fold risk of all-cause mortality, most of which was due to CHD • There is a dose-response gradient for future CHD events evident for CAC scores even among younger adults aged 32-46 years over 12.5 years of follow up. • Presence of risk factors for CVD in early adult life identified those above the median risk for developing CAC and, if applied, in a selective CAC screening strategy could reduce the number of people screened for CAC by 50% and the number imaged needed to find 1 person with CAC from 3.5 to 2.2.

			• Any CVD event (108 events/37,599 p-y) Any CAC: 38 events/3555 p-y CAC=0: 70/34,045p-y Adjusted HR 3.0, 95% CI, 1.9-4.7 • All-cause mortality (107 events/38330 p-y) Any CAC: 25 events/3847 p-y CAC=0: 82 events/34,847 p-y Adjusted HR 1.6, 95% CI 1.0-2.6 • **CAC score ranges vs. CAC=0** • All CHD CAC 1-19: 7 events/1844 p-y Adjusted HR 2.6, 95% CI: 1.0, 5.7 CAC 20-99: 10 events/1177 p-y Adjusted HR 5.8, 95% CI 2.6-12.1 CAC ≥100: 13 events/623-py Adjusted HR 9.8, 95% CI 4.5-20.5 • Any CVD event CAC 1-19: 11 events/1814 p-y Adjusted HR 1.8, 95% CI 0.9-3.4 CAC 20-99: 13 events/1150 p-y Adjusted HR 3.6, 95% CI 1.8-6.5 CAC >100: 14 events/591 p-y Adjusted HR 5.7, 95% CI 2.8-10.9 • All-cause mortality CAC 1-19: 8 events/1897 p-y Adjusted HR 1.1, 95% CI 0.5-2.1 CAC 20-99: 4 events/1243 p-y Adjusted HR 0.9, 95% CI 0.3-2.7 CAC≥100: 13 events/706 p-y Adjusted HR 3.7, 95% CI 1.5-10.0 • When participants were stratified into 3 tiers of Framingham CHD risk score (≤4%, 5%-11%, and ≥12%), CAC score further stratified CHD incidence density, with those	• Selective use of screening for CAC in adults before the age of 50, based on the presence of risk factors in young adulthood, might be considered to inform discussions on primary prevention. • Limitations: Small number of events given younger age of cohort

			with lower CAC scores experiencing substantially lower event rates than those with higher CAC scores, especially when CAC score ≥100 at 10-year CHD risk levels >5% and when CAC score ≥20 at 10-year CHD risk levels ≥12% • Among participants predicted to be at lower risk for CAC>0 in middle age (based on being below the median in predicted CAC risk from risk factor levels in early adulthood), CAC prevalence was 13.2% for number needed to screen to find CAC>0 of 7.7 • Among participants predicted to be at higher risk for CAC>0 in middle age (above the median in predicted CAC risk), CAC prevalence was 44.7% for number needed to screen to find CAC>0 of 2.2	
MESA Flueckiger P, et al. (73) 2017 27859433	**Study type:** Prospective cohort **Size:** 5002 participants	**Inclusion criteria:** • Untreated MESA participants (adults age 45-84 years) who underwent CAC screening at baseline **Exclusion criteria:** • Lipid-lowering medication use • Missing data • Age >75 years	**1° endpoints:** Sensitivity/specificity/NPV/PPV of several risk scores/guideline recommendations for detecting CAC at baseline; Incident CHD (for ATP III – defined as fatal/nonfatal MI or fatal CHD) Incident ASCVD (for ACC/AHA – defined as including fatal/nonfatal myocardial infarction (MI), coronary heart disease (CHD) death, fatal/nonfatal stroke); ASCVD death (for ESC/EAS – defined as all fatal ASCVD events, including MI, stroke, occlusive atherosclerotic disease, and sudden cardiovascular death) Follow up of 10 years **Results:** **Using Class I recommendations for lipid-lowering therapy by different guidelines for detection of CAC at baseline:**	• ACC/AHA approach using PCE appears to have the best balance between sensitivity and specificity for detecting CAC and for predicting incident CVD events compared with ATP III and ESC/EAS. • There were modest differences by sex (more sensitive in men), age (more sensitive in older adults), and race (minimal differences), but these differences appear largely driven by risk. • The proportion with baseline CAC=0 was high for all Class I recommendation groups, but similar across groups: ATP III (57%), PCE (58%), and SCORE (60%).

			• Sensitivity/Specificity/NPV/PPV for CAC>0 2004 ATP III: 35.0%/80.7%/62.9%/57.0% 2013 ACC/AHA: 69.8%/63.2%/74.2%/58.1% 2016 ESC/EAS: 39.1%/80.8%/64.5%/59.7% • Sensitivity/Specificity/NPV/PPV for CAC≥100 ATP III: 40.2%/77.1%/85.9%/27.1% ACC/AHA: 83.1%/56.1%/94.0%/28.6% ESC/EAS: 48.5%/76.8%/87.5%/30.7% • Sensitivity/Specificity/NPV/PPV for CAC≥300 ATP III: 41.1%/75.5%/93.3%/13.4% ACC/AHA: 87.2%/52.6%/97.8%/14.5% ESC/EAS: 54.1%/74.8%/94.6%16.6% • Sensitivity/Specificity/NPV/PPV for CAC≥300 + 75th %ile for age/sex/race ATP III: 36.3%/77.2%/80.1%32.4% ACC/AHA: 66.3%/53.9%/84.2%/30.2% ESC/EAS: 39.4%/75.9%/80.6%/33.0% **Using Class I recommendations for lipid-lowering therapy by different guidelines for prediction of incident events (risk score-specific outcomes)** • HR (95% CI) for incident events (absolute event rates not reported) among statin eligible compared with statin not eligible: ATP III: HR 2.24, 95% CI 1.74-2.88 ACC/AHA: HR 4.10, 95% CI 3.01-5.60 ESC/EAS: HR 2.41, 95% CI 1.87-3.10 • Sensitivity/Specificity/NPV/PPV for incident events ATP III: 45.8%/75.1%/96.3%/8.9% ACC/AHA: 79.6%/50.7%/98.0%/7.7% ESC/EAS: 50.5%/72.9%/98.7%/3.6% AUC (95% CI) for statin eligibility and incident events	

			ATP III: 0.59, 95% CI 0.56, 0.62 ACC/AHA: 0.66, 95% CI 0.63-0.68 ESC/EAS: 0.63, 95% CI 0.60-0.66	
MESA Fudim M, et al. (88) 2016 26909370	**Study type:** Prospective cohort (MESA) **Size:** 6742 participants	**Inclusion criteria:** • MESA participants at baseline exam **Exclusion criteria:** • Missing data	**1° endpoint:** Hard CVD events, which included myocardial infarction, death due to myocardial infarction, resuscitated cardiac arrest, stroke and death from stroke; Median follow up of 7.5 years **Results:** **Metrics for utility of addition of CAC score to PCE for prediction of CVD in subgroups:** • Men: 6.1 per 1000 p-y Increase in C-statistic: 0.025, P=0.047 Hosmer-Lemeshow X2: 8.587, P=0.38 Categorical NRI: 0.080, P=0.037 IDI: 0.0117, P=0.001 • Women 3.7 per 1000 p-y Increase in C-statistic: 0.018, P=0.019 Hosmer –Lemeshow X2: 16.715, P=0.033 Categorical NRI: 0.095, P=0.039 IDI: 0.0069, P=0.032 • Caucasian: 5.4 per 1000 p-y Increase in C-statistic: 0.019, P=0.18 Hosmer -Lemeshow X2: 11.9, P=0.16 Categorical NRI: 0.111, P=0.02 IDI: 0.012, P=0.001 • Black 5.0 per 1000 p-y Increase in C-statistic: 0.033, P=0.11 Hosmer-Lemeshow X2: 12.3, P=0.14 Categorical NRI: 0.024, P=0.61 IDI: 0.006, P=0.23 • Chinese-American: 2.5 per 1000 p-y Increase in C-statistic: 0.013, P=0.66 Hosmer-Lemeshow X2: 4.9, P=0.77 Categorical NRI: -0.121, P=0.11 IDI: 0.005, P=0.27 • Hispanic 5.0 per 1000 p-y	• Addition of CAC to PCE modestly improved discrimination, calibration, categorical and continuous net reclassification, and integrated discrimination, similarly across sex and race/ethnicity subgroups

			Increase in C-statistic: 0.009, P=0.45 Hosmer-Lemeshow X2: 12.3, P=0.14 Categorical NRI: 0.024, P=0.61 IDI: 0.006, P=0.23	
Gupta A, et al. (89) 2017 28797402	**Study type:** Systematic review **Size:** 8 studies identified (7 observational, 1 RCT) but only 6 studies (11,256 participants) included due to data availability. Single arm (CAC measurement) of EISNER study included. Note 2 reports from 1 study with different outcomes	**Inclusion criteria:** • Studies that evaluated the influence of CAC scores on subsequent lifestyle modifications or medication usage for primary prevention of CVD **Exclusion criteria:** • N/A	**1° endpoint:** Use of preventive interventions (both initiation and continuation), including aspirin, blood pressure lowering, lipid lowering, and behavioral changes **Results:** • Compared with individuals with CAC=0, individuals with CAC>0 had: • Aspirin initiation OR 2.6, 95% CI 1.8-3.8 (30% vs. 15%, 4 studies with 1.6 to 6 years of follow up, I^2=86%) • Lipid lowering medication initiation OR 2.9, 95% CI 1.9-4.4 (20% vs. 10%, 3 studies with 1.6 to 6 years of follow up, I^2=89%); • Blood pressure lowering medication initiation OR 1.9, 95% CI 1.6-2.3 (19% vs. 11%, 2 studies with 1.6 to 4 years of follow up, I^2=15%). • Aspirin continuation OR 1.3, 95% CI 0.8-2.2 (66% vs. 65%, 3 studies with 3.2 to 6 years of follow up, I^2=75%); • Lipid lowering medication continuation OR 2.3, 95% CI 1.6-3.3 (75% vs. 69%, 4 studies with 3 to 6 years of follow up, I^2=52%); • Blood pressure lowering medication continuation OR 1.4, 95% CI 0.9 to 2.2 (73% vs. 64%, 2 studies with 3.2 to 4 years of follow up, I^2=34%).	• Identification of coronary atherosclerosis by coronary calcium scanning is significantly associated with the likelihood of initiation or continuation of pharmacological and lifestyle therapies for prevention of CVD in follow up of up to 6 years. Limitations: Self-reported use of medications in at least half of studies; degree of exercise increase and dietary change ill-defined; predominantly Caucasian participants; variable means for informing participants of CAC presence and score

			• Increase in exercise OR 1.8, 95% CI 1.4-2.4 (51% vs. 32%; 3 studies with 3 to 6 years of follow up, I^2=43%); • Dietary change OR 1.9, 95% CI 1.5-2.5 (45% vs. 27%, 2 studies with 3 to 6 years of follow up, I^2=0%)	
Han D, et al. (90) 2017 28531241	**Study type:** Retrospective registry (KOICA, Korea, 2002-2014) **Size:** 31,375 patients	**Inclusion criteria:** • Adults age 40-75 years **Exclusion criteria:** • Prevalent CVD • LDL<70 mg/dL • Lipid lowering medication use • Missing risk factor or CAC data	**1° endpoint:** All-cause mortality; Median follow-up of 5 years (IQR 3-7 years) **Results:** **All-cause mortality** • Statin recommended group (n=13,888; 10-year predicted risk ≥7.5% or LDL-C 190 mg/dL or diabetes) • CAC=0 (reference) 68 events/7083 participants • Any CAC 110 events/6805 participants Adjusted HR 1.29, 95% CI 0.93-1.77 • CAC 1-100 63 events/4583 participants Adjusted HR 1.14, 95% CI 0.80-1.63 • CAC>100 47 events/2222 participants Adjusted HR 1.60, 95% CI 1.07-2.38 • Statin considered group (n=4046; 10-year predicted risk 5.0%-<7.5%) • CAC=0 (reference) 13 events/2428 participants • Any CAC 12 events/1618 participants Adjusted HR 1.19, 95% CI 0.53-2.66 • CAC 1-100 6 events/1214 participants Adjusted HR 0.76, 95% CI 0.28-2.02	• Presence of CAC and CAC score stratified risk for all-cause mortality in different statin-eligibility groups as assigned by ACC/AHA 2013 guidelines in a Korean population • Limitations: Retrospective study; patients self-referred for CAC; predominantly male; no data on ASCVD events; use of preventive therapy during follow up unknown;

			• CAC>100 6 events/404 participants Adjusted HR 2.98, 95% CI 1.09-8.13 • Statin not recommended group (n=13,441; 10-year predicted risk <5%) • CAC=0 (reference) 36 events/10,484 participants • Any CAC 12 events/3091 participants Adjusted HR 1.21, 95% CI 0.61-2.39 • CAC=1-100 8 events/2554 participants Adjusted HR 0.93, 95% CI 0.43-2.06 • CAC>100 4 events/537 participants Adjusted HR 3.14, 95% CI 1.08-9.17	
Hong JC, et al. (91) 2017 28797417	**Study type:** Microsimulation model (based on MESA participants) **Size:** N/A	**Inclusion criteria:** • Individuals were modeled based on AHA/ACC cholesterol treatment guideline using data from MESA **Exclusion criteria:** N/A	**1° endpoint:** Lifetime direct and indirect costs (societal perspective; 1 year intervals) comparing 2 strategies: 1) CAC testing among statin eligible individuals, where long-term statin therapy is guided by the reclassification of risk; versus 2) treating all statin-eligible individuals according to the ACC/AHA guideline recommendations **Results:** • CAC testing-based strategy Costs: $11,579, 95% CI $5,417-$19,183 QALYs: 11.859, 95% CI: 10.859-12,838 • Treat per guideline-based strategy Costs: $11,498, 95% CI $2,048-$19,135 QALYs: 11.849, 95% CI $10.834-$12,829 • Both strategies had similar costs and QALYs. CAC resulted in increased costs (+$81) and near-equal QALY (+0.01) for an	• Modeling suggests "both approaches have generally similar clinical and economic consequences." • "Clinicians should account for individual preferences in context of shared decision making when choosing the most appropriate strategy to guide statin decisions." • "CAC testing can supplement the shared decision-making process through more accurate risk prediction and help avoid low-value pharmacological therapy." Limitations: Microsimulation study; Multiple assumptions regarding costs, benefits and utility;

			incremental cost-effectiveness ratio of $8,100/QALY compared with the guideline strategy. • For 10,000 patients, guideline-based strategy would avert 21 ASCVD events prevented and would add 47,294 person-years of statins	
Kavousi M, et al. (92) 2016 27846641	**Study type:** Individual participant data meta-analysis **Size:** Meta-analysis of 5 prospective, community-based cohorts (Dallas Heart Study, FHS, MESA, Heinz Nixdorf, Rotterdam), 6739 participants	**Inclusion criteria:** • Women with low predicted ASCVD risk using PCE variables (< 7.5% predicted event rate over 10 years) **Exclusion criteria:** • In all cohorts, previous history of coronary artery disease, stroke, chronic kidney disease with glomerular filtration rate less than 30 mL/min/1.73m2, treatment with statin, LDL-C ≥190 mg/dL , and age older than 79 years	**1° endpoint:** Incident ASCVD, including nonfatal myocardial infarction, coronary heart disease (CHD) death, and stroke; Median follow-up of 7 to 11.6 years **Results:** • **Primary event rate** - CAC=0 (reference) 62 events/4304 participants/44,043 p-y - CAC>0 103 events/2435 participants/23,785 p-y Incidence rate difference 2.92, 95% CI 2.02- 3.83 Adjusted HR 2.04, 95% CI 1.44-2.90 - CAC 1-100 59 events/1951 participants/19,238p-y Incidence rate difference 1.66, 95% CI 0.80-2.52 Adjusted HR 1.53, 95% CI 1.02-2.29 - CAC>100 44 events/484 participants/4546 p-y Incidence rate difference 8.27, 95% CI 5.39- 11.15 Adjusted HR 4.02, 95% CI 2.61-6.19 • C-statistic with CAC added to base model: 0.77, 95% CI 0.74-0.81 • Increase in C-statistic with CAC added to base model: 0.02, 95% CI 0.00-0.05	• In women from 5 cohort studies at low predicted 10-year ASCVD risk (<7.5%), CAC was present in approximately one-third and was associated with increased risk of ASCVD and modest improvement in prognostic accuracy compared with traditional risk factors. • Limitations: Relatively few events; predominantly Caucasian; women only

			• Continuous NRI with CAC: 0.20 (95% CI 0.09, 0.31) • Results evaluating CHD as outcome similar but generally more robust	
Mahabadi AA, et al. 2017 (93) 27665163	**Study type:** Prospective cohort (Heinz-Nixdorf, 2000-2003) **Size:** 3745 participants	**Inclusion criteria:** • Asymptomatic adults age 45-75 years from 3 German cities **Exclusion criteria:** • Prevalent ASCVD, lipid lowering therapy, or missing risk factor or CAC data	**1° endpoint:** Incident coronary events, stroke, or cardiovascular death comparing strategies of 2012 ESC and 2013 ACC/AHA guidelines for statin eligibility; Median follow up of 10.4 years **Results:** • Low CAC score (<100) was common (60%) among those recommended for statin therapy by both guidelines • **Events by guideline** - 2012 ESC guideline statin not indicated, n=2457 CAC, median (IQR): 2 (0, 43) CVD events: 97 events (4.0%) Coronary events: 60 events (2.4%) - 2012 ESC guideline statin indicated, n=1288 CAC, median (IQR): 59 (5, 244) CVD events: 144 events (11.2%) Coronary events: 71 events (5.5%) - 2013 PCE statin not indicated, n=1254 (plus 396 with predicted risk=5-7.5%) CAC, median (IQR): 0 (0, 15) CVD events: 35 events (2.1%) Coronary events: 19 events (1.2%) - 2013 PCE statin indicated, n=2095 CAC, median (IQR): 46 (3, 200) CVD events 206 events (9.8%) Coronary events 112 events (5.3%) • **By CAC** - CAC=0, n=1272 CVD events: 30 (2.4%) Coronary events: 17 (1.3%)	• "Quantification of CAC score in addition to the guidelines improves stratification between subjects at high versus low risk for coronary events, indicating that CAC scoring may help to match intensified risk factor modification to atherosclerotic plaque burden as well as actual risk while avoiding therapy in subjects with low coronary atherosclerosis that have low 10-year event rate." • Limitations: Limited racial/ethnic diversity

			- CAC 1-100, n=555 CVD events: 88 (5.7%) Coronary events: 8 (2.4%) - CAC 100-399, n601 CVD events: 58 (9.7%) Coronary events: 36 (6.0%) - CAC≥400, n=17 CVD events: 65 (20.5%) Coronary events: 40 (12.6%) • **By guideline + CAC** - 2012 ESC statin indicated CAC=0: 5.7 per 1,000 p-y, 95% CI 2.7-8.7 CAC 1-99: 7.8 per 1,000 p-y, 95% CI 5.5-10.0 CAC≥100: 17.4 per 1,000 p-y, 95% CI 14.1-20.7 - 2012 ESC statin not indicated CAC=0: 1.5 per 1,000 p-y, 95% CI 0.8-2.2 CAC 1-99: 4.3 per 1,000 p-y, 95% CI 3.1-5.5 CAC≥100: 8.7 per 1,000 p-y, 95% CI 6.0-11.5 - 2013 PCE statin indicated CAC=0: 5.4 per 1,000 p-y, 95% CI 3.2-7.5 CAC1-99: 7.5 per 1,000 p-y, 95% CI 5.8-10.9 CAC≥100: 14.6 per 1,000 p-y, 95% CI 12.2-17.1 - 2013 PCE statin not indicated CAC=0: 0.8 per 1,000 p-y, 95% CI 0.3-1.2 CAC 1-99: 2.8 per 1,000 p-y, 95% CI 1.5-4.0 CAC≥100: 6.5 per 1,000 p-y, 95% CI 2.2-11.8) • Number needed to screen to detect 1 individual with CAC>100 ESC statin indicated: 2.4 ESC statin not indicated: 6.3 ACC/AHA statin indicated: 2.6	

			ACC/AHA statin not indicated: 13.9	
McClelland RL, et al. 2015 (94) 26449133	**Study type:** Prospective cohort studies (MESA, Dallas Heart, Heinz-Nixdorf Recall Studies), risk score derivation and validation **Size:** 6727 participants in derivation cohort; 3692 and 1080 in validation cohorts	**Inclusion criteria:** • Adults age 45-84 years in derivation cohort; 45 to 75 years in HNR; 45-65 years in DHS **Exclusion criteria:** • Prevalent CVD • Missing data	**1° endpoint:** Incident hard CHD, including MI, resuscitated cardiac arrest, fatal CHD, and revascularization in setting of angina; Median follow up 10.2 years in derivation cohort **Results:** • 422 CHD events in derivation cohort • Compared MESA score with traditional risk factors to MESA score + ln(CAC+1) • In MESA, MESA score model performance vs. MESA score + CAC: C-statistics 0.75 and 0.80 Discrimination slopes 0.052 and 0.086 Calibration slopes 0.834 and 0.857 Hosmer-Lemeshow P > 0.22 for both models • In HNR and DHS, MESA score + CAC performed well with good to excellent discrimination and excellent calibration C-statistic 0.78 and 0.82 Discrimination slopes 0.095 and 0.078 Calibration slopes 0.899 and 1.19 Hosmer-Lemeshow P > 0.22 for both models	• Routine addition of CAC score to traditional risk scores in contemporary cohorts added significant utility to risk prediction • Limitations: Implies universal CAC screening; targeted usage of preventive therapies for higher risk individuals may have resulted from intensive screening for CAC in these cohorts
Mortensen MB, et al. 2016 (95) 27561760	**Study type:** Prospective Observational Cohort study (BioImage Study, 2008-2009) **Size:** 5805 participants	**Inclusion criteria:** • Men 55-80 years and women 60-80 years **Exclusion criteria:** • Prevalent ASCVD	**1° endpoints:** Incident CHD, including MI, unstable angina, and coronary revascularization; Incident ASCVD, including CVD death, CHD or ischemic stroke; Median follow up of 2.7 years **Results:** • Assessed strategy of using ACC/AHA statin eligibility recommendations based on PCE, and added reclassification strategy of	• A simple theoretical reclassification strategy using CAC ≥100 to up-risk intermediate or CAC=0 to de-risk individuals with 10-year risk ≥7.5% and <15% by PCE led to significant improvements in reclassification and correct assignment of therapy

			down-classifying (to non-statin eligible) those with 10-year predicted risk ≥7.5% but with CAC=0, and up-classifying (to statin eligible) those with 10-year predicted risk 5% to <7.5% and CAC score ≥100. • 91 CHD events; 138 ASCVD events • Among these older participants, 86% were eligible for statins per ACC/AHA guideline recommendations • After reclassification by CAC, 64% were eligible for statins • NRI of reclassification strategy was 0.20 for CHD and 0.14 for ASCVD overall (both P<0.0001) • Among participants with predicted 10-year risk <15%, CAC-guided reclassification strategy led to gain of 1% in sensitivity (P=0.56) and gain of 10% in specificity (P<0.0001) for correct prediction of CHD (NRI = 0.11, P<0.0001)) • Among participants with predicted 10-year risk <15%, CAC-guided reclassification strategy led to loss of 2% in sensitivity (P=0.26) and gain of 10% in specificity (P<0.0001) for correct prediction of ASCVD (NRI = 0.08, P<0.0001)	
MESA **Nasir K, et al. 2015 (82)** 26449135	**Study type:** Prospective Observational Cohort study (MESA) **Size:** N=4758 participants,	**Inclusion criteria:** • All MESA participants, **Exclusion criteria:** • Participants on lipid-lowering medications, >75yo, missing key covariates, LDL-C <70 mg/dL	**1° endpoint:** Incident CHD: MI, resuscitated cardiac arrest, or CHD death; Incident ASCVD: CHD or fatal/non-fatal stroke Median follow up 10.3 years **Results:** • 247 ASCVD Events; 155 hard CHD events	• CAC =0 is prevalent (≥35%), and reclassifies risk to <7.5% for all strata of predicted risk <20% and for patients recommended for or considered for statins under ACC/AHA 2013 guideline recommendations. • CAC >100 identifies individuals with 10-year event rates ≥7.5%, even among those not recommended for statin therapy.

			• Prevalence of CAC =0 among participants stratified by statin recommendation status using 2013 ACC/AHA recommendations (based on PCE)
			  • 41% of ppts recommended for moderate to high-intensity statin Rx had CAC = 0; 29% had CAC >100.
			  • 57% of ppts considered for moderate-intensity statin had CAC = 0; 12% had CAC >100.
			  • 79% of ppts not recommended for statin had CAC = 0; 4% had CAC >100.
			
			• Prevalence of CAC =0 among participants stratified by predicted 10-year ASCVD risk (based on PCE)
			  • 7.5% - 9.9%: 55% of ppts had CAC = 0; 17% had CAC >100.
			  • 10.0% - 14.9%: 43% of ppts had CAC = 0; 24% had CAC >100.
			  • 15.0% - 19.9%: 35% of ppts had CAC = 0; 33% had CAC >100.
			  • ≥20%: 26% of ppts had CAC = 0; 46% had CAC >100.
			
			• Observed 10-year ASCVD Event Rates by Statin Recommendation Groups:
			  • Statin recommended: 8.2% overall; 4.9% with CAC=0; 13.3% with CAC >100.
			  • Statin considered: 3.9% overall; 1.5% with CAC=0; 6.0% with CAC >100.
			  • Statin not recommended: 1.6% overall; 1.3% with CAC=0; 9.6% with CAC >100.
			
			• Observed 10-year ASCVD Event Rates by Predicted 10-Year Risk Stratum:
				• In middle-aged people who are statin naïve, the addition of CAC scoring can help stratify risk and appropriately reclassify intermediate risk into lower risk categories and low risk into higher risk categories.
				• Limitations: Overprediction of ASCVD risk by PCE in MESA has been described and is present in this analysis. This might over-estimate the reclassification benefits of CAC = 0.

			• 7.5% - 9.9%: 2.7% with CAC=0; 7.3% with CAC >100. • 10.0% - 14.9%: 6.4% with CAC=0; 11.1% with CAC >100. • 15.0% - 19.9%: 4.4% with CAC=0; 20.5% with CAC >100. • ≥20%: 11.7% with CAC=0; 19% with CAC >100.	
Framingham **Pursnani A, et al. 2015 (96)** 26172893	**Study type:** Prospective Observational Cohort study **Size:** N=2435 participants	**Inclusion criteria:** • Framingham Offspring or Gen3 participants; men 35 and older, women 40 and older, weighted towards families with larger numbers in cohort **Exclusion criteria:** • Participants with prevalent CVD or on lipid-lowering therapy	**1° endpoint:** Incident ASCVD Median follow up 9.4 years **Results:** • Among participants recommended for statin therapy by 2013 AC/AHA guidelines, 33% had CAC=0, with an associated ASCVD event rate of 1.6% over 9.4 years	• CAC = 0 identified individuals recommended for statin therapy who had very low ASCVD event rates.
Qureshi W.T. et al. 2015 (97) 26482753	**Study type:** Systematic review and meta-analysis of published studies **Size:** N=8 studies of CAC and N=22 studies of hsCRP	**Inclusion criteria:** • Studies examining change in discrimination for CVD events with addition of CAC or hsCRP to models with traditional CVD risk factors **Exclusion criteria:** N/A	**1° endpoint:** Incident CVD **Results:** • Meta-analysis of change in area under the ROC curve: With addition of hsCRP: 0.012, 95% CI, 0.008-0.017, P<0.001 With addition of CAC: 0.063, 95% CI, 0,042-0.084	• Addition of CAC score to models containing traditional risk factors changes the area under the ROC curve for prediction of CVD events significantly and substantially, and by more than addition of hsCRP.
Jackson Heart Study **Shah R.V., et al. 2017 (98)** 28315622	**Study type:** Prospective Observational Cohort study **Size:** N=2812 (N=1743 with CAC score) participants	**Inclusion criteria:** • African American men and women age 40-75 years **Exclusion criteria:** • Prevalent CVD, on statin therapy, missing data	**1° endpoint:** Incident ASCVD Median follow up 10 years **Results:** • 55 incident ASCVD events among those with CAC score	• Among those who were recommended for statin by the ACC/AHA 2013 guideline, presence of CAC identified those with 10-year event rates >7.5%, whereas absence of CAC was associated with event rates <7.5%. Among those not recommended for statin, 10-year event rates were <1.0%.

			• CAC >0 prevalence increased in a dose dependent fashion from ~13% in those with 10-year predicted risk (by PCE) of 2.5% to ~75% in those with predicted risk ≥15% • ASCVD event rate for participants recommended for statin by ACC/AHA 2013 guideline: With CAC: 8.1/1000 p-y Without CAC: 3.1/1000 p-y; P=0.02 • ASCVD event rate for participants not recommended for statin by ACC/AHA 2013 guideline: With CAC: 0.9/1000 p-y Without CAC: 0.8/1000 p-y; P>0.99	
St. Francis Heart Study **Waheed S., et al. 2016 (99)** 27693004	**Study type:** Post hoc analysis of RCT **Size:** N=990 participants	**Inclusion criteria:** • Individuals aged 50-70 years with CAC score ≥80th percentile for age and sex enrolled in RCT of atorvastatin, vitamin C, and vitamin E vs placebos **Exclusion criteria:** • Prevalent ASCVD, diabetes, extreme values of cholesterol or blood pressure	**1° endpoint:** Incident CVD (non-fatal myocardial infarction or coronary death, coronary revascularization, stroke, and peripheral arterial revascularization) Median follow up 4.8 years **Results:** • CVD incidence rates (per 100 p-y) by statin eligibility, randomization status and CAC score: Statin ineligible by ACC/AHA 2013 guideline CAC <100 and treated: 0 CAC <100 and untreated: 0 CAC 100-300 and treated: 5 CAC 100-300 and untreated: 5 CAC >300 and treated: 17 CAC >300 and untreated: 23 Statin eligible by ACC/AHA 2013 guideline CAC <100 and treated: 0 CAC <100 and untreated: 0 CAC 100-300 and treated: 20 CAC 100-300 and untreated: 26	• No CVD events were observed among those with CAC <100, regardless of statin eligibility. CAC scores >100 were associated with higher event rates, especially among those who were deemed statin eligible. Limitations: Post-hoc analysis, restricted population with high CAC for age and sex

			CAC >300 and treated: 22 CAC >300 and untreated: 34	
MESA **Yeboah J., et al.** 2015 (100)	**Study type:** Prospective Observational Cohort study (MESA) **Size:** N=4185 participants with recalibrated (to MESA sample) PCE 10-year risk score <7.5%	**Inclusion criteria:** • MESA participants age 45-84 years **Exclusion criteria:** • Missing data, participants receiving statin at baseline	**1° endpoint:** Incident ASCVD Median follow up 10 years **Results:** • CAC ≥300 or ≥75th percentile for age, sex and race, hsCRP ≥2 mg/dl, AMBI <0.9, LDL-C ≥160 mg/dL, or positive family history of ASCVD each identified small proportions (<10%) of participants with predicted 10-year risk <7.5% who had observed 10-year event rates >7.5%. Of these additional tests, CAC identified the largest proportion.	• Among individuals with low predicted 10-year risk not expected to be in a statin benefit group, CAC ≥300 or ≥75th percentile for age, sex and race identified a subgroup with observed event rate >7.5%, and performed better than other additional tests or biomarkers.
MESA **Yeboah J., et al.** (101) 2016	**Study type:** Prospective Observational Cohort study (MESA) **Size:** N=5185 participants with recalibrated (to MESA sample) PCE score	**Inclusion criteria:** • MESA participants age 45-84 years **Exclusion criteria:** Missing data, participants receiving statin at baseline	**1° endpoint:** Incident ASCVD Median follow up 10 years **Results:** • CAC, ABI, and family history were associated with ASCVD events independent of recalibrated PCE. • Harrell's C statistic with addition to recalibrated PCE: Recalibrated PCE alone: 0.74 + CAC score: 0.76 (P=0.04) + ABI: 0.75 (P=0.55) + hsCRP: 0.74 (P=0.25) + Family history: 0.74 (P=0.98) • NRI for threshold of 7.5% 10-year risk with addition to recalibrated PCE: + CAC score: 0.119, 95% CI 0.080-0.256 + ABI: 0.017, 95% CI -0.031-0.058	• CAC improved discrimination and NRI beyond recalibrated PCE whereas other non-traditional risk markers did not.

			+ hsCRP: 0.025, 95% CI -0.015-0.067 + Family history: 0.051, 95% CI 0.000-0.109	

Data Supplement 16. Evidence Tables for Borderline and Intermediate Risk Group (5-<7.5%; 7.5 to 20%) (Section 4.4.2)

Acronym; Study Author; Year Published	Aim of Study; Study Type; Study Size (N) Duration	Patient Population	Study Intervention/ Study Comparator Definition of Outcomes Primary/Secondary	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2ºEndpoints (if any); Study Limitations; Adverse Events
HOPE 3 Yusuf S, et al., 2016 (12) 27040132	Determine net benefit of moderate intensity statin therapy in intermediate ASCVD risk group; **Study type**: RCT **Size:** 12,705 participants Duration: 5.6 y	**Inclusion Criteria:** Men: ≥ 55 y Women ≥ 65 y with one of the following CV Risk factors: -Elev. waist/hip ratio, -History of low HDL-C; -Current or recent tobacco use -Dysglycemia, -Family Hx premature coronary disease, -Mild renal dysfunction Women ≥ 60 with 2 or more such risk factors. **Exclusion Criteria:** •Cardiovascular disease (CVD) • Indication for CVD drugs such as statins, angiotensin-receptor blockers, angiotensin-converting–enzyme inhibitors, or thiazide diuretics	**Intervention:** G1: Rosuvastatin 10 mg/d (6361) G2: Comparator: Placebo (6364) 46.4% Female in GI 46.1% Female in G2 Definitions of Outcomes -First co-primary outcome or "hard ASCVD" -Second co-primary outcome: -Secondary outcome First primary outcome: composite of death from CVD causes, nonfatal MI, or nonfatal stroke, Second primary outcome: included revascularization, heart failure, and resuscitated cardiac arrest. Secondary outcome –Above second co-primary outcome plus angina with evidence of ischemia	**Frist primary outcome:** G1: 3.7% G2: 4.8% 0.76 (0.64-0.91) p 0.002 **Second primary outcome:** G1: 4.4% G2: 5.7% 0.75 (0.66-0.88); p<0.001 LDL-C Changes with G1 lower than G2 at 1-y 39.6 mg/dL (1.02) 3 y: 34.7 mg/dl ((0.90 Overall mean diff: 34.6 mg/dl [0.90) 26.5%; p<0.001) ASCVD Risk Placebo Group (%/y) First primary outcome = 4.8%/5.6 y =8.6 Second primary outcome = 5.7%/5.6 y =10.1	**Secondary outcome:** G1: 4.8% G2: 6.2% 0.77 (0.66-0.89); p< 0.001 Hospitalized for cardiovascular causes G1: 281 [4.4%] G2: 369 [5.8%], p<0.001) Total number of CVD hospitalizations G1: 444 G2: 596 **Study limitations:** Short duration of treatment and time to 1st event may underestimate events Despite decreased adherence with time, the reduction of risk of CVD increased with time **Adverse events** Muscle pain or weakness G1 (367 [5.8%] G2: 296 [4.7%], p=0.005) Muscle symptoms G1 (83 [1.3%] G2 76 [1.2%] p=0.63) Cataract surgery G1 241 [3.8%] vs. G2 194 [3.1%];

					p=0.02 Deep-vein thrombosis or pulmonary embolism G1 14 vs. G2 31; HR: 0.45; 95% CI: 0.24 to 0.84; p=0.01. No excess of: DM: G1: 3.9% vs. 3.8% Rhabdomyolysis or myopathy; G1 2 vs. G2: 1 case Cancer G1 267 vs. G2 286
AFCAPS-TEXCAPS Downs JR, et al., 1998 (102) 9613910	Does lowering of LDL-C with statins benefit men, women, elderly with normal TC levels. **Study Type:** RCT 6805 Participants Size: 5608 men and 997 women. **Duration:** 5.2 y Included Hispanics, African Ameri-cans, and older persons (baseline mean age, 58.2 y; upper limit, 73 y; 21% older than 65 y).	**Inclusion Criteria:** Men aged 45-73 y; Postmenopausal Women aged 55-73 y; Men: 85%; Women 15%. **Exclusion Criteria:** Uncontrolled hypertension, secondary hyperlipidemia, type 1 or type 2 diabetes mellitus managed with insulin, a glycol-hemoglobin level ≥ 10%, or body weight ≥ 50% greater than the desirable limit for height. **Lipid entry criteria** TC 180-264; (4.65 - 6.82) LDL-C, 130-190 (3.36- 4.91) HDL-C: men: <45 mg/dl (1.16) HDL-C: women <47 mg/dl (1.22) TG<400 mg/dl; (4.52) at both 4 and 2 wk before randomization, with <15% change in LDL-C values. In addition, those with LDL-C between 125-129 mg/dl (3.23 and 3.34) were included if the ratio of TC to HDL-C > 6.0.	G1: Lovastatin 20 or 40 mg/d N=3304 G2: Placebo N=3301 **Definition of Outcomes:** Primary outcome (PO) First acute major coronary event defined as fatal or nonfatal myocardial infarction, unstable angina, or sudden cardiac death. AFCAPS found that approximately equal numbers present with unstable angina or MI.	**Primary Outcome** G1 116/3301; 3.5% G2: 183/3304; 5.5% 0.63; (0.50-0.70) p<0.001 Rates per 1000 patient y G1 6.8% vs. G2 10.9% The differences between the 2 treatment groups appeared as early as 1 y (40 w/events in G2 vs.23 in G1 For the primary end point, these rates correspond to cumulative incidences of 4.0% and 6.8% for the lovastatin and placebo groups, respectively, during the study period (p 0.001). LDL-C changes G1: LDL-C 151 (3.89) (lower by 25% reduced to 115 (2.96)	Primary end point risk reduction with lovastatin was apparent across all baseline LDL-C tertiles with no threshold to benefit observed across baseline LDL-C levels LDL-C ≤142 (3.67); 143-156 (3.67-4.05) ≥157 (>4.05) There were no clinically relevant differences in safety parameters between treatment groups. **Study Limitations**: Inclusion of unstable angina in the primary endpoint; but in this trial equal numbers presented with unstable angina or non-fatal MI. New Onset of Diabetes G1: 74 G2: 72

Nakamura H, et al., 2006 (103) 17011942	Effect of primary prevention with statin in clinical practice in Japan **Study Type**: Prospective, randomized, open-label, blinded endpoint study **Duration**: 5.3 y	**Inclusion Criteria:** Men, Postmenopausal women AGE: 40-70 y Men: (31%) Women: (69%) Body wt >40 kg; Total cholesterol levels measured on 2 or 3 occasions during ≥ 4 wk washout period on a low fat, low cholesterol diet Baseline cholesterol level required to be 220-270 mg/dl (5.7-6.96) **Major exclusion criteria** those with familial hyper-cholesterolaemia; history of coronary heart disease or stroke; diagnosis of congenital or rheumatic heart disease; chronic atrial fibrillation; current diagnosis of malignancy; severe liver (chronic active hepatitis and cirrhosis) or renal (creatinine ≥4 mg/dl) disease; poorly controlled hypertension or diabetes mellitus; secondary hyperlipidemia; current use of oral or parenteral corticosteroids.	G1 Diet + pravastatin (3866 participants) Initial 10 mg/d or 20 mg if TC >221 mg/dl G2: Diet (3966 participants) **Primary composite endpoint:** First occurrence of coronary heart disease, which included fatal and non-fatal myocardial infarction, angina, cardiac and sudden death, and a coronary revascularization procedure. Secondary endpoints included stroke, coronary heart disease plus cerebral infarction, all cardiovascular events, and total mortality.	Coronary heart disease (CHD) was significantly lower in G1 than in the G2 groups. G1 66 events G2 101 events HR: 0·67; 95% CI: 0·49–0·91; p=0·01). **Adherence** 1 y: 95% 5 y 90% 9 y: 89% Mean dose of pravastatin was 8·3 mg. Mean LDL-C reductions: G1: 18%; 157 to 128 (4.05-3.31) G2: 3.2%; 157 to 151 (4.05-3.9).	**Secondary end-points** Included: stroke and transient ischemic attack, all cardiovascular events and total mortality. Stroke HR: 0.83; 95% CI: 0.57-121; p=0.33 Incidence CHD +cerebral infarction HR: 0.70; 95%CI: (0.54-0.90) p=0.05; NNT 91 Total mortality HR: 0.72; 95% CI: (0.72; 0.51-1.01; p=0.055) **Study limitations**: Open label No significant safety issues No significant difference between the two groups in the incidence or primary site of malignancy, or for the site of malignant neoplasms.
JUPITER Ridker PM, et al., 2008 (11) 18997196	Would people with elevated high-sensitivity C-reactive protein levels but without hyperlipidemia (LDL-C ≥ 130) benefit from statin treatment. **Study Type:** RCT	**Inclusion Criteria:** Men ≥ 50 Women ≥60 with no history of cardiovascular disease and at initial screening visit LDL-C <130 mg/dl (3.4 mm) and CRP ≥ 2.0 mg/L Men ≥ 50 y **Exclusion criteria** Those with previous or current use	G1: rosuvastatin 20 mg/d (high intensity) G2: Placebo N=8901 37.9% women Definition of Outcomes **Primary Outcome:** occurrence of the combined primary end point of MI, stroke, arterial revascularization, hospitalization for unstable angina, or death from CVD cause	LDL-C At 12 mo G1; LDL-C -50% **Primary outcome:** G1: 0.77, G2: 1.36 per 100 person-y of follow-up (HR: 0.56; 95% CI: 0.46-0.69; p<0.00001), Hard CHD G1: 108/8901; 1.2%	Death from any cause G1 1.00; G2 1.25 (HR: 0.80; 95% CI: 0.67 to 0.97; p=0.02). **Study Limitations:** Independent data and safety monitoring committee stopped the Trial early (median follow-up 1.9

	Study Size Participants:1782 **Duration**: median follow-up of 1.9 y (maximum, 5.0).	of lipid-lowering therapy, current use of post- menopausal hormone-replacement therapy, evidence of hepatic dysfunction (an alanine amino transferase level > twice the upper limit of normal range), a creatine kinase level > three times the upper limit of the normal range, a creatinine level > 2.0 mg/deciliter (176.8 µmol/liter), diabetes, uncontrolled hypertension (systolic blood pressure >190 mm Hg or diastolic blood pressure >100 mm Hg), cancer within 5 years before enrollment (with the exception of basal-cell or squamous-cell carcinoma of the skin), uncontrolled hypothyroidism (a thyroid-stimulating hormone level >1.5 times the upper limit of the normal range), and a recent history of alcohol or drug abuse or another medical condition that might compromise safety or the successful completion of the study. Also excluded were those with inflammatory conditions such as severe arthritis, lupus, or inflammatory bowel disease and those taking immunosuppressant agents such as cyclosporine, tacrolimus, azathioprine, or long-term oral glucocorticoids.		G2: 189/8901; 2.1% HR: 0.57; 95% CI: [0.45, 0.72] MI: G1 vs. G2 0.17 and 0.37 (HR: 0.46; 95% CI: 0.30 to 0.70; p=0.0002), Stroke: G1 vs. G2 0.18 and 0.34 (HR: 0.52; 95% CI: 0.34 to 0.79; p=0.002), Revasc/UA: G1 vs. G2 0.41 vs. 0.77 (HR: 0.53; 95% CI: 0.40 to 0.70; p<0.00001). Combined end point of myocardial infarction, stroke, or death from cardiovascular causes G1 0.45; G2 0.85 (HR: 0.53; 95% CI: 0.40-0.69; p<0.00001).	y) due to persistent significant difference in primary endpoint. Longer duration of the trial may have provided a more refined estimate of efficacy and safety. (The magnitude of benefit may be overestimated if an RCT is terminated early.) **Adverse events:** Physician Reported DM more frequent in the rosuvastatin group G1: 270 (3%) G2: 216 (2.4%) p=0.01 G1 did not have a significant increase in myopathy or cancer Non-significant increase In rhabdomyolysis G1: one non-fatal case of rhabdomyolysis occurred G2: No cases Can't rule out that adverse events would have been more with longer exposure to intervention.

Data Supplement 17. Evidence Tables Monitoring in Response to LDL-C–Lowering Therapy (Section 4.4.3)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results(P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)

Benner JS, et al.(104) 15669150	**Study type:** Retrospective cohort trial **Size:** 19 422 men (50%) and women (50%) Ages % 45-54. 22. 9 55-64. 21.8 65-74. 25.4 ≥. 75. 16.5 Clinical Diagnosis. % 1) Angina or coronary angiography 4.9% 2) PTCA, CABG, chronic CHD 3) Acute MI in past year. 1.8% 4) HTN: 34.1% 5) CHF. 3.8% 6) DM: 19.9% 7) Stroke. 3.9%	**Inclusion criteria:** Enrollees in a US managed care plan who initiated statin treatment between October 1999 & August 2001. Computerised pharmacy, medical and laboratory records used to study patterns and predictors of adherence with lipid therapy for up to 3 years	**1° endpoint:** Adherence checked at 3-monthly intervals. Patients considered "adherent" if ≥ 80% of days were covered by lipid-lowering therapy. **Results:** First 3 months: % of patients 40% had follow-up lipid tests; 21% had follow-up lipid visits ; 14% had both. Those who received followup care were substantially more likely to be adherent in subsequent intervals. Relative odds of adherence of those with vs. those without followup Odds 1.42 if one or more lipid tests Odds 1.27 if one or more lipid visits, (95% confidence intervals [CI] 1.33, 1.50 and 1.16, 1.39). P In other words, patients who received a follow-up visit and lipid test were 45% more likely to be adherent (95% CI 1.34, 1.55). Similar associations were observed when lipid tests and dyslipidaemia visits occurred later in therapy.	**Conclusions:** Early and frequent follow-up and especially if associated with lipid testing, was associated with improved adherence to lipid therapy. **Limitations:** Not a randomized prospective trial

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention(# patients) /Study Comparator(# patients)	Endpoint Results(Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any);Study Limitations; Adverse Events

Chiavaroli L et al (105) 29807048	Aim: To determine the effectiveness of a Portfolio Dietary added to a Step II diet in reducing LDL-C Study type: Systematic review and meta-analysis of controlled trials Size: Eligibility criteria were met by 7 trial comparisons in 439 participants with hyperlipidemia,	Inclusion criteria: Randomized and non-randomized controlled trials Exclusion criteria: Limited to human studies with no language restriction	Intervention: The combination of a portfolio dietary pattern and NCEP Step II diet • The Portfolio dietary pattern had to include these components as the intended intervention: 1) 1–3 g/day plant sterols (plant-sterol containing margarines, supplements), 2) 15–25 g/day viscous fibres (gel-forming fibres, such as from oats, barley, psyllium, legumes, eggplants, okra), 3) 35–50 g/day plant protein (such as from soy and pulses) and 4) 25–50 g/day nuts (including tree nuts and peanuts). Comparator: • NCEP Step II Diet	1 endpoint: LDL-Cholesterol Results: The Portfolio dietary pattern lowered LDL-C by 17% (7 trial comparisons, MD = −0.73 mmol/L [95% CI: −0.89 to −0.56 mmol/L], p b 0.0001) There was evidence of substantial heterogeneity (I2 = 67%, P-heterogeneity = 0.006). Saw reduction in high-density lipoprotein cholesterol, apolipoprotein B, total cholesterol, triglycerides, systolic and diastolic blood pressure, C-reactive protein, and estimated 10-year coronary heart disease (CHD) risk, compared with an NCEP Step 2 diet alone ($p < 0.05$). No effect on HDL-C or body weight.	Study strength Using the GRADE criteria, the certainty in the evidence was high for LDL-C, TC, TG, non-HDL-C, apoB and body weight Study limitations: Using the Grade criteria it was only moderate for HDL-C, SBP, DBP, CRP and 10-year CHD risk. This was due to downgrades in certainty for serious imprecision.
Stone NJ et al (106) 24239923	2013 Cholesterol Guideline Systematic Review and Meta-analysis Evidence Statement 45	In randomized controlled trials (RCTs) of high-intensity compared with moderate-intensity statins (clinical CVD), moderate-intensity statin compared with placebo (diabetes, primary prevention), high-	Participants were seen at visits that occurred at 4 – 13 weeks after randomization, and then every 3–6 months thereafter.	Endpoints 1. Assessed for adherence to study medication at every visit. 2. Assessed for adverse effects by history and laboratory measurements at every visit or every other visit	Study Strength: Evidence Statement 45 is a complete analysis of the effects of follow-up visits and lipid testing in the RCTS reviewed by the 2013 ACC-AHA Guideline Panel that were selected by an independent

		intensity statin compared with placebo (secondary and primary prevention), or statin-niacin versus placebo,			contractor chosen by the National Heart Lung Institutes Study limitations: Included only those RCTs available to the panel for the 2013 ACC-AHA guideline

Data Supplement 18. Evidence Table to discontinue therapy (Section 4.4.4.1)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study comparator	Endpoint Results (Absolute Event Rates, p values, OR or RR, and 95% CI)
Qi K, et al., 2015 (107) 26047944	**Aim:** To study the feasibility of deprescribing statins in adults aged ≥65 **Study Type:** Cross-sectional observational study **Size:** N=180 median age of 78 y, (interquartile range 71–85 y)	**Inclusion criteria:** adults aged ≥65 y, admitted to hospital (cardiology, geriatric, orthopedics, gen med) **Exclusion criteria:** Cognitively or functionally impaired as judged by the nurses on each study ward or refused to participate.	**Intervention:** Interview	**1° Endpoint:** qualitative assessment regarding their willingness to discontinue statin
Garfinkel D, et al., 2010 (108) 20937924	**Aim:** to study the impact of medication de-prescription in older adults **Study Type:** prospective cohort **Size**: N=70 43 patients (61%) had 3 or more and 26% had 5 or more comorbidities.	**Inclusion criteria:** Patients referred by their family physician or family for comprehensive geriatric assessments **Exclusion criteria:** patients with advanced disease (cancer or noncancer) in whom the initial estimate of life expectancy was <3 mo and patients in whom follow-up availability was <4 mo.	**Intervention:** removing medication	**1° Endpoint:** • Successful discontinuation of all meds was achieved in 81%; discontinuation of statins in 72% • No significant adverse events or deaths were attributable to discontinuation • 88% of patients reported global improvement in health.
Todd A, et al., 2016 (109) 26822776	**Aim:** to explore the lived experience of patients, caregivers and healthcare	**Inclusion criteria:** Patients attending a day care center at a specialist palliative care unit	Patient interview	• Medication formed a significant part of a patient's day-to-day routine; this was also apparent for their caregivers who took on an

	professionals in the context of medication use in life-limiting illness. **Size:** N=12, 50% aged >70 y and 2 aged >80 y.	To be included in the study, patients and caregivers had to be aged >18 y of age and healthcare professionals had to be responsible for prescribing medication to this general patient group.		active role-as a gatekeeper of care-in managing medication. • Patients described the experience of a point in which, in their disease journey, they placed less importance on taking certain medications; healthcare professionals also recognize this and refer it as a 'transition'.
Kutner JS, et al., 2015 (110) 25798575	**Aim:** To evaluate the safety, clinical and cost impact of discontinuing statin medications for patients in the palliative care setting **Study Type:** Multicenter, parallel-group, unblinded pragmatic clinical trial **Size:** 381 enrolled (189 discontinued statin and 192 continued statin). Mean age 74.1 y (SD 11.6)	**Inclusion criteria:** English-speaking, receiving statin for ≥3 mo for 1° or 2° prevention, documented diagnosis of advanced, life-limiting illness (life expectancy 1-12 mo), and reduced functional capacity **Exclusion criteria:** Physician opinion that the patient had active CVD or sufficient CVD risk to require ongoing statin therapy, or symptoms of myositis, liver function test (aspartate aminotransferase, alanine aminotransferase, or alkaline phosphatase) or creatine kinase levels of >2.5 times the upper limits of normal, or other contraindications to continuing statins.	**Intervention:** Statin removed from patients randomized to the discontinuation group vs. continued in the continuation group	• Discontinuing statin was associated with improved QOL, reduced non-statin medications, and reduced medication costs.
Tjia J, et al., 2017 (111) 28520522	**Aim:** The aim of this study was to quantify the perceived benefits and concerns of statin discontinuation among patients with life-limiting illness. **Size:** 297 participants, Mean age 72 y (SD 11)	**Inclusion criteria:** English-speaking, receiving statin for ≥3 mo for 1° or 2° prevention, with documented diagnosis of advanced, life-limiting illness (life expectancy 1-12 mo), reduced functional capacity, cognitively intact. (defined as a Short Portable Mental Status Questionnaire score ≥6) **Exclusion criteria:** Physician opinion that the patient had active CVD or sufficient CVD risk to require ongoing statin therapy, or symptoms of myositis, liver function test (aspartate aminotransferase, alanine aminotransferase, or alkaline phosphatase) or creatine kinase levels of >2.5 times the upper limits of normal, or other contraindications to continuing statins.	**Intervention:** Responses to a 9-item questionnaire addressing patient concerns about discontinuing statins were collected.	• Few participants expressed concerns about discontinuing statins; many perceived potential benefits. Cardiovascular disease patients perceived greater potential positive impact from statin discontinuation.

Data Supplement 19. Evidence Table for Statin therapy for adults >75 years (Section 4.4.4.1)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention	Endpoint Results (Absolute Event Rates, p values, OR or RR, and 95% CI	Relevant 2° endpoints (if any); Study limitations; Adverse events
JUPITER Ridker D, et al., 2008 (11) 18997196 Glynn RJ, et al., 2010 (112) 20404379	**Aim:** Study of primary prevention with rosuvastatin **Study Type:** RCT **Size:** 17,802 men and women 5695 (32%) ≥70 y of age (mean age 74 y)	**Inclusion criteria:** free of CVD with LDL cholesterol levels <130 mg/dL and high-sensitivity C-reactive protein levels >2 mg/L. (Intermediate risk) **Exclusion criteria:** intolerant to rosuvastatin	**Intervention:** rosuvastatin 20 mg **Comparator:** placebo	**1° endpoint:** • Overall trial: the JUPITER trial overall reported a 47% reduction in atherosclerotic CV events (nonfatal MI, nonfatal stroke, or CV death) (HR: 0.53; 95% CI: 0.40–0.69; p<0.0001), as well as a 20% reduction in all-cause mortality (HR: 0.80; 95% CI: 0.67–0.97; p=0.02). • Participants ≥70 y (mean age 74 y): amounted to 32% of the total JUPITER population, but suffered 55% of all the hard atherosclerotic cardiovascular events occurring in the trial • In adults >70: 39% reduction in risk atherosclerotic CV events (HR: 0.61; 95% CI: 0.43–0.86; p=0.004) • Nonsignificant 20% reduction in all-cause mortality in the older age strata (HR: 0.80; 95% CI: 0.62–1.0; p=0.09)	• **Limitations:** • median follow-up of only 1.9 y • Relatively younger older adult cohort.
HOPE-3 Yusuf, S, et al., 2016 (12) 27040132	**Aim:** To evaluate benefits of statins in an intermediate-risk, ethnically diverse population without cardiovascular disease **Study Type:** RCT **Size:** 12,705 men ≥55 and women ≥65 with 1 or more risk factor ~50% ≥65 (mean age 71 y) 3086 ≥70 y of age	**Inclusion criteria:** Free of CVD but with intermediate risk **Exclusion criteria:** intolerant to statins	**Intervention:** rosuvastatin 10 mg **Comparator**: placebo	**1° Endpoint:** • Overall trial: hard atherosclerotic cardiovascular events: 24% reduction in risk (HR: 0.76; 95% CI: 0.64–0.91; p=0.002) and a 7% nonsignificant reduction in all-cause mortality (HR: 0.93; 95% CI: 0.80–1.08; p=0.32) over 5.6 y. • Subjects ≥70 y of age represented 24% of the total trial population yet suffered 43% of all the hard atherosclerotic cardiovascular events • Among those ≥70 ye: Comparable nonsignificant 17% reduction in risk was found for the combined cardiovascular end point (HR: 0.83; 95% CI: 0.64–1.07; p=0.16),	N/A

				• Comparable nonsignificant 9% reduction in all-cause mortality (HR: 0.91; 95% CI: 0.73–1.13; p=0.38). **Safety Endpoint:** Rates of drug withdrawal in the rosuvastatin groups were 21.4%, 23.1%, and 29.1% among those <65, 65 to <70, and >70 y of age, respectively	
PROSPER Shepherd J, 2002 (113) 12457784	**Aim:** risk factors for CVD or Hx CHD or to pravastatin 40 mg daily or placebo **Study Type:** RCT **Size:** 5804 men and women aged 70-82 --subgroup with ASCV risk elevated due to tobacco, hypertension, DM	**Inclusion criteria:** high risk **Exclusion criteria:**	**Intervention:** Pravastatin 40 mg **Comparator:** placebo	**1° Endpoint:** • Pravastatin therapy reduced the primary endpoint of CHD death, non-fatal MI and fatal or non-fatal stroke (HR: 0.85; 95% CI: 0.74–0.97, p=0.014). • 3.2 y of average follow-up,	N/A
Physicians Health Study Orkaby, J, 2017 (114) 28892121	**Aim:** to determine whether statin use for primary prevention is associated with a lower risk of cardiovascular events or mortality **Study Type:** Prospective cohort study **Size:** 7,213 male physicians Median age 77 (77-102)	**Inclusion criteria:** ≥70 y without a history of cardiovascular disease (CVD) **Exclusion criteria:** 2,670 participants were excluded because of prevalent CVD (MI, stroke, or peripheral vascular disease) and an additional 105 were excluded due to missing information on statin use at baseline.	**Intervention:** Completed annual questionnaires from 1999, the year a specific question regarding statin use was added. **Comparator:** Non-users were matched to 1,130 statin users.	**1° Endpoint:** Statin use was associated with a significant lower risk of mortality in older male physicians ≥70 and a nonsignificant lower risk of CVD events. Results did not change in those who were >76 y at baseline or according to functional status. There was a suggestion that those with elevated total cholesterol may benefit. Median follow-up was 7 y.	N/A
Health Protection Study 2002 (115) 19442259	Aim: CHD or at high risk for CHD with diabetes,	**Inclusion criteria:** **Exclusion criteria**:	**Intervention:** Simvastatin **Comparator:**	**1° Endpoint:** • reduced all-cause mortality and CHD death with treatment with simvastatin 40 mg daily as	

	Study Type: RCT **Size:** N=20,536 patients aged 40–80 y. N=5806 aged ≥65 y			compared to placebo (12.9% vs. 14.7%, p=0.0003) and (5.7% vs. 6.9%), respectively. • In 5806 patients aged ≥65, major CV events were reduced by absolute rates of 6.3% in patients aged 65–69 and 5.1% in patients 70–80.	
CARDS Neil HA, 2006 (116) 17065671	**Aim:** primary prevention in older pts with DM **Study Type:** **Size:** 1129 diabetic patients aged 65-75	**Inclusion criteria:** DM and at least one risk factor **Exclusion criteria:**	**Intervention:** atorvastatin 10 mg **Comparator:** placebo	**1° Endpoint:** • Overall 37% CHD risk reduction • In, the older group, treatment with atorvastatin reduced the risk of first major CHD events by 38%; 95% CI: 58–8, p<0.017	No significant change in all cause morality
MEGA Nakaya N, 2011 (8) 21815708	**Aim:** to evaluate the relationships between age, baseline patient characteristics, and pravastatin treatment with respect to the development of cardiovascular disease (CVD) in the MEGA study **Study Type:** RCT **Size:** 7832 patients (ages women up to 80, men 40–70); 6 age groups: <45, 45–49, 50–54, 55–59, 60–64 and ≥65 y.	**Inclusion criteria:** men and postmenopausal women aged 40–70 y with hypercholesterolaemia (TC levels of 5.7–7.0 mmol/L), no history of CHD and stroke, **Exclusion criteria:**	**Intervention:** pravastatin 10–20 mg daily **Comparator**: placebo	**1° Endpoint:** • 30–40% reduction in clinical events across multiple age ranges including in patients greater than 65 y • Pravastatin (10–20 mg/d) reduced the risk of CVD by about 30–40% across all age groups (including those >65), and there was no difference between men and women. • Of particular note in this analysis, CVD risk lowering benefits (old vs. young) similar in men, but CVD risk lowering older women significantly greater in older vs. younger women.	N/A

ALLHAT-LLT Han BH, 2017 (90) 28531241	**Aim:** to study benefits of statins among adults aged 65–74 and ≥75 in ALLHAT-LLT **Study Type:** post hoc secondary analysis of older adults in ALLHAAT-LLT, an RCT **Size:** 2867 (mean age 71.3 y)	**Inclusion criteria:** Moderate hyperlipidemia and HTN in adults without evidence of atherosclerotic cardiovascular disease	**Intervention:** Pravastatin 40 **Comparator:**	**1° Endpoint:** • All-cause mortality: HR for all-cause mortality in the pravastatin group vs. the UC group were 1.18; 95% CI: 0.97–1.42; p=0.09 for adults ≥65 y • HR: 1.08; 95% CI: 0.85–1.37; p=0.55 for adults aged 65-74 y, • HR: 1.34; 95% CI: 0.98–1.84; p=0.07 for adults ≥75 y.	**Major limitation:** Significantly confounded by contamination with newer and more potent statins in the control group, with the effect that CHD event rates were not significantly different among the groups.
Cardiovascular Health Study Lemaitre RN, 2002 (117) 12076239	**Aim:** To assess effects of statins on CV events and all-cause mortality **Study Type:** Observational **Size:** 1914 elderly men and women older than 65 y (average 72)	**Inclusion criteria:** Subjects with no CVD **Exclusion criteria:**	**Intervention:** Statin therapy **Comparator:** No statin	**1° Endpoint:** 56% lower risk of incident CVD events (HR: 0.44, 95% CI: 0.27–0.71) and 44% lower mortality (HR: 0.56, 95% CI: 0.36–0.88). A subgroup aged >75 y had same benefit.	N/A
Jupiter—Hope-3 Ridker PM, 2017 (118) 28385949	**Aim:** To clarify efficacy of primary statin prevention in older adults **Study Type:** Meta-analysis Jupiter and Hope-3 **Size:** 30,507 subjects; 8781 aged ≥70 y	**Inclusion criteria:** Low risk subjects with no CVD **Exclusion criteria:**	**Intervention:** Rosuvastatin (20 mg, Jupiter and 10 mg, Hope-3) **Comparator:** Placebo	**1° Endpoint:** • 26% relative risk reduction observed for those >70 y for the end point of nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death (HR: 0.74; 95% CI: 0.61–0.91; p=0.0048 • The much higher event rates in those ≥70 y of age, along with the comparable relative rate reductions, i.e., larger absolute rate reductions associated with statin treatment and hence smaller numbers needed to treat to prevent an event in older compared with younger people. • In neither of these analyses was evidence of heterogeneity by age observed • Rates of drug withdrawal in the rosuvastatin groups were 14.3%, 17.0%, and 21.6% among	For an expanded endpoint that includes revascularization, effects were virtually identical in those >70 y of age (HR: 0.74; 95% CI: 0.61–0.89; p=0.0016).

				those <65 y, 65 to <70 y, and ≥70 y of age, respectively. **Safety Endpoint:** • Effects consistent across age groups, and a formal test for heterogeneity was nonsignificant. • Uncertainties remain with regard to hemorrhagic stroke, cognitive function, drug interactions, adherence, quality of life, and cost-effectiveness. • concerns regarding DM	
Savarese GJ, 2013 (119) 23954343	**Aim:** Study of CV endpoints and mortality using statins in older adults **Study Type:** Meta-analysis of RCT **Size:** 24,674 subjects age ≥65. 42.7% females; mean age 73.0	**Inclusion criteria:** RTC comparing statins versus placebo with --all-cause and CV mortality, MI, stroke, and new cancer onset in elderly subjects **Exclusion criteria:** 38 studies excluded: 25 trials enrolled patients with established CVD; 7 trials reported duplicate data; 2 trials reported no clinical endpoint; 1 trial excluded patients age >70 y; 1 randomized clinical study having missing information that we could not obtained	**Intervention:** Statin **Comparator:** Placebo	**1° Endpoint:** • Statins significantly reduced the risk of MI by 39.4% (RR: 0.606; 95% CI: 0.434–0.847; p= 0.003) and the risk of stroke by 23.8% (RR: 0.762; 95% CI: 0.626–0.926; p=0.006). • Risk of all-cause death (RR: 0.94; 95% CI: 0.856–1.035; p=0.210) and of CV death (RR: 0.907; 95% CI: 0.686–1.199; p=0.493) were not significantly reduced. **Safety Endpoint (if relevant)** • New cancer onset did not differ between statin- and placebo-treated subjects (RR: 0.989; 95% CI: 0.851–1.151; p=0.890).	**Limitations:** 2.9 y; mean follow up 3.5±1.5 y)
TENG M, et al., 2015 (120) 26245770	**Study Type:** Meta-analysis RCT **Size:** 8 studies 25,952 **Subjects**: aged ≥65 y. Mean age 72.7 y (range 69–75.5 y)	**Inclusion criteria:** participants aged ≥65 y and without established CVD The proportion of patients with diabetes and hypertension was 51.2 and 56.8 %, respectively. --22% current smokers **Exclusion criteria:** younger patients	**Intervention:** statin therapy **Comparator:** placebo or usual care	**1° Endpoint:** • Statins significantly reduced the risks of composite major adverse CV events (RR: 0.82, 95% CI: 0.74–0.92), nonfatal MI (0.75, 0.59–0.94) and total MI (0.74, 0.61–0.90). • Treatment effects of statins were statistically insignificant in fatal MI (0.43, 0.09–2.01), stroke (fatal: 0.76, 0.24–2.45; nonfatal: 0.76, 0.53–1.11; total: 0.85, 0.68–1.06) and all-cause mortality (0.96, 0.88–1.04). **Safety Endpoint:** No significant differences in myalgia (0.88, 0.69–1.13), elevation of hepatic transaminases (0.98,	**Limitation:** The occurrence of myopathy, rhabdomyolysis and cognitive impairment was largely unreported in the included trials.

				0.71–1.34), new–onset diabetes (1.07, 0.77–1.48), serious adverse events (1.00, 0.97–1.04) and discontinuation due to adverse events (1.10, 0.85–1.42).	
CTT Cholesterol Treatment Trialists' Collaborators, 2012 (121) 22607822 PMC3437972	**Study Type:** Meta-analysis of RCT **Size:** 22 RCT. N=134,537	**Inclusion criteria:** A trial was eligible if it 1. it included at least one intervention whose main effect was to lower LDL cholesterol concentration 2. it was unconfounded with respect to this intervention (i.e., no other differences in risk factor modification between the treatment groups were intended) 3. it recruited at least 1000 participants with scheduled treatment duration of at least 2 y.	**Intervention:** statin therapy **Comparator:** control	**Overall:** • Reduction of LDL cholesterol with a statin reduced the risk of major vascular events (RR: 0·79, 95% CI: 0·77–0·81, per 1·0 mmol/L reduction) • Among adults ≥70, effects on major vascular events per 1.0 mmol/L reduction in LDL cholesterol (RR: 0.83; 95% CI: 0.78 − 0.87; p<0.0001)	NA
Ridker PM, et al., 2017 (118) 28385949	**Aim:** To describe the role of statin therapy in the elderly **Study type:** Fixed-effects meta-analysis of age-specific data from JUPITER and HOPE-3 **Size:** 30,507	**Inclusion criteria:** • Participants in the JUPITER trial (rosuvastatin 20 mg daily vs. placebo) and H trial (rosuvastatin 10 mg daily vs. placebo) -All subjects were free of CVD and were divided into age groups <65 y (n=13, 517), 65-<70 y (n=8,218) and >70 y (n=8,781). • Those >70 y comprised 32% and 24% of the J and H study populations respectively and suffered 55% and 43% of the CVD events **Exclusion criteria:** N/A	**Intervention:** Rosuvastatin 20 mg or 10 mg **Comparator:** Placebo	**1° endpoint:** non-fatal MI. non-fatal stroke and CVD death **Results:** • Rates of primary outcome/100 pt.-y for rosuva/placebo and pooled HR: (95% CI): • <65 y; • JUPITER: 0.27/0.59 • HOPE-3: 0.46/0.53 • 0.75 (0.5; 0.97) • 65-<70 y: • JUPITER: 0.24/0.61 • HOPE-3: 0.50/0.91 • 0.51 (0.38; 0.69) • >70 y; • JUPITER: 0.82/1.36 • HOPE-3: 1.25/1.50 • 0.74 (0.61; 0.91)	•In subjects >70 y of age there was a 26% RRR in the primary and in the expanded endpoint (included revascularizations) •There was no heterogeneity by age •The higher event rates in those >70 y of age implies larger absolute rate reductions and therefore lower NNTs **Limitations:** • The upper age cut-off was 70 y not 75 y

				• Rates of drug withdrawal in those <65, 65-<70 and >70 y of age: • JUPITER: 14.3, 17.0, 21.6 y H: 21.4, 23.1, 29.1 y	Adverse event rates by age group are not provided, but >70 y old had higher drug withdrawal than younger groups

Data Supplement 20. Nonrandomized Trials, Observational Studies, and/or Registries of Q4: Evidence regarding the cost-effectiveness of screening for familial hypercholesterolemia (Section 4.4.4.3)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Ademi Z, et al., 2013 (122) 23490080	**Study type:** Systematic review **Size:** 6 published studies	**Inclusion criteria:** English literature studies performing economic evaluations of screening for FH (defined by Dutch Lipid Clinic Network or modified UK Simon Broome criteria). **Exclusion criteria:** Studies with duplicated data.	**1° endpoint:** Cost estimates of screening strategies. **Results:** • When compared with no screening, the incremental cost-effectiveness ratio (123) of screening ranged from €3177–€29,554 per life year gained.	• Screening of relatives of those with diagnosed FH is cost effective compared with no screening across a range of assumptions and geographic locations. • Across studies, results were sensitive to the prevalence of FH, the utility (sensitivity and specificity) of the screening test used and the assumed price and efficacy of lipid-lowering therapy. • Specific studies included in this systematic review are also included in the table below (and indicate by an asterisk) for greater clarification of findings. Limitations: Numerous assumptions inherent in cost-effectiveness analysis.
Ademi Z, et al., 2014 (124) 25110220	**Study type:** Decision and cost-effectiveness analysis	**Inclusion criteria:** Consecutive index cases and newly screened relatives, 2008 - 2013	**1° endpoint:** ICER per quality-adjusted life year (QALY) gained and per year of life saved (YoLS) for screening vs. no screening of relatives of index cases with FH.	• Cascade screening for FH using a combination of genetic and phenotypic testing represents a cost-effective means of preventing CHD in at-risk families.

	Size: 81 consecutive index cases of FH and 175 1st and 2nd degree relatives, Royal Perth Hospital, used to model cost-effectiveness in Australian general population	**Exclusion criteria:** N/A	**Results:** • Cascade screening for FH would prevent 1 CHD event over 10 y for every 7.4 people screened. The number needed to screen (125) to prevent one CHD-related death would be 18.3. In the population of relatives identified as having FH by cascade screening, the NNS to prevent one CHD event would be 4.0. • The authors estimated that for every 100 people undergoing cascade screening in Australia (including the 45.7% of those without underlying FH), there would be an overall gain of 24.9 life y and 29.1 QALYs (discounted) over a 10-y period. • ICERs over a 10-y period were AUD (Australian) $4154 per YoLS and AUD $3565 per QALY gained. • In sensitivity analyses, using age- and gender- adjusted LDL-C thresholds (only) for diagnosis of close relatives with FH for cascade screening was deemed to be a cost-effective strategy compared with no screening. In this strategy, the yield of FH relatives detected per index case was comparable to genetic testing (1.09 vs. 1.17), with incrementally lower costs (because no DNA tests would be used). There was an 86.9% concordance between genetic testing and using age-gender adjusted LDL-C cutoffs for the detection of FH in relatives.	Analysis using only plasma LDL-C for cascade screening found cascade screening to be a cost-effective approach when compared with no screening. • ICERs were sensitive to the prevalence of FH, assumptions regarding annual risks of CHD and relative benefits of statins, but still led to favorable ICERs compared with no screening. • Extending the time frame of this model to 20 or 30 y (compared with the 10-y examined in this analysis) would lead to even greater estimates of cost-effectiveness. Limitations: Did not consider children; uncertain generalizability beyond Australian population; sensitivity and specificity of genetic testing assumed to be 100%; numerous assumptions inherent in cost-effectiveness analysis.
Chen CX, et al., 2015 (126) 25569270	**Study type:** Decision and cost-effectiveness analysis **Size:** Analysis from US male population	**Inclusion criteria:** N/A **Exclusion criteria:** N/A	**1° endpoint:** Cost-effectiveness of genetic screening and lipid-based screening with statin adherence measures compared to lipid-based screening alone in the US. **Results:** • For each man with a family history of FH:	• Results support implementation of enhanced lipid cascade screening, potentially with additional statin adherence measures, while showing that genetic cascade screening is currently not cost-effective in US males. • At a US willingness-to-pay threshold of $150,000/QALY Genetic Screening is not

	perspective with lifetime horizon. initial cohort of 1000 Caucasian male adults with a family history of FH followed in a Markov model simulation		- Genetic Screening cost $15,594 for 18.29 QALYs - Lipid Screening with adherence measures cost $16,385 for 18.77 QALYs - Lipid Screening alone cost $10,396 for 18.28 QALYs • The ICER for Genetic Screening versus Lipid Screening alone was $519,813/QALY. • The ICER for Lipid Screening with adherence measures versus Lipid Screening alone was $12,223/QALY, which would generally be considered cost effective.	cost-effective compared with Lipid Screening alone. • Lipid screening alone and lipid screening with enhanced adherence measures dominated genetic screening for men with a history of FH in this model. • Sensitivity analyses showed that results were robust to reasonable variations in model parameters. Costs of DNA testing had the largest effects on the model. Limitations: Study performed at a time when there were limited data on CHD incidence rates in US population with FH; men only; numerous assumptions inherent in cost-effectiveness analysis.
Marang-van de Mheen PJ., et al., 2002 (127) 12473254	**Study type:** Cost-effectiveness analysis **Size:** 2229 relatives of 137 FH probands.	**Inclusion criteria:** Individuals aged ≥16 y who were related to genetically identified FH probands from a closed cohort in the Netherlands, 1994-1997 **Exclusion criteria:** N/A	**1° endpoint:** Life years gained and life time costs of the screened cohort of relatives, theoretically subjected to various strategies of treatment compared with a strategy of no screening. **Results:** • Depending on the treatment strategy implemented, costs per year of life gained varied between 25,600 and 32,200 Euros	• At the time of the study, statin costs were the major determinant of costs and cost-effectiveness. The ICER for genetic screening and treatment therefore exceeded the recommended threshold for cost-effectiveness for Dutch guidelines at the time. The authors recommended a screening and treatment approach based solely on LDL-C levels as a result. Statin costs have declined since this analysis was undertaken. Limitations: Generalizability beyond this Dutch population; time effects of costs given this is an older analysis; numerous assumptions inherent in cost-effectiveness analysis.
Marks D, et al., 2002 (128) 12039822	**Study type:** Cost-effectiveness analysis **Size:** Simulated population aged 16-54 y in England and Wales.	**Inclusion criteria:** Simulated population aged 16-54 y in England and Wales, using a lifetime event horizon. **Exclusion criteria:** N/A	**1° endpoint:** Cost per life year gained using a lifetime horizon comparing different screening strategies: universal screening (all in the population), opportunistic screening in primary care (fasting lipid panel in those with non-fasting total cholesterol >95th percentile), screening of people admitted to hospital with premature	• Family tracing of FH-affected individuals followed by lipid screening and possible genetic confirmation was the most cost-effective strategy when compared with universal screening, screening of premature CHD patients, and opportunistic screening of those identified through routine lab testing.

			myocardial infarction, or tracing family members of known FH-affected patients and inviting them for screening. **Results:** • Tracing of family members and lipid screening was the most cost-effective strategy (at £3097/€5066/$4479 per life year gained) with a NNS of 2.6 to identify one case. If the genetic mutation was known within the family then the cost per life year gained (£4914) was only slightly increased by genetic confirmation of the diagnosis. Universal population screening was least cost effective (£13 029 per life year gained) with a NNS of 1365 to identify one case. • For each strategy it was more cost effective to screen younger people and women. • Universal lipid screening of 16-y old's (only) in this hypothetical population had similar cost-effectiveness to family tracing.	Limitations: Generalizability beyond UK population; older study with high assumed drug costs; numerous assumptions inherent in cost-effectiveness analysis.
Marks D, et al., 2003 (129) 12669918	**Study type:** Cost-effectiveness analysis **Size:** Simulated population aged 16-54 y in England and Wales	**Inclusion criteria:** Simulated population aged 16-54 y in England and Wales, using a 10-y event horizon **Exclusion criteria:** N/A	**1° endpoint:** Cost per life year gained using a 10-y horizon comparing two different screening strategies: universal screening of all 16-y-old individuals in the population vs. tracing family members of known FH-affected patients and inviting them for screening. **Results:** • Screening all 16-y-olds in this population would result in an estimated 470 new diagnoses of FH and would avert 11.7 deaths over 10 y at a cost of £6,176,649 (including 10-y drug costs of £1,584,918.	• Although the two approaches compared in this study appeared similar in cost-effectiveness over a lifetime (see Marks 2002 analysis, above), results from this shorter-term (10-y) cost-effectiveness clearly favored the family tracing strategy. Limitations: Generalizability beyond UK population; older study with high assumed drug cost; numerous assumptions inherent in cost-effectiveness analysis.

			The cost per case identified and treated would be £13141. • Screening first-degree relatives of known FH cases would result in 13248 new diagnoses, 560 deaths averted over 10 y, at a cost of £46 430 681. The cost per case identified and treated would be £3 505 (including 10-y drug costs of £44 645 760).	
Nherera L, et al., 2011 (130) 21685482	**Study type:** Cost-effectiveness analysis **Size:** Simulated cohort of 1000 people in the UK suspected of having FH aged 50 y for index cases and 30 y for relatives, followed for a lifetime.	**Inclusion criteria:** N/A **Exclusion criteria:** N/A	**1° endpoint:** Costs, QALYs and ICERs comparing different cascade screening strategies: using LDL-C levels only (cholesterol method); cascading only in patients with a causative mutation identified and using DNA tests to diagnose relatives (DNA method); DNA testing combined with LDL-cholesterol testing in families with no mutation identified, only in patients with clinically defined 'definite' FH (DNA+DFH method); and DNA testing combined with LDL-cholesterol testing in no-mutation families of both 'definite' and 'probable' FH patients (DNA+DFH+PFH). **Results:** • All DNA-based methods were considered more cost-effective than the cholesterol only method. • The DNA+DFH+PFH method had an ICER of £3666/QALY compared with DNA alone and of £4145/QALY compared with the cholesterol method.	• In this study, the DNA+DFH+PFH method was the most cost-effective cascade screening strategy as a result of lower DNA screening costs compared with the higher number of Limitations: Assumptions based on 50-y old probands and 30-y old relatives; generalizability beyond UK population; numerous assumptions inherent in cost-effectiveness analysis.
Oliva J, et al., 2009 (131) 19150015	**Study type:** Cost-effectiveness analysis **Size:** Representative data from 503 individuals with FH and national data from Spain	**Inclusion criteria:** N/A **Exclusion criteria:** N/A	**1° endpoint:** Costs and ICER per Life Year Gained (LYG) comparing genetic screening and treatment of 1st degree relatives of probands with genetically diagnosed FH compared with no screening. **Results:**	• Genetic screening of 1st degree relatives of those with FH appeared to be favorable in terms of cost-effectiveness compared with no screening of relatives. • In sensitivity analyses, cost-effectiveness of genetic screening was favorable across a

			• For the base case, the results were: Group Cost Life Years Screened €8891 56.7 Not screened €4298 55.4 Increment €4593 1.34 ICER = €3423 per LYG	wide range of assumptions and was sensitive to the cost of statins. Limitations: Generalizability beyond Spanish populations; numerous assumptions inherent in cost-effectiveness analysis.
Wonderling D, et al., 2004 (132) 15199439	**Study type:** Cost-effectiveness analysis **Size:** Data from nationwide screening program for FH in the Netherlands 1994-2002	**Inclusion criteria:** N/A **Exclusion criteria:** N/A	**1° endpoint:** Costs per Life Year Gained (LYG) comparing genetic screening and treatment of relatives of probands with genetically diagnosed FH compared to national data, with a lifetime perspective. **Results:** • Compared with no screening, DNA testing of families with a known genetic defect was cost effective. • Individuals with newly-diagnosed FH as a result of the screening program appeared to gain, on average, 3.3 y of life each at an average cost of US $7500 per new case identified. • The cost per life-year gained was US$8700.	• Genetic screening of families of those with FH appeared to be favorable in terms of cost-effectiveness compared with no screening of relatives. • In sensitivity analyses, cost-effectiveness of genetic screening was favorable across a wide range of assumptions and was sensitive to the cost of statins. Limitations: Numerous assumptions inherent in cost-effectiveness analysis.

Abbreviations:
Search Terms and Date of Search: Author to provide

Data Supplement 21. RCTs Comparing Screening of Children and Adolescents (Section 4.4.4.3)

Study Acronym; Author; Year Published; PMID	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
Kusters DM, et al., 2015 (133) 25841542	**Aim:** To evaluate the safety and efficacy of ezetimibe monotherapy in young children with Heterozygous FH **Study type:** multicenter double-blind placebo controlled 12 wk RCT **Size:** 138, 2:1 randomization strategy ezetimibe 10 mg (n = 93) or placebo (n = 45)	**Inclusion criteria:** age 6-10 y diagnosed heterozygous FH or clinically important non-FH (LDL ≥160 mg/dL) **Exclusion criteria:** TG >300 mg/dL, evidence of secondary causes of hyperlipidemia, elevated LFTs, hypersensitivity or contraindication to ezetimibe or other major diagnoses	**Intervention:** Ezetimibe 10 mg per day **Comparator:** Placebo	**1° endpoint:** Compared to placebo, Ezetimibe lowered LDL by 27%, TC by 21%, non-HDL by 26%, and apolipoprotein B by 20% (all p<0.001) **Safety endpoint (if relevant):** N/A	• Ezetimibe reduced markers of cholesterol absorption (placebo adjusted changes at wk 12: sitosterol, -63%; campesterol, -65%; cholestanol, -32%; p<0.001) and increased a marker of cholesterol synthesis (lathosterol, +24%; p<0.001) • Well tolerated without significant safety effects. One girl experienced persistent elevated mild elevations in ALT that led to ezetimibe discontinuation.
APPLE Schanberg LE, et al., 2012 (134) 22031171 Ardion SP, et al., 2014 (135) 23436914	**Aim:** determine the 3-year efficacy and safety of atorvastatin in preventing subclinical atherosclerosis progression measured by mean-mean common carotid intima-media thickening (CIMT) in pediatric-onset SLE	**Inclusion criteria:** SLE, weight ≥25 kg, English or Spanish language **Exclusion criteria:** active nephrotic syndrome, myositis, liver disease, renal insufficiency, or hypercholesterolemia (total cholesterol >350 mg/dl) or were being	**Intervention:** atorvastatin 10 or 20 mg per day **Comparator: placebo**	**1° endpoint:** No difference in the rate of progression of mean-mean common CIMT between treatment groups (0.0010 mm/y for atorvastatin versus 0.0024 mm/y for placebo; p=0.24). **Safety endpoint:** N/A	• The atorvastatin group achieved lower hsCRP (p=0.04), TC (p<0.001), and LDL-C (p<0.001) levels compared with placebo. • Post-pubertal patients with high hCRP seemed to benefit the most in post-hoc analyses • CIMT progressed in the placebo group over time (0.0023-0.0144 mm/y; p<0.05). • No significant safety concerns.

	Study type: double blind RCT **Size:** 221 youth with SLE (ages 10-21 y), 182 completed the trial	treated with cyclosporine or tacrolimus, unwilling to follow AHA therapeutic lifestyle changes diet or use approved birth control methods			• Patients ineligible for participation were at the highest risk of progression, and possibly could have demonstrated the most benefit
STRIP Niinikoski H, et al., 2007 (136) 17698729	**Aim:** effect of a dietary intervention on lipid levels **Study type:** randomized, controlled atherosclerosis-prevention study **Size:** complete data were available at age 15 (n=394), 17 (n=376), and 19 (n=298) y	**Inclusion criteria:** **Exclusion criteria:**	**Intervention:** repeated dietary counseling and anti-smoking advice starting infancy up to age 14 y **Comparator:** biannual clinical visits without diet or smoking counseling	**1° endpoint:** Saturated fat intakes, TC, and LDL-C values were lower ($p<0.001$) in the intervention than in control children over 14 y of follow-up. • HDL-C levels did not differ between the 2 groups. • Boys had lower TC and LDL-C than girls throughout childhood ($p<0.001$), • The intervention effect on serum cholesterol concentration was larger in boys than girls. • TC and HDL-C decreased from 4.5 and 1.4 mmol/L, respectively in Tanner stage 1 (prepubertal) boys to approximately 3.9 and approximately 1.1 mmol/L in Tanner stage 4 (late pubertal) boys. **Safety endpoint:** The 2 study groups showed no difference in growth, body mass index, pubertal development, or age at menarche (median, 13.0 and 12.8 y in the intervention and control girls, respectively; p=0.52).	N/A
STRIP Pahkala K, et al., 2013 (137) 23613255	**Aim:** post hoc analysis of the effect of a dietary intervention on ideal cardiovascular health; relationship with intima-	**Inclusion criteria:** **Exclusion criteria:**	**Intervention:** repeated dietary counseling and anti-smoking advice starting infancy up to age 20 y	**1° endpoint:** Adolescents in the control group had an increased risk of low ideal cardiovascular health (≤3 metrics) compared with the intervention adolescents (risk	• No participants had all 7 ideal cardiovascular health metrics in adolescence. • At least 5 ideal metrics were found in 60.2%, 45.5%, and 34.2% of the

	media thickness and elasticity **Study type:** longitudinal, randomized, controlled atherosclerosis-prevention STRIP study **Size:** complete data were available at age 15 (n=394), 17 (n=376), and 19 (n=298) y		**Comparator:** biannual clinical visits without diet or smoking counseling	ratio=1.35; 95% confidence interval=1.04-1.77). **Safety endpoint:** N/A	adolescents at 15, 17, and 19 y of age, respectively. • Number of ideal cardiovascular health metrics was inversely associated with aortic IMT (p<0.0001) and directly associated with elasticity (p=0.045). • Adolescents with a low number of metrics (≤3) had nearly double the risk of having high intima-media thickness (>85th percentile) compared with those with a higher score (risk ratio: 1.78; 95% confidence interval: 1.31-2.43).
Iannuzzi A, et al., 2009 (138) 20108073	**Aim:** to test the effect of hypocaloric diets with varying glycemic index on weight loss and subclinical atherosclerosis (aortic IMT) in obese children **Study type:** 6-mo RCT **Size:** 26 divided between the 2 groups	**Inclusion criteria:** obese children enrolled in an outpatient weight management clinic **Exclusion criteria:**	**Intervention:** hypocaloric low-glycemic index diet **Comparator:** hypocaloric high-glycemic index diet	**1° endpoint:** No differences were detectable in fasting TG, TC, and HDL-C **Safety endpoint:** N/A	• All participants: BMI decreased from 28.3 +/- 3.1 to 25.8 +/- 3.3 kg/m(2), SBP from 119 +/- 12 to 110 +/- 11 mmHg (p<0.001), DBP from 78 +/- 8 to 74 +/- 7 mmHg (p<0.001), IMT from 0.48 +/- 0.05 to 0.43 +/- 0.07 mm (p<0.001), stiffness from 3.57 +/- 1.04 to 2.98 +/- 0.94 mm (p= 0.002), and CRP from 1.5 +/- 0.9 (values log transformed) to 0.4 +/- 1.1 (p<0.001). • Insulin resistance (calculated by HOMA) was reduced only in the low-glycemic-index diet group (p<0.04).
Murphy EC, et al., 2009 (139) 19922034	**Aim:** To determine whether an exercise intervention using an active video game (Dance Dance Revolution) improves endothelial dysfunction and other risk factors in overweight children **Study type:** RCT **Size:** 35 children total	**Inclusion criteria:** BMI ≥85th percentile with endothelial dysfunction **Exclusion criteria:**	**Intervention:** 12-wk of aerobic exercise using dance dance revolution **Comparator:** non-exercising delayed-treatment	**1° endpoint:** Exercise group experienced significant improvements in FMD (5.56+/-5.04% compared with 0.263+/-4.54%, p=0.008) **Safety endpoint:** N/A	• Intervention group had an increase exercise time on the graded exercise test (53.59+/-91.54 compared with -12.83+/-68.10 seconds, p=0.025), mean arterial pressure (MAP) (-5.62+/-7.03 compared with -1.44+/-2.16 mmHg, p=0.05), weight (0.91+/-1.53 compared with 2.43+/-1.80 kg, p=0.017) and peak VO(2) (2.38+/-3.91 compared with -1.23+/-3.18 mg/kg/min, p=0.005) compared with control.

Farpour-Lambert NJ, 2009 (140) 20082930	**Aim:** to determine the effects of physical activity on SBP and subclinical atherosclerosis in pre-pubertal obese children **Study type:** 3-month RCT with a modified crossover design **Size:** 44 overweight or obese children (exercise (n = 22) or a control group (n = 22). 22 lean children for baseline comparison	**Inclusion criteria:** pre-pubertal obese children (BMI >97th percentile) **Exclusion criteria:** pubertal stage > Tanner 1, involved in any weight control, physical activity, or behavioral therapy, had a familial history of dyslipidemia or essential hypertension, took any medications or hormones that might influence cardiovascular function, body composition, or lipid or glucose metabolism, had an orthopedic affection limiting physical activity, had a genetic disorder or a chronic disease, or were followed a therapy for psychiatric problems.	**Intervention:** trained 60 min 3 times/wk during 3 mo **Comparator:** no training Then, both groups trained twice/wk during 3 mo.	**1° endpoint:** Exercise group at 3 months experienced a decrease in BMI z-score (-5.5%), whole body (-3.6%) and abdominal fat (-4.2%), TC (-3.7%), LDL-C (-4.2%), HDL-C (-5.3%), office SBP (-2.0%) and DBP (-4.1%), and 24-h SBP (-4.9%) and DBP (-3.2%). Fat-free mass (+4.6%) and VO2max (+6.0%) increased during the intervention ($p < 0.05$). ● At 6 mo, change differences in arterial stiffness and IMT were significant. **Safety endpoint:** N/A	● Obese children had higher BP, arterial stiffness, body weight, BMI, abdominal fat, insulin resistance indexes, and C-reactive protein levels, and lower flow-mediated dilation, VO(2)max, physical activity, and high-density lipoprotein cholesterol levels than lean subjects.
Velázquez-López L, et al., 2014 (141) 24997634	**Aim:** to assess the efficacy of the Mediterranean style diet to decrease cardiovascular risk factors in children and adolescents with obesity **Study type:** RCT – 16 wk dietary advice **Size:** 24 assigned to intervention, 25 to control	**Inclusion criteria:** BMI ≥95th percentile and any metabolic syndrome component, according to modified International Diabetes Federation (IDF) criteria for children and adolescents **Exclusion criteria:** chronic illness, pharmacological treatment for obesity or comorbidities	**Intervention:** 16 wk dietary advice on following a Mediterranean style diet rich in polyunsaturated fatty acids, fiber, flavonoids and antioxidants (60% of energy from carbohydrate, 25% from fat, and 15% from protein, (n = 24); **Comparator:** standard diet (55% of carbohydrate, 30% from	**1° endpoint:** Mediterranean diet group had a significantly decrease in BMI, lean mass, fat mass, glucose, TC, TG, HDL-C and LDL-C. ($p < 0.05$); **Safety endpoint:** N/A	● The standard diet group decrease in glucose levels and frequency of glucose >100 mg/dL ($p < 0.05$). ● dietary compliance increased consumption of omega 9 fatty acids, zinc, vitamin E, selenium, and decreased consumption of saturated fatty acids ($p < 0.05$) ● Excluded non-adherent participants from the analysis

			fat and 15% from protein, (n = 25), Individualized caloric intake goals		
Singhal A, et al., 2013 (142) 23817470	**Aim:** test the hypothesis that DHA supplementation improves endothelial function and CVD risk factors **Study type:** RCT 16 wk **Size:** n=328, vascular data available on n=268	**Inclusion criteria:** Healthy volunteers, aged 18 to 37 y **Exclusion criteria:** chronic disease likely to affect endothelial function (e.g., insulin-dependent diabetes), pregnancy, on unusual diets, or taking regular medication or n-3 LC-PUFA supplements	**Intervention:** 1.6 g DHA/d (from a microalgae source) together with 2.4 g/d carrier oil **Comparator:** 4.0 g/d olive oil	**1° endpoint:** Brachial Flow-mediated endothelium-dependent vasodilation (FMD) was the same at randomization (mean, SD; 0.27, 0.1 mm), but was higher after the intervention in the control group (0.29, 0.1 mm) compared with intervention (0.26, 0.1 mm; mean difference -0.03 mm; 95% CI: -0.005 to -0.06 mm; p=0.02) **Safety endpoint:** N/A	• Of other outcomes, only TG (mean difference -28%, 95% CI: -40% to -15%; p<0.0001) and VLDL concentrations improved
Vuorio A, et al., 2017 (143) 28685504	**Aim:** to describe the effectiveness and safety of statins in children with inherited high cholesterol in children and adolescents with heterozygous FH **Study type:** meta-analysis of RCTs through Feb 20th, 2017 **Size:** 9 RCTs including 1177 participants	**Inclusion criteria:** RCTs of children up to age 18 y **Exclusion criteria:** poor quality studies and non-RCTs	**Intervention:** statin,12-104 wk interventions **Comparator:** placebo or diet alone	**1° endpoint:** The mean change in serum LDL-C was 32.15% lower (95% CI: 34.90% lower to 29.40% lower) in the stains group (moderate quality evidence) **Safety endpoint:** • AST, ALT, CK levels did not differ between treated and placebo groups at any time points (low quality evidence) • Risks of myopathy (low quality evidence) and other adverse effects (moderate quality evidence) were low • no significant differences between statins and placebo with regard to pubertal progression	• The mean change in carotid IMT was 0.01 mm lower (0.03mm lower to 0.00mm lower) in the stains group (low quality evidence) • The mean change in brachial flow-mediated dilatation was 2.70% higher (0.42% to 4.98% higher) in the statins group (low quality evidence)

Lozano P, et al., 2016 (144) 27559556	**Aim:** To systematically review the evidence on benefits and harms of treating adolescents and children who have heterozygous FH with a statin (USPSTF) **Study type:** systematic review through April 8, 2016 **Size:** 2 to 18 studies depending on the question addressed	**Inclusion criteria:** Fair and good quality studies in English with participants ages 0 to 20 y **Exclusion criteria:** poor quality studies and non-RCTs	**Intervention:** Statins, ezetimibe and bile acid binding resins **Comparator:** Placebo	**1° endpoint:** meta-analysis of 8 placebo trials of statin drugs (n = 1071, 6-104 wk) found LDL-C decreases of 20% to 40% **Safety endpoint:** • Statins are well tolerated (18 studies) • Adverse effects were minimal aside from those experienced by individuals in studies of bile acid-sequestering agents.	• statins decrease cIMT 1% more than placebo (p=0.02) • 3 placebo trials of bile acid–sequestering agents (n = 332, 8-52 wk) showed LDL-C reductions of 10%to 20%. • bile-acid binding resins decreased LDL-C 10-20% • ezetimibe decreased LDL-C 28% (monotherapy) or an additional 14% over and above simvastatin
DISC Obarzanek E, et al., 2001 (145) 11158455 **DISC 1995** (146) 7723156 Obarzanek E, et al., 1997 (147) **Disc 3 y Results** Lavigne JV, et al., 1999 (148) 10619534 **DISC Follow-up Study** Dorgan JE, et al., 2011 (149) 21994964	**Aim:** to evaluate the effect of a modified Step II diet of cholesterol in childhood **Study type:** RCT **Size:** 663 (334 intervention, 329 control)	**Inclusion criteria:** Prepubertal (age 8-10 y) with LDL ≥80th and <98th %tile for age and sex recruited from public and private elementary schools with TC level was ≥4.5 mmol/L (175 mg/dL) or greater (approximately the 75th age- and sex-specific percentile) with fasting LDL-C≥ 70th and ≤99th age and sex-specific percentiles Final lipid eligibility criterion was the average of the 2 screening LDL-C values ≥80th and ≤98th percentiles for age and sex. **Exclusion criteria:** medical condition or medication that might	**Intervention:** modified NCEP Step II delivered via family-based counseling for 0-3 y old's and lower intensity counseling age 4-8 yrs. **Comparator:** feedback to parent about child's baseline cholesterol and written heart healthy diet materials	**1° endpoint:** • At 7 y of follow-up reductions in dietary total fat, saturated fat, and cholesterol were greater in the intervention than in the usual care group. •At 1 y, 3 y, and 7 y, the intervention compared with the usual care group had 4.8 mg/dL (.13 mmol/L), 3.3 mg/dL (.09 mmol/L), and 2.0 mg/dL (.05 mmol/L) lower LDL-C, respectively. • Follow-up of female participants at age ~18 y found Metabolic syndrome was uncommon, and its prevalence did not differ by treatment group. • After adjustment for nondietary variables, mean ABP of intervention and control group participants were 107.7- and 110.0-mm Hg, respectively (p=0.03), whereas mean fasting plasma glucose levels were 87.0 and 89.1 mg/dl, respectively (p=0.01).	• At 3 y dietary total fat, saturated fat, and cholesterol levels decreased significantly in the intervention group compared with the usual care group (all p<0.001). • Both groups experienced small increases in TG levels ~1 mg/dl) that were not statistically different or clinically important.

		affect growth or blood cholesterol, behavior problems in the child or family likely to reduce adherence, onset of puberty, or plans to move within the 3 study years		• Intervention group participants also had lower concentrations of large VLDL particles compared with control group participants. **Safety endpoint:** There were no differences at any data collection point in height or serum ferritin or any differences in an adverse direction in red blood cell folate, serum retinol and zinc, sexual maturation, or body mass index. • No significant differences between the groups in adjusted mean height or serum ferritin levels (P > .05) or other safety outcomes up to 18 y after randomization	
Shivakumar S, 2015 (150) 25847553	**Aim:** to explore the efficacy of plant-based formulation in the management of adolescent obesity and its associated biomarkers **Study type:** RCT **Size:** 130 obese adolescents of both sexes, with	**Inclusion criteria:** adolescents, BMI above 25kg/m^2 **Exclusion criteria:**	**Intervention:** plant-based formulation two 500mg capsule containing test formulation **Comparator:** two 500mg of cellulose powder containing capsule daily for 3 mo	**1° endpoint:** statistically significant differences mean (95% CI:) were seen in the treatment group in TC mg/dl (-20.9±5.0 (-30.8 to -11.0), TG mg/dl (-12.9±5.7 (-23.9 to -1.2), HDL-C mg/dl (7.2±0.8 (5.6-8.8)) **Safety endpoint:** no significant differences between the groups in adjusted mean height or serum ferritin levels (P > .05) or other safety outcomes	• Plant-based test formulation may prevent the future cardio vascular risk incidence in obese adolescents by reducing inflammation, overweight, lipid profile and by regulating adipokines. • Other differences in favor of the plant-based extract include CRP mg/l (-1.0±0.01 (-1.2 to -0.8)), adiponectin µg/ml (4.9±0.4 (4.2-5.7)), leptin ng/ml (-8.0±1.4 (-10.7 to -5.3)), DBP mmHg (-10.4±0.8 (-12.0 to -8.7)) and SBP mmHg (-6.7±0.7 (-8.1 to -5.3)).
Kelishadi R, et al., 2010 (151) 21028969	**Aim:** to evaluate the effects of zinc sulfate in comparison with placebo on markers of insulin resistance, oxidative stress, and inflammation in a sample of obese prepubescent children.	**Inclusion criteria:** children with BMI >25kg/m^2 **Exclusion criteria:**	**Intervention:** 8 wk zinc supplement **Comparator:** placebo	**1° endpoint:** decrease in Apo B/ApoA-I ratio, ox-LDL, leptin and malondialdehyde, total and LDL-cholesterol after receiving zinc, without significant change after receiving placebo. **Safety endpoint:** N/A	• hs-CRP and insulin resistance significantly after receiving zinc but increased after receiving placebo. • In both groups, the mean body mass index (BMI) Z-score remained high, • After receiving zinc, the mean weight, BMI, BMI Z-score decreased significantly, whereas these values increased after receiving placebo.

	Study type: RCT double blind **Size:** 60 youth from Iran				
Horner K, 2015 (152) 26181766	**Aim:** To compare the effects of aerobic, resistance, and no exercise on Pulse wave velocity, carotid IMT, LV mass indexed and cardiometabolic risk factors **Study type:** RCT **Size:** 81 pts, 3 mo of aerobic (n = 30), resistance (n = 27) or a control group (n = 24)	**Inclusion criteria:** 12-18 y old, obese (BMI >95th%tile) **Exclusion criteria:**	**Intervention:** aerobic exercise, resistance exercise **Comparator:** no exercise	**1° endpoint:** • significant reductions in total fat and improvements in cardiorespiratory fitness in the AE and RE groups • aPWV, cIMT, LVMI, BP, lipids and body weight did not change compared to controls (p>0.05 for all) **Safety endpoint (if relevant):** N/A	• Baseline the strongest correlates of aPWV were body weight (r = .31) and diastolic BP (r = .28); of cIMT were body weight (r=0.26) and CRF (r=-0.25); and of LVMI was CRF (r=0.32) (p<0.05 for all)
de Ferranti SD, 2015 (153) 26337820	**Aim:** to compare the effects of a reduced-calorie low glycemic diet to a low saturated fat diet in youth with overweight/obesity and cardiometabolic risk factors **Study type:** RCT of home delivered food and nutritional counseling **Size:** 27 adolescents;	**Inclusion criteria:** 12-17 y old, obese (BMI >95th%tile) **Exclusion criteria**: known endocrine diagnoses or other conditions associated with lipid abnormalities or insulin resistance	**Intervention:** calorie restricted low glycemic diet **Comparator:** calorie restricted low saturated fat diet	**1° endpoint:** Overall, participants (n = 27) showed substantial improvement during the Intensive Phase, including InsAUC (-59 ± 18.2 µU/ml × 120 min, p=0.004), total cholesterol (-9.9 ± 3.6 mg/dl, p=0.01), weight (-2.7 ± 0.5 kg, p<0.001), waist circumference (-3.1 ± 0.8 cm, p<0.001), HOMA-IR (-1.7 ± 0.4, p<0.001), SBP (-5 ± 1.4 mm Hg, p=0.002), and CRP (-0.1 ± 0.1 mg/dl, p=0.04). • There were minimal between-group differences; the LF group showed greater declines in HDL (p=0.005) and fasting glucose (p= 0.01) compared to the LGL group. • Improvements waned during 4-mo maintenance period.	• Home delivery of LF or LGL diets resulted in improvements in CV risk factors that diminished without food delivery and did not differ based on dietary intervention.

				Safety endpoint (if relevant): N/A	
Gidding SS, 2014 (154) 25008950	**Aim:** To evaluate the effect of omega-3 fatty acids supplements on TG levels in hypertriglyceridemic adolescents. **Study type:** 8 wk double-blind, crossover RCT **Size:**42 adolescents	**Inclusion criteria:** hypertriglyceridemia and low-density lipoprotein (LDL) cholesterol <160 mg/dL **Exclusion criteria**:	**Intervention:** 8 wk fish oil **Comparator**: 8 wk placebo	**1° endpoint:** TG levels decreased on fish oil treatment compared with placebo but did not reach statistical significance (-52 ± 16 mg/dL vs. -16 ± 16 mg/dL). • Large VLDL particle number decreased (-5.83 ± 1.29 nmol/L vs. -0.96 ± 1.31 nmol/L; p<0.0001). • No change in LDL particle number or size. • Trend towards a lower prothrombotic state (lower fibrinogen and plasminogen activator inhibitor-1; 10 > p>0.05); **Safety endpoint (if relevant):** N/A	• Fish oil (4 g/d) may lower TG slightly and may have an antithrombotic effect without an effect on LDL particles. • Likely underpowered
de Ferranti SD, 2014 (155) 24707021	**Aim:** To evaluate the effect of omega-3 fatty acids supplements on TG levels in hypertriglyceridemic adolescents. **Study type:** 6 mo double-blind RCT **Size:** 25 adolescents	**Inclusion criteria:** 10-19 y, TG levels 150 to 1000 mg/dL **Exclusion criteria**:	**Intervention:** Lovaza (~3360 mg docosahexaenoic acid + eicosapentaenoic acid per day) **Comparator:** placebo (corn oil)	**1° endpoint:** TG levels declined at 3 mo in the Lovaza group by 54 ± 27 mg/dL (mean ± standard error; p=0.02) and by 34 ± 26 mg/dL (p=0.16) in the placebo group. The difference in TG lowering between groups was not significant (p=0.52). There were no between-group differences in endothelial function, blood pressure, body mass index, C-reactive protein, or side effects. **Safety endpoint (if relevant):**	• High-dose omega-3 fatty acid supplements are well tolerated in adolescents. However, declines in TG levels did not differ significantly from placebo • Likely underpowered

Abbreviations: 1° indicated primary; CI, confidence interval; HR, hazard ratio; N/A, not available; OR, odds ratio; RCT, randomized controlled trial; and RR, relative risk. ICVH – Ideal cardiovascular health
HOMA HOmeostatic Model Assessment index
Search Terms and Date of Search: Author to provide

Data Supplement 22. Nonrandomized Trials, Observational Studies, and/or Registries of Metabolic Syndrome of Children and Adolescents (Section 4.4.4.3)

Study Acronym; Author; Year Published' PMID	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Gunnarsdottir T, 2014 (156) 24636901	**Study type:** Weight loss obs. **Size:** 84 obese children (age-range: 8-13 y) and a participating parent	**Inclusion criteria:** **Exclusion criteria:**	**1° endpoint:** body-mass index standard deviation score - Laeknabladid. 2014 Mar; 100(3):139-45. – Article in Icelandic… **Results:** Among treatment completers BMI-SDS (body-mass index standard deviation score) decreased significantly from pre- to post- treatment (F (2.60) =110.31, p<0.001) which was maintained at one-y (F (2.60) =1.33; p=0.253) and two-y (F (2.60) = 3, 19; p=0.079) post treatment.	• Among a subsample (n=23) of participants, significant reductions were observed in fasting insulin levels, (t (22) =6.1, p<0.05), triglycerides (t (22) =0.31, p<0.05) and total cholesterol (t (22) =0.35, p<0.05). •Analysis was done only among study completers. • Written in Icelandic
Viitasalo A, et al., 2014 (157) 24463933	**Study type:** Factor analyses of metabolic syndrome definition **Size:** 491 children, 1,900 middle-aged men, 614 older women and 555 older men from Finland	**Inclusion criteria:** **Exclusion criteria:**	**1° endpoint:** incident type 2 diabetes, myocardial infarction, and cardiovascular and overall death in middle-aged men **Results:** The risk of type 2 diabetes, myocardial infarction, cardiovascular death and overall death increased 3.67-, 1.38-, 1.56- and 1.44-fold, respectively, for a 1 SD increase in the MetS score.	• Factor analysis was used to develop a metabolic syndrome score which was related to hard outcomes.
Benson M, et al., 2012 (158) 22819275	**Study type:** cross sectional description of lipoprotein subtypes in lean and obese children **Size:** 162 pediatric subjects—75 were lean (41 prepubertal and 34 pubertal, 43 boys and 32 girls) and 87 obese (39 prepubertal and 48	**Inclusion criteria:** Obese children (BMI >95%) with normal BP, fasting glucose, TC (<200 mg/dL) and TG (<130 mg/dL) and normal or mildly decreased HDL-C. Lean children were age and puberty matched and were healthy, on no medications or herbal remedies and without 1st degree relatives with	**1° endpoint:** lipoprotein sub-fractions using a novel ion mobility assay **Results:** Lean children had higher HDL-large (76%), HDL-small (13%), and HDL-total (27%) compared with obese (p<0.01), and lower LDL-medium (-30%, p<0.01) and medium + small (-21%, p=0.02) as well as LDL-total (-13%, p=0.035).	• In both groups, the LDL component was higher in males and pubertal children (p<0.01). • Prepubertal children had a higher HDL component than pubertal ones (p<0.004). • Adjusting for sex and pubertal status LDL component was positively, and HDL component negatively, correlated with obesity (p<0.004). • Despite relatively normal triglycerides and cholesterol measured with standard assays at

	pubertal, 58 boys and 29 girls)	obesity, type 2 diabetes, hypertension, or dyslipidemia. **Exclusion criteria:** Genetic and endocrine causes of obesity		screening, ion mobility analysis showed significant differences in lipid and apolipoprotein sub-fractions between lean and obese children, even before puberty.
Elkiran O, et al., 2013 (159) 22014414	**Study type:** Substudy of a cross sectional school-based survey of Turkish schoolchildren **Size:** 123 children; 67 obese and 24 overweight and 32 healthy weight	**Inclusion criteria:** 6th, 7th and 8th graders from 18 schools in eastern Turkey with available clinical data. **Exclusion criteria:** no subject or parental consent	**1° endpoint:** carotid intima-media thickness (IMT) **Results:** • Carotid IMT was significantly higher in overweight (0.52±0.008 mm) and obese (0.53±0.008 mm) groups compare to the controls (0.36±0.009 mm) (p=0.001). • Carotid IMT was significantly correlated to the body mass index (r=0.396, p=0.001), fat mass percentage (r=0.257, p=0.036), waist circumference (r=0.390, p=0.001), diastolic BP (r=0.266, p=0.030), glucose (r=0.250, p=0.042), and high-sensitivity C-reactive protein levels (r=0.269, p=0.001) in the obese group. Waist circumference (p=0.045), and diastolic BP (p=0.031) persisted in multivariable analyses.	• Obesity is related to cardiovascular risk factors leading to subclinical measures of atherosclerosis in schoolchildren. • Central obesity measured by waist circumference and diastolic BP were significant determinants.
Dalili S, et al., (160) 25249405	**Study type:** Cross sectional **Size:** 859 children age 12 y; 550 boys and 309 girls	**Inclusion criteria:** 12-y-old junior students referred to 15 urban health centers of Rasht, Iran **Exclusion criteria:**	**1° endpoint:** correlates of hypertension in childhood **Results:** weight, waist and hip circumferences, insulin levels, high TG and low HDL were correlated with high blood pressure.	• Children with one cardiovascular risk factor (elevated BP) should be screened for additional risk factors
de Jong M, et al., (161) 26086641	**Study type:** observational longitudinal cohort **Size:** 38 very low birth weight (VLBW) children and 82 term born children, 64 average for gestational	**1° endpoint:** Metabolic syndrome components in early childhood in children born at VLBW, SGA and AGA. **Results:**	**1° endpoint:** Metabolic syndrome components in early childhood in children born at VLBW, SGA and AGA. **Results:** • At age 2 y corrected, VLBW children had lower BMI and higher glucose level compared to AGA children.	• In early childhood, VLBW and term SGA children already have a high prevalence of some metabolic syndrome components compared to term AGA children. • Body fat was a significant correlate of cardiovascular risk factors in children born at low birth weight.

	age (AGA)/18 small for gestational a birth weight **Inclusion criteria:** very low birth weight (VLBW), small for gestational age (SGA) and average for gestational age (AGA) **Exclusion criteria:** N/A	• At age 2 y corrected, VLBW children had lower BMI and higher glucose level compared to AGA children. • SGA children had lower BMI at 1 and 2 y of age and a high prevalence of high TG levels at 1 y of age compared to AGA children. • Total body fat was a significant determinant of HDL cholesterol and TG and birth weight was a significant determinant of glucose at 2 y corrected age.	• SGA children had lower BMI at 1 and 2 y of age and a high prevalence of high TG levels at 1 y of age compared to AGA children. • Total body fat was a significant determinant of HDL cholesterol and TG and birth weight was a significant determinant of glucose at 2 y corrected age	
Ma CM, et al., 2015 (162) 25809784	**Study type:** cross-sectional population-based study **Size:** 3136 Han adolescents age 13-17 y	**Inclusion criteria:** **Exclusion criteria:**	**1° endpoint:** Elevated TC (≥5.18 mmol/L), high LDL-C (≥3.37 mmol/L), low HDL-C (<1.03 mmol/L), and high non-HDL-C (≥3.76 mmol/L) could be used as screening tools for the identification of adolescents characterized by atherogenic lipid profile. **Results:** adolescents with waist-to-height ratio (WHtR) ≥0.48 for boys and ≥0.46 for girls and TG levels ≥1.47 mmol/L were more likely to have hypercholesterolemia (odds ratio (OR) = 7.8, 95 % confidence interval (CI:) = 3.5-17.3, P < 0.001), high LDL-C (OR = 9.4, 95 % CI: = 2.8-31.2, P < 0.001), low HDL-C (OR = 10.8, 95 % CI: = 6.9-17.0, P < 0.001), and high non-HDL-C (OR = 22.9, 95 % CI: = 10.0-52.2, P < 0.001) than those adolescents with normal WHtR and normal serum TG	• hypertriglyceridemic waist-to-height ratio phenotype identified Han adolescents with atherogenic lipid profile in a non-age dependent fashion
de Lima Sanches P, et al., 2011 (163) 21124323	**Study type:** non-randomized 1 y weight loss intervention	**Inclusion criteria:** post-pubertal (Tanner 5) obese adolescents	**1° endpoint:** common carotid artery intima-media thickness (IMT) **Results:**	• The weight-loss program promoted a significant improvement in body composition, insulin concentration, HOMA-IR, lipid profile, BP and inflammatory state, in addition to

	Size: 29 post pubertal adolescents	**Exclusion criteria:** other metabolic or endocrine diseases; chronic alcohol consumption; previous use of drugs, such as anabolic androgenic steroids or psychotropics that may affect appetite regulation; pregnancy	• 1-y interdisciplinary weight-loss program including nutrition and aerobic and resistance exercise programming improved cIMT (-0.06 mm, P≤0.01) • Change in HOMA-IR (ΔHOMA-IR) was negatively correlated with concomitant changes in the adiponectin concentration (Δadiponectin; r=-0.42; p=0.02) and positively correlated with changes in common carotid artery IMT (Δcarotid IMT; r=0.41; p=0.03).	significantly decreasing the common carotid artery IMT. • Only reported results on participants completing >75% of the exercise sessions
HEALTHY study Bauer KW, et al., 2015 (164) 25515620	**Study type:** Cross-sectional 42 US middle schools with student populations at increased risk for type 2 diabetes, i.e., with at least 50% of students eligible for free or reduced-price lunch or belonging to a racial or ethnic minority group. **Size:** 6097 adolescents	**Inclusion criteria:** 10-13 y-old with available data **Exclusion criteria:**	**1° endpoint:** cardio-metabolic risk among youth defined as glucose ≥ 100 mg/dL, fasting insulin ≥ 30 µU/mL, SBP or DBP ≥95th percentile, TC ≥200 mg/dL, LDL ≥130 mg/dL, triglycerides ≥ 130 mg/dL, and HDL ≤40 mg/dL **Results:** • Discriminatory ability of BMI percentile was good (area under the curve [AUC] ≥ 0.80) for elevated insulin and clustering of ≥3 risk factors, with optimal cut-points of 96 and 95, respectively. • BMI percentile performed poor to fair (AUC = 0.57-0.75) in identifying youth with elevated glucose, TC, LDL, BP, TG and HDL. • WC percentile and WtHR performed similarly to BMI percentile.	• Obesity defined by BMI ≥95th%tile identifies elevated insulin and a clustering of ≥3 cardio-metabolic risk factors. • Evidence does not support WC percentile or WtHR as superior screening tools compared with BMI percentile for identifying cardio-metabolic risk

Abbreviations: 1° indicated primary; CI, confidence interval; HR, hazard ratio; N/A, not available; OR, odds ratio; RCT, randomized controlled trial; and RR, relative risk.
Search Terms and Date of Search: Author to provide

Data Supplement 23. Nonrandomized Trials, Observational Studies, and/or Registries of Treatment (Section 4.4.4.3)

Study Acronym; Author; Year Published' PMID	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)

Braamskamp MJ, et al., 2015 (165) 26079405	**Study type:** observational **Size:** 88 cases, 62 unaffected siblings	**Inclusion criteria:** Children age 8-18 previously randomized to pravastatin and their unaffected siblings **Exclusion criteria:** Current OCP use	**1° endpoint:** testosterone, estradiol, LH, FSH, DHEAS levels, **Results:** No difference in hormone levels between FH patients treated with pravastatin and their unaffected siblings.	•Statin use in children and adolescents does not affect gonadal steroid and gonadotropin levels
Pratt RE, et al., 2014 (166) 24636177	**Study type:** retrospective review of clinical practice **Size:** 53 patients	**Inclusion criteria:** 6 to 18 y of age with diagnosis of combined dyslipidemia cared for in a pediatric lipid clinic with at least 2 visits, ≥2 lipid values exceeding the upper limit of normal for TC, TG, non-HDL-C, or LDL-C ± HDL-C below the lower limit of normal. **Exclusion criteria:**	**1° endpoint:** lipid levels, BMI **Results:** mean follow-up 9.2 mo. Lipid parameters (mean ± SD, mg/dL) improved significantly (p<0.001): TC 209 ± 39 to 181 ± 32; TG 255 ± 119 to168 ± 99; non-HDL-C 167 ± 35 to 138 ± 30 and LDL-C 121 ± 43 to 106 ± 30. HDL-C was unchanged. • BMI decreased in 58% and mean BMI decreased 0.67 kg/m (2) (p<0.05).	• Focused lifestyle changes significantly improved combined dyslipidemia in obese children • . With no direct weight loss approach, body mass index decreased in 58%.
Zachariah JP, et al., 2016 (167) 27810053	**Study type:** retrospective review of clinical practice **Size:** 501 youth with lipid disorders	**Inclusion criteria;** seen a preventive cardiology clinic for lipid disorder with at least one follow-up visit **Exclusion criteria:**	**1° endpoint:** change in lipid levels from first to most recent visit **Results:** Over a median follow-up of 231 d Depending on baseline lipid levels: LDL decreased 3% to 15% TG decreased 2% to 27% HDL increased 9% to decreased 2% BMI z-score= -0.05; interquartile range: -0.22 to 0.05; p<0.0001; proportion obese 39% vs. 36%, p=0.03.	• Lifestyle interventions delivered in a pediatric subspecialty lipid clinic can improve lipid levels • Change in BMI explained some but not all of the improvements (moderately elevated LDL and elevated TG patients)

Abbreviations: 1° indicated primary; CI, confidence interval; HR, hazard ratio; N/A, not available; OR, odds ratio; RCT, randomized controlled trial; and RR, relative risk.
Search Terms and Date of Search: Author to provide

Data Supplement 24. Nonrandomized Trials, observational studies and / Registries for African Americans. (Section 4.5.1)

Study Acronym; Author; Year Published	Study Type /Design; Study Size	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary /Conclusion Comment(s)
Muntner P, et al., 2014 (81) 24682252	**AIM:** Assess the calibration and discrimination of the PCE in a contemporary US cohort.	REGARDS study: 45-79 y old. **Inclusion**: Regards participants with characteristic similar to	**Primary Outcome:** adjudicated atherosclerotic CVD incidence (nonfatal myocardial infarction, coronary heart	The Pooled Cohort Equation is well calibrated in African Americans and Whites and

	Study Type: Prospective study **Study Size:** N= 10,997 (African Americans = 7,705)	participants used to develop the Pooled Cohort Equation **Exclusion**: h/o prior atherosclerotic cardiovascular disease (ASCVD) or DM, LDLC ≥190mg/dl and not on statin at baseline	disease [CHD] death, nonfatal or fatal stroke) at 5 y **Results:** Observed and Predicted 5-y ASCVD incidence /1000-person y of persons with 10y predicted ASCVD risk: <5% = 1.9(1.3-2.7) and 1.9 5-7.5% = 4.8(3.4-6.7) and 4.8 7.5-10% = 6.1(4.4-8.6) and 6.9 >10% = 12.0(10.6-13.6) and 15.1 (Hosmer-Lemeshow $\chi 2$ = 19.9, p=0.01). C-statistics =0.72; 95% CI: 0.70-0.75. Medicare Linked: Observed and Predicted 5-y ASCVD incidence /1000-person y of persons with 10y predicted ASCVD risk: <7.5%= 5.3(2.8-10.1) and 4.0 7.5-10% = 7.9(4.6-13.5)and 6.4 ≥10% = 17.4(15.3-19.8) and 16.4. C-statistics of 0.67(0.64-0.71). (Hosmer-Lemeshow $\chi 2$ = 5.4, p=0.71	demonstrate moderate to good discrimination.
Fox ER, et al., 2016(168) 27437649	**Aim:** develop and validate risk prediction models for CVD incidence in black adults, incorporating standard risk factors, biomarkers, and subclinical disease. **Study Type:** Prospective study **Study Size:** N= 3689 African Americans	Jackson Heart Study. **Inclusion:** Participants who JHS examination # 1 and had available data on key covariates considered for prediction models	**Primary Endpoint**: First occurrence of MI, CHD death, CHF, stroke, incident angina, or intermittent claudication. **Results:** C- Statistics of the Pooled Cohort Equation = 0.75(0.71-0.79). The event and Non-Event NRI of: PCE vs. Model 1: were 0.016 and 0.007 PCE vs. Model 6: were 0.00 and 0.024	The Pooled Cohort Equation (PCE) has good discrimination in African Americans. The discriminative ability of the PCE in African Americans was not improved by the 6 models built and validated in this study using other subclinical markers
George MD, et al., 2016 (169) 27537560	**Aim:** Evaluate clinical factors associated with CK among healthy individuals and to develop practical reference ranges for important subgroups to improve test interpretation **Study Type**: Cross-sectional	National Health and Nutrition Examination Survey (NHANES) 2011–2014. **Exclusion**: Pregnant, <20y old, strenuous exercise in the last 3 d.	**Primary Outcome:** None **Results:** Provided data on 90%, 95% and 97.5% percentile and their corresponding confidence intervals. Males Race 95TH %tile White 312(268,356)	African Americans have a high CK levels compared with other race/ethnic groups. The 95th percentile or the 97.5th in sex and race specific subgroups provides a practical guide for clinicians interpreting CK levels

	Study Size: N = 10,096 (3156 used to derive the race/ethnicity and sex specific normal CK levels)	**Note:** thyroid disease, cholesterol medications, heavy alcohol use not excluded because they were not associated with higher levels in their models. Exclusion did not substantially change the percentile estimates.	Black 712(530,894) Hispanic 394(258, 530) Asian 378(185,571) Females 95%tile White 188(122,254) Black 323(218,428) Hispanic 207(176,238) Asian 162(139,185)	
Yeboah J, et al., 2016 (100) 26791059	**Aim:** To assess the predictive accuracy and improvement in reclassification gained by the addition of the coronary artery calcium (133) score to the Pooled Cohort Equation in the Multi Ethnic Study of Atherosclerosis (MESA). **Study Type:** Prospective cohort Study **Study Size:** N=5,185(1402 were African Americans)	MESA participants were free of clinical cardiovascular disease at baseline **Inclusion:** All MESA participants age 40-75y during baseline exam and has complete data **Exclusion:** Older than 75 y, missing data, those taking statins during the baseline examination.	**Primary Outcome:** Composite of myocardial infarction, coronary heart disease–related death, or fatal or nonfatal stroke **Results:** CAC was an independent predictor of atherosclerotic cardiovascular (ASCVD) events. HR(95%CI): 1.58(1.40-1.79), p<0.001 CAC improved the C statistics of the calibrated PCE: 0.74 vs. 0.76, p=0.04. CAC improved Net Reclassification Index (NRI): Event NRI: 0.178(0.080-0.256) and Non-Event NRI: -0.059(-0.075-0.030).	In this Multi-Ethic Cohort which included African Americans, CAC improved ASCVD risk assessment.
Paixao ARM, et al., 2015 (170) 26476504	**Aim :** To assess the effect of coronary artery calcium (133) on coronary heart disease risk prediction in a younger population **Study type:** Prospective cohort study **Study Size:** N=2084(956 were African Americans)	DHS (Dallas Heart Study), a multiethnic probability-based population sample of Dallas County Adults with deliberate oversampling of African Americans. **Inclusion:** All participants free of cardiovascular disease and diabetes mellitus **Exclusion:** Uninterpretable CT scans, prior CHD, End stage renal disease, missing data,	**Primary outcome:** composite of CHD death, myocardial infarction, coronary revascularization after 9.2 y of follow up. **Results:** Mean age 44 y. CAC was an independent predictor of CHD events: HR: 1.90; 95%CI: 1.51-2.38; p<0.0001. CAC improved the C statistics of the base traditional risk factor model: 0.86(0.83-91) vs. 0.89(0.86-0.93), p=0.03. CAC also improved the Net reclassification index of the base model. NRI = 0.216, p=0.012	CAC improved coronary heart disease risk classification in this multi-ethnic younger cohort (included ~46% African Americans)

		incomplete follow up data and diabetes mellitus.		
Carr JJ, et al., 2017 (87) 28196265	**Aim:** To determine if CAC in adults aged 32 to 46 y is associated with incident clinical CHD, CVD, and all-cause mortality during 12.5 y of follow-up **Study type:** Prospective cohort study **Study Size**: N= 3980 had CAC ever measured (1918 were African American).	The Coronary Artery Risk Development in Young Adults (171) study enrolled black and white men and women aged 18-30 y from 3/1985-6/1986. **Inclusion**: All participants who had CT scanning in the CARDIA study **Exclusion:** Participants who died before their 15th recruitment anniversary, unable to be contacted, never had a CT scan and those ineligible for CT scanning: i.e. pregnant, weight above the limit for the CT scan table.	**Primary outcome:** Incident CHD included fatal or nonfatal myocardial infarction, acute coronary syndrome without myocardial infarction, coronary revascularization, or CHD death. Incident CVD included CHD, stroke, heart failure, and peripheral arterial disease. Death included all causes. **Results:** 57 CHD, 108 CVD events occurred CAC vs. CAC=0: For CHD: HR: 5.0; 95% CI: 2.8-8.7; p<0.001 Similar association for CVD For all- cause mortality: HR: 1.6; 95% CI: 1.0-2.6; p=0.05	The presence of CAC among individuals aged 32-46 was independently associated with incident CHD, CVD and death in this cohort which included African Americans.

Data Supplement 25. Nonrandomized Trials, Observational Studies, and/or Registries of Pooled Cohorts Equation Risk Estimation in Adults of Asian Descent (Section 4.5.1)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Cho YK, et al., 2016 (172) 27543305	**Study type:** Retrospective cohort study **Size:** 1,246 1019 male (82%)	**Inclusion criteria:** Adults aged 20-79 y **Exclusion criteria:** CVD; Prescribed statins	**1° endpoint:** Risk Assessment and CAC progression **Results:** The 10-y FRS and 10-y PCE score were significantly higher in CAC progressors than nonprogressors Individuals with PCE score ≥7.5% were more likely to have progression of CAC When compared to those recommended to take a statin under ATP III guideline, subjects considered statin eligible by PCE had a higher OR for CAC progression:	The PCE predicts CAC score progression in a Korean population.

			2.73 (95% CI: 2.07– 3.61) versus 2.00 (95% CI: 1.49–2.68). The PCE predicted CAC progression more accurately than the ATP III guideline (p=0.006)	
Rana JS, et al., 2016 (83) 27151343	**Study type:** Retrospective cohort study **Size:** 307,591 52,917 Asian/Pacific Islander	**Inclusion criteria:** Adults aged ≥21 y; LDL 70-189 mg/dL **Exclusion criteria:** Unknown sex or race/ethnicity; Prescribed statins or other lipid-lowering therapies within 5 y before the index date Prior hospitalization for acute myocardial infarction, ischemic stroke, or receipt of CABG or PCI; <12 mo of continuous membership and pharmacy benefit before the index date (to ensure more complete information on clinical characteristics; <5 y of complete f/u, except if due to death; Missing SBP, TC, or HDL data; Patients who received statins during follow-up if used for primary prevention of ASCVD (i.e., statin initiated before a documented ASCVD event)	**1° endpoint:** Risk Assessment **Results:** Overall observed 5-y ASCVD risk was substantially lower than predicted in each risk category: 0.20% for predicted risk <2.50% 0.65% for predicted risk 2.50 to 3.74% 0.90% for predicted risk 3.75 to 4.99% 1.85% for predicted risk ≥5.00% The observed 5-y ASCVD risk was also lower than predicted in Asian/Pacific Islanders: 0.20% for predicted risk <2.50% 0.75% for predicted risk 2.50 to 3.74% 0.75% for predicted risk 3.75 to 4.99% 1.65% for predicted risk ≥5.00%	The PCE substantially overestimated actual 5-y ASCVD risk in eligible adults without diabetes, known ASCVD and with LDL 70 to 189 mg/dL c-statistic 0.72 for Asian/Pacific Islander
Jung KJ, et al., 2015 (74) 26255683	**Study type:** Retrospective cohort study **Size:** 192,605 114622 males (60%)	**Inclusion criteria:** Adults aged 40-79 y without clinical ASCVD who were registered in the Republic of Korea **Exclusion criteria:** Age <40 ; Receiving lipid-lowering medication at baseline; CVD or stroke; Missing values of variables such as BP, TC, HDL, glucose, smoking status or BMI	**1° endpoint:** Risk Assessment **Results:** The PCE distinguished cases from non-cases. In men, the AUROCs were 0.727; 95% CI: 0.721-0.734; using the white model and 0.725; 95% CI: 0.718-0.731 using the AA model. In women, the AUROCs were 0.738; 95% CI: 0.729-0.746, using the white model and 0.739; 95% CI: 0.731-0.747 using the AA model 10-y ASCVD risk for men was overestimated by 56.5% in the white model and 74.1% in the AA model,	The PCE statistically overestimated the ASCVD event rates observed in a Korean cohort

			10-y ASCVD risk for women was underestimated by 27.9% in the white model and overestimated by 29.1% in the AA model	
Lee CH, et al., 2015 (77) 26350809	**Study type:** Population-based prospective cohort study **Size:** 1753 Male 804 (46%)	**Inclusion criteria:** Chinese men and women aged 25-74 y **Exclusion criteria:** Age<40 y or >79 y; CVD; LDL>190 mg/dl	**1° endpoint:** Risk Assessment **Results:** The AUROC of the PCE was 0.714; 95% CI: 0.657–0.770 in men and 0.765; 95% CI: 0.690–0.840 in women, The AUROC of the Framingham CV risk equation was 0.773, 95% CI: 0.742–0.802, in men and 0.788, 95% CI: 0.724–0.852, in women. The calibration scores of both models were suboptimal	The predictive power of the PCE was poor when applied to the Chinese population in Hong Kong
MASALA Kandula NR, et al., 2014 (173) 25277669	**Study type:** Longitudinal cohort study **Size:** 906 Male 486 (54%)	**Inclusion criteria:** Self-identify as South Asian ethnicity; Speak English, Hindi, or Urdu; 40-84 y **Exclusion criteria:** Clinical ASCVD, HF, pacemaker, current atrial fibrillation, active treatment for cancer; Live in nursing home; Life expectancy < 5y; Impaired cognitive ability; Plans to move out of study region in next 5 y; Weight >300 lbs.	**1° endpoint:** Risk Assessment **Results:** Using the PCE for risk stratification, 49% of South Asian men and 13% of women had a high 10-y predicted risk. The majority of South Asian men (79%) and women (70%) had a high lifetime predicted risk of ASCVD. High 10-y predicted risk was associated with higher CAC prevalence (68%) and greater adjusted odds ratio of CAC (OR: 1.81; 95%CI: 1.0-3.3) compared with low 10-y risk in men. In women, the high 10-y predicted risk group also had a greater CAC burden than women in the low 10-y risk group, but this did not meet statistical significance.	South Asian men and women with high 10-y predicted risk using the PCE had a greater CAC burden than those with low 10-yr risk. South Asians with high lifetime predicted risk had increased odds for CAC higher than 0 (OR: men 1.97; 95% CI: 1.2 to 3.2; women 3.14; 95% CI: 1.5, 6.6).
Chia YC, et al., 2014 (65) 25410585	**Study type:** Retrospective cohort study **Size:** 922 Male 307 (33%)	**Inclusion criteria:** Adults aged 40-79 y without clinical ASCVD who were registered in the outpatient primary care clinic of University Malaya Medical Centre **Exclusion criteria:** Age<40 or >79 y; Lack of all clinical variables to calculate the pooled cohort	**1° endpoint:** Risk Assessment **Results:** High 10-y risk (≥7.5%) with the PCE agreed with FRS >10% in 98% of the subjects The PCE does not appear to overestimate cardiovascular risk as compared to FRS The AUC for the PCE was 0.63.	Overall cardiovascular risk was overestimated as the observed event rate was significantly less than the predicted event rate, but this may be a treatment effect

		risk score; Missing data on the ASCVD event		

Abbreviations: 1° indicated primary; AA African American; ASCVD atherosclerotic cardiovascular disease; ATP, Adult Treatment Panel; AUC area under curve; AUROC area under receiver operating curve; BMI body mass index; CABG coronary artery bypass grafting; CAC coronary artery calcium; CI, confidence interval; CVD, cardiovascular disease; FRS Framingham risk score; HF heart failure; HR, hazard ratio; N/A, not available; OR, odds ratio; PCE pooled cohort equation; PCI percutaneous coronary intervention; RCT, randomized controlled trial; and RR, relative risk; SBP systolic blood pressure; TC total cholesterol.
Search Terms and Date of Search: Risk Calculator, Asians 5/20/2017

Data Supplement 26. Nonrandomized Trials, Observational Studies, and/or Registries of Hispanic (Section 4.5.1)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
MESA Qureshi WT, et al., 2016 (174) 27445216	**Aim:** Compare accuracy of the PCE, modified FRS and the SCORE, and their impact on statin eligibility using the ≥7.5% 10-y risk threshold recommended in the new ACC/AHA cholesterol guidelines. **Study type:** Prospective cohort study **Size:** 6,814 initially 5,654 after exclusion criteria.	**Inclusion criteria:** Adults between 45 and 84 y with no cardiovascular disease. **Exclusion criteria:** Being on cholesterol reducing medication. Missing characteristics (n = 1,160) Characteristics were age, gender, race/ethnicity, family **Intervention:** Calculation of the 10-y risk of incident ASCVD for each individual using FRS, SCORE and PCE. For Hispanics white race estimates were used. Participants were followed from baseline through December 31, 2012. Median follow up of 8.5 y FRS, SCORE and PCE history of coronary artery disease, smoking, measurements of total cholesterol and high-density lipoprotein cholesterol and blood pressure.	**1 endpoint:** Incident of ASCV, composed of fatal and nonfatal myocardial infarction, other fatal and nonfatal coronary heart disease, fatal and nonfatal cerebrovascular disease, and fatal/nonfatal other atherosclerotic disease. 342 (6%) of which 22 % were Hispanic.	· Impact of replacing the PCE with either the modified FRS or the SCORE. Study shows PCE to have the best discrimination. **Limitations** · Not relevant in determining special considerations for Hispanics. Hispanics were not classified by their race and were applied the white race estimates.
MESA	**Aim:** Evaluated the ASCVD risk score	**Inclusion criteria:** Adults between the ages of 45 and 79 y.	**1º endpoint:**	· Overestimation was observed in all race/ethnic groups, men and women

DeFilippis AP, et al., 2017 (71) 27436865	among four different race/ethnic groups and to ascertain which factors are most associated with risk overestimation by the AHA-ACC-ASCVD score. **Study type:** Prospective cohort study **Size:** 6441	**Exclusion criteria:** Adults age 80 and over. Participants with missing data required for risk score calculation (n=53, 1%) or no follow up after baseline (n=3, <1%) **Intervention:** Calculation of the predicted 10 y ASCVD risk. Observation of the 10 y ASCVD. **Comparator:** Discordance between predicted and observed 10 y risk. Impact of individual risk factors on the discordance.	Risk discrimination was similar for women (100%0 and men (93%). Observed rates were roughly half of that predicted by the risk score. Overestimation was highest among Chinese (252% for women and 314% for men) and lowest in White women (72%) and Hispanic men (67%). The lowest discordance between observed and calculated ASCVD event rats was seen in Hispanic men (71%) and women (49%)	**Limitations** · Risk score specifically recommended for White Americans used for Hispanics, not considering that there are White and Black Hispanics.
Rana JS, et al., 2016 (83) 27151343	**Aim:** Evaluated the accuracy of the 2013 ACC/AHA risk equation within a large, multiethnic population in clinical care. **Study type:** prospective **Size:** 307,591 Also identified 4,242 patients that were diabetic and did not have prior lipid-lowering therapy, known ASCVD or any other exclusion criteria. **Duration:** 2008-2013	**Inclusion criteria:** Adults between 40 and 75 y of age. LDL between 70 and 189 mg/dl **Exclusion criteria:** Unidentified sex or race/ethnicity. Having known ASCVD or diabetes. Statin use. Missing systolic blood pressure, total cholesterol or high-density lipoprotein cholesterol information. Compared predicted versus observed 5-y risks of ASCVS events, overall and within sex and ethnic subgroups	1 **endpoint:** Among the patient without diabetes, 2,061 events were observed. Observed incidence was lower that the predicted risk in each category: 0.20% (95% CI: 0.20% to 0.25%) for predicted risk <2.50%; 0.65% (0.55% to 0.70%) for predicted risk 2.50% to <3.75%; 0.90% (0.75% to 1.00%) for predicted risk 3.75% to <5.00%: and 1.85% (1.75% to 1.95%) for predicted risk ≥5.00% Overestimation was similar in both men and women and across the 4 major ethnic groups. Poor calibration reported in each subgroup.	Overestimation was similar in both men and women and across the 4 major ethnic groups. Poor calibration reported in each subgroup. **Limitations** 5 y instead of 10 y FU Poor calibration Hispanics were not classified by their race and were applied the white race estimates.

NHANES Mercado C, et al., 2015 (175) 26633047 Data analyzed from the 2005-2012 surveys	**Study type:** Cross sectional **Size:** 8644 Identify sexual and ethnic disparities on cholesterol treatment for patients that are treatment eligible	**Inclusion criteria:** Adults age 21 and older **Exclusion criteria:** Pregnant women Missing fasting laboratory specimen. Not able to determine treatment eligibility.	**1 endpoint:** Half of treatment eligible adults were receiving cholesterol lowering medication. There were significant differences on treatment eligibility between racial/ethnic groups in (24.2% for Mexican-Americans, 38.4% for whites, and 39.5% for blacks; p<0.001). There were also significant differences on the proportion of adult taking cholesterol lowering medication between racial/ethnic groups. (58.0% for whites, 47.1% for Mexican-Americans, and 46.0% for blacks; p<0.001) Significant differences were also found among men and women and subgroups of age, poverty-to-income ratio, body mass index and presence of diabetes or hypertension. **Results:** Prevalence of cholesterol-lowering medication use among adults eligible for treatment varied within racial/ethnic subgroups, with the lowest prevalence (5.7%) among blacks without health care access and the highest among persons who reported making lifestyle modifications.	Cholesterol use medication lower for Mexican Americans than no Hispanic whites. Cholesterol use medication was lowest among blacks. **Limitations** Adults in nursing homes not included Limited data on estimation of lifestyle modifications. Recall bias. Potential for overestimation of eligibility in following the 2013 ACC/AHA guidelines. Patient taking cholesterol lowering medication included any type of medication. ·More studies are needed to determine disparities and programs are needed to increase screening and management of hyperlipidemia.

Abbreviations: 1 indicated primary; CI, confidence interval; HR, hazard ratio; N/A, not available; OR, odds ratio; RCT, randomized controlled trial; and RR, relative risk; HCHS/SOL Hispanic Community Health Study. /Study of Latinos; ACC/AHA American College of Cardiology/ American Heart Association; ATP Adult Treatment Panel; MESA Multi-Ethnic Study of Atherosclerosis; PCE Poole Cohort Equation; FRS Framingham Risk Score; SCORE Systematic Coronary Risk Evaluation

Search Terms and Date of Search: ASCVD RISK and Hispanic, 6/28/17

Data Supplement 27. Nonrandomized Trials, Observational Studies, and/or Registries of Hispanic (Section 4.5.1)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
HCHS/SOL Qureshi, WT, et al., 2017 (176) 28495699	**Study type:** Cross sectional **Size:** 16415	**Inclusion criteria:** Hispanic/Latino adults aged 18 to 74 y at recruitment, recruited from 4 US metropolitan areas.	**1° endpoint:** Out of 16415 participants. 4160 (26.9%; 95% CI: 25.7-28.0%) were statin eligible under the 2013 ACC/AHA guidelines compared to 2609 (15.9%; 95 CI: 15.0-16.7 %) under the NCEP/ATP III	• Among participants that were eligible the prevalence of statin use was 7.9%; 95% CI: 7.2-8.6%. That is only about one third for ATP III guidelines (28.2%; 95% CI: 26.3-30.0%) and about one fifth for 2013 ACC/AHA guidelines (20.6%; 95% CI: 19.4-21.9%)

	Determine statin eligibility under 2013 ACC/AHA criteria and NCEP/ATP III. Characteristics of Hispanic/Latinos treated and non-treated. Predetermined using black risk estimates for Dominicans, Puerto Ricans, Cuban and central Americans.	**Exclusion criteria:** None **Aim:** Prevalence of statin eligibility among Hispanic/Latinos living in the US under the new 2013 ACC/AHA guidelines. Comparison with NCEP/ATP III guidelines.		It was noticed too that using the 10 y ASCVD risk for White non-Hispanics, one fourth were statin eligible (26.9%; 95% CI: 5.8-28.0%); and using the black coefficient for Dominicans, Puerto Ricans and Central Americans, 28.2%; 95% CI: 27.0-29.4%; were statin eligible, which is a 1.3 % absolute increase in statin eligibility. **LIMITATIONS** Hispanic not well defined. Hispanic is not a race and the study does not take into consideration the race. Hispanics are classified by geographical area, not by ancestry.
HCHS/SOL Mattei J, WT, et al., 2016 (177) 27605403	**Study type:** Cross sectional **Size:** 12,406	**Inclusion criteria:** Hispanic/Latino, aged 18 -74 free of diabetes. (Multicenter population-based) **Exclusion criteria:** Diabetes, self-report or in the laboratory values. Aimed to compare diet quality, using AHEI, Range 0-110 lowest to highest quality. With the association of MetS and its cardiometabolic components across 6 groups of Hispanic/Latinos. Mexicans Puerto Ricans Cuban Dominicans Central Americans South Americans	**1° endpoint:** The prevalence of Metabolic Syndrome was 23.2% overall. Adjusted odds (95% CI) of having MetS were 22% (9%-33%) lower for each 10 – unit increase in AHEI. **Results:** Adjusted mean AHEI differed by ethnic background ($p<0.001$), ranging from 43.0 for Puerto Ricans to 52.6 for Mexicans. Lower odds observed only for Mexicans (30%; 95%CI: 13%, 44%) and Central Americans (42%; 95% CI: 9%, 64%). AHEI inversely associated with waist circumference, blood pressure and glucose among Mexicans and Puerto Ricans and with triglycerides among Mexicans only.	• Diet varies with Hispanic/Latino background. This is important because a healthier diet is associated with lower odds of MetS. Association of AHEI and cardio metabolic risk factors, varies by ethnic background. • The conclusion of the studies is that research and interventions should be different among ethnically diverse groups. There is a need to consider individual ethnic backgrounds to optimized results. • CVD prevention strategies should address the fact that Hispanics have high rates of multiple risk factors and that interventions should differ by individual ethnic background. • Ethnicity-specific analysis helps clarify inconsistent results of diet-disease association in Hispanics as a group and it will help tailor disease prevention. Suggest types of foods and nutrients targeted for specific ethnic groups.

		Previous studies reported one ethnicity or put them all together	AHEI positively associated HDL cholesterol among Puerto Ricans and Central Americans (all p<0.05) Most ethnicities had unhealthy intake of sugar-sweetened beverages, and fruit juices, whole grains and whole fruit and favorable intakes of trans fats and nuts and legumes. It helps understand why previous studies have inconsistent results. Understand ethnic differences in diet and health and direct culturally appropriate diet quality components	Overall reinforce reducing sugar sweetened beverages and increasing whole grains and fruits. Reduce sodium intake among Cubans, Increase vegetable intake among Puerto Ricans AVOID GENERALIZATIONS on diet and cardiometabolic health for Hispanics. Variation of diet among geographical areas but it was consistently best for Mexicans and poor for Puerto Ricans. LIMITATIONS Cross sectional Recall bias AHEI is a measurement that is not specific for Hispanic population
HCHS/SOL Daviglus ML, et al., 2016 (178) 27543802 HCHS data allow a level of granularity in examining the US Hispanic/Latino population by ethnic background and other characteristics that was not available previously.	**Study type:** cross sectional **Size:** 14,757 Aims to determine the prevalence of Low cardiovascular risk profile among Hispanics and its association with acculturation. (SASH short acculturation Scale for Hispanics) Low cardiovascular risk was defined by favorable levels of serum cholesterol, blood pressure and BMI and by not having diabetes and not currently smoking.	**Inclusion criteria:** adults aged 18 to74 Hispanic/Latino background and free of CVD **Exclusion criteria:** CVD or diabetes Missing data for LR Lack of self-identification as any of the 6 Hispanic backgrounds.	**1° endpoint:** Prevalence of LR profile among Hispanics is low, (8.4% overall; 5.1% for men, 11.2% for women), and varied by background, (4.2% for Mexican men versus 15.0% in women of Cuban heritage). Acculturation is associated with higher odds of a LR only among women. **Results:** OR of having LR were 1.64% (95% CI: 1.24-2.17) for foreign born versus US-born women and 1.96 (95% CI: 1.49-2.58) for women residing in the US less than 10 y versus 10 or more years. Lack of current smoking the most predominant favorable risk factor. LR was higher among women	• Prevalence of LR is low • Lower acculturation is associated with higher odds of a LR profile among women but no men. • In general, LR adults were younger and more educated. • Variations across Hispanic backgrounds. Men with Dominican and Mexican background had the lowest LR prevalence. Women with Puerto Rican background had the lowest rate of favorable risk factors. Almost 1 in 4 Hispanic adult men and women (ranging from 15% Puerto Rican women to 36% South American men) have unfavorable or borderline risk status. This together with the fact that almost half of men and more than half of women have no health insurance, points to the need of developing public health initiatives to lower CVD risk in this growing population.

				Further research need to understand acculturation.
HCHS/SOL Qi, Q, et al., 2015 (107) 26416808	**Study type:** Cross sectional **Size:** 12,083	**Inclusion criteria:** adults aged 18 to74 Hispanic/Latino background Complete data on cardiometabolic biomarkers **Exclusion criteria:** Not adherent to accelerometer protocol **UNIQUE CONTTRIBUTIONS** -Objectively measured, not self-reported -Differences between Hispanic/Latino background groups. -Analysis stratified by physical activity.	**1° endpoint:** sedentary lifestyle associated with decreased HDL cholesterol, cholesterol and increased blood pressure, elevated TG, 2-H glucose, fasting insulin, HOMA-IR and CRP (all p for trend p<0.0001) After adjustment for MVPA, association attenuated but still significant for HDL cholesterol (p=0.04), triglycerides (p<0.0001), 2-H glucose (p<0.0001), fasting insulin (p<0.0001), and HOMA-IR (p<0.0001). After further adjustment for BMI and waist to hip ratio, only the association with elevated TG, 2-H glucose, fasting insulin, and HOMA-IR (p<0.0001) remain significant. Even among those who met physical activity guidelines, sedentary lifestyle was detrimentally associated with several cardiometabolic biomarkers (diastolic blood pressure, high-density lipoprotein cholesterol, fasting and 2-H glucose, fasting insulin and homeostatic model assessment of insulin resistance; all p<0.05). **Results:** Strong association between sedentary behavior and cardiometabolic risk. Across Hispanic/Latino background groups.	• Association between sedentary life and elevated TG and insulin resistance. No association with blood pressure or cholesterol levels. • Need to reduce sedentary behaviors for the prevention of cardiometabolic disease, even among those who meet physical activity guidelines. **LIMITATIONS** Accelerometers placement and not discernment between sitting and standing up. Epoch length Self-reporting of some cardiovascular risk factors Cross sectional…….
Kershaw K, et al., 2012 (179) 23036519	**Study type:** Cross sectional **Size:** 8693	**Inclusion criteria:** **Exclusion criteria:** missing data on study covariates, pregnant women.	**1° endpoint:** No differences in low risk among foreign born Mexican-Americans versus non-Hispanic White Americans when adjusted for sex and age (OR: 0.90; 95% CI: 0.62-1.33).	•HEALTHY MIGRANT HYPOTHESIS Foreign born Mexican-Americans more likely to be low risk than Whites when adjusting for education and insurance status. Healthier, but education and insurance suppresses this, and

	Ethnic and nativity related differences in the prevalence of low cardiovascular risk and its relationship with acculturation, socioeconomic position and lifestyle.	HEI Healthy Eating Index form 2005 US Department of Agriculture. 0-100 0-50 poor 51-80 needs improvement >80 good Only 1% good poor vs. needs improvement	When adjusted for education odds of being low risk was 1.40 (95% CI: 0.92, 2.12) higher for foreign born Mexican-Americans versus non-Hispanic Whites. Unchanged after adjusting for diet and physical activity. When adjusted for sex and age, being low risk was lower (OR: 0.49; 95% CI: 0.34, 0.71) among US-born Mexican-American compared to non-Hispanic Whites. Adjustment for education attenuates the difference but remains significant (OR: 0.59; 95% CI: 0.41, 0.84). Language of the questionnaire not associated with low risk, but language spoken at home is Spanish versus English or a mixture of Spanish and English (OR: 2.25; 95% CI: 1.20-4.23) The language spoken at home attenuated the association between low risk and nativity Living less than 10 y foreign born Mexican-Americans are more likely to be low risk than US born Mexican-Americans 4.30 (95% CI: 2.61-7.10). Living more than 10 y decreased the ratio to 1.61 (95% CI: 0.99-2.61) **Results:** Low CV risk prevalence among men was less common for US born Mexican-Americans and non-Hispanic Whites. Low CV risk	makes that without adjusting there is no difference in low risk between Mexican-Americans and Whites • In contrast disparities between US born Mexican Americans and Whites persist after adjusting, suggesting that there are other factors, like discrimination and the stress associated with acculturation. Language associated with close communities, where there might be less discrimination and more support. • Ethnic and nativity variations • Effect of acculturation **LIMITATIONS** Cross sectional, so it does not capture changes over time. Measure of acculturation. Influence of discrimination not measured.

			prevalence among women was less common for foreign born and US born Mexican-American versus non-Hispanic Whites. Acculturation attenuates the effect of nativity.	

Abbreviations: 1° indicated primary; CI, confidence interval; HR, hazard ratio; N/A, not available; OR, odds ratio; RCT, randomized controlled trial; and RR, relative risk.
HCHS/SOL, Hispanic Community Health Study/Study of Latinos; ACC/AHA, American college of cardiology/American Heart Association; NCEP/ATP III 3rd National cholesterol Education Program Adult Treatment Panel; MetS M, metabolic syndrome; AHEI, Alternate Healthy Eating Index; LR, low risk; CVD, cardiovascular disease; LDL low density lipoprotein; HDL, High Density Lipoprotein; BMI, Body Mass Index, HOMA – IR Homeostatic Model Assessment of Insulin Resistance; CRP, C-reactive protein; CV, cardiovascular; NHANES, National Health and Nutrition Examination Survey
Search Terms and Date of Search: Cholesterol guidelines and Hispanic, 6/28/17

Data Supplement 28. Nonrandomized Trials, Observational Studies, and/or Registries of Hispanic (Section 4.5.1)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Yoshida YX, et al., 2016 (180) 27524787	**Study type:** Cross sectional **Size:** 622 Association of nutrition recommendations by ADA with sociodemographic factors and acculturation in Hispanic patients Nutrition is an important factor in cardiovascular risk prevention	**Inclusion criteria:** Hispanic, 20 y or older, with a previous diagnosis of diabetes. **Exclusion criteria:** NA Diet recommendation based on daily intake of saturated fat, cholesterol sodium, fiber and alcohol intake Acculturation measured based on spoken language, country of birth and number of years in the US	**1° endpoint:** Only 51%, 18% and 38% of HA with diabetes met saturated fat, fiber and sodium intake recommendations. Female HA were more likely to reach recommendations for cholesterol and sodium intake. The lowest achievement was among individuals between the ages of 20 to 45 y. **UNEXPECTED RESULTS** Low education had higher frequencies of meeting, fat, fiber , sodium, and three or more target recommendations No insurance and public insurance had higher frequencies of meeting fiber, sodium, and alcohol intake target recommendations. Poverty had higher frequency of meeting fiber, sodium, and three or more criteria.	•Only 49% of Hispanic met 3 recommendation criteria. Poor recommendation adherence associated with male gender and younger age (equal or less than 45). • Female HA with diabetes more likely to achieve recommendation for cholesterol sodium and alcohol intake. • Older HA with diabetes more likely to achieve recommendation for fiber, sodium and three or more recommendations. Interesting positive association with low socioeconomic status, lack of insurance and lower education. **LIMITATIONS** -Cross sectional (not causality)

			Results: Male lower odds to achieve daily cholesterol and sodium reductions recommendations than female (OR: 0.3; CI: 0.1– 0.5 and OR: 0.4; CI: 0.2–0.6, respectively). Age between 45-60 and over 60 higher odds of achieving dietary fiber and sodium recommendations than younger than 45 (OR 4.0; CI: 2.0–7.9 and OR: 6.2; CI: 3.2– 11.9, respectively) Highest income 50% lower odds of meeting dietary fiber recommendation than individuals under the poverty line (OR1: 0.5; CI: 0.2-0.9) Lower odds for acculturated individuals to achieve saturated fat (OR: 0.5; CI: 0.2–0.7), fiber (OR: 0.5; CI: 0.2– 0.9), sodium (OR 0.5; CI: 0.3–0.9) and cholesterol intake (OR 0.5; CI: 0.3–0.8) recommendations than less acculturated individuals	-Self reported, so individuals with undiagnosed diabetes not included. Not motivated for diet if not diabetic ·Type I and II -Study does not include undocumented immigrants. Female and older ROLE OF FAMILY IN HISPANIC CULTURE important to develop programs
Rana JS, et al.,2016 (83) 27151343	**Study type:** Prospective cohort **Size:** 307,591 subset of 4/242 with diabetes	**Inclusion criteria:** Adults 40-75 **Exclusion criteria:** Known ASCVD, diabetes mellitus, LDL less than 70 or more than 190, prior use of lipid lowering therapy or incomplete 5 y follow up. Sex or race. Ethnicity unknown missing criteria	**1° endpoint:** Observed 5-y ASCVD incidence was lower than the predicted risk in each category: 0.20% vs. 1.04% (95% CI: 0.20 to 0.25) for predicted risk <2.50%; 0.65% vs. 3.08% (95% CI: 0.55 to 0.70) for predicted risk 2.50% to <3.75%; 0.90% vs. 4.34% (95% CI: 0.75 to 1.00) for predicted risk 3.75% to <5.00%; and 1.85% vs. 8.72% (95% CI: 1.75 to 1.95) for predicted risk ≥5.00% **Results:** Overestimation and poor calibration with moderate discrimination observed in sex, racial/ethnic, and socioeconomic status subgroups (C statistic: 0.68 to 0.74)	•Overestimation across gender, ethnic/race groups and socioeconomic status **LIMITATIONS** 5 y

			Better calibration for adults with diabetes but worse discrimination	
Rivera-Hernandez M, et al., 2016 (181) 27111865	**Study type:** Cross sectional **Size:** 7.35 million MA enrollees Of those 14/4% were Hispanic. 25.1% of all Hispanic reside in Puerto Rico, more than in any state. (99% of Puerto Ricans self-identify as Hispanic.)	**Inclusion criteria:** MA enrollees. **Exclusion criteria:** -Younger than 65 -Enrollees that were not Hispanic or non-Hispanic White -Not residents in Puerto Rico or the United States -Puerto Ricans enrolled in an MA plan outside of Puerto Rico -Puerto Rican residents who were not Hispanic	**1° endpoint:** For 15 of the 17 measures, MA enrollees in Puerto Rico, received worse care than Hispanics in the United States. BP control was worse for Hispanics in Puerto Rico versus Hispanics in the United States by 5.3% percentage points (95%CI: -9.7to -0.8) **Results:** Measures related to cardiovascular disease. 1. LDL screening among persons with ischemic heart disease 2. LDL levels less than 100 among persons with ischemic heart disease 3. Beta blocker use 6 mo following MI 4. Blood pressure less than 140/90 among persons with Hypertension	• Slight differences between white and Hispanic MA enrollees in the United States but it was substantially worse for enrollees in Puerto Rico.
Adedinsewo D, et al., 2016 (182) 27505443	**Study type:** cross sectional **Size:** 5319 Prevalence of statin use for adults with diabetes mellitus and dyslipidemia. (defined as low density lipoprotein equal or over 70); defined as statin benefit group 1 (SBG1) and adults with atherosclerotic cardiovascular disease, defined as statin benefit group 2 (SBG2)	**Inclusion criteria:** Adults 20 y and older who completed the interview **Exclusion criteria:** NA	**1° endpoint:** Uninsured and Hispanic persons were less likely to be on statin compared to non-Hispanic whites (ORs 0.33 and 0.70 respectively) (no CIs reported) **Results:** Persons in SBG1 and persons in SBG2 were as likely to be on a statin (ORs 4.15 and 4.96, respectively) (no CIs reported) Uninsured and Hispanic persons were less likely to be on statin compared to non-Hispanic whites (ORs 0.33 and 0.70 respectively) (no CIs reported) There was no significant difference between non-Hispanic whites and non-Hispanic blacks.	• Hispanic ethnicity and lack of insurance remain barriers to statin use.

Abbreviations: 1° indicated primary; CI, confidence interval; HR, hazard ratio; N/A, not available; OR, odds ratio; RCT, randomized controlled trial; and RR, relative risk. NHANES, National Health and Nutrition Examination Survey; ADA< American Diabetes Association; US, United States; HA Hispanic American; ASCVD Atherosclerotic cardiovascular disease; LDL, Low density lipoprotein; MA, Medicare Advantage; HEDIS Healthcare Effectiveness Data and Information set; MI, myocardial infarction;
Search Terms and Date of Search: Cholesterol treatment and Hispanic, 6/28/17

Prevalence and Factors Associated With Statin Use Among a Nationally Representative Sample of US Adults: National Health and Nutrition Examination Survey, 2011-2012.
Another major knowledge gap is the lack of accurate ASCVD risk estimation specific to persons of Asian/Pacific Islander and Hispanic ethnicities, who are currently combined with the white population in the Pooled Cohort Risk Equation

Data Supplement 29. Nonrandomized Trials, Observational Studies, and/or Registries of Hispanics (Section 4.5.1)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
HCHS/SOL Daviglus M, et al., 2014 25242694	**Study type:** cross sectional **Size:** 5079 Study the burden of CV risk factors among HL Compare with previous studies done in MA	Participants of the HCHS/SOL	**Results:** HTN NHANES data MA lower prevalence among MA HCHS/SOL Dominican men highest prevalence of HTN followed by Puerto Rican women SA, both men and women, had the lowest rates. Awareness, rate of treatment and control vary by group, lowest for Central Americans Hypercholesterolemia HCHS/SOL Mean levels higher for HL than non-Hispanic whites and blacks. Highest for CA men and Puerto Rican women Diabetes Higher rates for HL in the NHANES HCHS/SOL Similar rates for all groups as a whole Highest for MA men and Puerto Rican women, lowest for SA men and women Obesity HCHS/SOL Highest for Puerto Rican women and lowest for SA women Smoking HCHS/SOL Higher rates of smoking than National average	• Large proportion of men and women (80% and 71% respectively) have at least one major CVD risk factor • Prevalence of 3 or more CV disease RF was highest among Puerto Ricans. • Prevalence of 3 or more CV disease RF higher among participants with lower education. • Acculturation associated to higher levels of CV RF BURDEN OF CV RISK FACTORS Marked variations HETEROGENEICITY OF HISPANIC GROUPS IS THE CONCLUSION OF THIS STUDY Previous studies underestimated the CVD burden and masked heterogeneity Rates in general higher The risk factors highly prevalent among HL are in this order MEN Hypercholesterolemia Obesity HTN Smoking WOMEN Obesity Hypercholesterolemia HTN

			Highest for men of Puerto Rican and Cuban background	
HCHS/SOL Daviglus M, et al., 2012 (183) 23117778	**Study type:** Cross sectional **Size:** 15079 RF association with CHD and stroke	Participants of the HCHS/SOL	**Results:** Same as above in RF distribution HTN and smoking associated with CHD In both sexes , hyperlipidemia and obesity in women and diabetes in men (ORs 1.5-2.2) HTN associated with stroke in both sexes, smoking in women and diabetes in men (ORs 1.7-2.6)	• Adverse CVD risk profile was higher among participants with Puerto Rican background, lower SES and higher levels of acculturation
HCHS/SOL Schneiderman N, et al., 2014 (184) 25212986	**Study type:** **Size:** 16415	Participants of the HCHS/SOL	**Results:** Diabetes associated with CHD and stroke Diabetes prevalence varied by group Less awareness and less control MetS significant variability in prevalence among participants of different HL background. Puerto Rican women highest prevalence and SA women the lowest. Prevalence increased with age Obesity, among HL women more likely to be obese than men HTN significant variability among groups, highest among Dominican men and lowest among SA women. Difference across geographical location. No variation with education level or income. Less awareness and control. Sleep disorders, unawareness and lack of treatment in consequence Smoking Highest among Puerto Ricans and Cuban Nutrition Puerto Ricans and Dominicans reported higher intakes of foods that are a risk for CVD and the opposite for SA	To be successful in preventing CVD among HL we need to understand the diversity within this population. Target of specific groups Attention to Access to health care and Lifestyle variables to lighten the burden of CVD RF and disease burdens among HL

Abbreviations: 1° indicated primary; CI, confidence interval; HR, hazard ratio; N/A, not available; OR, odds ratio; RCT, randomized controlled trial; and RR, relative risk; HCHS/SOL, Hispanic Community Health Study/Study of Latinos; NHANES, Hispanic Health and Nutrition Examination; CV, cardiovascular; CVD, cardiovascular Disease; HL, Hispanic/Latino; MA, Mexican-American; SA, South American; CA, Central American; RF Risk factors; HTN, Hypertension; MetS, Metabolic Syndrome
Search Terms and Date of Search: Cardiovascular disease risk factors and Hispanic

Data Supplement 30 Nonrandomized Trials, Observational Studies, and/or Registries of Hispanic (Section 4.5.1)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
HCHS/SOL Arguelles W, et al., 2015 (185) 25745986	**Study type:** cross sectional **Size:** 15,825 To see if distinct subtypes of MetS could be identified and how these subtypes relate to CVD prevalence	HCHS/SOL participants Excluded participants who had missing data on HL background or self-reported as more than one heritage Covariates: age, sex, HL background, smoking, family History of CHD and stroke, education and family income	**Results:** Including covariates, changed classification, more individuals classified as MetS. 1. Being older (OR: 1.32 for men and OR: 1.29 for women) and having family history of CHD (OR: 1.12 for men and OR: 1.16 for women) increases the odds of belonging to the MetS cluster. 2. Being of SA compared to Mexican descent associated with lower odds (OR = 0.46 for men and 0.61 for women) of belonging to the MetS cluster 3. In women, Lower education (OR:0.77), lower income (OR:0.87), never smoking (OR: 0.72) and being Puerto Rican compared to Mexican descent associated with higher odds of belonging to the MetS cluster (OR: 2.01) This is consistent with previous studies, except for the non-smoking. Family History of stroke and other backgrounds did not affect classification Mexicans had the highest prevalence of MetS in MESA< followed by Puerto Ricans	• Unable to distinguish subtypes of MetS in HL. • waist circumference cut off may not optimize diagnosis for HL women (Elevated WC among HL women with an otherwise healthy CV profile, clustered in the non-MetS Ethnic specific cut offs? Aschner et al. (reference) suggest 90 cm instead of 88 cm, but this reduces de prevalence by only 1-2%) • HDL differentiates poorly between US HL with and without MetS (mean= 45.4 vs. 44.6 mg/dL for men and 51.3 vs. 52.0 mg/dL for women) CURRENT CRITERIA MAY NOT OPTIMIZE DIAGNOSIS OFMETABOLIC SYNDROME AMONG HL NOT CONSENSUS in the role of MetS as screen for risk of CV disease. Use individual cardiovascular risk factors, whether they occur alone or in clusters.
HCHS/SOL Heiss G, et al., 2014 (184) 25061141	**Study type:** cross sectional **Size:** 16,319 Prevalence of MetS higher among HL, but unknown	HCHS/SOL participants Excluded participants who had missing data on HL background or self-reported as more than one heritage	**Results:** Different prevalence by age, sex and HL background Worse with age. Increased more with age for women Highest among Puerto Rican women and lowest among women and men SA.	• Prevalence of MEtS higher for HL than non-white but varies with age, sex and HL background • Abdominal adiposity is the main contributor for women. WC cutoff discussion need for sex race and ethnic specific thresholds.

	variation by HL background 34% in men and 36% in women		Abdominal obesity was higher in women than men (96% vs. 73%). Hyperglycemia was worse among men than women (73% vs. 62%)	• Not consensus in the role of MetS as screen for risk of CV disease. Use individual cardiovascular risk factors, whether they occur alone or in clusters.
HCHS/SOL Llabre MM, et al., 2015 (185) 25818844	**Study type:** Cross sectional **Size:** 15.823 PREVIOUS STUDIES Most studies before on Mexican-American. MESA showed that Mexican-American had a higher prevalence of MetS compared to Puerto Ricans. Hispanic higher incidence of obesity, diabetes and elevated TG and low HDL, but HDL does not predict myocardial infarction in HL. HTN lower. CVD lower among Mexican- Americans, Do RF and cut off values apply to HL?	HCHS/SOL participants Excluded participants who had missing data on HL background or self-reported as more than one heritage	**Results:** Of all the indicators HDL has the weakest association with the others No variation in clustering among subgroups Association with diabetes OR: 2.39 (95% CI: 2.25-2.55) for men and OR: 2.78 (95% CI: 2.60-2.97) for women. The odds of having diabetes with MetS increase by 130 % both for men and women. Association with CHD OR: 1.18 [95% CI: 1.08-1.29] for men and OR: 1.22 (95% CI: 1.11-1.35) for women. The odds of having CHD with MetS increase by 20% for both men and women.	• Current indicators of MetS cluster together in HL. Similarity for men and women, except for BP, stronger indicator for women. • HDL does not cluster together as strong as the other risk factors that define MetS. HDL is a weak indicator. (UNEXPECTED) Correlation with cardio protection not seen in HL. Not all components equally important for HL • Not difference across HL ancestry groups for the components of MetS. The cluster of risk factors is comparable across subgroups. DESPITE what it was shown in the study by Heiss et al prevalence of MetS different for groups but the clustering does not vary • MetS associated with CHD and Diabetes. Needs studies to determine sensitivity and specificity of cut-points for HL

Abbreviations: 1° indicated primary; CI, confidence interval; HR, hazard ratio; N/A, not available; OR, odds ratio; RCT, randomized controlled trial; and RR, relative risk. HCHS/SOL, Hispanic Community Health Study/Study of Latinos; HL, Hispanic/Latinos; US, United States; MetS, Metabolic Syndrome; SA, South American; WC< waist circumference; HDL, High Density Lipoprotein; NCEP ATP, National Cholesterol Education Program Adult Treatment Panel; CHD, Coronary Heart Disease; MESA, Multi-ethnic Study of Atherosclerosis;
Search Terms and Date of Search: Metabolic syndrome and Hispanic

Data Supplement 31. Hypertriglyceridemia: RCT, Meta Analyses (4.5.2)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
HOPE-3 Yusuf S, et al., 2016 (12) 27040132	**Aim**: Assess impact of moderate intensity statin on ASCVD risk in an intermediate risk population Double blind RCT N=12,705	**Inclusion criteria**: Men age ≥55 y and women ≥ 65 y with at least one of the following cardiovascular risk factors: elevated waist-to-hip ratio, history of a low level of HDL-C, current or recent tobacco use, dysglycemia, family history of premature coronary disease, and mild renal dysfunction. Also enrolled women age 60 y or older with at least two of the above risk factors. **Exclusion criteria**: 1. Clinical atherothrombotic CVD 2. Symptomatic hypotension 3. Chronic liver disease 4. Inflammatory muscle disease creatine kinase (CK > 3 x ULN) 5. Moderate renal dysfunction defined as serum creatinine > 2.0 mg/dL (180µmol/L) or eGFR <45ml/min/1.73m² 6. Treatment with cyclosporine or fibrates	Rosuvastatin 10 mg daily (6361 subjects) vs. Placebo (6344 subjects) followed over a median of 5.6 y	**Co-primary endpoints**: 1. Composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. 2. Revascularization, heart failure, and resuscitated cardiac arrest. **Results**: 1. Composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke occurred in 235 subjects (3.7%) in the rosuvastatin group and in 304 subjects (4.8%) in the placebo group (hazard ratio, 0.76; 95% CI: 0.64 to 0.91; p=0.002; NNT 91) 2. Revascularization, heart failure, and resuscitated cardiac arrest occurred in 277 subjects (4.4%) in the rosuvastatin group and in 363 subjects (5.7%) in the placebo group (HR: 0.75; 95% CI: 0.64 to 0.88; p<0.001; NNT 73) 3. Median predicted 5-y major vascular event rate in placebo group for first co-primary endpoint: 4.28%; for secondary co-primary endpoint: 5.09%	NA
Frick MH, et al., 1987 (Frick, 1987 #3268) 3313401	**Aim:** To assess the effect of gemfibrozil therapy on incident cardiac events.	**Inclusion criteria:** Finnish men age 40-55y with no clinical cardiovascular disease and	**Intervention/Comparator** Gemfibrozil 600 mg twice daily (2051 subjects) vs. placebo (2030	**1ºendpoint:** Fatal and non-fatal myocardial infarction and cardiac death. **Results:**	No increase in incidence of cancer or total mortality

	Study Type: Placebo controlled, double blind RCT N=4081	non-HDL-C ≥200 mg/dL on 2 successive measurements. **Exclusion criteria:** Clinical coronary heart disease, electrocardiographic abnormalities or other diseases that would impact study outcomes.	subjects) over a mean follow-up period of 60.4 mo.	1. Incidence of cardiac endpoints in gemfibrozil group was 27.3/1000 person-y vs. 41.4/1000-person y in the placebo group (p<0.02). 2. 10% reduction in LDL-C, 14% reduction in non-HDL-C; 43% reduction in triglycerides. 3.Median predicted 5-y incidence of fatal and non-fatal MI and cardiac death 4.1% in the placebo group.	
VOYAGER Nicholls SJ, et al., 2010 (Nicholls, 2010 #3272) 20102893	**Aim**: To assess dose-dependent reductions in levels of atherogenic lipids /lipoproteins in statin-treated patients. **Study Type**: Individual patient data pooled analysis N= 32,258	**Inclusion criteria**: 37 studies assessing fasting atherogenic lipids/lipoproteins in studies involving fixed-dose comparisons of rosuvastatin with either atorvastatin or atorvastatin and recording data at baseline and on therapy for which individual patient data were available. **Exclusion criteria**: N/A	**Intervention/Comparator**: Lipids/lipoproteins in subjects taking rosuvastatin vs. atorvastatin v. simvastatin	**Results**: 1. Doubling the dose of each statin resulted in a 4-7% greater reduction in all atherogenic lipids/lipoproteins 2. Mean reduction in non-HDL-C with moderate intensity simvastatin, atorvastatin or rouvastatin was ≥30.1%	N/A
Cholesterol Treatment Trialists Collaborators 2012 (Cholesterol Treatment Trialists, 2012 #3245) 22607822	**Aim**: To assess the effect of statin therapy on incident ASCVD in "low risk" individuals. **Study Type**: Meta-analysis of individual participant data from statin RCT ASCVD outcomes trials N=174,179	**Inclusion criteria**: Major statin primary prevention trials with at least 1,000 participants with 5-y risk of major vascular events of <10%, with a minimum follow-up of 2 y. **Exclusion criteria**: N/A	**Intervention/Comparator**: 22 RCT's statin versus control (N=134,537, median follow-up 4.8 y) and 5 RCT's of more versus less statin (N=39,612, median follow-up 5.1 y)	**1º endpoint**: Effect of statin therapy on non-fatal MI or coronary death, strokes or coronary revascularization, cancer incidence and cause-specific mortality. **Results**: 1. Statins reduce the risk of vascular events (relative risk 0.79, 95% CI: 0.77-0.81) irrespective of age, gender, baseline LDL-C or previous vascular disease and of vascular and all-cause mortality 2. Specifically in the intermediate risk group (5- to <10 % 5 y risk) the relative risk reduction with statins was 0.69 (99% CI: 0.60-0.79) 3. Reported 5 y major vascular event rates in statin RCT's:	N/A

				JUPITER: 4.4%; AFCAPS/TEXCAPS: 5.2%; ASCOT-LLA: 8.1% 4. Statin therapy had no effect on cancer incidence, cancer mortality or other non-vascular mortality	

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
VOYAGER Nicholls SJ, et al., 2010 (186) 20102893	**Aim**: To assess dose-dependent reductions in levels of atherogenic lipids/lipoproteins in statin- treated patients. **Study Type**: Individual patient data pooled analysis N= 32,258	**Inclusion criteria**: 37 studies assessing fasting atherogenic lipids/lipoproteins in studies involving fixed-dose comparisons of rosuvastatin with either atorvastatin or atorvastatin and recording data at baseline and on therapy for which individual patient data were available. **Exclusion criteria**: N/A	**Intervention/Comparator**: Lipids/lipoproteins in subjects taking rosuvastatin vs. atorvastatin v. simvastatin	**Results**: 1. Doubling the dose of each statin resulted in a 4-7% greater reduction in all atherogenic lipids/lipoproteins 2. Mean reduction in non-HDL-C with moderate intensity simvastatin, atorvastatin or rouvastatin was ≥30.1%	N/A
Cholesterol Treatment Trialists Collaborators 2012 (121) 22607822	**Aim**: To assess the effect of statin therapy on incident ASCVD in "low risk" individuals. **Study Type**: Meta-analysis of individual participant data from statin RCT ASCVD outcomes trials N=174,179	**Inclusion criteria**: Major statin primary prevention trials with at least 1,000 participants with 5-y risk of major vascular events of <10%, with a minimum follow-up of 2 y. **Exclusion criteria**: N/A	**Intervention/Comparator**: 22 RCT's statin versus control (N=134,537, median follow-up 4.8 y) and 5 RCT's of more versus less statin (N=39,612, median follow-up 5.1 y)	**1º endpoint**: Effect of statin therapy on non-fatal MI or coronary death, strokes or coronary revascularization, cancer incidence and cause-specific mortality **Results**: 1. Statins reduce the risk of vascular events (relative risk 0.79; 95% CI: 0.77-0.81) irrespective of age, gender, baseline LDL-C or previous vascular disease and of vascular and all-cause mortality	N/A

				2. Specifically in the intermediate risk group (5- to <10 % 5 y risk) the relative risk reduction with statins was 0.69 (99% CI: 0.60-0.79) 3. Reported 5 y major vascular event rates in statin RCT's: JUPITER: 4.4%; AFCAPS/TEXCAPS: 5.2%; ASCOT-LLA: 8.1% 4. Statin therapy had no effect on cancer incidence, cancer mortality or other non-vascular mortality	
Cholesterol Treatment Trialists Collaborators 2010 (Cholesterol Treatment Trialists, 2010 #3244) 21067804	**Aim**: Assess the safety and efficacy of more intensive statin therapy. **Study Type**: Meta-analysis of individual participant data from statin RCT with ASCVD outcomes **N**=169,138	**Inclusion criteria**: Major statin primary and secondary prevention trials with at least 1000 participants with a minimum follow-up of 2 y, including trials of more versus less intensive statin regimens (five trials; 39, 612 subjects; median follow-up 5.1 y) and statin versus control (21 trials; 129 526 subjects; median follow-up 4.8 y). **Exclusion criteria:** For acute coronary syndrome subjects, revascularization not related to recurrent ischemia or occurring <30 d from the time of randomization	**Intervention/Comparator**: Statin versus control More intense versus less intense statin	**1º endpoint**: Cause-specific mortality, major coronary event defined as coronary death or non-fatal MI percutaneous coronary intervention or bypass grafting), stroke (subdivided by type), and new cancer diagnosis (subdivided by site). **Results**: 1. More intensive versus less intensive regimens produced a 15% (95% CI: 11-18; p<0.0001) further reduction in major vascular events, including a 13% (95% CI: 7-19; p<0.0001) further reduction in coronary death or non-fatal MI, a 19% (95% CI: 15-24; p<0.0001) reduction in coronary revascularization, and a 16% (95%CI: 5-26; p=0.005) in ischemic stroke 2. For every 39 mg/dL reduction in LDL-C, there was a 22% (rate ratio 0.78; 95% CI: 0.76-0.80; p<0.0001) reduction in the relative risk of major vascular events. 3. All-cause mortality was reduced by 10% for every 39 mg/dL LDL-C reduction (rate ratio 0.9; 95% CI: 0.87-0.93; p<0.0001) primarily due to reduction in coronary heart disease death (risk ratio 0.8, 99% CI: 0.74-0.87;	N/A

				p<0.0001) and other cardiac causes (risk ratio 0.89; 99% CI: 0.89-0.98; p=0.002). 3. No effect on death due to stroke or other vascular causes and no effect on death due to cancer, death from non-vascular causes or on cancer incidence	
MARINE Trial Bays HE, et al., (187) 21683321	**Aim:** to investigate the efficacy and safety of omega-3 EPA ethyl ester in reducing triglyceride levels and other lipid parameters in patients with fasting triglycerides ≥ 500 in mg/dL in patients treated with omega 3 EPA ethyl ester or placebo **Study Type**: Multi-center, placebo-controlled, randomized, double-blind, 12-wk study with an open-label extension **N**= 229	**Inclusion criteria**: Men or women >18 y of age with diet-stable patients with triglycerides >500 mg/dl and <2,000 mg/dl (with or without background statin therapy) willing to maintain a stable diet and not alter their normal physical activity level throughout the study. **Exclusion criteria:** Women who were pregnant, planning to become pregnant, or breastfeeding; history of pancreatitis; body mass index >45 kg/m2; weight change >3 kg during the lead-in period; hemoglobin A1c >9.5% (patients with diabetes mellitus were required to be receiving stable therapy); history of stroke, myocardial infarction, life-threatening arrhythmia, or coronary vascularization within 6 mo before screening; TSH >1.5X upper limit of normal; clinical hypothyroidism or thyroid hormone therapy not been stable for >6 wk before screening; ALT or AST > 3 times upper limit of normal; an unexplained creatine kinase concentration >3 times	**Intervention/comparator**: Omega 3 EPA ethyl ester 4 g/d, or 2 g/d, or placebo.	**1º endpoint:** placebo-corrected median percentage of change in TG from baseline to wk 12 in the 2 active treatment groups compared to placebo. **Results:** In the setting of baseline triglycerides of 680, 657, and 703 mg/dl for omega 3 EPA ethyl esters 4 g/d, 2 g/d, and placebo, placebo-corrected triglyceride levels were reduced by 33.1% (n =76, p <0.0001) and 19.7% (n =73, p=0.0051). For a baseline TG level >750 mg/dl, omega 3 EPA ethyl esters 4 g/d reduced placebo-corrected TG levels by 45.4% (n = 28, p<0.0001) and 2 g/d by 32.9% (n =28, p<0.0016). AMR101.	**Other relevant Endpoints**: LDL-C did not change significantly. Side effect profile similar to placebo. **Study limitations**: Short duration; Open label extension study

		upper limit of normal or creatine kinase elevation due to known muscle disease; the consumption of >2 alcoholic beverages per day after screening; a history of illicit drug use within 1 y before screening; a history of symptomatic gallstone disease unless treated with cholecystectomy; known nephrotic syndrome or >3 g/d proteinuria; and use of a variety of weight loss or triglyceride- raising drugs			

Data Supplement 32. Hypertriglyceridemia: Observational Studies (Section 4.5.2)

Study Acronym Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Hokanson JE and Austin MA, 1996 (188) 8836866	**Study Type**: meta-analysis of 17 prospective population-based studies N=57,277.	**Inclusion criteria**: 46,413 men; 10,864 women; Age 15-81 y; Caucasians only; multinational	**Primary endpoint**: Incident fatal and non-fatal cardiovascular endpoints relative to fasting triglycerides (TG); average follow-up in men 8.4 y; in women 11.4 y. **Results**: Men: Univariate RR for TG: 1.32 (95% CI: 1.26-1.39; p<0.05) Women: Univariate RR for TG: 1.76 (95% CI: 1.50-2.07; p<0.05) With adjustment for HDL-C: Men: Univariate RR for TG: 1.14 (95% CI: 1.05-1.28; p<0.05) Women: Univariate RR for TG 1.37 (95% CI: 1.13 -1.66; p <0.05)	**Conclusions**: Suggest TG is a risk factor for cardiovascular disease events for Caucasian men and women, independent of HDL-C **Limitations:** Study limited to Caucasians
The Emerging Risk Factors Collaboration 2009 (189) 19903920	Patient level meta-analysis of 68 long-term prospective studies, mostly in North America and Europe. N=302,430.	**Inclusion criteria**: At baseline: Men and women with no history of MI, angina or stroke who had complete information on total cholesterol, HDL-C, triglycerides and risk factors including age, sex, smoking status, history of diabetes mellitus, systolic blood pressure and body mass index. Outcomes based on death certificates, medical records, autopsy findings, and "other supplementary sources to classify deaths." Stroke diagnosis based on clinical features and characteristic findings on brain imaging, and all studies attempted to classify stroke subtype.	**1º outcome (regarding triglycerides)**: Hazard ratios, adjusted for conventional risk factors, calculated for 1-standard deviation higher values of 0.52 $\log_e$ triglyceride. Within-study meta regression analysis adjusted for within person variation and combined using meta-analysis. **Results:** Mean age 59 ± 8 y. 43% women. 60% Western European, 32% North American. CHD rates per 1,000 person-y in the bottom and top thirds of baseline lipids, respectively, were 2.6 and 6.2. Highest usual mean TG level was 250 mg/dL. Unadjusted hazard ratio for CHD of fasting or non-fasting triglycerides for CHD was 1.37 (95% CI: 1.31-1.42) after adjustment for non-lipid risk factors, but after additional adjustment for HDL-C and non- HDL-C was 0.99 (95% CI: 0.94-1.05) for CHD, and for ischemic stroke 1.02 (95% CI: 0.94-1.11).	Population-wide fasting or non-fasting triglyceride concentrations are not independently related to CHD or ischemic stroke risk when controlling for standard risk factors and HDL-C and non-HDL-C.

		Exclusion criteria: N/A		
Nordestgaard, BG, et al., 2007 (190) 17635890	Prospective cohort study N=13,981	**Inclusion criteria**: 7587 men and 6394 women from the general population of Copenhagen, Denmark; age 20-93 y; followed from baseline (1976-1978) until 2004. **Exclusion criteria**: N/A	**1º endpoint**: Hazard ratios for incident MI, ischemic heart disease (IHD) and total death over a mean follow-up of 28 y, according the 88.5 mg/dL quintiles of non-fasting triglycerides (TG), as compared to those with TG <88.5 mg/dL. **Results**: **MI**: Women: age (and multifactorially adjusted) HR's for each quintile: 2.2 (1.7); 4.4 (2.5), 3.9 (2.1); 5.1 (2.4); 16.8 (5.4). For both, P for trend <.001. Men: 1.6 (1.4), 2.3 (1.6), 3.6 (2.3), 3.3 (1.9) and 4.6 (2.4). For both, P for trend <.001. **IHD:** Women: 1.7 (1.4), 2.8 (1.8), 3.0 (1.8), 2.1 (1.2), 5.9 (2.6). For both trend, P for trend <.001. Men: 1.3 (1.1), 1.7 (1.3), 2.1 (1.3), 2.0 (1.2), 2.9 (1.5). P for trend <.001 for age adjusted and p=0.03 for multifactorially adjusted. **Total death**: Women: 1.3 (1.3), 1.7 (1.6), 2.2 (2.2), 2.2 (1.9) and 4.3 (3.3), for both P for trend<.001 Men: 1.3 (1.2), 1.4 (1.4), 1.7 (1.5), 1.8 (1.6) and 2.0 (1.8); for both, trend <.001).	Elevated age and multifactorially-adjusted non-fasting TG concentration is associated with increased risk of MI, IHD and death in men and women in a large Danish population. **Limitations**: White population only. Relatively small sample size and wide CI's in the quintile with the highest TG levels.
Freiberg JJ, et al., 2008 (191) 19001625	Prospective cohort study N=13,956 in the prospective study; N=9,367 in the cross-sectional study	**Inclusion criteria**: Men and women age 20-93 y of age in the Copenhagen City Heart Study, with enrollment initiating in 1976 and with follow-up through July 2007. Cross sectional study of men and women attending the 1991-1994 examination of the prospective study. **Exclusion criteria:** NA	**Primary endpoint**: Prospective study: Baseline non-fasting TG (NFTG), other risk factors at baseline and at follow-up examination and incidence of ischemic stroke. Cross sectional study: NFTG, levels of remnant cholesterol and prevalence of ischemic stroke. **Results:** Prospective study: Incidence of ischemic stroke versus those with NFTG <89 mg/dl: Men with NFTG 89-176 mg/dL: multivariable-adjusted HR: (MAHR) 1.3 (95% CI: 0.8-1.91); 177-265 mg/dL: MAHR: 1.6 (95% CI: 1.0-2.5);	In this Danish population in both a prospective cohort study and in a cross- sectional study, NFTG levels predicted ischemic stroke risk.

			266-353 mg/dL: MAHR 1.5 (95% CI: 0.9-2.7); 354-442 mg/dL: MAHR 2.2 (95% CI: 1.3-4.8); ≥ 443 mg/dL: MAHR 2.5 (95% CI: 1.3-4.8). p<0.001 for trend. Women with NFTG 89-176 mg/dL: MAHR 1.3 (95% CI: 0.9-1.7); 177-265 mg/dL: MAHR 2.0 (95% CI: 1.3-2.9); 266-353 mg/dL: 1.4 (95% CI: 0.7-2.9); 354-442 mg/dL: MAHR 2.5 (95% CI: 1.0-6.4); ≥443 mg/dL: 3.8 (95% CI: 1.3-11); p<0.001 for trend. Absolute 10-y risk of ischemic stroke in men/women <age 55 y and NFTG <89 mg/dL: 2.6%/1.9%; in men/women >age 55 y with NFTG ≥ 443 mg/dL: 16.7%/12.2%. Cross sectional study: Men with previous ischemic stroke versus controls had NFTG 191 (IQR, 131-259/) mg/dL vs. 148 (IQR: 104-214) mg/dL (p<0.01). For women: NFTG 167(IQR 121-229) mg/dL vs. 127 (IQR 91-181) mg/dL (p<0.05).	
Karlson, BW, et al., 2016 (192) 26969416	Cohort study of Individual patient data extracted from a patient level meta-analysis examining LDL-C and triglyceride reductions in patients receiving treatment with different statins and doses N=15,800	**Inclusion criteria**: Subjects with baseline fasting triglycerides of ≥177 mg/dL derived from The VOYAGER (Of Statin Therapy in At-Risk Groups: Effects of Rosuvastatin, Atorvastatin and Simvastatin) database who were treated with daily doses of rosuvastatin 5, 10, 20 and 40 mg; atorvastatin 10, 20, 40 and 80 mg; and simvastatin 10, 20, 40 and 80 mg	**Primary endpoint**: Percent changes from baseline in LDL-C and triglycerides and least square means calculated. Percentage of patients reaching on treatment triglycerides of <150 mg/dL was calculated after adjusting for study and baseline triglyceride level **Results:** 1. The mean percent reduction in triglycerides ± standard error of the means across all statins and all doses ranged from -15.1% (3.2%) to -31.3% (1.4%) 2. Atorvastatin 80 mg produced greater triglyceride reduction than rosuvastatin 10 mg (p=0.003) 2. Triglyceride reduction with atorvastatin 20 and 40 mg were similar to that seen with rosuvastatin 20 and 40 mg (P non-significant). 3. Triglyceride reduction with atorvastatin 80 mg was similar to that seen with rosuvastatin 40 mg (P non-significant)	1. High-intensity statin therapy is associated with triglyceride reductions of up to 31% in patients with baseline triglycerides 2. High-intensity statins therapy produces greater triglyceride reduction than moderate intensity statins **Limitations:** 1. No cardiovascular outcomes data available 2. Short duration of the individual studies (typically 4-6 wk)

Pederson SB, et al., 2016 (193) 27820614	Prospective cohort study N=116,550	**Inclusion criteria**: 98,649 subjects from the Copenhagen General Population Study in 2003 to 2015 and 17,901 from the Copenhagen City Heart Study from 1976-8 with follow-up examinations in 1981-3, 1991-4 and 2001-3. All followed until occurrence of an event, death, emigration or end of follow-up in November 2014. Median follow-up 6.7 y. **Exclusion criteria**: NA	**1º endpoint**: Hazard ratio (HR) for acute pancreatitis (N=434) and myocardial infarction (N=3,942) **Results**: As compared to those with non-fasting TG <89 mg/dL, the multivariable adjusted HR for acute pancreatitis/myocardial infarction: TG 89-176 mg/dL: 1.6 (95% CI: 1.0-2.6; 4.3 events/10,000-person y). For MI:1.6 (95% CI: 1.4-1.9; 41 events/10,000 person-y) TG 177-265 mg/dL: 2.3 (95% CI: 1.3-4.0; 5.5 events/10,000-person y). For MI: 2.2 (95% CI: 1.9-2.7; 57 events /10,000-person y) TG 266-353 mg/dL: 2.9 (95% CI: 1.4-5.9; 6.3 events/10,000-person y). For MI: 3.2 (95% CI: 2.6-4.1; 72 events /10,000-person y) TG 354-442 mg/dL: 3.9 (95% CI: 1.5-10.0; 7.5 events/10,000-person y). For MI:2.8 (95% CI: 2.0-3.9; 68 events/10,000-person y) TG ≥ 443 mg/dL: 8.7 (95% CI: 3.7-20.0; 12 events per 10,000-person y) (trend P=6 x 10^{-8}). For MI: 3.4 (95% CI: 2.4-4.7; 78 events per 10,000-person y) Multivariable adjusted HR for acute pancreatitis was 1.17 (95% CI: 1.10-1.24) per 89 mg/dL higher triglycerides.	Non-fasting TG above 177 mg/dL predicts and increased risk of acute pancreatitis, with incremental risk proportionate to NFTG level.
Rhodes KS, et al., 2015 (194) 26228674	Prospective outcomes study N=168	**Inclusion criteria**: New patients referred to a University Medical Center lipid management program with fasting triglycerides ≥500 mg/dL between September 10, 2001 and October 5, 2007. Patents received fasting baseline lipid, lipoprotein, apolipoprotein, and additional screening blood testing followed by a 75 min.	**1ºoutcome**: Triglyceride level achieved at the second visit and the median percent change in triglyceride level from the first to the second visit. **Results**: 1. Outside physicians initiated fibric acid derivatives for 15 patient and other lipid-lowering medications for 8 patients during the period between the first and second visits.	A lifestyle intervention comprised of dietary change focusing on low simple and refined carbohydrates, high soluble fiber (>10 g/d), low saturated and minimal trans-fat, limited or no alcohol, and aerobic exercise of 30-60 min. most days of the week is associated with significant short-term reduction of fasting triglycerides in patients with severe hypertriglyceridemia, regardless of the absence or presence of concomitant lipid lowering therapy

		nutrition assessment and initiation of an individualized dietary and exercise intervention. A second nutrition consultation was provided one month later, with repeat lipid profile **Exclusion criteria**: Age <20 y, pregnant or lactating, history of organ transplant, creatinine >1.5 mg/dL	2. With median baseline triglycerides of 961.5 mg/dL at first visit, 123 (78%) achieved greater than 20% reduction in triglyceride levels. 3. The reduction in median fasting triglyceride level from the first to the second visit was 468.5 mg/dL, representing a 48.8% (IQR -73.3 to -23.2) Wilcoxon P <0.0001 4. Among those whose lipid-lowering medication regimen remained stable between the first and second visits, there was no difference in the median percentage reduction in triglycerides after lifestyle intervention between those not taking lipid medication, those taking a fibrate, those taking other lipid-lowering medication, or those on combination lipid-lowering therapy (p=0.376)	**Limitations**: Short follow-up period does not assure maintained long term adherence to the lifestyle change program
Christian JB, et al., 2012 (195) 23009781	Retrospective cohort study N=41,210	**Inclusion Criteria**: Patients ≥ age 18 y of age enrolled from January 2001 through December 2010 in >46 different health care plans with full insurance coverage for professional, hospital and outpatient prescription medication services with continuous enrollment with medical and pharmacy claims for 6 mo before the index date and at least 90 d after the index date. Had to have baseline triglyceride result and follow-up triglyceride result between 6 and <24 wk after the index date. **Exclusion criteria**: Medical claims indicating pregnancy during the study period.	**Primary outcomes**: Incidence of: Cardiovascular events Pancreatitis episodes Diabetes-related events Combined chronic kidney disease and end-stage renal disease Disease-related health care costs among those patients whose follow-up triglyceride levels: 1) remained ≥ 500 mg/dL (8,493 patients) vs. 2) fell to <500 mg/dL (32,217 patients) **Results**: Those with triglycerides ≥ 500 mg/dL had a greater rate of 1. Pancreatitis episodes (hazard ratio [HR:]1.79; 95% confidence interval [CI:] 1.47-2.18) 2. Cardiovascular events (HR: 1.19; 95% CI: 1.10-1.28) 3. Diabetes-related events (HR: 1.42; 95% CI: 1.27-1.59) 4. Kidney disease (HR: 1.13; 95% CI: 1.04-1.22)	**Conclusions**: The group with triglycerides <500 mg/dL had a lower rate of clinical events as compared to those with triglycerides that remained ≥ 500 mg/dL **Limitations**: 1. Retrospective design and potential for measured and unmeasured residual confounding 2. Etiology of high triglyceride levels could not be determined 3. Smoking and body mass index information not available

			Those with triglycerides <500 mg/dL had lower adjusted all-cause and cardiovascular related costs in the first three years of follow-up	

Data Supplement 33. Randomized Trials of Statins in Women for Primary Prevention of CVD (Section 4.5.3.)

Study Acronym Author Year	Aim of Study Study Type Study Size (N)	Patient Population	Study Intervention (include # patients) Study Comparator (include # patients)	Endpoint Results (include Absolute Event Rates, P value; OR or RR; and 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
AFCAPS/TexCAPS Downs JR, et al., 1998 (102) 9613910	**Aim:** To compare lovastatin with placebo for prevention of first acute major coronary event in men and women without clinically evident atherosclerotic cardiovascular disease with average total cholesterol and LDL-C levels and below average HDL-C levels.	**Inclusion criteria:** • Men 45-73 y old, women 55-73 y old • TC 180-264 mg/dL, LDL-C 130-190 mg/dL, HDL-C ≤ 45 mg/dL for men and ≤ 47 for women, TG < 400 mg/dL. • When LDL-C 125-129 mg/dL, if TC/HDL-C ratio > 6.0, subjects were included. **Exclusion criteria:**	**Intervention:** AHA Step I diet + lovastatin 20-40 mg daily (2805 men, 499 women) **Comparator:** AHA Step I diet alone + placebo (2803 men, 498 women) • Consecutive LFT > 3 times ULN	**1° endpoint:** First acute major coronary event (fatal or nonfatal MI, unstable angina, sudden cardiac death) • Lova 116 events (6.8 per 1000 patient-y), placebo 183 events (10.9 per 1000 patient-y) • RR for lova 0.63; 95% CI: 0.50 to 0.79), p<0.001 • No sex differences in treatment effects	**Secondary Endpoints** Coronary revascularizations • Lova 106 events (6.2 per 1000 patient-y), placebo 157 events (9.3 per 1000 patient-y) • RR for lova 0.67; 95% CI: 0.52 to 0.85), p=0.001 Unstable angina • Lova 60 events (3.5 per 1000 patient-y), placebo 87 events (5.1 per 1000 patient-y)

	Study type: RCT **Size:** 5608 men and 997 women	• Clinical evidence of CVD • Secondary hyperlipidemia • IDDM • Uncontrolled HTN • Ventricular ectopy requiring medication • Impaired hepatic transaminase > 20% above normal • Body weight > 50% over ideal for height Use of other lipid-lowering or investigational agents.	rare (< 1% in both groups) • Myalgia leading to discontinuation 0.3% for both groups • CK > 10 times ULN rate (< 1% in both groups) 3 cases of rhabdo (2 in placebo group, 1 in lova group).	**Safety endpoint:** • Total mortality: 80 lova (4.6 per 1000 person-y), 77 placebo 4.4 per 1000 person-y • Cardiovascular mortality: 17 lova (1.0 per 1000 person-y), 25 placebo 1.4 per 1000 person-y • Noncardiovascular mortality: : 63 lova (3.6 per 1000 person-y), 52 placebo 3.0 per 1000 person-y • Fatal and nonfatal cancer: 252 lovastatin (15.1 per 1000 person-y), 259 placebo (15.6 per 1000 person-y); p=0.75	• RR for lova 0.68; 95% CI: 0.49 to 0.95), p=0.02 Fatal and nonfatal MI • Lova 57 events (3.3 per 1000 patient-y), placebo 95 events (5.6 per 1000 patient-y) • RR for lova 0.60; 95% CI: 0.43 to 0.83), p=0.002 All cardiovascular events • Lova 194 events (11.5 per 1000 patient-y), placebo 255 events (15.3 per 1000 patient-y) • RR for lova 0.75; 95% CI: 0.62 to 0.91), p=0.003 All coronary events • Lova 163 events (9.6 per 1000 patient-y), placebo 215 events (12.8 per 1000 patient-y) • RR for lova 0.75; 95% CI: 0.61 to 0.92), p=0.006 **Adverse events** • Any adverse event leading to discontinuation similar in both groups (Lova 13.6%, placebo 13.8%). • Consecutive LFT > 3 times ULN rare (< 1% in both groups) • Myalgia leading to discontinuation 0.3% for both groups • CK > 10 times ULN rate (< 1% in both groups) 3 cases of rhabdo (2 in placebo group, 1 in lova group).
AFCAPS/TexCAPS Clearfield M, et al., 2001 (196) 11788107	**Aim:** To examine the efficacy and safety of long-term lovastatin treatment in the 997 women enrolled in AFCAPS/TexCAPS	**Inclusion criteria:** • Men 45-73 y old, women 55-73 y old • TC 180-264 mg/dL, LDL 130-190 mg/dL, HDL ≤ 45	**Intervention:** AHA Step I diet + lovastatin 20-40 mg daily (2805 men, 499 women)	**1° endpoint:** First acute major coronary event (fatal or nonfatal MI, unstable angina, sudden cardiac death)	**Secondary Endpoints in Women** Coronary revascularizations • RR for lova 0.89; 95% CI: 0.32-2.44; p=0.814 Unstable angina

	Study type: RCT **Size:** 5608 men and 997 women	mg/dL for men and ≤ 47 for women, TG < 400 mg/dL. • When LDL-C 125-129 mg/dL, if TC/HDL-C ratio > 6.0, subjects were included. **Exclusion criteria:** • Clinical evidence of CVD • Secondary hyperlipidemia • IDDM • Uncontrolled HTN • Ventricular ectopy requiring medication • Impaired hepatic transaminase > 20% above normal • Body weight > 50% over ideal for height Use of other lipid-lowering or investigational agents.	**Comparator:** AHA Step I diet alone + placebo (2803 men, 498 women)	• Women: 2.65 per 1000 person-y for lova vs. 4.92 for placebo • Men: 7.57 per 1000 person-y for lova vs. 11.95 for placebo • Risk of first acute major coronary event was 3.4 times greater in men than in women • Women: RR 0.54; 95% CI: 0.22 to 1.35; p=0.183 • Men: RR: 0.63; 95% CI: 0.50 to 0.81; p<0.001 • Heterogeneity, p=0.859 **Safety endpoint in women:** • Total mortality: 11 lova (4.11 per 1000 person-y), 7 placebo (2.61 per 1000 person-y) • Noncardiovascular mortality: all of the above except for 1 death in lova group • Fatal and nonfatal cancer: 32 lova (12.38 per 1000 person-y), 28 placebo (10.71 per 1000 person-y); p=0.69 (pre-existing cancer was not an exclusion)	• RR for lova 0.34; 95% CI: 0.09 to 2.14; p=0.085 Fatal and nonfatal MI • RR for lova 0.67; 95% CI: 0.19 to 2.37; p=0.532 All cardiovascular events • RR for lova 0.67; 95% CI: 0.34 to 1.31; p=0.236 All coronary events • RR for lova 0.56; 95% CI: 0.25-1.28; p=0.164 **Study Limitations** • Women comprised only 15% of the total cohort • Insufficient power to detect a treatment group difference in the primary endpoint in women • Small number of events in women • 54% of women took HRT during the trial (?? Effect) **Adverse events** • Fewer women taking lova than placebo had serious cardiovascular adverse events (5.2% vs. 8.6%; p=0.034) • Consecutive LFT > 3 times ULN rare (< 1% in both groups) • CK > 10 times ULN rare (1 woman in each group) • No cases of myopathy or rhabdo
MEGA Nakamura H, et al., 2006 (103) 17011942	**AIM**: To evaluate the usefulness of pravastatin in the primary prevention of CVD in daily clinical practice in Japan.	**Inclusion criteria:** • Men and postmenopausal women aged 40-70 y (mean age: 59.7 women, 55.2 men)	**Intervention:** NCEP step I diet plus pravastatin 10-20 mg daily (2638 women, 1228 men)	**1° endpoint:** Composite of first occurrence of CHD (fatal and nonfatal MI, cardiac and sudden death, coronary revascularization procedure, and angina)	**Secondary Endpoints** • Stroke: 50 events in the diet plus prava group vs. 62 events in the diet alone group (HR: for prava 0.83; 95% CI: 0.57 to 1.21; p=0.33)

	Study type: RCT **Size:** 7832 men and women	• Body weight of 40 kg or more • Hypercholesterolemia (total cholesterol 220 mg/dL to 270 mg/dL) **Exclusion criteria:** • History of CVD or cerebrovascular disease • Familial hypercholesterolemia • Current diagnosis of malignancy • Secondary hyperlipidemia	**Comparator:** NCEP step I diet alone (2718 women, 1248 men)	• Follow-up of 5 y plus an additional 5 y to increase events) • Diet plus prava 66 events, diet alone 101 events • HR: for prava 0.67; 95% CI: 0.49 to 0.91; p=0.011 • Treatment-by-sex interaction using a sex-stratified Cox proportional-hazards model was nonsignificant (p=0.71).	• CHD plus cerebral infarction: 98 events in the diet plus prava group vs. 144 in the diet alone group (HR: for prava 0.70; 95% CI: 0.54 to 0.90; p=0.005) • Total mortality: 55 in the diet plus prava group vs. 79 in the diet alone group (HR: for prava 0.72; 95% CI: 0.51 to 1.01; p=0.055 **Adverse Events** • No difference in severe adverse events between groups • Incidence rate of cancer: 119 in diet + prava vs. 126 in diet only; p=0.81 • ALT > 100 IU/L occurred in 107 (2.8%) patients in the diet plus prava group vs. 104 (2.8%) patients in the diet only group • CK > 500 IU/L occurred in 111 (3.1%) in the diet plus prava group vs. 98 (2.6%) in the diet only group
MEGA Mizuno K, et al., 2008 (197) 18172039	**AIM**: To summarize the comparison of the results of the MEGA study between men and women. **Study type:** RCT **Size:** 5356 women, 2476 men	**Inclusion criteria:** • Men and postmenopausal women aged 40-70 y (mean age: 59.7 women, 55.2 men) • Body weight of 40 kg or more • Hypercholesterolemia (total cholesterol 220 mg/dL to 270 mg/dL) **Exclusion criteria:** • History of CVD or cerebrovascular disease • Familial hypercholesterolemia • Current diagnosis of malignancy	**Intervention:** NCEP step I diet plus pravastatin 10-20 mg daily (2638 women, 1228 men) **Comparator:** NCEP step I diet alone (2718 women, 1248 men)	**1° endpoint:** Composite of first occurrence of CHD (fatal and nonfatal MI, cardiac and sudden death, coronary revascularization procedure, and angina) • Women: 2.2 per 1000 person-y for diet + prava vs. 2.9 for diet only • Men: 5.7 per 1000 person-y for diet + prava vs. 8.9 for diet only • Women: HR: 0.75; 95% CI: 0.45-1.25; p=0.27 • Men: HR: 0.65; 95% CI: 0.41-1.02; p=0.06 • P for heterogeneity 0.67	**Secondary Endpoints** Stroke • Women: HR: 0.63; 95% CI: 0.67 to 1.10; p=0.10 • Men: HR: 0.66; 95% CI: 0.37 to 1.20; p=0.17 • Heterogeneity, p=0.90 • Women ≥ 60 y: HR: 0.36; 95% CI: 0.17 to 0.77; p=0.008 CHD plus cerebrovascular disease • Women: HR: 0.74; 95% CI: 0.50 to 1.12; p=0.15. • Men: HR: 0.59; 95% CI: 0.40 to 0.87; p=0.007. • Heterogeneity p=0.42 • Women ≥ 60 y; HR: 0.50; 95% CI: 0.31-0.83; p=0.007.

		• Secondary hyperlipidemia		• Women ≥ 60 y: HR: 0.55; 95% CI: 0.30-1.01; p=0.054	Total mortality • Women: HR: 0.59; 95% CI: 0.35 to 1.00; p=0.046. • Men: HR: 0.81; 95% CI: 0.46 to 1.43; p=0.46. • heterogeneity p=0.43 • Women ≥ 60 y; HR: 0.52; 95% CI: 0.28-0.97; p=0.04 **Study Limitations** • Lower percentage of women with risk factors is probably associated with less incidence of events in women compared with men. • Insufficient number of younger women were enrolled. • Analyses in subgroups of women by age are exploratory because of small numbers of events. • Japanese people have a lower CVD risk compared with other countries. **Adverse Events** • No difference in the incidence of severe adverse events in women in the diet plus prava group (252; 9.6%) vs. diet only group (242; 8.9%) • Total incidence of cancer did not differ between the diet plus prava group (74; 5.46 per 1000 person-y) vs. diet only group (78; 5.55 per 1000 person-y)
JUPITER Ridker PM, et al., 2008 (198) 18997196	**Aim:** To investigate whether treatment with rosuvastatin, 20 mg daily, as compared with placebo, would decrease the rate of	**Inclusion criteria:** • Women ≥ 60 y of age • Men ≥ 50 y • LDL-C < 130 mg/dL • hsCRP ≥ 2.0 mg/L	**Intervention:** Rosuvastatin 20 mg daily (3426 women; 5475 men)	**1° endpoint:** First major cardiovascular event (MI, stroke, hospitalization for unstable angina, arterial	**Secondary Endpoints** • Fatal or nonfatal MI: 0.17 and 0.37 per 100 person-y for rosuva vs. placebo (HR: for rosuva 0.46; 95% CI: 0.30 to 0.70; p=0.0002)

	first major cardiovascular events. **Study Type:** RCT **Size:** 17,802 men and women	• TG < 500 mg/dL. **Exclusion criteria:** • Prior history of CAD, stroke or DM • ALT > twice the ULN • CK > 3 times ULN • Creatinine > 2.0 mg/dL • Uncontrolled HTN • Cancer within 5 y • Uncontrolled hypothyroidism • Recent history of alcohol or drug abuse • Inflammatory conditions such as arthritis, lupus, or inflammatory bowel disease • Current use of hormone therapy • Previous or current use of lipid-lowering therapy • Immunosuppresent agents.	**Comparator:** Placebo (3375 women; 5526 men)	revascularization, cardiovascular death) • After 1.9 y median follow-up; maximal follow-up 5 y • Rosuva 142 events (0.77 per 100 person-y), placebo 251 (1.36 per 100 person-y) • HR: for rosuva 0.56; 95% CI: 0.46-0.69; p<0.00001 • Relative hazard reductions in the rosuvastatin group were similar for women (46%) and men (42%)	• Fatal or nonfatal stroke: 0.18 and 0.34 per 100 person-y for rosuva vs. placebo (HR: 0.52; 95% CI: 0.34 to 0.70; p=0.002) • Arterial revascularization or unstable angina: 0.41 and 0.77 per 100 person-y for rosuva vs. placebo (HR: 0.53; 95% CI: 0.40 to 0.70; p<0.00001) • Nonfatal MI, nonfatal stroke, or death from cardiovascular causes: 0.45 and 0.85 per 100 person-y for rosuva vs. placebo (HR: 0.53; 95% CI: 0.40 to 0.69; p<0.00001) **Potential limitations** • Did not include people with low hsCRP along with low LDL-C (unlikely to show a benefit). • Trial was stopped early (median follow up <2 y); effect of longer-term therapy is not known. • Trial evaluated the use of rosuvastatin for the prevention of first CV events; absolute event rates are lower than expected among patients with vascular disease; must consider cost effectiveness of statins in patients with low LDL-C but elevated hsCRP. **Adverse Events** • Similar total number of adverse events in the rosuva (1352) and placebo (1377) groups; p=0.60 • 19 myopathic events in rosuva vs. 9 in placebo groups; p=0.82

					• One nonfatal case of rhabdomyolysis in the rosuva group • No sign between-group differences in newly diagnosed cancer, ALT elevation > 3 times ULN, or intracranial hemorrhage • Physician-reported diabetes was more frequent in the rosuva (270 cases) vs. the placebo (216 cases) group; p=0.01.
JUPITER Mora S, et al., 2010 (199) 20176986	**AIM:** 1) To conduct a prespecified sex-specific analysis in JUPITER comparing the efficacy and safety of rosuvastatin therapy in women vs. men; 2) Perform an updated met-analysis of statin therapy for the primary prevention of CVD events and total mortality in women **Study type**: RCT and meta-analysis **Size**: 6801 women, 11,0001 men	**JUPITER** **Inclusion criteria:** • Women ≥ 60 y of age • Men ≥ 50 y • LDL-C < 130 mg/dL • hsCRP ≥ 2.0 mg/L • TG < 500 mg/dL. **Exclusion criteria:** • Prior history of CAD, stroke or DM • ALT > twice the ULN • CK > 3 times ULN • Creatinine > 2.0 mg/dL • Uncontrolled HTN • Cancer within 5 y • Uncontrolled hypothyroidism • Recent history of alcohol or drug abuse • Inflammatory conditions such as arthritis, lupus, or inflammatory bowel disease • Current use of hormone therapy • Previous or current use of lipid-lowering therapy • Immunosuppresent agents.	**JUPITER** **Intervention:** Rosuvastatin 20 mg daily (3426 women; 5475 men) **Comparator:** Placebo (3375 women; 5526 men) **Meta-analysis** Statin vs. placebo	**JUPITER** **1° endpoint:** First major cardiovascular event (MI, stroke, hospitalization for unstable angina, arterial revascularization, cardiovascular death) • Women: 0.56 per 100 person-y for rosuva vs. 1.04 for placebo • Men: 0.88 per 100 person-y for rosuva vs. 1.54 for placebo • Women**:** HR: 0.54; 95% CI: 0.37 to 0.80; p=0.002 • Men: HR: 0.58; 95% CI: 0.45 to 0.73; p<0.001 • Treatment-by-sex interaction using a sex-stratified Cox proportional-hazards model was nonsignificant (p=0.80). **Meta-analysis** CVD in exclusively primary prevention women (AFCAPS/TexCAPS, MEGA, JUPITER)	**JUPITER** **Secondary Endpoints** Revascularization/unstable angina • Women: HR: 0.24; 95% CI: 0.11 to 0.51 • Men: HR: 0.63; 95% CI: 0.46 to 0.85; • Heterogeneity, p=0.01 Nonfatal stroke • Women: HR: 0.84; 95% CI: 0.45 to 1.58 • Men: HR: 0.33; 95% CI: 0.17 to 0.63 • Heterogeneity, p=0.04) All-cause death • Women: HR: 0.77; 95% CI: 0.55 to 1.06 • Men: HR: 0.82; 95% CI: 0.66 to 1.03 • Significant only when men and women were combined Adverse Events • *Muscle weakness, stiffness, pain, myopathy* – no difference in women vs. men regardless of treatment assignment • *Newly diagnosed cancer* -- no difference in women vs. men regardless of treatment assignment

		Meta-analysis **Inclusion criteria**: • RCTs through 2009 • Predominantly or exclusively primary prevention individuals • Mean follow-up > 1 y • Sex-specific clinical outcomes on CVD or total mortality		• RR 0.63; 95% CI: 0.49-0.82; p<0.001 • Heterogeneity, p=0.56 CVD in predominantly and exclusively primary prevention women (+ ALLHAT-LLT, ASCOT-LLA) • RR: 0.79; 95% CI: 0.59-1.05; p=0.11 • Heterogeneity, p=0.05 Total mortality in exclusively primary prevention women • RR: 0.78; 95% CI: 0.53-1.15; p=0.21 • Heterogeneity, p=0.20 Total mortality in predominantly and exclusively primary prevention women • RR: 0.86; 95% CI: 0.67-1.12; p=0.27 • Heterogeneity, p=0.13.	• *Cancer deaths* – no difference in women based on treatment assignment; more deaths in placebo group for men (p=0.03) • *Hepatic disorder* -- no difference in women based on treatment assignment; more adverse events in men assigned to rosuva than placebo (p=0.02) • *Physician reported diabetes* – Higher in women on rosuva vs. placebo (1.53 vs. 1.03 per 100 person-y; HR: 1.49; 95% CI: 1.11 to 2.01; p=0.008). Men on rosuva vs. placebo (1.36 vs. 1.20 per 100 person-y; HR: 1.14; 95% CI: 0.91 to 1.43; p=0.24). Test for heterogeneity of DM by sex was not significant (heterogeneity, p=0.16).
Kostis WJ, et al., 2012 (200) 22300691	**Aim:** Meta-analysis of sex-specific outcomes in controlled randomized clinical trials of statin therapy **Study type:** Meta-analysis **Size:** 18 studies (8 primary prevention, 10 secondary prevention); 5 primary prevention studies included patients with CVD. Overall, 141,235	**Inclusion criteria:** • Controlled, randomized trials • Investigator- and patient-blinded • Data presented by sex. **Exclusion criteria:** • Studies with fewer than 100 patients • Fewer than deaths per randomized group	**Intervention:** • Statin • Analyses were done separately for primary prevention and secondary prevention trials, by level of baseline risk and by type of endpoint. **Comparator:**	**1° endpoint:** All-cause mortality and the primary end-point as defined by the investigators of each study. • Women -- OR 0.81; 95% CI: 0.75 to 0.89, p<0.0001 • Men – OR: 0.77; 95% CI: 0.71-0.83, p<0.0001 • Interaction effect p=0.1837 • Women, secondary prevention trials – OR: 0.78; 95% CI: 0.70-0.88; p<0.0001	NA

	patients were included, 21,468 primary events, 13,710 events (3898 deaths in studies with sex-specific mortality data).		• Placebo or lower intensity statin	• Women, primary prevention trials --: OR: 0.85; 95% CI: 0.75-0.98; p=0.0209 • Interaction, p=0.3397. **Women, Meta-analysis by level of risk:** • High risk – OR: 0.88; 95% CI: 0.81-0.95; p=0.0014 • Medium risk – OR: 0.75; 95% CI: 0.64-0.89; p=0.0011 • Low risk – OR: 0.59; 95% CI: 0.41-0.87; p=0.006.	
Taylor F, et al., 2013 (201) 23440795	**Aim:** To assess the effects, both harms and benefits, of statins in people with no history of CVD **Study type:** Systematic review **Size:** 18 RCTs, 15,934 patients	**Inclusion criteria:** • RCTs comparing treatment with statins for at least 12 mo with placebo or usual care • Men and women (aged 18 or more) with no restrictions on total, low- or high-density lipoprotein cholesterol levels • RCTs with less than or equal to 10% of patients with a previous history of CVD **Exclusion criteria:** Trials in which statins were used to treat or control chronic conditions (e.g. Alzheimer's disease, rheumatoid arthritis, renal disease, macular degeneration, aortic stenosis)	**Intervention:** Statins **Comparator:** Placebo or usual care	**1° endpoints:** • Total mortality – OR: 0.86; 95% CI: 0.79-0.94 • Total CHD events – RR: 0.73; 95% CI: 0.67-0.80 • Total number of CVD events – RR: 0.75; 95% CI: 0.70-0.81 • Total number of stroke events – RR: 0.78; 95% CI: 0.68-0.89 • Total number of fatal and nonfatal CHD, CVD and stroke events –RR: 0.65; 95% CI: 0.58-0.73 • Number of study participants who underwent revascularization – RR: 0.62; 95% CI: 0.54-0.72	**Adverse events:** • No difference in adverse events between groups (RR: 1.00; 95% CI: 0.97 to 1.03 • No difference in participants who stopped treatment due to adverse events (RR: 0.86; 95% CI: 0.65 to 1.12 • No difference in study participants who developed cancer (RR: 1.01; 95% CI: 0.93 to 1.10 • No difference in study participants who developed myalgia (RR: 1.03; 95% CI: 0.97 to1.09 • No difference in study participants who developed rhabdo (RR: 1.00; 95% CI: 0.23 to 4.38 • No difference in study participants who developed diabetes (RR: 1.18; 95% CI: 1.01 to1.39

				**** Analyses based on sex were initially considered but abandoned due to lack of adequate reporting**	• No difference in study participants who developed hemorrhagic stroke (RR: 0.97; 95% CI: 0.54 to1.75 No difference in study participants who developed elevated liver enzymes (RR: 1.16; 95% CI: 0.87 to1.54
CTT Collaboration Fulcher J, et.al., 2015 (202) 25579834	**Aim:** To provide a more detailed assessment of the effects of statin therapy on particular vascular and non-vascular outcomes in men and women in the settings of both primary and secondary prevention. **Study type:** Meta-analysis **Size:** 27 trials; 174,149 patients (26.8% women)	**Inclusion criteria:** • Studies reported up to 2010 • Trials of statin therapy vs. control and trials comparing statin regimens of differing intensity • Main effect of at least one of the trial interventions was to reduce LDL-C; trial was unconfounded with respect to this intervention • Trial investigators aimed to recruit 1000 or more participants • Treatment duration of at least 2 y.	**Intervention:** Statin or high-intensity statin **Comparator:** Placebo or lower intensity statin	**1° endpoint:** Major vascular events, major coronary events (non-fatal MI or coronary death), coronary revascularization (angioplasty or bypass grafting), stroke, site-specific cancers, cause-specific mortality. **Overall Result for Primary and Secondary Prevention Trials (**irrespective of vascular risk or subtype of vascular outcome)**:** • Women -- Proportional reduction in major vascular events per 1.0 mmol/L LDL-C reduction (RR 0.84; 99% CI: 0.78 to 0.91) • Men -- Proportional reduction in major vascular events per 1.0 mmol/L LDL-C reduction (RR 0.78; 99% CI: 0.75 to 0.81	**Secondary endpoints:** Major vascular events (% annum) in women and men without history of vascular disease • Women -- 593 (1.3%) statin vs. 669 (1.4%) control (RR per 1 mmol/L reduction in LDL-C = 0.85; 99% CI: 0.72 to 1.00 • Men -- 1313 (1.5%) statin vs. 1756 (2.1%) control (RR per 1 mmol/L reduction in LDL-C = 0.72; 99% CI: 0.66-0.80) • Adjusted heterogeneity, p=0.02 All women -- RR per 1.0 mmol/L reduction in LDL-C based on vascular risk at baseline • < 10 % = 0.74 (0.59-0.93) • 10 to <20% = 0.88 (0.77-1.00) Major Coronary Events in all women --RR per 1.0 mmol/L reduction in LDL-C based on vascular risk at baseline • < 10 % = 0.72 (0.49-1.06) • 10 to <20% 0.85 (0.70-1.03) Coronary revascularization in all women -- RR per 1.0 mmol/L reduction in LDL-C based on vascular risk at baseline • < 10 % = 0.58 (0.38-0.89) • 10-<20% = 0.83 (0.67-1.04)

					Ischemic stroke in all Women --RR per 1.0 mmol/L reduction in LDL-C based on vascular risk at baseline • < 10 % = 0.73 (0.50-1.07) • 10-<20% = 0.92 (0.67-1.25) All-cause mortality in combined primary and secondary prevention studies) • Women -- 9% reduction with statin per 1.0 mmol/L reduction in LDL-C (RR: 0.91; 99% CI: 0.84 to 0.99) • Men -- 10% (RR: 0.90; 99% CI: 0.86 to 0.95) **Study Limitations** • Fewer women than men recruited for clinical trials • Primary prevention trials/subjects were difficult to tease out in this meta-analysis • Fewer events in women, particularly low-risk women
HOPE-3 Yusuf S, et al., 2016 (a) (203) 27039945	**Aim:** To evaluate the effects of a moderate dose of a potent statin (without lipid monitoring) versus placebo, a fixed combination of moderate doses of an angiotensin-receptor blocker plus a diuretic (without blood pressure targets) versus placebo, and the combination of both treatments versus dual placebo on the	**Inclusion criteria:** • Men 55 y of age or older, women 65 y of age or older • No cardiovascular disease • At least 1 additional risk factor besides age (elevated waist-to-hip ratio, history of low HDL-C, current or recent tobacco use, dysglycemia, family history of premature coronary disease, mild renal dysfunction) • Women 60 y of age or older were included if they had at	**Intervention** • Candesartan 16 mg- HCTZ 12.5 mg per day plus rosuvastatin 10 mg per day (N=3180, 1465 women) • Rosuvastatin 10 mg per day plus placebo (N=3181) • Candesartan 16 mg-HCTZ 12.5 mg per day plus placebo (N=3176)	**Primary endpoint #1:** Composite of death from cardiovascular causes, nonfatal MI, or nonfatal stroke • 3.6% in combined therapy group vs. 5.0% in dual placebo group • HR: for combined therapy 0.71, 95% CI: 0.56 to 0.90, p=0.005 • Women: HR: for combined therapy 0.70; 95% CI: 0.48 to 1.03	**Secondary outcome:** Composite of cardiovascular death, nonfatal MI, nonfatal stroke, resuscitated cardiac arrest, heart failure, revascularization, or angina with objective evidence of ischemia • 4.6% in combined therapy group vs. 6.5% in placebo group • HR: for combined therapy 0.71; 95% CI: 0.57 to 0.87, p=0.001 **Adverse events:** • Muscle weakness and dizziness were more common in the combined therapy than in the dual placebo group

	prevention of major cardiovascular events. **Study type:** RCT with a 2 x 2 factorial design **Size:** 12,705 (women 5874, men 6831)	least 2 of the above risk factors. **Exclusion criteria:** • Cardiovascular disease • An indication for or contraindication to statins, angiotensin-receptor blockers, angiotensin-converting enzyme inhibitors, or thiazide diuretics.	**Comparator** • Placebo plus placebo (N=3168, 1478 women)	• Men: HR: for combined therapy 0.71; 95% CI: 0.52 to 0.97 • Subgroup analyses showed no significant heterogeneity in the effects of combination therapy according to sex (p=0.980). **Primary endpoint #2:** Composite of the above events plus resuscitated cardiac arrest, heart failure or revascularization • 4.3% in combined therapy group vs. 5.9% in dual placebo group • HR: for combined therapy 0.72; 95% CI: 0.57 to 0.89, p=0.003 • Women: HR: for combined therapy 0.71; 95% CI: 0.49 to 1.01 • Men: HR: for combined therapy 0.72; 95% CI: 0.54 to 0.95 • Subgroup analyses showed no significant heterogeneity in the effects of combination therapy according to sex (p=0.936) **Safety endpoints:** • No difference in cancer, myopathy, or total hospitalizations between	• Rates of permanent discontinuation for any reason did not differ between the combined therapy group (26.3%) and the dual placebo group (28.8%)

				the combined therapy and dual placebo groups • Hospitalizations for cardiovascular causes were higher in the dual placebo group (6.0%) vs. combined therapy (4.4%); p=0.005	
HOPE-3 Yusuf S, et al., 2016 (b) (12) 27040132	**Aim:** To evaluate the long-term effects of rosuvastatin 10 mg per day (without dose adjustment or lipid targets) among persons of various ethnic backgrounds on six continents who did not have cardiovascular disease and were at intermediate risk. **Study type:** RCT with a 2 x 2 factorial design (including both cholesterol lowering and blood pressure lowering arms) **Size:** 12,705 (women 5874, men 6831)	**Inclusion criteria:** • Men 55 y of age or older, women 65 y of age or older • No cardiovascular disease • At least 1 additional risk factor besides age (elevated waist-to-hip ratio, history of low HDL-C, current or recent tobacco use, dysglycemia, family history of premature coronary disease, mild renal dysfunction) • Women 60 y of age or older were included if they had at least 2 of the above risk factors. **Exclusion criteria:** • Cardiovascular disease • An indication for or contraindication to statins, angiotensin-receptor blockers, angiotensin-converting enzyme inhibitors, or thiazide diuretics.	**Intervention:** Rosuvastatin 10 mg per day (N=6361) **Comparator:** Placebo (N=6344)	**Primary endpoint #1:** Composite of death from cardiovascular causes, nonfatal MI, or nonfatal stroke • 3.7% in rosuva group vs. 4.8% in placebo group • HR: for rosuva 0.76; 95% CI: 0.64 to 0.91, p=0.002 • Women: HR: for rosuva 0.83; 95% CI: 0.64 to 1.09 • Men: HR: for rosuva 0.72; 95% CI: 0.58 to 0.90 • Subgroup analyses showed no significant heterogeneity in the effects of rosuva according to sex (p=0.427). **Primary endpoint #2:** Composite of the above events plus resuscitated cardiac arrest, heart failure or revascularization • 4.4% in combined therapy group vs. 5.7% in dual placebo group • HR: for rosuva 0.75; 95% CI: 0.64 to 0.88, p<0.001	**Secondary outcome:** Composite of cardiovascular death, nonfatal MI, nonfatal stroke, resuscitated cardiac arrest, heart failure, revascularization, or angina with objective evidence of ischemia • 4.8% in rosuva group vs. 6.2% in placebo group • HR: for rosuva 0.77; 95% CI: 0.66 to 0.89; p<0.001 **Limitations:** • Relatively short mean duration of treatment (5.6 y); may underestimate the benefits of longer-term statin treatment. **Adverse events:** • Muscle pain or weakness were higher in the rosuva group (5.8%) than in the placebo group (4.7%); p=0.005 • Rates of permanent discontinuation due to muscle symptoms were similar in both groups (rosuva 1.3%, placebo 1.2%; p=0.63) • Rates of rhabdo and myopathy were similar • Rates of cataract surgery were higher in the rosuva group (3.8%) than in the placebo group (3.1%); p=0.02

				• Women**:** HR: for rosuva 0.82; 95% CI: 0.64 to1.06 • Men**:** HR: for rosuva 0.72; 95% CI: 0.59 to 0.87 • Subgroup analyses showed no significant heterogeneity in the effects of rosuva according to sex (p=0.404) **Safety endpoints for rosuva vs. placebo:** • No difference in cancer, myopathy, or total hospitalizations between rosuva and placebo groups • Hospitalizations for cardiovascular causes were higher in the placebo group (5.8%) vs. rosuva group (4.4%); p=0.0004 • No difference in death from any cause • No different in new-onset diabetes • CHD was higher in placebo group (2.2%) than in rosuva group (1.7%); p=0.02	

Abbreviations: AFCAPS/TexCAPS indicates Air Force/Texas Atherosclerosis Prevention Study; AHA, American Heart Association; ALLHAT-LLT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial--Lipid Lowering Trial; ALT, alanine aminotransferase; ASCOT-LLA, Anglo-Scandinavian Cardiac Outcomes Trial--Lipid-Lowering Arm; atorva, atorvastatin; CARDS, Collaborative Atorvastatin Diabetes Study; CHD, coronary heart disease; CI, confidence interval; CK, creatinine kinase; CVA, cerebrovascular accident; CVD, cardiovascular disease; CTT, Cholesterol Treatment Trialists' Collaboration; DM, diabetes mellitus; HbA1C, hemoglobin A1C; HDL-C, high density lipoprotein cholesterol; HOPE-3 , Heart Outcomes Prevention Evaluation-3; HR, hazard ratio; hsCRP, high sensitivity C-reactive protein; HTN, hypertension; IDDM, insulin dependent diabetes mellitus; JUPITER, Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin; LDL-C, low density lipoprotein cholesterol; LFT, liver function tests; lova, lovastatin; MEGA, Primary

Prevention of Cardiovascular Disease with Pravastatin in Japan; mg/dL, milligram per deciliter; MI, myocardial infarction; mmol/L, millimole per liter; NCEP, National Cholesterol Education Program; PAD, peripheral arterial disease; patient-y, patient-years; prava, pravastatin; RCT, randomized controlled trial; rhabdo, rhabdomyolosis; rosuva, rosuvastatin; RR, relative risk; TC, total cholesterol; TG, triglycerides; ULN, upper limit of normal.

Data Supplement 34. Nonrandomized Studies of the Utility of Coronary Artery Calcium in Women (Section 4.5.3)

Study Acronym Author Year Published	Study Type/Design Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR & 95% CI	Summary/Conclusion Comments
MESA McClelland RL, et al., 2006 (204) 16365194	• Prospective cohort study designed to investigate subclinical CVD in a multiethnic cohort free of clinical CVD • 6110 participants, 53% female, average age 62 y	Inclusion Criteria • 45 to 84 y of age • Self-identified as white, black, Hispanic, or Chinese • Free of clinically apparent CVD Exclusion Criteria • Treated diabetes • Pregnancy • Active treatment for cancer • Weight > 300 pounds • Cognitive inability as judged by interviewer • Living in a nursing home • Plans to leave the community within 5 y • Language barrier • CT scan of chest within past year • Any serious medical condition that would prohibit long-term participation	CAC measured by either EBT or MDCT • Men had higher CAC than women, greatest difference for whites • Amount and prevalence of calcium increased with age • Women – whites had highest percentiles, Hispanics had lowest • Distribution curves are presented according to age, sex, race/ethnicity	Substantial differences for CAC distribution were observed among the 4 race/ethnicity groups, as well as significant interactions for both age and gender with race/ethnicity.
MESA Jain A, et al., 2011 (205) 21068189	• Prospective cohort study to compare 3 noninvasive imaging tests (CAC, carotid intima-media thickness, left ventricular mass and geometry) for their	Inclusion Criteria • Men and women aged 45 to 84 y • Free of clinically recognized CVD at enrollment	CVD events considered separately: all CHD (MI, resuscitated cardiac arrest, definite angina, probable angina if followed by revascularization, CHD death), stroke, heart failure, all CVD	Compared with carotid IMT and LV mass and geometry, CAC was the most strongly associated with CHD and CVD in both men and women.

	overall and sex-specific ability to predict CVD. • 4965 participants, 2600 women)	• Available measures of CAC, carotid IMT, and LV mass and volume	• Men had a higher burden of subclinical disease at baseline (p<0.001 for all measures) • 297 incident CVD events occurred over 5.8 y follow-up; men experienced a higher incidence of CHD, HF, and CVD than women (p<0.05) • CAC was most strongly associated with CHD in men (HR: 2.4 per 1 SD; 95% CI: 1.9 to 2.9) and women (HR: 2.2 per 1 SD; 95% CI: 1.5 to 3.1); p≤0.001 • CAC was most strongly associated with all CVD in men (HR: 1.9 per 1 SD; 95% CI: 1.6 to 2.3) and women (HR: 1.5 per 1 SD; 95% CI: 1.2 to 1.8); p≤0.001 • No significant interactions for imaging measures with sex and ethnicity • For women, compared with traditional risk factors alone, CAC added most to AUC for CHD prediction (0.805 vs. 0.835; p=0.04)	
Kelkar AA, et al., 2016 (206) 27072301	• Prospective cohort study to determine long-term prognostic use of CAC in asymptomatic women and men with a low-intermediate Framingham Risk Score (FRS) • 2363 participants, 1072 women	Inclusion Criteria • Patients referred for CAC scanning • Without CAD diagnosis or symptoms suggestive of CAD • Calculated low-intermediate FRS (10-y risk of CAD, 6%-9.9%)	Time to all-cause mortality • Women were older than men (55.6 vs. 46.7 y; p<0.0001) • CAC scores ≥ 100 occurred in 18.8% of women and 15.1% of men • Cumulative 15-y mortality was 8.8% for women and 6.0% for men; p<0.0001 (HR: for women 1.44, p=0.022) • Mortality in relation to CAC scores: **women** 5% for CAC score of 0, 23.5% for CAC score ≥ 400 (p<0.001); **men** 3.5% for CAC score of 0, 18.0% for CAC score ≥ 400 (p<0.001) • Multivariate model for **women** (covariates include age, family history, HTN, dyslipidemia, smoking, DM) – HR: (95% CI:; p-value) for CAC score: 1-10 1.92: (0.82-4.47; p=0.13) 11-99 2.37: (1.29-4.35; p=0.005)	CAC may effectively risk stratify women who are classified as low- to intermediate-risk according to FRS. In this cohort, women had a greater prevalence of CAC, an elevated mortality, and an increased relative hazard for 15-y death when compared with men.

			100-399 2.99: (1.60-5.60; p=0.001) ≥ 400 6.53 (3.50-12.21; p<0.001)	
Kavousi M, et al., 2016 (92) 27846641	• Meta-analysis of 5 cohorts: Dallas Heart Study, Framingham Heart Study, Heinz Nixdorf Recall Study, MESA, Rotterdam Study • To assess the potential utility of CAC testing for CVD risk estimation and stratification among low-risk women • 6739 women mean age 44 to 63 y	Inclusion Criteria • Availability of CAC data • Women with 10-y ASCVD risk < 7.5% Exclusion Criteria • Previous history of CAD, stroke, chronic kidney disease • Treatment with statin • LDL-C ≥ 190 mg/dL • > 79 y of age	Incident ASCVD (composite of nonfatal MI, death due to CHD, stroke) • CAC was present (CAC > 0) in 36.1% of all low-risk women • 165 ASCVD events occurred in 7.0 to 11.6 y follow-up (total ASCVD incidence rate 1.5 to 6.0 per 1000 person-y • CAC presence = ASCVD incidence rate 4.33 per 1000 person-y vs. CAC absence = ASCVD incidence rate 1.41 per 1000 person-y (difference 2.92; 95% CI: 2.02-3.83) • HR for CAC > 100 vs. CAC absence = 4.02; 95% CI: 2.61-6.19 (fixed effects) • Addition of CAC to the base model (risk factors from pooled cohort equation) resulted in an increase in C statistic in all 5 cohorts (overall C statistic increased from 0.73; 95% CI: 0.69-0.77, to 0.77; 95% CI: 0.74-0.81	CAC was present in a large proportion of women with a 10-y risk < 7.5%. The hazard of a woman having an ASCVD event was higher when CAC was present. CAC has the potential to further risk stratify asymptomatic women categorized as having low 10-y ASCVD risk.
Nakanishi R, et al., 2016 (207) 26705490	• Prospective cohort study to examine the relationship between CAC and all-cause mortality, used as a proxy for CVD risk, in a cohort with a median follow-up of at least 10 y. • 13,092 participants, 4379 women, mean age 58 ± 11 y	Inclusion Criteria • No known CAD • Referred for a CAC scan Exclusion Criteria • Age < 20 y • Chest pain • Prior known CVD • Follow-up of ≤ 365 d	All-cause mortality • Compared to men, women were older (58.7 ± 11.3 vs. 57.7 ± 11.5 y, p=0.0001). • Women had a greater number of risk factors (1.77 ± 0.99 vs. 1.64 ± 1.01, p=0.0001). • Compared to women, men had higher CAC across age groups. • Among both genders, patients with more risk factors had increased CAC burden. • 522 (4%) died; no significant difference in mortality risk between men and women. • Mortality rate was low in patients with CAC=0 for men (1.6%) and women (1.8%) and increased with each CAC category for both men and women (p<0.001).	Increasing CAC was strongly associated with increased long-term mortality risk in young and middle-aged men and women. Long-term risk stratification of CAC was lower in older patients, however even in older patients, those with 0 or lower CAC had a lower risk of mortality than the general population. This was a single center study.

			• HR: (95% CI:) for men 45-74 y: *CAC 1-99* 1.8 (1.1-2.8), *CAC 100-399* 2.5 (1.5-4.0), *CAC ≥ 400* 4.5 (2.8-7.1) • HR: (95% CI:) for women 55-74 y: *CAC 1-99* 2.4 (1.2-4.8), *CAC 100-399* 3.8 (1.8-7.9), *CAC ≥ 400* 5.8 (2.8-12.4) • In men and women, CAC showed an incremental prognostic value over traditional risk factors alone at 15 y (men: AUC 0.723 vs. 0.656, p<0.0001; women: AUC 0.690 vs. 0.624, p<0.0001).	
MESA Mortensen MB, et al., 2017 (80) 28624395	• Prospective cohort study to determine whether CAC could be used to optimize statin allocation among individuals for whom trial-based evidence supports efficacy of statin therapy. • 5600 participants, 2965 women, ages 53-69 y, 10-y follow-up	Inclusion Criteria • Free of clinical ASCVD • 45-84 y of age	ASCVD events (MI, resuscitated cardiac arrest, CHD death, stroke) • 1929 women (65%) were eligible for statin therapy based on 7 RCTs • Of statin eligible women, 54% had no CAC, 27% had CAC score of 1-100, 20% had CAC score > 100 • Event rate per 1000 person-y in women: CAC=0, 3.77 (2.72-5.23); CAC 1-100, 9.37 (6.95-12.63); CAC > 100, 17.89 (13.74-23.31) • HR: for ASCVD event when CAC > 100 vs. 0 in women: 4.99 (3.27-7.62)	CAC=0 at baseline was associated with low ASCVD event rates for at least 10 y in women, whereas CAC > 100 was associated with a high event rate. Since evidence from RCTs supports primary prevention with statins in nearly all women > 55 y of age, and over half of women eligible for statin therapy have a CAC score of 0 and a low event rate, having a CAC score may help patients and providers in shared decision-making regarding treatment with statins.
FHS, MESA, CHS Yano Y, et al., 2017 (208) 28746709	• Prospective cohort study using pooled individual participant data from 3 US cohorts (FHS, MESA, CHS), examined the predictive ability of CAC score vs. age for ASCVD, including CHD and stroke. • 4778 participants, 2582 women, aged ≥ 60 y	Inclusion Criteria • Adults older than 60 y • Without known CVD at baseline • Participant in FHS, MESA, or CHS Exclusion Criteria: • Younger than 60 y of age • Known CHD, stroke, or heart failure at baseline	Incident ASCVD during follow-up, including CHD and stroke • 598 ASCVD events during median 10.7 y follow-up • Event rates increased across CAC strata • 11% of ASCVD events (8% of CHD, 16% of stroke) occurred with CAC=0; 42% of ASCVD events (45% of CHD, 38% of stroke) occurred with CAC ≥ 300 • CAC score vs. age had greater association with incident CHD (C statistic, 0.733 vs. 0.690; C statistics difference, +0.043; 95% CI: 0.009-0.075) and modestly improved prediction of stroke.	In older adults without known CVD, CAC score instead of chronological age provided better discrimination for incident ASCVD, especially CHD, over an 11-y follow-up period. When deciding to initiate statin therapy for primary prevention, obtaining a CAC score may assist in shared decision-making for patients ≥ 60 y of age.

			• Cox analysis including CAC score and all risk factors including age and an interaction term suggested no significant interaction between CAC score and sex. Sex-specific C statistics analyses showed similar results.	
Catov JM et al., 2007 (209) 17917602	**Study type:** Cross-sectional sub study **Size:** 446 women in this analysis	**Inclusion criteria:** Age 70-79 years, self-report of no difficulty walking one-quarter mile or climbing 10 steps without resting, no difficulty performing basic activities of daily living, no use of assistive devices to ambulate, no history of active treatment for cancer in the past 3 years, no plans to move out of the area in the subsequent 3 years. **Exclusion criteria:** None specified	**1° endpoint:** CVD status at the time of interview **Results:** • 6% of women reported delivering a preterm infant and 9% reported having a term infant weighing less than 2500 g. • Compared with delivering a term infant ≥ 2500 g, a preterm delivery was associated with a higher prevalence of CVD (OR 2.05; 95% CI 0.93-4.52); adjusted OR was 2.85 (95% CI 1.10-6.85) • Delivery of a small term infant -- OR of CVD of 1.33 (0.66-2.70) • Delivery of a preterm and < 2500 g infant – OR of CVD 2.55 (0.99-6.60); adjusted OR 3.31 (1.06-10.37)	•Women who reported delivering a preterm first birth had an increased prevalence of CVD after adjusting for demographics, smoking, and other cardiovascular risk factors. •This effect was greater in women who delivered both small and preterm infants. Authors suggest that earlier preterm delivery or preterm birth with growth restriction are associated with a greater CVD risk. •These results suggest that women who deliver a preterm infant may benefit from early CVD risk screening and intervention.
Grandi SM et al., 2017 (210) 28816365	**Study type:** Population-based cohort study using data extracted from the United Kingdom's Clinical Practice Research Datalink **Size:** 146,748 women	**Inclusion criteria:** Women between 15 and 45 years of age; first recorded delivery between January, 1990 and December, 2013 **Exclusion criteria:** Record of a previous delivery; diagnosis of hypertension before 18 weeks gestation for the first pregnancy; history of CVD; had ≥ 2 measures of SBP ≥ 140 mmHg or DBP ≥ 90 mmHg prior to 18 weeks gestation; had a DBP ≥110 mmHg prior to 18 weeks	**1° endpoint:** Incident CVD – any diagnosis of cerebrovascular disease, coronary artery disease, coronary revascularization, myocardial infarction, peripheral arterial disease, transient ischemic attack, stroke **Results:** • 1.8% (6433 women) had one pregnancy affected by hypertensive disorders of pregnancy (HDP) • 997 women had incident CVD during 902,897 person-years of follow-up • In women with HDP, rate of subsequent CVD was 2-fold higher	•Women who experienced HDP had an approximate 2-fold increased rate of incident CVD and a 5-fold increased rate of hypertension. •As a result of a higher CVD risk, women with HDP may warrant a close long-term follow-up for early risk factor identification and management.

		gestation; younger than 15 or older than 45 years at first pregnancy; used an anti-hypertensive medication before 18 weeks gestation	than in women with no history of HDP (HR 2.2, 95% CI 1.7, 2.7) • In women with a HDP, rate of hypertension was 5 times that of women without HDP (HR 5.6, 95% CI 5.1, 6.3) • In the time-fixed analyses for CVD and hypertension, none of the potential confounders were found to change the point estimate more than 10%	
Shostrom DC et al., 2017 (211) 28694789	**Study type:** Population-based cross-sectional survey: NHANES **Size:** 8127 women	**Inclusion criteria:** Female, aged 20 years or older, prior history of pregnancy **Exclusion criteria:** Individuals who reported a diagnosis of CVD or diabetes present before or during the same time as diagnosis of gestational diabetes (GDM)	**1° endpoint:** CVD, self-reported during interview: congestive heart failure, coronary heart disease, angina, heart attack, stroke **Results:** • 787 women developed CVD among 7572 women without a history of GDM; 42 women developed CVD among 555 women with a history of GDM • Compared to women without a history of GDM, women with a history of GDM were more lifely to develop CVD (multivariable-adjusted OR 1.63, 95% CI 1.02, 2.62). *Association was attenuated and became non-significant after adjustment for BMI.*	•Women with a history of GDM are at greater risk of developing CVD later in life than women without a history of GDM, however this association may be explained, in part, by BMI. •Targeted interventions may be implemented to reduce CVD risk at a young age for women with a history of GDM. • •

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; AUC, area under the curve; CAC, coronary artery calcium; CAD, coronary artery disease; CHD, coronary heart disease; CHS, Cardiovascular Health Study; CI, confidence interval; CT, computed tomography; CVD, cardiovascular disease; DM, diabetes mellitus; EBT, electron beam tomography; FHS, Framingham Heart Study; FRS, Framingham Risk Score; HR, hazard ratio; HTN, hypertension; IMT, intima-media thickness; LDL-C, low density lipoprotein cholesterol; LV, left ventricular; MDCT, multidetector computed tomography; MESA, Multi-Ethnic Study of Atherosclerosis; person-y, person-years; RCT, randomized controlled trial.

Data Supplement 35. CAC to guide therapy (Section 4.5.3)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients)/Study comparator (#patients)	Endpoint Results (Absolute Event Rates, p values, OR or RR, and 95% CI)
BioImage Mortensen MB, et al., 2016 (95) 27561760	**Aim:** Disease-guided reclassification **Study Type:** prospective observational cohort **Size:** 5,805 adults men and women 55–80 y; mean 68.9±6 Follow-up: median follow-up of 2.7 y.	**Inclusion criteria:** without known ASCVD at baseline examination	**Intervention:** those with an estimated 10 y ASCVD risk ≥7.5% were down-classified from statin eligible to ineligible if imaging revealed CAC=0 Intermediate-risk individuals were up-classified from optional to statin eligibility if CAC was ≥100	• **1° Endpoint:** • With CAC-guided reclassification, specificity for coronary heart disease events improved • 22% (p<0.0001) without any significant loss in sensitivity, yielding a binary net reclassification index (NRI) of 0.20 • (p<0.0001). • CAC scores of 0 were common (32%) and • were associated with low event rate
MESA Nasir, K, et al., 2015 (82) 26449135	**Aim:** to determine whether quantification of CAC score may discriminate risk in subjects with and without statin indication according to AHA/ACC guidelines **Study Type:** population-based prospective longitudinal cohort study **Size:** 4758 subjects (59±9 y of age, 47% men)	**Inclusion criteria:** MESA is a prospective observational cohort of 6,814 men and women, 45–84 y of age, without known CVD at enrollment.	**Intervention:** N/A **Comparator:** N/A	• A total of 247 (5.2%) • ASCVD and 155 (3.3%) hard coronary heart disease events occurred over a median (interquartile range) follow-up of 10.3 • 9.7–10.8 y. • The absence of CAC reclassifies approximately one-half of candidates as not eligible for statin therapy • The new ACC/AHA guidelines recommended 2,377 (50%) MESA participants for moderate- to high intensity statins; the majority (77%) was eligible because of a 10-y estimated ASCVD risk ≥7.5%. Of those recommended statins, 41% had CAC=0 and had 5.2 ASCVD events/1,000 person-y. Among 589 participants (12%) considered for moderate-intensity statin, 338 (57%) had a CAC=0, with an ASCVD event rate of 1.5/1,000 person-y. Of participants eligible (recommended or considered) for statins, 44% (1,316 of 2,966) had CAC=0 at baseline and an observed 10 y ASCVD event rate of 4.2 /1,000 person-y.

Data Supplement 36. Nonrandomized Trials, Observational Studies, and/or Registries of Chronic Kidney Disease and Cardiovascular Risk (Section 4.5.4)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Tonelli M, et al., 2012 (125) 22717317	**Study type:** Observational cohort; medical claims data in Alberta, Canada **Size:** 1,268,029 DM and CKD: 15,368 CKD: 59,117	**Inclusion criteria:** Persons with measures of eGFR and proteinuria in Alberta, Canada between 2002-2009, age >18 **Exclusion criteria:** no kidney measures, ESRD, eGFR<15	**1° endpoint:** hospital admission for MI **Results:** • 11340 admitted with MI (1% of cohort) • Rates of MI per 1000-person y • Prior MI: 18.5 • With no prior MI: Diabetes and no CKD: 5.4 (5.2 to 5.7) CKD no diabetes: 6.9 (6.6. to 7.2) • When eGFR <45 used to define CKD Diabetes no CKD: (approx.7.5) CKD no DM: 10 • Absolute rates of MI increased with more severe CKD (especially if also had proteinuria). Risks higher than diabetes without CKD • Specific data on proteinuria: Moderate proteinuria (ACR >=30 or trace on dipstick); Severe proteinuria (ACR>=300 or dipstick >=2+) • Figure appendix eFigure3: CKD stage 1-4 (Rate about 5 per 1000PY)- similar to diabetes with no CKD If egfr <60 and severe proteinuria and no diabetes, rate >10 per 1000PY and this is higher than diabetes with no CKD (5.4) • Note: from same cohort, published in the KDIGO guideline, table 3 CKD stage g1-g2, rates of coronary death or non-fatal MI 9.7 per 1000 PY (higher for age >50; rate 12.9 age >50)	• Among persons with no prior MI: Rates of hospitalized MI higher for persons with CKD-absolute rates even higher than persons with diabetes (and no CKD)
Matsushita K, et al., 2010 (212) 20483451	**Study type:** Observational cohort Meta-analysis **Size:** • 1,128,310 from 7 studies with dipstick	**Inclusion criteria:** study N≥1000 participants from a general population with eGFR and urine albumin concentrations or dipstick proteinuria, and information on	**1° endpoint:** all cause and cardiovascular mortality **Results:** • HR for CVD mortality elevated starting at eGFR 75- associations stronger with more severely reduced eGFR • HR for CVD mortality linearly increases for ACR	• egfr and albuminuria are each independently associated with all cause and CVD mortality, independent of traditional CVD risk factors (and independent of each other)

	information- (4,732,110 person-y) • 105,872 participants (730,577 person-y) from 14 studies with urine ACR	all-cause mortality or cardiovascular mortality **Exclusion criteria:** Studies that selected participants on the basis of cardiovascular disease or risk factors for cardiovascular disease	• For example, compared with eGFR ≥95, HR: 1.5, 2, and about 3 for eGFR 60, 45 and 15, respectively (these are estimated from Figure 2) • Compared with ACR <5, HR: 1.5, 2, 2.5 for ACR 10, 30, 300 • eGFR and albuminuria were multiplicatively associated with risk of mortality and CVD mortality, with no evidence for interaction • Notes on albuminuria with preserved eGFR • For CVD mortality: among persons with eGFR 90-104, compared with ACR <10 ACR 30-330 HR: 1.8; HR: 4.7 if ACR ≥300	○ Association appears around eGFR 75 and is linear and monotonic for albuminuria • Association is multiplicative
van der Velde M, et al., 2011 (213) 21307840	**Study type:** Meta-analysis of observational cohorts **Size:** 266,975 patients from 10 cohorts	**Inclusion criteria:** patients from 10 cohorts, selected because of increased risk for chronic kidney disease, defined as a history of hypertension, diabetes, or CVD **Exclusion criteria:** Low risk persons	**1° endpoint:** all cause and cardiovascular mortality **Results:** • Compared with eGFr >95, HR for all cause and CVD death increased at eGFRs of 60, 45, and 15 ml/min. • Log albuminuria was linearly associated with log risk for all-cause and CVD mortality without thresholds. Albuminuria and eGFR were multiplicatively associated with all-cause mortality, without evidence for interaction.	• In persons at high CVD risk (hypertension, DM, CVD), eGFR and ACR are independently association with all cause and CVD death. Risk is multiplicative by eGFR/ACR
Fox CS, et al., 2012 (214) 23013602	**Study type:** Meta-analysis of observational cohort studies **Size:** 1,024,977 30 general population and high-risk CVD cohorts and 13 chronic kidney disease cohorts.	**Inclusion criteria:** cohorts with >1000 persons, at least 50 events of interest with information on eGFR and albuminuria (ACR or dipstick); Age >18 **Exclusion criteria:** N/A	**1° endpoint:** • All cause death, ESRD CVD death in cohorts with this outcome • CVD death included deaths due to myocardial infarction, heart failure, sudden cardiac death, or stroke **Results:** • In the 23 studies with data for cardiovascular mortality, 21,237 deaths occurred from cardiovascular disease during a mean follow-up of 9·2 y (SD 4·9). • Finding #1-Persons with DM at higher risk than without diabetes across eGFr and ACR spectrum (HR: 1.2 to 1.9) Finding #2 (figure 1) -All-cause mortality and CVD death increased with lower eGFR and higher albuminuria categories in both the diabetes and no diabetes groups. No interaction by DM • Examples from figure 1	• Lower eGFR (threshold around 60) and albuminuria (no threshold) are independently associated with cardiovascular mortality in persons with and without diabetes • The association of CKD with CVD death is similar magnitude as that seen in persons with diabetes and no CKD

			Compared with category eGFR >95 and no diabetes, HR for CVD death for eGFR 60 no diabetes 1.3, eGFR 60 diabetes 2.0, eGFR 45 no diabetes 1.5, eGFR 45 diabetes 2.0 • Figure 2: Risk for ACR linear Compared with category no DM and ACR <5 ACR 30 no DM: HR: 1.5 ACR 30 DM: HR: 3 • Table 2 All-cause mortality and cardiovascular mortality increased with lower eGFR and higher albuminuria categories in both the diabetes and no diabetes groups Risk multiplicative • Notes on albuminuria with preserved egFr (>60) For example: Among persons with no diabetes, compared with egfr >95 and ACR <5: Acr 30-299 and egfr 75-89: 1.6 ACR >300 and egfr 75-89 HR: 2.57	
Colantonio LD, et al., 2015 (215) 25395432	**Study type:** Observational cohort **Size:** 4,726	**Inclusion criteria:** age 50-79 with CKD (eGFR <60 or ACR ≥30) not on dialysis **Exclusion criteria:** missing information on kidney function, CVD risk equation variables or outcomes	**1° endpoint:** incident ASCVD events - adjudicated **Results:** • Among 1,110 participants age 50-80 not already on statin, free of ASCVD and diabetes and LDL 70-89 • 24% had pooled risk equation <7.5% • If eGFR <60, 17.6% had <7.5% predicted risk • Pooled risk cohort well calibrated • Incidence rate for ASCVD for eGFR <60 was 14.3 (9.4 to 19.2) per 1,000-person y, ACR ≥30 15.8 (11.7 to 19.7) • if ASCVD predicted risk <7.5%, incidence rates <5 per 1000-person y • if ASCVD predicted risk >7.5%, persons with CKD had observed ASCVD rates >15% per 1,000-person y eGFR <60 or ACR ≥30 17.7 per 1,000-person y (13.6 to 21.7), eGFR <60 17.3 per 1000-person y (11.4 to 23.2) • ACC/AHA would recommend statin for 92% of participants for whom statins recommended by KDIGO • The 8% with predicted risk <7.5%, risk low even if CKD where not recommended low risk (<0 to 4 depending on CKD definition)	• Risk equation well calibrated in CKD • Majority of persons with CKD have estimated risk >7.5% • If risk predicted >7.5%, observed rates >15% • If predicted risk <7.5%, observed risk is low • The simpler guideline by KDIGO would potentially overtreat a very small proportion of persons with CKD • No data on persons age <50 Limited data on persons with estimated risk 5-7.5%

Data Supplement 37. RCTs Comparing PLACEBO VS. Statin (or Statin plus another agent) to reduce CVD events in persons with CKD (Section 4.5.4)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
SHARP Baigent C, et al., 2011 (13) 21663949	**Aim:** To assess safety and efficacy of reducing LDL in persons with CKD Placebo vs. simvastatin 20mg + ezetimibe 10 mg daily **Study type:** RCT **Size:** 9,270 randomized Study duration: 4 y (median 4.9 y)	**Inclusion criteria:** • Age ≥40, Cr 1.7 men, 1.5 women, With or without dialysis • Total randomized: 9,438 **Exclusion criteria:** • 6 wk run-in period with placebo to identify noncompliers • Prior CVD • Note re egfr: among non-dialysis, mean eGFR was 26.6 (SD 13). 36% stage 3, 43% stage 4, 20% stage 5 20% ACR <30, 38% 30-300 and 42% >300 • 33% on dialysis • 23% diabetes	**Intervention:** Placebo (N=4,620) vs. simvastatin 20mg + ezetimibe 10 mg daily (N=4,650) **Comparator:** • Placebo, N=4620 • Duration: median 4.9 y	**1° endpoint:** • major atherosclerotic events (non-fatal MI or coronary death, non-hemorrhagic stroke, arterial revascularization) • Placebo: 619 (13.4%) • Intervention: 526 (11.3%) • RR 0.83 (0.74 to 0.94), p 0.0021 • LDL chol. reduction for intervention: Overall, -1.08 y 1, -0.84 at 44 mo • 1.1 mmol/ L for non-dialysis (39%), - 0.75 for dialysis • Effects consistent across eGFR category • No statistically significant differences by CKD stage **Dialysis subgroup:** 3023 on dialysis (2527 hemodialysis, 496 peritoneal dialysis) • Intervention: 230 (15%) • Placebo: 246 (16.5%) • RR 0.90 (0.75 to 1.08) **Safety endpoint (if relevant):** • No differences in Cancer, cancer mortality, CK concentration, myopathy, rhabdomyolysis, persistently raised transaminases, hepatitis, gallstones, pancreatitis	• lack of power for dialysis subgroup • Crossover: 33% discontinued intervention, 14% in placebo started non-statin therapy • Few persons on peritoneal dialysis Important Note: initially randomized 3 ways (placebo, statin alone, ezetimibe plus simva) – the statin only was then re-randomized to intervention vs. placebo after 1 y

				• Note: 34% transitioned to ESRD during the trial	
Cholesterol Treatment Trialists' (CTT) Collaboration* Herrington WG, et al., 2016 (216) 27477773	**Aim:** Compare Effect of statin by renal function - Please check the ref is the following **Study type:** Meta-analysis **Size:** 28 trials, N=183,419	**Inclusion criteria:** Included all trials in renal populations, primary and secondary prevention **Exclusion criteria:** trials with no information on kidney measures	**Intervention:** Statin vs. placebo 23 trials 5 trials compared statin dose **Comparator:** Placebo	**1° endpoint:** • Major vascular events (non-fatal MI, coronary death, stroke, coronary revascularization) Note: able to readjudicate AURORA coronary deaths) • Estimates as rate ratios per mmol/L of LDL lowering • Overall, RR 0.79 (0.77 to 0.81) • Smaller relative effects as GFR declined (p=0.008 for trend), benefit not seen on dialysis N, % events per year, and RR by eGFR • eGFR 45-60 (N=34,417) 4.6% vs. 3.6% 0.76 (0.70 to 0.81) • eGFR 30-45 (N=10,634) 5.2 vs. 4.5% 0.85 (0.75 to 0.96) • eGFR <30 (5,368) 3.5 vs. 3.0 0.85 (0.71 to 1.02) • Dialysis (N=7053) 5.0 vs. 4.7 0.94 (0.79 to 1.11)	• Particular strength: considers differences in achieved LDL levels across trials, uniform definition of outcome in dialysis trials (coronary death) **Limitation:** • Concern over agreement of causes of vascular death adjudication in patients with kidney disease
Palmer SC, et al., 2012 (217) 22910937	**Aim:** To summarize benefits and harms of statin therapy in CKD And whether effects vary by CKD stage **Study type:** Meta-analysis of RCT	**Inclusion criteria:** RCT statin vs. placebo (or no therapy or standard care) or another statin **Exclusion criteria:** <8 wk follow-up, pediatric	**Intervention:** Statin **Comparator:** Placebo or no treatment, standard care (86 comparisons) Vs. other statin (9 comparisons)	**1° endpoint:** Focus here on CVD mortality, major cardiovascular events, MI, stroke Event Rates (Estimate of control group risk per year) • CKD not on dialysis:	• Statins beneficial Benefit varies by CKD severity (dialysis vs. not) **Limitations:** • Included secondary prevention trials

	Size: 89 trials 56,857 participants total Size differed by comparison and outcome considered			Major CV events: 2.0 CV mortality 1.5% • On dialysis: Major vascular event: 15% CV death: 10% • CVD mortality: 27 comparisons, 35417 patients • CKD not dialysis- 8 studies RR 0.78 (0.68 to 0.89) • Dialysis 13 studies RR 0.94 (0.82 to 1.07) • Major CV events 7899 patients (included data from SHARP) • Stat significant difference by CKD stage p <0.001: • CKD not on dialysis 14 studies or subsets • Statin 2525/17912 (14%) vs. 3361/18121 (18.5%) • RR 0.76 (0.73 to 0.80) • Dialysis 4 studies • 0.95 (0.87 to 1.03) • LDL reduction: -43.1 (-49.5 to -36.7) **Safety endpoint:** • Cancer, elevated CKD, abnormal liver function, withdrawal from treatment, LDL reduction • Adverse events (33 comparisons, 45,568 patients) • No differences from statin Cancer 0.96 (0.89 to 1.04) Elevated CK 1.11 (0.80 to 1.56)	• Estimates for CKD not on dialysis includes posthoc subgroup of prior trials • Risk of bias: highest risk for selective outcome reporting For CKD not on dialysis not all reported concealment, 8 trials were post hoc analyses of general population Overall related high-quality evidence • Limited by not able to report risk reduction per unit of LDL lowering
Upadhyay 2012 (218) 22910936	**Aim:** synthesize evidence of lipid lowering on clinical outcomes in persons with CKD	**Inclusion criteria:** • RCT 1 or more lipid lowering agent vs. no treatment or other lipid lowering	**Intervention:** Statin **Comparator:** Placebo or no treatment, usual care	**1° endpoint:** • For Cardiovascular events 9 trials composite fatal and non-fatal CV events or need for revascularization	• Mostly report across all studies (dialysis and not dialysis) • Good quality evidence • Not enough participants on peritoneal dialysis

	Study type: Meta-analysis **Size:** 18 trials	Adults and children with CKD of any stage • f/u minimum 6 mo >100 with CKD per group for adults **Exclusion criteria:** trials of dietary supplements, binders, sterols.		• RR 0.78 (0.71 to 0.86) estimate across studies Did not report for dialysis studies only • 9 trials on MI RR 0.74 (0.67 to 0.81) Consistent across all studies • 9 trials on stroke RR 0.90 (0.63 to 1.27) **Safety endpoint:** Adverse events 14 trials No differences	• Heterogeneity in study populations • Subgroup analyses are majority of CKD data- can introduce bias • Combined LIPID, WOSCOPS AND CARE and used meta-analysis estimates for these studies published together
Major RW, et al., 2015 (219) 25833405	**Aim:** Meta-analysis of RCT Focused on Primary Prevention in CKD **Study type:** Meta-analysis **Size:** 8,834 persons in 6 trials	**Inclusion criteria:** RCT of lipid lowering, CKD patients usually seen in primary care, with no CVD, minimum 6 mo follow up **Exclusion criteria:** trials that included persons on dialysis, or persons with macroalbuminuria (ACR ≥300) or primary renal pathologies	**Intervention:** Statin **Comparator:** Placebo	**1° endpoint:** • In CKD stage 1-3 Major cardiovascular events RR 0.59 (0.48 to 0.72) • Total events 409 32,846-person y of f/u • No statistical heterogeneity	• Excluded SHARP • Represents a lower CVD risk group of CKD patients but also those more likely to be seen in primary care
Baigent C, et al., 2010 (13) 21067804	**Aim:** safety and efficacy of more intensive LDL lowering **Study type:** meta-analysis of RCT **Size:** >170,000	**Inclusion criteria:** • RCT that included >1000 participants At least 2 y follow up • More vs. less intensive statin (5 trials) OR Statin vs. control (12 trials) • Note: included trials of persons with known CVD **Exclusion criteria:** N/A	**Intervention: Statin (or higher dose)** **Comparator:**	**1° endpoint:** • (of relevance to this section) report by eGFR Major vascular event (first occurrence of any major coronary event, stroke or revascularization) • eGFR <60 statin group 2712 events (4.1% per y) vs. 3354 (5.15 per y), RR: 0.77 (0.72-0.83) • no heterogeneity when considering eGFR 60-90 or >90; p=0.9 **Safety endpoint:** not reported for CKD subgroup	Benefit of statin does not differ by GFR (when comparing egFR >90, 60-90, <60)

Wanner C, et al., 2005 (220) 16034009	**Aim:** Effectiveness and safety of statin use in persons with type 2 diabetes on dialysis **Study type:** RCT Multicenter, double blind **Size:** 1,255	**Inclusion criteria:** • 18-80 y, type 2 diabetes, on dialysis for <2 y • Total N= 1255 randomized **Exclusion criteria:** LDL<80 or >190, triglycerides >1000, LFTs >3x normal limit, congestive HF, vascular intervention, MI within 3 mo, unsuccessful kidney transplant, resistant HTN	**Intervention:** N=619 Placebo run-in period 4 wk (discontinued any prior lipid lowering medication) Placebo vs. atorvastatin 20 mg **Comparator:** Placebo N= 636	**1° endpoint:** • Composite of death from cardiac causes, fatal stroke, nonfatal MI or stroke (only 1 event per patient) • Secondary endpoint: all cause death, all cardiac events combined, all cerebrovascular events combined • LDL reduction: 42% in intervention vs. 1.3% in placebo • Cumulative incidence of primary outcome: 31.9 at 3 y in intervention vs. 30.5% in placebo 0.92 (0.77 to 1.10), p=0.37 • Secondary endpoint of all cardiac events combined 0.82 (0.68 to 0.99) but not significant for cerebrovascular events combined (RR: 1.12; 95% CI: 0.81-1.55) or total mortality, RR: 0.93; 95% CI: 0.79-1.08. **Safety endpoint:** No cases of rhabdomyolysis or severe liver dysfunction in either group No differences in cancer No differences in myalgia, myopathy CK levels 3-5 x normal (3 in placebo vs. 11 in statin	• IF LDL fell below 50, atorvastatin dose reduced to 10 mg • Higher rate of stroke in atorvastatin group RR: 2.03 (1.05-3.93) • Revascularization procedures not included in primary outcome
AURORA Fellström BC, et al., 2009 (221) 19332456	**Aim:** Effect of rosuvastatin to reduce CV events in patients on hemodialysis **Study type:** multicenter, double blind RCT **Size:** 2,776	**Inclusion criteria:** Age 50-80 On hemodialysis at least 3 mo **Exclusion criteria:** Prior statin therapy within prior 6 mo Expected kidney transplant within 1 y Serious hematologic, neoplastic, gastrointestinal, infectious or metabolic	**Intervention:** Rosuvastatin 10 mg daily **Comparator:** Placebo	**1° endpoint:** • LDL reduction 43% in statin group • Follow-up mean 3.2 y • Time to major CV event (non-fatal MI or stroke or death from CV causes) Event rate: 9.2 statin vs. 9.5 placebo (per 100 patient y) HR: 0.96 (0.84-1.11) • Selected Secondary endpoints (event rates per 100-person-y rosuvastatin vs. placebo): total	• Excluded patients already on statins (and so could have recruited lower risk HD population) • Lower event rate than 4D, lower than observed in population and lower than expected • Relatively high rate of drug discontinuation • Uncertainty on adjudication of vascular deaths

		disease, malignancy, active liver disease, elevation in CK		mortality (13.5 vs. 14), nonfatal MI (2.1 vs. 2.5), stroke 1.2 vs. 1.1), procedures for stenosis or thrombosis (10.9 vs. 10) of vascular access, death from cardiovascular causes (7.2 vs. 7.3). **Safety endpoint:** • Serious adverse events requiring permanent discontinuation of drug (31.5 vs. 32.1), p=0.78 • No significant differences in CK levels, LFTs, rhabdomyolysis	

Data Supplement 38. RCTs Comparing PLACEBO VS. Statin (or Statin plus another agent) to reduce CVD events in persons with Albuminuria and preserved eGFR (Section 4.5.4)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
Colhoun HM, et al., 2009 (222) 19540640	**Aim:** Subgroup analysis of major RCT to evaluate whether eGFR or albuminuria status modify effect of statin to reduce CVD **Study type:** Posthoc subgroup of RCT **Size:** 2,838	**Inclusion criteria:** • Type 2 diabetes +1 risk factor (hypertension, retinopathy, albuminuria, smoking) • No prior CVD **Exclusion criteria:** • Cr >1.7 • HgbA1c >12% • LD >160 mg/dL	**Intervention:** Atorvastatin 10 mg **Comparator:** Placebo	**1° endpoint:** • Major CVD event (median 4 y) • No difference in CVD reduction with statin by eGFR at baseline • No difference in treatment effect by albuminuria Major CV events Albuminuria 13.8 vs. 8.7%, HR: 0.59 (95% CI: 0.36-0.99) No albuminuria: 7.8 vs. 5.1%, HR: 0.64 (95% CI:0.46-0.89)	Note: eGFR<60 had no increased incidence of CV events or death compared with eGFR >60
Asselbergs FW, et al., 2004 (223) 15492322	**Aim:** assess ability of fosinopril and pravastatin to reduce CVD events in persons with microalbuminuria	**Inclusion criteria:** Persistent microalbuminuria (15 to 300 mg/24 H) BP <160/100 No use of antihypertensive medication	**Intervention:** 2x2 factorial Pravastatin 40 mg Fosinopril Placebo	**1° endpoint:** • Combined incident CV mortality, hospitalization for CV morbidity (non-fatal MI or ischemia, congestive HF, PAD or CVA) • In pravastatin vs. placebo	Fewer events than expected Study powered to detect 35% reduction in events for statin vs. placebo assuming incidence rate of 15% in placebo

	Study type: 2x2 factorial RCT Single center Double blind **Size:** 864, <3% had diabetes	No use of lipid lowering meds Cholesterol <8.0 mmol/L (<5 if prior MI) **Exclusion criteria:** • Crl Cl <60% or normal age adjusted and use of ACE/ARB • Duration: 46 mo	**Comparator:** Placebo	LDL reduction in pravastatin group 4.1 to 3.1 (25%) mmol/L at 4 y • Primary endpoint: Rate of events 5.2% (N=45) over mean 46 mo. • 4.8% in statin vs. 5.6% placebo • RR 0.87 (0.49 to 1.57) **Safety endpoint:** Intolerability of statin (5.1 in placebo vs. 3.0 in statin)	

Data Supplement 39. Nonrandomized Trials, Observational Studies, and/or Registries of HIV/Inflammatory Diseases (Section 4.5.5)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Mantel A, et al., 2015 (224)28279294	**Study type:** Population-based cohort of patients with rheumatoid arthritis (RA) with matched general population comparators who developed an ACS **Size:** 1,135 with RA and 3184 matched comparators	**Inclusion criteria:** • Age ≥18 living in Sweden • with >2 medical visits with a diagnosis of actively monitored RA • developed an acute coronary syndrome (ACS) • Population comparators matched for age, sex, education level, and area of residency **Exclusion criteria:** If clinical visit did not occur from 2006-9	**1° endpoint:** Short-term mortality **Results:** • Within first wk after ACS, 10.4% of RA cases vs. 6.7% of population cases died (age/sex-adjusted HR:1.65; 95% CI: 1.32-2.08 • Rates of deaths within 1 month after ACS was 15.7% among RA cases vs. 10.7% of population cases (age/sex-adjusted HR:=1.57; 95% CI: 1.30-1.89) • After adjustment for prior comorbidities, demographics, education, 7-d (HR:1.50; 95% CI: 1.19-1.90;, 30-d HR: 1.43; 95% CI: 1.18-1.72)	• Patients with RA sustained more severe ACS with increased short-term mortality as compared with general population. They have worse outcomes after ACS, and this can only partly be explained by increased event severity. • RA patients may have an increased frequency of vulnerable plaques as well as markers of endothelial damage, and prothrombotic factors. • RA patients have an increased incidence of ACS
Westerweel PE, et al., 2007 (225) 17469095	**Study type:** review of prospective and retrospective studies looking at CVD endpoints in adults with systemic	**Inclusion criteria:** Studies that reported CV endpoints for populations with SLE vs. general population or those vs. healthy controls	**1° endpoint:** Incidence of CVD **Results:** • Incidence of MI was considerably higher in all age groups of women with SLE with	• The increased CVD risk in adults with SLE is likely related to a propensity for thrombotic complications and accelerated atherosclerosis.

	lupus erythematosus (SLE) **Size:** 14,421 patients with SLE	**Exclusion criteria:** N/A	a 7-fold higher incidence in the Framingham cohort • Longer disease duration and treatment with glucocorticoids was associated with a higher MI incidence	•Adults with SLE tend to develop subclinical atherosclerosis at an earlier age. •Hypertension and Dyslipidemia are more prevalent in adults with SLE.
Mehat NN, et al., 2010 (226) 20037179	**Study type:** Cohort study using the General Practice Research Database **Size:** 3,603 adults with severe psoriasis and up to 4 patients without psoriasis from the same United Kingdom practices and start dates for each adult with psoriasis	**Inclusion criteria:** Patients with severe psoriasis who were ≥18 y of age between 1987-2002 **Exclusion criteria:** Psoriasis patients who did not receive systemic therapy	**1° endpoint:** CV death defined as diagnoses consistent with MI, CVA, PVD, arrhythmia, or left ventricular thrombus **Results:** • When adjusting for age, smoking, diabetes, sex, hypertension, and hyperlipidemia, severe psoriasis was an independent risk factor for CV mortality (HR: 1.57; 95% CI: 1.26-1.96) • Severe psoriasis patients sustained 1 extra CVD death per 283 patients per y after adjusting for major risk factors	•Adults with severe psoriasis have a higher risk of CV mortality, independent of traditional CV risk factors. •Counselling and aggressive management of risk factors in patients with severe psoriasis is warranted.
Hanna DB, et al., 2016 (227) 27444412	**Study type:** Surveillance registry **Size:** 145,845 HIV-infected adults	**Inclusion criteria:** Individuals diagnosed with HIV infection in the New York City HIV Surveillance Registry compared with those without HIV In the New York City Vital Statistics Registry **Exclusion criteria:** If persons were <13 y old	**1° endpoint:** Age-specific and age-standardized mortality rates due to major CVD events **Results:** • 10% of the 29,588 deaths were caused by CVD; 42% were due to ischemic heart disease, 27% to hypertension, and 10% were due to cerebrovascular disease. • Proportionate mortality due to CVD among HIV+ persons increased from 6% in 2001 to 15% in 2012 • CVD mortality rate was highest among viremic persons (adjusted rate ratio [RR], 3.53; 95% CI: 3.21-3.87), but still elevated among virally suppressed (<400 copies/ml) persons (adjusted RR, 1.53; 95% CI: ?! (227)) compared with general population	Clinicians who care for patients with HIV should aggressively manage traditional CVD risk factors and focus on viremic control via ART.

Triant VA, et al., 2007 17456578	**Study type:** Cohort study **Size:** 3,851 HIV and 1,044,589 non-HIV patients in a large data registry	**Inclusion criteria:** Patients who were seen at one of two hospitals in the Partners HealthCare System at least 2 times **Exclusion criteria:** Individuals who were not billed for their encounter	**1° endpoint:** Occurrence of AMI **Results:** • AMI rates per 1000 person-y were increased in HIV vs. non-HIV patients (11.13; 95% CI: 9.58-12.68) vs. 6.98; 95% CI: 6.89-7.06) • RRs (for HIV vs. non-HIV) were 2.98 (95% CI: 2.33-3.75) for women and 1.40 (95% CI: 1.16-1.67) for men after adjustment for age, race, hypertension, gender, diabetes, and dyslipidemia	AMI rates and CVD risk factors are increased in HIV + patients vs. non-HIV patients, especially among women.
Fernandez-Montero JV, et al., 2016 (228) 26390144	**Study type:** Retrospective, observational study of individuals with HIV and/or HCV infection **Size:** 567 HIV-monoinfected, 70 HCV-monoinfected, and 499 HIV/HCV-coinfected adults	**Inclusion criteria:** Consecutive individuals with HIV and/or HCV seen at outpatient clinic in Madrid, Spain as compared to a control group with HCV monoinfection **Exclusion criteria:** Patients with HCV who had been treated	**1° endpoint:** Composite endpoint of angina, MI, CVA, or CVD death **Results:** • HIV/HCV-coinfected patients had a higher incidence of CVD events and/or death than HIV-monoinfected adults (4% vs. 1.2%, p=0.004) and HCV-monoinfected persons (4% vs. 1.4%, p=0.5) • After adjustments for demographics, traditional CVD risk factors, and viral parameters, both HIV/HCV coinfection (HR: 2.91; 95% CI: 1.19-7.12) and hypertension (HR: 3.65; 95% CI: 1.34-9.94) were independently associated with CVD events and/or death in HIV+ adults	•Chronic hepatitis C and hypertension are independently associated with increased CVD risk in adults with HIV. •Treatment of chronic hepatitis C should be prioritized in HIV/HCV-coinfected patients regardless of any liver fibrosis staging.
Dregan A,Chowienczyk P, and Molokhia M. 2017 (229) 28601812	**Study type:** Cross-sectional study to estimate cardiometabolic risk and a prospective cohort study to estimate mortality risk **Size:** 19,082 with a chronic inflammatory disorder out of a total study population of 502,641	**Inclusion criteria:** Participants in the UK Biobank with diagnosis of RA, SLE, psoriasis, AS, systemic vasculitis, and inflammatory bowel disease composed the exposed group; those with none of these disorders were the comparison group. **Exclusion criteria:** N/A	**1° endpoint:** MI, type 2 diabetes mellitus, PAD, and VTE events; all-cause mortality and CVD-related mortality. **Results:** • SLE had the strongest association with risk of cardiometabolic disease (RR: 6.36; 95% CI: 4.37-9.25), followed by RA (RR: 1.70; 95% CI: 1.59-1.83), AS (RR: 1.28; 95% CI: 1.09-1.52), vasculitis (RR:	•Inflammatory disorders increase risk of cardiovascular events •Excess risk varies with use of anti-inflammatory therapy and duration of the underlying inflammatory disorder •Increased risk associated with inflammatory disorders is similar to that of diabetes or chronic kidney disease

			1.64; 95% CI: 1.42-1.90), and psoriasis (RR: 1.25; 95% CI: 1.16-1.35). • Magnitude of association was higher among adults on anti-inflammatory drugs or corticosteroids with risk greatest in SLE patients (RR: 12.35; 95% CI: 7.18-21.24) followed by RA patients (RR: 3.06; 95% CI: 2.44-3.85) • Patients with SLE had the highest adjusted HR: for all-cause mortality (HR: 2.06; 95% CI: 1.37-3.10) vs. comparison group.	
Bartels CM, et al., 2011 (230) 21305507	**Study type:** Retrospective cohort study **Size:** 3,298 RA patients enrolled in Medicare	**Inclusion criteria:** Age ≥ 65 who were alive from 1/1/04-12/31/06 and had a diagnosis of RA who were considered eligible for lipid screening **Exclusion criteria:** no baseline CVD, diabetes mellitus, or hyperlipidemia	**1° endpoint:** Primary lipid screening by the relative frequency of primary care and rheumatology visits or seeing a primary care provider (PCP) at least once a year. **Results:** • Primary lipid screening was performed in just 45% of RA patients. Any primary care predicted more lipid screening than care by a rheumatology practice alone (26% [21-32]). • Not seeing a PCP at least annually decreased lipid screening by 22% (adjusted risk ratio 0.78; 95% CI: 0.71-0.84)	• Lipid screening was performed in less than half of eligible adults with RA. •Annual visits to a PCP improved lipid screening; there needs to be better partnerships between rheumatologists and PCPs for assessing CVD risk
Feinstein MJ, et al., 2017 (72) 28002550	**Study type:** Multicenter cohort study of HIV patients **Size**: 11,288 adults	**Inclusion criteria**: Patients age 18 or older with HIV enrolled in Centers for AIDS Research Network of Integrated Clinical Systems 9CNICS) **Exclusion criteria**: Prior ASCVD	**1° endpoint:** MI rates and accuracy of the 2013 Pooled Cohort Equations (PCE) vs. two data-derived model incorporating HIV-specific covariates **Results**: • MI rates were increased in black men (6.9/1000 person-y and black women (7.2/1000 person-y) as compared to white men and women (4.4 and 3.3 per 1000 person-y, respectively) and subjects who were not virally suppressed (6.3 vs. 4.7 per 1000 person-y for	• The PCE discriminated MI risk and were only moderately calibrated in this multi-center HIV cohort •The addition of HIV-specific factors did not improve model performance. •As more ASCVD events accrue in this cohort, HIV-specific risk estimation models should be compared again to the PCE in this population

			persons with and with detectable viral load, respectively.) • PCE adequately discriminated MI risk (C statistic 0.75 [95% CI: 0.71-0.78], while two data-derived models with HIV-specific covariates did not discriminate risk any better. • The PCE predicted consistently lower MI rates than what occurred.	
Arts EE, et al., 2015 (231) 24389293	**Study type**: Retrospective cohort study based on prospectively collected data **Size**: 1050 patients with RA	**Inclusion criteria:** Adults with RA enrolled in Nijmegen, early RA inception cohort in The Netherlands **Exclusion criteria:** Patients who had a CV event before they were diagnosed with RA	**1° endpoint:** First CV event – either ACS, MI, angina pectoris, CVA, TIA, PVD, and heart failure and discriminatory ability for CV risk prediction was estimated by ROC curves; calibration, sensitivity and specificity were also calculated. **Results**: • Areas under the ROC curve were 0.78-0.80, indicating moderate discrimination between those with and without a CVD event. The Systematic Coronary Risk Evaluation (SCORE), Framingham risk score (FRS), and Reynolds Risk Score (RRS) generally underestimated CV risk and low and middle observed risk levels and mostly overestimated risk at higher observed risk levels. • Depending on the model, up to 32% of observed CVD events occurred in RA patients who were classified as low risk for CVD.	•Established risk models like the Systematic Coronary Risk Evaluation, Framingham Risk, and Reynolds Risk Scores generally underestimate CVD risk in RA patients, especially in the lower two-thirds of predicted risk. •The QRisk II score is the only standard algorithm tends to overestimate CV risk in RA patients. •Underestimation of risk would likely lead to suboptimal implementation of statin and aspirin therapy in RA patients •There is a need to develop and test a RA-specific CV risk model
Yu HH, et al., 2015 (232) 26342937	**Study type:** Nationwide population-based cohort study **Size:** 4,095 adults with SLE and hyperlipidemia and 935 who had never been on lipid lowering therapy	**Inclusion criteria:** Adults with SLE and hyperlipidemia and matching set of patients who had never used lipid-lowering medications and a separate group of statin uses	**1° endpoint:** Development of coronary artery disease (CAD), CVD, ESRD, or mortality **Results:** • Multivariate adjusted HRs for statin users, as compared with patients never on lipid lowering medication were 0.67 [0.54-0.83] for death from any cause.	•Statin therapy in SLE patients may reduce risk of mortality, CVD, and ESRD •This hypothesis needs to be demonstrated and proven in a large prospective study with long-term follow-up

		Exclusion criteria: SLE that was not diagnosed between 1/1/97 and 12/31/08	• High dose statin for >1 y reduced risk of mortality (HR: 0.44 [0.32-0.60]); CAD (HR: 0.20; 95% CI: 0.13-0.31); CVD (HR: 0.14; 95% CI: 0.08-0.25) with similar results in the nested matched study.	
Ou HT, et al., 2017 (233) 28062146	**Study type:** Nationwide longitudinal cohort study **Size:** 945 HIV-infected patients	**Inclusion criteria:** Patients who had started on a statin after a diagnosis of HIV; 801 without history of CVD and 144 with prior CVD. **Exclusion criteria:** Those who had used statin therapy within 1 y before the index date (date of first statin treatment) after HIV diagnosis	**1° endpoint:** Composite of hospitalizations with diagnosis of ischemic CVA, CAD, or heart failure. **Results:** • In HIV + persons with history of CVD, the high-dose statin group had a lower CVD risk compared to that of the low-dose group (HR: 0.88; 95% CI: 0.39-1.99). • The high-potency group showed a lower CVD risk compared to that of the low-potency group (HR: 0.42; 95% CI: 0.06-3.13). • For those without a history of CVD, the HR values were 0.64 (95% CI: 0.30-1.35) and HR: 0.67 (95% CI: 0.16-2.87). • No muscle complaints or dementia was observed in statin users. • New-onset diabetes in the high-dose statin group was higher than in the low-dose statin group (15.3% vs. 8.3%).	•There is a strong trend for lower CVD risk in HIV patients on intensive statin therapy •The results observed with intensive statin regimens in HIV + adults are consistent with those in non-HIV populations •It is important to monitor the metabolic profiles in HIV patients on high intensity statin therapy. Weight loss and improved exercise habits should be encouraged in overweight individuals.
Klein DB, et al., 2015 (234) 25595743	**Study type:** Cohort study of Kaiser members **Size:** 24,768 HIV+ and 257,600 HIV– subjects	**Inclusion criteria:** Enrollees age >18 in Kaiser Permanente in Southern and Northern California **Exclusion criteria:** HIV+ adults who were not in care	**1° endpoint:** Occurrence of MI **Results:** • The adjusted MI rate ratio for HIV status declined over time and reached 1.0 [95% CI: 0.7-1.4] in 2011; this was down from 1.8 [95% CI: 1.3-2.6] from 1996-9. • There were 320 MIs among HIV+ (268 cases/100,000 person-y) and 2,483 MIs among HIV-negative (165 cases/100,000 person-y) with an adjusted RR:1.4 [95% CI: 1.2-1.6].	•The improved rate of CVD in HIV+ positive patients is likely related to better access to care and broadly disseminated CVD risk reduction initiatives in the Kaiser system •The increased use of more tolerable ART regimens has also contributed to reduced risk of CVD in HIV+ subjects.

			• Prescriptions for lipid-lowering therapy increased for HIV+ subjects from 5.5% in 1996-9 to 31.5% in 2010-11.	
Myasoedova E, et al., 2011 (235) 21216812	**Study type:** Population-based incidence cohort **Size:** 651 adults with RA	**Inclusion criteria:** Residents of Olmstead County, MN at least 18 y of age with RA **Exclusion criteria:** Those who did fulfill the 1987 ACR criteria for RA	**1° endpoint:** Interactions between lipids and risk of CVD **Results:** There was a significant non-linear association for TC with CVD risk with 3.3-fold increased risk for TC <4 mmol/l and in increased risk of CVD for TC >4 mmol/l. There was no increased risk of CVD for LDL-C ≥2 mmol/l	•Lipids may have paradoxical associations with CVD risk in RA; lower TC and LDL-C are associated with increased CVD risk. •Patients with lower TC and LDL-C levels have increased CVD risk. •The associations of lipids with CVD in RA likely confounded by inflammation
Post WS, et al., 2014 (236) 24687069	**Study type:** Cross-sectional study **Size:** 1001 men underwent non-contrast CT and 759 has coronary CT angiography (CTA)	**Inclusion criteria:** HIV-infected and uninfected men who had sex with men, Age: 40-70 y, weighed <300 lbs. **Exclusion criteria:** Prior coronary revascularization	**1° endpoint:** Presence of any coronary atherosclerotic plaque and degree of any stenosis on CTA. **Results:** • After adjustments for age, race, center, and cohort, HIV-infected men had a greater prevalence of CAC (Prevalence ratio (PR): 1.21; 95% CI: 1.08-1.35) as well as any plaque (PR=1.14), including non-calcified plaque (PR =1.28) and mixed plaque (PR=1.45) than HIV-uninfected men. • HIV-infected men also had a greater extent of non-calcified plaque after CAD risk factor adjustment (p=0.026). • Longer duration of ART and lower nadir CD4+ T-cell count were associated with coronary stenosis diameter >50%.	•Independent of traditional CHD risk factors, coronary arterial plaque, especially non-calcified plaque, is more extensive and prevalent in HIV-infected men. •Men with more advanced HIV infection (lower nadir CD4+ T cell count and higher number of years on ART have a higher prevalence of more advanced CAD.
Kao AH, et al., 2008 (237) 18774002	**Study type:** Cross-sectional **Size:** 157 women with SLE, 181 women with RA, and 157 healthy controls	**Inclusion criteria:** Women with SLE or RA in the Univ. of Pittsburgh Arthritis Network **Exclusion criteria:** No history of a CVD event or diabetes in control group	**1° endpoint:** Presence of CAC in age- and race-matched women with SLE, RA, or in controls and its relationship with CHD risk factors **Results:** • The prevalence of any CAC was higher in asymptomatic women with either SLE	•There is generally a higher burden of CAC in patients with chronic inflammatory diseases. •Inflammation and endothelial cell activation may play significant role in excess risk of CVD in women with RA or SLE.

			or RA (both 48%) compared with controls (35%). • Independent of traditional risk factors, women with SLE or RA were more likely to have any CAC as well as more extensive CAC as compared to age- and race-matched controls. • After adjustments for levels of C-reactive protein and /or soluble intercellular adhesion molecule-1, women with RA or SLE no longer had increased odds of having any CAC compared with controls.	
Kawai VK, et al., 2015 (238) 25371313	**Study type:** Cohort study **Size:** 98 adults with RA	**Inclusion criteria:** Ages 40-75, LDL-C < 190 mg/dL **Exclusion criteria:** Prior CVD event, statin use, history of diabetes	**1° endpoint:** Accuracy of the 2013 ACC/AHA PCE compared to FRS and RRS to identify RA patients with high CAC **Results:** • All 3 risk scores were higher in patients with high CAC (>300 Agatston units or > 75th percentile of expected CAC for age, sex, and ethnicity, p<0.05 • The percentage of patients with high CAC correctly assigned to the elevated risk category was similar among the 3 scores (FRS 32%, RRS 32, PCE 41%). • The C-statistics for each score predicting high CAC were nearly identical (0.65-0.66)	•The PCE did not outperform the FRS or RR in the identification of RA patients with high CAC. •Standard risk prediction models do not accurately identify many RA patients with high CAC
Lerman JB, et al., 2017 (239) 28483812	**Study type:** Prospective observational cohort study **Size:** 105 adults with psoriasis, 100 adults with hyperlipidemia, and 25 healthy volunteers	**Inclusion criteria:** adults with psoriasis, adults with hyperlipidemia eligible for statin Rx by ATP III, and healthy volunteers matched by age and sex to those with psoriasis. **Exclusion criteria:** age ≤ 18, eGFR < 30, pregnancy, lactating women	**1° endpoint:** Assessment of coronary plaque burden on CTA **Results:** • Subjects with psoriasis had increased noncalcified coronary plaque burden (NCB) (1.18±0.33 vs. 1.11±0.32, p=0.02) and similar prevalence of high-risk plaque (HRP) (p=0.58), despite being younger with lower traditional risk factors. • Compared to healthy volunteers, subjects with psoriasis had increased total coronary plaque burden (1.22±0.31 vs. 1.04±0.22),	•As assessed by CTA, patients with psoriasis tend to have greater volume of NCB and HRP prevalence as compared to healthy volunteers and equivalent HRP prevalence as older subjects with hyperlipidemia. •Reductions in skin inflammation was associated with decreases in NCB at 1 y. This suggests that changes in remote sites of inflammation may correlate with changes in CAD risk.

			p=0.001), NCB (1.18±0.33 vs. 1.03±0.21), p=0.001), and prevalence of HRP beyond traditional risk. • After a year, improvement in psoriasis severity was associated with improvement in total coronary plaque burden and NCB beyond traditional risk factors.	• Aggressive management of CVD risk factors in person with moderate to severe psoriasis is warranted.
Navarro-Millan I, et. al 2013 (240) 23460074	**Study type:** Data from TEAR RCT: a 2-year, investigator-initiated, randomized, 4-arm, placebo-controlled trial of 755 patients with early RA and no prior treatment with disease-modifying anti-rheumatic drugs **Size:** 459 patients RA disease duration: (mean ± SD 3.8 ± 1.1 months) White: 80% Female: 73.6%; 76.9% & 70.8% in three groups DAS28-ESR 5.8 ± 1.1 On prednisone: 40% in each treatment group No significant baseline differences between treatment groups.	**Inclusion criteria:** • Participants naive to treatment with disease-modifying antirheumatic drugs (DMARDs). Patients randomized to 4 different treatment groups MTX plus etanercept (n = 155) Triple therapy (n = 78) MTX monotherapy (n = 226) And a Placebo arm; Two arms included MTX monotherapy aggressively titrated to 20 mg/week, with "step-up" to MTX plus etanercept 50 mg/week or to triple therapy at 6 months for patients who did not achieve a low Disease Activity Score in 28 joints using the erythrocyte sedimentation rate (DAS28-ESR; <3.2 at 6 months). The other two arms were MTX plus etanercept initiated at baseline and triple therapy initiated at baseline. Triple therapy: 1) MTX (titrated to 20 mg/week) 2) SSZ 500 mg twice a day. If this was tolerated, then escalated to 1,000 mg twice a	**1° endpoint:** Lipid levels at 24 weeks. **Results:** Significant changes in total cholesterol, HDL-C, and LDL-C levels (all in mg/dL) compared to baseline ($p<0.0001$) Mean decrease in Total Cholesterol to HDL-C compared to baseline ($p<0.0001$) MTX plus etanercept LDL-C 31.4 Triple therapy LDL-C 28.7 MTX monotherapy LDL-C 30.0 **TC/HDL-C TC/HDL-C TC/HDL-C** −0.1. -0.3. -0.2 ($P = 0.012$ versus baseline) for first group ($P < 0.0001$ versus baseline for each comparison) 2nd and 3rd groups Within each treatment group, the changes in lipid levels at 24 weeks were not significantly different comparing those with DAS28-ESR <3.2 and those with DAS28-ESR ≥3.2	Although lipid levels increase with intensive treatment of RA with 3 different protocols, the ratio of TC/HDL-C, a robust lipid measure of risk actually decreased slightly in all treatment arms Comments: Strength of study was use of a blinded (TEAR) study comparing various rgimens for patients with early RA. Caution: Significant number of patients on prednisone that increases all lipid fractions including HDL-C Study suggests that lipid levels are worth watching, although in these patients there can be multiple factors that can affect lipid levels.

		day, plus HCQ 200 mg twice a day		

Abbreviations:
RA = rheumatoid arthritis, ACS = acute coronary syndrome, HR = hazard ratio, CVD = cardiovascular disease, CI = confidence interval, MI = myocardial infarction; CVA = cerebrovascular accident, PVD = peripheral vascular disease, VTE = venous thromboembolic, PCP = primary care provider, ROC = Receiver Operator Characteristic, SCORE = Systematic Coronary Risk Evaluation; FRS = Framingham Risk Score; RRS = Reynold's Risk Score, ESRD = end stage renal disease, CTA = Computed Tomographic Angiography, NCB = noncalcified coronary plaque burden

Data Supplement 40. RCTs Comparing Statin Safety and Statin Associated Side Effects (Section 5)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
HOPE 3 Yusuf S, et al., 2016 (12) 27040132 NCT00468923	**Aim:** Determine net benefit **Study type:** RCT **Size:** 12,705 participants 46.4% female G1 46.1% female G2	**Inclusion criteria:** Men > 55yrs, Women > 65 y with at least 1 CVRF; Women > 60 with 2 RFs Worldwide recruitment 21 countries **Exclusion criteria:** • Pts with CVD Indications or contraindications to statins, ARBs, ACE-I or thiazide diuretics	**Intervention:** G1: Rosuvastatin 10 mg/d (6361) **Comparator:** G2: placebo (6344)	**1° endpoint:** Composite of CV death, nonfatal MI/nonfatal stroke (G1:3.7% vs. G2: 4.8%; HR: 0.76; 95% CI: 0.64-0.91; p=0.002; NNT=91) **Second co- 1° endpoint:** composite of CV death, MI, stroke, resuscitated cardiac arrest, heart failure or revascularization (G1 4.4% vs. G2 5.7%; HR: 0.75; 95% CI: 0.64-0.88; p<0.001; NNT=73) LDL-C with G1 lower than G2 at 1 y: 39.6 (1.02) 3 y: 34.7 (0.90) Overall mean Diff: 34.6 (0.9) 26.5%; p=0.001 ASCVD Risk G2 (%/y) PO1=4.8%/5.6 y=8.6 PO2=5.7%/5.6 y=10.1	•**Muscle pain or weakness** G1: 5.8% vs. G2: 4.7%; p=0.005 •Cataract surgery G1:3.8% vs. G2 3.1%; p=0.02 **No excess of:** •New-onset DM: G1:3.9% vs. 3.8%, p=0.82 •Muscle symptoms leading to discontinuation of treatment: G1: 1.3% vs. G2: 1.2%, p=0.63 •Rhabdomyolysis or myopathy: G1 2 cases vs. G2:1 case •Cancer: G1 267 vs. G2 286

					•No excess risk of functional abnormalities of the liver in G1.
STOMP Parker BA, et al., 2013 (241) 23183941 NCT00609063	**Aim:** To study the effect of statins on muscle symptoms, strength and exercise performance **Study type:** RCT **Size:** 420 51% women	**Inclusion criteria:** Healthy, statin-naive men and women **Exclusion criteria:** Cancer within 5 y, baseline ALT>2x ULN, Cr level >2 mg/dL, abnormal thyroid function, CVD, DM, pretreatment muscle symptoms, disability limiting exercise testing	**Intervention:** atorvastatin 80 mg for 6 mo (203) **Comparator:** placebo for 6 mo (217)	**1° endpoint:** incidence of myalgias in atorvastatin vs. placebo groups (19 vs. 10; p=0.05) **Secondary endpoint:** •Change in serologic markers including creatine kinase levels (average CK increase of 20.8 U/L from baseline in atorvastatin group; p<0.0001), liver enzymes (average ALT increase of 15.7 U/L in the atorvastatin group; p<0.0001). •Muscle strength and performance (no effect of atorvastatin or placebo; p>0.17)	•No subject on atorvastatin had CK levels>10x ULN •No effect on vitamin D levels at 6 mo
GAUSS-3 Nissen SE, et al., 2016 (242) 27039291 NCT01984424	**Aim:** Identify patients with statin induced muscle symptoms with statin re-challenge and compare effectiveness of evolocumab and ezetimibe in patients with muscle related statin intolerance **Study type:** Two-stage RCT **Size:** 491	**Inclusion criteria:** •Phase A: pts 18 to 80 y unable to tolerate a statin Phase B: Patients with muscle related symptoms or CK ≥10x ULN on statin re-challenge during phase A: •LDL-C≥100 mg/dl with CHD or ≥130 mg/dl with ≥2 risk factors, ≥160 mg/dl with ≥1 risk factor, or ≥190 mg/dl with no risk factors **Exclusion criteria:** •MI, unstable angina, coronary revascularization or stroke within 3 mo before randomization •NYHA class III or IV heart failure	**Intervention:** Phase A: Atorvastatin 20 mg for first 10 wk then cross over to placebo Phase B: Evolocumab 420 mg monthly (145) **Comparator:** Phase A: Placebo for first 10 wk then cross over to atorvastatin Phase B: ezetimibe 10 mg daily (73)	**1° endpoint:** •Mean % change in LDL-C from baseline to wk 24 with evolocumab vs. ezetimibe (-52.8% vs. -16.7%, p<0.001) • % change in LDL-C from baseline to means of wk 22 and 24 with evolocumab vs. ezetimibe (-54.5% vs. -16.7%, p<0.001)	•Muscle symptoms occurred in 209 of 491 (42.6%) of patients while on atorvastatin but not on placebo during phase A •Muscle related symptoms in evolocumab vs. ezetimibe: 20.7% vs. 28.8% P>0.05 •Drug discontinuation due to muscle symptoms in evolocumab vs. ezetimibe: 0.7% vs. 6.8% •CK ≥10x ULN with evolocumab vs. ezetimibe: 2.8% vs. 1.4%, P>0.05

		•Uncontrolled hypertension or cardiac arrhythmia •Type 1 DM •Poorly controlled Type II DM •Uncontrolled thyroid disease			
ODYSSEY ALTERNATIVE Moriarty PM, et al., 2015 (243) 25499937 NCT01709513	**Aim:** study the safety and efficacy of LDL-C reduction with alirocumab vs. ezetimibe in patients with statin intolerance and primary hypercholesterolemia **Study type:** RCT **Size:** 314	**Inclusion criteria:** •Statin intolerance (inability to tolerate at least 2 statins due to muscle related symptoms, including one at the lowest dose) with LDL-C ≥ 70 mg/dL (very high CV risk) or ≥ 100 mg/dL (moderate/high CV risk). **Exclusion criteria:** •Non-statin related muscle symptoms during single-blind placebo run-in period •Uncontrolled thyroid disease •Use of fibrates other than fenofibrate within 6 wk before screening. •Hx of rhabdomyolysis or known myopathy other than statin-associated myopathy.	**Intervention:** alirocumab 75 mg SQ Q2W plus oral placebo (126) **Comparator:** ezetimibe 10 mg daily plus SQ placebo Q2W (125) or atorvastatin 20 mg daily plus SQ placebo Q2W (63)	**1° endpoint:** % LDL-C change from baseline to wk 24 in alirocumab vs. ezetimibe group (-45% vs. -14.6%, difference of 30.4%, p<0.0001)	•Muscle related side effects were lower in alirocumab vs. atorvastatin groups (HR: 0.61, 95% CI: 0.38-0.99, p=0.042) •27% had myalgias, 6.3% had muscle weakness and 11.1% had muscle spasms in the atorvastatin group
N-of-1 Trial Joy TR, et al., 2014 (244) 24737272 NCT01259791	**Aim:** compare effect of statin rechallenge in patients with Hx of statin-related myalgia **Study type:** RCT, 3 double-blind, crossover comparisons **Size:** 8	**Inclusion criteria:** pts ≥ 18 y age with hypercholesterolemia and statin-related myalgia without clinically significant elevation in CK levels (<3x ULN or <3x the baseline value) **Exclusion criteria:** •Hx of rhabdomyolysis, metabolic or inflammatory myopathy or neuropathy	**Intervention:** Re-challenge with previously intolerant statin (80) **Comparator:** placebo (80)	**1° endpoint:** difference in mean visual analogue scale (VAS) myalgia score between statin treatment and placebo (No statistically significant difference in VAS myalgia score between the two groups, p>0.05) **Secondary outcome:** mean difference in symptom specific VAS score, pain severity score (PSS) and pain interference score (PIS) (No statistically significant differences between statin treatment and placebo groups, p>0.05).	•No statistically significant difference in CK or liver enzyme levels between statin treatment and placebo groups

Taylor BA, et al., 2015 (245) 25545331 NCT01140308	**Aim:** to study the effect of coenzyme Q10 (CoQ10) supplementation on statin associated muscle symptoms, strength and performance **Study type:** RCT **Size:** 41	**Inclusion criteria:** Pts ≥ 20 y age with confirmed statin myalgia on simvastatin during lead-in trial **Exclusion criteria:** • subjects with muscle pain on placebo during lead-in trial •cancer within 5 y of recruitment •hypo- or hyperthyroidism •liver disease (ALT >2x ULN) •renal disease (Cr >2 mg/dL) •medications known to affect muscle metabolism (corticosteroids)	**Intervention:** simvastatin 20 mg/d and CoQ10 600 mg/d (20) **Comparator:** simvastatin 20 mg/d and placebo (18)	**1° endpoint:** muscle pain assessed by Pain Severity Score (PSS) and Pain Interference Score (PIS) •More subjects reported pain in the CoQ10 vs. placebo group (70% vs. 39; p=0.05) •Increase in PSS and PIS in both groups (p<0.01) with statin therapy however no difference with CoQ10 or placebo (p=0.53 and p=0.56) **Secondary endpoint:** •No change in CK, muscle strength or aerobic performance between statin+CoQ10 vs. statin+placebo groups (all p>0.10) •No difference in time to pain onset in CoQ10 vs. placebo groups (3.0 ± 2.0 wk vs. 2.4 ± 2.1 wk; p=0.55)	•Of the 120 patients enrolled in the lead-in phase, -35.8% had myalgia on simvastatin but not on placebo -17.5% had no symptoms on simvastatin or placebo -29.2% experienced pain on placebo but not on simvastatin -17.5% experienced pain on both simvastatin and placebo -time to pain onset was shorter in those with confirmed statin myalgia compared to non-myalgia patients who developed pain on simvastatin (1.7 ± 1.4 wk vs. 3.0 ± 1.8 wk; p<0.01)
JUPITER-Diabetes risk Ridker PM, et al., 2012 (246) PMC3774022	**Aim:** to evaluate the balance between net CV benefit versus incident DM risk with rosuvastatin in pts with none or ≥ 1 risk factors for DM (fasting glucose >100 mg/dL but <126 mg/dL, metabolic syndrome, BMI ≥ 30 kg/m^2 or glycated hemoglobin A1c >6%) **Study type:** RCT **Size:**17,603	**Inclusion criteria:** Healthy men ≥50 y age and women ≥ 60 y age with LDL-C <130 mg/dL and high sensitivity C-reactive protein (hsCRP) ≥ 2 mg/L **Exclusion criteria:** • history of DM • history of CVD • previous or current use of lipid-lowering therapy • current use of post-menopausal HR:T • liver dysfunction (ALT > 2x ULN) •CK>3x ULN •Cr >2.0 mg/dL	**Intervention:** rosuvastatin 20 mg **Comparator:** placebo	**1° endpoint:** MI, stroke, hospitalization for unstable angina, revascularization, or CV death Individuals without major risk factors for DM (rosuvastatin vs. placebo): •52% reduction in 1° endpoint (HR: 0.48; 95% CI: 0.33-0.68; p=0.0001) Individuals with ≥ 1 risk factor for DM (rosuvastatin vs. placebo): • 39% reduction in 1° endpoint (HR: 0.61; 95% CI: 0.47-0.79; p=0.0001) **Secondary endpoint:** Individuals without major risk factors for DM (rosuvastatin vs. placebo):	•More frequent incident DM in rosuvastatin vs. placebo group (270 vs. 216, HR: 1.25; 95% CI: 1.05-1.49; p=0.01) •Average time to DM diagnosis for rosuvastatin vs. placebo group was 84.3 wk vs. 89.7 wk respectively • for every 54 new cases of diabetes diagnosed, 134 vascular events or deaths avoided with rosuvastatin in those with risk factors for DM •for individuals without risk factors for DM, 86 vascular events or deaths avoided without any new cases of DM

		●uncontrolled hypertension (SBP >190 mmHg or DBP >100 mmHg) ●Cancer within 5 y before enrollment ●Uncontrolled hypothyroidism ●Hx of alcohol or drug abuse ●Pts with inflammatory conditions (arthritis, lupus or inflammatory bowel disease) ●Pts taking immunosuppressant agents (cyclosporine, tacrolimus, azathioprine, long term oral glucocorticoids)		● 53% reduction in VTE (HR: 0.47; 95% CI: 0.21-1.03; p=0.05) ● 22% reduction in total mortality (HR: 0.78; 95% CI: 0.59-1.03; p=0.08) ●No increase in incident DM (0.99; 95% CI: 0.45-2.21; p=0.99) Individuals with ≥ 1 risk factor for DM (rosuvastatin vs. placebo): ●36% reduction in VTE (HR: 0.64; 95% CI: 0.39-1.06; p=0.08) ●17% reduction in total mortality (HR: 0.83; 95% CI: 0.64-1.07; p=0.15) ● 28% increase in incident DM (HR: 1.28 (95% CI: 1.07-1.54; p=0.01)	
St. Francis Heart Study RCT Foster T, et al., 2011 (247) 20842109	**Aim:** to evaluate the effectiveness of statin therapy for non-alcoholic fatty liver disease (NAFLD) **Study type:** RCT **Size:**455	**Inclusion criteria:** Healthy men and women between ages 50-70 y **Exclusion criteria:** ● history of CAD, insulin dependent DM, bleeding diathesis, severe anemia ●cancer within 5 y prior to enrollment ●condition likely to lead to death within 5 y of enrollment ●use of anticoagulants or cyclosporine ●LDL >174 mg/dL or <90 mg/dL ●Systolic blood pressure >180 mmHg ●diastolic blood pressure >100 mmHg ●elevated transaminases >1.5x ULN ●pts without both visible liver and spleen on imaging	**Intervention:** atorvastatin 20 mg, vitamin C 1g and vitamin E 1000 IU (n=229) **Comparator:** placebo (n=226)	**1° endpoint:** effect of atorvastatin, vitamin C and Vitamin E vs. placebo on NAFLD ●reduced odds of NAFLD in the intervention group vs. placebo (70% vs. 34%, OR: 0.29; p<0.001)	●Only 3 patients had transaminase elevation >2x ULN that resolved on follow up

Data Supplement 41. Nonrandomized Trials, Observational Studies, Meta-analyses and/or Registries of Statin Safety and Statin-Associated Side Effects (Section 5)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
ASCOT-LLA Gupta A, et al., 2017 (248) 28476288	**Study type:** Non-blinded, non-randomized extension of ASCOT-LLA RCT **Size:** 9899 patients • 6409 (65%) in atorvastatin user group • 3490 (35%) non-atorvastatin user group	**Inclusion criteria:** •pts aged 40–79 y with hypertension and three or more CVD risk factors •fasting total cholesterol concentrations 6·5 mmol/L or lower and not taking a statin or fibrate • no hx of MI and were not being treated for angina **Exclusion criteria:** •Prior MI •currently on angina treatment cerebrovascular event within 3 mo •fasting TG>4.5 mmol/L •heart failure •uncontrolled arrhythmias •clinically important hematological or biochemical abnormality on screening	**1° endpoint:** compare rates of AEs in blinded vs. non-blinded phase of the study **Results:** **Blinded phase:** •Muscle related AEs were similar between atorvastatin and placebo groups (2.03% vs. 2.0%/y, HR: 1.03; 95% CI: 0.88-1.21; p=0.72) •Erectile dysfunction (1.86% vs. 2.14%/y, HR: 0.88; 95% CI: 0.75-1.04; p=0.13) •Sleep disturbance lower in atorvastatin group vs. placebo (1.0% vs. 1.46%, HR: 0.69, 95% CI: 0.56-0.85; p=0.0005) •Few cases of reported cognitive impairment (not statistically reliable for analysis per authors) **Unblinded phase**: •Muscle related AEs higher in patients on atorvastatin vs. those not on it (1.26% vs. 1.0%/y, HR: 1.41; 95% CI: 1.10-1.79; p=0.006) •No significant differences between statin and non-statin users for erectile dysfunction, sleep disturbance or cognitive impairment	• muscle related adverse effects were higher when patients were unblinded suggesting nocebo effect
Banach M, et al., 2015 (249) 25440725	**Study type:** Meta-analysis of RCTs **Size:** 6 studies with 302 patients receiving statin therapy, 5 studies with 226 participants evaluating the effect of CoQ10 on plasma CK, and 5 studies with 253 participants assessing the	**Inclusion criteria:** Randomized, placebo-controlled, parallel or crossover trial; adults 18 y and older; intervention group received CoQ10 and comparison group received placebo; availability of data on CK levels or severity of myopathic pain	**1° endpoint:** impact of CoQ10 on plasma CK activity and muscle pain **Results:** • Non-significant increase in plasma CK activity increased after CoQ10 supplementation (mean difference 11.69 U/L; 95% CI: -14.25 to 37.63 U/L; p=0.38)	• No significant benefit of CoQ10 supplementation in improving statin-induced myopathy

	effect of CoQ10 on muscle pain	**Exclusion criteria:** Not conducted in statin-treated individuals; no numerical values; no control group; ongoing trial; inadequate details of study methods or results**:**	• Non-significant decrease in muscle pain after CoQ10 supplementation (standardized mean difference =-0.53; 95% CI: -1.33 to 0.28; p=0.20)	
Preiss D, et al., 2011 (250) 21693744	**Study type:** Meta-analysis of RCTs **Size:** 5 trials of 32,752 participants	**Inclusion criteria:** trials of 1000 or more participants without DM exposed to moderate or intensive dose statin therapy with a minimum mean follow-up of 1 y **Exclusion criteria:** Placebo-controlled trials, patients with diabetes, other agents or treatments	**1° endpoint:** •incident DM, determined by an adverse event report of new diagnosis during the trial, participant starting glucose-lowering medication during the trial or 2 fasting plasma glucose values of 126 mg/dL or greater during the trial • composite of CV events (CV death, nonfatal MI, nonfatal stroke, CABG or PCI) **Results:** •Participants receiving intensive dose statin were more likely to develop new-onset DM compared with moderate-dose statin (OR: 1.12; 95% CI: 1.04-1.22; I^2=0%) • Participants receiving intensive dose statin vs. moderate dose statin had OR: 0.84; 95% CI: 0.75-0.94; I^2=74% for CV events.	•Intensive-dose statin therapy was associated with an increased risk of new-onset diabetes compared to moderate-dose statin therapy •2 additional cases of DM per 1000 patient-y vs. 6.5 fewer cases of CV events per 1000 patient-y in the intensive statin therapy group •NNH=498 for new onset DM and NNT=155 for CV events in intensive-dose statin therapy group
Navarese EP, et al., 2013 (251) 23352266	**Study type:** Meta-analysis of RCTs **Size:** 17 RCTs including a total of 113,394 patients	**Inclusion criteria:** RCTs comparing either a statin vs. placebo or high-dose vs. moderate-dose statin therapy **Exclusion criteria:** Trials investigating surrogate markers, patients already diagnosed with DM, new-onset DM data not published, different follow-up per group	**1° endpoint:** the incidence of new-onset DM with different type and doses of statins **Results:** •Pravastatin 40 mg/d was associated with the lowest risk of new-onset DM compared to placebo (OR: 1.07; 95% CI: 0.86-1.30) •Rosuvastatin 20mg/d associated with increased risk for new-onset DM compared to placebo (OR: 1.25; 95% CI: 0.82-1.90 •Atorvastatin 80mg/d was associated with increased risk of DM compared to placebo (OR: 1.15; 95% CI: 0.90-1.50)	• Various doses of different types of statins show varying potential to increase the incidence of DM

Sattar N, et al., 2010 (252) 20167359	**Study type:** Meta-analysis of RCTs **Size:** 13 trials with 91140 participants	**Inclusion criteria:** RCTs of more than 1000 patients, identical follow-up in both groups, and duration of more than 1 y **Exclusion criteria:** Trials of patients with organ transplants or needed hemodialysis	**1° endpoint:** Incident DM **Results:** •Statin therapy associated with an increased risk for incident DM (OR: 1.09; 95% CI: 0.02-1.17) with little heterogeneity between trials (I^2=11%) • one case of DM for every 255 patients (0.4% absolute increase) treated with statins for 4 y • Incidence of DM was 12.3 cases/1000 patient-y in the statin group and 11.25 cases/1000 patient-y in the control group	•Statin therapy was associated with a slightly increased risk of diabetes development. • Absolute risk of DM development is low and low-risk when compared with the reduction in coronary events
Taylor F, et al., 2013 (201) 21249663	**Study type:** Systematic Review and Meta-Analysis **Size:** 18 RCTs with 19 groups; 56,934 participants	**Inclusion criteria:** RCTs of statins vs. placebo or usual care in adults ≥ 18 y age; with treatment duration of ≥ 12 mo and follow-up ≥ 6 mo; 10% or less had a history of CVD **Exclusion criteria:** Studies in which >10% of patients had previous CVD Studies where statins were used to control/treat chronic conditions	**1° endpoint:** All-cause mortality, fatal and non-fatal CHD, CVD and stroke, combined endpoints (fatal and non-fatal CHD, CVD and stroke), revascularization • Adverse events (253) included cancer, DM Type 2. **Results: AEs** (statin vs. control) • Pooled event rates from 12 trials showed no difference in overall rate of AEs (RR: 1; 95% CI: 0.97-1.03). •No excess risk of cancer from pooled estimate from 11 trials (RR: 1.01; 95% 0.93-1.10) and no heterogeneity. •No excess risk of myalgia and rhabdomyolysis from pooled estimate of 9 trials (RR: 1.03; 95% CI: 0.97-1.09) with some heterogeneity (I^2 41%) •Excess risk of Type 2 DM observed from only two trials (RR: 1.18; 95% CI: 1.01-1.39). • No excess risk of hemorrhagic stroke from pooled estimate of 2 trials (RR: 0.97; CI: 0.54-1.75). •Weak evidence for elevation in transaminases from pooled estimate of 10 studies (RR: 1.16; 95% CI: 0.87-1.54). •Weak evidence for renal dysfunction from pooled estimate of 4 studies (RR: 1.11; 95% CI: 0.99-1.26). • Weak evidence for arthritis from pooled estimate of 2 studies (RR: 1.2; 95% CI: 0.82-1.75) .	•In patients without CVD, statins reduce all-cause mortality, major vascular events and revascularization without a significant increase in AEs.

Richardson K, et al., 2013 (254) 24247674	**Study type:** Systematic Review and Meta-Analysis **Size:** 27 studies (3 RCTs, 16 cohort, 4 case–control, and 4 cross-sectional) were included in meta-analysis	**Inclusion criteria:** Studies evaluating cognitive function in adults receiving statins	**1° endpoint:** Incidence of dementia, Alzheimer's disease, or mild cognitive impairment in statin vs. placebo treated patients **Results:** •Moderate-strength evidence showed no increased risk for dementia with statins - One RCT of statin vs. placebo – RR: 1.00; 95% CI: 0.61-1.64 - pooled analysis of 10 cohort studies showed statins were associated with decreased risk for dementia (RR: 0.87; CI: 0.82-0.92) • Low-strength evidence demonstrates no association between statins and increased risk of Alzheimer disease - Pooled analysis of 10 cohort studies suggest statins are associated with decreased risk of Alzheimer disease (RR: 0.79; CI: 0.63-0.99) •Moderate-strength evidence suggests no increase in risk of mild cognitive impairment (MCI) or cognitive impairment without dementia with statins - One RCT showed no significant difference in incidence of MCI with statin therapy vs. placebo (RR: 0.98; 95% CI: 0.93-1.03) - Pooled analysis of 4 cohort studies showed a decrease in risk with statin therapy (RR: 0.66; CI: 0.51-0.86)	• Lack of large RCTs to evaluate effect of statin therapy on cognitive function • currently available data does not suggest adverse effect of statins on cognitive function
Ganga HV, et al., 2014 (255) 24952854	**Study type:** Systematic Review **Size:** 42 trials (113,695 patients)	**Inclusion criteria:** Placebo controlled studies with a minimum follow-up of 6 mo. and published from 1990 through November 2012. **Exclusion criteria:** nonrandomized trials, observational studies, case	**1° endpoint:** Incidence of muscle symptoms in patients treated with statin vs. placebo **Results:** •Incidence of any muscle problems was 12.7% (n = 7,544) in 59,237 statin treatment group and 12.4% (n = 6,735) in 54,458 placebo group (p=0.06)	• incidence of muscle symptoms is almost identical in statin and placebo-treated patients in clinical trials (about 13% of the participants) • statin related adverse effects are less frequent in clinical trials compared to clinical practice

		series, review articles, editorials, and duplicates	•CK>3 times ULN reported in 0.5% (63/13,734) of statin group vs. 0.3% (42/13,740) of the placebo group (p=0.04) •CK >10 times ULN reported in 0.2% (77/39,893) of the statin group vs. 0.16% (55/34,499) of the placebo group (p=0.28) •Rhabdomyolysis occurred in 0.03% (15/49,691) of the statin group vs. 0.02% (12/52,301) of the placebo group (p=0.48)	
GREACE Athyros VG, et al., 2010 (23) 21109302	**Study type:** Post-hoc analysis of the GREACE population randomized to statin or usual care **Size:** 1600 patients	**Inclusion criteria:** Patients with coronary artery disease, aged <75 y, with LDL-C>2·6 mmol/L and triglycerides <4·5 mmol/L	**1° endpoint:** safety and effectiveness of statin therapy in risk reduction for first recurrent CV event in patients with abnormal liver tests **Results:** • 227patients with abnormal liver tests, treated with a statin had improvements in liver tests from baseline (p<0.0001) •210 patients with abnormal liver tests, not treated with statin had increase in liver tests from baseline (p<0.0001) •<1% (7/880 pts) who received a statin discontinued due to elevation in transaminases >3x ULN •CV events occurred in 10% of patients with abnormal liver tests receiving statin compared to 30% of patients with abnormal liver tests not receiving a statin (p<0.0001)	•Statin treatment appears to be safe in patients with abnormal liver tests and reduces CV mortality
Kralis DG, et al., 2016 (256) 27678424	**Study type:** Systematic Review **Size:** 16 studies (5 case series, 3 cohort studies, 3 registry-based studies, 1 RCT and 4 systematic reviews)	**Inclusion criteria:** English language studies related to statin exposure and pregnancy **Exclusion criteria:** Single case reports Animal studies Studies only published in abstract form, and non-English language	**1° endpoint:** Teratogenicity associated with statin use **Results:** No clear relationship in congenital anomalies with statin use in pregnancy	•No clear relationship between statin use and congenital anomalies in pregnancy •More studies are needed to determine the safety of statins in pregnancy

Data Supplement 42. RCTs Comparing Patient Interventions to Usual Care (Section 6)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
Park LG, et al., 2014 (257) 24321403	**Aim:** To determine the effectiveness of a mobile text messaging intervention in improving adherence to antiplatelet and statin medications. **Study type:** Parallel randomized controlled clinical trial **Size:** N recruited = 90 N randomized = 90 N reported outcomes = 84	**Inclusion criteria:** • ≥ 21 y of age • Hospitalized for non-ST elevation MI, ST elevation MI, or PCI • Prescribed an antiplatelet medication • Prescribed a statin medication • Owned mobile phone with text messaging capability • Able to speak, read, understand English **Exclusion criteria:** • Cognitive impairment that limited ability to understand and complete questionnaires • Inability to operate a mobile phone	**Intervention:** • TM for medication reminders and education (n = 30) • Educational TM only (n = 30) **Comparator:** • No TM (n = 30)	**1° endpoint:** Comparison of medication adherence using TM response rates and MEMS data over 30-d intervention period. • Patients receiving educational and reminder text messages for antiplatelets had a higher percentage of correct doses taken (p=0.02) and percentage of prescribed doses taken on schedule (p=0.01) compared to the No TM group. • TM response rates were significantly higher for anti-platelets than statins (p=0.005), which authors attribute to the fact that statins are prescribed for the evening.	**Study limitations:** (1) Low frequency of analyzable MEMS data caused by poor usage among patients recruited in acute-settings and/or patients resistant to changing habit of using pill organizers. (2) Small convenience sample could undermine external validity of the findings to a more diverse group. (3) Short follow-up period does not allow for measurement of long-term adherence trends or clinical outcomes. (4) Use of MEMS may have added attention to medication-taking habits across all groups.
ORBITAL Willich SN, et al., 2009 (258) 19174696	**Aim:** To measure the effect of a compliance-enhancing program on the level of lipid control for patients taking rosuvastatin. **Study type:** Parallel randomized controlled clinical trial	**Inclusion criteria:** • LDL-C ≥ 115 mg/dl if statin naïve • LDL-C ≥ 125 mg/dl otherwise • Participants had one of the following risk factors: history of CHD or other atherosclerotic disease, 10-	**Intervention:** Rosuvastatin 10/20 mg with compliance program (videotape, educational leaflet, information about free phone patient helpline and website, labels with reminder to take medication) (n = 4064)	**1° endpoint:** Medication adherence, expressed as proportion of participants who were adherent at 3, 6, and 12 mo • Compliance program effective among statin-naïve patients at 3 mo (80% vs. 76%, p<0.01) and 6 mo (78% vs. 73%, p<0.01), when	**Study limitations:**

	Size: N recruited = 8108 N randomized = 8108 N reported outcomes = 6872	y CHD risk Z20%, or diabetes **Exclusion criteria:** • Fasting triglycerides > 400 mg/dl • Familial or secondary hypercholesterolemia • Active liver disease (elevations of aspartate aminotransferase or alanine aminotransferase)	**Comparator:** Rosuvastatin 10/20 mg without compliance program (n = 4044)	compared with control group, but had no significant effect at 12 mo.	
Ma Y, et al., 2010 (259) 21490915	**Aim:** To evaluate the efficacy of a pharmacist-delivered intervention in improving LDL-C goal attainment. **Study type:** Parallel randomized controlled clinical trial **Size:** N recruited = 689 N randomized = 689 N reported outcomes = 559	**Inclusion criteria:** • 30-85 y of age • CHD (defined as ≥ 1 coronary lesion ≥ 50% at the time of coronary angioplasty) **Exclusion criteria:** • Unable or unwilling to give informed consent in English • History of intolerance to two or more statin drugs • Planned to move out of the area within 1 y of recruitment • Estimated life expectancy < 5 y • Major psychiatric illness • No telephone	**Intervention:** Pharmacist-delivered intervention (PI). Initial inpatient contact and 5 patient-centered pharmacist-delivered telephone counseling calls after discharge (n = 338) **Comparator:** Routine care as determined by provider (UC) (n = 331)	**1° endpoint:** Percentage of patients with serum LDL-C < 100 mg/dl at 12 mo. • There was not a significant difference between patients who received the intervention (64.51) when compared to those receiving routine care (60.15) (p=0.293, FET) in terms of meeting cholesterol targets.	**2° endpoint:** CMA for statin medication use was 0.88 (SD = 0.3) for PI group vs. 0.90 (SD = 0.03) for UC (p=0.51). **Study limitations:** (1) Small sample size available for LDL-C outcome limited power to detect level of LDL-C difference; (2) Limitations of using pharmacy refill data – no information to indicate whether dispensed medications were actually taken by patients, no information for patients who did not fill prescriptions; (3) No data on cost of medication or insurance coverage; (4) Study does not account for effects of co-management (e.g., by pharmacists, cardiologists, etc.); (5) No lipid levels at baseline to account for the drop in LDL-C following acute CHD event; (6) Majority of study patients Caucasian, limiting generalizability; (7) Possibility of selection bias, explaining high adherence rate in control group.

Nieuwkerk PT, et al., 2012 (253) 22621795	**Aim:** To evaluate the potential for nurse-led counseling to improve statin adherence and lipid levels without increasing anxiety levels. **Study type:** Parallel randomized controlled clinical trial **Size:** N recruited = 201 N randomized = 201 N reported outcomes = 181	**Inclusion criteria:** • ≥ 18 y of age • Indication for statin use (1° or 2° prevention of cardiovascular event) **Exclusion criteria:** • Severe fasting dyslipidemia (total cholesterol >9.0 mmol/L or triglyceride >4.0 mmol/L) • Statin use >3 mo before inclusion • History of drug and/or alcohol abuse • Pregnant or breastfeeding	**Intervention:** Extended Care (EC). Patients received multifactorial (modifiable and non-modifiable) risk-factor counselling by NP. Counselling focused on increasing medication adherence, reducing overweight, smoking cessation, and increasing physical activity. Data summarized in "personal risk-factor passport," a graphical presentation of 10-y CVD risk. (n = 100) **Comparator:** Routine Care (RC). Measurement of body weight, blood pressure, capillary lipid profile at each visit. All patients received 10 mg atorvastatin, unless baseline cholesterol levels indicated more aggressive therapy. Subsequent dose escalation was allowed, as deemed fit by providers. (n = 101)	**1° endpoints:** Serum LDL; Adherence to lipid lowering medication (subjects asked what percentage of their prescribed lipid-lowering medications they took during the past month, 1 = <30%, 9 = 100%). Both measures were averaged over follow-up (mo 3, 9, and 18). • Among 1° prevention patients, LDL levels were significantly lower for EC group (3.0 ± 0.10 mmol/L) vs. RC group (2.66 ± 0.10 mmol/L) (p<0.05). • Adherence to statins was significantly higher for EC (4.90 ± 0.05) vs. RC (4.60 ± 0.05) (p<0.01).	**2° endpoints**: Anxiety was significantly lower (p<0.01) in the intervention group. **Study limitations:** (1) Self-report was used to assess adherence to statin, known to over-estimate adherence when compared to more objective measures. Authors note significant association between self-reported adherence and LDL cholesterol, however, which supports the validity of their measure. (2) Framingham risk score may not be appropriate estimate for cardiovascular disease among patients with known CVD. (3) Multiple comparisons may have produced false-positive results. (4) Target levels for LDL cholesterol are currently lower than they were at the time of the study.
Kooy MJ, et al., 2013 (260) 3665928	**Aim:** To evaluate the ability of an ERD with or without counseling to improve adherence for statin treatment in non-adherent patients.	**Inclusion criteria:** • ≥ 65 y of age • Started statin therapy at least 1 y prior to study • Non-adherent in the year prior to study (refill rate between 50-80%).	**Intervention:** • ERD: Patients received ERD by mail with written instructions for use. ERD beeped at the same time every day until patient turned it off. (n = 131)	**1° endpoint:** Refill adherence for statin treatment for 360-d period after inclusion (refill rate ≥ 80% considered adherent) • The proportion of adherent patients was not significantly higher in the	**Study limitations**: (1) Some pharmacists did not follow study protocol. Only 54 of the 116 invited patients actually received the counseling; (2) Small sample size could limit power to demonstrate statistically significant effect;

	Study type: Parallel randomized controlled clinical trial **Size:** N recruited = 399 N randomized = 399 N reported outcomes = 381	**Exclusion criteria:** • Persons not personally responsible for medication intake • Life expectancy < 5 y • < 65 y of age • Patients who had changed statins in the 540 d before inclusion	• ERD and Counseling: Patients participated in 10-min counseling session with pharmacist based on stages of change model. Patients received ERD device and instructions for use. (n = 134) **Comparator:** Usual Care (UC). Patients received information about therapy and medication at start of therapy. (n = 134)	ERD group (72.4%, p=0.18) or the ERD and counseling group (69.2%, p=0.55), when compared to the control group (64.8%). • For women using statins for 2° prevention, adherence was significantly higher among those in the ERD group (86.1%), when compared to the control group (52.6%) (p<0.005).	(3) Some patients may have been selected as non-adherent who were actually more than 80% adherent; (4) Researchers were unaware of whether or not patients who received ERD with the instructions actually utilized the device; (5) Odds ratio overestimates the effect size when interpreted as relative risk.
Pladevall M, et al., 2015 (261) 28000212	**Aim:** To determine whether the provision of adherence information with or without motivation interviewing has a positive effect on diabetes and lipid control. **Study type:** Parallel randomized controlled clinical trial **Size:** N recruited = 3799 N randomized = 1692 N reported outcomes = 1692	**Inclusion criteria:** • ≥ 18 y of age • Member of health plan with prescription coverage • ≥ 1 HbA1c measurement with the last value ≥ 7% • ≥ 1 LDL-C measurement with the last value ≥ 100 mg/dL • ≥ 1 Prescription for both an oral diabetes medication and a lipid-lowering medication. **Exclusion criteria:** • Hospice care or hospitalized ≥ 90 d • Participation in any other study involving diabetes management or medication adherence • Primary care provider did not consent to participate	**Intervention:** • Adherence information provided to clinicians to discuss with patients (AI). (n = 569) • Adherence information provided to clinicians and motivational interviewing provided to patients via nurses and pharmacists in "adherence clinic" (AI + MI). (n = 556) **Comparator:** Usual care (UC) (n = 567)	**1° endpoints:** HbA1c; LDL-C at 18 mo. • HbA1c not significantly different for AI (7.91 ± 1.53, p=0.763) or AI + MI (7.79 ± 1.34, p=0.285), when compared with UC (7.88 ± 1.53) • LDL-C not significantly different for AI (87.27 ± 35.67, p=0.380) or AI + MI (85.56 ± 32.86, p=0.084), when compared with UC (89.02 ± 32.11)	**Study limitations**: (1) Possibility of selection bias toward individuals already motivated to change; (2) Study carried out in single integrated health system, may not be generalizable to other systems; (3) Significant baseline differences between randomized groups, although not thought to be clinically significant; (4) Measurement of primary laboratory outcome measures was not standardized and relied on PCPs ordering tests during routine care.

Abbreviations: 1° indicated primary; 2° indicated secondary; CHD, coronary heart disease; CMA, continuous multiple interval; ERD, electronic reminder device; FET, Fisher's exact test; HbA1c, hemoglobin A1c; LDL-C, low density lipoprotein cholesterol; MEMS, medication event monitoring system; MI, myocardial infarction; N/A, not available; NP, nurse practitioner; PCI, percutaneous coronary intervention; PI, pharmacist-delivered intervention; RCT, randomized controlled trial; and TM, text message.
Search Terms: Cholesterol, adherence, compliance
Date of Search: 9/17

Data Supplement 43. RCTs Comparing System Interventions to Usual Care (Section 6)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
Tamblyn R, et al., 2010 (262) 19675319	**Aim:** To determine whether integrating a cardiovascular medication tracking and alert system into electronic medical records would increase drug profile review by PCP, increase likelihood of therapy change, or improve adherence. **Study type:** Parallel cluster-randomized controlled trial **Size:** N screened = 2138 N randomized = 2004 N reported outcomes = 1921	**Inclusion criteria:** • Insured with provincial drug insurance program • ≥ 1 active lipid-lowering or antihypertensive drug prescribed by study physician in 3 mo. prior to index visit. **Exclusion criteria:** • N/A	**Intervention**: PCP provided with detailed drug profile (total medication cost per month, out of pocket expenditure for patient, graphic representation of unfilled prescriptions, and days of supply for each medication); patient adherence calculated at each visit; physician alerted to check for potential adherence problems if treatment adherence < 80% (n = 1002). **Comparator:** PCP had access only to current list of prescribed and dispensed drugs; PCPs did not receive alerts for low adherence (n = 1002).	**1° endpoints:** Review of drug profile by physician; change in drug therapy (increase or discontinuation of therapy) • Participants in the intervention group were more likely to have their drug profile reviewed when compared to the control group (44.5% vs. 35.5%, OR: 1.4; 95% CI: 1.21- 1.76; p<0.0001) • The intervention did not have a significant effect on increased drug therapy (28.5% vs. 29.1%; OR: 0.98; 95% CI: 0.80 to 1.21; p=0.86) or discontinuation of therapy (2.3% vs. 2.0%; OR: 1.18; 95% CI: 0.63 to 2.19; p=0.61).	**2° endpoint:** Adherence rates to cardiovascular medications in the 6 mo before and after the intervention. Measured as difference in post-pre-compliance rates. • The intervention did not have a significant effect on adherence (-6.2 vs. -6.4; SD = 24.1; 95% CI: -1.8, - 2.1; p=0.90) **Study limitations**: (1) Insufficient number of new users to evaluate whether there is greater benefit of adherence monitoring tools for new users; (2) Insufficient statistical power to assess clinically important changes to therapy; (3) Risk of contamination due to study design (i.e., physicians reviewing drug profiles for non-adherent patients in control group).

Choudhry NK, et al., 2011 (263) 22080794	**Aim:** To determine whether eliminating the costs associated with prescriptions improves medication adherence. **Study type:** Parallel randomized controlled clinical trial **Size:** N recruited = 6768 N randomized = 5855 N reported outcomes = 5216	**Inclusion criteria:** • Patients discharged following MI • Patients received medical and prescription drug benefits tough Aetna. **Exclusion criteria:** • N/A	**Intervention**: Participants' pharmacy benefits were changed so that they had no cost sharing for any statins, betablockers, ACE inhibitors, or ARBs after randomization. All copayments were waived at point of care. (n = 2845). **Comparator:** Usual copayment arrangements (n = 3010)	**1° endpoint:** Fatal or nonfatal vascular event or revascularizations (rate/100 person-y). • The rate of total fatal or nonfatal vascular events was lower in the intervention group (21.5) than in the control group (23.3) (HR: 0.89, 95% CI: 0.80 to 0.99; p=0.03).	**2° endpoint:** Medication adherence rates (full adherence defined as having a supply of medications available on ≥ 80% of days during follow-up); Cost of intervention. • Rates of full adherence for statins were significantly higher in the full-coverage group (49.3%) than the usual care group (41.9%) (OR: 1.36; 95% CI: 1.18 to 1.56; p<0.001). • The elimination of co-payments for intervention group did not increase the total spending for the health system (USD 66,008 in full-coverage group vs. USD 71,778 for usual coverage group). (Relative spending 0.89; 95% CI: 0.50 to 1.56; p=0.68). • Participants in the full coverage group paid significantly less for drugs and other services (Relative spending 0.75; 95% CI: 0.68 to 0.80; p<0.001). **Study limitations**: (1) Reliance on administrative claims to identify patients and evaluate outcomes may have diminished the observed effect of the intervention. (2) Nature of sample (relatively young patients, insured by large national insurer) may limit generalizability to other groups.

Abbreviations: ACE, angiotensin-converting-enzyme; ARB, angiotensin-receptor blocker; CI, confidence interval; HR, hazard ratio; N/A, not available; OR, odds ratio; PCP, primary care provider; RCT, randomized controlled trial; and SD, standard deviation.
Search Terms: Cholesterol, adherence, compliance
Date of Search: 9/17

Data Supplement 44. RCTs Comparing Small Number of Pills/Day to Large Number of Pills/Day (Section 6)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
Brown BG, et al., 1997 (264) 9230143	**Aim:** To evaluate the efficacy, safety, and tolerability of a moderate dose, 3-drug lipid-lowering regimen. **Study type:** Cross-over randomized controlled clinical trial **Size:** N recruited = 31 N randomized = 31 N reported outcomes = 29	**Inclusion criteria:** • Male • ≤ 65 y of age • High risk for future cardiac events (apoprotein B ≥ 125 mg/dl; ≥ 1 coronary lesion ≥ 50% stenosis or 2 lesions ≥ 30% stenosis; family history of premature cardiovascular events). **Exclusion criteria:** • N/A	Preliminary treatment: For first 12 mo, all enrolled patients received 3-drug regimen (niacin, lovastatin, colestipol). At 12 mo, patients were randomly assigned to intervention/control groups. At 20 mo, intervention status was reversed. **Intervention**: Reduced daily dosage: Intervention group changed to controlled-release niacin, administered twice daily, rather than 4 times/d. (n = 31) **Comparator:** Continued regular niacin at dosage established during first 12 mo. (n = 31)	**1° endpoint:** Lipid levels • Target LDL of < 100 mg/dl was achieved at 8 mo by 83% of participants on controlled-release niacin compared to 52% of participants on regular niacin (p<0.01)	**2° endpoint:** Medication adherence • Reducing medication intake from 4 times/d to 2 times/d improved mean medication intake by 11% (96% in intervention vs. 85% in control; p=0.01) **Study limitations**: Small sample size limits statistical power and generalizability of findings.
FOCUS Castellano JM, et al., 2014 (265) 25193393	**Aim:** To compare the effects of an FDC polypill (aspirin, simvastatin, rampiril)	**Inclusion criteria:** Participants previously included in Phase 1 (cross-sectional study of FOCUS)	**Intervention**: FDC polypill containing aspirin 100 mg, simvastatin 40 mg, and rampiril 2.5, 5, or	**1° endpoint:** Attending final visit with MAQ of 20 and high pill count (80% to 110%)	**2° endpoints:** • Among study participants, the risk of being non-adherent (MAQ < 20) was associated with younger age, depression, complex

	with administering the 3 drugs separately. **Study type:** Parallel randomized controlled clinical trial **Size:** N recruited = 695 N randomized = 695 N reported outcomes = 695 for intention-to-treat analysis; 458 completed all visits for per protocol analysis	but not in Phase 2 (RCT of FOCUS) **Exclusion criteria:** • Secondary dyslipidemia • Contraindication to polypill • Participation in another trial • Previous percutaneous transluminal coronary angioplasty with drug eluting stent within previous year • Severe congestive heart failure • Serum creatinine > 2 mg/dl • Life expectancy < 2 y • Pregnancy • Premenopausal	10 mg, given once daily. (n = 350) **Comparator**: Received aspirin, simvastatin, and rampiril as 3 separate drugs, administered once daily (n = 345)	• The intervention group showed improved adherence over the control group at 9 mo in the intention-to-treat population (50.8% vs. 41.0%; p=0.019) and per protocol population (65.7% vs. 55.7%; p=0.012)	medication regimen, poorer health insurance coverage, and lower levels of social support. • No significant differences were seen between intervention and control for mean LDL-C (89.9 mg/dl vs. 91.7 mg/dl) or mean SBP (129.6 mmHg vs. 129.6 mmHg). **Adverse events:** No difference in adverse events or serious adverse events in groups receiving polypill (35.4%, 6.0%) or the 3 drugs separately (32.5%, 6.6%). There was 1 death in each group (0.3% vs. 0.3%).
Patel A, et al., 2015 (266) 24676715	**Aim:** To determine whether FDC polypills of generic drugs would promote use of preventive drugs for individuals at high risk of CVD. **Study type:** Parallel randomized controlled clinical trial **Size:** N recruited = 731 N randomized = 623 N reported outcomes = 623	**Inclusion criteria:** • ≥ 18 y of age • High CVD risk (established CVD or estimated 5-y Framingham CVD risk of 15%) •Indications for all and no contraindications to any component of at least 1 of 2 polypills **Exclusion criteria:** • Participants for whom it was clinically inappropriate to alter medications	**Intervention**: Intervention group received a polypill containing aspirin 75 mg, simvastatin 40 mg, lisinopril 10 mg, and either atenolol 50 mg or hydrochlorothiazide 12.5 mg. (n = 311) **Comparator** Usual care. Medications administered as separate doses, as prescribed by physician. (n = 312)	**1° endpoint:** Use of treatment after median of 18 mo. • Participants in the intervention group demonstrated greater use of treatment compared to those who received the drugs as separate doses (70% vs. 47%; RR: 1.49, 95% CI: 1.30 to 1.72; p<0.0001).	**2° endpoint:** • No significant differences between intervention and control for total cholesterol levels (0.08 mmol/l; 95% CI: 0.06-0.22; p=0.26) or SBP (1.5 mmHg; 95% CI: 4.0-1.0; p=0.24). **Adverse events:** ≥ 1 serious adverse event reported in 46.3% of intervention participants and 40.7% of control participants (p=0.16)

Pill Collaborative Group, et al., 2011 (267) 21647425	**Aim:** To evaluate the effect of a polypill on systolic BP, LDL-C, and tolerability. **Study type:** Parallel randomized controlled clinical trial **Size:** N recruited = 859 N randomized = 378 N reported outcomes = 373	**Inclusion criteria:** • Raised cardiovascular risk (7.5% using Framingham risk equation) • No contraindication to polypill • ≥ 18 y of age **Exclusion criteria:** • Patients taking other antiplatelet, blood pressure lowering, or cholesterol lowering medicine • Patients with diabetes mellitus	**Intervention**: Intervention group received polypill containing aspirin 75 mg, lisinopril 10 mg, hydrochlorothiazide 12.5 mg, and simvastatin 20 mg. (n = 189) **Comparator:** Placebo (n = 189)	**1° endpoints:** Change in SBP, LDL-C, and tolerability (withdrawal from study) measured at 12 wk. • There was a reduction in SBP (9.9 mmHg; 95% CI: 7.7-12.1) and LDL-C (0.8 mmol/L; 95% CI: 7.7-12.1) with the polypill, as compared to the placebo. • Discontinuation rates were higher in polypill group (23%) than the placebo group (18%) (RR: 1.33; 95% CI: 0.89-2.0; p=0.2).	**2° endpoint:** • Treatment adherence (% of prescribed treatment according to pill counts) was 82% for polypill group and 86% for control group (p=0.1). **Study limitations:** (1) Short follow-up period did not allow for assessment of long-term drop-out rates. (2) Narrow sample may limit generalizability of findings. **Adverse events:** 58% of participants in the intervention group reported adverse events compared to 42% in control group (p=0.001). Authors note that reported side effects were consistent with known side effects of medications within the polypill. Within each group, 4 serious adverse events were reported (polypill: chest pain, newly diagnosed Type II diabetes, removal of wisdom teeth, syncope; placebo: syncope, depression, transient ischemic attack; hip fracture).
Selak V, et al., 2014 (268) 24868083	**Aim:** To evaluate the effectiveness of FDC treatment in improving adherence and risk factor control among high risk cardiovascular patients.	**Inclusion criteria:** • 18-79 y of age • High risk of CVD (established coronary, cerebrovascular, or peripheral vascular disease; or ≥ 15% 5-y risk of cardiovascular event) • PCP determined all drugs in at least 1 of the 2	**Intervention**: FDC treatment was administered by PCP. PCPs could choose between 2 FDCs: (1) aspirin 75 mg, simvastatin 40 mg, lisinopril 10 mg, atenolol 50 mg; or (2) aspirin 75 mg, simvastatin 40 mg, lisinopril 10 mg,	**1° endpoint:** Adherence rate at 12 mo • FDC was associated with higher adherence compared to usual care (81% vs. 46%; RR: 1.75, 95% CI: 1.52 to 2.03; p<0.001).	**2° endpoint:** Mean change in LDL-C, SBP • There was not a significant difference in LDL-C levels between the intervention and control groups (-0.05 mmol/L; 95% CI: -0.17, 0.08; p=0.46).

	Study type: Parallel randomized controlled clinical trial **Size:** N recruited = 513 N randomized = 513 N reported outcomes = 513	versions of the FDC treatment were recommended • Patients had started statins ≥ 1 y prior to inclusion, and were non-adherent in the year prior to inclusion (refill rate between 50% and 80%) **Exclusion criteria:** • Contraindications to any components of FDC • Congestive heart failure, hemorrhagic stroke, active stomach or duodenal ulcer, receipt of oral anticoagulant • Concerns of PCP about risk of study • Participant unlikely to complete the trial (i.e., terminal illness)	hydrochlorothiazide 12.5 mg. (n = 256) **Comparator:** Cardiovascular drug regimen was prescribed according to PCP's usual method. (n = 257)		• There was a significant reduction in SBP for the intervention group compared to the control group (-2.6 mmHg; 95% CI: -4.0, -1.1 mmHg; p<0.001). **Study limitations:** (1) Moderate statistical power limits ability to rule out small increases or decreases in risk factor levels. (2) Baseline treatment rates were higher than national averages, limiting ability to test FDC among patients currently taking few or no preventive drugs. (3) Open label trial design may have contributed to differential treatment or reporting between groups. **Adverse events:** There was not a significant difference in serious adverse events between the intervention group (99) and the control group (93) (p=0.56). There were 4 deaths in the intervention group and 6 in the usual care group (p=0.75)
Thom S, et al., 2013 (269) 24002278	**Aim:** To determine whether FDC therapy improves long-term adherence, SBP, and LDL-C when compared to usual care. **Study type:** Parallel randomized controlled clinical trial	**Inclusion criteria:** • ≥ 18 y of age • High cardiovascular risk (history of coronary heart disease, ischemic cerebrovascular disease, or peripheral vascular disease; or estimated 5-y CVD risk ≥ 15%) **Exclusion criteria:**	**Intervention**: Patients were assigned to an FDC of either (1) aspirin 75 mg, simvastatin 40 mg, lisinopril 10 mg, and atenolol 50 mg; or (2) aspirin 75 mg, simvastatin 40 mg, lisinopril 10 mg, and hydrochlorothiazide 12.5. (n = 1002)	**1° endpoint:** Self-reported adherence (defined as taking medication for ≤ 4 d during week preceding visit); mean changes in LDL-C and SBP at 15 mo • Adherence was significantly greater for patients receiving FDC, when compared to the usual care (86% vs. 65%, RR: 1.33, 95% CI: 1.26 to 1.41; p<0.001).	**Study limitations:** (1) Participants selected based on their willingness/ability to attend study visits, which may limit the generalizability of the findings. (2) High level of adherence reported at baseline findings when compared with the general population. **Adverse events:** There was no significant different in adverse

	Size: N recruited = 2138 N randomized = 2004 N reported outcomes = 1921	• Low cardiovascular risk • Contraindications to switching medication • Inability to complete trial	**Comparator:** Usual care (n=1002)	• There was a significant difference in LDL-C, favoring the intervention (-4.2 mg/dL, 95% CI: -6.6 to -1.9; p<0.001). • There was a significant difference in SBP, favoring the intervention (-2.6 mmHg, 95% CI: -4.0 to -1.1 mmHg; p<0.001)	events between the FDC group (5%) and the usual care group (3.5%) (p=0.09). There were 17 deaths in the FDC group compared to 15 in the usual care group (p=0.72).

Abbreviations: 1° indicated primary; CI, confidence interval; CVD, cardiovascular disease; FDC, fixed-dose combination; HR, hazard ratio; LDL-C, low density lipoprotein cholesterol; MAQ, Morisky Green questionnaire; N/A, not available; OR, odds ratio; PCP, primary care provider; RCT, randomized controlled trial; and RR, relative risk; and SBP, systolic blood pressure.
Search Terms and Date of Search:

Data Supplement 45. RCTs for Implementation (Section 6)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
Choudhry, NK, et al., 2011 (263) 22080794	**Study type:** investigator-initiated, cluster-randomized, controlled policy study **Size:** 5855 patients (2845 full prescription coverage; 3010 patients with usual prescription coverage)	**Inclusion criteria:** Patients received both medical and prescription drug benefits through Aetna, discharged from the hospital with a principal or secondary diagnosis code of International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) 410 (except when the fifth digit was 2), and a length of stay of 3 to 180 d. **Exclusion criteria** Patients enrolled in a health savings account offering full coverage for the study medications or	**1° endpoint:** First major vascular event or revascularization. **Results:** Primary endpoint - no difference 17.6 per 100 person-y in the full-coverage group vs. 18.8 in the usual coverage group; HR: 0.93; 95% CI: 0.82-1.04; p=0.21. • Secondary endpoints better for full-coverage total major vascular events or revascularization (21.5 vs. 23.3; HR: 0.89; 95% CI: 0.90 to 0.99; p=0.03) • Rate of first major vascular event or revascularization (11.0 vs. 12.8; HR: 0.93; 95% CI: 0.82–1.04).	• Elimination of copayments improved adherence and secondary outcomes. • Although out-of-pocket costs to the patient were reduced, total spending did not increase.

		≥ 65 y of age at time of hospital discharge, since Medicare was primary health insurer	• Adherence rates statins, beta-blockers, ACE inhibitors, and ARBs for all comparisons (p<0.001) No difference in total spending between groups ($66,008 for the full-coverage group vs. $71,778 for the usual-coverage group; relative spending, 0.89; 95% CI: 0.50-1.56; p=0.68).	

Abbreviations: 1° indicated primary; CI, confidence interval; HR, hazard ratio; N/A, not available; OR, odds ratio; RCT, randomized controlled trial; and RR, relative risk.
Search Terms and Date of Search: Author to provide

Data Supplement 46. Nonrandomized Trials, Observational Studies, and/or Registries for Implementation (Section 6)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
ACC/AHA Special Report: Clinical Practice Guideline Implementation Strategies, 2017 (270) 28132746	**Study type:** Summary of systematic reviews (SR) **Size:** 39 SR 16 overviews of SR	**Inclusion criteria:** For critical questions (CQ) 1,2: SRs focused on implementation of guidelines or clinical practice directly affecting patient care + aimed at clinicians [4 interventions: • audit and feedback (any summary of clinical performance over a specified time period; may include recommendations for clinical active); • educational outreach visits (academic detailing = trained person met with providers in their practice setting to give information with the intent of changing practice; the information may have included feedback on performance); • reminders (patient or encounter specific information given verbally or on paper/computer screen, which was designed to prompt information recall; computer-aided decision support and drug doses are included); • provider incentives (pay for performance = direct or indirect financial reward/benefit to the individual for doing a specific action).	**1° endpoint:** Critical questions 1,2: • Generally effective: > 2/3 studies had positive intervention effects • Mixed effectiveness: 1/3 to 2/3 studies had positive intervention effects • Generally ineffective: < 1/3 studies had positive intervention effects Critical questions 3, 4: Conclusions are drawn from contractor's qualitative coding of included reviews during abstraction process for a variety of categories of contextual factors identified a priori. **Results:** Generally effective for improving process of care and clinical outcomes: • audit and feedback (15 of 21 reviews; 7 of 12 reviews) • educational outreach visits (12 of 13 reviews; 3 of 5 reviews) Generally effective for cost reduction: • outreach visits (2 of 2 reviews) • reminders (3 of 4 reviews) • provider incentives (1 of 1 review) Generally effective for cost-effectiveness outcomes:	• Gaps exist in the evidence of effectiveness of implementation strategies. • Audit and feedback and educational outreach visits were generally effective in improving process of care and clinical outcomes. • Educational outreach visits were generally effective for cost reduction and cost effectiveness outcomes. • Reminders and provider incentives were generally effective for cost reduction. • Reminders and provider incentives showed mixed effectiveness for improving process of care. • Implementation strategies may not be effective across all practice settings. • It may take multiple strategies to implement guidelines in clinical practice.

		For critical questions (CQ) 3,4: SRs and overviews of SRs focused on contextual issues affecting guideline implementation. **<u>Exclusion criteria</u>:** Studies focused on interventions targeting patients (e.g. patient education/reminders).	• educational outreach visits (1 of 1 review) and provider incentives (1 of 1 review) . Mixed effectiveness for improving process of care and clinical outcomes: • provider incentives (3 of 4 reviews; 3 reviews equally distributed between generally effective, mixed, and generally ineffective). Mixed effectiveness for improving process of care and generally ineffective for clinical outcomes: • reminders (27 reviews with 11 mixed and 3 generally ineffective results; 18 reviews with 6 mixed and 9 generally ineffective results). Facilitating factors to adoption/adherence: • guideline characteristics, e.g. format, resources, and end-user involvement (6 reviews/overviews). • involving stakeholders (5 reviews/overviews). • leadership support (5 reviews/overviews) scope of implementation (5 reviews/overviews). • organizational culture such as multidisciplinary teams and low-baseline adherence (9 reviews/overviews).	

			• electronic guidelines systems (3 reviews). Barriers to adoption/ adherence: • time constraints (8 reviews/overviews) limited staffing resources (2 overviews). • timing (5 reviews/overviews) • clinician skepticism (5 reviews/overviews). • clinician knowledge of guidelines (4 reviews/overviews). • higher age of the clinician (1 overview).	
Fischer, F, et al., 2016 (271) 27417624	**Study type:** Scoping review **Size:** 69 articles (42 studies, 27 reviews)	**Inclusion criteria:** articles published through 2015 and listed in PubMed (English, German). **Exclusion criteria:** If did not include: • generalizable strategies • direct reference to strategies/barriers for guideline implementation • clinical guidelines • comparability (e.g. developing countries) • study protocol	**Results:** Physician factors • Barriers: knowledge (lack of awareness or familiarity); attitudes (lack of agreement, self-efficacy, skills, learning culture, outcome expectancy, or motivation). • Strategies: dissemination (standardize notification process, training material), continuing education/meetings, active learning with expert opinion leaders, individualized audit and feedback, group performance audit, quality circle, financial, standing orders Guideline-related factors • Barriers: lack of evidence, applicability, or clear intervention goals; plausibility of	• Publication and dissemination of guidelines does not ensure guideline implementation. • An implementation strategy for guidelines is needed. • Barriers to guideline implementation and adherence need to be analyzed in advance, so implementation strategies may be tailored to the setting and target group.

			recommendations; complex/too theoretical; focus on patients with single disease or excludes comorbidities, difficult to implement. • Strategies: use evidence-based medicine in guideline development, communication strategies, marketing outreach visits, computerized decision-support systems, reminders, pilot projects. External factors • Barriers: organizational constraints, lack of resources or collaboration, social and clinical norms. • Strategies: standing orders, improvements in organization of care, local adaption/consensus groups, incorporation into established structures.	
Stacey D, et al., 2017 (272) 28402085	**Study type:** Updated search (2012 to April 2015) in CENTRAL; MEDLINE; Embase; PsycINFO; and grey literature; includes CINAHL to September 2008. **Size:** 105 studies, 34,043 participants	**Inclusion criteria:** RCTs comparing decision aids to usual care and/or alternative interventions. **Exclusion criteria:** Studies comparing detailed versus simple decision aids.	**1° endpoint:** Difference in attributes of choice made and the decision-making process. **Results:** Decision aids improved these attributes compared to usual care: **Choice made** • participants' knowledge (mean difference 13.27/100; 95% CI: 11.32 - 15.23; 52 studies; N = 13,316; high-quality evidence), • accuracy of risk perceptions (risk ratio 2.10; 95% CI: 1.66 - 2.66; 17	After using a decision aid, • knowledge improved • patients had more accurate risk perception • More patients were willing to start a new medication. Decision aids added 2.6 min to the consultation time.

			studies; N = 5096; moderate-quality evidence) • congruency between informed values and care choices (risk ratio 2.06; 95% CI: • 1.46 to 2.91; 10 studies; N = 4626; low-quality evidence) <u>Decision-making process</u> • decisional conflict related to feeling uninformed (mean difference −9.28/100; 95% CI: −12.20 to −6.36; 27 studies; N = 5707; high-quality evidence) • indecision about personal values (mean difference −8.81/100; 95% CI: −11.99, −5.63; 23 studies; N = 5068; high-quality evidence) • Proportion of people who were passive in decision making (risk ratio 0.68; 95% CI: 0.55-0.83; 16 studies; N = 3180; moderate-quality evidence). <u>Relevant secondary outcomes</u> • increased those choosing to start new medications for diabetes (risk ratio1.65; 95% CI: 1.06 to 2.56; 4 studies; N =447). • median effect of decision aids on length of consultation was 2.6 min longer (24 versus 21; 7.5% increase).	

Michelis,KC, et al., 2011 (273) 21462218	**Study type:** retrospective cohort study **Size:** 796 patients with baseline LDL-C not at goal	**Inclusion criteria:** ≥18 y old; ≥ 2 patient encounters, with primary care provider, cardiologist, or endocrinologist, and lipid panels drawn in 2007. **Exclusion criteria:** LDL-C could not be determined (triglycerides > 400 mg/dL); LDL-C goal could not be determined.	**1° endpoint:** LDL-C goal attainment with e-prescription with formulary decision support (FDS) versus manual prescription. **Results:** Patients with e-prescription using FDS reached LDL-C goal more often (51%) than patients with manual prescription (44%), OR: 1.59 (95% CI: 1.12-2.25).	• Use of e-prescription with formulary decision support may increase adherence and LDL-C goal attainment • Generic statin prescribed more often with an e-prescription using FDS than with a manual prescription (38% vs. 22.9%; p=0.0004) • For each $10 increase in prescription price, the likelihood of being at goal decreased by 5% (OR: 0.95; 95% CI: 0.93-0.98).
Watanabe JH, 2014 (274) 24372459	**Study type:** retrospective cohort study **Size:** 4886 patients	**Inclusion criteria:** New users of statins (no active statin prescription in 6 mo prior), dyslipidemia (International Classification of Diseases, Ninth Revision, Clinical Modification ICD-9-CM code 272), within the Veterans Integrated Service Network 22 for at least 2 y prior, and initiated a statin between November 30, 2006, and December 2, 2007. Required to have medical and pharmacy benefits throughout the study period. Study subjects were required to have at least 1 primary care visit prior to index date, at least 2 primary care visits after index date, and at least 1 prescription prior to index date. Patients included in the analysis were required to have complete data for exposure, outcome, and regression adjustment variables. **Exclusion criteria:** N\A	**1° endpoint:** Adherence rate [determined via the medication possession ratio (MPR), defined as number of days supplied with prescription medication divided by days of observation]. **Results:** Patients with copayment for their statin had higher adherence rates (≥0.8 MPR and ≥0.9 MPR) than patients with copayments, odds ratios (OR) of 1.19 (95% CI: 1.03-1.37) and 1.28 (95% CI: 1.11-1.48).	• Elimination of copayments increased adherence rate.
Navar AM, et al., 2017 (275) 28973087	**Study type:** Retrospective, cohort study using pharmacy claims transactional data **Size:** 45,029 patients	**Inclusion criteria:** New PCSK9 inhibitor prescription from 8/1/15 to 7/31/16 **Exclusion criteria:** N\A	**1° endpoint:** Proportion of PCSK9 inhibitor prescriptions approved and abandoned **Results:** • 20.8% approved on first day; 47.2% ever received approval	• About 1/3 of approved prescriptions for PCSK9 inhibitors were not filled because of cost.

			• Of those approved, 65.3% filled the prescription • 30.9% of those prescribed PCSK9 inhibitor ever received therapy Prescription abandonment by patients associated with cost • 7.5% with copay = $0 • 75% with copay ≥ $350	
Hess GP, et al., 2017 (276) 29084735	**Study type:** Retrospective, descriptive cohort study using pharmacy claims linked to electronic medical records from nationwide data warehouse **Size:** 51,446 patients who had PCSK9 inhibitor prescription submitted (451 individual health plans)	**Inclusion criteria:** ≥18 y old; ≥1 submitted claim for PCSK9 inhibitors from 7/1/15 to 8/31/2016, ≥1 private practitioner or facility medical claims from 1/1/2010 to 7/31/15, and >1 LDL-C test result (≤ 400 mg/dL) from 7/1/2015 to the patient's index date. **Exclusion criteria:** N\A	**1° endpoint:** Percentage of patients approved or rejected for PCSK9 inhibitor **Results:** • 47% of PCSK9 inhibitor prescriptions were approved for coverage by payer Variables associated with PCSK9 inhibitor approval: • > 65 y of age (p<0.01) • history of ASCVD (p<0.01) • prescription from cardiologist or nonprimary care provider (p<0.01) • statin intolerance (p=0.03) • longer statin duration (p=0.01) • noncommercial payers (p<0.01) Approval rates • Highest: Medicare (60.9%) • Lowest: commercial third-party payers (24.4%)	Cost to the patient (mean patient responsibility) influenced therapy possession and abandonment • Approved/possessed: $202.87±12.92 • Approved/abandoned: $478.83±27.32

Abbreviations: 1° indicated primary; CI, confidence interval; HR, hazard ratio; N/A, not available; OR, odds ratio; RCT, randomized controlled trial; and RR, relative risk.

Search Terms and Date of Search: Author to provide

Data Supplement 47. Cost-Effectiveness Models of PCKS9 Inhibitors in Secondary Prevention (Section 7)

Study	Design	Patient Population	Incremental Lifetime Cost	Incremental Effectiveness	Value	Summary/Conclusions
Kazi DS, et al., 2016 (277) 27533159	State-transition Markov Model (CVD Policy Model)	ASCVD with LDL>=70 despite maximally tolerated statin therapy (including individuals who are statin intolerant)	$ 3,282 x 10^9 (US Population)	7.92 x 10^6 Quality Adjusted Life Years (US Population)	$414,000/QALY added (relative to ezetimibe) $316,000/QALY (relative to statin standard of care)	"Assuming 2015 [US] prices, PSCK9 inhibitor use…did not meet generally accepted incremental cost-effectiveness thresholds"
Kazi DS, et al., update (278) 28829863	State-transition Markov Model (CVD Policy Model)	ASCVD with LDL>=70 despite maximally tolerated statin therapy (including individuals who are statin intolerant)	$ 2,500 x 10^9 (US Population)	5.56 x 10^6 Quality Adjusted Life Years (US Population)	$450,000/QALY added (relative to ezetimibe) $339,000/QALY (relative to statin standard of care)	"PCSK9 inhibitor use in patients with ASCVD was not cost-effective at 2017 [US] prices… Reducing annual drug costs by 71% (to ≤$4215) would be needed for PCSK9 inhibitors to be cost-effective at a threshold of $100 000/QALY"
Gandra SR, et al., 2016 (279) 27092712	State-transition Markov Model	ASCVD with LDL >70 mg/dl despite maximally tolerated statin therapy	$158,307 (per patient)	1.12 Quality Adjusted Life Years (per patient)	$141,700/QALY (relative to statin standard of care)	"Evolocumab added to standard of care may provide a cost-effective treatment option for lowering LDL-C"
Toth PP, et al., 2017 (280) 28097904	State-transition Markov Model	ASCVD with a prior CV event, LDL >=70 mg/dl despite maximally tolerated statin therapy	$127,088 (per patient)	0.68 Quality Adjusted Life Years (per patient)	$190,400/QALY (relative to statin standard of care)	"The expected value-based price for evolocumab is higher than its current annual cost, as long as the payer discount off list price is greater than 20%"
Fonarow GC, et al., 2017 (281) 28832867	State-transition Markov Model	ASCVD with a prior CV event, LDL >=70 mg/dl despite maximally tolerated statin therapy	$105,398 (per patient)	0.39 Quality Adjusted Life Years (per patient)	$268,600/QALY (relative to statin standard of care)	"At its current list price of $14 523, the addition of evolocumab to standard background therapy in patients with atherosclerotic cardiovascular disease exceeds generally accepted cost-effectiveness thresholds."

Arrieta A, et al., (282) 28081164	State-transition Markov Model	Patients who would have been eligible the OSLER (Open-Label Study of Long-Term Evaluation against LDL Cholesterol) study	$231,918 (per patient)	0.66 Quality Adjusted Life Years (per patient)	$348,800/QALY (relative to statin standard of care)	"At current prices, our study suggests that PCSK9 inhibitors do not add value to the U.S. health system…to be the breakthrough drug in the fight against cardiovascular disease, the current price of PCSK9 inhibitors must be reduced by more than 70%"
Arrieta A, et al., update (282) 29049467	State-transition Markov Model	Patients who would have been eligible the FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) trial	$136,101 (per patient)	0.36 Quality Adjusted Life Years (per patient)	$337,700/QALY (relative to statin standard of care)	"At current prices, the addition of PCSK9 inhibitor to statin therapy is estimated to provide an additional quality-adjusted life year for $337,729. Significant discounts are necessary to meet conventional cost-effectiveness standards."

Data Supplement 48. Cost-Effectiveness Models of PCKS9 Inhibitors in Primary Prevention (Familial Hypercholesterolemia) (Section 7)

Study	Design	Patient Population	Incremental Lifetime Cost	Incremental Effectiveness	Value	Summary/Conclusions
Kazi DS, et al., 2016 (277) 27533159	State-transition Markov Model (CVD Policy Model)	Heterozygous familial hypercholesterolemia with either: (1) a family history of premature CHD and LDL-C >= 190 mg/dL without statin therapy or >= 150 mg/dL with statin therapy OR (2) no family history of premature CHD and LDL-C >= 250 mg/dL without statin therapy or >= 200 mg/dL with statin therapy	$ 316 x 10^9 (US Population)	628 x 10^3 Quality Adjusted Life Years (US Population)	$503,000/QALY added (relative to ezetimibe)	"Assuming 2015 [US] prices, PSCK9 inhibitor use…did not meet generally accepted incremental cost-effectiveness thresholds"
Gandra SR, et al., (279) 27092712	State-transition Markov Model	Heterozygous familial hypercholesterolemia with LDL > 100 md/dl	$153,289 (per patient)	2.02 Quality Adjusted Life Years (per patient)	$75,900/QALY (relative to statin standard of care)	"Evolocumab added to standard of care may provide a cost-effective treatment option for lowering LDL-C"

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