2019 ACC/AHA Guideline on Primary Prevention of Cardiovascular Disease 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 April through July 2018, that included literature published through July 2018. Key search words included but were not limited to the following.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. RCTs of Patient-Centered Approaches for Providing Comprehensive ASCVD Prevention (Section 2.1)

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 value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
Carter BL, et al., 2009 (1) 19858431	**Study Aim:** To determine the potency of interventions for blood pressure involving nurses or pharmacists **Study type:** Systematic review and meta analysis N=37 controlled clinical trials	**Inclusion criteria:** • Quasi-randomized trials, controlled before-after studies, interrupted time-series studies, patient-randomized trials, cluster randomized trials • Published January 1, 1970 through February 5, 2009 • Intervention of team based care of hypertension involving pharmacists or nurses	**Intervention:** Team based care of hypertension involving pharmacists or nurses. Because components varied, reviewers assigned a potency score of the predicted potency of the combination of effects of the interventions **Comparison:** Not specified	**1° endpoint:** Net change in BP Net change in BP Control (control was BP lower than 140/90 mm Hg for uncomplicated BP and lower than 130/80 mm Hg for those with diabetes mellitus or chronic kidney disease) A significant predicted reduction in SBP was found in interventions including pharmacist recommended medication to physician (-27.21 mm Hg, p=0.002), counseling about lifestyle modification (-12.63 mm Hg, p=0.03), pharmacist performed intervention (-11.70 mm Hg, p=0.03), use of a treatment algorithm (-8.46 mm Hg, p<0.001), completion of a drug profile and/or medication history (-8.28 mm Hg, p-0.01), and overall intervention potency score assigned by reviewers (p<0.001). A significant predicted reduction in DBP was found for interventions including: referral made to a specialist (-19.61 mm Hg, p0.04), providing patient education about BP medications (-17.60 mm Hg, p=0.003), completion of a drug profile and/or medication history (-7.27 mm Hg, p=0.006), pharmacist performed intervention (-4.03 mm Hg, p=0.04), nurse performed intervention (-3.94 mm Hg, p=0.04).	**Study Limitations:** The analysis included studies with varying trial designs and varying interventions There was no formal test of heterogeneity, but at least one study had an extremely high OR (OR=29.71), though sensitivity analysis revealed potential for a change to the OR for community pharmacy intervention to 1.8

				In a non-parametric analysis, the only intervention component significantly associated with a reduction in BP was education about BP medications, which was associated with a median 8.75 mm Hg reduction in SBP (IQR: -11.90 to -4.25) and a median 3.60 reduction in DBP (IQR: -7.03 to -1.00). In meta regressions examining the outcome of controlled BP, there were significant effects of team-based interventions regardless of whether they involved nurses, community pharmacies, or primary care clinic pharmacists, though the strongest effect was in community pharmacies. In trials of nurse-led interventions, the overall OR for control of SBP in the intervention vs. control group=1.69 (95% CI 1.48-1.93). In trials of community pharmacies, the OR=2.89 (95% CI 1.83-4.55), and in pharmacists in primary care clinics OR=2.17 (95% CI 1.75-2.68). In nonparametric analyses, in nursing studies, the mean reduction in SBP=5.84 mm Hg compared to 7.76 in pharmacists in primary care clinics and 9.31 mm Hg in interventions with community pharmacists. Comparable reductions in DBP were 3.46 mm Hg, 4.18 mm Hg, and 4.59 mm Hg, respectively.	
Chen Z, et al., 2013 (2) 23614849	**Study Aim:** To compare indices of 24-hour blood pressure following a physician-pharmacist collaborative intervention and to describe the associated changes	**Clinic Inclusion criteria:** • Community-based family medicine offices with clinical pharmacists on staff who had worked in offices at least 3 years **Patient Inclusion criteria:** • 21 or older	**Intervention:** N=3 practices Physician-pharmacist comanagement. Clinical pharmacists evaluated medications and BP at baseline and 1	**1° endpoint:** Pre-post and intervention vs control comparison of Measurement of BMI, assessment Drug therapy changes (diuretic added, nondiuretic added, switch within same class, dose increased, dose decrease, drug discontinued)	**Study Limitations:** Small number of randomized clinics Data analyzed at patient level though randomization was done at clinic level

	in antihypertensive medications **Study type:** secondary analysis of a cluster randomized clinical trial N=6 clinics (n=374 patients)	• Had a diagnosis of essential hypertension • Taking 0-3 antihypertensive medications without changes in the prior 4 weeks • Uncomplicated hypertension with SBP 140-179 mm Hg or diastolic BP 90 to 109 mm Hg, or hypertension with diabetes mellitus or chronic kidney disease with SBP 130 to 179 mm Hg or DBP 80-109 mm Hg **Patient Exclusion criteria:** • Serious renal or hepatic disease • Cognitive impairment • Poor prognosis (life expectancy <3 years) • Recent myocardial infarction or stroke	month, had a 3-month check in with more frequent contact of BP remained poorly controlled. Pharmacist-identified issues and recommendations were shared with patient's physician, typically face to face. Therapy changed had to be accepted by physician. **Control:** N=3 practices Usual care. Office pharmacists did not make therapy recommendations except typical drug information questions.	Compared ambulatory BPs for patients not taking diuretic at baseline but had a diuretic added with those who never had a diuretic added At the end of the study (6 months), mean 24-hour SBP was significantly lower in the co-managed group than the control group (122.8 vs. 134.4, p<0.001), as was mean nighttime SBP (114.8 vs. 123.7, p<0.001), and mean overall 24-hour SBP (120.4 vs. 131.8, p<0.001). The percent of patients with controlled SBP was significantly higher in the co-managed group than the control group for mean daytime SBP (79.6% s. 57.6%, p<0.001), for mean nighttime SBP (67.9% vs. 48.1%, p<0.001), and mean overall 24-hour SBP (75.6% vs. 50.0%, p<0.001). The mean number of antihypertensive medications was significantly greater in the co-managed than control group (1.3 to 2.3 vs. 1.9 to 2.2, p<0.01). Significantly greater number of drug changed were initiated in the co-managed group than in the control group (mean=2.7 vs. 1.1, p<0.001). 95% of pharmacist recommendations for antihypertensive regimen changes were accepted and implemented by physicians. Significantly greater percentages of co-managed than control patients had a diuretic added (41.5% vs. 15.2%, p<0.001), a nondiuretic drug added (64.8% vs. 20.2%, p<0.001), had a dose increased (55.7% vs. 30.8%, p<0.001),	

				had a dose decreased (15.9% vs. 5.1%, p<0.001), had a drug discontinued (18.2% vs. 10.1%, p=0.024), and had a switch within class (6.8% vs. 2.0%, p=0.022). The specific class of antihypertensive medication used in co-managed vs control patients were: diuretics (79.6% vs. 62.6%, p<0.001), β-blockers (42.1% vs. 47.0%, p≥0.05), angiotensin-converting enzyme inhibitors (51.1% vs. 51.5%, p≥0.05), calcium channel blockers (33.0% vs. 29.3%, p≥0.05), α-Blockers (0.0% vs. 5.6%, p<0.01), angiotensin receptor blockers (11.9% vs. 10.1%, p≥0.05), centrally acting α-blockers (1.1% vs. 3.0%, , p≥0.05), vasodilators (0.0% vs. 2.0%, p≥0.05), aldosterone receptor blockers (4.0% vs. 1.0%, p≥0.05)) <u>Effect of adding a diuretic: baseline vs 6 months</u> *Daytime ambulatory blood pressure* No diuretic added 137.1 vs. 129.6 mm Hg Diuretic added in first month: 138.9 vs. 122.5 mm Hg (p<0.01 vs. no diuretic added group) Diuretic added between months 1-3: 151.4 vs. 135.5 mm Hg Diuretic added between 3-6 months: 150.5 vs. 132.3 mm Hg Diuretic added any time: 141.4 vs. 124.9 mm Hg *Nighttime ambulatory blood pressure*	

				No diuretic added 126.5 vs. 121.7 mm Hg Diuretic added in first month: 126.7 vs. 111.8 mm Hg (p<0.001 compared to no diuretic added group) Diuretic added between months 1-3: 140.0 vs. 123.9 mm Hg Diuretic added between 3-6 months: 134.4 vs. 124.3 mm Hg Diuretic added any time: 128.6 vs. 114.2 mm Hg (p<0.01 compared to no diuretic added group) *Overall 24-hour ambulatory blood pressure* No diuretic added 134.2 vs. 127.4 mm Hg Diuretic added in first month: 135.4 vs 119.2 mm Hg Diuretic added between months 1-3: 148.7 vs. 133.3 mm Hg Diuretic added between 3-6 months: 145.2 vs. 129.4 mm Hg Diuretic added any time: 137.8 vs. 121.8 mm Hg (p<0.05 compared to no diuretic added group)	
Fazel MT, et al., 2017 (3) 28573873	**Study Aim:** To conduct a comprehensive systematic review and meta-analyses	**Inclusion criteria:** • Studies involving patients aged 18 and older • Type 1 or type 2 diabetes • Pharmacist interventions	**Intervention:** Pharmacist interventions providing direct patient care within a	**1° endpoint:** Hemoglobin A1C N=7417 from 36 study arms in 35 studies	**2° endpoint:** Systolic blood pressure LDL cholesterol *SBP*:

	examining the impact of pharmacist interventions as part of health care teams on diabetes therapeutic outcomes in ambulatory care settings **Study type:** Systematic review and meta-analysis of studies with comparative designs (controlled and non-controlled trials and pre-post studies) N=42 in systematic review, N=35 in meta analysis	• Ambulatory care setting • Usable data on HbA1C, systolic blood pressure, or LDL cholesterol • English language article **Exclusion criteria:** • Gestational diabetes • Review articles, systematic reviews, meta analyses, abstracts, poster/seminar presentations	health care team in an ambulatory care setting (could be educational, clinical, or both) **Comparison:** alternative or usual care	Overall SMD=0.57, p<0.01 (difference of 1.1% in HbA1C, 95% CI 0.88-1.27) Evidence of heterogeneity (I^2=92%). No significant differences in results by study design (SMD for RCT=0.59, retrospective non randomized controlled trial=0.48, pre-post=0.73, retrospective pre-post=0.61, p for difference=0.48) SMD for results stratified by baseline HbA1C: Low baseline=0.49, medium=0.52, high=1.08, p=0.18 Differences in SMD for results stratified by age <59 vs >59 not significant (p=0.75) No evidence of publication bias	N=14 studies with 4275 participants Overall SMD=0.31 (p<0.01) (difference=4.3 mm Hg, 95% CI 4.3-6.2) Evidence of heterogeneity (I^2 =84%) No evidence of publication bias *LDL cholesterol*: N=19 studies with 5029 participants Overall SMD=0.32 (p<0.01) (difference=106 mg/dL, 95% CI 7.1-14.1) Evidence of heterogeneity (I^2 =83%) No evidence of publication bias
Hirsch JD, et al., 2014 (4) 25085406	**Study Aim:** To examine blood pressure control in hypertensive patients managed by a newly formed PharmD-PCP MTM team versus usual care in a university-based primary care clinic **Study type:** Randomized pragmatic trial N=166	**Inclusion criteria:** • Age 18+ • Diagnosis of hypertension • Most recent BP measurement ≥140/≥90 mm Hg (≥130/≥80 mm Hg with comorbid diabetes mellitus) • Current treatment with 1+ antihypertensive medication • At least 1 visit in 6 months before screening • English speaking/able to complete a questionnaire in English **Exclusion criteria:**	**Intervention:** PharmD-PCP collaborative care **Comparison:** Usual care	**1° endpoint:** Change in systolic blood pressure at 6 months *PharmD-PCP vs. usual care: month 6* -7.1 vs. 1.6 (p=0.008) *PharmD-PCP vs. usual care: month 9* -5.2 vs. -1.7, p=0.22	**2° endpoint:** Percent of patients at BP goal Change in diastolic BP LDL HDL Number and types of medication changes Number and types of anti-hypertensive drug therapy problems identified Patient satisfaction with clinical pharmacist using 22-item Pharmacist Service Questionnaire PharmD-PCP vs. usual care *Diastolic BP* Month 6: -3.8 vs. 1.7 p=0.006 Month 9: -2.5 vs. -0.3, p=0.27

		• Did not meet provisions of clinical collaborative-practice protocol in the opinion of the patients PCP or the clinical pharmacist			*LDL cholesterol* Month 6: 0.1 vs. 4.6, p=0.21 Month 9: -3.5 vs. -3.1, p=0.95 *HDL cholesterol* Month 6: 2.4 vs. 0.3, p=0.54 Month 9: -1.0 vs. 0.4, p=0.67 *Percent of patients at BP goal* Month 6: 81% vs. 44%, p<0.001 Month 9: 70% vs. 52%, p=0.02 Number of total visits (PCP+pharmacist)=4.4 in PharmD-PCP group vs. 4.2 in usual care group (p=0.38) PharmD-PCP baseline vs post intervention *Drug therapy problem identified* Baseline: 45.2% (42% of whom needed additional therapy, 33.3% needed dose increase, 15.2% had nonadherence, 6.1% had adverse drug reaction) Month 6: 20.0% (58.3% of whom needed additional therapy, 25.0% needed dose increase, 8.3% had nonadherence, 16.7% had adverse drug reaction) Month 9: 7.8% (25.0% of whom needed additional therapy, 25.0% needed dose increase, 25.0% had nonadherence, 0% had adverse drug reaction) *Medication change at visit* Baseline: 34.2% (60.0% of whom increased dosage, 32.0% added

					medication, 12.0% changed medication, 8.0% decreased dose) Month 6: 11.7% (42.9% of whom increased dosage, 28.6% added medication, 14.3% changed medication, 14.3% decreased dose) Month 9: 3.9% (3.9% of whom increased dosage, 100.0% added medication, 0% changed medication, 0% decreased dose) *Satisfaction with pharmacist* Month 6: 92.4 Month 9: 92.7
Hunt JS, et al., 2008 (5) 18815843	**Study Aim:** To assess the impact of co-located physician-pharmacist team-based care on blood pressure control, quality of life and patient satisfaction in patients cared for by all physicians practicing in multiple community-based clinics over a 1-year period. **Study type:** prospective, single-blind randomized controlled trial N=463	**Inclusion criteria:** • patients with an office visit within the past 2 years • diagnosis of hypertension (ICD-9 of 410.*) • last systolic blood pressure ≥160 mmHg and/or a last diastolic blood pressure ≥100 mmHg **Exclusion criteria:** • no blood pressure reading in the chart in the previous 2 years • attended a visit with a pharmacy practitioner in the previous 6 months, • had transferred care out of the Network	**Intervention:** Physician-pharmacist collaborative model (N=230) **Comparison:** Usual care (N=233)	**1° endpoint:** Difference in mean systolic and diastolic blood pressure between intervention and control Systolic Blood Pressure *Study exit visit measurement* 137 intervention vs. 143 control (p=0.007) *ITT* 142 intervention vs. 148 control (p=0.002) Diastolic Blood Pressure Study exist visit measurement 75 intervention vs. 78 control, p=0.003 ITT 77 intervention vs. 80 control (p=0.003)	**2° endpoints:** Proportion of subjects achieving target blood pressure <140/90 mmHg Self-management knowledge and behavior Medication adherence Use of home blood pressure monitoring device Healthcare utilization HRQoL Satisfaction with treatment General healthcare utilization: intervention vs. control Mean Number PCP visits 3.2 vs. 4.7, p<0.0001 Mean number pharmacist visits 4.0 vs. 0.2, p<0.0001 Mean total visits per patient 7.2 vs. 4.9, p<0.0001

					Hypertension-related healthcare utilization: intervention vs. control Mean Number PCP visits 1.8 vs. 2.9, p<0.0001 Mean number pharmacist visits 4.0 vs. 0.2, p<0.0001 Mean total visits per patient 5.8 vs. 3.1, p<0.0001 Pharmacotherapy: intervention vs. control Mean number antihypertensive medications 2.7 vs. 2.4, p=0.02 Mean pills per patient per day 2.4 vs. 2.5, p=0.87 Percent using generic antihypertensive agent 50.7% vs. 39.7%, p=0.008 Goal attainment <140/90 mmHg *Study exit visit measurement* 62% intervention vs 44% control (p=0.003) *ITT* 54% intervention vs. 42% control (p=0.005) HRQOL (SF-36): Intervention vs. control Physical functioning: 44 vs. 42, p=0.33 Role limitation, physical: 48 vs. 49, p=0.49 Bodily pain: 32 vs. 33, p=0.43 General health: 42 vs. 44, p=0.01 Vitality: 48 vs. 49, p=0.20

					Social functioning: 35 vs. 35, p=0.70 Role limitations, emotional: 49 vs. 48, p=0.32 Mental health: 44 vs. 42, p=0.15 Physical component summary: 41 vs. 42, p=0.12 Mental component score: 45 vs. 44, p=0.16 Satisfaction with treatment Overall: 8.6 intervention vs. 8.5 control, p=0.75 No significant between-group difference on any of the 11 satisfaction measures, no association between satisfaction and blood pressure goal attainment (p=0.4)
Chisholm-Burns M, et al., 2010 (6) 20720510	**Study Aim:** To conduct a comprehensive systematic review with focused meta-analyses to examine the effects of pharmacist-provided direct patient care on therapeutic, safety, and humanistic outcomes. **Study Design:** Systematic review and meta analysis N=298 studies	**Inclusion criteria:** • Published through January 2009 • Evidence of pharmacist involvement in direct patient care • Comparison group present • Patient related outcomes reported (therapeutic, safety, or humanistic) • No restrictions by age (26 studies included patients <18 years) **Exclusion criteria:** • Non-US studies • Descriptive studies with no comparison group • Systematic reviews, meta analyses, clinical drug trials, commentaries, letters, editorials, books, book chapters, meeting abstracts, case studies, guidelines, online exams, bibliographies,	**Intervention:** Direct patient care by pharmacist **Comparison:** Not specified	**1° endpoint:** *Hemoglobin A1c* SMD=0.6, p=0.005. Mean difference between intervention and comparison=-1.8% (95% CI -2.7 to -0.9). No evidence of publication bias *LDL*: SMD=0.3, p-0.01. Mean difference between intervention and comparison=-6.3 mg/dL (95% CI -6.5 to -6.0). No evidence of publication bias *Diastolic BP*: SMD=0.3, p=0.001. Mean difference between intervention and comparison=-2.9 mm Hg (95% CI -3.8 to -2.0). Some evidence of publication bias. *Systolic BP*: SMD=0.5, p<0.001. Mean difference between intervention and comparison=-7.8 mm Hg (95% CI -9.7 to -5.8). No evidence of publication bias *Adverse drug events*: OR=0.53 (p=0.01) indicating significant reduction in	**2° endpoint** Summary estimates were not produced for other study outcomes, including hospitalization/readmission, length of hospital stay, emergency department visit, INR/PT/aPTT, mortality, BMI, blood glucose, appropriate medication use, lab monitoring/screening, appropriate medication dose, aspirin use, primary care/urgent care visit, asthma measures, eye exam, adverse drug reactions, medication errors, and patient satisfaction

		dissertations, lectures, theses, book reviews, news articles		pharmacist-provided care group. No evidence of heterogeneity or publication bias *Medication adherence*: SMD=0.6, p=0.001. Evidence of heterogeneity. No evidence of publication bias *Patient knowledge*: SMD=1.1, p=0.001. Evidence of heterogeneity. No evidence of publication bias *QoL-general health*: SMD=0.1, p=0.003. No evidence of heterogeneity. Some indication of publication bias, but non-significant Kendall's tau (p=0.327)	
Study of Cardiovascular Risk Intervention by Pharmacists-Hypertension (SCRIP-HTN) McLean DL, et al., 2008 (7) 19029501	**Study Aim:** To determine the efficacy of a community-based multidisciplinary intervention on BP control in patients with diabetes mellitus **Study Type:** Randomized controlled trial N=227	**Inclusion criteria:** • Adults • Diabetes • BP higher than 130/80mmHg on 2 screening visits separated by 2 weeks **Exclusion criteria:** • institutionalized (or had their medications administered by a professional caregiver) • refused consent • declined attendance at follow-up visits for BP measurements	**Intervention:** Pharmacists and nurse **Comparison:** Usual care	**1° endpoint:** Difference in change in systolic BP between baseline and 24 weeks Mean change of -10.1 mm Hg intervention vs. -5.0 mm Hg control Mean adjusted difference=5.6 mm Hg (p=0.008)	**2° endpoints:** *achievement of BP targets of 130/80 mm Hg or less* Significant increases from baseline in both groups (2.6% at baseline in Intervention group to 47.0% at follow up, p<0.001; 3.6% at baseline in control group to 33.0% at follow up, p<0.001. 14% absolute difference between intervention and control, p=0.02) *The addition, or dosage increase, of antihypertensive drug therapy* Diuretics: Intervention=8.7% baseline to 9.6% follow up. Control=12.5% baseline to 15.2% follow up

					β-blockers: Intervention=21.7% baseline to 23.5% follow up. Control=13.4% baseline to 13.4% follow up Calcium channel blockers: Intervention=24.3% baseline to 23.5% follow up. Control=22.3% baseline to 23.2% follow up ACE inhibitors: Intervention=40.0% baseline to 39.1% follow up. Control=42.9% baseline to 42.9% follow up Angiotensin receptor blockers: Intervention=30.4% baseline to 32.2% follow up. Control=26.8% baseline to 29.5% follow up *The proportion of patients prescribed an angiotensin-converting enzyme inhibitor or angiotensin receptor antagonist* Intervention: 61.7% baseline to 59.1% follow up. Control:65.2% baseline to 67.0% follow up. *the difference in change in systolic BP between baseline and 24 weeks in patients with baseline systolic BP greater than 160 mm Hg* -27.4 mm Hg Intervention vs. -3.3 mm Hg Control (adjusted mean difference=24.1 mm Hg, p<0.001)
Mills KT, et al., 2018 (8) 29277852	**Study Aim:** To assess the comparative effectiveness of 8	**Inclusion criteria:** • Randomized controlled trial • Study participants were adults with hypertension (average systolic BP ≥ 140 mmHg, average diastolic	**Intervention:** Health coaching, home BP monitoring, provider training, audit and	**1° endpoint** Difference in change in systolic BP between Intervention and Control groups at follow up	**2° endpoint:** None specified

	implementation strategies for blood pressure control in adults with hypertension **Study Type:** Systematic review and meta analysis of RCTs N=100 articles (n=55,920 patients)	BP ≥ 90 mmHg, and/or use of antihypertensive medication) • A main trial outcome was the net change in systolic BP or diastolic BP • The trial intervention targets barriers to hypertension control at one or more of the patient, provider, and healthcare system levels • The control group received usual care or minimal education • The trial duration was at least six months • Variance of BP changes (or data to calculate it) was reported • If a trial was cluster-randomized, clustering must be accounted for in the analysis.	feedback, electronic decision support systems, multilevel strategies without team based care, team based care with physicians titrating medications, team based care with non-physician providers titrating medications **Comparison:** Usual care or minimal education	*Net Change in Systolic BP* Health coaching: -3.9 mm HG (95% CI: -5.4 TO -2.3, P<0.001) Home BP monitoring: -2.7 mm Hg (95% CI: -3.6 to -1.7, p<0.001). Provider training: -1.4 mm Hg (95% CI: -3.6 to 0.7, p>0.05) Audit and feedback: --0.8 mm Hg (95% CI: -2.1 to 0.5, p>0.05) Electronic decision support systems: -3.7 mm Hg (95% CI: -5.2 to -2.2, p<0.001) Multilevel strategies without team based care: -5.0 mm Hg (95% CI: -8.0 to -2.0, p=0.001) Team based care with physicians titrating medications: -6.2 mm Hg (95% CI: -8.1 to -4.2, p<0.001). Team based care with non-physician providers titrating medications: -7.1 mm Hg (95% CI: -8.9 to -5.2, p<0.001) *Net Change in Diastolic BP* Health coaching: -2.1 mm HG (95% CI: -2.9 TO -1.3, P<0.001) Home BP monitoring: -1.5 mm Hg (95% CI: -2.3 to -0.8, p<0.001).	

				Provider training: -1.0 mm Hg (95% CI: -2.2 to 0.1, p>0.05) Audit and feedback: --0.6 mm Hg (95% CI: -1.3 to 0.1, p>0.05) Electronic decision support systems: -1.5 mm Hg (95% CI: -1.9 to -1.1, p<0.001) Multilevel strategies without team based care: -2.9 mm Hg (95% CI: -5.4 to -0.4, p=0.025) Team based care with physicians titrating medications: -2.7 mm Hg (95% CI: -3.8 to -1.5, p<0.001). Team based care with non-physician providers titrating medications: -3.1 mm Hg (95% CI: -4.1 to -2.2, p<0.001) *Adjusted Difference in Blood Pressure Reduction with Team based care with titration by non-physician compared to other interventions* Vs Team based care with titration by physician: DBP -0.48 mm Hg (95% CI: -1.95 to 0.99), SBP -0.88 mm Hg (95% CI -3.58 to 1.80) vs. Multilevel strategy without team-based care: DBP -0.28 mm Hg (95% CI -2.84 to 2.26); SBP -2.05 mm Hg (95% CI -5.53 to 1.43)	

				Vs. Health coaching: DBP -1.08 mm Hg (-2.29 to 0.14); SBP -3.22 mm Hg (95% CI -5.72 to -0.72, p<0.05) Vs. Electronic decision support system DBP -1.68 mm Hg (95% CI -2.65 to -0.72, p<0.001); SBP -3.35 mm Hg (95% CI -5.75 to -0.96, p<0.01) Vs. Home blood pressure monitoring DBP -1.60 mm Hg (95% CI -2.71 to -0.48, p<0.01); SBP -4.41 mm Hg (95% CI -6.50 to -2.32, p<0.001) Vs. Provider training: DBP -2.12 mm Hg (95% CI -3.57 to -0.68, p<0.01); SBP -5.63 mm Hg (95% CI -8.57 to -2.69, p<0.001) Vs. Audit and feedback: DBP -2.52 mm Hg (95% CI -3.54 to -1.51, p<0.001); SBP -6.29 mm Hg (95% CI -8.52 to -4.05, p<0.001)	
CAPTION Polgreen LA, et al., 2015 (9) 26527048	**Study Aim:** to examine the cost effectiveness of the intervention implemented in the CAPTION Trial **Study type:** Economic analysis of RCT intervention N=625	**Inclusion criteria:** • Spoke either English or Spanish • At least 18 years old • Had uncontrolled hypertension (BP ≥ 140 mmHg systolic or ≥ 90 mmHg diastolic, or for patients with diabetes or chronic kidney disease, these cut offs were ≥ 130 and ≥ 80 mmHg)	**Intervention:** Physician-Pharmacist-collaborative model **Comparison:** Usual care	**1° endpoint:** Intervention cost Incremental cost-effectiveness ratio *Health care costs: Intervention vs. Control* Changed hypertension medications $272.45 vs $170.75, p=0.0352 Hypertension medication: $951.46 vs $972.52, p=0.7848 Total drug cost: $1223.91 vs. $1146.27, p=0.4715 Pharmacist cost: $140.62 vs. $0, p<0.001	N/A

				Physician cost: $98.34 vs. $113.67, p=0.1774 Total cost: $1462.87vs. $1259.94, p=0.0759 *Cost effectiveness* Compared to the control group, the cost to lower systolic BP by 1 mm Hg was $33.27 and to lower diastolic BP by 1 mm Hg was $69.98. The cost to increase BP control by one percentage point was $22.55. In subgroup completing 9 month intervention, cost to lower systolic BP by 1 mm Hg was $38.82 and cost to lower diastolic BP by 1 mm Hg was $81.66. The cost to increase BP control by one percentage point was $26.31 Using deflated drug costs, cost to lower systolic BP 1 mm Hg was $26.54 and cost to lower diastolic BP 1 mm Hg was $44.82. Deflated cost to increase BP control by one percentage point was $17.99	
Proia KK, et al., 2014 (10) 24933494	**Study aim:** To examine the effectiveness of team-based care in improving blood pressure outcomes **Study type:** Systematic review of RCTs and observational studies	**Inclusion criteria:** • Met the definition of team-based care as described in the conceptual framework; • Were in English; • Were not in the Walsh et al.(2006) review; • Were conducted in a high-income economy consistent with Community Guide methods; • Reported at least one BP outcome of interest (i.e., proportion of patients with controlled BP,	**Intervention:** Team based care (adding new staff or changing the roles of existing staff to work with a primary care provider) **Comparison:** Usual care	**1° endpoint:** Proportion of patients with controlled BP (<140/90 mm Hg or <130/80 mm Hg for those with diabetes) Reduction in SBP and DBP *Proportion of patients with controlled BP:* Median effect estimate=12 percentage points (IQI=3.2-20.8 percentage points). By location: US=10.0 percentage point, Non-US=15.6 percentage points	**2° endpoints:** Medication adherence Satisfaction with care Changes in lipids and diabetes outcomes *Medication adherence* High medication adherence increased by median of 16.3 percentage points *Satisfaction with care* One of the two studies found an improvement of 14.0 percentage points

	N=80 studies (n=52 newly identified studies and n=28 studies from Walsh et al, 2006)	reduction in SBP, or reduction in DBP); • Included a comparison group or had an interrupted time-series design with at least two measurements before and after the intervention; • Targeted populations with primary hypertension or populations with comorbid conditions such as diabetes as long as the primary focus of the intervention was BP control; • Did not include populations with secondary hypertension (e.g., pregnancy) or with a history of CVD (e.g., myocardial infarction).		By setting: Similar improvement in healthcare and community settings (median=12.0 percentage points for both). By team member added: Nurse=8.5 percentage point, pharmacist=22.0 percentage points, nurse+ pharmacist=16.2 percentage points, other=2.6 percentage points By type of team member role related to medication: Independent=17.4 percentage points, PCP approval=15.0 percentage points, support only=7.9 percentage points By number of team members added: PCP+ 1 team member=10.5 percentage points, PCP+2 team members=13.5 percentage points, PCP+3 or more team members=17.0 percentage points By baseline level of percentage with controlled BP: 0=14.0 percentage points, ≤50=14.0 percentage points, >50=1.1 percentage points *Reduction in SBP* Median reduction=5.4 mm Hg (IQI=2.0-7.2 mm Hg) By location: US=5.8 percentage points, Non-US=4.9 percentage points By setting: Healthcare= 5.7 percentage points, Community-based=4.5 percentage points By team member added: Nurse=5.4 percentage point, pharmacist=5.0	(p<0.001), while the other found similarly high satisfaction in both groups *Total cholesterol*: -3 mg/dL change in mean, 13.0 percentage point increase in proportion of patients at goal *LDL cholesterol*: -4.3 mg/dL change in mean, 3.2 percentage point increase in proportion of patients at goal *HDL cholesterol*: 1.3 mg/dL change in mean, -6.0 percentage point change in proportion of patients at goal *Triglycerides*: -7.9 mg/dL change in mean *A1C level*: -0.3% change in mean, 10.0 percentage point increase in proportion of patients at goal *Blood glucose*: -7.0 mg/dL change in mean

				percentage points, nurse+ pharmacist=5.6 percentage points, other=3.2 percentage points By type of team member role related to medication: Independent=7.2 percentage points, PCP approval=5.0 percentage points, support only=3.8 percentage points By number of team members added: PCP+ 1 team member=5.6 percentage points, PCP+2 team members=5.3 percentage points, PCP+3 or more team members=5.9 percentage points By baseline SBP: ≥140 mm Hg=5.9 percentage points, <140 mm Hg=5.0 percentage points *Reduction in DBP* Median reduction=1.8 mm Hg (IQI=0.7-3.2 mm Hg) By location: US=1.8 percentage points, Non-US=1.7 percentage points By setting: Healthcare= 1.8 percentage points, Community-based=0.5 percentage points By team member added: Nurse=2.9 percentage point, pharmacist=1.7 percentage points, nurse+ pharmacist=3.5 percentage points, other=0.4 percentage points By type of team member role related to medication: Independent=3.5 percentage points, PCP approval=1.7 percentage points, support only=1.0 percentage points	

				By number of team members added: PCP+ 1 team member=1.4 percentage points, PCP+2 team members=3.2 percentage points, PCP+3 or more team members=3.0 percentage points By baseline DBP: ≥90 mm Hg=3.3 percentage points, <140 mm Hg=1.6 percentage points	
Buhse S, et al., 2015 26567256	**Study aim:** To evaluate an informed shared decisionmaking programm (ISDM-P) for people with type 2 diabetes under high fidelity conditions **Study type:** Single blind RCT N=154	**Inclusion criteria:** • registered in the German Disease Management Programme (DMP) for type 2 diabetes • were 40–69 years old, had glycated haemoglobin (HbA1c) values between 6% and 9% • had no history of ischaemic heart disease (International Classification of Diseases (ICD) I20-I25) or stroke (ICD I63) • had previously participated in structured diabetes education sessions as typically provided within the DMP **Exclusion criteria:** • had proliferative retinopathy, chronic kidney disease stage 3 or higher • had metastatic cancer • were addicted to alcohol • were cared for by a legal guardian	**Intervention:** Evidence-based decision aid for patients on the prevention of heart attack, structured patient teaching provideed by diabetes educators, and provider training (n=77) **Comparison:** usual care supplemented with 90 minute teaching module on sports, nutrition, and stress issues (n=77)	**1° endpoint:** Patient comprehension of relevant risk information after the teaching session *Risk comprehension*: Mean difference between ISDM and control group=5.63 (95% CI 4.82-6.44, p<0.001) *Realistic expectations*: Mean difference between ISDM and control group=3.67 (95% CI 3.23-4.11, p<0.001) *Sufficient risk comprehension*: Percentage difference between ISDM and Control group=48.6% (95% CI 37.0% vs. 60.2%, p<0.001)	**2° endpoints:** Comprehension, including realistic expectations, at 6 months Adherence to individual treatment goals related to use of statins, levels of office systolic blood pressure, and HbA1c, and smoking Adherence to prioritized treatment goals related to statin uptake, office blood pressure values, and HbA1c levels at follow up with the treatment goals the patients set and prioritized at the end of the teaching session *Risk comprehension* Mean difference=0.98 (95% CI 0.15-1.80, p=0.021) *Realistic expectations* Mean difference=0.51 (95% CI 0.09-0.93, p=0.018) *Treatment goals after teaching* Taking statins: mean difference=28.7% (95% CI: 12.9-44.5, p=0.001)

					Stop smoking: mean difference=13.6% (95% CI: -31.2 to 58.5, p=0.552) Average group systolic blood pressure: mean difference= -0.9 %(95% CI: -3.5 to 1.7, p=0.419) Average group HbA1c: mean difference=0.07 (-0.11 to 0.25, p=0.492) *Achievement of treatment goals at 6 months (mean difference between ISDM and control group):* Statin: 7.6% (95% CI: -3.4% to 18.6%, p=0.203) Blood pressure value between 80-120% of defined goal: -2.4% (-17.7% to 12.9%, p=0.856) HbA1c: 10.1% (95% CI 0.6% vs. 19.5%, p=0.046) Smoking: -8.3% (95% CI -52.9% - 36.2%, p=1.000) Prioritized goal: -3.4% (95% CI -15.3%-8.5%, p=0.627)
Cooper LA, et al., 2011 21732195	Study Aim To compare the effectiveness of patient centered interventions targeting patients and physicians with the effectiveness of minimal interventions	*Physicians* Inclusion criteria • general internists and family physicians who saw patients at least 20 hours per week at one of the participating study sites. Exclusion Criteria • Physicians were excluded if they intended to leave the practice within 12 months	*Physicians* Intervention Physician communication skills program with personalized feedback based on videotaped performance with simulated patient.	1° endpoint -Physician Communication Behaviors -Patient Ratings of Physicians' Participatory Decision-Making Style -Patient Involvement in Care -Systolic and diastolic blood pressure -Blood pressure control *Physician Communication Behaviors*	2° endpoint None specified

	for underserved groups. Study type RCT N=41 physicians, N=279 patients	*Patients* Inclusion criteria • Patients recruited for the study were adults aged 18 years and older • diagnosis of hypertension (at least one claim with the ICD-9 code 401 in the preceding year) • able to provide contact information for themselves and at least one other person. Exclusion criteria • too acutely ill, disoriented, or unresponsive to complete the baseline assessment medical conditions that might limit participation in the study (e.g., AIDS/HIV, schizophrenia, cancer (except skin), Alzheimer's or other form of dementia; end-stage renal disease, congestive heart failure, or active tuberculosis)	Comparison No feedback after videotaped performance with simulated patient. *Patients* Intervention Patient intervention included pre-visit coaching Comparison Usual care+newsletter (received by all study participants)	Verbal dominance: Change in Intensive vs. Minimal physician intervention group: -1.67 vs. -1.94 (p=0.35) Patient Centerdness ratio: Change in Intensive vs. Minimal physician intervention group -0.52 vs. -0.82, p-0.04 *Participatory Decision Making: Change at 12 months* Physician+Patient Intensive: 6.2 (95% CI -0.5-12.9, p compared to physician+patient minimal=0.03) Physician minimal/patient intensive: -3.2 (95% CI -4.8-11.3, p compared to physician+patient minimal =0.13) Physician intensive/patient minimal: -3.1 (95% CI -3.9-10.2, p compared to physician+patient minimal =0.12) Physician+patient minimal: -5.2 (95% CI: -13.0-2.5) *Patient Involvement in Care* <u>Doctor facilitation: Change at 12 months</u> Physician+Patient Intensive: 0.22 (95% CI 0.00-0.43, p compared to physician+patient minimal=0.03) Physician minimal/patient intensive: 0.12 (95% CI -0.15-0.39, p compared to physician+patient minimal =0.11) Physician intensive/patient minimal: 0.09 (95% CI -0.14-0.33, p compared to physician+patient minimal =0.14)	

				Physician+patient minimal: -0.17 (95% CI: -0.43-0.09) <u>Information exchange: change at 12 months</u> Physician+Patient Intensive: 0.32 (95% CI 0.08-0.56, p compared to physician+patient minimal=0.005) Physician minimal/patient intensive: 0.16 (95% CI -0.14-0.45, p compared to physician+patient minimal =0.08) Physician intensive/patient minimal: 0.13 (95% CI -0.13-0.38, p compared to physician+patient minimal =0.08) Physician+patient minimal: -0.22 (95% CI: -0.51-0.07) <u>Patient decision making: change at 12 months</u> Physician+Patient Intensive: 0.21 (95% CI -0.03-0.44, p compared to physician+patient minimal=0.08) Physician minimal/patient intensive: 0.07 (95% CI -0.23-0.36, p compared to physician+patient minimal =0.35) Physician intensive/patient minimal: 0.16 (95% CI -0.10-0.41, p compared to physician+patient minimal =0.14) Physician+patient minimal: -0.13 (95% CI: -0.42-0.16)	

				Medication adherence on Morisky scale at 12 months: Physician+Patient Intensive: 0.75 (95% CI -0.62-0.84, p compared to physician+patient minimal=0.75) Physician minimal/patient intensive: 0.80 (95% CI -0.65-0.90, p compared to physician+patient minimal =0.76) Physician intensive/patient minimal: 0.66 (95% CI -0.53-0.77, p compared to physician+patient minimal =0.22) Physician+patient minimal: 0.77 (95% CI: -0.63-0.87) *Systolic BP: Change at 12 months* Overall Physician+Patient Intensive: -2.8 (95% CI -9.5-3.8, p compared to physician+patient minimal=0.58) Physician minimal/patient intensive: -6.5 (95% CI -14.2-1.2, p compared to physician+patient minimal =0.24) Physician intensive/patient minimal: -2.3 (95% CI 8.7-4.0, p compared to physician+patient minimal =0.65) Physician+patient minimal: -0.1 (95% CI: -7.5-7.4) Uncontrolled at baseline	

				Physician+Patient Intensive: -13.2 (95% CI -23.1 to -3.4, p compared to physician+patient minimal=0.14) Physician minimal/patient intensive: -16.8 (95% CI -28.0 to -5.6, p compared to physician+patient minimal =0.07) Physician intensive/patient minimal: -10.6 (95% CI -21.5 to 0.3, p compared to physician+patient minimal =0.27) Physician+patient minimal: -2.0 (95% CI: -13.2 to 9.2) *Diastolic BP: Change at 12 months* <u>Overall</u> Physician+Patient Intensive: 0.2 (95% CI 3.7-4.1, p compared to physician+patient minimal=1.0) Physician minimal/patient intensive: -0.9 (95% CI -5.4-3.6, p compared to physician+patient minimal =0.72) Physician intensive/patient minimal: -1.4 (95% CI –5.1-2.3, p compared to physician+patient minimal =0.57) Physician+patient minimal: 0.2 (95% CI: -4.1-4.6) <u>Uncontrolled at baseline</u> Physician+Patient Intensive: -5.2 (95% CI -11.1-0.7, p compared to physician+patient minimal=0.24)	

				Physician minimal/patient intensive: -5.4 (95% CI -12.1-1.3, p compared to physician+patient minimal =0.26) Physician intensive/patient minimal: -5.2 (95% CI –11.7-1.3, p compared to physician+patient minimal =0.27) Physician+patient minimal: 0.0 (95% CI: -6.7 to 6.7) *% with BP controlled: Change at 12 months* <u>Overall</u> Physician+Patient Intensive: 0.53 (95% CI 0.38-0.68, p compared to physician+patient minimal=0.92) Physician minimal/patient intensive: 0.61 (95% CI 0.43-0.77, p compared to physician+patient minimal =0.58) Physician intensive/patient minimal: 0.65 (95% CI 0.50-0.78, p compared to physician+patient minimal =0.35) Physician+patient minimal: 0.55 (95% CI: 0.37-0.71) <u>Uncontrolled at baseline</u> Physician+Patient Intensive: 0.44 (95% CI 0.19-0.73, p compared to physician+patient minimal=0.52) Physician minimal/patient intensive: 0.63 (95% CI 0.28-0.88, p compared to physician+patient minimal =0.15)	

				Physician intensive/patient minimal: 0.39 (95% CI 0.17-0.67, p compared to physician+patient minimal =0.67) Physician+patient minimal: 0.31 (95% CI: 0.11-0.63)	
Beauchamp, A et al., 2010 20562629	Study Aim: To determine whether key interventions for CVD prevention and treatment are effective among lower socioeconomic groups, to describe barriers to their effectiveness and the potential or actual impact of these interventions on the socioeconomic gradient in CVD. Study type: Systematic review (narrative synthesis) N=49 studies	Inclusion criteria • used quantitative outcomes to examine the effectiveness of the particular intervention among groups or individuals according to SES. • Published between January 1, 1996 and October 31, 2008 • Adult populations Exclusion criteria • studies of interventions among children and adolescents studies of sex or ethnicity-related inequalities, unless participants were specifically described as being of lower SES	Intervention Smoking reduction strategies among the well population Absolute risk assessment to identify those who are asymptomatic but at most risk Secondary prevention medications and cardiac rehabilitation Heart failure self-management programs Comparison	1° endpoint changes in rates of smoking prevalence or consumption for absolute risk equations, their predictive performance or changes in the proportion of people assessed at being at high risk of CVD for secondary prevention medications, cardiac rehabilitation and heart failure programs, outcomes included changes in mortality rates, further CVD events or hospital readmissions, changes in cardiovascular risk factors, or behavioral modification NO QUANTITATIVE SUMMARY	Overall, only limited evidence was found for the effectiveness of the interventions examined and there was little exploration of SES-related barriers to their uptake. Summarized conclusions: *Potential successes* Combining population-based strategies with those specifically directed to disadvantaged groups may reduce the SES-smoking gradient Heart failure self-management programs are effective among lower SES groups possibly because they allow for an intensive and personalized approach *Potential opportunities* Creative and innovative approaches to improve uptake of interventions are needed, such as those that increase access (home-based cardiac rehabilitation programs), or those that remove cost (free NRT), or those that are tailored towards lower SES groups (heart failure self-management programs) Lower SES individuals could be more appropriately identified as being at high risk of CVD either through inclusion of SES into absolute risk equations, or by lowering their thresholds for treatment

					Future directions for policy makers and researchers Many barriers to the effectiveness and utilization of CVD interventions in lower SES groups are directly related to the underlying factors associated with disadvantage. More efforts towards identification of these barriers are required Approaches that have been shown to work among the disadvantaged need further research into the causes of their effectiveness, for example, reasons underlying the declines in educational inequalities in smoking in the UK The increased burden of CVD associated with lower SES is likely to be cumulative. Emphasis must be on intervening as early as possible within the CVD continuum
Havranek EP, et al., 2015 26240271	Study Aim To increase awareness of the influence of social factors on the incidence, treatment, and outcomes of CVD; to summarize the current state of knowledge about these factors; and to suggest future directions in research, particularly research on effective interventions to attenuate or eliminate these	Inclusion Criteria N/A		No primary or quantitative outcomes Recommendations and Conclusions: *Socioeconomic Position* •No single parameter fully captures SEP; income, education, and occupation have been used successfully. •Measures of socioeconomic position may vary by race/ethnic groups, and these synergistic effects should be considered. •Novel markers of socioeconomic position should be investigated for broader use in understanding CVD. *Race/Ethnicity* •Race/ethnicity is a social construct with little biological or genetic basis.	Author's Conclusions The focus on the causes of CVD has to be broadened to incorporate the social determinants of health. Failure to demonstrate awareness of this will result in a growing burden of CVD, especially in those with the least means to engage in the healthcare system

	adverse social influences Study Type Scientific Statement N= N/A			•The concepts of implicit bias and stereotype threat are real phenomena that affect health and disease and may be root causes of disparate care • Effective interventions to improve patient-provider communication and patient satisfaction/trust across racial lines are clearly needed. *Social Support and Social Networks* •Although diminished social support contributes to CVD, effective interventions for low support have not been demonstrated. •Mechanisms by which social networks affect health are unknown and a significant opportunity for future research. • Engaging individuals and their support networks may be a powerful intervention tool and is worth future investigation. *Access to Care* •Barriers to access are many and include issues involving patient beliefs, literacy, culture, and language. • There is a poor geographic distribution of cardiac services. • Barriers to improving access to subspecialty care for patients with Medicaid are a critical issue for cardiovascular specialists. • Although access to health insurance is necessary, it is not a sufficient intervention for improving cardiovascular health. • Improving access is a multifaceted task that will require not only the provision of insurance coverage but also a better distribution of services. *Residential Environments*	

				•Residential environments characterized by diminished socioeconomic resources, access to healthy foods and resources for physical activity have a measurable effect on CVD and the density of CVD risk factors. •Proactive efforts to change the built environment may reduce the burden of CVD risk. *Psychological, Behavioral, and Biological Mechanisms* •Psychological factors such as depression and a comprehensive set of psychosocial stressors may mediate associations between social determinants and cardiovascular outcomes and should be investigated more in future studies. •Although cardiovascular health behaviors vary across social groups, they do not fully account for social group differences in cardiovascular outcomes. •Physiological and anatomical effects of early disadvantage affect risk for CVD in adulthood. • Effective interventions to reduce the impact of early disadvantage will require organizational partnerships that currently are uncommon.	
Vilhelmsson A, Östergren PO, 2018 29659598	Study Aims to assess the magnitude of evidence regarding intervention evaluations with high-quality designs concerning health-related behavior, which have shown a	Inclusion criteria • Published between 1990-2015 • published in English in international peer-reviewed scientific journals • populations from countries with developed welfare systems (i.e., from countries in Europe, North America, Australia, and New Zealand)	Intervention of non-healthcare-based interventions regarding health-related behavioral factors among different educational groups Comparison	1° endpoint Health related behavior (smoking, dietary intake, physical activity, mental health, mammography) reductions by educational level NO QUANTITATIVE SUMMARY	Author's Conclusions: Smoking cessation:, could not draw any decisive conclusions Limited evidence for decreasing inequality through interventions regarding dietary intake, physical activity, and mental health

	higher impact among individuals with a low educational level, as well as the potential of reducing health inequality Study Type: Rapid review N=9 studies	• evaluations of non-healthcare-based interventions regarding health-related behavioral factors among different educational groups • studies comparing those receiving the intervention with a control group (randomized controlled trials or non-randomized trials with a cohort design) • N≥100 Exclusion criteria • Did not measure educational status • No original data • Lacked data on outcomes of interest	Not specified		Mammography: only one study identified, concluded that there is not enough scientific evidence concerning the potential for increased health equity for this approach
Schultz WM, et al., 2018 29760227	Study Aims To review the current state of knowledge on the impact of SES on the incidence, treatment, and outcomes of CVD in high-income societies, suggest future research directions aimed at the elimination of these adverse factors, and the integration of measures of SES into the customization of	Inclusion criteria N/A Exclusion criteria N/A	Intervention Various (none prespecified) Comparison Various (none prespecified)	1° endpoint None specified NO QUANTITATIVE SUMMARY	Author's Conclusions SES has a measurable and significant impact on cardiovascular health. Individuals of low SES carry a substantial burden of CVD and are more likely to experience increased event rates and poorer outcomes. Current models do not adequately account for the risk conveyed by low SES. The independent association between SES and mortality is comparable in strength and consistency to that of the traditional major risk factors.

	cardiovascular treatment Study Type Non-systematic literature summary N=N/A				There is a need for increased focus on effective and sustainable interventions informed by clinical and population science insights from SES research. Further research is required to better understand the underlying mechanisms of CVD risk that disproportionately affect individuals of low SES.

Data Supplement 2. Nonrandomized Trials, Observational Studies, and/or Registries of Patient-Centered Approaches for Providing Comprehensive ASCVD Prevention (Section 2.1)

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Chen EH, et al., 2010 (11) 20737236	Study Aim To implement and evaluate the Teamlet Model, which uses health coaches working with primary care physicians to improve care for patients with diabetes and/or hypertension in an academic practice Study type: Non-randomized intervention N=541	Inclusion criteria • Transferred from graduating third year resident to an incoming first year resident (control group had and kept second or third year resident providers) • Had at least one visit in prior 2 years • Spoke English, Spanish, Cantonese, or Mandarin Diagnosed with diabetes and/or hypertension	1° endpoint Intervention vs. control comparisons of mean daytime, nighttime, and overall 24-hour ambulatory SBP and control rates *Change in intervention group from the year prior to the intervention year*: BP ≤goal: 48.7% vs. 56.5%, p=0.22 HbA1c≤ goal: 26.7% vs. 36.7%, p=0.12 LDL ≤ goal: 49.1% vs. 58.6%, p=0.07 HbA1c measured: 86.9% vs. 88.9%, p=0.82 LDL measured: 74.0% vs. 84.9%, p=0.02 BMI measured: 3.4% vs. 88.4%, p<0.001 Smoking status assessed: 4.1% vs. 86.9%, p<0.001 Self-management plan made: 19.9% vs. 55.5%, p<0.001 *Difference in change between intervention group and control group for year prior vs. year of intervention*:	Summary Teamlet model was implemented without decreases in efficiency

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			BP ≤goal: +3.8%, p=0.06 HbA1c≤ goal: +1.8%, p=0.83 LDL ≤ goal: +3.2%, p=0.79 HbA1c measured: +5.6%, p=0.17 LDL measured: -5.8%, p=0.001 <u>2° endpoint</u> First year residents provided an average of 146 patient visits during the year compared to 136 on average for the previous residency class	
CAPTION trial (subanalysis) Isetts BJ, et al., 2016 <u>26893135</u>	Study aim to describe the components of pharmacists' work in the management of hypertension with a physician-pharmacist collaborative model Study type Descriptive analysis of components of intervention in a cluster randomized trial (present report is on pharmacists' work in intervention group) N=32 medical offices (n=390 patients)	Inclusion criteria • uncontrolled BP	<u>1° endpoint</u> 3.44 hours/patient for face-to-face care visits Pharmacists spent a mean of 33 minutes/patient in face-to-face time in initial counter and 28 minutes/patient in face-to-face time in each follow-up encounter. Pharmacists also spent an average of 4.05 minutes for pre-visit and 8.85 minutes for post visit time per encounter, representing 31% of pharmacists' work. Total time spent was 4.99 hours per patient in 9 months. 12.3% of patients were at BP goal on initial assessment, despite uncontrolled BP assessed by the study coordinators' structured measurements at the time of study enrollment	Summary: The physician-pharmacist collaborative care model required an average of 4.99 hours of pharmacist time per patient per 9 months. The intervention resulted in a greater number of medication increases or additions than in the control group, which were nearly always accepted by the physician, and no greater frequency of adverse events.

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			0% of patients' blood pressure goals were achieved at baseline compared to 43% at 9 months 2.6 dose increases or medication additions in intervention group compared to 0.8 in control group, p=0.0001 98.6% of recommendations made to alter drug therapy were accepted by physicians 43% of patient encounters involved patient-specific drug therapy problem resolution recommendations Monitoring by medical monitors and a Data and Safety Monitoring Board indicated no significant difference in adverse events in the intervention group compared to the control group (p=0.500) 392 adverse events were assessed, 64 of which were possibly medication-related	
Kravetz JD, et al., 2016 27106631	Aim to determine whether proactive panel management within a Patient Aligned Care Team (PACT) could improve blood pressure control in a primary care population compared to usual care	Inclusion criteria • Blood pressure >160/100 mm Hg • Patient at West Haven Veterans Affairs Medical Center	1° endpoint Change in systolic BP Change in diastolic BP % with lower systolic BP at 4-month follow up % with lower diastolic BP at 4-month follow up % who did not return to follow up *Change in systolic BP: Intervention vs. Control*	Summary The team approach resulted in a significantly greater reduction in blood pressure compared to usual care

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
	Study type Non-randomized intervention trial N=665		-15.6 vs. -9.9 mm Hg, p<0.001. (-15 vs. -7.3 mm Hg, p<0.001 when excluding patients with medication changes) *Change in diastolic BP: Intervention vs. Control* -5.4 vs. -4.6 mm Hg, p=0.32 (-5.2 vs. -3.6 mm Hg, p=0.079 when excluding patients with medication changes) *% with lower systolic BP at follow up: Intervention vs. Control* 61.1% vs. 41.0%, p<0.001 *% with lower diastolic BP at follow up: Intervention vs. Control* 53.7% vs. 37.5%, p<0.001 *% who did not return for follow up: Intervention vs. Control* 32.0% vs. 48.0%, p<0.001 Mean increase in number of blood pressure medications from 1.37 to 1.5 (p=0.01) in intervention group (change in control group not reported)	
Olomu A, et al., 2016 27484348	Study Aim to evaluate: 1) feasibility of the Office-GAP program among patients with diabetes and CHD in a Federally Qualified Healthcare Center (FQHC); 2) the	Inclusion criteria • Adults aged 18 or older • could provide informed consent • sought care from September 2009 to December 2011 • diagnosis of 1) Diabetes mellitus. 2) Coronary heart disease.	1° endpoint Implementation of program elements Patient satisfaction with communication and confidence in decision Medication Use *Implementation* All providers and staff attended the 90 minute training	Summary The use of Office-GAP program to teach SDM and use of DAs in real time was demonstrated to be feasible in FQHCs. It has the potential to improve satisfaction with physician communication and confidence in decisions and to improve medication use.

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
	impact on a) patient satisfaction with physician communication and confidence in decisions; and b) use of guidelines-based medication for CHD prevention Study type: Pre-Post quasi experimental design N=95	Exclusion criteria Adults with cognitive impairment, dementia and psychosis as determined by ICD codes	81.1% of patients who attended first 90 minute group visit completed Office-GAP provider visit and 63.2% completed final visit Office-GAP checklist completed in 98.7% of medical records *Patient satisfaction with communication and confidence in decision: hierarchical model coefficients vs. baseline* <u>Satisfaction</u> 3 months: model coefficient=4.55 (95% CI 2.63-6.46, p<0.001) 6 months: model coefficient: 5.03 (95% CI 3.09-6.97, p<0.001) <u>Confidence</u> 3 months: model coefficient=3.70 (95% CI 1.33-6.07, p<0.01) 6 months: model coefficient 5.48 (95% CI 2.96-8.00, p<0.001 Medication use (OR vs. baseline) <u>3 months</u>: Aspirin/Plavix OR=1.50 (95% CI 1.05-2.15) Statin OR=1.12 (95% CI 1.00-1.25) ACB/ABR OR=1.21 (95% CI 0.84-1.75) Beta blocker OR=1.31 (95% CI 0.91-1.89) Global medication adherence OR=1.19 (95% CI 0.85-1.66) <u>6 months</u> Aspirin/Plavix OR=1.92 (95% CI 1.27-2.92) Statin OR=1.34 (95% CI 0.99-1.81) ACB/ABR OR=1.38 (95% CI 0.92-2.09)	

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			Beta blocker OR=1.75 (95% CI 1.07-2.85) Global medication adherence OR=1.52 (95% CI 1.01-2.29) <u>12 months</u> Aspirin/Plavix OR=1.81 (95% CI 1.17-2.79) Statin OR=1.52 (95% CI 1.07-2.16) ACB/ABR OR=1.13 (95% CI 0.72-1.78) Beta blocker OR=1.75 (95% CI 1.07-2.85) Global medication adherence OR=1.34 (95% CI 0.87-2.06)	
Parchman ML, et al., 2010 <u>20843882</u>	Study aim To assess a causal pathway among the relationships between physicians' participatory decision-making style, patient participation in the encounter, and outcomes Study type Prospective cohort N=141	Inclusion criteria • Patients at one of 5 independent primary care practices Diagnosis of type 2 diabetes in past 12 months	<u>1° endpoint</u> *- Effect of medication adherence on clinical outcomes* *-Effect of patient activation on medication adherence:* *-Effect of participatory decision making on patient activation at follow up* *Effect of medication adherence on clinical outcomes* HbA1c: regression coefficient=0.04, p=0.05 Systolic Blood Pressure: regression coefficient=0.04 (p=0.80) LDL Cholesterol: regression coefficient=1.08 (p=0.04) *Effect of patient activation on medication adherence:* HbA1c model: regression coefficient=-0.04 (p=0.02) Systolic Blood Pressure model: regression coefficient=-0.004 (p-0.02)	Participatory decision making during primary care encounters by patients with type 2 diabetes resulted in improvements in hemoglobin A1c levels and LDL cholesterol values by improving patient activation, which in turn improved medication adherence. This relationship was not observed for systolic blood pressure.

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			LDL cholesterol model: regression coefficient=-0.04 (p=0.02) *Effect of participatory decision making on patient activation at follow up* HbA1c model: regression coefficient=0.44 (p=0.03) Systolic Blood Pressure model: regression coefficient=0.43 (p=0.04) LDL cholesterol model: regression coefficient=0.42 (p=0.04)	
Backholer K, et al., 2017 27974445	Study Aim to ascertain the most reliable estimate of the sex differences in the relative risks of SES on the risk of incident CHD, stroke and CVD in the general population Study Type: Systematic review and meta-analysis N=116 cohorts (over 22 million individuals)	Inclusion criteria • Cohort studies • Reported sex-specific RRs, or equivalent, together with a measure of variability, on the relationship between any indicator of SES and CHD, stroke or CVD • Adult populations Exclusion criteria • available results were not adjusted for at least age selected on the basis of a prior CVD event or an underlying pathological disorder	1°Endpoint combined fatal and non-fatal incident CHD, stroke or CVD (where studies reported results for fatal outcomes only, we used this end point in our analyses 2°Endpoints Pooled RRs (highest vs. lowest SES) for each sex both adjusted for age, without other CVD risk factors Multiple adjusted RRs with adjustment sets that most closely matched to the conventional CVD risk factors (ie, smoking, diabetes, total cholesterol, high-density lipoprotein cholesterol and systolic blood pressure), while avoiding adjustment sets that included other measures of SES 1°Endpoint *CHD* *Education* Female: RR=1.66 (95% CI 1.46-1,88)	

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			Male: RR=1.30 (95% CI 1.15-1.48) *Area Deprivation* Female: RR=1.83 (95% CI 1.61-2.07) Male: RR=1.50 (95% CI 1.38-1.63) *Occupation* Female: RR=1.59 (95% CI 1.26-1.97) Male: RR=1.50 (95% CI 1.25-1.80) *Income* Female: RR=2.48 (95% CI 1.53-4.00) Male: RR=2.01 (95% CI 1.47-2.74) Age adjusted RRR comparing women vs. men: RRR=1.24 (95% CI 1.09-1.41), and adjusting for major CVD risk factors RRR comparing women vs. men RRR=1.34 (95% CI 1.09-1.63). *Stroke* *Education* Female: RR=1.34 (95% CI 1.07-1,69) Male: RR=1.53 (95% CI 1.27-1.86) *Area Deprivation* Female: RR=1.60 (95% CI 1.21-2.12) Male: RR=1.63 (95% CI 1.35-1.96) *Occupation* Female: RR=1.81 (95% CI 0.91-3.62) Male: RR=1.50 (95% CI 0.96-2.36) *Income* Female: RR=1.64 (95% CI 1.36-1.96) Male: RR=1.73 (95% CI 1.33-2.24)	

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			Age adjusted RRR comparing women vs. men: RRR=0.93 (95% CI 0.72-1.18), and adjusting for major CVD risk factors RRR comparing women vs. men RRR=0.79 (95% CI 0.53-1.17). *CVD* *Education* Female: RR=1.66 (95% CI 1.43-1,92) Male: RR=1.42 (95% CI 1.25-1.63) *Area Deprivation* Female: RR=1.75 (95% CI 1.55-1.98) Male: RR=1.60 (95% CI 1.45-1.76) *Occupation* Female: RR=1.80 (95% CI 1.51-2.40) Male: RR=1.74 (95% CI 1.38-2.20) *Income* Female: RR=1.46 (95% CI 1.43-1.50) Male: RR=1.36 (95% CI 1.34-1.39) Age adjusted RRR comparing women vs. men: RRR=1.18 (95% CI 1.03-1.36), and adjusting for major CVD risk factors RRR comparing women vs. men RRR=1.21 (95% CI 1.04-1.42). No evidence of publication bias (p=0.68)	
Khaing W et al., 2017	Study Aim to pool the effects of low to high education	Inclusion criteria • assessed associations between education/income and	1°Endpoint	Summary: In general, groups with low to medium education and income are at higher risk of CAD, CVE, stroke and cardiovascular death than those with high education and income

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
28406328	and income on various cardiovascular outcomes by including more studies conducted in developing countries Study type Systematic review and Meta analysis N=72 studies	cardiovascular outcomes in general adults or specific diseases • measured education or income • had at least one outcome of interest (i.e. coronary artery diseases, cardiovascular events, strokes and cardiovascular deaths) • had contingency data between education/income and cardiovascular outcomes, or a beta-coefficient. • Published 1982 through July 31, 2016 Exclusion criteria • data for education and income were combined income was based on ownership of car/house/health insurance/zip-code.	CVDs including CAD (e.g. acute MI, IHD, coronary heart disease (CHD)), CVE (e.g. HF, hospital admission due to cardiac causes, revascularization and composite CVDs (e.g. IHD or stroke)), strokes (ischemic or hemorrhagic strokes), and cardiovascular deaths. 45 out of 72 (62%) had a low risk of bias and 27 out of 72 (38%) had a high risk of bias Coronary artery diseases *Education* Medium vs High RR=1.21 (95%CI 1.06-1.40) Low vs. High RR=1.36 (95% CI 1.11-1.66) Effects were heterogeneous (I^2=94%-96%) Medium vs. High USA RR=1.21 (95% CI 0.97-1.51) Low vs. High USA RR=1.51 (95% CI 0.93-2.45) (I^2=47-75%) *Income* Medium vs high RR=1.27 (95% CI 1.10-1.47) Low vs. high RR=1.49 (95% CI 1.16-1.91) Effects were heterogeneous (I^2=95%-98%) Cardiovascular events *Education* Medium vs high RR=1.27 (95% CI 1.09-1.48)	

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			Low vs high RR=1.50 (95% CI 1.17-1.92) Effects were heterogeneous (I^2=83%-99%) Medium vs. high USA RR=1.07 (95% CI 0.69-1.66) (I^2=78%) *Income* *Medium vs. high RR=1.05 (95% CI 0.98-1.13)* *Low vs. high RR=1.17 (95% CI 0.96-1.44)* *Effects were heterogeneous* (I^2=97%-99%) <u>Strokes</u> *Education* Medium vs. high RR=1.17 (95% CI 1.01-1.35) Low vs. high RR=1.23 (95% CI 1.06-1.43) Effects were heterogeneous (I^2=83%-99%) Medium vs. high USA RR=0.98 (95% CI 0.81-1.19) Low vs high USA RR=0.99 (95% CI 0.83-1.20) (I^2=53%-89%) *Income* Medium vs. high RR=1.24 (95% CI 1.00-1.53) Low vs high RR=1.30 (95% CI 0.99-1.72) Effects were heterogeneous (I^2=98%-99%) Medium vs. high USA RR=0.89 (95% CI 0.62-1.27) Low vs. high USA RR=0.91 (95%CI 0.58-1.41) (I^2=49%-78%)	

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			Cardiovascular deaths *Education* Medium vs. high RR=1.21 (95% CI 1.12-1.30) Low vs. high RR=1.39 (95% CI 1.26-1.54) Effects were heterogeneous (I^2=98) Medium vs. high USA RR=1.30 (95% CI 1.14-1.49) Low vs. high USA RR=1.69 (95% CI 1.28-2.22) (I^2=72%-95%) *Income* Medium vs. high RR=1.34 (95% CI 1.17-1.64) Low vs. high RR=1.76 (95% CI 1.45-2.14) Effects were heterogeneous (I^2=96%-99%)	
Pollitt RA, et al., 2005 15661071	Study Aim: To describe the major groups of conceptual life course SES models, categorize and summarize studies that examine the associations between life course SES and CVD risk Study type: Systematic review N=49 studies	Inclusion criteria • publication date between January 1966 and July 2003 • SES or related measures as independent variables outcomes of subclinical CHD, CVD morbidity and/or mortality, or traditional CVD risk factors	NO QUANTITATIVE SUMMARY Early SES: All 19 studies conducting unadjusted or age adjusted analyses reported a point estimate consistent with an inverse association between early-life SES and risk of one or more of the adult cardiovascular outcomes Social trajectory studies: Of 10 studies carrying out statistical analyses, six did not report associations between upward or downward mobility and either elevated levels of CVD risk factors or increased CVD morbidity or mortality when compared to stable low-SES or high-SES trajectories	Conclusions The literature identified modestly supports the existence of life course SES effects on risk of adult CVD

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			Cumulative SES: All 7 papers reviewed reported that participants' cumulative life course exposure to low SES conditions was associated with increases in CVD outcome. Several studies indicated that cumulative SES was a more powerful predictor of CVD morbidity and/or mortality than adult or early-life SES alone	
Wan EYF et al., 2018 29138274	Study Aim: To evaluate the 5-year effectiveness of a multidisciplinary Risk Assessment and Management Programme–Diabetes Mellitus (RAMP-DM) in primary care patients with type 2 diabetes Study Type Prospective cohort study N=53,436	Inclusion criteria • age at least 18 years • clinical diagnosis of type 2 DM • no prior CVD or microvascular complications Exclusion criteria	1°Endpoint all cause mortality 2°Endpoints incidences of CVD events (coronary heart disease, heart failure, or stroke), microvascular complications (retinopathy, nephropathy, neuropathy, end-stage renal disease, and sight-threatening diabetic retinopathy), and service use rates. All cause mortality: 1.68 per 100 person-years in RAMP-DM (95% CI 1.61-1.75) vs. 5.07 per 100 person years in usual care (95% CI 4.95-5.20). HR=0.339 (95% CI 0.321-0.357), p<0.001 Any CV or microvascular complications: 4.34 per 100 person years (4.22-4.46) in RAMP-DM vs. 7.73 (95% CI 7.57-7.90) in usual care. HR=0.594 (95% CI 0.572-0.617), p<0.001 CVD: 2.47 per 100 person years (2.38-2.55) in RAMP-DM vs. 5.58 (95% CI 5.44-5.72) in usual care. HR=0.434 (95% CI 0.414-0.455), p<0.001	Summary RAMP-DM led to significantly greater reductions in CVD/ microvascular complications and secondary/ tertiary care service uses compared with usual care

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			CHD: 1.11 per 100 person years (1.05-1.17) in RAMP-DM vs. 2.79 (95% CI 2.70-2.89) in usual care. HR=0.383 (95% CI 0.358-0.410), p<0.001 Heart failure: 0.71 per 100 person years (95% CI 0.67-0.76) in RAMP-DM vs. 1.75 (95% CI 1.68-1.83) in usual care. HR=0.401 (95% CI 0.368-0.436), p<0.001 Stroke:1.00 per 100 person years (95% CI 0.95-1.06) in RAMP-DM vs. 1.92 (95% CI 1.84-1.99) in usual care. HR=0.533 (95% CI 0.495-0.574), p<0.001 Any microvascular complications:2.23 per 100 person years (95% CI 2.15-2.31) in RAMP-DM vs. 2.95 (95% CI 2.85-3.05) in usual care. HR=0.881 (95% CI 0.834-0.930), p<0.001 Retinopathy: 0.81 per 100 person years (95% CI: 0.76-0.86) in RAMP-DM vs. 0.87 (95% CI 0.82-0.92) in usual care. HR=1.256 (95% CI 1.144-1.379), p<0.001 Nephropathy: 1.50 per 100 person years (95% CI 1.44-1.57) in RAMP-DM vs. 2.24 (95% CI 2.16-2.33) in usual care. HR=0.742 (95% CI 0.696-0.791), p<0.001 Neuropathy: 0.10 per 100 person years (95% CI 0.08-0.12) in RAMP-DM vs. 0.25 (95% CI 0.22-0.28) in usual care. HR=0.391 (95% CI 0.314-0.488), P,0.001	

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			ESRD: 0.11 per 100 person years (95% CI 0.09-0.13) in RAMP-DM vs. 0.28 (95% CI 0.25-0.31) in usual care. HR=0.384 (95% CI 0.311-0.474), p<0.001 STDR: 0.11 per 100 person years (95% CI 0.09-0.13) in RAMP-DM vs. 0.34 (95% CI 0.31-0.38) in usual care. HR=0.412 (95% CI 0.334-0.509), p<0.001 Hospitalization: 32.49 per 100 person years in RAMP-DM vs.64.35 in usual care. HR=0.415 (95% CI 0.403-0.428), p<0.001 A&E attendance: 52.41 per 100 person years in RAMP-DM vs. 80.43 in usual care. HR=0.588 (95% CI 0.575-0.602), p<0.001 SOPC attendance: 210.79 per 100 person years in RAMP-DM vs.307.47 in usual care. HR=0.650 (95% CI 0.636-0.664), p<0.001 GOPC attendance: 456.95 per 100 person years in RAMP-DM vs. 354.34 in usual care. HR=1.326 (95% CI 1.311-1.340), p<0.001 HRs were presented for 21 strata for each outcome (by age, smoking, duration of DM, eGFR level, control of HbA1c, BMI, control of BP, control of LDL-C, level of CVD risk). In general, RAMP-DM participants in all subgroups observed a 40% greater risk reduction in each CVD/microvascular complications and a	

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			55–85% risk reduction in all-cause mortality compared to usual care subjects. RAMP-DM participants in all subgroups had significantly fewer hospitalizations, A&E attendances, and SOPC attendances but more GOPC attendances than usual care patients. RAMP-DM participants ,<65 years of age with a DM duration of <2 years or with low/medium CVD risks received the greatest benefits from the RAMP-DM. The number needed to treat to prevent one CVD event was 8 and the number needed to treat for all-cause mortality was 6	

Data Supplement 3. Nonrandomized Trials, Observational Studies, and/or Registries of Assessment of Cardiovascular Risk (Section 2.2)

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Lloyd-Jones et al., 2006 (12) 16461820	Aim: To estimate the lifetime risk for CVD and to examine overall survival in the presence and absence of established risk factors. Study type: prospective cohort	Inclusion criteria: • Free of CVD before their earliest examination • examined at least once between 50 and 94 years of age had follow-up after their earliest eligible examination	1° Endpoint: All atherosclerotic CVD events (MI, coronary insufficiency, death from CHD, angina pectoris, atherothrombotic stroke, intermittent claudication, or other cardiovascular death) Hard atherosclerotic CVD events (excluding angina and claudication) *Men:*	The absence of established risk factors at 50 years of age is associated with very low lifetime risk for CVD and markedly longer survival

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
	N=7926		In men free of CVD at 50 years of age, lifetime risk of all ASCVD events to 95 years of age=51.7% (95% CI 49.3-54.2), and median overall survival=30 years. Lifetime risk of hard CVD=41.2% (95% CI 38.8-43.7) Lifetime risk to age 75 increased with increasing total cholesterol (26.2% for <180 mg/dL, 29.2% for 180-199 mg/dL, 34.5% for 200-239 mg/dL, and 45.3% for ≥240 mg/dL), with decreasing HDL cholesterol (23.6% ≥40 mg/dL, 34.0% <40 mg/dL), with increasing systolic or diastolic blood pressure (26.6%<120 or <80, 31.8% 120-139 or 80-89, 46.4% 140-159 or 90-99, and 51.3% ≥160 or ≥100 or treated), with diabetes (30.2% nondiabetic vs 67.1% diabetic), with smoking (27.8% nonsmoking vs. 34.0% smoking), and with increasing BMI (27.5% <25, 30.4% 25-29.9, and 41.8% ≥30). Lifetime risk at age 50 years to 95 years by risk factor status: All optimal risk factors: 5.2% (95% CI 0-12.2) (median survival>39 years) ≥1 Not optimal risk factor: 36.4% (95% CI 23.1-49.6) (median survival=36 years) ≥ Elevated risk factor: 45.5% (95% CI 38.0-53.1) (median survival=35 years)	

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			1 Major risk factor: 50.4% (95% CI 46.2-54.5) (median survival=30 years) ≥2 Major risk factors: 68.9% (95% CI 61.7-73.2) (median survival=28 years) *Women* In women free of CVD at 50 years of age, lifetime risk of all ASCVD events to 95 years of age=39.2% (95% CI 37.0-41.4), and median overall survival=36 years. Lifetime risk of hard CVD= 28.8% (95% CI 26.6-30.8). Lifetime risk to age 75 increased with increasing total cholesterol (9.1% for <180 mg/dL, 11.3% for 180-199 mg/dL, 16.7% for 200-239 mg/dL, and 30.0% for ≥240 mg/dL), with decreasing HDL cholesterol (11.0% ≥50 mg/dL, 15.9% <50 mg/dL), with increasing systolic or diastolic blood pressure (10.5%<120 or <80, 17.9% 120-139 or 80-89, 28.8% 140-159 or 90-99, and 35.0% ≥160 or ≥100 or treated), with diabetes (16.3% nondiabetic vs 57.3% diabetic), with smoking (14.2% nonsmoking vs. 20.6% smoking), and with increasing BMI (14.7% <25, 18.1% 25-29.9, and 21.9% ≥30). Lifetime risk at age 50 years to 95 years by risk factor status:	

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			All optimal risk factors: 8.2% (95% CI 0-22.3) (median survival>39 years) ≥1 Not optimal risk factor: 26.9% (95% CI 18.4-35.5) (median survival=39 years) ≥ 1 Elevated risk factor: 39.1% (95% CI 33.0-45.1) (median survival=39 years) 1 Major risk factor: 38.8% (95% CI 35.0-42.6) (median survival=35 years) ≥2 major risk factors: 50.2% (95% CI 44.7-55.7) (median survival=31 years)	
Yano et al., 2017 28746709	Aim: To examine the predictive ability of coronary artery calcium (CAC) score vs age for incident ASCVD and how risk prediction changes by adding CAC score and removing only age from prediction models Study type: Pooled analysis of US population based studies N=4778 in US studies, N=4990 in European studies	Inclusion criteria: • Framingham Heart Study, Multi-Ethnic Study of Atherosclerosis (MESA), Cardiovascular Health Study (CHS) data, as well as Rotterdam Study and Heinz Nixdorf Recall Study for comparison • ≥60 years • Without known cardiovascular diseases at baseline (including CHD, stroke, and heart failure) Exclusion criteria: • Missing CAC data • Missing covariates	1° Endpoint: Incident ASCVD, CHD, and stroke Median follow up=10.7 years The probability of remaining ASCVD event free during 12-year follow up increased with increasing CAC category. In those with CAC=0, probability of remaining ASCVD event free>90% 11% of ASCVD events occurred in those with CAC score=0, 42% of ASCVD events occurred in those with CAC≥300. ASCVD Event: Compared to a base model, a model excluding age and including CAC categories resulted in a significant change (C statistic=0.027, 95% CI 0.005-0.048), and a model excluding age and including continuous CAC resulted in a	Summary: CAC score had a greater association with incident CHD and a modest association with stroke; use of traditional cardiovascular risk factors with CAC score and without age improved discrimination for incident CHD and modestly improved discrimination for stroke; including age and CAC score without cardiovascular risk factors improved discrimination for incident CHD but not for stroke; CAC score improved risk reclassification for incident ASCVD more than age

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			significant change (C statistic=0.025, 95% CI 0.004-0.047) CHD event: Compared to a base model, a model excluding age and including CAC categories resulted in a non-significant change (C statistic=0.030, 95% CI -0.0004-0.060), and a model excluding age and including continuous CAC resulted in a significant difference (C statistic=0.032, 95% CI 0.002-0.062) Stroke event: Compared to a base model, a model excluding age and including categorical CAC resulted in a non-significant change (C statistic=0.013, 95% CI -0.015-0.041) and a model excluding age and including continuous CAC resulted in a non-significant change (C Statistic=0.017, 95% CI -0.011-0.045) CAC score had a greater association with incident CHD than age (C statistic 0.733 vs. 0.690, C statistic of difference=0.043, 95% CI 0.009-0.075) and was somewhat greater for stroke (C statistic=0.695 vs 0.670, C statistic for difference=0.025, 95% CI -0.015 to 0.064). Replacing CAC score for risk factors but retaining age improved model fit and discrimination for CHD (C statistic=0.740 vs 0.703, C statistic difference=0.037,	

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			95% CI 0.012-0.062), but reduced discrimination or incident stroke No significant interactions between CAC score and sex, race/ethnicity, or age Category free NRI in those who experienced ASCVD events for CAC=0.390 (95% CI 0.312-0.469) and for age=0.098 (95% CI -0.001-0.181). Category-free NRI in those who did not experience ASCVD events for CAC=0.105 (95% CI 0.08-0.137) and for age=0.199 (95% CI 0.171 – 0.225). In European cohort, CAC had greater association with incident CHD than age, while age had greater association with stroke than CAC. Including CAC and excluding age provided improved discrimination for CHD but not stroke. Replacing risk factors with CAC in a model with age improved fit and discrimination for CHD but reduced discrimination for stroke.	
Wilkins et al., 2012 23117780	Aim To calculate LTR estimates of tCVD by index age [45, 55, 65, 75 years(y)] and risk factor strata and to estimate years lived free of CVD across risk factor strata Study type	Inclusion criteria: Framingham Heart Study, Framingham Offspring Study, Cardiovascular Health Study, Atherosclerosis Risk in Communities study, and Chicago Heart Association Detection Project in Industry Study.	1° Endpoint: Lifetime risk of total CVD At index age of 45 years: overall lifetime risk through age 95=60.3% (95% CI 59.3-61.2) for men and 55.6% (95% CI 54.5-56.7 for women).	Summary: At index age 45, overall remaining lifetime risk estimates for total CVD to age 95 years were approximately 60% in men and 55% in women. Risks for were greater in men than women at all but the oldest index ages. Lifetime risks were high regardless of index age. Lower aggregate risk factor burden was associated with a lower lifetime risk through age 95 years regardless of index age. Even those with optimal risk factor profiles had lifetime risks greater than 30%, but maintenance of low risk factor burden at middle age was

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
	Pooled analysis of prospective cohort studies N=905,115 person years	• Studies had to include cause-specific or cardiovascular mortality, and ascertainment of non-fatal cardiovascular events Exclusion criteria pre-existing CVD	At index age of 55 years: overall lifetime risk=60.2% (95% CI 59.1-61.2) for men and 56.3% (95% CI 55.2-57.4) for women At index age 65 years: overall lifetime risk=59.0% (95% CI 57.6-60.4) for men and 56.1% (54.7-57.5) for women At index age 75 years: overall lifetime risk=54.5% (95% CI 52.2-56.9) for men and 52.3% (95% CI 50.3-54.3) for women For all but index age 75, lifetime risk through age 95 was greater than 50% in those with 1 or more elevated risk factor, 1 major risk factor, and 2 or more major risk factors in both men and women. In those with "not optimal" risk factors at age 55 and 65, lifetime risk were >40% for men and >30% for women. At index age 55, men with optimal risk factor profiles had remaining lifetime risks >40% and women had risks close to 30% to age 85 years of age. Compared to those with 2 or more major risk factors, those with optimal risk factor levels had longer CVD-free and overall survival, though the difference in years lived free of CVD decreased with increasing age. At age 45, those with optimal risk factor profiles lived up to 14 years longer CVD free than those with 2 or more risk factors.	associated with a delay in age at onset of total CVD by as much as 14 years for younger adults.
Valenti et al., 2015 26189116	Aim:	Inclusion criteria	1° Endpoint:	Summary: The presence of CAC was a strong predictor of incident mortality, even when considering clinical risk scores by

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
	To examine long-term prognosis of a zero coronary artery calcium (CAC) score among asymptomatic individuals and its associated warranty period <u>Study type:</u> prospective cohort N=9,715	• No known coronary artery disease (CAD) • referred by their physicians for CAD evaluation underwent CAC testing electron beam computed tomography (EBCT) at a single site.	All cause mortality CAC>0 HR=2.67 (95% CI 2.29-3.11, p<0.001). Stratified analyses: CAC=0 Age HR=1.03 (95% CI 1.02-1.04, p<0.001) Female HR=1.01 (95% CI 0.78-1.32, p=0.92) Hypertension HR=1.48 (95% CI 1.21-2.06, p=0.001) Dyslipidemia HR=0.83 (95% CI 0.63-1.08, p=0.16) Diabetes HR=2.53 (95% CI 1.74-3.69, p<0.001) Family history HR=0.3 (95% CI 0.70-1.23) Smoking HR=1.95 (95% CI 1.50-2.53, p<0.001) CAC>0 Age HR=1.05 (95% CI 1.04-1.05, p<0.001) Female HR=0.93 (95% CI 0.80-1.09, p=0.37)	Framingham or NCEP ATP III methods. CAC=0 confers a 15-year warranty period against mortality among individuals at low-to-intermediate risk, which is unaffected by age or gender. Furthermore, in individuals considered at high-risk by clinical risk scores the presence of CAC=0 confers better survival than in individuals at low-to-intermediate risk but with any CAC

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			Hypertension HR=1.62 (95% CI 1.39-1.89, p<0.001) Dyslipidemia HR=0.65 (95% CI 0.56-0.75, p<0.001) Diabetes HR=2.15 (95% CI 1.79-2.57, p<0.001) Family history HR=0.71 (95% CI 0.61-083, p<0.001) Smoking HR=1.77 (95% CI 1.52-2.05, p<0.001) Risk of all cause mortality in those with CAC>0 and low cardiovascular risk: FRS: HR=3.3, 95% CI 2.49-4.32, NCEP ATP III HR=3.09, 95% CI 2.45-3.90. Risk of all cause mortality in those with CAC=0 and high cardiovascular risk: FRS HR=2.8, 95% CI 2.05-3.92, NCEP ATP III HR=2.94, 95% CI 2.15-4.01 *Adjusting for FRS*: Compared with CAC=0: CAC 1-99 HR=2.08 (95% CI 2.08, p<0.001) CAC 100-399 HR=3.42 (95% CI 2.83-4.14, p<0.001) CAC 400-999 HR=4.93 (95% CI 3.98-6.12, p<0.001)	

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			CAC ≥1000 HR=6.79 (95% CI 5.29-8.72, p<0.001) Adjusting for NCEP-ATPIII Compared with CAC=0 CAC 1-99 HR=2.03 (95% CI 1.70-2.42, p<0.001) CAC 100-399 HR=3.32 (95% CI 2.74-4.02, p<0.001) CAC 400-999 HR=4.81 (95% CI 3.87-5.97, p<0.001) CAC ≥1000 HR=6.99 (95% CI 5.46-8.95, p<0.001) CAC=0 associated with >15 year warranty period with observed rate of mortality <1% during entirety of follow up. Mean event rate=0.3% events/year in initial 12 year, 0.4% events/year in 13th year, 0.58% events/year in 14th year. No apparent disparity among genders. Observed warranty period in CAC=0 slightly shorter for those 60 years and older. CAC=0 and high cardiovascular risk had warranty period of 5-6 years. Compared with base model of FRS or NCEP ATP III alone, discrimination improved significantly with addition of CAC (AUC=0.71 vs. 0.64 for FRS and AUC=0.72 vs. 0.64 for NCEP ATP III,	

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			p<0.001). CAC improved risk classification for those at risk versus not at risk for incident mortality (net reclassification improvement p<0.001 overall and when stratified by risk category)	
Framingham Heart Study Pencina et al., 2009 19506114	Aim: To develop a tool for estimating 30-year risk of hard CVD events among individuals free of the condition at baseline Study type Prospective cohort N=4,506	Inclusion criteria • Participants in the Framingham Offspring Study • Between 20 and 59 years of age • Free of CVD and cancer at baseline • Not lost to follow up Had complete risk factor profile	1° Endpoint: Effect of risk factors measured at baseline on 30-year risk of hard CVD 2° Endpoint: Effect of risk factors measured at baseline on 30-year risk of all CVD Main model: Male sex, HR=1.73 (95% CI 1.45-2.07) Age HR=2.09 (95% CI 1.88-2.31) Systolic BP HR=1.29 (95% CI 1.19-1.39) Antihypertensive treatment HR=1.48 (95% CI 1.10-2.00) Smoking HR=2.01 (95% CI 1.72-2.35) Diabetes HR=2.49 (95% CI 1.82-3.41) Total cholesterol HR=1.33 (95% CI 1.23-1.44) HDL cholesterol HR=0.78 (95% CI 0.72-0.84)	Summary: Standard risk factors were strongly related to hard CVD over extended followup. 30-year functions offer additional risk burden information over 10-year risk

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			BMI (in place of total cholesterol and HDL cholesterol in simple model) HR=1.20 (95% CI 1.10-1.30) 30-year risk model showed high discrimination (cross-validated c statistic=0.803, 95% CI 0.786-0.820, internally validated c statistic=0.802, 95% CI 0.772-0.832) and good calibration (cross-validated chi square=4.25, p=0.894; internally validated chi square=3.98, p=0.913) Mean estimated 30-yuear risk=7.9% for women and 18.0% for men. Ignoring competing risk of non-cardiovascular death, mean risks increased to 8.6% and 20.4%.	
MESA Patel et al., 2015 26047825	Aim: To determine whether the extent of subclinical atherosclerosis burden (by either CAC or CIMT) could better stratify risk for ASCVD and CHD events beyond traditional risk factors among individuals with a self-reported FH of premature CHD Study type: Prospective cohort	Inclusion criteria • 45 to 84 years of age • Caucasian, African American, Hispanic, or Chinese American • Free of clinical ASCVD at baseline Exclusion criteria: Missing data from visit 1 or 2 (when family history and CAC were obtained)	1° Endpoint: Hard CHD (MI, resuscitated cardiac arrest, or coronary heart disease death) Hard ASCVD: hard CHD plus stroke or stroke death Median follow up time of 10.2 years *CAC* *Hard ASCVD events (no significant interaction by family history, p=0.28):* In those with negative family history: Compared to CAC=0, HR for CAC 1-99=1.75 (95% CI 1.22-2.50), CAC 100-	CAC testing is more effective than CIMT at stratifying absolute and relative risk for both ASCVD and CHD in those with a family history of premature CHD. The addition of CAC added significant prognostic information for discrimination for CHD events in persons with a family history of premature CHD, while the addition of CIMT did not.

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
	N=6,125		399=2.78 (95% CI 1.91-4.06), CAC >400=3.23 (95% CI 2.15-4.86) In those with positive family history: Compared to CAC=0, HR for CAC 1-99=1.64 (95% CI 0.94-2.87), CAC 100-399=2.45 (95% CI 1.31-4.58), CAC >400=2.80 (1.44-5.43). Compared to those without FH, those with FH HR=1.35 (95% CI 1.07-1.71). After adjusting for CAC, association remained significant (HR=1.30, 95% CI 1.03-1.64). There was no significant interaction between race and family history (HR white=1.08, 95% CI 0.74-1.56; HR black=2.09, 95% CI 1.37-3.19, HR Hispanic=1.34, 95% CI 0.85-2.13, HR Chinese=0.95, 95% CI 0.21-4.22) *Hard CHD events (no significant interaction by family history, p=0.49)* In those with negative family history: Compared to CAC=0, HR for CAC 1-99=2.35 (95% CI 1.46-3.78), CAC 100-399=3.54 (95% CI 2.14-5.85), CAC >400=4.87 (95% CI 2.88-8.24) In those with positive family history: Compared to CAC=0, HR for CAC 1-99=1.93 (95% CI 0.91-4.10), CAC 100-399=3.52 (95%CI 1.58-7.84), CAC >400=3.85 (95% CI 1.65-9.02) Compared to those without FH, those with FH HR=1.41 (95% CI 1.05-1.88).	

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			After adjusting for CAC, association remained significant (HR=1.33, 95% CI 1.00-1.78) <u>*CIMT*</u> *Hard ASCVD events (no significant interaction by family history, p=0.21):* In those with negative family history: Compared to CIMT≤50th percentile, HR for CIMT 51-75th percentile=0.93 (95% CI 0.67-1.29), CIMT 75-90th percentile HR=1.27 (95% CI 0.90-1.80), CIMT >90th percentile HR=1.11 (95% CI 0.75-1.63) In those with positive family history: Compared to CIMT≤50th percentile, HR for CIMT 51-75th percentile HR=1.18 (95% CI 0.71-1.95), CIMT 75-90th percentile HR=1.30 (95% CI 0.74-2.28), CIMT >90th percentile HR=0.76 (95% CI 0.39-1.50) *Hard CHD events (no significant interaction by family history, p=0.51)* In those with negative family history: Compared to CIMT≤50th percentile, HR for CIMT 51-75th percentile HR=0.70 (95% CI 0.46-1.08), CIMT 75-90th percentile HR=1.20 (95% CI 0.79-1.84), CIMT >90th percentile HR=0.94 (95% CI 0.58-1.52) In those with positive family history: Compared to CIMT≤50th percentile, HR	

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			for CIMT 51-75th percentile HR=1.02 (95% CI 0.54-1.94), CIMT 75-90th percentile HR=1.29 (95% CI 0.64-2.60), CIMT >90th percentile HR=0.87 (95% CI 0.38-1.96) The addition of CAC to the base model comprising the variables from the pooled cohort equation for ASCVD risk estimation led to an increase in the Harrell's C-statistic for hard CHD from 0.74 to 0.77 (p=0.0005), while the addition CIMT was not significant (p=0.97). Similar results for hard ASCVD were obtained when either CAC or CIMT were added to the base model [base AUC = 0.75; base plus CAC = 0.77 (p=0.0004) and base plus CIMT = 0.75 (p=0.70)]	
MESA Budoff, et al., 2018 29688297	Aim: to evaluate the contribution of CAC using the population-based MESA cohort with over 10 years of follow-up for ASCVD events, and whether the association of CAC with events varied by sex, race/ethnicity, or age category. Study Type: Prospective cohort	Inclusion criteria: • Free of clinical cardiovascular disease • Age 45-84 at baseline • White, Black, Hispanic, Chinese	1° Endpoint: Total events: Incident ASCVD events (definite or probably MI, resuscitated cardiac arrest, fatal CHD, fatal and non-fatal stroke (not TIA), other atherosclerotic death, other CVD death) Hard ASCVD: MI, fatal or non-fatal strokes (not TIA), resuscitated cardiac arrest, fatal CHD • Median 11.1 years follow up At 10 years of follow-up, all participants with CAC> 100 were estimated to have >7.5% risk regardless of demographic subset	Summary: • CAC is consistently associated with risk with the same magnitude of effect in all races, age groups, both sexes, and in people on and off lipid lowering therapy Limitations: • Authors note a limitation in the use of electron beam tomography (EBT) and 4- and 16-detector CT systems

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
	Size: N=6814		Ten-year ASCVD event rates increase with increasing CAC overall and across race/ethnicity, age, sex, and education. 10 year ASCVD event rates in the CAC=0 group range from 1.3-5.6% vs. 13.1-25.6% in the CAC>300 group Hard ASCVD: • adjusting for CAC in multivariable models attenuated associations, but associations between age, sex, and race and Hard ASCVD outcomes were still significant. Doubling of CAC HR=1.14 (1.11-1.17, p<0.001) • association of CAC with risk of ASCVD did not vary by age, sex, race/ethnicity, or lipid lowering medication at baseline (p for interaction all non significant)	
Multi-Ethnic Study of Atherosclerosis (MESA) Blaha et al., 2016 26801055	Aim: to compare the relative value of various negative risk markers in a contemporary, multi-ethnic cohort Study Type: Prospective Cohort N=6,814	Inclusion criteria • MESA participants were 45 to 84 years of age Free of clinical CVD at recruitment	1° endpoint mean diagnostic likelihood ratios (DLRs) for the thirteen negative risk markers for the entire MESA population as well as for important subgroups (CAC=0, Low CIMT, Normal FMD, Normal ABI, hsCRP<2mg/L, homocysteine <10μmol/L, NT-ProBNP <100 pg/mL, no microalbuminuria, healthy lifestyle, no family history, no family history of premature CHD, no metabolic syndrome)	Among a wide range of negative risk markers including atherosclerosis imaging techniques, serum biomarkers clinical features, and other tests, CAC=0 resulted in the greatest reduction in post-test risk. The conclusions were consistent across gender and 10-year ASCVD risk categories, and using different baseline multivariable models. Carotid ultrasound imaging with a normal result showed the best performance after CAC=0, whereas the performance of the other negative risk markers was minimal or modest. CAC=0 also yielded the largest, most accurate reclassification of risk to below commonly accepted treatment thresholds. After CAC=0, low CIMT showed the best performance. Absence of any family history of CHD was most informative of the clinical characteristics.

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			NRI was calculated for each of the negative risk markers using different risk thresholds Mean follow up time=10.3 years Among all negative risk markers, CAC=0 showed the best performance with the greatest pre-test to post-test risk shift. CAC=0 had stable risk factor adjusted DLRs across clinical characteristics (0.36 in men, 0.46 in women). CAC=0 was particularly informative in older ages and in those with higher pre-test predicted 10-year ASCVD risk. DLR adjusted for traditional risk factors: All CHD events: CAC: 0.41, CIMT: 0.65 No carotid plaque: 0.84 FMD: 0.94 Ankle Brachial Index: .98 HsCRP: 0.90 Homocysteine: 0.96 NT-ProBNP: 0.86 No microalbuminura: 0.96 No family history of CHD: 0.76 No family history premature CHD: 0.97 No metabolic syndrome: 0.90 Healthy lifestyle: 0.90	

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			DLR adjusted for traditional risk factors: Hard CHD events CAC: 0.51 CIMT: 0.78 No carotid plaque: 0.88 FMD: 0.86 Ankle Brachial Index: 0.97 HsCRP: 0.98 Homocysteine: 0.94 NT-ProBNP: 0.79 No microalbuminura: 0.97 No family history of CHD: 0.78 No family history premature CHD: 0.99 No metabolic syndrome: 0.91 Healthy lifestyle: 0.87 All CVD events CAC: 0.54 CIMT: 0.75 No carotid plaque: 0.88 FMD: 0.91 Ankle Brachial Index: 1.00 HsCRP: 0.89 Homocysteine: 0.96 NT-ProBNP: 0.88 No microalbuminura: 0.97 No family history of CHD: 0.81 No family history premature CHD: 0.96 No metabolic syndrome: 0.91 Healthy lifestyle: 0.98	

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			NRI analyses also showed CAC=0 as the largest, most accurate downward risk reclassification.	
Cardiovascular Lifetime Risk Pooling Project Berry et al., 2012 22276822	Aim To report lifetime risks of cardiovascular disease have not been reported across the age spectrum in black adults and white adults Study type Meta analysis of cohort studies N=18 studies (257,384 participants)	Inclusion criteria • Represented either community-based or population-based samples or large volunteer cohorts • Included at least one baseline examination with direct measurement of physiological and anthropometric (e.g., weight) variables • Included 10 or more years of follow-up for fatal or nonfatal cardiovascular events or both	1° endpoint *Lifetime risk of cardiovascular disease* Lifetime risk was higher among men than women (36.1% white men, 33.0% black men, 26.6% white women, 27.1% black women) Lifetime risk of death from cardiovascular disease and coronary heart disease or nonfatal MI were approximately two times as high in men, lifetime risk of fatal stroke or nonfatal stroke did not vary by sex. In men at 55 years of age, white and black men with optimal risk factor profiles (total cholesterol <180 mg per deciliter, <120 mm HG systolic and 80 mm HG diastolic blood pressure, non smoking, and nondiabetic) had lower lifetime risks than those with two or more major risk factors (7.7% vs. 29.6% in all men, 4.0% vs 26.6% for white men, 9.9% vs 27.9% in black men, 6.4% vs. 20.5% in all women). Adjusting for competing risks substantially decreased the lifetime risk (in men with 2+ major risk factors, unadjusted Kaplan-Meier estimate=81.8% without adjustment for competing risk and 44.5% after adjustment for competing risk). The 20-year adjusted risk of death from cardiovascular disease at age 55 decreased with increasing year of birth	Summary: Risk factors were associated with significant increases in the long-term risk of cardiovascular disease, and optimal risk factor status was associated with a very low lifetime risk. The effect of risk factors was consistent across birth cohorts. Accounting for risk factors, the lifetime risks of cardiovascular disease were similar between blacks and whites .

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			cohort (e.g., men in NHANES I compared to men in NHANES III had 17.7% vs. 10.5% 20-year adjusted risk; women from NHANES I compared to women from NHANES III had 12.2% VS. 7.0% 20-year adjusted risk). The 20-year adjusted risk for each risk factor profile did not show evidence of change over time.	
Mahabadi AA, et al., (8) 2017 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%)	• "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

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

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			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., (9) 2015 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	• 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

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			• 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	
Kavousi M, et al., (7) 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	• 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

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			• Increase in C-statistic with CAC added to base model: 0.02, 95% CI 0.00-0.05 • Continuous NRI with CAC: 0.20 (95% CI 0.09, 0.31) • Results evaluating CHD as outcome similar but generally more robust	
CARDIA Carr J, et al., 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 • 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>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. • 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

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

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			• 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	
Mortensen MB, et al., 2016 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 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	• 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

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			• 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)	
Framingham Pursnani A, et al., 2015 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.
MESA Yeboah J., et al., 2016 26791059	Study type: Prospective Observational Cohort study (MESA)	Inclusion criteria: • MESA participants age 45-84 years	1° endpoint: Incident ASCVD Median follow up 10 years Results:	• CAC improved discrimination and NRI beyond recalibrated PCE whereas other non-traditional risk markers did not.

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
	Size: N=5185 participants with recalibrated (to MESA sample) PCE score	Exclusion criteria: Missing data, participants receiving statin at baseline	• 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 + hsCRP: 0.025, 95% CI -0.015-0.067 + Family history: 0.051, 95% CI 0.000-0.109	
Gupta A, et al., 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	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%)	• 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

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
	EISNER study included. Note 2 reports from 1 study with different outcomes		• 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%). • 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%)	
Jackson Heart Study Shah R.V., et al., 2017 28315622	Study type: Prospective Observational Cohort study	Inclusion criteria: • African American men and women age 40-75 years Exclusion criteria:	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%.

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
	Size: N=2812 (N=1743 with CAC score) participants	Prevalent CVD, on statin therapy, missing data	• 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	
JUPITER Ridker PM, et al., 2008 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-	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	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

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
	blind placebo controlled clinical trial Size: 17,802 subjects	• 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		
Ference BA, et al., 2018 30165986	Study Aim: describe the cumulative effect of lipid carrying lipoproteins on the risk of cardiovascular disease, estimate the magnitude of the potential clinical benefit that can be achieved by maintaining optimal lipid levels, identify the most effective timing for implementing strategies designed to achieve and maintain optimal lipid levels, and suggest specific strategies to help people	Inclusion criteria N/A Exclusion criteria N/A	1° endpoint: Not specified, and no quantitative summary conducted	Author's Conclusions The causal effect of LDL and other apo B–containing lipoproteins on the risk of cardiovascular disease is determined by both the magnitude and the cumulative duration of exposure to these lipoproteins. The goal of maintaining optimal lipid levels throughout life is to keep the concentration of circulating LDL and other apo B–containing lipoproteins low to minimize the number of particles that become retained in the arterial wall and thereby minimize the rate of progression of atherosclerotic plaques. Because apo B–containing lipoproteins have both causal and cumulative effects on the risk of atherosclerotic cardiovascular disease, the most effective strategy to prevent cardiovascular events by slowing the rate of atherosclerotic plaque progression would be to achieve optimal lipid levels as early in life as possible and maintain those optimal lipid levels throughout life.

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
	Study Type Narrative review N=N/A			
Multi-Ethnic Study of Atherosclerosis (MESA) Patel, J. et al., 2018 29555305	Study Aim To determine whether family history of coronary heart disease (FH) definitions differ in their association with atherosclerotic cardiovascular disease events Study type Prospective cohort N=6200	Inclusion criteria Age 45-84 Race: white, black, Hispanic, or Chinese American Free of clinical ASCVD at baseline Provided data on family history (attended visits at baseline and visit 2)	1° endpoint: • hard CHD (myocardial infarction, resuscitated cardiac arrest, or CHD death) • Angina (definite, probable, or absent). • Stroke (fatal or nonfatal due to hemorrhage or infarct) • Peripheral artery disease (PAD): • Congestive heart failure (CHF) *CHD* Any FH: HR=1.37 (95% CI 1.06-1.77) Premature FH: HR=1.33 (95% CI 0.96-1.83) Moderate familial risk (vs. weak) HR=1.40 (95% CI 1.00-1.96) Strong familial risk (vs. weak) HR=1.37 (95% CI 1.00-1.87 Addition of FH status to base model led to increase in C statistic from 0.736 to 0.737 for premature FH (p=0.09). Addition of Familial Risk Assessment to the base model improved C statistic from 0.736 to 0.739 (p=0.05) *Angina* Any FH: HR=1.60 (95% CI 1.24-2.06) Premature FH: HR=1.58 (95% CI1.17-2.14)	Summary All the approaches to defining FH considered in this analysis seemed to perform similarly in improving CHD risk prediction The association of FH and events was limited to CHD and angina, and other noncoronary cardiovascular outcomes were not statistically significantly associated

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			Moderate familial risk (vs. weak): HR=1.33 (95% CI 0.94-1.87) Strong familial risk (vs. weak): HR=1.80 (1.35-2.40) *Stroke*: No significant differences *PAD*: No significant differences *CHF*: No significant differences *Composite ASCVD* Any FH: HR=1.28 (95% CI 1.10-1.49) Premature FH: HR=1.29 (95% CI 1.07-1.55) Moderate familial risk (vs. weak): HR=1.20 (95% CI 0.98-1.47) Strong familial risk (vs. weak): HR=1.35 (95% CI 1.13-1.61) Addition of FH status to base model led to increase in C statistic from 0.740 to 0.743 ($p<0.001$) for any FH and from 0.740 to 0.742 for premature FH ($p<0.05$). Addition of Familial Risk Score to base model improved C statistic from 0.740 to 0.744 ($p=0.001$) and provided improved discrimination over premature FH (C statistic increased from 0.742 to 0.744, $p=0.05$) NRI Analysis for incident cardiovascular events with addition of FH to Framingham risk score	

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			Total population *CHD* FRS+ any FH NRI=0.162 (95% CI 0.061-0.264) FRS+premature FH NRI=0.069 (95% CI -0.106-0.179) FRS+FH risk strata NRI=0.164 (95% CI 0.067-0.260) Composite ASCVD *CHD* FRS+any FH NRI=0.166 (95% CI 0.094-0.243) FRS+premature FH NR=0.076 (95% CI 0.014-0.135) FRS+FH risk strata NRI=0.165 (95% CI 0.090-0.237) Population at intermediate risk by FRS *CHD* FRS+any FH NRI=0.160 (95% CI -0.200p0.323) FRS+premature FH NRI=0.064 (95% CI -1.90-0.206) FRS+FH risk strata NRI+0.159 (95% CI -0.201-0.318) *Composite ASCVD* FRS+any FH NRI=0.143 (95% CI 0.041-0.244) FRS+premature FH NRI=0.036 (95% CI -0.108-0.111)	

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			FRS+FH risk strata NRI=-0.209 (-0.155 to 0.205)	
ORALE (Outcome of Rheumatoid Arthritis Longitudinal Evaluation) del Rincon, ID. Et al., 2001 11762933	Study Aim To compare the incidence of cardiovascular (CV) events in persons with rheumatoid arthritis (RA) with that in people from the general population, adjusting for traditional CV risk factors Study type Prospective cohort study N=236	Inclusion criteria - presented for a scheduled appointment with a rheumatologist at 1 of 3 participating clinical centers -met the American College of Rheumatology 1987 revised criteria for the classification of RA -Non-RA cohort were those in the San Antonio Heart Study (SAHS) cohort	1° endpoint: CV event (any hospitalization due to myocardial infarction, stroke or other arterial occlusive events, or arterial revascularization procedures; death due to CV causes (immediate or first underlying cause of death)) Incidence in ORALE cohort=3.43 per 100 patient years vs. 0.59 per 100 person years in SAHS cohort *Incidence Rate Ratio ORALE RA cohort vs. SAHS non-RA cohort* Women 25-54 IRR=4.61 (95% CI 0.11-27.39) Women 55-65 IRR=1.68 (95% CI 0.04-9.83) Men 25-54 IRR=9.57 (95% CI 0.24-55.86) Men 55-65 IRR=4.70 (95% 1.24-12.58) Weighted Mantel-Haenszel IRR=3.96 (95% CI 1.86-8.43) Multivariate analysis IRRs: ORALE vs. SAHS cohort IRR=3.17 (95% CI 1.33-6.36) Age IRR=2.15 (95% CI: 1.83-2.55) Sex (men vs. women) IRR=1.99 (95% CI 1.50-2.66) Diabetes mellitus IRR=2.28 (95% CI 1.65-3.12)	Summary increased incidence of CV events in RA patients is independent of traditional CV risk factors

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			Systolic blood pressure IRR=1.18 (95% CI 1.03-1.33) Body mass index IRR=-1.13 (95% CI 0.99-1.28) Cigarette smoking IRR=1.37 (95% CI 1.01-1.83) Hypercholesterolemia IRR=1.35 (95% CI 1.01-1.82)	
Manzi, S. et al., 1997 9048514	Study Aim Determined age-specific incidence rates of cardiovascular events, including myocardial infarction and angina pectoris, in women with systemic lupus erythematosus Study Type Retrospective cohort study N=498 women with systemic lupus erythematosus N=2,208 women in Framingham Offspring Study	Inclusion criteria -consecutive female patients with a diagnosis of systemic lupus erythematosus seen at the University of Pittsburgh Medical Center between January 1, 1980, and December 31, 1993 -met the 1982 revised American College of Rheumatology criteria for classification as having definite or probable lupus -Comparison group were women of similar age in the Framingham Offspring Study Exclusion criteria -patients residing outside a 100-mile radius of the medical center	1° endpoint: Incidence rates of cardiovascular events *Myocardial Infarction* RR age 35-44=52.43 (95% CI 21.6-98.5) RR age 45-54=2.47 (95% CI 0.8-6.0) RR age 55-64=4.21 (95% CI 1.7-7.9) *Angina* RR age 25-34=1.96 (95% CI 0.0-9.0) RR age 35-44=2.35 (95% CI 0.4-11.1) RR age 45-54=1.03 (95% CI 0.2-4.6) RR age 55-64=2.33 (95% CI 0.9-5.5) *Death rates in women with systemic lupus erythematosus* Rate age 15-24 =12.6 (95% CI 1.5-45.6) Rate age 25-34=14.6 (95% CI 7.6-25.5) Rate age 35-44=9.9 (95% CI 5.3-16.9) Rate age 45-54=11.2 (95% CI 4.5-23.1) Rate age 55-64=39.1 (95% CI 21.3-65.6) Rate age 23.8 (95% CI 8.7-51.8)	Summary -Rates of cardiovascular events were higher in women with lupus -High rates of cardiovascular disease were found in young women with lupus
Wu, P. et al., 2017	Study Aim	Inclusion criteria	1° endpoint:	Summary

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
28228456	to systematically evaluate and quantify the evidence on the relationship between preeclampsia and the future risk of cardiovascular diseases. Study Type Systematic review and meta analysis N=22 studies (>6.4 million women)	-studies investigating the long-term cardiovascular outcomes of women with and without preeclampsia -published in English -published between 2005 and August 2015 - no restriction on the definition of preeclampsia -had at least 2 groups (1 with preeclampsia and 1 without preeclampsia) - reported sufficient data to allow for accurate risk estimates to be calculated. Exclusion criteria -Studies assessing outcomes during antepartum or before 6 weeks postpartum	heart failure; coronary heart disease; death because of coronary heart disease; composite cardiovascular disease defined as a combination of cardiac, cerebrovascular, and peripheral vascular disease; death because of composite cardiovascular disease; stroke; and stroke death. *Heart Failure* Pooled RR for adjusted studies=4.19 (95% CI 2.09-8.38) Heterogeneity I^2=71% Pooled RR for unadjusted studies=3.08 (95% CI 1.67-5.69) I2=76% Overall pooled RR adjusted and unadjusted=3.62 (95% CI 2.25-5.85) I^2=83% RR for adjusted studies with <1 year follow up=4.10 (95% CI 2.90-5.80), 1-10 years=8.42 (95% CI 4.39-16.17), and >10 years follow up=1.60 (95% CI 0.73-3.50) Sensitivity analysis controlling for Age RR=3.89 (95% CI 1.83-8.26), controlling for BMI/Weight RR=1.84 (95% CI 1.23-2.74), controlling for diabetes RR=2.16 (95% CI 1.03-4.52), controlling for smoking RR=1.56 (95% CI 1.11-2.20), and controlling for hypertension RR=3.84 (95% CI 0.81-18.16) *Coronary heart disease*	There was an association of preeclampsia with future incident coronary heart disease, composite cardiovascular disease, heart failure, stroke, and deaths because of coronary heart disease. The adjusted risk ranged between 1.8-and 2.5-fold compared with those without a history of preeclampsia in all cardiac outcomes, except in heart failure, where a 4-fold increase in risk was found

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			Pooled RR for adjusted studies=2.50 (95% CI 1.43-4.37) I^2=89% Pooled RR for unadjusted studies=2.04 (95% CI 1.61-2.59) I^2=70% Overall pooled RR adjusted and unadjusted=2.11 (95% CI 1.60-2.77). I^2=87% RR for adjusted studies with <1 year follow up=3.10 (95% CI 1.56-6.15), 1-10 years=3.78 (95% CI 0.43-77.30), and >10 years follow up=1.46 (95% CI 0.95-2.25) RR adjusting for age=2.63 (95% CI 1.74-3.98) *CVD Mortality* RR=2.21 (95% CI 1.83-2.66) I^2=54% Sensitivity analysis controlling for age RR=2.21 (95% CI 1.83-2.66) *Stroke* Pooled RR for adjusted studies=1.81 (95% CI 1.29-2.55) I^2=74%	

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			Pooled RR for unadjusted studies=1.60 (95% CI 1.47=1.74) (note: estimate based on one study) I^2=N/A Overall pooled RR adjusted and unadjusted=1.71 (95% CI 1.38-2.11) I^2=69% RR for adjusted studies with <1 year follow up=2.22 (95% CI 1.73-2.85), 1-10 years follow up=3.56 (95% CI 0.52-24.28), and >10 years=1.18 (95% CCI 0.95-1.46) Sensitivity analysis controlling for age RR=2.04 (95% CI 1.60-2.60), controlling for BMI/Weight RR=1.94 (95% CI 1.42-2.65), controlling for diabetes RR=2.46 (95% CI 1.11-5.43), and controlling for smoking RR=1.64 (95% CI 1.12-2.40)	
Nurses' Health Study II (NHSII) Tanz, LJ., et al., 2017 28153993	Study Aim To evaluate the association between preterm delivery and CVD (myocardial infarction or stroke) and whether this association is accounted for by postpartum development of traditional CVD risk factors (chronic	Inclusion criteria -participant in Nurses' Health Study Exclusion criteria -Self-reported pre-baseline CVD -did not complete 2001 or 2009 questionnaires documenting reproductive history -nulliparous in 2009 -<age18 or >45 at first birth	1° endpoint: Composite cardiovascular events (myocardial infarction and stroke) 2° endpoint: Coronary revascularization 1° endpoint: *All subjects* HR preterm (<37 weeks) for cardiovascular events=1.42 (95% CI 1.16-1.72)	Summary Women who deliver a preterm infant are at a 40% increased risk of future CVD events while those who deliver before 32 weeks experience a doubling of CVD risk, even after accounting for pre-pregnancy sociodemographic, lifestyle and CVD risk factors. This increased risk is only partially explained by the subsequent development of traditional CVD risk factors such as chronic hypertension, hypercholesterolemia, weight gain and T2DM in the years after the delivery

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
	hypertension, hypercholesterolemia, type 2 diabetes mellitus (T2DM), and BMI). Study type Prospective cohort study N=70,182	-missing information on gestation length or year of pregnancy	HR moderate preterm (≥32 to <37 weeks)=1.22 (95% CI 0.96-1.54) HR very preterm (<32 weeks)=2.01 (95% CI 1.47-2.75) P<0.0001 for trend *Those without hypertensive disorders of pregnancy in first pregnancy* HR preterm (<37 weeks) for cardiovascular events=1.35 (95% CI 1.06-1.72) HR moderate preterm (≥32 to <37 weeks)=1.12 (95% CI 0.83-1.52) HR very preterm (<32 weeks)=2.01 (95% CI 1.38-2.93) *Among women with no births at age 40+ HRs compared to referent group with First pregnancy term/2nd+pregnancies term* 1st pregnancy term/2nd+ preterm HR=1.34 (95% CI 1.01-1.76) 1st pregnancy term/no 2nd+prengnacies HR=1.21 (95% CI 0.99-1.46)	

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			1st pregnancy preterm/2nd + pregnancies term HR=1.38 (95% CI 1.00-1.90) 1st pregnancy term/2nd+pregnancies preterm HR=1.65 (95% CI 1.20-2.28) 1st pregnancy preterm/ no 2nd+pregnancies HR=1.45 (95% CI 0.97-2.17) When examining a model adjusted for age at first birth, age in 1989, race/ethnicity, and parental education, the proportion of the association accounted for by the intermediates of chronic hypertension hypercholesterolemia, type 2 diabetes mellitus, and BMI was 13.3% (95% CI 7.9-21.4) for <37 weeks, 17.1% (95% CI 5.5-42.5) for ≥32 to <37 weeks, and 12.0% (95% CI 8.6-16.5) for <32 weeks. When examining a model adjusted for age at first birth, age in 1989, race/ethnicity, parental education, pre-pregnancy BMI, pre-pregnancy smoking, pre-pregnancy Alternative Healthy Eating Index score, pre-pregnancy alcohol intake, physical activity at age 18, pre-pregnancy oral contraceptive use, and family history of MI or stroke before age 60, the proportion of the association accounted for by the intermediates of chronic hypertension	

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			hypercholesterolemia, type 2 diabetes mellitus, and BMI was 12.8% (95% CI 7.1-21.9) for <37 weeks, 14.5% (95% CI 4.0-41.1 for ≥32 to <37 weeks, and 13.1% (95% CI 9.0-18.7) for <32 weeks. When examining a model adjusted for age at first birth, age in 1989, race/ethnicity, parental education, pre-pregnancy BMI, pre-pregnancy smoking, pre-pregnancy Alternative Healthy Eating Index score, pre-pregnancy alcohol intake, physical activity at age 18, pre-pregnancy oral contraceptive use, and family history of MI or stroke before age 60, the proportion of the association accounted for by the intermediates of chronic hypertension hypercholesterolemia, type 2 diabetes mellitus, BMI, and breastfeeding was 15.9% (95% CI 8.7-27.3) for <37 weeks, 20.7% (95% CI 5.5-53.8) for ≥32 to <37 weeks, and 14.0% (95% CI 9.5-20.1) for <32 weeks.	
Multi-Ethnic Study of Atherosclerosis (MESA) Wellons, M. et al., 2012 22692332	Study Aim to determine if a self-reported early menopause (menopause at an age <46) identifies women as at risk for future coronary heart disease or stroke	Inclusion criteria -female -identified themselves as white, black, Hispanic, or Chinese, -reported that they were free of CVD at baseline -45 to 84 years of age at baseline Exclusion criteria	1° endpoint: Incident CHD (definite or probable MI, resuscitated cardiac arrest, definite CHD death), Incident stroke (fatal and non-fatal) *CHD Events* Annualized rate in group with early menopause=7.33/1000/yr	Summary early menopause is a moderate predictor of CHD and stroke, even after adjusting for traditional CVD risk factors in a diverse population of US women

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
	Study type Prospective cohort study N=2509	-hysterectomy without oophorectomy Missing data -inconsistent data regarding menopausal status	Annualized rate in group without early menopause=3.22/1000/yr HR fully adjusted model=1.85 (95% CI 1.01-3.37), p=0.045 C-statistics for traditional risk factors=0.68, when early menopause is added, C-statistic=0.70 (p=0.55) *Stroke Events* Annualized rate in group with early menopause=1000/yr Annualized rate in group without early menopause=/1000/yr HR fully adjusted model=2.03 (95% CI 1.00-4.10), p=0.049 Adjustment for type of menopause did not alter results (data not shown) No evidence of interaction between early menopause and use of hormone therapy, type of menopause, or ever drinking (data not shown)	
Multi-Ethnic Study of Atherosclerosis (MESA) Uddin, SMI. Et al., 2018 29891569	Study Aim to examine the value of self-reported erectile dysfunction for predicting incident coronary heart disease and CVD in those free of these	Inclusion criteria -Male -MESA participants - attended visit 5 and answered the single Massachusetts Male Aging Study question 3 on erectile dysfunction symptoms Exclusion criteria	1° endpoint: CHD hard events CVD hard events *CHD hard events* Proportion of participants with and without ED who experienced an event=3.4% vs. 1.4%, p<0.001)	Summary ED was found to be a significant predictor of hard CVD events after adjustment for traditional CVD risk factors, depression, and β-blocker use

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
	CVD events at baseline Study type Prospective cohort N=1914	-CVD event prior to visit 5	Unadjusted HR=2.5, 95% CI 1.3-4.8 Fully adjusted HR=1.8, 95% CI 0.8-4.0 *CVD hard events* Proportion of participants with and without ED who experienced an event =6.3% vs. 2.6%, p<0.001 Unadjusted HR=2.6, 95% CI 1.6-4.1 Fully adjusted HR=1.9, 95% CI 1.1-3.4 Time shifted cross-sectional analysis, OR between prior CVD event and ED at visit 5=2.1, 95% CI 1.4-3.2 (OR=1.7, 95% CI 1.1-2.6 when adjusted for medication use and depression)	
Partners HIV cohort Triant, VA. Et al., 2018 29444987	Study Aim to assess the performance of 3 established CVD risk prediction functions in a longitudinal cohort of HIV infected men Study type Prospective cohort N=1272	Inclusion criteria -males -HIV positive -≥1 clinical encounter in calendar years 2006 to 2008 -a blood pressure measurement available in 2006 to 2008 -lipid laboratory values available in calendar years 2004 to 2008 -smoking status available at baseline (2006–2008) -first HIV code that occurred before the start of observation for each individual Exclusion criteria	1° endpoint: Hard CHD (MI or coronary death) ASCVD (MI, stroke, or coronary death) Global CVD (MI, stroke, coronary death, coronary insufficiency, angina, transient ischemic attack, peripheral artery disease, or heart failure 1° endpoint: The 5-year hard CHD event rate was 3.8% (48/1272), and the 5-year ASCVD event rate was 6.1% (78/1272). *Framingham Health Study CHD model*: C-statistic original=0.68 (95% CI 0.61-	Conclusions The three models evaluated systematically underestimate CVD risk in HIV. Discrimination and calibration were both suboptimal when applying the functions to a cohort of largely antiretroviral therapy–treated men engaged in HIV care. Established CVD risk functions do not provide an accurate estimation of risk in the setting of HIV disease and may fail to identify patients at elevated CVD risk who would benefit from aggressive risk reduction.

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
		-history of a CVD event before the start of observation -<30 or >74 years of age for the FHS CHD and ASCVD functions, and <40 or >79 years of age for the ACC/AHA ASCVD function	0.75), C-statistic HIV=0.73 (95% CI 0.67-0.81). For the FHS CHD function, the calibration χ2 statistic=13.6 (P=0.019). *ACC/AHA ASCVD model*: C-statistic original=0.65 (95% CI 0.59-0.71), C-statistic HIV=0.66 (95% CI 0.60-0.73) For the ACC/AHA function, the calibration χ2 statistic=23.9 (P=0.001). *FHS ASCVD*: c-statistic original=0.6 (95% CI 0.61-0.73), c-statistic HIV 0.67 (95% CI 0.61-0.73) For the FHS ASCVD function, the calibration χ2= 24.6 (P=0.0004). Observed risk exceeded predicted risk for all categories in all three functions except for >7.5% predicted risk for the FHS hard CHD function (data presented in graphs) FHS and ACC/AHA models were recalibrated to attempt to improve the model fit by using baseline survival and mean risk factor values from the HIV cohort instead of the FHS or ACC/AHA cohorts values. After recalibration, goodness of fit remained poor for all functions, and model performance did not improve (data not shown). To further confirm that each function poorly	

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			discriminated and underestimated risk in the HIV cohort, we conducted analyses stratified by race and showed that discrimination remained moderate and calibration remained poor -generated a new model (HIV function) among men and women combined, including significant interaction terms with sex for each risk factor	
Volgman, AS. Et al., 2018 29794080	Study Aim To summarize literature on demographics and biological and nonbiological mechanisms contributing to excess ASCVD, health behaviors, and interventions in South Asians Study type Narrative summary N=N/a	Inclusion criteria -English-language studies - Inductive methods and descriptive studies that focused on ASCVD outcomes incidence, prevalence, treatment response, and risks	1° endpoint: None specified, no quantitative outcomes	Authors' conclusions -A majority of the risk in South Asians can be explained by the increased prevalence of known risk factors, especially those related to insulin resistance, and no unique risk factors in this population have been found -Although several population-specific risk assessment tools exist, none of the currently available models are derived from or prospectively validated in US South Asians. Risk calculators underestimate CVD risk in South Asians because they have not been derived from or validated in this higher-risk group

Data Supplement 4. RCTs of Nutrition and Diet (Section 3.1.)

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 value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events

PREDIMED Estruch, 2018 (re-analysis) (13) 29897866	Aim: Randomized controlled trial N=7,447	Inclusion criteria: Men 55 to 80 years of age and women 60 to 80 years of age with type 2 diabetes mellitus or at least three risk factors (smoking, hypertension, elevated LDL cholesterol, low HDL cholesterol, overweight or obesity, or family history of premature coronary heart disease	Intervention Mediterranean diet training, supplemented with extra-virgin olive oil (~1 liter/week) or 30 g of mixed nuts Mediterranean diet recommendations were olive oil (>=4 tbsp/day), tree nuts and peanuts (>=3 servings/wk), fresh fruits (>=3 servings/day), vegetables (>=2 servings/day), fish/seafood (>=3 servings/wk), legumes (>=3 servings/wk), sofrito (>=2 servings/wk), white meat (instead of red meat), wine with meals (optional, >=7 glasses/wk) Discouraged: Soda drinks, commercial bakery goods, sweets, and pastries, spread fats, and red and processed meats Comparator Low-fat diet training Low-fat dietary products (>=3 servings/day), bread/potatoes/pasta/rice (>=3 servings/day), fresh fruits (>=3 servings/day), vegetables (>=2 servings/day), lean fish/seafood (>=3 servings/wk)	1° endpoint: CV death, nonfatal MI, or nonfatal stroke A: Mediterranean diet with extra virgin olive oil: 3.8% (96/2,543) B: Mediterranean diet with nuts: 3.4% (83/2,454) C: Low-fat diet: 4.4% (109/2,450) Adjusted HR A vs. C: 0.69 (95% CI 0.53 to 0.91) B vs. C: 0.72 (95% CI 0.54 to 0.95) A or B vs. C: 0.70 (95% CI 0.55 to 0.89) [Annual cardiovascular event risk (%) in placebo arm: 1.12 (CV death, nonfatal MI, or nonfatal stroke)] CV Death A: Mediterranean diet with extra virgin olive oil: 1.0% (26/2,543) B: Mediterranean diet with nuts: 1.3% (31/2,454) C: Low-fat diet: 1.2% (30/2,450) Adjusted HR A vs. C: 0.62 (95% CI 0.36 to 1.06) B vs. C: 1.02 (95% CI 0.63 to 1.67) A or B vs. C: 0.80 (95% CI 0.51 to 1.24) Stroke A: Mediterranean diet with extra virgin olive oil: 1.9% (49/2,543) B: Mediterranean diet with nuts: 1.3% (32/2,454) C: Low-fat diet: 2.4% (58/2,450) Adjusted HR A vs. C: 0.65 (95% CI 0.44 to 0.95) B vs. C: 0.54 (95% CI 0.35 to 0.82)	2° endpoints Adherence Score for adherence to Mediterranean diet ~10.5 to 11 from year 1 to year 6 in Mediterranean diet groups and ~8.8 to 9.3 in low-fat diet group All-Cause Mortality A: Mediterranean diet with extra virgin olive oil: 4.6% (118/2,543) B: Mediterranean diet with nuts: 4.7% (116/2,454) C: Low-fat diet: 4.7% (114/2,450) Adjusted HR A vs. C: 0.90 (95% CI 0.69 to 1.18) B vs. C: 1.12 (95% CI 0.86 to 1.47) A or B vs. C: 0.98 (95% CI 0.77 to 1.24) Fatal or non-fatal MI A: Mediterranean diet with extra virgin olive oil: 1.5% (37/2,543) B: Mediterranean diet with nuts: 1.3% (31/2,454) C: Low-fat diet: 1.6% (38/2,450) Adjusted HR A vs. C: 0.82 (95% CI 0.52 to 1.30) B vs. C: 0.76 (95% CI 0.47 to 1.25) A or B vs. C: 0.80 (95% CI 0.51 to 1.24) Comments Re-analysis due to deviations from randomization protocol in ~20% of sample. Model stratified according to sex, recruiting site, and educational level, and adjusted for age, smoking

			Discouraged: Vegetable oils (including olive oil), commercial bakery goods/sweets/pastries, nuts/fried snacks, red/processed meats, visible fat in meats and soups, fatty fish/seafood canned in oil, spread fats, sofrito	A or B vs. C: 0.58 (95% CI 0.42 to 0.82)	status, HTN, dyslipidemia, DM, family history of premature CHD< BMI, waist-to-height ratio, physical activity, and propensity score (based on 30 variables) for intervention group assignment. Adherence adjusted estimated for Mediterranean diet vs. control diet on primary outcome 0.42 (95% CI 0.24 to 0.63); absolute differences 0.67, 1.38, and 2.00 percentage points at 12, 24, and 36 months, respectively.
Trials of Hypertension Prevention long-term follow-up Cook, 2007 17449506	Aim: to investigate long term effects of dietary sodium reduction on cardiovascular disease outcomes Study type: 2 RCTs with long-term follow-up after study completion N=2,415 long-term follow-up	Inclusion criteria: TOHP I: Men and women 30 to 54 years of age, mean DBP 80-89 mm Hg TOHP II: Men and women 30 to 54 years of age, 110-165% of desirable weight, and DBP 83-89 and SBP <140 mm Hg	Intervention: Low salt diet counseling, goal urinary sodium excretion 80 mmol (1800 mg)/24 hours Comparator: Usual care	1° endpoint: CV death, nonfatal MI, or revascularization CV death: Low salt diet: 0.7% (10/1,518). Usual care: 0.9% (15/1,608). Adjusted HR: 0.62 (95% CI 0.28 to 1.40) Nonfatal MI: Not reported	2° endpoint: All-cause mortality: Low salt diet: 2.3% (35/1,518) Usual care: 2.6% (42/1,608) Adjusted HR: 0.80 (95% CI 0.51 to 1.26)
Sacks et al, 2001 11136953	Aim: to investigate the extent to which the reduction of the sodium level, in the context of a typical United States diet and in combination with the DASH diet, lowers blood pressure Study type: RCT N=412	Inclusion criteria: • Age 22 or older • Average systolic BP on 3 screening visits of 120-159 mm Hg • Average diastolic BP 80-95 mm Hg Exclusion criteria: • Heart disease • Renal insufficiency • Poorly controlled hyperlipidemia or diabetes • Diabetes requiring insulin	Intervention: 2 diets: Control (typical American diet) (N=204) DASH diet (N=208) Participants provided with all food, energy intake adjusted to ensure weight remained constant	1° endpoint: systolic blood pressure at end of each 30 day period Systolic blood pressure: Significant interaction between diet group and sodium level (p<0.001), with nearly twice the effect of dietary sodium on blood pressure in control than DASH diet. Control diet+high sodium vs. DASH+low sodium= -11.5 mm Hg in those with hypertension vs -7.1 mm Hg in those without hypertension (p=0.004), and -6.8 mm Hg	2° endpoint: Diastolic blood pressure Diastolic blood pressure decreased between High and Intermediate dietary sodium periods in both the Control group (-1.1; 95% CI -1.9 to -0.2) and the DASH diet group (-2.5; 95% CI -4.1 to -0.8, and between the Intermediate and Low dietary sodium periods in both the Control group (-2.4; 95% CI -3.3 to -1.5) and the DASH diet group (-1.0; 95% CI -1.9 to 0.1).

		• Special dietary requirements • Intake >14 alcoholic drinks/week • Use of antihypertensive drugs or other mediations that would affect blood pressure or nutrient metabolism	Within diet groups, participants ate at each of three sodium levels for 30 consecutive days in random order: High sodium (target 150 mmol per day with energy intake of 2100 kcal) Intermediate (target of 100 mmol per day) Low (target of 50 mmol/day) <u>Comparator:</u> Usual	in men vs. -10.5 mm Hg in women (p=0.02) *Effect of Sodium Level* SBP decreased between High and Intermediate dietary sodium periods in both the Control group (-2.1; 95% CI -3.4 to -0.8) and the DASH diet group (-1.3; 95% CI -2.6 to 0.0), and between the Intermediate and Low dietary sodium periods in both the Control group (-4.6; 95% CI -5.9 to -3.2) and the DASH diet group (-1.7; 95% CI -3.0 to -0.4). Effects of sodium greater in those with hypertension (interaction p=0.01 on control diet, p-0.003 on DASH diet), in Blacks on control diet than those of other races on control diet (interaction p=0.007), and in women on DASH than men on DASH (interaction p=0.04) *Effect of Control vs. DASH diet* High Sodium Level: -5.9 (95% CI -8.0 to -3.7) Intermediate Sodium Level: -5.0 (95% CI -7.6 to -2.5) Low Sodium level: -2.2 (95% CI -4.4 to -0.1)	Control vs. DASH diet High Sodium Level: -2.9 (95% CI -4.3 to -1.5) Intermediate Sodium Level: -2.5 (95% CI -4.1 to -0.8) Low Sodium Level: -1.0 (95% CI -2.5 to 0.4) <u>Adverse events</u> Headache: 47% during the high sodium phase of the control diet, 39% during low-sodium phase of the control diet, 36% during the low-sodium phase of the DASH diet (P<0.05 for both comparisons with the high-sodium phase of control diet) Number not completing intervention period similar during all three sodium levels

Data Supplement 5. Nonrandomized Trials, Observational Studies, and/or Registries of Nutrition and Diet (Section 3.1.)

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Intake of trans fat and all-cause mortality in the Reasons for Geographical and Racial Differences in Stroke (REGARDS) cohort Kiage, 2013 (14) 23553155	Study type: Cohort study N=18,513	Inclusion criteria: REGARDS	1° endpoint: Age, sex, smoking status, race, region, alcohol use, education, waist circumference, physical activity, DM, CHD, HTN, stroke, heart failure, chronic kidney disease, statin use, total energy intake, energy adjusted intake of saturated fatty acids, monounsaturated fatty acids, polyunsaturated fatty acids, proteins, and carbohydrates Age: p for interaction=0.6 Sex: p for interaction=0.36	
Southern Dietary Pattern is Associated With Hazard of Acute Coronary Heart Disease in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study Shikany, 2015 26260732	Study type: Cohort study N=17,418	Inclusion criteria: REGARDS (no CHD at baseline)	1° endpoint: Age, sex, race, education, household income, region, total energy intake, smoking, physical activity, BMI, waist circumference, HTN, dyslipidemia, DM	
Association of Specific Dietary Fats With Total and Cause-Specific Mortality Wang, 2016	Study type: Cohort study N=126,233	Inclusion criteria: NHS and HPFS (no CV disease or DM at baseline)	1° endpoint: Age, race, marital status, BMI, physical activity, smoking status, alcohol consumption, multivitamin use, vitamin E use, aspirin use, family history of MI, family history of DM, family history of cancer, HTN, hypercholesterolemia, intake of total energy and dietary cholesterol, percentage of energy intake from dietary	Comments: Replacing 5% of energy from saturated fats with equivalent energy from PUFA or MUFA was associated with esimated reductions in total mortality of 27% (adjusted HR 0.73, 95% CI 0.70 to 0.77) and 13% (adjusted HR 0.87, 95 5CI 0.82 to 0.93), respectively

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
27379574			protein, menopausal status/hormone use, percentage of energy intake from other fatty acids All-cause mortality: Adjusted HR, quintile 5 versus quintile 1 A: 0.95 (95% CI 0.94 to 0.96) B: 1.08 (95% CI 1.04 to 1.11) C: 0.85 (95% CI 0.83 to 0.87) D: 0.73 (95% CI 0.69 to 0.77) E: 0.90 (95% CI 0.87 to 0.94) F: 1.16 (95% CI 1.09 to 1.24) G: 0.90 (95% CI 0.88 to 0.93) H: 0.88 (95% CI 0.86 to 0.91) I: 0.58 (95% CI 0.47 to 0.73) J: 0.97 (95% CI 0.94 to 0.99) K: 0.98 (95% CI 0.94 to 1.02) L: 0.93 (95% CI 0.89 to 0.98) M: 1.00 (95% CI 0.99 to 1.00	
Prospective Urban Rural Epidemiology (PURE) study Dehghan et al, 2017 28864332	Study type Cohort Study N=135,335	Inclusion: • Households in one of 18 low-, middle-, and high-income countries with at least one member was between 35 and 70 years of age, and the household • Householders intended to stay in the current address for another 4 years • plausible energy intake (500–5000 kcal per day) • no missing values on age and sex. Exclusion:	1° endpoint total mortality and major cardiovascular events (fatal cardiovascular disease, non-fatal myocardial infarction, stroke, and heart failure). Secondary outcomes were all myocardial infarctions, stroke, cardiovascular disease mortality, and non-cardiovascular disease mortality. Median follow-up of 7.4 years *Total carbohydrate intake for quintile 5 vs quintile 1:* Total mortality; HR=1.28 (95% CI: 1.12-1.46; p for trend=0.0001)	Summary: High carbohydrate intake was associated with higher risk of total mortality, whereas total fat and individual types of fat were related to lower total mortality. Total fat and types of fat were not associated with cardiovascular disease, myocardial infarction, or cardiovascular disease mortality, whereas saturated fat had an inverse association with stroke.

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
		• follow-up information was not available • history of cardiovascular disease	Major cardiovascular disease; HR=1.01 (95% CI 0.88-1.15, p for trend=0.62) Myocardial infarction; HR=0.90 (95% CI 0.73-1.10, p for trend 0.40) Stroke: HR=1.11 (95% CI 0.92-1.35, p for trend=0.10) Cardiovascular disease mortality: HR=1.13 (95% CI 0.89-1.44, p for trend=0.50) Non-cardiovascular disease mortality: Total carbohydrate intake HR=1.36 (95% CI 1.16-1.60, p for trend <0.0001) *Total fat intake for quintile 5 vs quintile 1* Total mortality: HR=0.77 (95% CI 0.67-0.87; p for trend<0.0001) Major cardiovascular disease: HR= (95% CI ; p for trend) Myocardial infarction: HR=1.12 (95% CI 0.92-1.37; p for trend0.40) Stroke: HR=0.82 (95% CI 0.68-1.00, p for trend=0.05). Cardiovascular disease mortality: HR= 0.92 (95% CI 0.72-1.16; p for trend 0.50) Non-cardiovascular disease mortality: HR=0.70 (95% CI 0.60-0.82, p for trend<0.0001) *Total protein intake for quintile 5 vs quintile 1* Total mortality: HR=0.88 (95% CI 0.77-1.00, p for trend=0.0030) Major cardiovascular disease: HR= 0.96 (95% CI 0.84-1.10; p for trend 0.86) Myocardial infarction: HR=1.02 (95% CI 0.83-1.24; p for trend 0.67) Stroke: HR= 0.90 (95% CI 0.74-1.09; p for trend 0.47)	

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			Cardiovascular disease mortality: HR= 0.90 (95% CI 0.71-1.15; p for trend 0.26) Non-cardiovascular disease mortality HR=0.85 (95% CI 0.73-0.99, p for trend=0.0022). *% energy from saturated fats quintile 5 vs quintile 1* Total mortality: HR=0.86 (95% CI 0.76-0.99; p for trend=0.0088) Major cardiovascular disease: HR= 0.95 (95% CI 0.83-1.10; p for trend=0.49) Myocardial infarction: HR= 1.17 (95% CI 0.94-1.45; p for trend 0.40) Stroke: HR= 0.79 (95% CI 0.64-0.98; p for trend 0.0498) Cardiovascular disease mortality: HR=0.83 (95% CI 0.65-1.07; p for trend=0.20) : Non-cardiovascular disease mortality HR= 0.86 (95% CI 0.79-1.01; p for trend=0.0108): *% energy from monounsaturated fats quintile 5 vs quintile 1* Total mortality: HR= 0.81 (95% CI 0.71-0.92; p for trend<0.0001) Major cardiovascular disease: HR= 0.95 (95% CI 0.84-1.09; p for trend=0.54) Myocardial infarction: HR= 1.12 (95% CI 0.92-1.38; p for trend=0.40) Stroke: HR= 0.85 (95% CI 0.70-1.03; p for trend=0.10) Cardiovascular disease mortality: HR=0.85 (95% CI 0.66-1.09; p for trend=0.10):	

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			Non-cardiovascular disease mortality HR=0.79 (95% CI 0.68-0.93; p for trend=0.0003): *% energy from polyunsaturated fats quintile 5 vs quintile 1* Total mortality: HR=0.80 (95% CI 0.71-0.89; p for trend<0.0001) Major cardiovascular disease: HR=1.01 (95% CI 0.90-1.14; p for trend=0.94) Myocardial infarction: HR=1.12 (95% CI 0.93-1.34; p for trend=0.40) Stroke: HR=0.92 (95% CI 0.78-1.09; p for trend=0.30) Cardiovascular disease mortality: HR=0.94 (95% CI 0.76-1.15; p for trend=0.20) : Non-cardiovascular disease mortality HR=0.75 (95% CI 0.65-0.86; p for trend=0.0002):	
Atherosclerosis Risk in Communities (ARIC) Seidelmann et al 2018 30122560	Study type Prospective cohort study (ARIC) and meta-analysis N=15,428 ARIC N=8 studies (432,179 participants) meta-analysis	Inclusion criteria • age 45-64 Exclusion criteria • incomplete dietary information • extreme caloric intake (<600 kcal or >4200 kcal per day for men and <500 kcal or >3600 kcal per day for women). Inclusion criteria meta-analysis: • published full-text report, observational study, or randomized controlled trial • minimum 1 year follow-up	1° endpoint: • Median length of follow up=25 years *All-cause mortality* • relationship between carbohydrate consumption and risk of mortality was significantly nonlinear (p<0·001), resulting in a U-shaped association, with the lowest observed risk associated with carbohydrate consumption of 50–55% • In the ARIC cohort and in meta analysis, increased consumption of animal-based protein and fat instead of carbohydrate was associated with a significant increase in all-cause mortality (p<0·0001;	Summary: mid-life dietary patterns marked by both low carbohydrate (<40% of energy from carbohydrate) and high carbohydrate (>70% of energy from carbohydrate) consumption were associated with increased mortality risk and shorter residual lifespan, with minimum risk observed with 50–55% of energy from carbohydrate. Low carbohydrate dietary patterns that replaced energy from carbohydrate with energy from animal-derived protein or fat were associated with greater risk. This association was reversed when energy from carbohydrate was replaced with plant-derived protein or fat.

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
		• reported relative risks (ie, HRs, risk ratios, or odds ratios with CIs) • adjusted for at least three of the following factors: age, sex, obesity, smoking status, diabetes, hypertension, hypercholesterolemia, history of cardiovascular disease, and family history of cardiovascular disease Exclusion criteria meta-analysis:	• Increased consumption of plant based protein and fat instead of carbohydrate was associated with a significant decrease in all-cause mortality (p<0·0001). • Animal and plant based findings were consistent for cardiovascular and non-cardiovascular mortality *Meta-analysis results*: • significantly increased risk of all-cause mortality among participants with low carbohydrate versus moderate carbohydrate consumption (pooled HR 1·20, 95% CI 1·09–1·32; p<0·0001). • High carbohydrate consumption was associated with a significantly higher risk of all-cause mortality compared with moderate carbohydrate consumption (1·23, 1·11–1·36; p<0·0001)	
Kim, 2018 29659968	Cohort study N= 11,879	Inclusion criteria • NHANES III Exclusion criteria • No stroke, MI, CHD, or DM at baseline	1° endpoint: Age, sex, race, total energy intake, education, federal poverty level, marital status, smoking status, physical activity, alcohol consumption, margarine intake, BMI, HTN, serum cholesterol, kidney function, menopause (for women) Men A: 1.04 (95% CI 0.99 to 1.07) B: 1.01 (95% CI 0.92 to 1.10) in subgroup less than median, 0.95 (95% CI 0.89 to 1.01) in subgroup at median or higher C: 1.01 (95% CI 0.98 to 1.06)	

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			Women A: 0.98 (95% CI 0.95 to 1.00) B: 1.09 (95% CI 0.98 to 1.19) in subgroup less than median, 0.94 (95% CI 0.88 to 0.99) in subgroup at median or higher C: 1.01 (95% CI 0.98 to 1.05) 2° endpoint: Cardiovascular Death Adjusted HR, per 10-unit increase A: 1.05 (95% CI 0.99 to 1.12), B: 1.02 (95% CI 0.97 to 1.08) C: 1.02 (95% CI 0.96 to 1.08) Men A: 1.08 (95% CI 0.99 to 1.17) B: 1.03 (95% CI 0.96 to 1.10) C: 1.04 (95% CI 0.96 to 1.13) Women A: 1.03 (95% CI 0.96 to 1.10) B: 1.00 (95% CI 0.93 to 1.07) C: 1.03 (95% CI 0.95 to 1.10 All-Cause Mortality Adjusted HR, per 10-unit increase A: 1.01 (95% CI 0.98 to 1.03) B: 1.04 (95% CI 0.97 to 1.12) in subgroup less than median, 0.95 (95% CI 0.91 to 0.98) in subgroup at or above median C: 1.00 (95% CI 0.98 to 1.04)	

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Reedy, 2014 24572039	Study Type: Cohort N=492,823	Inclusion Criteria: NIH-AARP Diet and Health Study (no heart disease at baseline)	1° endpoint: Age, race/ethnicity, education, marital status, physical activity, smoking, energy intake, BMI, DM, alcohol (HEI-2010 and DASH). Analyses stratified by sex. 2° endpoint: Adjusted HR, quintile 5 versus quintile 1 All-cause mortality Men A: 0.78 (95% CI 0.76 to 0.80) B: 0.76 (95% CI 0.74 to 0.78) C: 0.77 (95% CI 0.75 to 0.79) D: 0.83 (95% CI 0.80 to 0.85) Women A: 0.77 (95% CI 0.74 to 0.80) B: 0.76 (95% CI 0.74 to 0.79) C: 0.76 (95% CI 0.73 to 0.79) D: 0.78 (95% CI 0.75 to 0.81) CV mortality Men A: 0.85 (95% Ci 0.80 to 0.89) B: 0.74 (95% CI 0.70 to 0.78) C: 0.80 (95% CI 0.76 to 0.84) D: 0.86 (95% CI 0.81 to 0.91) Women A: 0.79 (95% CI 0.73 to 0.85) B: 0.72 (95% CI 0.67 to 0.78) C: 0.78 (95% CI 0.72 to 0.84) D: 0.78 (95% CI 0.72 to 0.83)	

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Satija, 2017 28728684	Study Type: Cohort N=209,298	Inclusion Criteria: NHS, NHS2, HPFS (no CHD at baseline)	1° endpoint: Age, smoking status, physical activity, alcohol intake, multiviamin use, aspirin use, family history of CHD, margarine intake, energy intake, baseline hypertension, hypercholesterolemia, and diabetes, BMI, post-menopausal hormone use (NHS and NHS2) and oral contraceptive use (NHS2) Age: Adjusted HR, decile 10 vs. decile 1 <55 years A: NR B: 0.59 (95% CI 0.43 to 0.82) C: 1.82 (95% CI 1.33 to 2.47) >=55 years A: NR B: 0.76 (95% CI 0.69 to 0.85) C: 1.27 (95% CI 1.14 to 1.42) BMI: Adjusted HR, decile 10 vs. decile 1 <30 A: NR B: 0.72 (95% CI 0.64 to 0.80) C: 1.27 (95% CI 1.13 to 1.43) >=30 A: NR B: 0.84 (95% CI 0.66 to 1.05) C: 1.38 (95% CI 1.11 to 1.72) Smoking status:	

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			Adjusted HR, decile 10 vs. decile 1 Ever smoker A: NR B: 0.66 (95% CI 0.58 to 0.75) C: 1.42 (95% CI 1.25 to 1.62) Never smoker A: NR B: 0.78 (95% CI 0.66 to 0.92) C: 1.30 (95% CI 1.10 to 1.52) 2° endpoint: Fatal or non-fatal MI: Adjusted HR, decile 10 vs. decile 1, and per 10 unit increase in index A: 0.92 (95% CI 0.83 to 1.01), 0.93 (95% CI 0.90 to 0.97) B: 0.75 (95% CI 0.68 to 0.83), 0.88 (95% CI 0.85 to 0.91) C: 1.32 (95% CI 1.20 to 1.46), 1.10 (95% CI 1.06 to 1.14)	
Sotos-Prieto, 2017 28700845	Study Type: Cohort N=73,739	Inclusion Criteria: NHS and HPFS (no CVD at baseline)	1° endpoint: Age, initial diet quality score, race, family history (MI, DM or cancer), use of aspirin or multivitamins, BMI, smoking status, pack-years of smoking, menopausla stsus and use of hormone replacement therapy in women, HTN, hypercholesterolemia, DM, weight change, cholesterol lowering medications, antihypertensive medications	

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			2° endpoint: CV death: Adjusted HR, per 20 percentile increase in score A: 0.85 (95% CI 0.76 to 0.96) B: 0.93 (95% CI 0.88 to 0.99) C: 0.96 (95% CI 0.88 to 1.05) All-cause mortality: Adjusted HR, quintile 5 versus quintile 3 and per 20 percentile increase in score A: 0.91 (95% CI 0.85 to 0.97), 0.83 (95% CI 0.78 to 0.88) B: 0.84 (95% CI 0.78 to 0.91), 0.92 (95% CI 0.89 to 0.95) C: 0.89 (95% CI 0.84 to 0.95), 0.90 (95% CI 0.86 to 0.94)	
Whalen, 2017 28179490	Study Type: Cohort N=21,423	Inclusion Criteria: REGARDS	1° endpoint: Age, sex, race, total energy intake, BMI, physical activity, smoking status, annual income, hormone replacement therapy use (women) Age: <=65 or >65 All-cause mortality A: p for interaction 0.99 B: p for interaction 0.15 Sex: All-cause mortality A: p for interaction 0.81 B: p for interaction 0.06	

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			BMI: All-cause mortality Underweight/normal vs. overweight/obese A: p for interaction 0.27 B: p for interaction 0.73 Smoking status: All-cause mortality Current smoker, former smoker, or never smoked A: p for interaction 0.04 B: p for interaction 0.86 2° endpoint: CV death: Adjusted HR, quintile 5 versus quintile 1 A: 0.78 (95% CI 0.61 to 1.00) B: 0.68 (95% CI 0.53 to 0.88) All-cause mortality: Adjusted HR, quintile 5 versus quintile 1 A: 0.77 (95% CI 0.67 to 0.89) B: 0.64 (95% CI 0.55 to 0.74)	
Bao, 2013 24256379	Study Type: Cohort N=118,962	Inclusion Criteria: NHS and HPFS (no heart disease or stroke at baseline)	1° endpoint: Age, race, BMI, physical activity, smoking status, physical exam for screening, multivitamin use, aspirin use family history (DM, MI, or cancer), history (DM, HTN, or hypercholesterolemia), intake (total energy, alcohol, red or processed meats, fruits, vegetables), menopausal status and hormone use (women)	

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			Age: Adjusted HR, any nut consumption >=2 times per week versus never consumed All-cause mortality >=60: 0.86 (95% CI 0.83 to 0.90) <60: 0.80 (95% CI 0.67 to 0.96) p for interaction 0.86 Sex: Adjusted HR, any nut consumption >=5 times per week versus never consumed All-cause mortality Women: 0.84 (95% CI 0.77 to 0.92) Men: 0.82 (95% CI 0.76 to 0.88) CV mortality Women: 0.82 (95% CI 0.66 to 1.01) Men: 0.73 (95% CI 0.64 to 0.83) BMI: Adjusted HR, any nut consumption >=2 times per week versus never consumed All-cause mortality <25: 0.91 (95% CI 0.86 to 0.96) 25 to <30: 0.76 (95% CI 0.68 to 0.84) >=30: 0.78 (95% CI 0.63 to 0.96) p for interaction 0.04 Smoking status: Adjusted HR, any nut consumption >=2 times per week versus never consumed All-cause mortality Ever: 0.83 (95% CI 0.79 to 0.88)	

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			Never: 0.89 (955 CI 0.84 to 0.95) p for interaction 0.61 <u>2° endpoint:</u> <u>CV death:</u> Adjusted HR, consumption five or more times per week versus never A: 0.75 (95% CI 0.62 to 0.84) B: NR C: NR <u>All-cause mortality:</u> Adjusted HR, consumption 2 or more times per week versus never consumed and five or more times per week versus never A: 0.86 (95% CI 0.82 to 0.89), 0.83 (95% 0.78 to 0.88) B: 0.88 (95% CI 0.84 to 0.93), NR C: 0.83 (95% CI 0.79 to 0.88), NR <u>Fatal MI:</u> Adjusted HR, consumption 2 or more times per week versus never consumed and five or more times per week versus never A: 0.74 (95% CI 0.68 to 0.81), 0.71 (95% CI 0.63 to 0.81) B: 0.76 (95% CI 0.68 to 0.84), NR C: 0.76 (95% CI 0.67 to 0.85), NR <u>Fatal stroke:</u> Adjusted HR, consumption 2 or more times per week versus never consumed and five or more times per week versus never	

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			A: 0.92 (95% CI 0.79 to 1.08), 0.89 (95% CI 0.67 to 1.19) B: 0.97 (95% CI 0.67 to 1.40), NR C: 0.96 (95% CI 0.78 to 1.19), NR	
Bernstein, 2010 (Circulation) 20713902	Study type: Cohort N=84,136	Inclusion criteria: NHS (no CVD or DM at baseline)	1° endpoint: Age, time period, total energy, cereal fiber, alcohol, trans fat, BMI, cigarette smoking, menopausal status, parental history of early myocardial infarction, multivitamin use, vitamin E supplement use, aspirin use at least once per week, physical exercise 2° endpoint: Fatal or non-fatal MI: Adjusted RR, 5th vs. 1st quintile and per 1 serving per day increase A: 1.22 (95% CI 1.06 to 1.40), 1.13 (95% CI 1.07 to 1.20) B: 1.29 (95% CI 1.12 to 1.49), 1.16 (95% CI 1.09 to 1.23) C: 1.13 (95% CI 0.99 to 1.30), 1.19 (95% CI 1.07 to 1.32) D: 0.92 (95% CI 0.80 to 1.06), 0.90 (95% CI 0.75 to 1.08) E: 0.81 (95% CI 0.72 to 0.90), 0.81 (95% CI 0.66 to 1.00) F: 1.26 (95% CI 1.11 to 1.43), NR G: 1.28 (95% CI 1.12 to 1.46), NR H: 1.09 (95% CI 0.97 to 1.22), 1.03 (95% CI 1.00 to 1.06) I: 0.90 (95% CI 0.80 to 1.01), 1.01 (95% CI 0.96 to 1.04)	

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			J: 0.96 (95% CI 0.85 to 1.09), 1.04 (95% CI 0.93 to 1.16) K: 0.68 (95% CI 0.60 to 0.76), 0.78 (95% CI 0.66 to 0.93) L: 0.89 (95% CI 0.80 to 0.99), 0.76 (95% CI 0.50 to 1.14) M: 1.02 (95% CI 0.90 to 1.14), 0.97 (95% CI 0.79 to 1.19) N: 0.91 (95% CI 0.82 to 1.02), 0.94 (95% CI 0.72 to 1.23) O: 1.03 (95% CI 0.91 to 1.15), 1.41 (95% CI 1.12 to 1.76) P: 1.11 (95% CI 0.99 to 1.23), 1.35 (95% CI 0.94 to 1.93) Q: 1.09 (95% CI 0.98 to 1.22), 1.23 (95% CI 1.01 to 1.49) R: 1.10 (95% CI 0.96 to 1.27), 1.08 (95% CI 0.92 to 1.27) S: 1.09 (95% CI 0.98 to 1.23), 1.42 (95% CI 1.10 to 1.84) T: 1.05 (95% CI 0.93 to 1.17), 1.20 (95% CI 1.03 to 1.40) U: 0.97 (95% CI 0.82 to 1.15), 1.05 (95% CI 0.72 to 1.54 V: NR, 0.96 (95% CI 0.37 to 2.52) W: 0.91 (95% CI 0.75 to 1.11), 0.88 (95% CI 0.52 to 1.49)	
Song, 2016 27479196	Study type: Cohort N=131,342	Inclusion criteria: NHS and HPFS (no CVD or DM at baseline)	1° endpoint: Age, sex, calendar time, total caloric intake, percentage of energy from saturated fat, polunsaturated fat, monounsaturated fat, and trans-fat, multivitamin use, smoking status, pack-years of smoking, BMI, physical activity,	Risk of mortality with replacing 3% of energy from processed red meat with plant protein: 0.66 (95% CI 0.59 to 0.75); for other animal protein sources HR's ranged from 0.81 to 0.94

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			alcohol consumption, hypertension diagnosis, intake of whole grains, total fiber, fruits, and vegetables, and protein source 2° endpoint: CV death: Adjusted HR, category 5 (>18% of total energy) vs. category 1 (<=10%) and per 10% increment (animal protein) or per 3% increment (plant protein) A: 1.09 (95% CI 0.99 to 1.20), 1.08 (95% CI 1.01 to 1.16) B: 0.85 (95% CI 0.74 to 0.97), 0.88 (95% CI 0.80 to 0.97) All-cause mortality: Adjusted HR, category 5 (>18% of total energy) vs. category 1 (<=10%) and per 10% increment (animal protein) or per 3% increment (plant protein) A: 1.09 (95% CI 0.99 to 1.20), 1.08 (95% CI 1.01 to 1.16) B: 0.85 (95% CI 0.74 to 0.97), 0.88 (95% CI 0.80 to 0.97)	
Tharrey, 2018 29618018	Study type: Cohort N=81,337	Inclusion criteria: Adventist Health Study 2 (no CVD at baseline)	1° endpoint: Variables adjusted for in the analysis: Age, sex, race, energy intake, BMI, physical activity, smoking status, alcohol consumption, income, education, marital status, type of diet on vegetarian spectrum, polyunsaturated fatty acids, saturated fatty acids, sodium, fiber, vitamins A, C, E, B6,	Each 18-g increase in animal protein associated with 12% increase in risk of CV mortality and each 18-g increase in protein associated with 5% decrease in risk of CV mortality

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			B9, and B12, fat from meat product and fat from nuts CV death: Adjusted HR, quintile 5 versus quintile 1 A: 0.93 (98.75% CI 0.76 1.13) B: 1.12 (98.75% CI 0.90 to 1.41) C: 1.46 (98.75% CI 0.98 to 2.18) D: 1.04 (98.75% CI 0.84 to 1.28) E: 0.56 (98.75% CI 0.38 to 0.81)	
Micha et al 2017 28267855	Study type: Risk model using data from various sources	Inclusion Criteria: Identified 17 dietary factors with associations with CHD, stroke, type 2 diabetes, BMI, or systolic blood pressure using Bradford-Hill criteria and considering consistency with other criteria for assessing potential causality of diet-disease relationships; 10 of the 17 were included (7 excluded based on major overlap for estimating joing effects) All observational studies used multivariable adjustment for other risk factors	1° endpoint: Absolute number and percentage of overall cardiometabolic deaths associated with suboptimal intake of each dietary factor *Associations with all US cardiometabolic deaths in 2012 vs. optimal consumption levels* The 10 dietary factors in combination: 45.4% of deaths High sodium: 9.5% of deaths (10.2% of CHD deaths; 10.7% of stroke deaths, 21.4% hypertensive heart disease) Low nuts/seeds: 8.5% of deaths (14.7% of CHD deaths) High processed meats: 8.2% of deaths (12.3% of CHD deaths, 17.5% type 2 diabetes deaths)	Summary Estimated 45.4% of all cardiometabolic deaths associated with suboptimal intakes of 10 dietary factors in 2012 in the US. Larger proportion of deaths due to diet in men than in women, younger vs older ages, among blacks and Hispanics vs whites, and among individuals with low and medium education vs high education

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			Low seafood omega-3 fats: 7.8% of deaths (14.7% of CHD deaths) Low vegetables: 7.6% of deaths (21.9% of stoke deaths) Low fruits: 7.5% of deaths (22.4% of stoke deaths) High sugar sweetened beverages: 7.4% of deaths (10.8% of CHD deaths, 14.8% of type 2 diabetes deaths) Low polyunsaturated fats: 2.3% of deaths High unprocessed red meats: 0.4% of deaths Low whole grains (17.1% of type 2 diabetes deaths) *Gender* Mortality associated with each dietary factor modestly higher in men than women because of higher proportion of men with unhealthy consumption levels. Men, suboptimal diet associated with 48.6% of deaths. Top 5 dietary factors associated with cardiometabolic deaths: excess processed meats (10.8% of deaths), excess sodium (10.0% of deaths), sugar sweetened beverages (9.3% of deaths), insufficient nuts/seeds (8.8% of	

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			deaths), seafood omega-3 fats (8.8% of deaths) Women: suboptimal diet associated with 41.8% of deaths. Top 5 dietary factors associated with cardiometabolic deaths: excess sodium (8.8%), insufficient nuts/seeds (8.1% of deaths), vegetables (7.4% of deaths), fruits (7.1% of deaths), omega-3 fats (6.7% of deaths. *Age* 25-64 year olds: Overall, suboptimal diet associated with 64.2% of cardiometabolic deaths. Dietary factors with highest associations with cardiometabolic deaths: excess sugar sweetened beverages, excess processed meats 65+: overall, suboptimal diet associated with 35.7% of cardiometabolic deaths. Top Dietary factors with highest associations with cardiometabolic deaths: excess sodium, insufficient nuts/seeds, insufficient vegetables *Race* Estimated proportion of deaths due to diet higher among Blacks and Hispanics than other races, except with omega-3 fats which were higher in whites. Rankings of dietary factors were similar by race. Associations of suboptimal diet with	

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			cardiometabolic mortality: Blacks=53.1%, Hispanics=50.0%, Whites=42.8%. *Educational level* Proportion of deaths due to diet generally higher in low or medium education vs. high education population (e.g.,low vs. high education effect of nuts/seseds=10.7% vs. 6.2%, sugar sweetened beverages=8.4% vs. 4.5%, fruits=8.5% vs. 6.4%). Suboptimal diet associated with 46.8% of deaths for low education, 45.7% of deaths for medium education, 39.1% for higher education Trends from 2002-2012 Total number of population-adjusted cardiometabolic deaths decreased by 26.5%. Improvements in intakes of polyunsaturated fats, nuts/seeds, SSBs, whole grains, and fruits led to decreases in numbers of diet-related cardiometabolic deaths. Estimated diet-associated mortality declined for polyunsaturated fats (-20.8%), nuts/seeds (-18.0%), SSBs (-14.5%), and increased for sodium (5.8%) and unprocessed red meats (14.4%). Trends were similar by sex and age. Insufficient nuts/seeds declined in whites only (10.0% to 7.9%), deaths due to insufficient whole grains declined in Hispanics only (12.9% to 7.6^%). Trends by education: percent associated with low nuts/seeds decline in high education group (8.7% to 6.2%),	

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			SSBs declined more in those with high education (5.9% to 4.5% compared to 9.2% to 8.4% in low education group)	
Epidemiological Study of Risk Factors for LADA and Type 2 Diabetes (ESTRID) study nested in ANDIS and ANDiU studies Lofvenborg et al, 2016 27926472	Aim to investigate sweetened beverage intake and risk of latent autoimmune diabetes in adults (LADA) and type 2 diabetes Population-based case-control study N=2864 (n=357 LADA, n=1136 type 2 diabetes, n=1371 controls)	Inclusion criteria All newly diagnosed cases of LADA and a random sample of incident type 2 diabetes cases (4:1 ratio diabetes to LADA). Exclusion criteria Incomplete information on exposure or main covariates Reported total daily energy intake that deviated more than 3 SD from log-transformed sex-specific mean energy intake	1° endpoint: *LADA* 2+ sweetened beverages/day vs. 0 servings OR=1.99 (95% CI 1.11-3.56). >5 servings/day OR=4.47 (95% CI 1.21-16.47). each daily serving OR=1.15 (95% CI 1.02-1.29). each daily serving sugar sweetened beverages OR=1.18 (95% CI 1.00-1.39) each daily serving artificially sweetened beverage intake OR=1.12 (95% ci 0.95-1.32) Increased risk observed after stratification by sex, age, family history of diabetes, BMI, median GADA levels association between servings per day of water consumption and LADA (OR=0.98, 95% CI 0.94-1.02) *Type 2 diabetes* 2+ sweetened beverages/day vs. 0 servings OR=2.39 (95% CI 1.39-4.09). >5 servings/day OR=10.53 (95% CI 2.75-40.33).	Summary Increased intake of sweetened beverages was associated with increased risk of LADA and type 2 diabetes. Effects were observed for sugar sweetened and artificially sweetened beverages

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			each daily serving OR=1.20 (95% CI 1.07-1.34). each daily serving sugar sweetened beverages OR=1.21 (95% CI 1.05-1.41) each daily serving artificially sweetened beverage intake OR=1.18 (95% ci 1.01-1.38) Increased risk observed after stratification by sex, age, family history of diabetes, BMI Association between servings per day of water consumption and type 2 diabetes (OR=0.99, 95% CI 0.96-1.03)	
NHANES and NHANES III Linked Mortality cohort Yang et al, 2014 24493081	Study Aims To examine time trends of added sugar consumption as percentage of daily calories in the United States and investigate the association of this consumption with CVD mortality Prospective cohort study	Inclusion Criteria Nonpregnant adults Exclusion Criteria Incomplete data on first-day 24 hour dietary recall History of MI, stroke, or CHF Diabetes or on diabetes medications Cancer BMI<18.5 Missing values on covariates	1° endpoint: Trends of consumption of added sugar as percentage of total daily calories Association between sugar consumption and CVD mortality *Trends*: Mean percentage off calories from added sugar increased from 15.7% (95% CI 15.0-16.4%, p) in 1988-1994 to 16.8% (16.0-17.7%, p<0.02) in 1999-2004, and decreased to 14.9% (14.2%-15.5%, p<0.001) in 2005-2010	Summary usual percentage of calories from added sugar among US adults increased from the late 1980s to 1999-2004 and decreased during 2005-2010. Most adults consumed more than 10% of their total calories from added sugar, and approximately 10% of adults consumed 25% or more of calories from added sugar in 2005-2010. Compared with those who consumed approximately 8.0% of calories from added sugar (quintile 1), those who consumed approximately 17% to 21% (quintile 4) of calories from added sugar had a 38% higher risk of CVD mortality, and those who consumed approximately 25% of calories from added sugar had double the risk (HR=2.03).

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
	NHANES III N=11,733 NHANES 1999-2004 N=8,786 NHANES 2005-2010 N=10,628		*Association between quintiles of usual percentage of calories from sugar and CVD mortality* Quintile 1 vs. 2: HR=1.07 (95% CI 1.02-1.12) Quintile 1 vs. 3: HR=1.18 (95% CI 1.06-1.31) Quintile 1 vs 4: HR=1.38 (95% CI 1.11-1.70) Quintile1 vs. 5: HR=2.03 (1.26-3.27) P for trend=0.004 Risk of mortality compared to those who consume 0 to<10% of calories from added sugar: 10 to <25% calories form added sugar HR=1.30 (95% CI 1.09-1.55) ≥25% of calories from added sugar HR=2.75 (95% CI 1.40-5.42) P for trend=0.004 Risk of mortality was increased in Quintile 5 vs. Quintile 1 in all subgroups of age, sex, race/ethnicity (except in Non-Hispanic Blacks, where risk was non significantly reduced), education, healthy eating index, physical activity, and BMI, though not always significantly Significant association between sugar sweetened beverage consumption and risk of CVD mortality (HR=1.29, 95% CI 1.04-1.60) in those with 7+ servings/week vs.	

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			those who consumed 1 serving per week or less	
EPIC (Greek component) Trichopoulou et al, 2007 17136037	Aim of Study To evaluate the effects on mortality of habitual low carbohydrate–high-protein diets that are thought to contribute to weight control Prospective cohort study N=22944	Inclusion criteria Greek resident Age 20-86 Exclusion criteria Missing data from dietary, anthropometric or lifestyle variables Lost to follow up History of coronary artery disease, diabetes mellitus, and/or cancer	1° endpoint: All cause and cause-specific mortality Mean follow up of 4.9 years Increasing LC/HP score was significantly associated with mortality (p=0.001). Increase in LC/HP score by 2 units Mortality Ratio=1.08 (95% CI 1.03-1.13). Increase of LC/HP score of five units (corresponding to increase of protein intake by 15 g/day and decrease of carbohydrates by 50 g/day) associated with 22% increase in overall mortality (95% CI 9-36%). Reference group LC/HP score≤6: LC/HP score 7-9, MR=1.20 (95% CI 0.89-1.62) LC/HP score 10-12, MR=1.42 (95% CI 1.06-1.89) LC-HP score 13-15, MR=1.56 (95% CI 1.13-2.13) LC/HP score≥16, MR=1.71 (95% CI 1.22-2.41) CVD deaths: Mortality Ratio=1.09 (95% CI: 1.01-1.17) Cancer deaths: Mortality Ratio=1.07 (95% CI 0.99-1.15)	Summary Individuals with habitual (not short term) diets low in carbohydrates and high in protein tend to have higher overall mortality, compared to individuals with habitual diets high in carbohydrates and low in protein Limitations Potential for residual confounding Potential for limited generalizability

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			Other causes of death: Mortality Ratio=1.11 (95% CI 1.00-1.23) In separate Greek EPIC population with CAD at baseline, model for a 2-unit increase in LC/HP score (energy-adjusted components) Mortality Ratio=1.05 (95% CI 0.96-1.14). Analogous model in population with diabetes at baseline, mortality ratio=1.06 (95% CI 0.95-1.17)	
Noto et al, 2013 23372809	Study Aims Systematic review and Meta analysis of observational studies N=17 studies (272,216)	Inclusion criteria Studies assessing risk of mortality or CVD incidence associated with low carbohydrate intake Published full text report RCTs or observational studies of 1 year+ follow up (no RCTs identified) Reported relative risks Adjusted for at least 3 of age, gender, obesity, smoking status, diabetes, hypertension, hypercholesterolemia, prior history of CVD, family history of CVD	1° endpoint: Pooled estimates of adjusted RRs for low carbohydrate intake and effect on all cause mortality and CVD incidence *All cause mortality* Pooled RR of low carbohydrate diet for all cause mortality from 4 studies=1.31 (95% CI 1.07-1.59) p=0.007, with significant heterogeneity I^2=53% (p=0.09). Among the sources of heterogeneity explored, RRs were significantly elevated in both the US (RR=1.12, 95% CI 1.01-1.24) and Europe (RR=1.42, 95% CI 1.18-1.72), studies with follow up 0of less than 10 years had significant RRs (RR=1.40, 95% CI 1.12-1.74) while those with longer follow up did not have significant RRs (RR=1.27, 95% CI 0.88-1.84). RR for men was significantly elevated (RR=1.19, 95% CI 1.08-1.31) while that for women was not (RR=1.34, 95% CI 0.96-1.87)	Summary low-carbohydrate diets were associated with a significantly higher risk of all-cause mortality, but not CVD mortality and incidence

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			CVD mortality RR low carbohydrate diet=1.10 (95% CI 0.98-1.24), p=0.12, I^2=0% (p=0.41). RR low carbohydrate diet in women=0.98 (95% CI 0.78-1.24), p=0.87, I^2=53% (p=0.09) RR using LC/HP score=1.53 (0.88-2.67), p=0.13, I^2=61% (p=0.05)	
Martinez-Gonzalez et al., 2014 24871477	Study Aim to identify the association between an a priori–defined provegetarian FP and all-cause mortality Study type RCT being analyzed as prospective cohort study N=7216	Inclusion criteria -men aged 55–80 y or women aged 60–80 y - no previously documented cardiovascular disease - at high cardiovascular risk (either type 2 diabetes or ≥ 3 major cardiovascular risk factors at baseline, including current smoking, hypertension (≥140/90 mm Hg or treatment with antihypertensive agents), high LDL cholesterol >160 mg/dL, low HDL cholesterol (<40 mg/dL), overweight/obesity [BMI ≥ 25], or a family history of premature CAD Exclusion criteria - previous medical diagnosis of CAD, stroke, or peripheral arterial disease	1° endpoint: All cause mortality Mortality rate by quintiles of baseline provegetarian food pattern Quintile 1 : 12.78/1000 person years Quintile 2: 11.68/1000 person years (HR=0.98, 95% CI 0.72-1.32) Quintile 3: 10.02/1000 person years (HR=0.81, 95% CI 0.57-1.14) Quintile 4: 8.31/1000 person years (HR=0.70, 95% CI 0.49-0.99) Quintile 5: 8.20/1000 person years (HR=0.66, 95% CI 0.46-0..96) P for trend=0.006 *HR of death by baseline provegetarian food pattern (compared to very low provegetarian food pattern (<30))* Low (30-34): HR=0.71 (95% CI0.50-1.02)	Summary the preference for plant derived foods in the customary diet was associated with reduced all-cause mortality during a 4.8-y follow-up compared with preferential selection of foods from animal sources

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
		-any severe chronic illness, drug or alcohol addiction -history of allergy or intolerance to olive oil or nuts - low predicted likelihood of changing dietary habits according to the stages-of- change model -illiteracy	Moderate (35-39): HR=0.68 (95% CI 0.48-0.96) High/very high (≥40): HR=0.59 (95% CI 0.40-0.88) P for trend=0.027 *HR of death by yearly updated provegetarian food pattern (compared to very low)* Low (30-34): HR=0.76 (95% CI 0.53-1.10) Moderate (35-39): HR=0.79 (95% CI 0.55-1.13) High/very high (≥40): HR=0.59 (95% CI 0.39-0.89) P for trend=0.028 *HR of death by adherence to the absolute serving based index (compared to low, <4)* Moderate (4): HR=0.85 (95% CI 0.65-1.11) High (>4): HR=0.70 (95% CI 0.51-0.95) P for trend=0.003	

Data Supplement 6. RCTs of Exercise and Physical Activity (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 value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
Orrow et al, 2012 (15)	Study type	Inclusion criteria • RCTs	Intervention: any intervention of	1° endpoint	Adverse events:

23243114	Systematic review and meta analysis N=15 randomized controlled trials (8.745 participants)	• adults aged 16 years or over • determined as sedentary during participant recruitment or baseline measurement at trial entry • recruited through primary care • study of any intervention of physical activity promotion, provided that the primary stated goal was to increase activity or fitness levels in participants • outcome of physical activity or fitness • minimum follow up of 12 months after randomization • reported intention to treat analysis results. Exclusion criteria • multifactorial interventions, such as promoting dietary modification in addition to physical activity	physical activity promotion, provided that the primary stated goal was to increase activity or fitness levels in participants control: no restrictions (in 7 studies control=no intervention, in 8 studies there was a comparator intervention)	Effect of physical activity promotion on self reported physical activity: (dichotomous data) OR=1.42 (95% CI 1.17-1.73) Effect of physical activity promotion on self reported physical activity at 12 months (continuous data) SMD=0.25 (95% CI 0.11-0.38) Effect of physical activity promotion on cardiorespiratory fitness at 12 months (SMD=0.51 (95% CI -0.18-1.20) Effect of physical activity promotion (exercise referral; dichotomous data) on self reported physical activity at12 months OR=1.38 (0.98-1.95) Effect of physical activity promotion (exercise referral; continuous data) on self reported physical activity at12 months OR=0.20 (-0.21-0.61) In studies that compared physical activity promotion to no intervention (n=6), significant intervention effect on self reported physical activity at 12 months (OR=1.74, 95% CI 1.39 to 2.18); SMD= 0.36 (95% CI 0.28 to 0.43) compared to non-significant effect in studies with comparator interventions (OR=1.18, 95% CI 0.95-1.48).	Only one study found a significant intervention effect on adverse events, reporting a relative 11% increase in falls and a 6% increase in injuries among intervention participants between baseline and 12 months' follow-up, compared with control participants
Sanchez et al (2015) 25263343	Study type Narrative summary of a systematic review of systematic reviews and meta-analyses N=10 studies	Inclusion criteria • literature reviews, systematic reviews, meta-analyses • adults aged 18 years and older • any intervention performed or initiated in a primary care setting with the goal of increasing the PA	Intervention any intervention performed or initiated in a primary care setting with goal of increasing the PA level of participation of	1° endpoint High-quality causal evidence of a positive effect of interventions on achieving the predetermined PA level was shown in five systematic reviews. Four of the five obtained a small to moderate mean standardized effect (0.17−0.28), but the	Limitations Narrative summary, no quantitative summary measure of effect

		level or participation of sedentary or insufficiently active adults; • comparison group: no intervention control, usual care control, or alternative intervention control • interventions initiated in a PC context with PC professionals as main intervention agents. • reported outcome of increase in PA level or proportion of patients meeting predefined PA level, with at least one post-intervention follow-up measurement Exclusion criteria • Clinical practice guidelines or recommendations involving no literature search and review of studies analyzing evidence; • Reviews in which primary studies carried out in PC did not constitute at least 50% of the included articles; • Studies conducted in settings that were not generalizable to primary care, including inpatient care, emergency departments, or occupational settings; • Reviews of secondary or tertiary prevention, or population studies focused only on pathology • Exercise referral schemes	sedentary or insufficiently active adults Control: no intervention, usual control, or alternative intervention	reviews on which these were based found evidence of a high degree of heterogeneity (I^2 range: 67% to 83.5%)l Of the three systematic reviews of average quality and with a moderate or low degree of evidence, only one reported acceptable evidence that the interventions that addressed PA behaviors in PC patients could achieve improvements No clear evidence of an association between patient characteristics and effectiveness of interventions	

Data Supplement 7. Nonrandomized Trials, Observational Studies, and/or Registries of Exercise and Physical Activity (Section 3.2.)

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Ekelund et al, 2016 (16) 27475271	Study type Systematic review and meta analysis N=16	Inclusion criteria • English-language, prospective cohort studies • had individual level exposure and outcome data, provided • data on both daily sitting or TV-viewing time and physical activity • reported effect estimates for all-cause mortality, cardiovascular disease mortality, or breast, colon, and colorectal cancer mortality	1° endpoint *All cause mortality* Sitting time All cause mortality increased with increasing siting time in all but the highest quartile of physical activity. The RR for sitting >8 h/day compared to <4 h/day in the four quartiles of physical activity were: 1st Quartile: RR=1.27 (95% CI 1.22-1.32) 2nd Quartile: RR=1.12 (95% CI: 1.07-1.17) 3r Quartile: RR=1.10 (95% CI 1.04-1.16) 4th Quartile: RR=1.04 (95% CI 0.98-1.10) When comparing each of the physical activity by sitting time subgroups to the reference group with the highest physical activity (≥35.5 MET-h/w) and lowest sedentary time (<4 h/day), most other groups had a greater all cause mortality risk: RRs increased with increasing sitting time regardless of PA, and decreased with increasing PA regardless of sitting time. 1st quartile PA: lowest PA/lowest sitting time (≤2.5 MET-h/w and <4 h/day) RR=1.27 (95% CI 1.22, 1.30) lowest PA/highest sitting time (≤2.5 MET-h/w and >8 h/day sitting) RR=1.59 (95% CI 1.52-1.66) 2nd quartile PA (16 MET-h/w) Risk significantly higher than referent category for all categories of sitting time	Summary: High levels of moderate intensity physical activity (ie, about 60–75 min per day) seem to eliminate the increased risk of death associated with high sitting time. However, this high activity level attenuates, but does not eliminate the increased risk associated with high TV-viewing time.

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			(e.g., RR 1.27, 95% CI 1.21-1.33 for >8 hours sitting) 3rd quartile PA (30 MET-h/w) Risk significantly higher than referent category for those sitting 4+ hours per day (e.g., RR 1.13, 95% CI 1.07-1.19 for >8 hours sitting 4th quartile PA (>35.5 MET-h/w) highest PA/highest sitting time (>35 MET-h/w and >8 h/day) RR=1.04 (95% CI 0.99, 1.10) Similar patterns were observed for TV viewing time, though the effect estimates were less precise All cause mortality increased with increasing TV time in all quartiles of physical activity. The RR for watching TV ≥5 h/day compared to <1 h/day in the four quartiles of physical activity were: 1st Quartile: RR=1.44 (95% CI 1.34-1.56) 2nd Quartile: RR=1.29 (95% CI: 1.19-1.39) 3r Quartile: RR=1.41 (95% CI 1.28-1.56) 4th Quartile: RR=1.15 (95% CI 1.05-1.27) Physical activity by TV time subgroups to the reference group with the highest physical activity (≥35.5 MET-h/w) and lowest sedentary time (<1 h/day): 1st quartile PA (≤2.5 MT-h/w): RRs significantly higher than referent category for all categories of TV time	

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			lowest PA/lowest TV time (≤2.5 MET-h/w and <1 h/day) RR=1.32 (95% CI 1.20, 1.46) lowest PA/highest TV time (≤2.5 MET-h/w and ≥5 h/day sitting) RR=1.93 (95% CI 1.76-2.01) 2nd quartile PA (16 MET-h/w) RRs significantly higher than referent category for all categories of TV time (e.g., RR 1.48, 95% CI 1.35-1.61 for ≥5 hours TV time) 3rd quartile PA (30 MET-h/w) RRs significantly higher than referent category for those watching TV 3+ hours per day (e.g., RR 1.35, 95% CI 1.23-1.49 for ≥5 hours TV time) 4th quartile PA (≥35.5 MET-h/w) highest PA/highest TV time (≥35.5 MET-h/w and ≥5 hours TV time) RR=1.16 (95% CI 1.05, 1.28) *CVD mortality* Sitting time Compared to the reference group with the highest physical activity (≥35.5 MET-h/w) and lowest sedentary time (<4 h/day), most other groups had a greater CVD mortality risk: RRs generally increased with increasing sitting time, and decreased with increasing PA regardless of sitting time.	

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			1st quartile PA: RRs significantly higher than reference category for all categories of sitting time lowest PA/lowest sitting time (≤2.5 MET-h/w and <4 h/day) RR=1.34 (95% CI 1.24, 1.43) lowest PA/highest sitting time (≤2.5 MET-h/w and >8 h/day sitting) RR=1.74 (95% CI 1.60-1.90) 2nd quartile PA (16 MET-h/w) RRs significantly higher than referent category for all categories of sitting time (e.g., RR 1.37, 95% CI 1.25-1.50 for >8 hours sitting) 3rd quartile PA (30 MET-h/w) RRs significantly higher than referent category for those sitting 4-<6 hours per day and those sitting >8 hours per day (RR 1.14, 95% CI 1.06-1.22 and RR 1.16, 95% CI 1.04-1.28, respectively) 4th quartile PA (≥35.5 MET-h/w) highest PA/highest sitting time (>35 MET-h/w and >8 h/day) RR=1.07 (95% CI 0.96, 1.20) Similar patterns were observed for TV viewing time 1st quartile PA (≤2.5 MT-h/w): RRs significantly higher than referent category for all categories of TV time	

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			lowest PA/lowest TV time (≤2.5 MET-h/w and <1 h/day) RR=1.45 (95% CI 1.21, 1.73) lowest PA/highest TV time (≤2.5 MET-h/w and ≥5 h/day sitting) RR=2.26 (95% CI 1.93-2.66) 2nd quartile PA (16 MET-h/w) RRs significantly higher than referent category for all categories of TV time (e.g., RR 1.71, 95% CI 1.46-2.01 for ≥5 hours TV time) 3rd quartile PA (30 MET-h/w) RRs significantly higher than referent category for those watching TV 3+ hours per day (e.g., RR 1.48, 95% CI 1.24-1.78 for ≥5 hours TV time) 4th quartile PA (≥35.5 MET-h/w) highest PA/highest TV time (≥35.5 MET-h/w and ≥5 hours TV time) RR=1.19 (95% CI 0.99, 1.24) *Cancer mortality* Sitting time 1st quartile PA (≤2.5 MET-h/w): RRs significantly higher than reference category for all categories of sitting time lowest PA/lowest sitting time (≤2.5 MET-h/w and <4 h/day) RR=1.12 (95% CI 1.06, 1.19)	

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			lowest PA/highest sitting time (≤2.5 MET-h/w and >8 h/day sitting) RR=1.22 (95% CI 1.13-1.31) 2nd quartile PA (16 MET-h/w) RRs not significantly higher than referent category for any category of sitting time (e.g., RR 1.07, 95% CI 0.98-1.16 for >8 hours sitting) 3rd quartile PA (30 MET-h/w) RRs not significantly higher than referent category for any category of sitting time (e.g., RR 0.99, 95% CI 0.90-1.08 for >8 hours sitting) 4th quartile PA (≥35.5 MET-h/w) highest PA/highest sitting time (≥35 MET-h/w and >8 h/day) RR=0.97 (95% CI 0.88, 1.06) Similar patterns were observed for TV viewing time 1st quartile PA (≤2.5 MT-h/w): RRs higher than referent category for all categories of TV time lowest PA/lowest TV time (≤2.5 MET-h/w and <1 h/day) RR=1.12 (95% CI 0.96-1.30) lowest PA/highest TV time (≤2.5 MET-h/w and ≥5 h/day sitting) RR=1.26 (95% CI 1.10-1.45)	

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			2nd quartile PA (16 MET-h/w) RRs significantly higher than referent category for highest category of TV time (RR 1.20, 95% CI 1.05-1.37 for ≥5 hours TV time) 3rd quartile PA (30 MET-h/w) RRs not significantly higher than referent category for any TV time category (e.g., RR 1.15, 95% CI 0.99-1.33 for ≥5 hours TV time) 4th quartile PA (≥35.5 MET-h/w) highest PA/highest TV time (≥35.5 MET-h/w and ≥5 hours TV time) RR=1.05 (95% CI 0.91, 1.22)	
Hamer et al, 2008 18048441	Study type Meta analysis N=18 studies (459,833 participants)	Inclusion criteria • English language full-length publication in a peer-reviewed journal; • Prospective cohort studies in healthy men and women at baseline • measures of CVD (fatal and nonfatal) and/or all-cause mortality at follow-up • measures of habitual walking volume (time/distance) or intensity at baseline	1° endpoint Incident CVD (death from coronary causes, myocardial infarction, angina pectoris, stroke, congestive heart failure, and coronary revascularization procedures) Results Mean 11.3 years follow up *CVD* Highest walking category (on average, 5.2 hours per week or more than 17.2 km per week, but varied by study) compared to lowest HR=0.69 (95% CI 0.61–0.77, p,0.001) with significant between study heterogeneity (p<0.001) and evidence of publication bias	Summary: There is an inverse relationship between walking and CVD and all cause mortality, including at moderate walking levels. The effect was stronger for walking pace than for walking volume (time and distance). There was no evidence of difference in effects by gender.

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			Analysis comparing moderate walking levels with the lowest category (average walking time/distance in the moderate walking categories was approximately 3 hours per week or 9.8 km per week, which equated to a casual or moderate walking pace of approximately 3 km per hour): pooled HR =0.84 (0.79 to 0.90, p,0.001, and 0.80 (0.71 to 0.91, p,0.001; x2 (9) = 29.78, p,0.001) for all-cause mortality. No significant differences in effect sizes between men and women *All cause mortality* Highest walking category (on average, 5.2 hours per week or more than 17.2 km per week, but varied by study) compared to lowest HR=0.68 (95% CI: 0.59–0.78, p,0.001) with significant between study heterogeneity (p<0.001) but no evidence of publication bias Analysis comparing moderate walking levels with the lowest category (average walking time/distance in the moderate walking categories was approximately 3 hours per week or 9.8 km per week, which equated to a casual or moderate walking pace of approximately 3 km per hour): pooled HR = 0.80 (95% CI: 0.71 to 0.91, p,0.001) No significant differences in effect sizes between men and women	

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			Volume and pace In a combined analysis of CVD and all-cause mortality the effects were more stronger for brisk walking pace ,HR = 0.52 (95% CI 0.48 to 0.57, p,0.001) compared with higher walking volume, HR = 0.74 (95% CI 0.69 to 0.80, p,0.001),. Effects were observed at lower levels of activity; moderate pace walking (HR=0.71, 95% CI 0.62 to 0.81, p,0.001) and lower levels of walking volume (HR=0.90, 95% CI 0.85 to 0.95, p,0.001).	
Kyu et al, 2016 27510511	Study type Systematic review and meta analysis N=174 studies (149,184,285 total person years; n=43 for ischemic heart disease and n=26 studies for ischemic stroke)	Inclusion • Published from 1980 to February 27, 2016 • English language publications and studies in humans • Prospective cohort studies • assessed physical activity as the exposure variable (total activity or domain specific activity that allowed conversion to total activity) • assessed at least one of the five chosen diseases as an outcome • provided risk estimates (relative risk, hazard ratio, or odds ratio) with confidence intervals or standard errors (or sufficient data to calculate them) Exclusion	1° endpoint Continuous physical activity: Higher levels of total physical activity were associated with lower risk of all outcomes. Major gains occurred at lower levels of activity, and the decrease in risk was minimal at levels higher than 3000-4000 MET minutes/week Categorical physical activity (reference is physical activity <*600 MET minutes/week)* *Breast Cancer*: 600-3999 MET minutes/week RR=0.967 (95% Uncertainty Interval 0.937-0.998) 4000-7999 MET minutes/week RR=0.941 (95% Uncertainty Interval 0.904 to 0.981) ≥8000 MET minutes/week RR=0.863 (95% Uncertainty Interval 0.829 to 0.900) No significant evidence of publication bias	Summary: higher levels of total physical activity were significantly associated with lower risk for all outcomes: major gains occurred at lower levels of activity and there were diminishing returns at levels higher than 3000-4000 MET minutes/week

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			Colon Cancer: 600-3999 MET minutes/week RR=0.903 (95% Uncertainty Interval 0.851-0.952) 4000-7999 MET minutes/week RR=0.833 (95% Uncertainty Interval 0.771 to 0.896) ≥8000 MET minutes/week RR=0.789 (95% Uncertainty Interval 0.735 to 0.850) No significant evidence of publication bias *Diabetes*: 600-3999 MET minutes/week RR=0.857 (95% Uncertainty Interval 0.816-0.902) 4000-7999 MET minutes/week RR=0.748 (95% Uncertainty Interval 0.701 to 0.799) ≥8000 MET minutes/week RR=0.722 (95% Uncertainty Interval 0.678 to 0.768) Egger's test for publication bias was significant (P<0.05). Results were similar in sensitivity analysis using trim-and-fill method to include missing studies *Ischemic Heart Disease*: 600-3999 MET minutes/week RR=0.837 (95% Uncertainty Interval 0.791-0.886) 4000-7999 MET minutes/week RR=0.769 (95% Uncertainty Interval 0.698 to 0.838) ≥8000 MET minutes/week RR=0.754 (95% Uncertainty Interval 0.704 to 0.809)	

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			Egger's test for publication bias was significant (P<0.05). Results were similar in sensitivity analysis using trim-and-fill method to include missing studies *Ischemic Stroke*: 600-3999 MET minutes/week RR=0.843 (95% Uncertainty Interval 0.779-0.918) 4000-7999 MET minutes/week RR=0.810 (95% Uncertainty Interval 0.690 to 0.937) ≥8000 MET minutes/week RR=0.736 (95% Uncertainty Interval 0.659 to 0.811) Egger's test for publication bias was significant (P<0.05). Results were similar in sensitivity analysis using trim-and-fill method to include missing studies	
Patterson et al (2018) 29589226	Systematic review and meta analysis of prospective observational studies N=34 studies	Inclusion criteria • assessed the association between total daily sitting/sedentary, TV viewing or leisure sitting time, and at least one of the outcomes of interest (all-cause, CVD or cancer mortality, incident (fatal and non-fatal) CVD and incident T2D). • primary research studies with a prospective design • at least an abstract in English • investigated non-diseased adults (≥ 18 years) in the general population	1° endpoint All-cause mortality CVD mortality Cancer mortality Type 2 diabetes Results *All-cause mortality* Non-linear association between sedentary behavior and all cause mortality Adjusted for physical activity RR=1.01 (95% CI 1.00-1.01) for each additional	Summary: increased risk for all-cause mortality and CVD mortality and incidence of T2D with higher levels of total sedentary time as well as TV viewing time, independent of physical activity. Associations with TV viewing were stronger than associations with sedentary time, with the strongest association being that between TV viewing and T2D.

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			hour of exposure below 8 h/day and RR=1.04 (95% CI 1.03-1.05) for each hour above 8 h/day Non-linear association between TV viewing time and all cause mortality. Adjusted for physical activity RR=1.03 (95% CI 1.01-1.04) per hour per day below 3.5 h/day and 1.06 (95% CI 1.05-1.08) per hour/day above 3.5 h/day Population attributable fraction associated with TV viewing=8% (6-10%) *CVD mortality* Non-linear association between sedentary behavior and CVD mortality Adjusted for physical activity RR=1.01 (95% CI 0.99-1.02) for each additional hour of exposure below 6 h/day and RR=1.04 (95% CI 1.03-1.04) for each hour above 6h/day Non-linear association between TV viewing time and CVD mortality. Adjusted for physical activity RR=1.02 (95% CI 0.99-1.04) per hour per day below 4 h/day and 1.08 (95% CI 1.05-1.12) per hour/day above 4 h/day Population attributable fraction associated with TV viewing=5% (1-8%) *Cancer mortality*	

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			Non-significant linear association between sedentary behavior and cancer mortality Adjusted for physical activity RR=1.01 (95% CI 1.00-1.02) Linear association between TV viewing time and cancer mortality adjusted for physical activity (RR=1.02, 95% CI 1.01-1.03) Population attributable fraction associated with TV viewing=5% (2-7%) *Type 2 diabetes* Linear association between sedentary behavior and type 2 diabetes Adjusted for physical activity RR=1.01 (95% CI 1.00-1.01) Equivocally linear association between TV viewing time and type 2 diabetes in physical activity adjusted estimate (RR=1.09; 95% CI 1.07-1.12) Population attributable fraction associated with TV viewing=29% (26-32%)	
Sattelmair et al (2011) 21810663	Study type Meta analysis N=33 studies	Inclusion criteria • prospective cohort studies • published in English • published between January 1, 1995, and July 31, 2009, • human adults • measured effect sizes (relative risks [RRs]) of CHD (primary prevention) by level of physical	1° endpoint Coronary heart disease Results Pooled RRs for highest vs. lowest (referent) categories. Overall estimated RR=0.75 (95% CI 0.71-0.79)	Summary: Individuals who met the basic US PA guideline had a 14% lower risk of CHD compared with those with no LTPA, while those meeting the advanced guideline had a 20% lower risk of CHD. Modest increments of risk reduction at higher levels of physical activity. Protective effects were observed at PA levels below the basic guideline.

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
		activity (providing either confidence intervals [CIs] or SEs). • All types of physical activity, including LTPA, time spent walking, walking pace, occupational physical activity, transport physical activity, nonleisure physical activity, and total physical activity, were included. • If multiple articles were published from the same cohort, article with the most detailed report for each type of physical activity was included	No evidence for publication bias *Leisure time PA* RR=0.74 (95% CI 0.69-0.78) RR for men =0.78 (95% CI 0.73-0.82) RR for women=0.67 (95% CI 0.61-0.74) Those who met the basic guideline (150 minutes of moderate intensity PA per week) had a 14% lower risk of CHD than those who engaged in no LTPA (RR, 0.86; 95% CI, 0.77 to 0.96). Those who met the advanced guideline (300 minutes of moderate intensity PA per week) had a 20% lower risk (RR, 0.80; 95% CI, 0.74 to 0.88). Risk for those who had PA at half the basic guideline (275 kcal/wk) RR=0.86, 95% CI 0.76-0.97 Men who met the basic guideline RR=0.91, 95% CI 0.79-1.04) Men who met the advanced guideline RR=0.82, 95% CI 0.74-0.91) Women who met the basic guideline RR=0.80, 95% CI 0.69-0.92) Women who met the advanced guideline RR=0.72, 95% CI 0.63-0.83) No interaction by geographic region, adjustment strategy for confounding variables, or CHD outcome *Walking time* RR=0.71 (95% CI 0.59-0.84) RR for men =*0.63* (95% CI 0.34-1.17) RR for women=0.65 (95% CI 0.55-0.76)	

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			Walking pace RR=0.53 (95% CI0.43-0.66) RR for men =*0.53* (95% CI 0.42-0.67) RR for women=not available *Occupational PA* RR=0.84 (95% CI 0.79-0.90) RR for men =*0.87* (95% CI 0.81-0.99) RR for women= Not available *Transport PA* RR=0.87 (95% CI 0.74-1.02) RR for men =*0.93* (95% CI 0.85-1.02) RR for women= 0.74(95% CI 0.57-0.97) *Total PA* RR=0.74 (95% CI0.62-0.90) RR for men =*0.79* (95% CI 0.59-1.07) RR for women=0.66 (95% CI 0.44-0.99)	
Wahid et al, 2016 27628572	Study type Systematic review and Meta analysis N=36 studies (3,439,874 participants)	Inclusion criteria • Prospective cohort studies • Measured PA in at least 2 domains (leisure, household, active travel, occupational activity) • Reported RR for incidence or mortality from incident CVD or T2DM • RR adjusted for a measure of body weight • English language • Published January 1981-March 2014 Exclusion criteria	1° endpoint CVD Incidence CVD mortality Stroke incidence CHD incidence CHD mortality Heart failure incidence MI incidence T2DM incidence Results Effect of an increase in PA of 11.25 MET h/week (equivalent to moving from inactivity to achieving current recommendations), adjusted for body	Summary: Increasing levels of PA were associated with a decrease in the risk of all cardiovascular outcomes and diabetes mellitus incidence. The RRs were only marginally attenuated when adjusting for a measure of body weight, suggesting that the majority of the health benefit from increasing PA is through mechanisms other than weight maintenance.

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
		• PA measure was one of fitness as opposed to a measure of time or volume of PA	weight, assuming a 0.25 power transformation *CVD Incidence* RR=0.83 (95% CI 0.77-0.89) *CVD mortality* RR=0.77 (95% CI 0.71-0.84) (evidence of significant heterogeneity) *Stroke incidence* RR=0.82 (95% CI 0.77-0.87) *CHD incidence* RR=0.80 (95% CI 0.75-0.86) *CHD mortality* RR=0.80 (95% CI 0.58-1.09) (evidence of significant heterogeneity) *Heart failure incidence* RR=0.81 (95% CI 0.76-0.86) *MI incidence* RR=0.75 (95% CI 0.62-0.89) *T2DM incidence* RR=0.74 (95% CI 0.72-0.77) Effect estimates for levels of PA compared to baseline of inactive behavior (low=0.1-11.5 METs h/week; medium=11.5-29.5 METs h/week; high=29.5+ METs h/week) *CVD Incidence* Low PA RR=0.89 (95% CI 0.82-0.98) Medium PA RR=0.79 (95% CI 0.69-0.89)	

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			High PA RR=0.75 (95% CI 0.64-0.87) *CVD mortality* Low PA RR=0.72 (95% CI 0.67-0.77) Medium PA RR=0.72 (95% CI 0.66-0.78) High PA RR=0.73 (95% CI 0.67-0.79) *Stroke incidence* Low PA RR=0.85 (95% CI 0.80-0.91) Medium PA RR=0.81 (95% CI 0.74-0.88) High PA RR=0.76 (95% CI 0.68-0.85) *CHD incidence* Low PA RR=0.87 (95% CI 0.80-0.95) Medium PA RR=0.78 (95% CI 0.74-0.82) High PA RR=0.70 (95% CI 0.66-0.75) *CHD mortality* Low PA RR= Not available Medium PA RR=0.76 (95% CI 0.63-0.93) High PA RR= Not available *Heart failure incidence* Low PA RR=Not available Medium PA RR=0.79 (95% CI 0.72-0.85) High PA RR=0.74 (95% CI 0.68-0.79) *MI incidence* Low PA RR= Not available Medium PA RR=0.76 (95% CI 0.66-0.87) High PA RR= Not available *T2DM incidence* Low PA RR=0.77 (95% CI 0.74-0.80) Medium PA RR=0.70 (95% CI 0.54-0.90) High PA RR= Not available	

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Zheng et al, 2009 19306107	Study type Meta analysis N=12 studies (295,177 participants)	Inclusion criteria • limited to English-language papers only. The search was restricted to 1954 to September • primary prevention studies • walking as exposure • CHD as outcome • Reported estimates and SEs or Cis of RRs of effect of waling on CHD or provided sufficient data to allow calculation of those estimates • Adjusted minimally for age as confounder • Only most recent publication chosen for papers based on the same study population Exclusion criteria • Walking combined with other types of PA • CVD as outcome instead of CHD	1° endpoint CHD Results No evidence of publication bias *Walking intensity (MET-hours/week)* Risk of CHD decreased by 11% (95% CI 4-18%) for increase of 8 MET-h/week, with no evidence of heterogeneity across studies *Walking Pace (km/h)* Increment of 2 km/h associated with 21% reduced risk of CHD (95% CI 15-27%), no evidence of heterogeneity *Walking time (hours/week)* Increment of 3.5 h/week of normal walking associated with 32% reduction in CHD (95% CI 11-48%), with no evidence of heterogeneity No evidence of heterogeneity in results by gender (p-0.67), mean age of study population (p-0.52), or follow-up duration (p=0.77)	Summary Walking was associated with a dose-responsive protective effect on CHD.
Biswas et al, 2015 25599350	Study aims: To quantify the association between sedentary time and hospitalizations, all-cause mortality, cardiovascular disease, diabetes, and cancer in adults	Inclusion criteria English language primary research articles Published through August 2014 Assessed sedentary behavior in adults, independent of physical activity, and correlated to at least 1 health outcome	1° endpoint All cause mortality, CVD incidence, CVD mortality, cancer incidence, cancer mortality, type 2 diabetes incidence All cause mortality. Statistical evidence of publication bias (Egger regression intercept=2.63, p-0.015). High vs. low sedentary time adjusted for physical	Summary Sedentary time (assessed as either daily overall sedentary time, sitting time, television or screen time, or leisure time spent sitting) was independently associated with a greater risk for all cause mortality, cardiovascular disease incidence or mortality, cancer incidence or mortality), and type 2 diabetes in adults after adjusting for physical activity. The increased risk associated with high sedentary time was stronger in those with low than high physical activity

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
	independent of physical activity Systematic review and meta analysis N=47 articles	Exclusion criteria Nonadult populations Didn't adjust for physical activity Only assessed sedentary behavior as reference category to effects of physical activity Measured sedentary behavior as lowest category of daily or weekly physical activity	activity HR=1.24 (95% CI 1.09-1.41). I^2=94.95, p<0.001. Participants with high levels of physical activity: association between sedentary time and all cause mortality HR=1.16 (95% ci 0.84-1.59) Participants with low levels of physical activity: association between sedentary time and all cause mortality HR=1.46 (95% CI 1.22-1.75) CVD incidence. High vs. low sedentary time adjusted for physical activity HR=1.14 (95% CI 1.00-1.30). I^2=82.12, p=0.004 CVD mortality. High vs. low sedentary time adjusted for physical activity HR=1.18 (95% CI 1.11-1.24). I^2=19.22, p=0.170 Cancer incidence Statistical evidence of publication bias (Egger regression intercept=0.957, p=0.156). High vs. low sedentary time adjusted for physical activity HR=1.13 (95% CI 1.05-1.21). I^2=0.00, p=0.39 Cancer mortality: High vs. low sedentary time adjusted for physical activity HR=1.16 (95% CI 1.10-1.22). I^2=0.23, p=0.54	Limitations Evidence for publication bias on all cause mortality and cancer incidence

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			Type 2 diabetes incidence. High vs. low sedentary time adjusted for physical activity HR=1.91 (95% CI 1.64-2.22)	
Women's Health Initiative Observational Study (WHI-OS) Chomistek et al, 2013 23583242	Study aims to examine the independent and joint associations of sitting time and physical activity with risk of incident cardiovascular disease (CVD). Prospective cohort study N=71,018	Inclusion criteria Age 50-79 at student entry Exclusion criteria Presence of any medical condition associated with predicted survival of less than 3 years Alcoholism Mental illness Dementia History of CVD or cancer at baseline Reported inability to walk at least one block Missing sedentary time or physical activity data	1° endpoint Incident CHD (including nonfatal MI and fatal CHD) and stroke *CHD* Sitting time ≥10 hours/day (vs. ≤5 hours/day) multivariable adjusted+adjustment for BMI and comorbidities HR=1.13 (95% CI 1.01-1.26), p for trend=0.04 Physical activity ≤1.7 MET hours/week (vs. >20 MET hours/week) multivariable adjusted+adjustment for BMI and comorbidities HR=1.43 (95% CI 1.25-1.63), p for trend<0.001 Stroke Sitting time ≥10 hours/day (vs. ≤5 hours/day) multivariable adjusted+adjustment for BMI and comorbidities HR=1.18 (95% CI 1.04-1.34), p for trend=0.008	Summary Sitting time was positively associated with risk of incident CHD, stroke, and total CVD, independent of leisure-time physical activity. Low levels of leisure-time physical activity were also associated with increased CVD risk, after adjusting for sitting time Limitations Generalizability unclear given restriction of study population to postmenopausal women Self reported sitting time and physical activity

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			Physical activity ≤1.7 MET hours/week (vs. >20 MET hours/week) multivariable adjusted+adjustment for BMI and comorbidities HR=1.30 (95% CI 1.13-1.50), p for trend<0.001 *Total CVD (CHD+Stroke)* Sitting time ≥10 hours/day (vs. ≤5 hours/day) multivariable adjusted+adjustment for BMI and comorbidities HR=1.15 (95% CI 1.05-1.25), p for trend=0.002. Continuous sitting time: each hour/day HR=1.02 (95% CI 1.01-1.03). No evidence of non-linearity of effect (p=0.87). In those who reported an increase in sitting time over a three year period vs. those who reported no change, HR=1.18 (95% CI 1.07-1.31). In those who decreased sitting time by 2+ hours/day, HR=1.01 (95% CI 0.91-1.13). Continuous increase in sitting time, for every 1 hour/day increase in sitting HR=1.014 (95% CI 1.001-1.027, p=0.03 Physical activity ≤1.7 MET hours/week (vs. >20 MET hours/week) multivariable adjusted+adjustment for BMI and comorbidities HR=1.35 (95% CI 1.23-1.493), p for trend<0.001. Continuous physical activity: each MET hour/week HR=0.990 (95% CI 0.987-0.992). No evidence of non-linearity of effect (p=0.60) *Interactions:*	

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			Sitting time x Physical activity: Highest risk in physically inactive women who also reported ≥10 hours/day of sitting (HR=1.63, 95% CI 1.39-1.90), but no significant interaction between sitting time and physical activity (p=0.94) No significant interactions of sitting time with CVD risk by employment status. Significant interaction between BMI and sitting time (significant association in women with BMI ≥25 but not BMI<25 (HR=1.26 vs HR=1.02). Significant interaction between sitting time and age (significant association in women 70+ but not <70 HR=1.22, 95% CI 1.09-1.3, p for trend< 0.001 vs. 1.08, 95% CI 0.94-1.25, p for trend=0.23	

Data Supplement 8. RCTs of Obesity and Being Overweight (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 value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
LeBlanc, 2018 (17) 30326501	Aim of Study: To support the U.S. Preventive Services Task Force (USPSTF) in updating their 2012 recommendation on screening for and treatment of adult	Inclusion Criteria: Key studies: • Overweight persons (BMI >25) who were 40 to 65 years old and had impaired glucose tolerance • >25 years, BMI >24 (>22 in Asians), and a fasting	Behavioral interventions Most interventions recommended diet and exercise with a goal of 5% weight loss, using a variety of forms, frequency and duration of counseling and support given individually, in groups, mixed group and	1° endpoint: Weight Loss and Maintenance: Behavioral Interventions (12-18 months) Mean difference (N = 67 RCTs): −2.39 kg, 95% CI −2.86 to −1.93, I2=90.0%	Adverse Events Behavioral Interventions Serious adverse events: None Overall adverse events: few ; no differences between groups Withdrawals due to AEs: NR Specific AEs: musculoskeletal events: Differences not consistently found

	obesity. Study type Systematic review 124 RCTs 89 RCTs of behavior-based weight loss: 80 RCTs of behavior-based weight loss and 9 RCTs of weight loss maintenance. 35 RCTs of medications for weight loss: 32 studies of medication for weight loss and 3 of weight loss maintenance. Key studies included: 4 RCTS N=8,902 1. DPS, Tuomilehto, 2001 2. DPP Research Group, 2002 3. Pi-Sunyer, 2015 4. Gadde, 2011	plasma glucose of 95 to 125 mg/dL and 140 to 199 mg/dL two hours after a 75-g oral glucose load • Adults without Type 1 or 2 Diabetes Mellitus with stable BMI ≥ 30, or ≥ 27 with dyslipidemia or hypertension • Overweight or obese adults (aged 18–70 years), with a body-mass index of 27–45 kg/m2 and two or more comorbidities (hypertension, dyslipidaemia, diabetes or prediabetes, or abdominal obesity)	individual, via technology or via written materials. Most also provided some other form of motivation (e.g. pedometer, videos). The median number of sessions for individual interventions was 12 in the 1st year, compared with 23 in group-based intervention studies (such as weight watchers). Medication interventions Liraglutide: 1.8 mg and 3.0 mg daily Lorcaserin: 10 mg twice daily Naltrexone/bupropion: 16/180 mg three times daily Orlistat 120 mg and 60 mg daily Phentermine/topiramate: 15/92 mg and 7.5/46 mg daily	Mean absolute change: Interventions: −0.5 kg to −9.3 kg; Controls: +1.4 kg to −5.6Kg Probability of losing 5% of baseline weight: (N = 38 RCTs) RR 1.94 (95% CI 1.70 to 2.22, I2=67.2%; NNT = 8) Weight loss maintenance (8 RCTs, 12-18 months) Mean difference: −1.59 kg (95% CI −2.38 to −0.79, I2=26.8%) Medication Interventions Liraglutide versus placebo (2 RCTs, 12-18 months) Mean absolute change in weight: −7.8 to −8.4 kg versus −2.0 to −2.8 kg; p<0.001) Probability of losing 5% of baseline weight: 63 to 79% versus 27 to 29% Weight loss maintenance (1 RCT, 13 months) Mean difference: -6.0 kg versus -0.1 kg; (p<.0001) Lorcaserin versus placebo (2 RCTs, 12 months) Mean absolute change in weight: LSM of -5.8 kg versus -2.2 to 2.9 kg; p<.001 Probability of losing 5% of baseline weight: 47% vs. 20-25%; p<.001 Naltrexone/Bupropion versus placebo (3 RCTs, 13 months) Mean difference: LSM −6.1 to −6.2 kg versus −1.3 to −1.4 kg; p<.001 Probability of losing 5% of baseline weight: 48 to 66% versus 16 to 42%; p<.01	Medication Interventions Liraglutide (12 to 36 months) versus placebo (3 RCTs) Serious AEs: 6 to 15% versus 3 to 13% Overall AEs: 80 to 96% versus 63 to 89% Withdrawal due to AEs: 8 to 33% versus 0 to 6% Specific AEs: gastrointestinal 77 to 79% versus 31 to 46%; pancreatitis: 0.7% versus 0.3% (1 RCT) Lorcaserin (1 to 12 months) versus placebo (4 RCTs) Serious AEs: 0 to 3% versus 0 to 2% Overall AEs: 12% at 1 month, 83% at 1 year versus 4% at 1 month, 75% at 1 year Withdrawal due to AEs: 7% versus 5 to 7% (1 RCT) Specific AEs: dizziness: 8 to 10% versus 4% Naltrexone and Bupropion (12 to 13 months) versus placebo (3 RCTs) Serious AEs: 0.3 to 2% versus 0 to 1% Overall AEs: 83 to 86% versus 69 to 75% Withdrawal due to AEs: 20 to 25% versus 10 to 14% Orlistat (6 to 18 ,months) versus placebo (17 RCTs, 2 observational studies) Serious AEs: 0 to 15% versus 2 to 26% (13 RCTs) Overall AEs: 80 to 96% versus 67 to 94% (8 RCTs, p<.05 in 3, NR in others)

				Orlistat 120 /60 mg TID versus placebo (11 RCTs, 12 months): Mean difference at 12 months: -1.0 to -4.4 kg Mean difference at 18-48 months: 120 mg −3.1 to −3.37 kg and 60 mg −2.3 to −2.81 kg ; p<.01 Probability of losing 5% of baseline weight: (N = 10 RCTs): 35 to 73% vs. 21 to 49%; p<0.05 Weight loss maintenance Mean difference at 12-18 months (N = 2 RCTs) 120 mg TID +2.6 to 2.8 kg vs. Placebo +4.4 to 4.7 kg 60 mg TID: +3.8 kg vs +4.4 kg Mean difference at 36 months (1 RCT): 120 mg TID +5.1 kg versus Placebo 7.1 kg; p=0.028 Phentermine and Topiramate (15/92 mg, 7.5/46 mg) versus placebo (2 RCTs, 12 months) Mean difference (kg): LSM: −8.1 kg with 15/92 mg, −10.2 kg with 7.5/46 mg, versus−1.4 kg with placebo; p<.0001 (1 RCT); Mean difference (% loss): LSM: 10.9% (doses combined) versus 1.5%; p<.0001 (1 RCT) Probability of losing 5% of baseline weight: 67 to 70% with 15/92 mg, 62% with 7.5/46 mg, and 17 to 21% with placebo; p<.0001 CV Behavioral Interventions versus control: All-Cause Mortality (4 RCTs)	Withdrawal due to AEs: 2 to 16% versus 0 to 7% (14 RCTs) Specific AEs: gastrointestinal: 63 to 91% versus 39 to 65% (16 RCTs, p<0.05 in 3, NR in others); beta carotene or vitamins A, D, or E deficiency: 0 to 12% vs. 0 to 8% (6 RCTs, p<0.01 in 1, NR in others) Phentermine and Topiramate (15/92 mg, 7.5/46 mg)(6 to 12 months) versus placebo (3 RCTs) Serious AEs: 2 to 5%, 1 to 3% versus 0 to 4% Overall AEs: 85% - 15/92 mg versus 73% placebo Withdrawal due to AEs: 16 to 21% - 15/92 mg, 12 to 15% - 7.5/46 mg versus 7 to 9% Specific AEs: anxiety: 4% -15/92 mg, 7.5/46 mg – “not increased” versus 1 to 2% placebo (p≤.01); Irritability: combined doses 2 to 5% versus <1 to 2% placebo (p<=.05); Insomnia: combined doses 6 to 12% versus 5 to 6% (p<=.05); disturbance in attention: combined doses 3 to 7% versus <1%(p<.001).

				DPP: (4.5 years): 0.1 versus 0.2 per 100 person-years TOHP II: 5 versus 2 events at 2 years Finnish DPS: 6 versus 10 deaths; HR, 0.57 (95% CI, 0.21 to 1.58) at 10 years TONE: (hypertensive adults aged 60 to 80): HR, 0.82 (95% CI, 0.55 to 1.22) at 16 years Cardiovascular Disease (stroke or myocardial infarction) DPP: nonfatal CV events: 2.2% (9.7 events/1000 patient-years) versus 1.7% (7.3 events/1000 patient-years) (not significant) CV-related deaths 2 versus 4 events Finnish DPS: 57 new CV events (22.9 per 1,000 person-years) versus 54 events (22.0 per 1,000 person-years); HR, 1.04 (95% CI, 0.72 to 1.51). Medication Interventions Cardiovascular Disease Liraglutide. 3 (0.12%) versus 3 (0.24%) at 13 months Subgroup with prediabetes at baseline: 2 additional CV events versus 0 at 36 months total Phentermine and topiramate: 0.4% versus 0.6% versus 0.7% at 13 months	
Ma, 2017 29138133	Aim of Study: To assess whether weight loss interventions for adults with obesity affect all cause, cardiovascular, and cancer mortality, cardiovascular	Inclusion Criteria: Key studies: • Moderately overweight individuals with high-normal diastolic BP (diastolic BP of 83 to 89 mm Hg, a systolic BP lower than 140 mm Hg, and a body mass index (the	Most were recommendations for a low fat weight reduction diet (usually ≤30% of energy as fat). Most also recommended reduction in saturated fats.	1° endpoint: Weight Loss and Maintenance: Weight change after one year (44 trials): Mean difference -3.42 kg (95% CI -4.09 to -2.75) Weight change after two years (20 trials): Mean difference -2.51 kg (95% CI -3.42 to -1.60)	

	disease, cancer, and body weight. Study type Systematic review 54 RCTs (N=30,206) All but 1 studied low fat diets for weight reduction (e.g., <30% of calories from fat, with most also recommending reducing saturated fat intake). Examples of diet programs used include the DASH diet, US Diabetes Prevention Program diet, and content based on the Dietary Guidelines for Americans. Most recommended increased exercise, but few offered specific programs. 2 RCTs (N = 316) included participants with prior CVD Key studies included: 4 RCTS (N=8,430)	weight in kilograms divided by the square of the height in meters) • Overweight and obese men and women age 60 or older with knee osteoarthritis • Men and women age 60 - 80 years with an average systolic blood pressure <145 mmHg and diastolic blood pressure <85 mmgHg taking a single antihypertensive agent or a single combination regiment of a diuretic and a non-diuretic. This study is a follow-up of the patients who were overweight or obese at randomization • 45 to 75 years old, type 2 diabetes, BMI >25.0 (>27.0 if on insulin); HbA1c < 11%; systolic blood pressure <160 mm Hg; diastolic blood pressure <100 mm Hg; triglycerides < 600 mg/dL; the ability to complete a valid maximal exercise test; and an established relationship with a primary care provider	4 trials were based on the DASH diet, and 8 were based on the diet in the US Diabetes Prevention Program. Most also recommended an exercise program, with 20 providing a program for participants to attend.	CV: All cause mortality (34 trials, 685 events): Risk ratio 0.82 (95% CI 0.71 to 0.95); 6 fewer deaths per 1000 participants (95% CI 2 to 10) Cardiovascular mortality (8 RCTs, 134 events): Risk ratio 0.93 (95% CI 0.67 to 1.31) New cardiovascular events (24 RCTs, 1,043 events: Risk ratio 0.93 (95% CI 0.83 to 1.04)	

	Largest studies with good methods for identifying CV events: 1. TOHP II, 2007 2. ADAPT, 2010 3. TONE, 2011 4. Look-AHEAD, 2013				

Data Supplement 9. Nonrandomized Trials, Observational Studies, and/or Registries of Obesity and Being Overweight (Section 4.1.)

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Health Professionals Follow-up Study & Nurses' Health Study Flint et al, 2010 21116472	Study type Meta-analysis from prospective cohort study N=69,393	Inclusion criteria: • Health Professionals Follow up Study includes male health professionals aged 40-75 at enrollment in 1986 with follow up data through 2004 • Nurses Health Study includes female nurses aged 30-55 at study entry, with follow up through 2004 Exclusion criteria: Health Professionals Follow up Study • known acute myocardial infarction • self-reported angina in 1986 or before • cancer diagnosis • missing data on BMI or waist circumference Nurses' Health Study	1° endpoint Incident CHD (acute non fatal myocardial infarction or fatal CHD outcome) by gender, BMI and waist circumference category Men *BMI* Compared to those with BMI 18.5-22.9 RR=1.22 (95% CI 1.04-1.43) for BMI 23.0-24.9 RR=1.53 (95% CI 1.31-1.78) for BMI 25.0-26.9 RR=1.71 (95% CI 1.44-2.02) for BMI 27.0-29.9 RR=1.81 (95% CI 1.48-2.22) for BMI 30+ *Waist circumference* Compared with waist circumference <84.0 RR=1.39 (95% CI 1.11-1.74) for WC 84.0-93.9 RR=1.55 (95% CI 1.23-1.95) for WC 94.0-102.0	Summary: BMI and WC predict future risk of CH, with both WC and BMI adding significantly to models containing the other measure in predicting CHD-risk. WC better predicted CHD risk than BMI, and became increasingly more predictive with increasing age. Lower WC cutoffs may be useful in identifying an ideal WC threshold .

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
		• known CHD in 1988 or before • cancer diagnosis • missing data on BMI or waist circumference, • death or withdrawal from follow-up prior to 1986	RR=2.25 (95% CI 1.77-2.84) for WC >102.0 40.4% of cases occurred in women with WC below 80.0 cm In model of WC deciles, CHD risk began to increase with the second decile of WC (approximately 84 cm) in men and with the third decile of WC (71 cm). Addition of aspirin intake or physical activity did not result in substantial change in estimates. Results were similar in analysis restricted to never smokers. In models with both BMI category and waist circumference, there were significant main effects of both BMI and WC (likelihood ratio test p<0.0001) , and addition of either resulted in attenuation of RR for the other. There was no significant interaction between WC and BMI on CHD risk. Women Compared to those with BMI 18.5-22.9 RR=1.10 (95% CI 0.93-1.30) for BMI 23.0-24.9 RR=1.34 (95% CI 1.11-1.61) for BMI 25.0-26.9 RR=1.53 (95% CI 1.27-1.84) for BMI 27.0-29.9 RR=2.16 (95% CI 1.81-2.58) for BMI 30+	

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			Compared with waist circumference <71.0 cm RR=1.57 (95% CI 1.26-1.95) for WC 71.0-79.9 cm RR=1.90 (95% CI 1.51-2.38) for WC 80.0-87.9 cm RR=2.75 (95% CI 2.20-3.45) for WC >88.0 cm 41.9% of cases occurred in women with WC below 80.0 cm In model of WC deciles, CHD risk began to increase with the third decile of WC (71 cm). Addition of aspirin intake or physical activity did not result in substantial change in estimates. Results were similar in analysis restricted to never smokers. In models with both BMI category and waist circumference, there were significant main effects of both BMI and WC (likelihood ratio test p<0.0001), and addition of either resulted in attenuation of RR for the other. There was no significant interaction between WC and BMI on CHD risk. A model including deciles of WC was compared to a model containing deciles of BMI; the model with WC fit the data better than the model using BMI deciles according to Akaike's Information Criterion (AIC)	

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Million Women Study Canoy et al, 2013 23723327	Study Aims To examine the prospective associations of BMI and waist circumference with CHD Prospective cohort study N=496,225	Inclusion criteria Female Had information on waist circumference and BMi No known heart disease, strsoke, or cancer (except non-melanoma skin cancer)	1° endpoint First hospital admission with diagnosis of CHD or death with CHD as underlying cause Average of 5.1 years of follow up Cumulative incidence of CHD over 20 years from age 55 was 9.7 (95% CI 9.5-9.9) per 100 women *Waist Circumference* Cumulative incidence <70 cm: 8.1 per 100 women (95% CI 7.1-9.1) 79-79.9 cm: 8.1 per 100 women (95% CI 9.1-10.0) ≥80 cm: 10.8 per 100 women (95% CI 9.8-11.9) Incidence increased with increasing waist circumference in every BMI category (p for trend <0.001 for each BMI category) Apolipoprotein B/A1 ratio increased with increasing BMI in Waist Circumference <70 and 70-79.9 cm groups (p for trend <0.001 in each), but not Waist Circumference ≥80 (p for trend=0.1) *BMI* Cumulative incidence <25: 8.8 per 100 women (95% CI 8.0-9.6) 25-29.9: 10.3 per 100 women (95% CI 9.8-10.8)	Summary Waist circumference and BMI were both positively associated with risk of a first onset of CHD. The risk for CHD was higher for women who reported larger waist circumference than those who have smaller waist circumferences, regardless of BMI Lilmitations Self reported BMI and waist circumference

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			≥30: 11.9 per 100 women (95% CI 10.5-13.3) Incidence increased with increasing BMI in each Waist Circumference category (p for trend <0.001 for each waist circumference category) Apolipoprotein B/A1 ratio increased with increasing waist circumference in BMI <25 (p for trend <0.001) and 25-29.9 (p for trend=0.03), but not BMI ≥30 (p for trend=0.6).	
Faith Activity and Nutrition program (FAN) Warren et al, 2012 22632742	Study Aims investigates the independent association of waist circumference with hypertension and diabetes in African American women Cross Sectional study N=843	Inclusion criteria African American women Members of participating churches in 4 districts in South Carolina 18+ years of age Free of serious medical conditions or disabilities that would make physical activity difficult Attend worship services 1+ times/month Planned to reside in area for next 2 years Exclusion criteria Missing data on study variables	1° endpoint Diabetes, hypertension *Hypertension* Compared to normal waist circumference, fully adjusted model: increased WC OR=2.79 (95% CI 1.44-5.41) Substantially increased WC OR=5.53 (95% CI 2.66-11.48), p for trend<0.001 *Diabetes* Compared to normal waist circumference, fully adjusted model: increased WC OR=3.25 (95% CI 1.19-8.88)	Summary After controlling for all variables, waist circumference was independently associated with a significant 3-5-fold risk in hypertension and diabetes in African American wome Limitations Self reported diabetes Cross-sectional design

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			Substantially increased WC OR=5.38 (95% CI 1.94-14.71), p for trend<0.001	
Czernichow et al, 2011 21521449	Study aims To examine whether the impact of adiposity on CVD and all cause mortality is independent of blood cholesterol, diabetes, and blood pressure, and to assess the difference in discriminative capability of these adiposity markers Meta analysis N=9 cross-sectional studies with follow up for mortality (n=82.864 participants)	Inclusion criteria Participants sampled from the general populations in Scotland and England	1° endpoint All cause mortality and CVD mortality Mean of 98.7 months mortality surveillance *All cause mortality* BMI: one SD higher BMI, fully adjusted model HR=0.95 (95% CI: 0.91-0.99), p-0.73. AUC=0.847 (95% CI 0.840-0.855) Waist Circumference: one SD higher WC HR=1.05 (95% CI 1.00-1.09), p<0.0001. AUC=0.847 (95% CI 0.839-0.855) Waist to Hip Ratio: one SD higher WHR HR=1.12 (95% CI 1.06-1.18), p<0.0001. AUC=0.848 (95% CI 0.840-0.856) Relative integrated discrimination improvement (RIDI) statistics WC vs. BMI=0.150 (95% CI 0.140-0.160) WHR vs BMI=0.335 (95% CI 0.321-0.348) WHR vs WC=0.184 (95% CI 0.175-0.193) *CVD mortality* BMI: one SD higher BMI HR=1.05 (95% CI 0.98-1.14), p=0.01. AUC=0.868 (95% CI 0.856-0.880) Waist Circumference: one SD higher WC HR=1.15 (95% CI 1.05-1.25), p<0.0001. AUC=0.868 (95% CI 0.86-0.880)	Summary BMi, WC, and WHR were associated with an increased risk of cardiovascular disease mortality. In a fully-adjusted model including adjustment for potentially mediating variables such as systolic blood pressure and diabetes status, the effects were not statistically significant at conventional levels for BMI, suggesting that some, if not all, of the impact of BMI on CVD risk occurs via these variables. In all models, WHR was the most strongly associated with CVD mortality compared to either WC or even BMI. Comparison of the discrimination capacity of the three adiposity indices indicated no differences using the AUC and a marginal benefit when using the RIDI statistic

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			Waist to Hip Ratio: one SD higher WHR HR=1.15 (95% CI 1.04-1.27). AUC=0.858 (95% CI 0.856-0.880) Relative integrated discrimination improvement (RIDI) statistics WC vs. BMI=0.543 (95% CI 0.524-0.563) WHR vs BMI=0.265 (95% CI 0.236-0.295) WHR vs WC=-0.276 (95% CI -0.302 to -0.250)	

Data Supplement 10. RCTs of Type 2 Diabetes Mellitus (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
Azadbakht et al, 2011 (18) 20843978	Aim: assessed how the DASH eating pattern affects cardiometabolic risks in type 2 diabetic patients Study Type: Crossover clinical trial N=31	Inclusion criteria: • age 50–75 years • fasting plasma glucose 126 mg/dl or was taking oral glucose lowering agents or insulin Exclusion criteria: • any secondary cause of hyperglycemia • use of estrogen therapy • untreated hypothyroidism • smoking • kidney or liver diseases	Intervention Diet: DASH diet Control diet: macronutrient composition of 50-60% carbohydrates, 15-20% protein, <30% total fat, and <5% of caloric intake from simple sugars.	1° endpoint: fasting blood glucose, AIC, weight, waist circumference, and lipid profiles Results: No significant difference between groups in calories, carbohydrates, protein, or fats. Control vs. DASH results: SBP: -3.1 vs. -13.6, (p=0.02) DBP: -.7 vs. -9.5 (p=0.04) Triglycerides -10.9 to -14.4, (p=0.79) HDL-C: 1.3 vs. 4.3 (p=0.001) LDL-C: -2.7 vs. -17.2 (p=0.02) Total cholesterol: -8.3 vs. 22.1 (p=0.11) .	Limitations: Patients unblinded, lab staff measuring outcomes were blinded. 31/44 enrolled completed the study (11 did not follow the study protocol) patients were given recommendations to follow a particular diet (rather than receiving prepared foods). Short-term (8 weeks) No control for physical activity

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
HART-D (Health Benefits of Aerobic and Resistance Training) in individuals with type 2 diabetes Church et al (2010) 21098771	Aim To examine the benefits of aerobic training alone, resistance training alone, and a combination of both on hemoglobin A1c (HbA1c) in individuals with type 2 diabetes Study Type RCT N=262	Inclusion criteria: • sedentary (defined as not exercising more than 20 minutes on 3 or more days a week • 30- to 75-years old • Type 2 diabetes and HbA1c levels of 6.5% to 11.0%. • Exclusion criteria: • body mass index ≥48.0 • blood pressure ≥160/100mmHg • fasting triglycerides ≥500 mg/dL, • use of an insulin pump, • urine protein >100 mg/dL, • serum creatinine >1.5 mg/dL, • history of stroke, advanced neuropathy or retinopathy, or any serious medical condition that prevented participants from adhering to the protocol or exercising safely N=262	Intervention: Resistance training 3 days a week (n=73) Aerobic exercise (expended 12 kcal/kg per week) (n=72) Combined aerobic and resistance training in which they expended 10 kcal/kg per week and engaged in resistance training twice a week (n=76) Comparator: Non exercise (offered weekly stretching and relaxation classes and was asked to maintain current activity during the 9-month study period) (n=41)	1° endpoint: change in HbA1c levels (assessed monthly). Results: Compared to changes in HbA1c in the control group, change in HbA1c was significantly greater in the combination training group (−0.34%; *P*=.03), while the differences in changes were not significant in the resistance training (resistance training vs. control=−0.16%; *P*=.32) or the aerobic exercise group(−0.24%; *P*=.14) compared to the control group	2° endpoints measures of anthropometry, fitness, strength, and changes in diabetes medications (assessed at baseline and follow-up only) Results (comparisons made between control group and each of three intervention groups for each outcome; only significant differences reported): Peak Vo2: combination group significantly greater increase than control and resistance only (p<0.05) Peak lean Vo2: combination group significantly greater increase than control and resistance only (p<0.05) Time on treadmill: combination group and aerobic group significantly greater increase than control and resistance only. Resistance only group significantly greater increase than control group (p<0.05) Speed/grade estimated MET: combination group and aerobic group significantly greater increase than control and resistance only. Resistance only group significantly greater increase than control group (p<0.05) Muscular work: combination group and resistance only group significantly

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
					greater change than all other groups ($p<0.05$) Muscular torque: combination and resistance only groups significantly greater increase than aerobic group ($p<0.05$) Body mass: combination group significantly greater decrease than control and resistance groups ($p<0.05$) Fat mass: resistance group significantly greater decrease than control group. Combination group significantly greater decrease than control and aerobic group ($p<0.05$) Lean mass: aerobic and combination group had significantly smaller increase than resistance group ($p<0.05$) Waist circumference: all exercise groups had significantly greater decreases than control group ($p<0.05$) <u>Adverse Events:</u> (control, 3 events; resistance training, 8 events; aerobic, 6 events; and combination taring, 4 events), including diverticulitis, emergency hysterectomy, lung cancer, 5 cardiovascular disease events (all reported to be unrelated to intervention), blood clot. No serious adverse event occurred during exercise

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
					training and only 1 was considered associated with exercise
SPREAD-DIMCAD (Study on the Prognosis and Effect of Antidiabetic Drugs on Type 2 Diabetes Mellitus with Coronary Artery Disease) Hong et al (2013) 23230096	Aim to compare the effects of the two major classes of blood glucose-lowering agents, sulfonylurea (glipizide) and metformin, on the cardiovascular events and mortality in 304 Chinese type 2 diabetic patients who had a history of coronary artery disease (CAD). Study Type RCT N=304	Inclusion criteria: • diagnosed with CAD by either having a history of acute myocardial infarction, diagnosed by a representative set of electrocardiograms, cardiac enzyme values, and typical symptoms or by angiographically identified stenosis of >50% of lumen diameter in at least one major epicardial coronary artery • diagnosed with type 2 diabetes (fasting plasma glucose ≥ 7 mmol/L and/or 2-h oral glucose tolerance test ≥11.1 mmol/L and fasting plasma glucose <15mmol/L); • no more than 80 years of age. Exclusion criteria: • severe liver dysfunction, including serum alanine aminotransferase concentration >2.5 times above the upper limit of normal range and abnormal renal function (serum creatinine >132 μmol/L); • severe dysfunction of the heart (New York Heart Association class >phase III); • psychiatric disease, severe infection, severe anemia, or neutropenia;	Intervention: metformin (≤1.5 g daily, mean 1.4 ± 0.2 g) plus glipizide placebo for 3 years (n=156) Comparator: glipizide(≤30 mg daily, mean 28.3 ±3.9mg) plus metformin placebo (n=148	1° endpoint: Composite recurrent cardiovascular events, including nonfatal myocardial infarction, nonfatal stroke or arterial revascularization by percutaneous transluminal coronary angioplasty (PTCA) or by coronary artery bypass graft, death from a cardiovascular cause, and death from any cause Results: Median follow-up period was 5.0 years The HR for the composite cardiovascular events for metformin treatment compared to glipizide was 0.54 (95%CI 0.30–0.90; P = 0.026) after adjustment for the duration of diabetes, duration of CAD, age, sex, and smoking history at baseline No significant difference in the mortality rate between the two groups (P = 0.55.) No significant between-group differences in glycated hemoglobin level, fasting plasma glucose, postload 2-h plasma glucose, systolic or diastolic blood pressure, total cholesterol, HDL cholesterol, LDL cholesterol, fasting serum triglyceride, or serum creatinine, glucose lowering medications, or other medications except statins for which the	2° endpoints new or worsening angina, new or worsening heart failure, new critical cardiac arrhythmia, and new peripheral vascular events Results: new or worsening heart failure: 6.8% glipizide group and 5.8% metformin group (adjusted HR 0.82, P = 0.677); new critical cardiac arrhythmia: 18.2% glipizide group and 19.2% metformin group (adjusted HR 1.01; P = 0.958); new or worsening angina: 48% glipizide group and 49.4% metformin group (adjusted HR 1.07; P = 0.696); and peripheral vascular events: 4.1% glipizide group and 0.6% metformin group (adjusted HR 0.13; P = 0.059). No significant between-group differences in number of patients who reported one or more hypoglycemic attacks (P = 0.651 overall, p=0.080 when excluding insulin users) Limitations:

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
		• other severe organic heart diseases, including, but not limited to, congenital heart disease, rheumatic heart disease, and hypertrophic or dilated cardiomyopathy; • pregnant or lactating; • allergic to study drugs; • using insulin therapy for type 2 diabetes and could not be changed to oral glucose-lowering drugs; • recent drug or alcohol abuse.		metformin group had significantly lower use at follow up (p=0.013). Metformin group had significantly lower BMI, body weight, and waist circumference at follow up than glipizide group (p<0.01)	secondary end points and adverse events were recorded only during the 3-year period of study drug administration
Huo et al, 2015 25369829	Study aim to conduct a comprehensive and updated overview of the effects of a Mediterranean-style diet (MSD) on glycemic control, weight loss and cardiovascular risk factors in patients with T2D Study type Meta-analysis N=9 studies (1178 patients)	Inclusion criteria: • RCTs • adult patients with diagnosed T2D, • evaluated the effect of MSD • intervention period ≥4 weeks • reported at least hemoglobin A1c (HbA1c) outcome data. Exclusion criteria: • no randomization or control diet group • cohort, case-control or cross-sectional design • included subjects with type 1 diabetes, gestational diabetes or at high risk for diabetes, • did not report relevant data • performed a post hoc analysis of previous studies	Intervention: Mediterranean style diet Comparator: Control diets included low-fat diet, usual dietary habits, nonrestricted calorie low-carbohydrate diet, the 2003 American Diabetes Association (ADA) diet and high-carbohydrate diet N=9 studies total, number of studies, arms, and patients varied by outcome	1° endpoint: • glycemic control including changes in HbA1c, fasting plasma glucose (FPG), fasting insulin and homeostasis model assessment of insulin resistance • weight control including changes in body weight, body mass index (BMI) and waist circumference • cardiovascular risk factors including changes in total cholesterol, triglyceride, high-density lipoprotein cholesterol and low-density lipoprotein cholesterol, systolic and diastolic blood pressure. Results: *Glycemic control*: MSD group had significantly greater reduction in HbA1c than control (mean difference, − 0.30; 95% CI, − 0.46 to − 0.14) (significant between-study heterogeneity).	2° endpoints Limitations: No evidence of substantial publication bias from Begg's test (P>0.05) for any outcome examined, but some evidence of potential publication bias for HbA1c (P = 0.001) and total cholesterol (P = 0.025) (Egger's test) Heterogeneity detected for multiple outcomes (HbA1c, FPG levels, triglycerides, and HDL No consistent control diet

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		• commentaries, reviews, letters, editorials, duplications, nonhuman studies and extensions of original studies		MSD group had significantly decreased FPG levels compared to control (−0.72 mmol/l; CI, − 1.24 to − 0.21) (significant between study heterogeneity). MSD group had significantly greater decrease than control in fasting insulin levels (−0.55 μU/ml; CI, − 0.81 to − 0.29) (no significant heterogeneity). No significant effect of MSD on homeostasis model assessment of insulin resistance (mean difference,− 0.55; CI, − 1.53 to 0.42) (non-significant moderate between study heterogeneity). *Weight control*: Significantly greater decrease in BMI in MSD that control patients (mean difference (− 0.29 kg/m2; 95% CI, − 0.46 to − 0.12). Significantly greater weight loss in MSD than control group (0.29 kg; CI, − 0.55 to − 0.04) No significant difference in reduction in waist circumference (−0.41 cm; CI, − 0.89 to 0.08) *Cardiovascular risk factors*: Significantly greater decrease in MSD than control group in total cholesterol (mean difference,− 0.14 mmol/l; 95% CI, − 0.19 to − 0.09) and triglyceride (−0.29	

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				mmol/l; CI, − 0.47 to − 0.10) and increased HDL (0.06 mmol/l; CI, 0.02 to 0.10). No significant difference between groups in change in LDL (−0.11 mmol/l; CI, − 0.24 to 0.01). Significantly greater decrease in MSD vs control in systolic blood pressure (−1.45mmHg; CI,− 1.97 to − 0.94) and diastolic blood pressure (−1.41 mmHg; CI, − 1.84 to − 0.97).	
Snowling et al, 2006 17065697	to meta-analyze the effects of different modes of exercise training on measures of glucose control and other risk factors for complications of diabetes Study type Meta analysis N=27 studies (1,003 patients)	Inclusion criteria: • published in English • through May 2006 • controlled trials • supervised exercise training programs • type 2 diabetic patients • at least one measure of glucose control Exclusion criteria: • lack of control group • control group of healthy subjected • exercise program interrupted • program participation did not significantly increase physical activity • insufficient data to calculate magnitude of mean effect or SE	Intervention: Aerobic, resistance, or combination exercise Comparator:	1° endpoint: HbA1c Fasting glucose Postprandial glucose Insulin sensitivity Fasting insulin Body mass Fat mass LDL cholesterol HDL cholesterol Total cholesterol triglycerides Systolic Blood pressure Diastolic blood pressure Results (only showing those that are small to large; all other comparisons were unclear or trivial. All results are beneficial unless otherwise noted) : HbA1c: -0.37 aerobic, --2.9 resistance, -0.43 combined	2° endpoints Limitations:

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		for at least one measure of glucose control		Fasting glucose: -0.20 aerobic, -0.53 combined Postprandial glucose: -0.44 aerobic, -0.28 combined Insulin sensitivity: 0.74 aerobic, 0.34 resistance, 2.20 combined Fasting insulin: -0.47 aerobic, -0.78 resistance Body mass: -0.32 combined Body fat: -0.35 aerobic, -0.46 combined LDL cholesterol: none HDL cholesterol: 0.49 combined Total cholesterol: none Triglycerides: -0.23 aerobic Systolic Blood pressure: -0.22 aerobic, -0.35 combined Diastolic blood pressure: -0.21 aerobic, -0.63 combined Total exercise time had trivial or unclear effects on the outcomes except for HDL cholesterol (0.23, representing a small harm) Exercise intensity had trivial or unclear effects on the outcomes except for HbA1c (-0.29), HDL cholesterol (-0.23), and body fat (0.23, small harm)	

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				Dietary co-interventions had trivial or unclear effects on the outcomes except fasting glucose (-0.27), waist circumference (0.25), total cholesterol (0.23, small harm), and LDL cholesterol (0.21, small harm)	
Maruthur, NM et al., 2016 27088241	Aim To evaluate the comparative effectiveness and safety of monotherapy (thiazolidinediones, metformin, sulfonylureas,dipeptidyl peptidase-4 [DPP-4] inhibitors, sodium–glucose cotransporter 2 [SGLT-2] inhibitors, and glucagon-like peptide-1 [GLP-1] receptor agonists) and selected metformin-based combinations in adults with type 2 diabetes Study type Meta analysis-(update of prior review). Updated findings where the strength of evidence changed from low or insufficient to moderate or high	Inclusion criteria: • date restrictions of April 2009 through March 2015 • .English • Nonpregnant adults • Type 2 diabetes • Evaluated 3+ months of use of a diabetes medication or drug combination of interest • RCTs or observational studies that adequately accounted for confounding • Included all cause mortality, macrovascular outcomes, microvascular outcomes, intermediate outcomes, or safety Exclusion criteria: • Did not specify adjunctive medications • Studies of acarbose	Intervention: head-to head monotherapy comparisons of metformin, thiazolidinediones, sulfonylureas, DPP-4 inhibitors, SGLT-2 inhibitors, and GLP-1 receptor agonists; comparisons of metformin alone with metformin-based combination; comparisons of metformin-based combinations where second medication was one of monotherapies studied or a basal or premixed insulin Comparator:	1° endpoint: All cause mortality CVD mortality CVD morbidity HbA1c Results: *All cause mortality*: low strength of evidence metformin was associated with lower risk compared with sulfonylureas. (Range of RRs from RCT=0.5 to 1.0; range in risk difference from RCTs=-5.0% to -0.1%; adjusted HR from observational studies=0.5 to 0.8). All other evidence for all of the other drug comparisons was of low strength or insufficient (data not presented). *CVD mortality*: moderate strength of evidence that metformin monotherapy was associated with lower long-term (≥2 years) cardiovascular mortality compared with sulfonylurea monotherapy (range in RR from RCTs=0.6 to 0.7, 2 studies with 3,199 participants; range in risk difference from RCTs=-2.9% to -0.1%, 2 studies with 3,199 participants); adjusted HR from observational studies (0.6 to 0.9, 3 studies with 115,105 participants). All	2° endpoints Limitations: About 45% of the RCTs did not report race/ethnicity. When reported, only 10% to 30% of the enrolled population was of nonwhite race. Most studies excluded older persons and those with clinically significant comorbid conditions Adverse Events/Safety: *Hypoglycemia*: Sulfonylureas were associated with increased risk for severe hypoglycemia as monotherapy (compared with metformin or thiazolidinedione) and in combination with metformin (compared with metformin plus a DPP-4 inhibitor or metformin plus an SGLT-2 inhibitor) Sulfonylureas alone and in combination with metformin increased the risk for mild, moderate, or total hypoglycemia compared with all other monotherapies and metformin-based combinations for which there was evidence. Metformin plus a basal or premixed insulin increased the risk for hypoglycemia over metformin plus a GLP-1 receptor agonist, and metformin plus a basal insulin conferred a lower risk for

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	N=204 studies (116 newly identified in updated review)			other evidence for all of the other drug comparisons was of low strength or insufficient (data not presented). *CVD morbidity*: low strength of evidence metformin was associated with lower risk compared with sulfonylureas (Range of RRs from RCT=0.7 to 1.6; range in risk difference from RCTs=-0.4% to 10.1%; adjusted HR from observational studies=0.3 to 0.9). All other evidence for all of the other drug comparisons was of low strength or insufficient (data not presented). *HbA1c*: Most diabetes medications used as monotherapy (metformin, thiazolidinediones, and sulfonylureas) reduced hemoglobin A1c to a similar degree in the short term, except for DPP-4 inhibitors, which were less effective than metformin or sulfonylureas. 2-drug combination therapies with metformin were more effective than metformin monotherapy in reducing hemoglobin A1c. the combination of metformin plus a GLP-1 receptor agonist reduced hemoglobin A1c more than metformin plus DPP-4 inhibitors. Most other combination therapy comparisons with moderate strength of evidence had no clinically meaningful between-group differences (≥0.3%) in hemoglobin A1c. Most of the evidence for the comparisons with GLP-1 receptor	hypoglycemia compared with the combination of metformin plus premixed insulin GI Side Effects: Metformin and GLP-1 receptor agonists, as monotherapy or in combination, were associated with more GI side effects than were all other medications with sufficient studies for comparison Metformin plus a GLP-1 receptor agonist yielded more GI side effects than metformin plus DPP-4 inhibitors and metformin plus thiazolidinediones. Nausea and vomiting were more common with GLP-1 receptor agonists than with metformin. Metformin resulted in more diarrhea than metformin plus a thiazolidinedione AEs with SGLT-2 Inhibitors: Metformin resulted in more diarrhea thanmetformin plus a thiazolidinedione. Risk for fracture for SGLT-2 inhibitors as monotherapy or in combination with metformin was of low or insufficient strength. comparative safety of SGLT-2 inhibitor–based comparisons regarding renal impairment, urinary tract infection, and volume depletion was also insufficient or of low strength Congestive Heart Failure:

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				agonists and comparisons with metformin plus injectables was insufficient or of low strength. *Body weight:* Metformin decreased body weight more than DPP-4 inhibitors, whereas sulfonylureas caused slightly less weight gain than thiazolidinediones. The SGLT-2 inhibitors decreased weight more than metformin and more than DPP-4 inhibitors. The combinations of metformin plus a GLP-1 receptor agonist and metformin plus an SGLT-2 inhibitor were both favored over the combination of metformin plus a DPP-4 inhibitor, and metformin plus a GLP-1 receptor agonist was favored over metformin plus a premixed insulin. Metformin plus a sulfonylurea had more favorable weight effects than metformin plus a premixed or basal insulin. Prior guideline's finding not updated that metformin reduced weight ~ 2.5 kg versus thiazolidinedione and sulfonylurea monotherapy, with high strength of evidence *Systolic BP and Heart Rate:* Evaluated for SGLT-2 inhibitors and GLP-1 receptor agonists only. moderate strength of evidence that the SGLT-2 inhibitors reduced systolic blood pressure by 3 to 5 mm Hg compared with other monotherapy when there were sufficient studies for pooling. metformin plus an SGLT-2 inhibitor and metformin	low strength of evidence that the risk for congestive heart failure was 1.2- to 1.6-fold greater with thiazolidinediones than with sulfonylureas (pooled odds ratio [OR], 1.6 [CI, 0.96 to 2.8]; range in risk difference, 0% to 2%) or metformin (2 short RCTs with no events and one 4-year RCT with a risk difference of 3%; range in hazards ratios, 1.2 to 1.5 in 2 observational studies with 6 to 8 years of follow-up). Low or insufficient strength of evidence on the comparative safety of DPP-4 inhibitors regarding congestive heart failure. Other: - The evidence on the outcomes of liver injury, lactic acidosis, pancreatitis, cancer, severe allergic reactions, and macular edema and decreased vision was of low strength or insufficient.

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				plus a GLP-1 receptor agonist reduced systolic blood pressure by 3 to 5 mm Hg more than metformin alone, with moderate to high strength of evidence heart rate, only 2 comparisons had sufficient data to grade the evidence as more than insufficient or low. Metformin plus an SGLT-2 inhibitor decreased heart rate more than metformin plus a sulfonylurea (pooled between-group difference in heart rate, 1.5 beats/min [95% CI, 0.6 to 2.3 beats/min]). The GLP-1 receptor agonists showed no between-group differences in heart rate compared with metformin monotherapy	
Metformin (seminal UKPDS study, also included in the metformin SR) 9742977	Study Type: RCT N=4,209 Country: UK	Inclusion Criteria: Age 25-65 with fasting plasma glucose >108 mg/dL on two occasions after being diagnosed as diabetic, and >120% of ideal body weight	Interventions: A. Metformin (n=279); A. Sulfylnurea + insulin (2,118)	1° endpoint: Any diabetes-related endpoint (sudden death, death from hyperglycemia or hypoglycemia, fatal or nonfatal MI, angina, heart failure, fatal or nonfatal stroke, renal failure, amputation, vitreous hemorrhage, retinal photocoagulation, blindness in one eye, or cataract extraction), diabetes-related death, death from all causes, MI, stroke, peripheral vascular disease, or microvascular disease	
Griffin, 2017 28770324	Aim: Efficacy of metformin to prevent cardiovascular events in diabetics Study Type: 13 RCTs N=2,079 allocated to metformin and "a similar			Results: Metformin vs. placebo/control All-cause mortality (6 trials): RR 0.96 (95% CI 0.84 to 1.09) CV mortality (5 trials): RR 0.97 (95% CI 0.80 to 1.16) MI (7 trials): RR 0.89 (95% CI 0.75 to 1.06)	Adverse Events: Not reported

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	number" of comparison subjects			Stroke (4 trials): RR 1.04 (95% CI 0.73 to 1.48)	
CANVAS Program Neal et al, 2017 28605608	Aim To detect plausible effects of canagliflozin on cardiovascular, kidney, and safety outcomes Study type Pooled analysis of RCTs N=10.142	Inclusion criteria Type 2 diabetes 30 years of age or older with history of symptomatic atherosclerotic cardiovascular disease OR 50 years or older with 2 or more of: diabetes for 10+ years, systolic blood pressure higher than 140 mm Hg while receiving antihypertensive agents, current smoking, microalbuminuria or macroalbuminuria, or HDL cholesterol less than 1 mmol per liter Estimated glomerular filtration rate at entry of more than 30 ml per minute per 1.73 m2 of body surface area Exclusion criteria	Intervention Canagliflozen (300 mg or 100 mg) Comparator placebo	1° endpoint: Composite of death from cardiovascular causes, nonfatal MI, or nonfatal stroke Mean follow up time of 188.2 weeks 29.2% assigned to canagliflozin and 29.9% assigned to placebo discontinued prematurely Differences between canagliflozin and placebo group for intermediate outcomes all p<0.001): glycated hemoglobin (-0.58%, , 95% CI -0.61 to -0.56); body weight (-1.60 kg; 95% CI -1.70 to -1.51); systolic blood pressure (-3.93 mm Hg, 95% CI -4.30 to -3.56); diastolic blood pressure (-1.39 mm Hg, 95% CI -1.61 to -1.17). Use of other antihyperglycemic agents 9.3% lower (95% CI -11.0 to -7.6) canagliflozin vs. placebo. HDL higher in canagliflozin vs placebo (2.06 mg per deciliter, 95% CI 1.77 to 2.33), LDL higher (4.68 mg per deciliter, 95% CI 3.64 to 5.73). Significantly lower composite death in canagliflozin than placebo group (36.9 vs 31.5 per 1000 patient years, HR=0.86, 95% CI 0.75 to 0.97, p<0.001 for non inferiority, p=0.02 for superiority).	2° endpoint: Death from any cause, death from cardiovascular causes, progression of albuminuria, composite of death from cardiovascular causes and hospitalization for heart failure Exploratory outcomes: nonfatal MI, nonfatal stroke, hospitalization for heart failure, regression of albuminuria, renal composite comprising 40% reduction in eGFR sustained for 2+ measures, need for renal replacement therapy, death from renal causes, total hospitalizations No significant superiority for death from any cause (p=0.24) so hypothesis testing discontinued; therefore differences in deathy from any cause and death from cardiovascular causes are not considered significant (HR=0.87, 95% CI 0.74 to 1.01; and HR=0.87, 95% CI 0.72 to 1.06). Death from cardiovascular causes: HR=0.87 (95% CI 0.72-1.06) Nonfatal stroke: HR=0.90 (95% CI 0.71-1.13) Nonfatal MI: HR=0.85 (95% CI 0.69-1.05)

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					Hospitalization for heart failure: HR=0.57 (95% CI 0.52-0..87) Death from any cause: HR=0.87 (95% CI 0.74-1.01) Albuminuria: HR=0.73 (95% CI 0.67-0.79) Composite of 40% reduction in eGFR, requirement for renal-replacement therapy, or death from renal causes: HR=0.60 (95% CI 0.47-0.77) <u>Adverse events:</u> Serious AEs less common in canagliflozin than placebo group (104.3 vs. 120.0 per 1000 patient years, HR=0.93, 95% CI 0.87-1.00) Higher risk in canaglilozin group of amputation of toes, feet or legs (6.3 vs 3.4 per 1000 patient years, HR=1.97, 95% CI 1.41-2.75) No difference in risk of hypoglycemia (50.0 vs 46.4 per 1000 patient year, p=0.20), hyperkalemia (6.9 vs 4.4 per 1000 patient year, p=0.10), acute kidney injury (3.0 vs 4.1 per 1000 patient year, p=0.33), pancreatitis (0.5 vs 0.4 per 1000 patient years, p=0.63), malignancies (p>0.17), venous thromboembolism (1.7 per 1000 patient years in both groups, p=0.63)

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					Differences in infections of male or female genitalia (p<0.001), volume depletion (p0.009), diruresis (p<0.001) Higher rate of all fractures (15.4 vs 11.9 per 1000 patient years, HR=1.26, 95% CI 1.04 to 1.52) and similar trend with low trauma fracture events (11.6 vs 9.2 per 1000 patient years, HR=1.23 95% CI 0.99 to 1.52) Small number of diabetic ketoacidosis (0.6 vs 0.3 per 1000 patient years, HR=2.33, 95% CI 0.75 to 7.17)
Marso et al, 2016 27295427	Aim To assess the long-term effects of liraglutide on cardiovascular outcomes and other clinically important events, Study Type RCT N=9340	Inclusion Criteria Patients with type 2 diabetes who had glycated hemoglobin of 7.0% or more Had not received drugs for the condition previously or had been treated with 1+ oral antihyperglyemic agents or insulin or a combination of these agents Age 50+ with at least one cardiovascular coesisting condition (CHD, cerebrovascular disease, peripheral vascular disease, chronic kidney disease stage 3 or greater, chronic heart failure class II or III) OR age 60+	Intervention Liraglitude (1.8 mg or maximum tolerated dose). N=4668 Comparator Placebo. N=4672 Randomization stratified on estimated glomerular filtration rate at screening (<30 or ≥30 ml per minute per 1.73 m2 of body surface area) Addition of any antihyperflycemic agents except FLP-	1° endpoint: Composite outcome: First occurrence of death from cardiovascular causes, nonfatal MI, or nonfatal stroke Median exposure 3.5 years, median 3.8 years follow up Changes in liraglutide vs placebo group at 36 months: glycated hemoglobin =-0.40 percentage points, 95% CI -0.45 to -0.34; greater weight loss=-2.3 kg (95% CI 2.5 to 2.0), lower systolic blood pressure (1.2 mm Hg, 95% CI 1.9 to 0.5), higher diastolic blood pressure (0.6 mm Hg, 95% CI 0.2 to 1.0), higher heart rate (3.0 beats per minute, 95% CI 2.5 to 3.4) Primary composite outcome occurred less frequently in liraglutide than placebo	2° endpoint: Expanded composite cardiovascular outcome (death from cardiovascular causes, nonfatal MI, nonfatal stroke, coronary revascularization, hospitalization for unstable angina pectoris or heart failure), death from any cause, composite renal and retinal microvascular outcome (nephropathy and retinopathy), neoplasms, pancreatitis *Expanded composite outcome*: 20.3 vs 22.7%, HR=0.88, 95% CI 0.81-0.96, p=0.005 *Death from cardiovascular causes*: lower in liraglutide group (4.7 vs 6.0%, HR=0.78, 95% CI 0.66-0.93, p=0.007)

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		with at least one cardiovascular risk factor (microalbuminuria or proteinuria, hypertension and left ventricular hypertrophy, left ventricular systolic or diastolic dysfunction, or ankle-brachial index of less than 0.9) Exclusion criteria Type 1 diabetes Use of GLP-1 receptor agonists Dipeptidyl peptidase 4 inhibitors, pramlintide, or rapid acting insulin Familial or personal history of multiple endocrine neoplasia type 2 or medullary thyroid cancer Occurrence of acute coronary or cerebrovascular event within 14 days before screening and randomization	1-receptor agonists, DPP-4 inhibitors, or pramlintide was permitted	group (13.0% vs 14.9%, HR=0.87, 95% CI 0.78n to 0.97, p<0.001 for noninferiority, p=0.01 for superiority).	*Death from any cause*: lower in liraglutide than placebo (8.2 vs 9.6%, HR=0.85, 95% CI 0.74-0.97, p=0.02) *Nonfatal MI*: 6.0 vs 6.8%, HR=0.88, 95% CI 0.75-1.03, p=0.11 *Fatal MI*: 0.4 vs. 0.6%, HR=0.60, 95% CI 0.33-1.10, p-0.10 *Silent MI*: 1.3 vs. 1.6%, HR=0.86, 95% CI 0.61-1.20, p=0.37 *TIA*: 1.0 vs. 1.3%, HR=0.79, 95% CI 0.54-1.16, p=0.23 *Coronary revascularization*: 8.7 vs. 9.4%, HR=0.91, 95% CI 0.80-1.04, p-0.18 *Nonfatal stroke*: 3.4 vs. 3.8%, HR=0.89, 95% CI 0.72-1.11, p=0.30) *Fatal stroke*: 0.3 vs. 0.5%, HR=0.64 95% CI 0.34-1.19, p=0.16 *Hospitalization for unstable angina*: 2.6 vs. 2.7%, HR=0.98 95% CI 0.76-12.6, p=0.87 *Hospitalization for heart failure*: 4.7 vs 5.3%, HR=0.87, 95% CI 0.73-1.05, p=0.14 *Microvascular event*: 7.6 vs. 8.9%, HR=0.84, 95% CI 0.73-0.97, p=0.02

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					Adverse Events Any AE: no significant difference between groups (62.3% vs 60.8%, p=0.12) Non significantly higher rates of benign (3.6 vs. 3.1%, p=0.18)) and malignant neoplasms (6.3% vs. 6.0%, p=0.46) in liraglutide vs placebo group (more patients in liaglutide than placebo had pancreatic cancer, fewer had prostate cancer and leukemia) Acute pancreatitis in 18 patients in liraglutide vs 23 in placebo Mean levels of serum amylase and lipase higher in liraglutide than placebo group Acute gallstone disease more common in liraglutide than placebo group Fewer in liraglutide treated with hypoglycemic medications than placebo Severe hypoglycemia less common in liraglutide than placebo (RR=0.69, 95% CI 0.51 to 0.93) Confirmed hypoglycemia less common in liraglutide (RR=0.80, 95% CI 0.74-0.88)

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					AEs leading to permanent discontinuation of trial regimen more common in liraglutide than placebo, apparently driven by GI disorders (9.5% vs 7.3%, p<0.001)
Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI 58 trial) Wiviott et al, 2018 30415602	Study Aim To evaluate the effects of dapagliflozin on cardiovascular and renal outcomes in a broad population of patients who had or were at risk for atherosclerotic cardiovascular disease Study Type RCT N=17.160	Inclusion criteria -40 years of age or older -type 2 diabetes, a glycated hemoglobin level of at least 6.5% but less than 12.0%, and a creatinine clearance of 60 ml or more per minute - had multiple risk factors for atherosclerotic cardiovascular disease or had established atherosclerotic cardiovascular disease (defined as clinically evident ischemic heart disease, ischemic cerebrovascular disease, or peripheral artery disease) .	Intervention 10 mg dapagliflozin daily (n=8582) Comparison Placebo (n=8578)	1° endpoints: Safety: Major adverse cardiovascular events (MACE) (cardiovascular death, myocardial infarction, or ischemic stroke). Efficacy: MACE and a composite of cardiovascular death or hospitalization for heart failure. 1° endpoints *Cardiovascular death or hospitalization for heart failure* 4.9% dapagliflozin vs. 5.8% placebo Rate=12.2/1000 patient years dapagliflozin vs. 14.7/1000 patient years placebo HR=0.83 (95% CI 0.73-0.95), p=0.005 for superiority HR ASCVD group=0.83 (95% CI 0.71-0.98) vs. HR=0.84 (95% CI 0.67-1.04) in multiple risk factors group, p for interaction=0.99 HR in those with history of heart failure=0.79 (95% CI 0.63-0.99), HR in	2° endpoints: Renal composite outcome (sustained decrease of 40% or more in estimated glomerular filtration rate (eGFR)), new end-stage renal disease, or death from renal or cardiovascular causes. Additional renal composite outcome included all these criteria except for cardiovascular .death All cause mortality 2° endpoints: *Renal composite* Rate=10.8/1000 patient years dapagliflozin vs. 14.1/1000 patient years placebo HR=0.76 (95% CI 0.67-0.87) *All cause mortality* 6.2% dapagliflozin vs. 6.6% placebo Rate=15.1/1000 person years dapagliflozin vs. 16.4/1000 person years placebo HR=0.93 (95% CI 0.82-1.04)

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				those with no history of heart failure=0.84 (95% CI 0.72-0.99), p for interaction=0.60 HR by eGFR ≥90=0.96 (95% CI 0.77-1.19) 60 to <90=0.79 (95% CI 0.66-0.95) <60=0.78 (95% CI 0.55-1.09) P for interaction=0.37 *MACE* 8.8% dapagliflozin vs. 5.8% placebo Rate=22.6/1000 patient years dapagliflozin vs. 24.2/1000 patient years placebo Met prespecified criterion for noninferiority (upper boundary of 95% CI <1.3, p<0.001) HR=0.93 (95% CI 0.84-1.03), p=0.17 for superiority HR ASCVD group=0.90 (95% CI 0.79-1.02) vs. HR=1.01 (95% CI 0.86-1.20) in multiple risk factors group, p for interaction=0.25 HR in those with history of heart failure=1.01 (95% CI 0.81-1.27), HR in those with no history of heart failure=0.92 (95% CI 0.82-1.02), p for interaction=0.46 HR by eGFR	*Cardiovascular death* 2.9% dapagliflozin vs. 2.9% placebo Rate=7.0/1000 patient years dapagliflozin vs. 7.1/1000 patient years placebo, HR=0.98 (95% CI 0.82-1.17) *noncardiovascular death* 2.5% dapagliflozin vs. 2.8% placebo Rate=6.0/1000 patient years dapagliflozin vs. 6.8/1000 patient years placebo, HR=0.88 (95% CI 0.73-1.06) Adverse Events *Serious adverse event, dapagliflozin vs. placebo (%)* 34.1% vs. 36.2%, HR=0.91 (95% CI 0.87-0.96), p<0.001 *AE leading to discontinuation of trial regimen* 0.7% vs. 1.0%, HR=0.68 (95% CI 0.49-0.95), p=0.01 *Major hypoglycemic event* 0.7% vs. 1.0%, HR=0.68 (95% CI 0.49-0.95), p=0.02 *Diabetic ketoacidosis* 0.3% vs. 0.1%, HR=2.18 (95% CI 1.10-4.30), p=0.02 *Amputation* 1.4% vs. 1.3%, HR=1.09 (95% CI 0.84-1.40), p=0.53 *Fracture*

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				≥90=0.94 (95% CI 0.80-1.10) 60 to <90=0.95 (95% CI 0.82-1.09) <60=0.92 (95% CI 0.69-1.23) P for interaction=0.99 *hospitalization for heart failure* 2.5% dapagliflozin vs. 3.3% placebo Rate=6.2/1000 patient year dapagliflozin vs. 8.5/1000 patient years placebo, HR=0.73 (95% CI 0.61-0.88) *myocardial infarction* 4.6% dapagliflozin vs. 5.1% placebo Rate=6.2/100 patient years dapagliflozin vs. 8.5//1000 patient years placebo, HR=0.89 (95% CI 0.77-1.01) *ischemic stroke* 2.7% dapagliflozin vs. 2.7% placebo Rate=6.9/1000 patient years dapagliflozin vs. 6.8/1000 patient year placebo, HR=1.01 (95% CI 0.84-1.21) *cardiovascular death* 2.9% dapagliflozin vs. 2.9% placebo Rate=7.0/1000 patient years dapagliflozin vs. 7.1/1000 patient years placebo, HR=0.98 (95% CI 0.82-1.17)	5.3% vs. 5.1%, HR=1.04 (95% CI 0.91-1.18), p=0.59 *Symptoms of volume depletion* 2.5% vs. 2.4%, HR=1.00 (95% CI 0.83-1.21), p=0.99 *Acute kidney injury* 1.5% vs. 2.0%, HR=0.69 (95% CI 0.55-0.87), p=0.002 *Genital infection* 0.9% vs. 0.1%, HR=8.36 (95% CI 4.19-16.68), p<0.001 *Urinary tract infection* 1.5% vs. 1.6%, HR=0.93 (95% CI 0.73-1.18), p=0.54 *Cancer* 5.6% vs. 5.7%, HR=0.99 (95% CI 0.87-1.12), p=0.83 *Bladder cancer* 0.3% vs. 0.5%, HR=0.57 (95% CI 0.35-0.93), p=0.02 *Breast cancer* 0.4% vs. 0.4%, HR=1.02 (95% CI 0.64-1.63), p=0.92 *Hypersensitivity* 0.4% vs. 0.4%, HR=0.87 (95% CI 0.54-1.40), p=0.57 *Hepatic event*

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					1.0% vs. 1.0%, HR=0.92 (95% CI 0.68-1.25), p=0.60
Hernandez et al, 2018 30291013	Study Aim To determine the safety and efficacy of albiglutide in preventing cardiovascular death, myocardial infarction, or stroke Study Type RCT N=9463	Inclusion criteria -aged 40 years or older -diagnosis of type 2 diabetes -established disease of the coronary (myocardial infarction, at least 50% stenosis in one coronary artery or more, or previous coronary revascularization), cerebrovascular (ischemic stroke, at least 50% carotid artery stenosis, or a previous carotid vascular procedure), or peripheral arterial circulation (intermittent claudication and an ankle to brachial index <0·9, non-traumatic amputation, or a previous peripheral vascular procedure) -glycated hemoglobin concentration of more than 7·0% (53 mmol per mole) Exclusion criteria -estimated glomerular filtration rate less than 30 mL/min per 1·73 m² -severe gastroparesis - previous pancreatitis or substantial risk factors for pancreatitis - a personal or family history of medullary carcinoma of the	Intervention Albiglutide 30-50 mg (n=4731) Comparison Placebo (n=4732)	1° endpoint composite outcome (death from cardiovascular causes, myocardial infarction, and stroke) 7% albiglutide vs. 9% placebo j Rate=4.57/100 person years albiglutide vs. 5.87/100 person years albiglutide HR=0.78 (95% CI 0.68-0.90), p for non-inferiority<0.0001, p for superiority=0.0006	2° endpoints Cardiovascular outcomes four-component composite (the primary composite, with the addition of urgent revascularization for unstable angina), the individual components of the primary endpoint the composite of cardiovascular death or hospital admission because of heart failure. Metabolic outcomes time to initiation of chronic insulin therapy time to the first occurrence of an important microvascular event changes in glycated hemoglobin and bodyweight proportion of participants who attained glycemic control without severe hypoglycemia and who gained less than 5% of their bodyweight by the end of the study. Safety outcomes change in blood pressure and heart rate

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
		thyroid or multiple endocrine neoplasia type 2 -a history of pancreatic neuroendocrine tumor - current use of a GLP-1 receptor agonist			change in eGFR adverse events of special interest, including development of prespecified malignancies (medullary thyroid cancer, pancreatic cancer, and hematological malignancies), pancreatitis, severe hypoglycemia, injection site reactions, immunological reactions, diabetic retinopathy, worsening renal function, and death from any cause <u>Results</u> *Expanded composite outcome* 8% albiglutide vs. 10% placebo Rate=5.06/100 person years albiglutide vs. 6.45/100 person years placebo HR=0.78 (95% CI 0.69-0.90), p=0.0005 *Death from cardiovascular causes* 3% albiglutide vs. 3% placebo Rate=1.61/100 person years albiglutide vs. 1.72/100 person years placebo HR=0.93 (95% CI 0.73-1.19), p=0.578 *Fatal or non-fatal myocardial infarction* 4% albiglutide vs. 5% placebo Rate=2.43/100 person years albiglutide vs. 3.26/100 person years placebo

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
					HR=0.75 (95% CI 0.61-0.90), p=0.578 *Fatal or non-fatal stroke* 2% albiglutide vs. 2% placebo Rate=1.25/100 person years albiglutide vs. 1.45/100 person years placebo HR=0.86 (95% CI 0.66-1.14), p=0.300 *Composite of death from cardiovascular causes or hospital admission for heart failure* 4% albiglutide vs. 5% placebo Rate=2.49/100 person years albiglutide vs. 2.92/100 person years placebo HR=0.85 (95% CI 0.70-1.04), p=0.113 *All cause mortality* 4% albiglutide vs. 4% placebo Rate=2.44/100 person years albiglutide vs. 2.56/100 person years placebo HR=0.95 (95% CI 0.79-1.16), p=0.644 Adverse events albiglutide vs. placebo *Severe hypoglycemia* 1% vs. 1%, RR=0.56 (95% CI 0.36-0.87) *Pancreatitis*

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
					<1% vs. <1%, RR=1.43 (95% CI0.54-3.75) *Injection site reactions* 2% vs. 1%, RR=2.96 (95% CI 1.95-4.51) *Thyroid cancer* 0% vs. 0% *Hematological neoplasia* <1% vs. <1%, RR=1.80 (95% CI 0.60-5.36) *Pancreatic cancer* <1% vs. <1%, RR=1.20 (95% CI 0.37-3.93) *Hypersensitivity syndrome or symptoms* 1% vs. 1%, RR=0.94 (95% CI 0.63-1.40) *Hepatobiliary disorders* 1% vs. 1%, RR=0.94 (95% CI 0.63-1.40) *Alanine aminotransferase of at least 3 times the ULN* <1% vs. 1%, RR=0.57 (95% CI 0.31-1.03) *Alanine aminotransferase of at least 5 times the ULN* <1% vs. <1%, RR=0.35 (95% CI 0.14-0.89)

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
					Bilirubin of at least twice the ULN <1% vs. <1%, RR=1.71 (95% CI 0.68-4.35) *Serious gastrointestinal events* 2% vs. 2%, RR=1.06 (95% CI 0.79-1.41) *Appendicitis* <1% vs. <1%, RR=0.37 (95% CI 0.10-1.41) *Atrial fibrillation or flutter* 2% vs. 3%, RR=0.82 (95% CI 0.64-1.06) *Pneumonia* 3% vs. 3%, RR=0.95 (95% CI 0.75-1.20) *Renal impairment* 6% vs. 7%, RR=0.87 (95% CI 0.75-1.02) *Diabetic retinopathy* 2% vs. 2%, RR=0.88 (95% CI 0.65-1.18)
Zelniker et al., 2018 30424892	Study Aim to combine data from all the large-scale placebo-controlled cardiovascular outcome trials of SGLT2i to gain more reliable estimates of the efficacy	Inclusion criteria -randomized, placebo-controlled, cardiovascular outcome trials of SGLT2i published up to Sept 24, 2018	Intervention SGLT2i Comparison Placebo	1° endpoint Efficacy endpoints Major adverse cardiovascular events (the composite of myocardial infarction, stroke, or cardiovascular death), the composite of cardiovascular death or	

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
	and safety of specific outcomes overall and in relevant subgroups. Study type Systematic review and meta analysis N=3 trials (34,322 patients)			hospitalization for heart failure, their individual components, and a standardized composite of renal outcomes including worsening eGFR, end-stage renal disease, or renal death. Safety endpoints non-traumatic lower limb amputations, fractures, and diabetic ketoacidosis. Results *Major adverse cardiovascular events composite* Patients with atherosclerotic cardiovascular disease: HR=0.86 (95% CI 0.80-0.93), p=0.0002 Patients with multiple risk factors: HR=1.00 (95% CI 0.87-1.16), p=0.98 Patients with eGFR <60 mL/min per m^2 HR=0.82 (95% CI 0.70-0.95), p=0.0077 Patients with eGFR 60 to <90 mL/min per m^2 HR=0.91 (95% CI 0.82-1.00), p=0.0520 Patients with eGFR ≥90 mL/min per m^2 HR=0.94 (95% CI 0.82-1.07), p=0.35 *Hospitalization for heart failure and cardiovascular death*	

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
				Patients with atherosclerotic cardiovascular disease: HR=0.76 (95% CI0.69-0.84), p<0.0001 Patients with multiple risk factors: HR=0.84 (95% CI 0.69-1.01), p=0.0634 Patients with history of heart failure: HR=0.71 (95% CI 0.61-0.84), p<0.0001 Patients with no history of heart failure: HR=0.79 (95% CI 0.71-0.88), p<0.0001 Patients with eGFR <60 mL/min per m^2 HR=0.60 (95% CI 0.47-0.77), p<0.0001 Patients with eGFR 60 to <90 mL/min per m^2 HR=0.69 (95% CI 0.57-0.83), p<0.0001 Patients with eGFR ≥90 mL/min per m^2 HR=0.88 (95% CI 0.68-1.13), p=0.31 *Composite of renal worsening, end stage renal disease, or renal death* Patients with atherosclerotic cardiovascular disease HR=0.56 (95% CI 0.47-0.67), p<0.0001 Patients with multiple risk factors HR=0.54 (95% CI 0.42-0.71), p<0.0001 Patients with eGFR <60 mL/min per m^2 HR=0.67 (95% CI 0.51-0.89), p=0.0054	

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
				Patients with eGFR 60 to <90 mL/min per m^2 HR=0.56 (95% CI 0.46-0.70), p<0.0001 Patients with eGFR ≥90 mL/min per m^2 HR=0.44 (95% CI 0.32-0.59), p<0.0001	
EMPA-REG Zinman et al., 2015 26378978	Study Aim To examine the effects of empagliflozin, as compared with placebo, on cardiovascular morbidity and mortality in patients with type 2 diabetes at high risk for cardiovascular events who were receiving standard care Study Type RCT N=7020	Inclusion criteria type 2 diabetes were adults (≥18 years of age) with a body-mass index of 45 or less and an estimated glomerular filtration rate (eGFR) of at least 30 ml per minute per 1.73 m2 of body-surface area, according to the Modification of Diet in Renal Disease criteria. All the patients had established cardiovascular disease (as defined in Section C in the Supplementary Appendix) and had received no glucose-lowering agents for at least 12 weeks before randomization and had a glycated hemoglobin level of at least 7.0% and no more than 9.0% or had received stable glucose-lowering therapy for at least 12 weeks before randomization	Intervention Empagliflozin (10 mg or 25 mg) Comparison Placebo	1° endpoint Composite (death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke) Results 12.1% placebo vs. 10.5% empagliflozin Rate=43.9/1000 patient year placebo vs. 37.4/1000 patient years empagliflozin HR=0.86 (95% CI 0.74-0.99), p=0.04 for superiority, p<0.001 for noninferiority p≥0.20 for interaction terms on sex, blood pressure control, estimated glomerular filtration rate, urine albumin-to-creatinine ratio, cardiovascular risk, insulin, statins or ezetimibe, antihypertensive therapy, ACE inhibitor or ARB, beta blocker, and diuretic P<0.20 for interaction terms on age, race, glycated hemoglobin, and BMI	2° endpoints composite of the primary outcome plus hospitalization for unstable angina *Composite (plus hospitalization for unstable angina)* 14.3% placebo vs. 12.8% empagliflozin Rate=52.5/1000 patient years placebo vs. 46.4/1000 patient years empagliflozin HR=0.89 (95% CI 0.78-1.01), p<0.001 noninferiority, p=0.08 superiority *Death from cardiovascular causes* 5.9% placebo vs. 3.7% empagliflozin Rate=20.2/1000 patient year placebo vs. 12.4/1000 patient years empagliflozin HR=0.62 (95% CI 0.49-0.77), p<0.001 p≥0.20 for interaction terms on age, sex, race, glycated hemoglobin, blood pressure control, urine albumin-to-creatinine ratio, cardiovascular risk, insulin, statins or ezetimibe, antihypertensive therapy, ACE inhibitor or ARB, Beta-blocker, or diuretic p<0.20 for interaction terms on BMI and estimated glomerular filtration rate

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
		and had a glycated hemoglobin level of at least 7.0% and no more than 10.0%.			*Death from any cause* 8.3% placebo vs. 5.7% empagliflozin Rate=28.6/1000 patient year placebo vs. 19.4/1000 patient year empagliflozin HR=0.68 (95% CI 0.57-0.82), P<0.001 *Hospitalization for heart failure* 4.1% placebo vs. 2.7% empagliflozin Rate=14.5/1000 placebo vs. 9.4/1000 patient years empagliflozin HR=0.65 (95% CI 0.50-0.85), p=0.002 Fatal or nonfatal myocardial infarction excluding silent myocardial infarction HR=0.87 (95% CI 0.70-1.09), p=0.23 Nonfatal myocardial infarction excluding silent myocardial infarction HR=0.87 (95% CI 0.70-1.09), p=0.22 Silent myocardial infarction HR=1.28 (95% CI 0.70-2.33), p=0.42 Hospitalization for unstable angina HR=0.99 (95% CI 0.74-1.34), p=0.97 Coronary revascularization procedure HR=0.86 (95% CI 0.72-1.04), p=0.11 Fatal or nonfatal stroke HR=1.18 (95% CI 0.89-1.56), p=0.26 Nonfatal stroke HR=1.24 (95% CI 0.92-1.67), p=0.16

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
					Transient ischemic attack HR=0.85 (95% CI 0.51-1.42), p=0.54 Hospitalization for heart failure HR=0.65 (95% CI 0.50-0.85), p=0.002 Hospitalization for heart failure or death from cardiovascular causes excluding fatal stroke HR=0.66 (95% CI 0.55-0.79), p<0.001 Adverse Events (placebo vs. empagliflozin 10 mg vs. empagliflozin 25 mg) Any adverse event: 91.7%, 90.1%, 90.4% Severe adverse event: 25.4%, 22.9%, 24.1% Serious adverse event (any): 42.3%, 37.4%, 39.0% Serious adverse event (death): 5.1%, 4.1%, 3.4% Adverse event leading to discontinuation of a study drug: 19.4% vs. 17.7% vs. 17.0% Confirmed hypoglycemic adverse event (any): 27.9% vs. 28.0% vs. 27.6% Confirmed hypoglycemic adverse event (requiring assistance): 1.5% vs. 1.4% vs. 1.3% Event consistent with urinary tract infection (male): 9.4% vs. 10.9% vs. 10.1%

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 value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
					Event consistent with urinary tract infection (female): 40.6% vs. 35.5% vs. 37.3% Complicated urinary tract infection (1.8% vs. 1.4% vs. 2.0% Event consistent with genital infection (male patients): 1.5% vs. 5.4% vs. 4.6% Event consistent with genital infection (female patients): 2.6% vs. 9.2% vs. 10.8% Event consistent with volume depletion: 4.9% vs. 4.9% vs. 5.3% Acute renal failure: 6.6% vs. 5.2% vs. 5.3% Acute kidney injury: 1.6% vs. 1.1% vs. 0.8% Diabetic ketoacidosis: <0.1% vs. 0.1% vs. <0.1% Thromboembolic event: 0.9% vs. 0.4% vs. 0.9% Bone fracture: 3.9% vs. 3.9% vs. 3.7%

Data Supplement 11. RCTs of High Blood Cholesterol (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
Baigent C, et al., 2010 (19) 21067804	Aim: To evaluate safety and efficacy of more intensive lowering of LDL cholesterol Study type: Individual patient-level meta-analysis of 26	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.	Intervention/Comparator: 1. Statin (n= 64744)/ placebo (n= 64782) [21 trials] 2. More (high) [n=19829] /less intense statin	Endpoints: Statin (S) / Placebo (P): Average LDL-C difference between statin and placebo = 1.07 mmol/L*	• 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)

	randomized trials of statin therapy Size: 170000 participants from 26 randomized trials of statin therapy	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% (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).	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) 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.	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). 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	-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 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).

				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). <u>Safety endpoint (if relevant)</u>: -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)].	●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 <u>≤</u>65 y, >65 y to <u>≤</u>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, GREACE) not available and therefore, not included.

				-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).	

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
Silverman MG, et al., 2016 27673306	Aim: To evaluate association between LDL cholesterol lowering and relative cardiovascular risk reduction employing statin and non-statin therapies Study type: Meta-analysis of RCT's Size: N=312,175	Inclusion criteria: 49 RCT's of 9 different approaches to LDL-C reduction with reported ASCVD outcomes that included myocardial infarction Exclusion criteria: RCT's of <6 mo duration or with fewer than 50 clinical events	Intervention/comparator: Drug vs. placebo	1^{o}endpoint: 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 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:	Limitations: PCSK9 inhibitor outcome trial results were not available to be included in the results of this study

				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 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 Study Design: Double blind placebo controlled RCT Size: N= 6595	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 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	Intervention/comparator: Pravastatin 40 mg daily vs. placebo over a mean follow-up period of 4.9 y	1^{o} 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. 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%)	2^{o} 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: 3-53%, 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

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 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 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 Exclusion criteria:	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: • The trial was terminated 2 y earlier than expected (median duration 3.9 y) because efficacy had been met	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; p=NR

	Study type: Randomized double-blind placebo-controlled clinical trial Size: 2,838	• 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%	• 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	• 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 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 • uncontrolled arrythmia	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) • Differences in LDL-C between treatment	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] ○ Placebo: 151(11.9%) [39.1]

	Study type: Randomized double-blind placebo controlled clinical trial Size: 10,305 subjects of whom 2532 had T2DM	• 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	groups not provided for diabetes subgroup	study trial secondary outcome, namely total CVD events	○ 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 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 ○ >65 y n=332 (35%)	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 • Placebo 1

	Size: 2,410 subjects with T2DM. 505 had CVD and 1,905 did not	○ diabetes duration 8 y ○ hypertension; 55% • Placebo: • mean age 60.4 y • >65 y n=305 (32%) • DM duration 8 y • hypertension; 53%			
de Vries FM, et al., 2012 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
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

AFCAPS-TEXCAPS Downs JR, et al., 1998 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 endpoint 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
SHARP Baigent C, et al., 2011 21663949	Aim: To assess safety and efficacy of reducing LDL in persons with CKD Placebo vs. simvastatin 20mg + ezetimibe 10 mg daily	Inclusion criteria: • Age ≥40, Cr 1.7 men, 1.5 women, With or without dialysis • Total randomized: 9,438 Exclusion criteria:	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	• lack of power for dialysis subgroup • Crossover: 33% discontinued intervention, 14% in placebo started non-statin therapy • Few persons on peritoneal dialysis

	Study type: RCT Size: 9,270 randomized Study duration: 4 y (median 4.9 y)	• 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		• 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 • Note: 34% transitioned to ESRD during the trial	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
Cholesterol Treatment Trialists' (CTT) Collaboration* Herrington WG, et al., 2016 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	• 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

				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)	
Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastain (JUPITER) Ridker et al, 2016 26916794	Aim: assess relationship of per cent reduction in LDLC with clinical outcomes in a contemporary randomized trial of rosuvastatin 20 mg when compared with placebo in the primary prevention of cardiovascular events Study type: RCT (secondary analysis) Size: 17.082	Inclusion criteria: •asyptomatic •Women ≥60 years •Men ≥50 years •LDLC <130 mg/dL •hsCRP≥2.0 mg/L •triglycerides <500 mg/dL Exclusion criteria: •history of CVD, diabetes, or use of lipid lowering therapy	Intervention: rosuvastatin 20 mg daily Comparator: placebo	1° endpoint: Composite endpoint of first occurrence of non-fatal myocardial infarction, non-fatal stroke, hospitalization for unstable angina, arterial revascularization, or cardiovascular death Results: *By LDLC reduction:* significant trend by group in incidence (p for trend<0.000001), and relationship between percent reduction in group on active rosuvastatin p=0.01. Placebo: 11.2 per 1000 person years (95% CI 9.7-12.9) No LDL reduction: 9.2 per 1000 person years (95% CI 5.6-15.3) (HR vs placebo=0.91, 95% CI 0.54-1.53), LDL reduction <50%: 6.7 per 1000 person years (95% CI 5.1-8.9) (HR vs placebo=0.61, 95% CI 0.44-0.83)	

				LDL reduction ≥50%: 4.8 per 1000 person years (95% CI 3.5-6.6) (HR vs placebo=0.42, 95% CI 0.30-0.60) *By non-HDLC reduction: significant trend by group in incidence (p for trend <0.000001)* , and relationship between percent reduction in group on active rosuvastatin p=0.046 Placebo: 11.1 per 1000 person years (95% CI 9.6-12.8) No Non-HDLC reduction: 10.0 per 1000 peson years (95% CI 6.1-16.3) (HR vs. placebo=0.99, 95% CI 0.60-1.66) Non-HDLC reduction <50%: 6.0 per 1000 person years (95% CI 4.7-7.6) (HR vs placebo 0.54, 95% CI 0.41-0.71) Non-HDLC reduction ≥50%: 5.2 per 1000 person years (95% CI 3.6-7.7) (HR vs placebo 0.46, 95% CI 0.31-0.70) By apolipoprotein B reduction: significant trend by group in incidence (p for trend, p<0.000001) , and relationship between percent reduction in group on active rosuvastatin p=0.024 Placebo: 11.0 per 1000 person years (95% CI 9.6-12.8)	

				No apoB reduction: 11.9 per 1000 person years (95% CI 7.0-20.1) (HR vs placebo 1.14, 95% CI0.66-1.97) <50% apoB reduction: 5.7 per 1000 person years (95% CI 4.6-7.2) (HR vs placebo=0.51, 95% CI0.39-0.67) ≥50% apoB reduction: 4.7 per 1000 person years (95% CI 2.8-7.9) (HR vs placebo=0.43, 95% CI 0.25-0.75)	
Taylor et al., 2013 23440795	Study Aim To assess the effects, both harms and benefits, of statins in people with no history of CVD Study Type N=18 trials	Inclusion criteria -randomized controlled trials of statins versus placebo or usual care control - minimum treatment duration of one year and follow-up of six months -adults (18 and older) - 10% or less had a 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 (HMG CoA reductase inhibitors) Comparator: placebo or usual care	1° endpoint: All cause mortality fatal and non-fatal CHD, CVD and stroke events; combined endpoint (fatal and non-fatal CHD, CHD and stroke events) change in blood total and low density lipoprotein cholesterol concentration revascularization adverse events quality of life costs Results *All cause mortality* 4.4% in statin vs. 5.1% in placebo. NNT for 5 years=96 (95% CI 64-244) OR=0.86 (95% CI 0.79-0.94). No heterogeneity observed. *Fatal and non-fatal CHD events*	Adverse Events 19% of all participants experienced an adverse event (range 0-97%). RR=1.00 (95% CI 0.97-1.03) *Cancer*: 5.8% of all participants. RR=1.01 (95% CI 0.93-1.10), no significant heterogeneity *Myalgia*: 3551/37939 participants RR=1.03 (95% CI 0.97-1.09), some heterogeneity (I^2=41%) *Rhabdomyolysis*: 3/19410 participants on statins RR=1.00 (95% CI 0.23-4.38) *Type 2 diabetes* 2.8% statins vs. 2.4% control/placebo. RR=1.18 (95% CI 1.01-1.39) *Hemorrhagic stroke* 0.2% of participants. RR=0.97 (95% CI 0.54-1.75) *Liver enzyme elevations*: RR=1.16 (95% CI 0.87-1.54)

				3.4% statin group vs. 4.6% placebo group. NNT for 5 years=56 (95% CI 46-75) RR=0.73 (95% CI 0.67-0.80) *Fatal CHD events* 1.1% statin vs. 1.3% placebo. RR=0.82 (95% CI 0.70-0.96). No significant heterogeneity observed. *Non-fatal CHD* 1.9% statin vs. 2.8%. RR=0.67 (95% CI 0.59-0.76). No significant heterogeneity observed. *Fatal and non-fatal CVD events* 9.3% statin vs. 12.2% placebo. RR=0.75 (95% CI 0.70-0.81). No evidence of significant heterogeneity. *Fatal CVD events* 17.4% statin vs. 20.8% placebo, RR=0.83 (95% CI 0.72-0.96). No significant heterogeneity. *Non-fatal CVD events* 3% statin vs. 4% placebo. RR=0.77 (95% CI 0.62-0.96). No significant heterogeneity. *Fatal and non-fatal stroke events* 17% statin group vs. 22% placebo group. RR=0.78 (95% CI 0.68-0.89) *Fatal stroke events* No observed difference. Significant heterogeneity (i^2=68%) *Non-fatal stroke events*	*Renal dysfunction*: RR=1.11 (95% CI 0.99-1.26) Arthritis: RR=1.20 (95% CI 0.82-1.75) *Treatment compliance*: 77% statins vs. 70% placebo. RR=1.08 (95% CI 0.98-1.18) *Quality of life* No reliable data

				1.3% statin vs. 2% placebo. RR=0.69 (95% CI 0.58-0.83) *Combined endpoint (fatal and non-fatal CHD, CHD and stroke events)* 2.4% statins vs. 3.8% placebo. RR=0.65 (95% CI 0.58-0.73) Cholesterol (total and low density lipoprotein cholesterol) Total cholesterol: net difference= -1.05 mmol/L (95% CI -1.35 to -0.76) (I^2=100%) LDL: net difference= -1.00 (95% CI -1.16 to -0.85). Heterogeneity (I^2=99%) *Revascularization* 1.4% statin vs. 2.2% placebo. RR=0.62 (95% CI 0.54-0.72)	
Heart Outcomes Prevention Evaluation (HOPE)–3 trial Yusuf et al., 2016 27040132	Study Aims evaluating the long-term effects of rosuvastatin at a dose of 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 N=12,705	Inclusion criteria 55 years of age or older (men) 65 years of age or older (women) (60+ for women with 2+ risk factors) At least one of the following cardiovascular risk factors: elevated waist-to-hip ratio, history of a low level of high-density lipoprotein cholesterol, current or recent tobacco use, dysglycemia, family history of premature coronary disease, and mild renal dysfunction	Intervention Rsuvastatin 10 mg per day without dose adjustment or lipid targets Comparison placebo	1° endpoint: composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke plus resuscitated cardiac arrest, heart failure, and revascularization Results *composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke*	2° endpoint: composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke plus resuscitated cardiac arrest, heart failure, revascularization, angina with evidence of ischemia all cause mortality new onset diabetes death from cardiovascular causes myocardial infarction stroke resuscitated cardiac arrest

		Exclusion criteria Cardiovascular disease an indication for or contraindication to statins, angiotensin-receptor blockers, angiotensin-converting–enzyme inhibitors, or thiazide diuretics		3.7% rosuvastatin vs. 4.8% placebo. HR=0.76 (95% CI 0.64-0.91), p=0.002 *composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke plus resuscitated cardiac arrest, heart failure, and revascularization* 4.4% rosuvastatin vs. 5.7% placebo. HR=0.75 (95% CI 0.64-0.88), p<0.001 Total number of events (first and recurrent). HR=0.75 (95% CI 0.64-0.89), p=0.001	revascularization heart failure angina with evidence of ischemia <u>Results</u> *composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke plus resuscitated cardiac arrest, heart failure, revascularization, angina with evidence of ischemia* 4.8% rosuvastatin vs. 6.2% placebo. HR=0.77 (95% CI 0.66-0.89), p<0.001 *all cause mortality* 5.3% rosuvastatin vs. 5.6% placebo. HR=0.93 995% CI 0.80-1.08), p=0.32 *new onset diabetes* 3.9% rosuvastatin vs. 3.8% placebo. HR=1.02 (95% CI 0.85-1.23), p=0.82 *death from cardiovascular causes* 2.4% rosuvastatin vs. 2.7% placebo. HR=0.89 (95% CI 0.72-1.11) *myocardial infarction* 0.7% rosuvastatin vs. 1.1% placebo. HR=0.65 (95% CI 0.44-0.94) *stroke*

					1.1% rosuvastatin vs. 1.6% placebo. HR=0.70 (95% CI 0.52-0.95) *resuscitated cardiac arrest* 0.1% rosuvastatin vs. 0.1% placebo. HR=0.99 (95% CI 0.25-3.97) *revascularization* *0.9%* rosuvastatin vs. 1.3% placebo. HR=0.68 (95% CI 48-0.95) *heart failure* *0.3%* rosuvastatin vs. 0.5% placebo. HR=0.72 (95% CI 0.41-1.26) *angina with evidence of ischemia* 0.9% rosuvastatin vs. 1.0% placebo. HR=0.87 (95% CI 0..61-1.24) *Coronary heart disease* 1.7% rosuvastatin vs. 2.2% placebo. HR=0.74 (95% CI 0.58-0.96). p=0.02 *Hospitalizations for cardiovascular causes* 4.4% rosuvastatin vs. 5.8% placebo. HR=0.75 (95% CI 0.64-0.88), p<0.001 *Hospitalizations for noncardiovascular causes* 13.9% rosuvastatin vs. 13.9% placebo. HR=1.00 (95% CI 0.91-1.10), p=0.99

Chou et al, 2016 27905702	**Study Aim** To assess the benefits of treatment with statins that target LDL-C versus other treatment strategies in adults age 40 years or older without prior CVD events (one review in a larger report with 5 study questions) **Study Type** Systematic Review, including meta analysis of some parameters N=19 studies (71,344 patients)	**Inclusion criteria** RCTs Asymptomatic adults (age ≥40 years) without prior CVD events (e.g., myocardial infarction, angina, revascularization, CVA, or transient ischemic attack), including persons who are at increased risk for CVD events based on 10-year or lifetime individualized CVD risk level or presence of specific CVD risk factors Treatment with statins vs. No treatment or usual care without statin Examined CHD and/or CVA-related morbidity or mortality; all-cause mortality Primary care or primary care–generalizable	**Intervention** Statins **Comparison** No treatment or usual care without statin	**1° endpoint** CHD and/or CVA-related morbidity or mortality; all-cause mortality *Findings* No study directly compared treatment with statins titrated to attain target cholesterol levels vs. other treatment strategies. There were no clear differences in risk of all-cause or CV mortality, MI, or stroke between 3 trials of statins vs. placebo or no statin that permitted limited dose titration and 16 trials of fixed-dose statin therapy. This finding was rated as being consistent, having high applicability to US primary care settings, but was limited by lack of direct evidence (all studies were evaluated as providing indirect evidence), and limited indirect evidence from 3 trials, and were of poor overall quality Meta analyses of statins vs. placebo (presented for separate questions in same review): All-Cause Mortality RR=0.86 (95% CI 0.80-0.93). I^2 =0% Cardiovascular Mortality RR=0.69 (95% CI 0.54-0.88). I^2 =54% Fatal and nonfatal stroke RR=0.71 (95% CI 0.62-0.82). I^2 =0% Fatal and nonfatal myocardial infarction	**Summary** No study directly compared treatment with statins titrated to attain target cholesterol levels versus other (e.g., fixed-dose) treatment strategies. There were no clear differences in risk of all-cause or cardiovascular mortality, MI, or stroke between three trials of statins versus placebo or no statin that permitted limited dose titration and 15 trials of fixed-dose statin therapy

				RR=0.64 (95% CI 0.57-0.71) I^2 =0% Revascularization RR=0.63 (95% CI 0.56-0.72) I^2 =0% Composite Cardiovascular Outcomes RR=0.70 (95% CI 0.63-0.78) I^2 =36%	
CTT Cholesterol Treatment Trialists' Collaborators, 2012 22607822	**Study Type:** Metaanalysis 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 2y.	**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)	N/A

Data Supplement 12. Nonrandomized Trials, Observational Studies, and/or Registries of High Blood Cholesterol (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)
Perak, AM, et al., 2016 (20) 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	1^{O}endpoint: 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%	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.

		LDL-C ≥ 190 mg/dL and referent <130 mg/dL Exclusion criteria: N/A	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)	2. Single measurement of LDL-C for inclusion 3. Secondary hypercholesterolemia was not excluded. 4. Limited family data available
Besseling J, et al., 2016 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.	1^{o}endpoint: 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 0.56 (95% confidence interval: 0.33 to 0.96).	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.
Rana JS, et al., 2016 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	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)	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

	Size: 1,586,061 adults of whom 138,507 had diabetes (ICD code diagnosis)		women 8.8 (95% CI: 8.58–9.14) • By age subgroups; - 40-49 y (n=19,746); men 9.0, 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)	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 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
Mulnier HE, et al., 2008 18581091	Study type: Prospective case- control observational cohort study Design: • 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	Inclusion criteria: • Men and women aged 35-89 y • Free of CHD Baseline characteristics: • 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	1° endpoint: 7 y Incident MI Results: Incident MI: rate/1000 pt. y (95% CI) over mean follow-up of 7 y • 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)	• 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 • 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

	Size: 40,727 subjects with and 194,913 without DM		○ 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)	
FHS, MESA, CHS Yano Y, et al., 2017 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. • 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.	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.
BioImage Mortensen MB, et al., 2016 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 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	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	

		optional to statin eligibility if CAC was ≥100		
General Practice Research Database (GPRD) Soedamah-Muthu et al, 2006 16567818	Aim: To estimate the absolute and relative risk of cardiovascular disease (CVD) in patients with type 1 diabetes in the U.K. Study Type: Prospective cohort Size: N=45,595	Inclusion criteria: • ≥6 months of data before January 1 1992 • Diagnosis of Type I diabetes (n=7479) or nondiabetic comparison group (n=38,116) (5 age and sex matched control per diabetic patient) or CVD Exclusion criteria: •	1° Endpoint: Cumulative incidence of a first major incident CVD event in Type 1 diabetic patients vs. comparison patients=3% vs. 0.76%. HR=4.5 (95% CI 3.8-5.4) *Acute Coronary Events* • Men; HR=3.0 (95% CI 2.2-4.1) • Women; HR=7.6 (95% CI 4.9-12.0) *Coronary revascularizations* • Men; HR=5.0 (95% CI 3.2-7.8) • Women; HR=16.8 (95% CI 7.3-37.5) *Stroke (fatal and non-fatal)* • Men, HR=3.7 (95% CI 2.6-5.3) • Women; HR=4.8 (95% CI 3.0-7.9) *Major CHD* • Men; HR=3.6 (95% CI 2.8-4.6) • Women; HR=9.6 (95% CI 6.4-14.5) *Fatal CVD* • Men; HR=5.8 (95% CI 3.9-8.6) • Women; HR=11.6 (95% CI 6.7-20.1) • Type I diabetic patients reach a 10-year risk of fatal CVD≥5% around 50 years of age vs. 60 years of age in nondiabetic comparison group (data presented in graph) *Major CVD* HR men vs. women=1.3 (95% CI 1.0-1.7, p=0.07) in type I patients vs. 2.6 (95% CI 2.0-3.4, p<0.0001) in nondiabetic comparison patients. Significant interaction between diabetes and gender (likelihood ratio test, p=0.0007) Men	Summary: • Increased risks of CVD morbidity and mortality were observed in patients with type 1 diabetes compared with those without diabetes. Increased risks were reached in patients with type 1 diabetes at a much younger age compared with nondiabetic patients Limitations: • Potential for loss to follow up

			• Overall HR=3.6 (95% CI 2.9-4.5) • Age: ≤35 HR=11.3 (95% CI 2.9-43.8) 35-45 HR=4.4 (95% CI 2.5-7.6) 45-55 HR=3.0 (95% CI 1.9-4.8) 55-65 HR=4.1 (95% CI 2.8-6.0) 65-75 HR=2.3 (95% CI 1.3-4.1) >75 HR=3.5 (95% CI 1.6-7.3) Women • Overall; HR=7.7 (95% CI 5.5-10.7) • Age ≤35 HR=9.8 (95% CI 1.8-53.6) 35-45 HR=15.4 (95% CI 5.0-47.3) 45-55 HR=10.1 (95% CI 5.0-20.4) 55-65 HR=5.7 (95% CI 3.2-10.4) 65-75 HR=8.3 (95% CI 4.0-17.2) >75 HR=4.0 (95% CI 1.4-11.2) *Major Coronary Events* Men: HR=1.3 (95% CI 0.9-1.7, p=0.2) Women; HR=3.0 (95% CI 2.1-4.2, p<0.0001) Significant interaction between diabetes and gender where gender difference was only found in those without diabetes (likelihood ratio p=0.0001)	
Willeit et al, 2014 25169167	Aim: To determine wether Lp(a) improves CVD risk prediction Study Type: Prospective cohort Size: N=826	Inclusion criteria: • Residents of Bruneck, Italy Exclusion criteria:	1° Endpoint: • Composite CVD endpoint of vascular death (ischemic stroke, myocardial infarction, sudden cardiac death, aortic aneurysm rupture), acute CAD (nonfatal MI, new onset unstable angina, crescendo angina or new onset severe angina, acute coronary interventions) and ischemic stroke ascertained 1995-2010 Mean Lp(a) No CVD No vs Yes CVD=23.3 vs. 39.1, p<0.001 High Lp(a) (>45 mg/dL) No CVD vs Yes CVD=16.8% vs 34.5%, p<0.001	Summary: • adding Lp(a) to the Framingham Risk Score and Reynolds Risk Score improves discrimination and reclassification of CVD risk in 15-year follow-up in a general population, particularly in those of intermediate risk.

			Overall incidence=15.0 per 1,000 person years (95% CI 12.8-17.7) Highest quintile of Lp(a) vs reminder adjusted for age and sex HR=2.34 (95% CI 1.67-3.29, p<0.001). HR per 1 SD higher level of Lp(a)=1.38 (95% CI 1.23-1.56; p<0.001). HRs remained significant after adjustment for remaining Framingham Risk Score variables, Reynolds risk Score Variables, and for apo(a) isoform major allele *Discrimination*: Addition of Lp(a) to Framingham model improved C-index by 0.0165 (95% CI 0.0019-0.0308, p=0.027). Replacement of "total" Lp(a) with allele-specific Lp(a) levels associated with low- versus high-molecular-weight apo9a) isoforms did not further increase C-index. C index for Reynolds Risk Score was 0.762 (95% CI 0.725-0.798); addition of Lp(a) improved C-index by 0.0155 (95% CI 0.0014-0.0297, p=0.031) Net Reclassification Improvement in those at intermediate risk (15-<30%) was 22.5% for noncases (95% CI 10.6-34.4) and 17.1% for cases (95% CI -1.4-35.6), and 39.6% overall (95% CI 17.6-61.6)). Analogous statistics in participations without diabetes are 18.9% in noncases (95% CI 6.1-31.7), 13.9% in cases (-5.7-33.5), and 32.8% overall (9.3-56.2). Allele specific Lp(a) levels did not add to predictive ability of Framingham Risk Score, Reynolds Risk Score, or Lp(a)	
MESA Malik et al, 2017 29117273	Aim: To compare improvement in long-term prognostication of incident CHD and ASCVD using	Inclusion criteria: • Ages 45-84 • No known CVD • White, African American, Hispanic, Chinese	1° Endpoint: Incident CHD events (MI, resuscitated cardiac arrest, CHD death) 2° Endpoint:	Summary: • addition of CAC score to global risk assessment was associated with significantly improved risk classification in those with MetS

	CAC scores among those with diabetes, MetS, or neither condition Study Type: Prospective cohort Size: N=6814	Exclusion criteria: •	ASCVD (CHD events and fatal or nonfatal stroke) • Mean follow up time of 11.1 years • In each group, stepwise increase in CHD and ASCVD events with increasing severity of CAC score CHD *Diabetes Group* HR CAC 1-99 vs CAC 0=2.13 (95% CI 1.13-4.73) HR CAC 100-399 vs CAC 0=3.52 (95% CI 1.66-7.46) HR CAC ≥400 vs CAC 0=5.60 (95% CI 2.79-11.23) *MetS without diabetes Group* HR CAC 1-99 vs CAC 0=2.63 (95% CI 1.46-4.73) HR CAC 100-399 vs CAC 0=5.43 (95% CI 3.03-9.74) HR CAC ≥400 vs CAC 0=6.42 (95% CI 3.38-12.2) *Group with neither diabetes nor MetS* HR CAC 1-99 vs CAC 0=2.33 (95% CI 1.44-3.78) HR CAC 100-399 vs CAC 0=5.07 (95% CI 3.11-8.27) HR CAC ≥400 vs CAC 0=7.87 (95% CI 4.74-13.08) ASCVD *Diabetes Group* HR CAC 1-99 vs CAC 0=1.64 (95% CI 0.98-2.77) HR CAC 100-399 vs CAC 0=2.51 (95% CI 1.44-4.35) HR CAC ≥400 vs CAC 0=3.48 (95% CI 2.06-5.86) *MetS without diabetes Group* HR CAC 1-99 vs CAC 0=1.87 (95% CI 1.21-2.90) HR CAC 100-399 vs CAC 0=2.81 (95% CI 1.78-4.45) HR CAC ≥400 vs CAC 0=3.16 (95% CI 1.91-5.22)	and diabetes, even if diabetes duration was longer than a decade Limitations: • CAC measurements are from baseline, not time-varying

			Group with neither diabetes nor MetS HR CAC 1-99 vs CAC 0=1.89 (95% CI 1.32-2.72) HR CAC 100-399 vs CAC 0=3.23 (95% CI 3.19-4.77) HR CAC ≥400 vs CAC 0=3.88 (95% CI 2.57-5.85) Discrimination: Diabetes group: NRI=0.23 (95% CI 0.10-0.37, p<0.001) MetS group: NRI=0.22 (95% CI 0.09-0.35) Neither diabetes nor MetS group: NRI=0.25 (95% CI 0.15-0.35)	
Sniderman et al, 2011 21487090	Aim: to determine the overall balance of the evidence comparing the standardized RRRs of apoB, non-HDL-C and LDL-C Study Type: Meta analysis Size: N=12 reports (233,455 subjects)	Inclusion criteria: • Studies reporting risks of non-HDL-C and apoB Exclusion criteria:	1° Endpoint: • apoB: RRR=1.43 (95% CI 1.35-1.51) p<0.001 • non-HDL-C RRR=1.34 (95% CI 1.24-1.44) p<0.001 • LDL-C RRR=1.25 (95% CI 1.18-1.33) p<0.001 • Overall, apoB RRR was 5.7% higher than non-HDL-C RRR (95% CI 2.4-9.1%, p<0.001). On average RRR of non-HDL-C was 5.0% greater than LDL-C RRR (95% CI 0.9% to 9.1!, p=0.017). On average RRR of apoB was 12.0% greater than RRR of LDL-C (95% CI 8.5% to 15.4%, p<0.0001). • Meta regression indicated no significant impact of year of publication (p=0.49), mean age (p=0.60), range of apoB (p=0.48), but there was a significant difference of mean HDL-C concentrations (HDL-C concentrations negatively associated with size of difference in RRR between apoB and non-HDL-C, p=0.064, R^2=0.565) • No significant evidence of publication bias	Summary: • apoB was the most accurate marker of cardiovascular risk, followed by non-HDL-C, which was followed by LDL-C • Authors calculate that over a 10-year period, using non-HDL-C as a marker would prevent 300,000 more events in the US than LDL-C, and using apoB would prevent 500,000 more events than a non-HDL-C strategy
Wong ND, et al., 2012 22377485	**Study type**: Cross sectional cohort analysis **Design**: Assessment of	**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:**	**Summary:** • 75% of subjects without CVD were at intermediate or high risk. • A minority of adults with T2DM and about

	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		• Among those without pre-existing CVD 27% had <10%, 23% had 10-20% and 50% had >20% 10 y risk. • Age subgroups: o 40-49 y, low risk 47%; high risk 15% o 50-59 y, low risk 17%; high risk 33% o 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.	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.
Khera AV, et al., 2016 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 LDLC ≥ 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	**1^{o}endpoint:** 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). 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	**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

			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., 2016 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.	**1^{o} endpoint**: 1-y risk of first recurrent coronary death or myocardial infarction after multivariable adjustment, assessed by telephone monitoring and by a followup 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 19001495	**Study Type:** Retrospective cohort study of 27 outpatient lipid clinics in the Netherlands. **Size:** 2146 patients	**Inclusion criteria:** Patients with phenotypic familial hypercholesterolemia identified in a Dutch cohort from 1/1/90 to 2002. Enrollees had to have no	**1^{o}endpoint:** Relative risk of myocardial infarction in statin treated patients and in those who were delayed in starting statin treatment compared with a Cox regression model in which statin use was a time dependent variable.	**Summary:** Statin therapy reduces incident myocardial infarction risk in subjects with familial hypercholesterolemia **Limitations:** 1. Possible selection bias favoring earlier treatment of patients with perceived higher

		documented coronary heart disease prior to 1/1/90. **Exclusion criteria:** Those with established coronary heart disease prior to 1/1/90.	**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).	risk. 2. Lack of placebo control 3. Intention to treat analysis was not employed
MESA Nasir K, et al., 2015 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; Not statin candidates (10-y predicted risk <5%): 1.62/1000 person-y, 95% CI: 1.2-2.3.	• 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
MESA Budoff, et al., 2018 29688297	Aim: to evaluate the contribution of CAC using the population-based MESA cohort with over 10 years of follow-up for ASCVD events, and whether the association of	Inclusion criteria: • Free of clinical cardiovascular disease • Age 45-84 at baseline • White, Black, Hispanic, Chinese	1° Endpoint: Total events: Incident ASCVD events (definite or probably MI, resuscitated cardiac arrest, fatal CHD, fatal and non-fatal stroke (not TIA), other atherosclerotic death, other CVD death) Hard ASCVD: MI, fatal or non-fatal strokes (not TIA), resuscitated cardiac arrest, fatal CHD	Summary: • CAC is consistently associated with risk with the same magnitude of effect in all races, age groups, both sexes, and in people on and off lipid lowering therapy Limitations:

	CAC with events varied by sex, race/ethnicity, or age category. Study Type: Prospective cohort Size: N=6814		• Median 11.1 years follow up At 10 years of follow-up, all participants with CAC> 100 were estimated to have >7.5% risk regardless of demographic subset Ten-year ASCVD event rates increase with increasing CAC overall and across race/ethnicity, age, sex, and education. 10 year ASCVD event rates in the CAC=0 group range from 1.3-5.6% vs. 13.1-25.6% in the CAC>300 group Hard ASCVD: • adjusting for CAC in multivariable models attenuated associations, but associations between age, sex, and race and Hard ASCVD outcomes were still significant. Doubling of CAC HR=1.14 (1.11-1.17, p<0.001) • association of CAC with risk of ASCVD did not vary by age, sex, race/ethnicity, or lipid lowering medication at baseline (p for interaction all non significant)	• Authors note a limitation in the use of electron beam tomography (EBT) and 4- and 16-detector CT systems

Data Supplement 13. RCTs of High Blood Pressure or Hypertension (Section 4.4.)

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
The Action to Control Cardiovascular Risk in Diabetes Study Group (2008) (21). 18539917	To examine whether intensive therapy to target normal glycated hemoglobin levels would reduce cardiovascular events in patients	Inclusion criteria • Type 2 diabetes • Glycated hemoglobin level of 7.5% or more • Either between ages 40-79 and had cardiovascular disease OR between ages 55 and 79 and had anatomical evidence of significant atherosclerosis,	Intervention: comprehensive intensive therapy targeting glycated hemoglobin level of less than 6.0% (n=5128)	1° endpoint First occurrence of nonfatal myocardial infarction or nonfatal stroke or death from cardiovascular causes (MI, heart failure, arrhythmia, invasive	2° endpoint All cause mortality All cause mortality: higher in intensive therapy group (5.0% vs 4.0%, HR=1.22, 95% CI 1.01-1.46, p-0.04)

	with type 2 diabetes who had either established cardiovascular disease or additional cardiovascular risk factors Study type: RCT N=10,251	albuminuria, left ventricular hypertrophy, or at least two of the following: dyslipidemia, hypertension, current smoker, or obesity <u>Exclusion criteria</u> • Frequent or recent serious hypoglycemic events • Unwillingness to do home gluose monitoring or inject insulin • BMI>45 • Serum creatinine level>1.5 mg per deciliter • Other serious illness	Comparison: standard therapy targeting glycated hemoglobin 7.0 (n=5123)	cardiovascular interventions, cardiovascular causes after noncardiovascular surgery, stroke, unexpected death presumed to be from ischemic cardiovascular disease occurring within 24 hours after onset of symptoms, death from other vascular disease) Rates of primary composite endpoint began to separate in the two groups after 3 years, but the trend was not significant (rate=6.9% in intensive therapy group and 7.2% in standard therapy group, HR=0.90, 95% CI 0.78-1.04, p=0.16). There was heterogeneity with patients who had not had a cardiovascular event before the study and those whose baseline glycated hemoglobin level was 8.0% or less having fewer events (p for interaction=0.04 and p for interaction=0.03, respectively) Nonfatal MI: lower in intensive therapy group	Adverse events: Intensive therapy group had significant higher rates of hypoglycemia (annualized rate of events requiring medical assistance=3.1% vs. 1.0% in standard therapy group), weight gain (3.5 kg at 3 years vs. 0.4 kg in standard therapy group), and fluid retention

				(3.6% vs 4.6%, HR=0.6, 95% CI 0.62-0.92, p=0.004) Death rate from cardiovascular causes: higher in intensive therapy group (2.6% vs 1.8%, HR=1.35, 95% CI 1.04-1.76, p=0.02). Non-fatal stroke: no significant difference, 1.3% in intensive therapy group vs. 1.2% in standard therapy group, HR=1.06, 95% CI 0.75-1.50, p-0.74)	
Appel LJ, et al., 1997 (22) 9099655	Aim: Study the effect of dietary patterns on BP Study type: • Multicenter RCT • 3 arm parallel design • 3 wk pre-randomization run-in phase • Feeding study with 8 wk of intervention Size: 459 adults, mean age 44 y. (326 normotensive)	Inclusion criteria: • Adults ≥22 y • SBP<160 mm Hg and DBP 80–95 mm Hg • No antihypertensive medication Exclusion criteria: • CVD event within 6 mo • Poorly controlled DM or hyperlipidemia • BMI ≥35 • Pregnancy or lactation • Chronic illness that would interfere with participation • Unwillingness to stop taking vitamins, mineral supplements, Ca++ Antacids • Consuming ≥14 alcoholic drinks with Renal insufficiency	Intervention: • Diet high in fruits and vegetables • "Combination" diet high in fruits, vegetables, low-fat dairy products, and reduced total fat, saturated fat and cholesterol. Comparator: Usual U.S. diet	1 endpoint: Compared to the control diet, both intervention diets reduced BP, with an overall mean (95% CI) reduction of: •Fruits and Veg. Diet: SBP: -2.8 (95% CI: -4.7– -0.9) DBP: -1.1 (95% CI: -2.4– -0.3) • Combination Diet: SBP: -5.5 (95% CI: -7.4– -3.7) DBP: -3.0 (95% CI: -4.3– -1.6) The BP changes in the subgroup with HTN were: • Fruits and Veg. Diet: SBP: -7.2 (-	• This trial was the first of several to document the value of the combination diet (later renamed the DASH diet). • The BP reductions noted with the DASH (combination) diet were substantial and well maintained. • Generalizability was limited due to the nature of the intervention (feeding study) and the relatively short period of intervention experience (8 wk)

				11.4, -3.0) DBP: -2.8 (- 5.4, -0.3) • Combination Diet: SBP: -11.4 (-15.9, -6.9) DBP: -5.5 (-8.2, -2.7) The corresponding changes in the subgroup of normotensives were: • Fruits and Veg. Diet: SBP: -0.8 (-2.7, 1.1) DBP: -0.3 (-1.9, 1.3) • Combination Diet: SBP: -3.5 (-5.3, -1.6) DBP: -2.1 (-3.6, -0.5) 1 Safety endpoint: Infrequent and similar occurrence of gastrointestinal symptoms in each group	
Sacks FM, et al., 2001 (77) 11136953	Aim: Study the effect of different levels of sodium intake on BP during consumption of a DASH or usual U.S. diet Study type: • Multicenter RCT with 2 parallel diet arms (DASH diet or usual U.S. diet) • Within each arm, randomized cross-over trial with 3 periods testing different levels of	Inclusion criteria: • Adults ≥22 y • Average SBP between 120–159 mm Hg and average DBP between 80–95 mm Hg • No use of antihypertensive medication Exclusion criteria: Heart disease, renal insufficiency, poorly controlled hyperlipidemia or DM, DM requiring insulin, special dietary requirements, >14 alcoholic drinks /wk.	Intervention: 3 levels of dietary sodium while consuming a DASH or usual U.S. diet. The target sodium intake levels for a daily energy intake of 2,100 kcal were: High: 150 mmol (3,450 mg)/d Intermediate: 100 mmol (2,300 mg)/d Low: 50 mmol (1,150 mg)/d The mean achieved levels of sodium during the high, intermediate and low sodium periods were 144,	1 endpoint: • At each level of sodium intake, SBP and DBP were lower during consumption of the DASH diet compared to the usual U.S. diet, the difference being greatest with high sodium intake and lowest with low sodium intake, with the mean SBP difference between the DASH and usual US diets during high, intermediate and low sodium intake being -5.9 (95% CI: -8.0– -3.7), -5.0 (95% CI: -7.6– -2.5),	This trial provided additional documentation of the effectiveness of a DASH diet in lowering BP in normotensives (and hypertensives) and the complementary benefit of consuming a reduced intake of sodium.

	sodium intake (no washout) Size: 412, with 59% (243) being normotensive		107 and 67 mmol/d in the DASH diet group and 141, 106, and 64 mmol/d in the usual U.S. diet group. Comparator: See description above	and -2.2 (95% CI: -4.4– -0.1). The corresponding differences for DBP were -2.9 (95% CI: -4.3– -1.5), -2.5 (95% CI: -4.1– - 0.8), and -1.0 (95% CI: -2.5, 0.4). • In both the DASH and usual U.S. diet arms, SBP and DBP were significantly lower during intermediate compared to high sodium intake, and during low compared to intermediate sodium intake, with the decrement being greater for the latter change. In comparison to consumption of a usual U.S. diet at the high level of sodium intake, the normotensive group consuming the DASH diet at the low level of sodium intake had a mean SBP difference of 7.1 mm Hg ($p<0.001$). 1 Safety endpoint: Participants tended to report less symptoms during periods of reduced sodium intake, with a statistically significant reduction in reports of headache ($p<0.05$) consistent with prior experience in the	

				TONE trial.	
Neter JE, et al., 2003 (103) 12975389	Aim: Study the effect of weight loss on BP Study type: Systematic review and meta-analysis Size: 25 RCTs (34 comparisons) with 4,874 pts; 17 of the comparisons were conducted in normotensive pts	Inclusion criteria: • RCT in humans • English language publication between 1966– 2002 • Nonpharmacologic intervention Exclusion criteria: • Duration <8 wk • Missing data • Objective not weight loss Concomitant intervention(s)	Intervention: Weight loss (calorie reduction, physical activity, or combination of both) Comparator: No weight loss prescription	1 endpoint: • For the overall group, mean baseline body weight was 88.3 kg and mean change in body weight following the application of the weight loss intervention was -5.1 (95% CI: -6.03– -4.25) kg. This represents a mean percent change of -5.8%. • There was strong evidence for a BP lowering effect of weight loss on BP, overall and in normotensive subgroup. In the normotensive group, the mean for change in SBP was 4.08 (95% CI: - 6.01– -2.16). • Overall, a 1 kg reduction in body weight was associated with a mean change in SBP of -1.05 (95% CI: -1.43– -0.66) mm Hg. 1 Safety endpoint: N/A	• Substantial evidence for a reduction in BP, overall and in normotensives. With the exception of the mean (95% CI) changes in BP, this paper provides limited data for the normotensive group
TOHP, Phase I 1992 (79) 1586398	Aim: Study the effect of weight loss on BP and prevention of HTN	Inclusion criteria: • Community-dwelling adults 30–54 y • Not on antihypertensive medication	Intervention: Behavior change intervention (combination of diet change and physical activity)	1 endpoint: Change in DBP 2 endpoint: Change in SBP	• Significantly lower DBP (2.3 mm Hg; p<0.01) and SBP (2.9 mm Hg; p<0.01) in the weight loss group

	Study type: Randomized, controlled factorial trial. Size: Overall, 2,182 adults, with the 308	• DBP 80-89 mm Hg • Healthy Exclusion criteria: Disease	Comparator: Usual care	Safety endpoint: CVD events, symptoms and general and well being	compared to usual care • Few CVD events • No difference in symptoms • Significant improvement in general well-being at 6 and 18 mo ($p<0.05$)
NUTRICODE Mozaffarian D, et al., 2014 (74) 25119608	Aim: Study the effect of sodium reduction on BP and CVD mortality Study type: Meta-regression analysis Size: 103 RCTs (107 comparisons) with 6,970 pts; 38 of the 107 comparisons were conducted in normotensive pts	Inclusion criteria: RCT in 2 previous Cochrane meta-analyses Exclusion criteria: • Duration <1 wk • Mean 24-h collections or estimates of urinary sodium reduced <20 mmol in the intervention group compared to control Concomitant interventions	Intervention: Sodium reduction Comparator: No sodium reduction	1 endpoint: • Strong evidence for a linear relationship between reduction in sodium intake and lower levels of SBP throughout the entire distribution of sodium studied, with larger reductions in older persons, blacks (compared to whites) and hypertensives (compared to normotensives). For a white, normotensive population at age 50 y, each reduction of 100 mmol/d (2.3 g/d) in dietary sodium lowered SBP by a mean: 3.74 (95% CI: 5.18–2.29). • Modeling based on global estimates of sodium intake, effect of sodium reduction on BP, and effect of BP reduction on CVD mortality attributed 1.65 million CVD deaths annually due sodium intake >2 g/d. this would represent 9.5%	• RCT meta-regression analysis that provides evidence for BP lowering following a reduction in dietary sodium intake, overall and in normotensive persons, with a more pronounced effect in those who were older, black and had a higher starting level of BP. • These findings are consistent with other reports. The modeling analysis suggested sodium reduction would yield important population health benefits but did not specify the magnitude of the potential benefit for pts within the normal BP range.

				(95% CI: 6.4–12.8) of all CVD mortality. Estimates were not provided separately for hypertensive and normotensive persons. 1 Safety endpoint: N/A	
He FJ, et al., 2013 (75) 22437256	Aim: Study the effect of sodium reduction on BP Study type: Systematic review, meta-analysis and meta-regression analysis Size: Overall study included 34 trials (37 comparisons) conducted in 3,230 pts. 12 of the RCTs (14 comparisons) were conducted in 2,240 normotensive pts.	Inclusion criteria: ● RCTs ● Healthy adults ≥18 y ● Trial duration ≥4 wk ● Sodium intake only difference between treatment and control group ● 24-h urine sodium ≥40 mmol less in treatment compared to control Exclusion criteria: Lack of above	Intervention: Sodium reduction Comparator: No sodium reduction	1 endpoint: In an overall pooled analysis, the change for SBP was -4.18 (95% CI: - 5.18– -3.18) mm Hg. In the trials of persons with HTN, the mean change was -5.39 (95% CI: -6.62– -4.15) mm Hg. In the trials conducted in normotensives, the change in SBP was -2.42 (95% CI: -3.56– -1.29) mm Hg. • In meta-regression analysis, change in 24-h urinary sodium was significantly associated with reduction in SBP (4.3 mm Hg for a 100 mmol reduction in 24-h urinary sodium). Safety endpoint: In the small number of relevant trials (which included both hypertensive and normotensive pts) that	● Study inclusion/exclusion criteria designed to yield a group of trials that would provide results that have relevance for clinical practice and public health. In this context, reduced sodium intake resulted in a significant and potentially important reduction in SBP. The meta-regression results were consistent with a dose- response relationship in normotensive pts

				provided safety endpoint measurements (4–14 trials), there was no change in total, LDL- or HDL- cholesterol, or triglyceride levels. There were small significant increases in plasma renin activity, aldosterone, and noradrenaline levels but these were consistent with expected physiologic responses to sodium reduction.	
TONE Whelton PK, et al., 1998 (107) 9515998	Aim: Study the effect of weight loss on BP and need for antihypertensive drug therapy Study type: RCT, factorial design Size: 585 (obese) participants	Inclusion criteria: • Community-dwelling adults 60–80 y • SBP <145 mm Hg and DBP <85 mm Hg on 1 antihypertensive medication Exclusion criteria: • Heart attack or stroke within 6 mo • Current angina, HF, insulin-dependent DM Inability to comply with protocol	Intervention: Behavior change intervention (combination of diet change and physical activity) Comparator: Usual care, with similar level of contact compared to active intervention group	1° endpoint: Recurrence of HTN following withdrawal of antihypertensive medication (or CVD event) 2° endpoint: BP (while still on antihypertensive medication prior to tapering of medication) Safety endpoint: CVD events, symptoms (including headaches), dietary composition	• Significant reduction in SBP prior to withdrawal of antihypertensive medication (mean±SE=-4.0±1.3 mm Hg) • 1° outcome significantly less common in weight loss group compared to usual care – Rel. HR: 0.70; 95% CI, 0.57–0.87; p<0.001 No overt evidence for adverse effects of intervention
Whelton PK, et al., 1997 (67) 9168293	Aim: Study the effect of potassium supplementation on BP Study type: Systematic review	Inclusion criteria: • Human RCT • Without HTN • Potassium supplementation vs. control • No concurrent interventions	Intervention: Potassium supplementation in 1,049 pts (potassium chloride tabs in 10 RCTs with 618 pts and diet in 2 RCT with 431 pts)	1° endpoint: • Significant reduction in BP. • Overall (hypertensives and normotensives), mean: 3.11 mm Hg; 95% CI: -4.32– -1.91 mm Hg.	• This is the most comprehensive presentation of the effects of potassium on BP, including experience in normotensives.

	and meta-analysis Size: ● Overall, 33 RCT (n=2,609) ● 2 RCTs (n=1,049) in normotensives	Exclusion criteria: Missing key data	Comparator: No potassium supplementation (placebo in 10 RCT and usual diet in 2 RCT)	• In the 12 trials conducted in normotensives, mean: -1.8 mm Hg; 95% CI: -2.9– -0.6 mm Hg for SBP and -1.0 mm Hg; 95% CI: -2.1–0.0 for DBP • In the 20 trials conducted in hypertensives, mean: -4.4 mm Hg; 95% CI: -6.6– -2.2 for SBP and -2.5 mm Hg; 95% CI: -4.9– -0.1 for DBP Safety endpoint: N/A	• Significant reduction in SBP overall and in the subgroups with and without HTN. • In a subsequent meta-analysis of 23 trials, Geleijnse JM, Kok FJ, and Grobbee DE (J Hum Hypertens. 2003;17:471-480) reported a similar effect of potassium on SBP in both hypertensives and nonhypertensives (mean of -3.2 and -1.4 mm Hg, respectively). • The 1 RCT conducted in African-Americans (n=87) identified a mean treatment effect size of -6.9 mm Hg; 95% CI: -9.3– -4.4 for SBP (p<0.001) and -2.5 mm Hg; 95% CI: -4.3– -0.8 for DBP (p=0.004). • In the entire cohort (trials conducted in pts with HTN and normotension), net changes in SBP and DBP were directly related to level of urinary sodium excretion during the trial.
Aburto NJ, et al., 2013 (68) 23558164	Aim: Study the effect of potassium supplementation on BP	Inclusion criteria: • RCT in humans • Duration ≥4 wk • 24-h collections of urinary potassium	Intervention: Potassium supplementation in 20 trials, supplements plus diet/education in 1 trial, and diet/education alone	1 endpoint: • Overall change in SBP=- 5.93; 95% CI: -10.15– -1.70. After removing outlier trials, the	• 1 trial (TOHP Phase I) incorrectly entered twice so only 2 trials really available. However, this does not

	Study type: Systematic review and meta-analysis Size: 21 RCTs (n=1,892); 16 in pts with HTN (n=818) and 3 RCTs in pts without HTN (n=757)	• No concomitant interventions Exclusion criteria: Pts who were acutely ill, HIV positive, hospitalized, or had impaired urinary excretion of potassium	in 2 trials. Comparator: No potassium supplementation (placebo or usual diet)	change was -3.49 mm Hg; 95% CI: -5.15– -1.82 mm Hg. • In 16 trials conducted in hypertensives, change in SBP was -5.32 mm Hg; 95% CI: -7.20– -3.43. In the 3 trials conducted in persons without HTN, change in SBP was 0.09 mm Hg; 95% CI: -0.77–0.95.	change overall finding. The negative results for normotensives in this meta-analysis (and difference with the findings by Whelton et al) probably reflects the requirement for a duration of ≥4 wk and the fact that few trials of this duration have been conducted in normotensives.
Cornelissen VA, et al., 2013 (97) 23525435	Aim: Study the effect of different types of physical activity on BP • Dynamic aerobic endurance • Resistance training - Dynamic - Static (Isometric) Study type: Systematic review and meta-analysis Size: Overall, 93 studies (>5,000 pts) • 59 Dynamic Aerobic Endurance studies • 13 Dynamic Resistance Training studies • 5 Combined Dynamic Aerobic and	Inclusion criteria: • Parallel arm RCTs • Adults≥18 y • Peer reviewed journals up to February 2012 • Trial duration ≥4 wk Exclusion criteria: Inadequate reporting of the data	Intervention: Physical activity Comparator: No prescription of physical activity	1 endpoint: Overall (trials in hypertensives and normotensive), pooled experience identified a significant reduction in BP with all forms of physical activity (aerobic and both forms of resistance training), with mean reductions in SBP of -3.5 mm Hg following aerobic endurance training, -1.8 mm Hg following dynamic resistance training, and -10.9 mm Hg following static (isometric) resistance training ($p<0.001$ for the difference between the effect size following static [isometric] and other forms of physical activity). In subgroup analysis, dynamic aerobic endurance and dynamic resistance training resulted in mean SBP	• Most recent in a series of progressively updated publications from Dr. Cornelissen and her colleagues. • The findings suggest a beneficial effect of all forms of physical activity on BP, with a disproportionately large effect of resistance training on BP. Many of the available RCTs have been small, of short duration, and of uncertain quality.

	Resistance training • 4 Static (Isometric) Resistance 12 Different interventions within 1 trial			changes of -2.1 (95% CI: -3.3– -0.83) and -4.3 (95% CI: -7.7– -0.90), respectively, in the pts with pre-HTN and smaller, nonsignificant reductions in the remaining pts with a normal BP. Safety endpoint: N/A	
Whelton SP, et al., 2002 (96) 11926784	Aim: Study the effect of aerobic exercise on BP Study type: Systematic review and meta-analysis Size: 38 reports (54 comparisons) with 2,419 pts; 27 of the comparisons were conducted in normotensive pts	Inclusion criteria: • English language publication between 1966–2001 • RCT in adults ≥18 y • Duration ≥2 wk • No concurrent interventions Exclusion criteria: Missing BP data	Intervention: Aerobic exercise Comparator: No exercise prescribed	1 endpoint: • For the overall group, a pooled analysis of experience in 53 trials identified a mean net change in SBP of - 3.84 (95% CI: -4.97– -2.72). In subgroup analysis, the effect was noted in different ethnic groups, in trials that employed different designs, durations, and sample sizes, in trials with obese, overweight or normal weight pts, and in trials that employed different types, intensity levels, and duration of aerobic exercise. In the subgroup of 15 trials in hypertensives, the mean net change in SBP was -4.94 (95% CI: -7.17– -2.70). • In the subgroup of 27 trials conducted in normotensives, the mean net change in SBP was -4.04 (95% CI: -5.32– -	● This meta-analysis provides the most comprehensive analysis of the effect of aerobic exercise on BP and provides strong evidence in support of aerobic exercise as an intervention to lower BP in normotensives. Recognizing this, many of the trials were small and of short duration.

				2.75). 1° Safety endpoint: N/A	
Roerecke M, et al., 2017 Lancet Public Health. 2017;2:e108-120. 29253389	Aim: Study the effect of reduced alcohol intake on BP. Study type: Systematic review and meta-analysis. Size: 36 RCT with 2865 participants. Design: • 15 parallel-arm trials • 21 crossover trials Setting: • 13 in hypertension • 13 in normotension • 12 HTN and NT Only 3 trials presented data for women.	Inclusion criteria: • RCT in adult humans • Publication on or before July 13, 2016. • Full text articles. Change in alcohol intake for ≥1 wk	Intervention: Reduction in alcohol consumption. Strategy varied from controlled inpatient administration to randomization to "light" alcohol to pragmatic primary care trials with counselling to reduce alcohol intake. Duration: Follow-up from 1 wk to 2 y (median 4 wk).	1° endpoint: • Overall, alcohol reduction was associated with a significant reduction in mean SBP of -3.31 (95% CI: -4.10– -2.52) and DBP of -2.04 (95% CI: -2.58– -1.49). • In the subgroup of 7 RCTs in persons with HTN, the mean changes in SBP and DBP were SBP: -3.13 (95% CI: -3.93– - 2.32) DBP: -2.00 (95% CI: -2.65– -1.35). • In meta-regression analysis, there was a strong relationship between the extent of BP reduction and change in BP, with no reduction in BP for those consuming 2 or less drinks at baseline but increasing reductions in BP for those with progressively higher intakes of alcohol at baseline. For instance, in those consuming ≥6 drinks/day and reducing their alcohol intake by approximately 50%, the estimated	N/A

				reduction in SBP and DBP were: SBP: -5.5 (95% CI: -6.70– -4.30) DBP: -3.97 (95% CI: -4.70– - 3.25). Similar patterns of the effect of baseline alcohol intake on treatment effect were noted for a variety of subgroups. 1 Safety endpoint: N/A	
Law MR, et al., 2009 (18) 19454737	Study type: Meta-analysis of use of BP- lowering drugs in prevention of CVD from 147 randomized trials Size: Of 147 randomized trials of 464,000 pts, 37 trials of BBs in CAD included 38,892 pts, and 37 trials of other antihypertensive drugs in CAD included 85,395 pts	Inclusion criteria: The database search used Medline (1966 to Dec. 2007) to identify randomized trials of BP-lowering drugs in which CAD events or strokes were recorded. The search also included the Cochrane Collaboration and Web of Science databases and the citations in trials and previous meta-analyses and review articles. Exclusion criteria: Trials were excluded if there were <5 CAD events and strokes or if treatment duration was <6 mo.	N/A	1 endpoint: CAD events; stroke Results: In 37 trials of pts with a history of CAD, BB reduced CAD events 29% (95% CI: 22%– 34%). In 27 trials in which BBs were used after acute MI, BB reduced CAD events 31% (95% CI: 24%–38%), and in 11 trials in which BB were used after long-term CAD, BB insignificantly reduced CAD events 13%. In 7 trials, BB reduced stroke 17% (95% CI: 1%–30%). CAD events were reduced 14% (95% CI: 2%–25%) in 11 trials of thiazide diuretics, 17% (95% CI: 11%–22%) in 21 trials of ACEIs, insignificantly 14% in 4 trials of angiotensin receptor blockers, and	With the exception of the extra protective effect of BB given shortly after a MI and the minor additional effect of CCBs in preventing stroke, all the classes of BP-lowering drugs have a similar effect in reducing CAD events and stroke for a given reduction in BP.

				15% (95% CI: 8%–22%) in 22 trials of CCB. Stroke was reduced 38% (95% CI: 28%–47%) in 10 trials of thiazide diuretics, 22% (95% CI: 8%–34%) in 13 trials of ACEI, and 34% (95% CI: 25%–42%) in 9 trials of CCB.	
Ettehad D, et al., 2016 (17) 26724178	Aim: This systematic review and meta-analysis aims to combine data from all published large-scale BP-lowering trials to quantify the effects of BP reduction on CV outcomes and death across various baseline BP levels, major comorbidities, and different pharmacological interventions. Study type: Meta- analysis of RCTs Size: 123 studies with 613,815 pts	Inclusion criteria: • RCTs of BP-lowering treatment that included a minimum of 1,000 pt-y of follow-up in each study arm. No trials were excluded because of presence of baseline comorbidities, and trials of antihypertensive drugs for indications other than HTN were eligible. • Eligible studies fell into 3 categories: 1st, random allocation of pts to a BP-lowering drug or placebo; 2nd, random allocation of pts to different BP-lowering drugs; and third, random allocation of pts to different BP-lowering targets. Exclusion criteria: <1,000 pt y of follow-up in each treatment group.	Intervention: BP-lowering meds Comparator: Placebo, active comparator or less intensive treatment	1 endpoint: • CVD. • Major CVD events, CHD, stroke, HF, renal failure, and all-cause mortality. • Standardized RR for 10 mm Hg difference in SBP • CVD RR: 0.80 (95% CI: 0.77–0.83) Other endpoints: CHD RR: 0.83 (95% CI: 0.78–0.88) Stroke RR: 0.73 (95% CI: 0.68–0.77) HF RR: 0.72 (95% CI: 0.67–0.78) Total deaths RR: 0.87 (95% CI: 0.84–0.91) Other results: • Benefit for CVD and other endpoints not different by baseline SBP, including <130 mm Hg fig 4 in paper CVD: 0.63; 95% CI: 0.50–	• BP-lowering significantly reduces vascular risk across various baseline BP levels and comorbidities. Our results provide strong support for lowering BP to SBP<130 mm Hg and providing BP-lowering treatment to individuals with a history of CVD, CHD, stroke, DM, HF, and CKD. • In stratified analyses, we saw no strong evidence that proportional effects were diminished in trials that included people with lower baseline SBP (<130 mm Hg), and major CV events were clearly reduced in high-risk pts with various baseline comorbidities. Both of these major findings—the efficacy of BP-lowering below 130 mm Hg and the similar proportional effects in

				0.80; p=0.22 CHD: 0.55; 95% CI: 0.42–0.72; p=0.93 Stroke: 0.65; 95% CI: 0.27–1.57; p=0.38 HF: 0.83; 95% CI: 0.41–1.70; p=0.27 Total deaths: 0.53; 95% CI: 0.37–0.76; p=0.79 • More precision around estimates of benefits in SBP 130–139 at baseline, fig 4 in paper • Results similar in trials of people with and without CVD at baseline figure 5 CVD+ 0.77 (95% CI: 0.71–0.81) CVD- 0.74 (95% CI: 0.67–0.83) Total deaths CVD+ 0.90 (95% CI: 0.83–0.98) CVD- 0.84 (95% CI: 0.75–0.93) Other outcomes similarly in figure 5 • In appendix, in general, benefits for CVD prevention seen in groups with and without baseline CHD, Stroke, DM, CKD and HF when examined separately, but no absolute risks provided to enable estimation of how far down the absolute risk curve these findings have	high risk populations—are consistent with and extend the findings of the SPRINT trial. <u>Limitations:</u> • Lack of individual pt data, which would have allowed a more reliable assessment of treatment effects in different pt groups. Interpretation: Lowering of BP into what has been regarded the normotensive range should therefore be routinely considered for the prevention of CVD among those deemed to be of sufficient absolute risk.

				been demonstrated. • Some evidence of BB inferiority to other med classes in figure 6. Did not report absolute risks so do not know lower level of risk in treated populations.	
Sundstrom J, BPLTTC, et al., 2014 (112) 25131978	Aim: We aimed to investigate whether the benefits of BP-lowering drugs are proportional to baseline CV risk, to establish whether absolute risk could be used to inform treatment decisions for BP-lowering therapy, as is recommended for lipid-lowering therapy. Study type: Meta-analysis of RCTs Size: 11 trials and 26 randomized groups with 67,475 pts (51,917 pts data available for the calculation of the risk equations)	Inclusion criteria: BPLTTC: trials were eligible if they met the original inclusion criteria specified in the protocol, 11 and were part of the subset of studies that randomly allocated pts to either a BP-lowering drug or placebo, or to a more intensive or less intensive BP regimen. Trials had to have a minimum of 1,000 pt-y of planned follow-up in each randomized group, and should not have presented their main results before the protocol was finalized in July, 1995. Exclusion criteria: Not stated	Intervention: BP-lowering meds Comparator: Placebo or less intensive treatment	1 endpoint: • Total major CV events, consisting of stroke (nonfatal stroke or death from cerebrovascular disease), CHD (nonfatal MI or death from CHD including sudden death), HF (resulting in death or admission to hospital), or CV morbidity. • The mean estimated baseline levels of 5-y CV risk for each of the 4 risk groups were 6.0% (SD: 2–0), 12.1% (1–5), 17.7% (1–7), and 26.8% (5–4). • In each consecutive higher risk group, BP-lowering treatment reduced the risk of CV events relatively by 18% (95% CI: 7–27), 15% (95% CI: 4–25), 13% (95% CI: 2–22), and 15% (95% CI: 5– 24), respectively (p=0·30 for trend) in each group with BP-lowering treatment for 5 y would prevent 14	Summary: • Lowering BP provides similar relative protection at all levels of baseline CV risk, but progressively greater absolute risk reductions as baseline risk increases. These results support the use of predicted baseline CVD risk equations to inform BP-lowering treatment decisions. Lowest risk group had >83% with a risk that exceeds 4%.

				(95% CI: 8–21), 20 (95% CI: 8–31), 24 (95% CI: 8–40), and 38 (95% CI: 16–61) CV events, respectively (p=0.04 for trend).	
Sundstrom J, et al., 2015 (19) 25531552	Aim: To investigate whether pharmacologic BP reduction prevents CV events and deaths in pts with grade 1 HTN. Study type: Meta- analysis of RCTs Size: 10 RTCs with 15,266 pts	Inclusion criteria: RCTs of at least 1 y duration; pts ≥18 y, at least 80% of whom had grade 1 HTN and no previous CVD (MI, angina pectoris, CABG, PCI, stroke, TIA, carotid surgery, peripheral arterial surgery, intermittent claudication, or renal failure); and compared an antihypertensive drug provided as monotherapy or a stepped-care algorithm vs. placebo or another control regimen. Exclusion criteria: Excluded trials did not contribute an event for any of the outcomes of interest.	N/A	1 endpoint: Total major CV events, comprising stroke (nonfatal stroke or death from cerebrovascular disease), coronary events (nonfatal MI or death from CHD, including sudden death), HF (causing death or resulting in hospitalization), or CV death; OR: 0.86 (95% CI: 0.74–1.01) Other endpoints: Each of the above outcomes independently; and total deaths. CHD 0.91 (95% CI: 0.74–1.12) Stroke 0.72 (95% CI: 0.55–0.99) HF 0.80 (95% CI: 0.57–1.12) CVD deaths 0.75 (95% CI: 0.57–0.98) Total deaths 0.78 (95% CI: 0.67–0.92) Only the first event for a pt was used for the	• BP-lowering therapy is likely to prevent stroke and death in pts with uncomplicated grade 1 HTN. 5 y risks in BPLTTC control groups CVD events 7.4%, CVD deaths 3.1%

				analysis of each outcome, but a pt who had >1 outcome type could contribute to more than 1 analysis. They also tabulated overall withdrawals and withdrawals due to adverse events.	
Xie X, et al., 2015 (21) 26559744	Aim: To assess the efficacy and safety of intensive BP-lowering strategies. Study type: Meta-analysis of RCTs Size: 19 RCTs with 44,989 pts	Inclusion criteria: RCTs with at least 6 mo follow-up that randomly assigned pts to more intensive vs. less intensive BP- lowering treatment, with different BP targets or different BP changes from baseline. Reference lists from identified trials and review articles were manually scanned to identify any other relevant studies. Exclusion criteria: N/A	Intervention: BP-lowering meds Comparator: • Less intensive treatment • BP difference 6.8/3.5 • The mean follow-up BP levels in the less intensive BP-lowering regimen group were 140/81 mm Hg, compared with 133/76 mm Hg in the more intensive treatment group.	1 endpoint: • CVD, other major CV events, defined as a MI, stroke, HF, or CV death, separately and combined; nonvascular and all-cause mortality; ESKD, and adverse events. Progression of albuminuria (defined as new onset of micro-albuminuria/macro-albuminuria or a change from micro-albuminuria to macro-albuminuria) and retinopathy (retinopathy progression of 2 or more steps) were also recorded for trials that were done in pts with DM • CVD RR: 0.86 (95% CI: 0.78– 0.96) Other endpoints: MI RR: 0.87 (95% CI: 0.76–1.00; p=0.042) Stroke RR: 0.78 (95% CI: 0.68–0.90) HF RR: 0.85 (95% CI:	Summary: Intensive BP-lowering, including to <130 mm Hg, provided greater vascular protection than standard regimens. In high-risk pts, there are additional benefits from more intensive BP- lowering, including for those with SPB <140 mm Hg at baseline. The net absolute benefits of intensive BP- lowering in high-risk individuals are large. Limitations: • Lack of individual pt data, which would have allowed a more reliable assessment of treatment effects in different pt groups. • Interpretation: Supports treating pt with and without CVD at threshold of 130 to <130. Supports treating

				0.66–1.11) CVD death RR: 0.91 (95% CI: 0.74–1.11) Total deaths RR: 0.91 (95% CI: 0.81–1.03) <u>Other results:</u> •Benefit for CVD not different by baseline SBP 120–139: 0.89 (95% CI: 0.76–1.05) 140–160: 0.83 (95% CI: 0.68–1.00) >160: 0.89 (95% CI: 0.73–1.09) p-heterogeneity: 0.60 • Benefit for CVD not different for more intensive and less intensive targets in intensive group <140 or <150 mm Hg: 0.76 (95% CI: 0.60–0.97) <120– <130 mm Hg: 0.91 (95% CI: 0.84–1.00) p-hetero: 0.06 • Absolute benefits were proportional to absolute risk. • For trials in which all pts had vascular disease, renal disease, or DM at baseline, the average control group rate of major vascular events was 2·9% per y compared with 0·9% per y in other trials, and the numbers needed to treat	at threshold of about 130 even down to a CVD event rate of 0.9% per y.

				were 94 (95% CI: 44–782) in these trials vs. 186 (95% CI: 107– 708) in all other trials. • Increase in severe hypotension: 0.3% vs. 0.1% per person y OR: 2.68 (95% CI: 1.21–5.89)	
SPRINT Wright JT Jr, et al., 2015 (114) 26551272	Aim: To test the effectiveness of a goal SBP<120 mm Hg vs. a goal SBP<140 mm Hg for the prevention of CVD in pts with SBP≥130 mm Hg at baseline. Study type: RCT Size: 9361 pts followed median of 3.26 y.	Inclusion criteria: SBP≥130 mm Hg, with upper limit varying as number of pre-trial BP-lowering meds increased. age ≥50 y Presence of at least 1 of the following: • Clinical or subclinical CVD • CKD stage ≥3 • Age≥75 • Framingham General CVD risk≥15% in 10 y Exclusion criteria: DM, history of stroke, ESRD (eGFR <20)	Intervention: Intensive BP- lowering treatment to goal SBP <120 mm Hg Comparison: • Standard BP-lowering treatment to goal SBP<140 mm Hg • Net treatment difference ~3 drugs (2.8) on average vs. 2 drugs (1.8) on average During the trial, mean SBP was 121.5 vs. 134.6.	1° endpoint: CVD (MI, ACS, stroke, HF, CVD death) HR: 0.75 (95% CI: 0.64, 0.89) Other endpoints: • Total deaths HR: 0.73 (95% CI: 0.60–0.90) • 1° or death HR: 0.78 (95% CI: 0.67–0.90) • Components of 1° composite mostly consistent in direction other than ACS – no difference. CKD outcomes: • 1° in CKD pts: reduction in GFR of ≥50% or ESRD HR: 0.89 (95% CI: 0.42, 1.87) • Incident albuminuria HR: 0.72 (95% 0.48, 1.07) • In pts without CKD: reduction in GFR ≥30% and to <60 • HR: 3.49 (95% CI: 2.44–5.10) • Incident albuminuria HR: 0.81	Summary: • More intensive SBP lowering to a goal of <120 mm Hg with achieved mean of approximately 121 mm Hg resulted in less CVD and lower total mortality over 3.26 y in comparison with a goal SBP <140 mm Hg and achieved SBP of ~135 mm Hg. • There were small increases in some expected SAEs. Perhaps unexpected, a sizable increase in reduced eGFR in the non-CKD group and AKI/ARF overall was observed in the intensive group. While of uncertain etiology and significance, there is speculation this could be an acute hemodynamic effect, especially given the findings regarding albuminuria.

				(95% CI: 0.63–1.04) Adverse events: • SAEs: 1.04; p=0.25 • Significant absolute increases seen in intensive group for hypotension (1%), syncope (0.6%), electrolyte abnormality (0.8%), acute kidney injury/acute renal failure (1.6%) over the study period. • 1.7% fewer pts had orthostatic hypotension in intensive group; p=0.01.	Limitations: Few pts were untreated at baseline ~9%, so SPRINT provides little if any insight at present regarding BP-lowering medication initiation for untreated people with SBP 130–139.
Czernichow S et al., 2011 (121) 20881867	Aim: The objective of this systematic review and meta-analysis was to compare the relative reductions in risk achieved with different starting levels of BP (and treatment regimens). Study type: Meta-analysis of RCTs Size: 32 trials with 201,566 pts (20,079 1° outcome events)	Inclusion criteria: RCTs of BP-lowering (drug vs. control or less intensive treatment) or different classes of drug therapy that included a minimum of 1,000 pt- y of follow-up in each study arm. Exclusion criteria: <1,000 pt-y of follow-up in each treatment group.	Intervention: BP-lowering meds Comparator: Placebo, active comparator or less intensive treatment	1 endpoint: • Major CVD events (stroke, CHD, and HF. No evidence of differences in the ratio of risk across varying levels of baseline BP (with all classes of BP-lowering medications).	Summary: • Effectiveness of BP-lowering regiments in reducing RR of major CVD events does not seem to be influenced by starting level of BP. Limitations: • The majority of the participants studied were at high risk for CVD. Information pertaining to the effect of treatment on absolute risk was not presented in this manuscript.
REIN-2 Ruggeneti P, et al., 2005 (171) 15766995	Aim: To determine whether intensive BP control will achieve further renoprotection (delayed progression to ESRD) compared	Inclusion criteria: • Adults, age 18–70 y, with nondiabetic nephropathy, persistent proteinuria (urinary protein excretion >1 g/24 h for ≥3 mo) and not on	Intervention: • Intensive: BP goal <130/80 mm Hg • Conventional: DBP goal <90 mm Hg,	1° endpoint • Time to ESRD; over 36 mo follow-up, median 19 mo 1° outcome: ESRD in	Limitations: The study was stopped at the 1st interim analysis for futility. Median time 19 mo

	to standard BP control in pts with chronic nephropathies Study type: Multicenter RCT of pts all placed on ACEI (ramipril) at maximum dose tolerated to achieve DBP <90 then assigned to conventional or intensified BP control. Add-on drug was dihydropyridine felodipine 5–10 mg/d Size: 335 (median time 19 mo)	ACEIs in previous 6 wk • Pts with proteinuria 1–3 g/24 h included if CrCl <70 mL/min/1.73 m^2 • For overall population, mean SBP, mm Hg (SD): Intensive: 137.0 (16.7) Conventional: 136.4 (17.0) • For overall population, mean DBP, mm Hg (SD): Intensive: 84.3 (9.0) Conventional: 83.9 (10.4) Exclusion criteria: Urinary tract infection, CHF class III–IV, treatment with corticosteroids, NSAIDs, immunosuppression, acute MI or stroke in prior 6 mo, severe uncontrolled HTN, suspicion for renovascular disease, obstructive uropathy, DM-1, collagen vascular disease, cancer, elevated aspartate transaminase, chronic cough, history of allergy or poor tolerance to study meds, alcohol abuse, pregnancy, breastfeeding, ineffective contraception.	irrespective of SBP • For baseline proteinuria subgroups, result BP values NR • For the overall population, achieved BP, mm Hg (SD) Intensive: 129.6/79.5 (10.9/5.3) Conventional: 133.7/82.3 (12.6/7.1) p=0.0019/<0.0001 • For the overall population, change in BP, mm Hg Intensive: -7.4/-4.8 Conventional: -2.7/-1.6 p=NR • For the overall population, BP difference between groups, mm Hg 4.1/2.8 p=NR Comparator: By BP goals	pts with baseline proteinuria 1–3 g/24 h HR (95% CI): 1.06 (95% CI: 0.51–2.20) p=0.89 • ESRD in pts with baseline proteinuria >3 g/24 h HR (95% CI): 1.09 (95% CI: 0.55–2.19) p=0.81 • 23% of intensive and 20% of conventional control groups progressed to ESRD. • Median rate of GFR decline, mL/min/1.73 m^2/mo (IQR) in pts with baseline proteinuria <3 g/24: Intensive: 0.18 (95% CI: 0.03–0.49) Conventional: 0.21 (95% CI: -0.03–0.40) p=0.89 Median rate of GFR decline, mL/min/1.73 m/mo (IQR) in pts with baseline proteinuria ≥3 g/24: Intensive: 0.51; 95% CI: 0.16–1.05 Conventional: 0.39; 95% CI: 0.030.98 p=0.39	Summary: In pts with non-DM proteinuric nephropathies receiving background ACEI therapy, no additional benefits from further BP reduction by felodipine could be shown. Dihydropyridine CCBs do not offer additional renoprotection to ACEIs or ARBs.
AASK Wright JT, et al., 2002 (172) 12435255	Aim: To compare the effects of 2 levels of BP and 3 antihypertensive drug classes on GFR decline in HTN	Inclusion criteria: • Adult African- Americans,18–70 y, with HTN (DBP ≥95) and GFR of 20–65 mL/min/1.73 m2, no DM • At entry: mean MAP, mm Hg: Low: 115 (27) Usual: 113 (15)	Intervention: • Low: MAP goal ≤92 mm Hg Usual: MAP goal 102–107 mm Hg • Initial treatment with a	1° endpoint: • 1° outcome: difference in mean slopes, acute GFR slope, mL/min/1.73 m^2/3 mo (SE): • 1.82 (0.54)	Limitations: • Based on DSMD recommendation, amlodipine arm halted early and those pts switched to open label

	Study type: • Randomized 3×2 factorial trial • Measured GFR with iothalamate Size: 1,094	• Mean SBP, mm Hg (SD): Low:152 (25) Usual: 149 (23) • Mean DBP, mm Hg: Low: 96 (15) Usual: 95 (14) Exclusion criteria: DBP<95, history of DM, Urinary protein/creatinine ratio >2.5, accelerated or malignant HTN, non-BP related cause of CKD, serious systemic disease, clinical CHF, specific indication or contraindication for a study drug or procedure	B Blocker (metoprolol), and ACEI (ramipril) or a dihydropyridine (amlodipine) with open label agents added to achieve BP goals • Study duration: 3–6.4 y • BP similar across drug groups except 2 mm Hg lower in amlodipine group • Mean from 3 mo to study end • MAP, mm Hg (SD) Low: 95.8 (8) Usual: 104 (7) • SBP/DBP, mm Hg (SD) Low: 128/78 (12/8) Usual: 141/85 (12/7) MAP change, mm Hg Low: -20 Usual: -9 • SBP/DBP change, mm Hg Low: -24/-8 Usual: -18/-10 • Achieved mean BP difference between groups, mm Hg MAP: 11 SBP: 16 DBP: 8 Comparator: N/A	in low BP group p<0.001 • 1° outcome: difference in mean slopes, chronic GFR slope, mL/min/1.73 m^2/y (SE): 0.21 (0.22) p=0.33 NS • Difference in mean slopes, total GFR slope, mL/min/1.73 m^2/y (SE): -0.25 (0.22) p=0.24 • Main 2º clinical composite outcome: GFR event, ESRD, or death, % risk reduction (95% CI): 2 (95% CI: -22–21) p=0.85 • GFR event or ESRD, % Risk Reduction: -2; 95% CI: -31–20; p=0.87 • ESRD or death, % risk reduction: 12; 95% CI: -13–32; p=0.31 • ESRD alone, % risk reduction: 6; 95% CI: -29–31; p=0.72 • 2º outcome: urine protein excretion Safety endpoint: ● Acute and chronic rate of change in GFR (slope): NS for chronic and total slope in subgroup analyses by	Rx, continued study schedule and same BP goals Summary: • No difference in GFR decline with lower BP goal and no difference in composite clinical endpoints • Average rate of GFR decline 2 mL/min/y is similar or slower than previous reports • There was a trend favoring the lower BP goal in subjects with higher baseline proteinuria and the opposite trend for those without proteinuria Ramipril treatment group had slower progression compared with metoprolol and amlodipine combined, less evident between ramipril and metoprolol

				baseline proteinuria strata ● Acute slope: p=0.08 for interaction ● Total slope: p=0.04 for interaction ● Chronic slope: p=0.16 for interaction ● Clinical composite outcome: includes reduction in GFR by 50% or by 25 mL/min/m², ESRD, death, NS in subgroup analyses by baseline proteinuria strata; p=0.007 for interaction ● For above outcomes, trends favored the lower BP goal over the usual goal in participants with higher baseline proteinuria and opposite trends in participants with little or no proteinuria Within each drug group, risk reductions for any 2º clinical outcome of the low vs. usual BP goal were not significantly different between pts with baseline urine protein to creatinine ratio ≤0.22 and >0.22 (p=NS)	
LV J, et al., 2013 (127) 23798459	Study type: MA of RTC that randomly assigned individuals to different target BP levels	N/A	N/A	7.5/4.5 mm Hg BP difference. Intensive BP lowering achieved. RR for ● Major CV events: 11%;	More intensive strategy for BP control reduced cardio-renal endpoint

	Size: 37,348 pts, 15 trials			95% CI: 1%–21%) • MI: 13%; 95% CI: 0%–25% • Stroke: 24%; 95% CI: 8%–37% • ESRD: 11%; 95% CI: 3%–18% • Albuminuria: 10%; 95% CI: 4%–16% Retinopathy 19%; 95% CI: 0%–34% p=0.051	
Arguedas JA, et al., 2013 (244) 24170669	Aim: To determine if "lower" BP targets (any target <130/85 mm Hg) are associated with reduction in mortality and morbidity compared to "standard" BP targets (<140–160/90–100 mm Hg) in pts with DM. Study type: Meta-analysis of RCTs. Size: 5 RCTs recruiting a total of 7,314 ps. Mean follow-up: 4.5 y	Inclusion criteria: RCTs in which individuals were randomized to a "lower" compared with a "standard" BP target. Exclusion criteria: Studies that did not meet the inclusion criteria. Excluded studies were UKPDS 1998, HTN in Diabetes Study IV 1996, SANDS 2008, Lewis 1999 and the Steno-2 study.	• Pts with HTN and DM were randomly assigned to the intensive or standard BP control group.	1 outcomes: Total mortality, total serious adverse events, MI, stroke, CHF, and ESRD. Results: Only 1 trial (ACCORD) compared outcomes associated with 'lower' (<120 mm Hg) or 'standard' (<140 mm Hg) SBP targets in 4734 pts. Despite achieving a significantly lower BP (119.3/64.4 mm Hg vs. 133.5/70.5 mm Hg, p<0.0001), and using more antihypertensive medications, the only significant benefit in the group assigned to 'lower' SBP was a reduction in the incidence of stroke: RR: 0.58; (95% CI: 0.39–0.88; p=0.009), absolute risk reduction 1.1%. The effect of SBP targets on	Conclusions: Evidence from RCTs does not support BP targets lower than standard targets in pts with HTN and DM.

				mortality was compatible with both a reduction and increase in risk: RR: 1.05 (95% CI: 0.84, 1.30), low quality evidence. Trying to achieve the 'lower' SBP target was associated with a significant increase in the number of other serious adverse events: RR: 2.58, (95% CI: 1.70–3.91; p<0.00001, absolute risk increase 2.0%. 4 trials (ABCD-H, ABCD-N, ABCD-2V, and a subgroup of HTN Optimal Treatment) specifically compared clinical outcomes associated with 'lower' vs. 'standard' targets for DBP in pts with DM. The total number of pts included in the DBP target analysis was 2580. Pts assigned to 'lower' DBP had a significantly lower achieved BP: 128/76 mm Hg vs. 135/83 mm Hg; p<0.0001. There was a trend towards reduction in total mortality in the group assigned to the 'lower' DBP target: RR: 0.73 (95% CI: 0.53–1.01), mainly due to a trend to lower non-CV mortality. There was no difference in stroke: RR: 0.67, (95% CI: 0.42–1.05), in MI: RR:	

				0.95 (95% CI: 0.64–1.40) or in CHF: RR: 1.06 (95% CI: 0.58–1.92), low-quality evidence. End-stage renal failure and total serious adverse events were not reported in any of the trials. A sensitivity analysis of trials comparing DBP targets <80 mm Hg (as suggested in clinical guidelines) vs. <90 mm Hg showed similar results. There was a high risk of selection bias for every outcome analyzed in favor of the 'lower' target in the trials included for the analysis of DBP targets.	
Margolis KL et al., 2014 (235) 24595629	Aim: To compare effects of combinations of standard and intensive treatment of glycemia and BP in the ACCORD trial. Study type: RCT Size: 4,733 pts, 4.7 y follow-up	Inclusion criteria: Type 2 DM with HgbA1c 7.5%; 40 y with CVD or 55 y with anatomical evidence of atherosclerosis, albuminuria, LVH, or at least 2 additional risk factors for CVD. Exclusion criteria: BMI 45, serum creatinine >1.5, and other serious illness.	Pts were randomly assigned to intensive therapy SBP<120 mm Hg or standard therapy SBP<140 mm Hg.	1 outcomes: Nonfatal MI, nonfatal stroke, or CV death. Results: In the BP trial, risk of the 1° outcome was lower in the groups intensively treated for glycemia HR: 0.67 (95% CI: 0.50, 0.91), BP HR: 0.74 (95% CI: 0.55, 1.00), or both HR: 0.71 (95% CI: 0.52, 0.96) compared with combined standard BP and glycemia treatment. For 2º outcomes, MI was	Limitations: 2 analysis; results analyzed across individual cells of a factorial design with shorter follow- up than originally intended reducing power to detect meaningful differences and interactions; results may not apply to younger, healthier diabetics. Conclusions: Either intensive BP or glycemia control reduced major CVD compared with combined standard

				significantly reduced by intensive glycemia treatment and stroke by intensive BP treatment; most other HRs were neutral or favored intensive treatment groups.	treatment, but the combination was no better than the individual intensive interventions.
Lewington S, et al., 2002 (16) 12493255	Aim: To describe the age-specific relevance of BP to cause-specific mortality Study type: Meta-analysis of cohort studies Size: 61 prospective studies with 12.7 million person-y of observation, 56,000 vascular deaths in 40– 89 y.	Inclusion criteria: Collaboration was sought from the investigators of all prospective observational studies in which data on BP, blood cholesterol, date of birth (or age), and sex had been recorded at a baseline screening visit, and in which cause and date of death (or age at death) had been routinely sought for all screens during more than 5,000 person-y of follow-up (see appendix A; http://image.thelancet.com/extras/01art8300webappendixA.pdf). Relevant studies were identified through computer searches of Medline and Embase, by hand- searches of meeting abstracts, and by extensive discussions with investigators. Exclusion criteria: To minimize the effects of reverse causality (whereby established disease could change the usual BP), studies were excluded if they had selected pts on the basis of a positive history of stroke or heart disease, and individuals from contributing studies were excluded from the present analyses if they had such a history recorded at baseline.	Intervention: N/A Comparator: N/A The exposures of interest were the level of SBP and DBP and age-group.	1° endpoint: • Not completely clear, but for our purposes, stroke and IHD death would be co-1°. Also looked at other vascular deaths. • HRs for stroke mortality for a 20 mm Hg lower SBP by age-group 40–49: 0.36 (95% CI: 0.32–0.40) 50–59: 0.38 (95% CI: 0.35–0.40) 60–69: 0.43 (95% CI: 0.41–0.45) 70–79: 0.50 (95% CI: 0.48–0.52) 80–89: 0.67 (95% CI: 0.63–0.71) • HRs for IHD mortality for a 20 mm Hg lower SBP by age-group 40–49: 0.49 (95% CI: 0.45–0.53) 50–59: 0.50 (95% CI: 0.49–0.52) 60–69: 0.54 (95% CI: 0.53–0.55) 70–79: 0.60 (95% CI: 0.58–0.61) 80–89: 0.67 (95% CI: 0.64–0.70) • HRs for other vascular mortality for a 20 mm Hg lower SBP by age- group	Summary: Throughout middle and old age, usual BP is strongly and directly related to vascular (and overall) mortality, without any evidence of a threshold down to at least 115/75 mm Hg.

				40–49: 0.43 (95% CI: 0.38–0.48) 50–59: 0.50 (95% CI: 0.47–0.54) 60–69: 0.53 (95% CI: 0.51–0.56) 70–79: 0.64 (95% CI: 0.61–0.67) 80–89: 0.70 (95% CI: 0.65–0.75) • Similar results for DBP also in figure 1. Similar results for men and women separately for stroke, figure 3, and IHD, figure 5.	
Kassai B, et al., 2005 (120) 17315403	Aim: Consideration of absolute risk has been recommended for making decisions concerning preventive treatment in HTN. Aim to estimate the benefit of antihypertensive therapy over a life-time. Study type: Meta-analysis on individual data in HTN and specific cause of death from national statistics. Disease-free survival curves until all pts have died were built using the "life-table" method. The treatment effect estimated from	Inclusion criteria: To estimate the rate of cv and non-CV deaths in a hypothetical U.S. population of untreated hypertensive pts, we used the following procedure: age-specific death rates in the U.S. general population were obtained from national vital statistics (1994), and in untreated hypertensive population they were obtained from the control groups of the INDANA database. This latter group represents a unique cohort of 14 942 untreated or placebo-treated hypertensive pts, 26–96 y with an average follow-up of 5 y Exclusion criteria: N/A	Intervention: The gain in life expectancy without stroke, CHD, and CV events was estimated from the area between the 2 survival curves of treated and control groups. The relative gain in life expectancy was defined as the ratio of gain in life expectancy to life expectancy.	1 endpoint: Stroke and CHD co- 1° Results: CHD Age ABb RGLEe Y RRa (%) NNTc GLEd (%) 40 0.86 0.3 333 20 4.1 50 0.88 1.0 100 17 4.3 60 0.90 1.9 53 13 3.4 70 0.91 3.9 26 10 5.4 Stroke Age ABb RGLEe Y RRa (%) NNTc GLEd (%) 40 0.80 0.4 250 32	Summary: Absolute gains in life expectancy are likely to be greater for younger, lower risk people with HTN than for older, higher risk people with HTN. However, the NNT to prevent an event will likely be greater especially in the short term in younger, lower risk people. This modeling analysis provides support for treating younger, lower risk individuals with HTN, but relies on the assumption that the relative benefits of treatments observed in short-term trials of higher risk individuals applies over a longer term to lower risk individuals.

	INDANA was applied to this curve to obtain the disease-free survival curve of the life-long treated population. Gains in event-free life expectancy were estimated from survival curves. A sensitivity analysis was performed to assess the impact of possible death misclassifications. Size: 6 RCTs, ~30,000 Pts			5.9 50 0.84 1.0 100 26 5.7 60 0.86 2.3 44 21 7.1 70 0.87 5.7 18 17 9.1 a RR at 10 y b Absolute benefit at 10 y c NNT to avoid 1 event. d Gain in life expectancy in mo without events. e Relative gain in life expectancy without events.	
Thomopolous C, et al., 2016 (54) 26848994	Study type: Meta-analysis of RTCs of more vs. less intense BP control	• 16 trials (52,235 pts) compared more vs. less intense treatment 34 (138,127 pts) active vs. placebo		More intense BP • Stroke RR: 0.71; 95% CI: 0.60–0.84) • CHD RR: 0.80; 95% CI: 0.68–0.95) • Major CV events RR: 0.75; 95% CI: 0.68–0.85 • CV mortality RR: 0.79; 95% CI: 0.63–0.97 Stratification of SBP cutoffs (150,140 and 130 mm Hg) showed that a SBP/DBP difference of 10/5 mm Hg across each cutoff reduced risk of all outcomes	Intensive BP reduction improves CV outcomes compared to less intense Achieved BP <130/80 may be associated with CV benefit.

Verdecchia P et al., 2016 27456518	Study type: Cumulative meta-analysis of RCTs to study benefit of more vs. less intensive BP lowering Size: 18 trials (n=53,405)	N/A	N/A	• Stroke, MI, HF, CVD mortality, and all-cause mortality • Difference in achieved SBP/DBP=7.6/4.5 mm Hg • For stroke and MI the cumulative Z score crossed the efficacy boundary after addition of the SPRINT results • For CVD mortality and HF, the cumulative Z curve crossed the conventional significance boundary (but not the sequential monitoring boundary) • For all-cause mortality, the cumulative Z curve did not reside in the futility are but did not cross the conventional significance boundary	The results strongly supported the benefit of intensive BP reduction for prevention of stroke and MI and suggested benefit for prevention of CVD mortality and HF
Bangalore S, et al., 2017 28109971	Study type: Network meta- analysis in which the authors attempted to compare the benefits and adverse effects resulting from intensive reduction in SBP Size: 17 trials (n=55,163)	N/A	N/A	• There was a significant reduction in stroke (RR: 0.54) and MI (RR: 0.68) • The point estimate favored all-cause mortality, CVD mortality and HF but the results did not achieve significance • SBP targets <120 and <130 mm Hg ranked #1 and #2 as the most efficacious • Serious adverse effects were more common at a	Overall, the beneficial effects of treatment were consistent with other reports. The cluster plots of treatment benefit vs. risk are difficult to interpret due to limitations of the available data base and the authors' decision to weight treatment benefits and potential adverse effects equally.

				lower SBP (120 vs. 150 or 140 mm Hg) • Cluster plots for combined efficacy and safety suggested a SBP <130 mm Hg as the optimal target for SBP reduction during treatment	
Bundy JD, et al., 2017 28564682	Study type: Network meta-analysis Size: 144,220 patients in 42 RCTs.	Inclusion criteria: • Random allocation into an antihypertensive medication, control or treatment target • Allocation to antihypertensive Antihypertensive treatment was independent of other treatment regimens • ≥100 patients in each treatment group • Trial duration ≥ 6 mo • One or more events for each treatment group reported • Minimum 5 mm Hg difference in SBP level between the 2 treatment groups Outcomes included major CVD, stroke, CHD, CVD mortality or all- cause mortality	N/A	• There were linear associations between mean achieved SBP and risk of cardiovascular disease and mortality, with the lowest risk at 120 to 124 mm Hg. Randomized groups with a mean achieved SBP of 120 to 124 mm Hg had a hazard ratio (HR) for major cardiovascular disease of 0.71 (95% CI: 0.60–0.83) compared with randomized groups with a mean achieved SBP of 130 to 134 mm Hg, an HR of 0.58 (95% CI: 0.48–0.72) compared with those with a mean achieved SBP of 140 to 144 mm Hg, an HR of 0.46 (95% CI: 0.34–0.63) compared with those with a mean achieved SBP of 150 to 154 mm Hg, and an HR of 0.36 (95% CI: 0.26–0.51) compared with those with a mean achieved SBP of 160 mm Hg or more.	This study suggests that reducing SBP to levels below currently recommended targets significantly reduces the risk of cardiovascular disease and all- cause mortality and strongly support more intensive control of SBP among adults with hypertension.

Lonn EM, et al., 2016 27041480	Aim: To assess efficacy of fixed-dose antihypertensive therapy in adults with intermediate CVD risk. Study type: Double-blind, placebo-controlled RCT, factorial design Size: 12,705 pts	Inclusion criteria: Men ≥55 y and women ≥60 y at intermediate risk for CVD. No BP restrictions. Exclusion criteria: • Known CVD • Indications or contraindications to study meds • Mod/advanced CKD Symptomatic hypotension	Intervention: FDC of ARB (candesartan 16 mg/d) and diuretic (hydrochlorothiazide 12.5 mg/d) or placebo Follow-up: Median=5.6 y	1 endpoint: 1 co-1° CVD composite outcomes • CVD mortality, nonfatal MI, nonfatal stroke Above plus cardiac arrest, HF, revascularization	Summary: • SBP/DBP reduction of 6.0/3.0 mm Hg • No difference in treatment effect • 1st co-1° 0.93 (0.79–1.10) • 2nd co-1° 0.95 (0.81–1.11) • Suggestion of a subgroup effect in tertile with the highest baseline BP and increased CVD risk.
Neaton JD, et al., 1993 (23) 8336373	Aim: To compare 6 antihypertensive drugs (representing different drug classes) Study type: Double-blind, placebo-controlled RCT Size: 902 pts with stage 1 HTN	Inclusion criteria: • Men and women 45–69 y • Not taking antihypertensive medications, with DBP 90–99 mm Hg Taking 1 antihypertensive medication, with DBP <95 mm Hg and between 85–99 mm Hg after withdrawal of BP medications	Intervention: Treatment (number): Once daily (AM): • Placebo (234) • Chlorthalidone 15 mg/d (136) • Acebutolol 400 mg/d (132) • Doxazosin 2 mg/d (134) • Amlodipine 5 mg/d (131) • Enalapril 5 mg/d (135) Follow-up: Median=4.4 y	1 endpoint: BP, QoL, side effects, chemistries, ECG, clinical events	Summary: • Drugs (plus diet) more effective compared to placebo (plus diet) for control of BP. Minimal differences between drug regimens
Whelton PK, et al., 1997 9168293	**Aim:** Study the effect of potassium supplementation on BP **Study type:**	**Inclusion criteria:** • Human RCT • Without HTN • Potassium supplementation vs. control • No concurrent interventions	**Intervention:** Potassium supplementation in 1,049 pts (potassium chloride tabs in 10 RCTs with 618 pts and diet in 2 RCT with 431 pts)	**1 endpoint:** • Significant reduction in BP. • Overall (hypertensives and normotensives), mean: 3.11 mm Hg; 95%	• This is the most comprehensive presentation of the effects of potassium on BP, including experience in

	Systematic review and meta-analysis **Size:** • Overall, 33 RCT (n=2,609) • 2 RCTs (n=1,049) in normotensives	**Exclusion criteria:** Missing key data	**Comparator:** No potassium supplementation (placebo in 10 RCT and usual diet in 2 RCT)	CI: -4.32– -1.91 mm Hg. • In the 12 trials conducted in normotensives, mean: -1.8 mm Hg; 95% CI: -2.9– -0.6 mm Hg for SBP and -1.0 mm Hg; 95% CI: -2.1–0.0 for DBP • In the 20 trials conducted in hypertensives, mean: -4.4 mm Hg; 95% CI: -6.6– -2.2 for SBP and -2.5 mm Hg; 95% CI: -4.9– -0.1 for DBP **Safety endpoint:** N/A	normotensives. • Significant reduction in SBP overall and in the subgroups with and without HTN. • In a subsequent meta-analysis of 23 trials, Geleijnse JM, Kok FJ, and Grobbee DE (J Hum Hypertens. 2003;17:471-480) reported a similar effect of potassium on SBP in both hypertensives and nonhypertensives (mean of -3.2 and -1.4 mm Hg, respectively). • The 1 RCT conducted in African-Americans (n=87) identified a mean treatment effect size of -6.9 mm Hg; 95% CI: -9.3– -4.4 for SBP (p<0.001) and -2.5 mm Hg; 95% CI: -4.3– -0.8 for DBP (p=0.004). • In the entire cohort (trials conducted in pts with HTN and normotension), net changes in SBP and DBP were directly related to level of urinary sodium excretion during the trial.

TOHP, Phase II Hypertension Prevention Collaborative Research Group, 1997 9080920	**Aim:** Study the effect of weight loss on BP and prevention of HTN. **Study type:** Randomized, controlled factorial trial. **Size:** 2,382 pts, of whom 1,192 were randomized to a weight loss intervention and 1,190 were randomized to a no weight loss intervention.	**Inclusion criteria:** Healthy community-dwelling adults 30–54 y • BMI between 110% and 165% of desirable body weight • Not taking BP-lowering medication • Mean SBP <140 mm Hg and DBP 83-89 mm Hg **Exclusion criteria:** • Taking antihypertensive medication • Heart disease, renal disease, poorly controlled hyperlipidemia or DM, DM requiring insulin, special dietary requirements >14 drinks/wk	**Intervention:** Behavior change intervention (combination of diet change and physical activity) aimed at studying the effects of a modest reduction in body weight during up to 48 mo (minimum 36 mo) of follow-up. **Comparator:** Usual care group	**1 endpoint:** Change in SBP Compared to usual care, the weight loss group experienced a significant mean reduction of -4.5 kg in body weight and -3.7 (SD: 0.5; p<0.001) mm Hg in SBP at 6 mo (-6.0 mm Hg in the weight loss group and -2.2 mm Hg in the usual care group). • A progressive reduction in the effect sizes for body weight and BP was noted over time, with mean for SBP at 18, 36 mo and termination of -1.8 (SD: 0.5; p<0.001), -1.3 (SD: 0.5; p=0.01), and - 1.1 (SD: 0.5; p=0.04). Prevention of HTN • At 6 mo of follow-up the incidence of new onset HTN was 42% lower in the participants randomized to weight loss compared to the usual care group (p=0.02). • During more prolonged follow-up, the effect size decreased but remained borderline significant after 48 mo of follow-up (13% reduction; p=0.06). Overall, the incidence of	• Largest trial of weight loss in prevention of HTN and also provides the longest duration of follow-up • The assumptions for a main effects factorial analysis (independence of the interventions) were not demonstrated. Given this finding, the most reliable analysis of this trial was comparison of the experience in each active intervention group with the usual care group. This results in a reduction in statistical power. • Consistent with the pattern in the proceeding TOHP I trial weight loss reduced BP and the incidence of HTN but the effect sizes for weight loss and BP as well as the difficulty of maintaining the intervention in highly motivated and extensively counselled participants underscores the difficulty of achieving and maintaining ideal body weight in the • general population by means of lifestyle change.

				HTN was reduced by 21% (p=0.02). **Safety endpoint:** N/A	
PREMIER Appel LJ, et al., 2003 (83) 12709466	**Aim:** Study the effect of 2 behavioral interventions, aimed at dietary change, on BP **Study type:** • Multicenter RCT with 3 parallel arms: • Established • Established plus DASH diet Advice only **Size:** 810 adults, with 62% (506) normotensive. At baseline, mean age, BMI and SBP/DBP were 50 y, 33 kg/m^2, and 135/85 mm Hg, respectively **Duration:** 6 mo, with observations at 3 and 6 mo.	**Inclusion criteria:** • Adults ≥25y • Average SBP between 120–159 mm Hg and average DBP between 80–95 mm Hg • No use of antihypertensive medication • BMI between 18.5 and 45 kg/m^2 **Exclusion criteria:** • Regular use of drugs that affect BP • Target organ damage or DM • Use of weight-loss meds • Hx CVD event • HF, angina, cancer, within 2 y • Consumption of >21 alcoholic drinks /wk Pregnancy, planned pregnancy, lactation	**Intervention:** • Structured behavioral interventions that used an identical format (4 individual and 14 group sessions) to facilitate adoption of "established" dietary recommendations for reduction in BP or "established" plus the DASH diet. The "established" dietary recommendations used in PREMIER were a) weight loss in overweight participants, b) sodium reduction, increased physical activity, reduced alcohol intake in pts consuming alcohol. • Compared to experience in the advice only (control) group, there was only modest achievement of intervention goals in the "established" group, with a MDs of 3.8 kg (8.4 lbs) for body weight, 11.6 mmol (267 mg)/d) for urinary sodium excretion, no change in physical activity (but better fitness), and no change	**1 endpoint** • Compared to control (advice only), SBP and DBP were significantly reduced with both active interventions but there was no significant difference in the effect size between the 2 active intervention groups. This was true for both the normotensive and hypertensive pts, with the effect size being larger in the hypertensive group. In the normotensives, the MD for change in SBP was identical for the "established" compared to "established plus DASH Diet" groups: -3.1 (95% CI: -5.1– -1.1) mm Hg The corresponding changes for DBP were -1.6 (95% CI: -2.9– -0.2) for the "established" intervention group and -2.0 (95% CI: -3.4– -0.6) for the "established intervention plus DASH Diet) group. • Overall, the incidence of HTN was lowest and the percent with optimal BP was highest in the	● This was an interesting trial which employed a behavior change approach to implement both active interventions. ● The investigators goal was to determine the additive value of the DASH Diet in persons already following key elements of conventional (established) recommendations for nonpharmacologic intervention to lower BP. ● The intervention approach in this trial was less effective in achieving weight loss and reduction in dietary sodium compared to the corresponding experience in the TOHP and TONE trials and the DASH Diet effects on intermediate variables (such as fruit and vegetable consumption) was less than that achieved in the DASH Diet feeding studies. Despite the modest intervention effects, both

			in alcohol consumption (but very low alcohol consumption at baseline). Weight loss was somewhat greater in the "established" plus DASH diet group, with a MD of 4.8 kg (10.6 lbs) for body weight. This group also manifested expected effects of the DASH diet, with significantly higher urinary potassium and phosphorous levels, greater consumption of fruits and vegetables, dietary calcium, dairy products, and a lower consumption of total fat and saturated fat. **Comparator:** Advice only	"established plus DASH" diet but the incidence of HTN was significantly less and the percent with optimal BP was higher in both active intervention groups compared to advice only. The difference between the 2 active intervention groups was not significant. In the normotensives, there was a nonsignificant trend towards less HTN and a significantly higher percent with optimal BP in both active intervention groups compared to advice only, with no significant difference for percent with optimal BP in the 2 active intervention groups. 1 **Safety endpoint**: N/A	SBP and DBP were significantly reduced with the conventional intervention approach (in normotensives as well as overall) and addition of the DASH diet did not have a significant effect on reduction of SBP or DBP. • There were some nonsignificant trends for slightly lower BP, less HTN, and more optimal BP in the "established plus DASH Diet" group compared to "established" group. The authors also cited use of the DASH Diet as a means to beneficially influence CVD risk factors in addition to BP.
Aburto NJ, et al., 2013 23558163	**Aim:** Study the effect of sodium reduction on BP **Study type:** Systematic review and meta-analysis **Size:** Overall study included 36 trials (49 comparisons) conducted in 6,736 pts. Of these, 3,263 were nonhypertensive. The	**Inclusion criteria:** ● RCT in humans ● Trial duration ≥4 wk ● 24-h urinary sodium ≥40 mmol/d less in treatment compared to control group ● No concurrent interventions ● Not acutely ill **Exclusion criteria:** Lack of above	**Intervention:** Sodium reduction **Comparator:** No sodium reduction	1 **endpoint:** In pooled analysis, the overall change in SBP was -3.39 (95% CI: -4.31– - 2.46) mm Hg. In the pts with HTN, the change was -4.06 (95% CI: -5.15– -2.96). In the normotensives, the change was -1.38 (95% CI: -2.74–0.02). **Safety endpoint:** In the small number of relevant trials, there was no significant effect of sodium	● Study inclusion/exclusion criteria designed to yield a group of trials that would provide results that have relevance for clinical practice and public health. In this context, reduced sodium intake resulted in a statistically significant but small reduction in SBP.

	results in normotensives in this table are based on experience in 7 RCTs conducted in 3,067 normotensive pts.			reduction on lipid levels (Total cholesterol, LDL-cholesterol, HDL-cholesterol, triglyceride levels; 11 trials) or on plasma (7 trials) or urinary catecholamine levels (2 trials). Experience in 4 trials (3 which could not be included in the meta-analysis) suggested a beneficial effect of sodium reduction on urinary protein excretion.	
Graudal NA, et al., 2012 (76) 22068710	**Aim:** Study the effect of sodium reduction on BP **Study type:** Systematic review and meta-analysis **Size:** Overall study included 167 trials. Of these, 71 RCTs were conducted in 5,577 normotensive pts, with the following characteristics: ● Median age: 27 y (13–67 y) ● Median trial duration: 7 d (4–1,100 d) ● 5,292 Whites (71 studies) ● 268 Blacks (7 studies) 215 Asians (3	**Inclusion criteria:** ● RCTs ● 24-h collections or estimates from ≥8 h collections of urinary sodium excretion **Exclusion criteria:** Systematic studies in unhealthy pts with diseases other than HTN	**Intervention:** Sodium reduction **Comparator:** No sodium reduction	**1 endpoint:** The overall effect of sodium reduction was not presented. A forest plot of 71 comparisons (from 61 trials) in the 4,919 normotensive whites assigned to sodium reduction compared to usual sodium intake identified a trend towards lower SBP in 50 (70%), no difference in 8 (11%), and higher SBP in 13 (19%). In a pooled analysis, sodium reduction compared to usual sodium intake in the normotensives yielded the following MDs in SBP: ● Whites: -1.27 (95% CI: -1.88– -0.66) ● Blacks: -4.02 (95% CI: -7.37– -0.68)	● Heterogeneous group of trials that included many small studies of short duration in young persons. ● Overall finding of lower BP in those assigned to a reduced intake of dietary sodium, with an apparently greater effect in Blacks compared to Whites and Asians. ● The hormone changes in this meta-analysis likely reflect a physiologic response to sodium reduction, especially in studies of short duration and rapid changes in sodium intake. The increases in total cholesterol and triglyceride levels were not noted in the meta-

	studies)			● Asians: -1.27 (95% CI: -3.07– -0.54) A corresponding analysis in the hypertensives yielded the normotensives yielded the following MDs in SBP: ● Whites: -5.48 (95% CI: -6.53– -4.43) ● Blacks: -6.44 (95% CI: -8.85– -4.03) ● Asians: -10.21 (95% CI: -16.98– -3.44) **Safety endpoint:** In the relevant trials (all cross-over studies and including comparisons in both hypertensive and normotensive participants) that provided safety endpoint measurements, significant increases in the standard MD for plasma renin activity (70 trials), aldosterone (51 trials), noradrenaline (31 trials), adrenaline (14 trials), and weighted MD for total cholesterol (24 trials), and triglyceride (18 trials) levels. There was no significant effect of sodium reduction on LDL-cholesterol (15 trials) and HDL-cholesterol	analyses conducted by Aburto et al. and He et al.

				(17 trials).	
Geleijnse JM, et al., 2003 (69) 12821954	**Aim**: Study the effect of potassium supplementation on BP **Study type**: Systematic review and meta- regression analysis **Size**: 27 RCTs; 19 in pts with HTN and 11 RCTs in pts without HTN	**Inclusion criteria**: • RCT in adults • Published after 1966 • Duration ≥2 wk • No concomitant interventions **Exclusion criteria**: • Disease Outlier results (1 trial)	**Intervention**: Potassium supplementation **Comparator**: No potassium supplementation	**1 endpoint**: • Overall change in SBP=- 2.42; 95% CI: -3.75– -1.08 • In the 19 trials conducted in hypertensives, change in SBP was -3.51 mm Hg; 95% CI: -5.31– -1.72 • In the 3 trials conducted in persons without HTN, change in SBP was 0.97 mm Hg; 95% CI: -3.07–1.14 **Safety endpoint**: N/A	• Imputation for missing data • In addition to the treatment effect difference by presence/absence of HTN, there was a trend toward a larger treatment effect in older age (≥45 y), and to a lesser extent higher baseline urinary Na (>150 mmol/24 h) and greater increase in urinary K (>44 mmol/24 h)
Carlson DJ, et al., 2014 (100) 24582191	**Aim:** Study the effect of physical activity on BP in children with obesity. **Study type:** Systematic review and meta-analysis. **Size:** 9 RCTs (223 pts: 127 intervention and 96 controls): 6 were conducted in normotensives.	**Inclusion criteria:** • Adults ≥18 y • RCT, including cross-over trials. • Duration ≥4 wk • Published in a peer reviewed journal between January 1, 1966 and July 31, 2013 **Exclusion criteria:** Studies that employed any intervention other than pure isometric exercise (e.g., dynamic resistance)	**Intervention:** Pure isometric exercise. **Comparator:** Use of a control group was a requirement but no additional specific information provided.	**1 endpoint:** • In the overall pooled analysis (hypertensive and normotensive trials), mean change in SBP was -6.77 (95% CI: -7.93– -5.62) mm Hg. • In the subgroup of 3 trials with hypertensive pts (all on antihypertensive medication), the mean change in SBP was -4.31 (95% CI: -6.42– -2.21) mm Hg. In the subgroup of 6 trials with normotensive pts, the mean change in SBP was -7.83 (95% CI: -9.21– -6.45)	• This study provides information regarding the effect of pure isometric exercise interventions on BP in adults. • The BP reductions reported in this meta-analysis are surprisingly large but the overall effect pattern is quite consistent with other meta-analyses of isometric exercise.

				mm Hg. **Safety endpoint:** N/A	
Garcia-Hermosa A, et al., 2013 (99) 23786645	**Aim:** Study the effect of exercise on BP in obese children. **Study type:** Systematic review and meta-analysis. **Size:** 9 RCTs (410 pts).	**Inclusion criteria:** • Children ≤14 y with obesity • RCT • Duration ≥8 wk • 1° outcome: change in BP **Exclusion criteria:** Concomitant intervention	**Intervention:** Physical activity, principally aerobic exercise. **Comparator:** No physical exercise, nutrition, education, or dietary restriction intervention	**1 endpoint:** Change in SBP: In pooled analysis, mean change in SBP was -0.4 (95% CI: -0.66– -0.24). **Safety endpoint:** N/A	• This meta-analysis focused specifically on the effect of physical activity on BP in children with obesity. Although it is not stated explicitly, it seems likely that all of the participants were normotensive and not receiving medication that could influence level of BP. • The findings are consistent with other meta-analyses of the effect of physical activity on BP. • Only limited information regarding study details is provided in this publication. The interventions were • heterogeneous in type, duration, and quality.
Rossi AM, et al., 2013 23541664	**Aim:** Study the effect of resistance exercise on BP **Study type:** Systematic review and meta-analysis **Size:** 9 RCTs (11 intervention groups	**Inclusion criteria:** • RCTs in adults (≥18 y) BP-lowering 1° outcome • Trial duration ≥4 wk • Resistance training only intervention **Exclusion criteria:** Handgrip/isometric exercise	**Intervention:** Dynamic resistance training but overall reporting of the details was poor. **Comparator:** No resistance training but not detailed in this article	**1 endpoint:** Pooled experience (hypertensive and normotensive pts) identified a small, nonsignificant reduction in mean SBP of -1.03 (95% CI: -3.44–0.39). The corresponding finding for DBP was -2.19 (95% CI: -3.87– -	• Suggests resistance training is effective in lowering BP and was the basis for recommending this intervention in the Canadian HTN Education Program recommendations. • The discrepancy in effect size between this meta-analysis and the 1

	and 14 comparisons) conducted in 452 pts. 10 (71%) of the 14 comparisons were conducted in normotensives			0.51). **Safety endpoint:** N/A	conducted by Cornelisson et al may have been due to the more restrictive requirement by Rossi et al that change in BP be the 1° outcome.
TOHP, Phase II Hypertension Prevention Collaborative Research Group, 1997 9080920	**Aim:** Study the effect of weight loss on BP and prevention of HTN. **Study type:** Randomized, controlled factorial trial. **Size:** 2,382 pts, of whom 1,192 were randomized to a weight loss intervention and 1,190 were randomized to a no weight loss intervention.	**Inclusion criteria:** Healthy community-dwelling adults 30–54 y • BMI between 110% and 165% of desirable body weight • Not taking BP-lowering medication • Mean SBP <140 mm Hg and DBP 83-89 mm Hg **Exclusion criteria:** • Taking antihypertensive medication • Heart disease, renal disease, poorly controlled hyperlipidemia or DM, DM requiring insulin, special dietary requirements >14 drinks/wk	**Intervention:** Behavior change intervention (combination of diet change and physical activity) aimed at studying the effects of a modest reduction in body weight during up to 48 mo (minimum 36 mo) of follow-up. **Comparator:** Usual care group	**1 endpoint:** Change in SBP Compared to usual care, the weight loss group experienced a significant mean reduction of -4.5 kg in body weight and -3.7 (SD: 0.5; p<0.001) mm Hg in SBP at 6 mo (-6.0 mm Hg in the weight loss group and -2.2 mm Hg in the usual care group). • A progressive reduction in the effect sizes for body weight and BP was noted over time, with mean for SBP at 18, 36 mo and termination of -1.8 (SD: 0.5; p<0.001), -1.3 (SD: 0.5; p=0.01), and - 1.1 (SD: 0.5; p=0.04). Prevention of HTN • At 6 mo of follow-up the incidence of new onset HTN was 42% lower in the participants randomized to weight loss compared to the usual care group (p=0.02). • During more	• Largest trial of weight loss in prevention of HTN and also provides the longest duration of follow-up • The assumptions for a main effects factorial analysis (independence of the interventions) were not demonstrated. Given this finding, the most reliable analysis of this trial was comparison of the experience in each active intervention group with the usual care group. This results in a reduction in statistical power. • Consistent with the pattern in the proceeding TOHP I trial weight loss reduced BP and the incidence of HTN but the effect sizes for weight loss and BP as well as the difficulty of maintaining the intervention in highly motivated and extensively counselled participants underscores

				prolonged follow-up, the effect size decreased but remained borderline significant after 48 mo of follow-up (13% reduction; p=0.06). Overall, the incidence of HTN was reduced by 21% (p=0.02). **Safety endpoint:** N/A	the difficulty of achieving and maintaining ideal body weight in the • general population by means of lifestyle change.
TOHP, Phase I 1992 1586398	**Aim:** Study the effect of weight loss on BP and prevention of HTN **Study type:** Randomized, controlled factorial trial. **Size:** Overall, 2,182 adults, with the 308 assigned to weight loss compared to 256 usual care controls	**Inclusion criteria:** • Community-dwelling adults 30–54 y • Not on antihypertensive medication • DBP 80-89 mm Hg • Healthy **Exclusion criteria:** • Disease • Inability to comply with the protocol	**Intervention:** Behavior change intervention (combination of diet change and physical activity) **Comparator:** Usual care	**1 endpoint:** Change in DBP **2 endpoint:** Change in SBP **Safety endpoint:** CVD events, symptoms and general and well being	• Significantly lower DBP (2.3 mm Hg; p<0.01) and SBP (2.9 mm Hg; p<0.01) in the weight loss group compared to usual care • Few CVD events • No difference in symptoms • Significant improvement in general well-being at 6 • and 18 mo (p<0.05)
Xin X, et al., 2001 11711507	**Aim:** Study the effect of alcohol reduction on BP **Study type:** Systematic review and meta-analysis **Size:** • 15 RCTs (25 comparisons) with 2,234 pts. • 6 trials were conducted in	**Inclusion criteria:** • RCT in humans • Publication between 1966-1999 • Duration ≥1 wk • Only pts regularly consuming alcohol • Only difference between the comparison groups was alcohol intake **Exclusion criteria:** Comparison of different doses of alcohol intake	**Intervention:** Reduction in alcohol consumption. In most trials this was achieved by randomization to "light" alcohol but some RCT were based on a behavioral intervention aimed at reducing the number of drinks consumed. **Comparator:** Usual consumption of alcohol	**1 endpoint:** • Overall, alcohol reduction was associated with a significant reduction in mean SBP of -3.31 (95% CI: -4.10– -2.52) and DBP of -2.04 (95% CI: -2.58– -1.49). • In the subgroup of 7 RCTs in persons with HTN, the mean changes in SBP and DBP were -3.9 (95% CI: -5.04– -2.76) and	• This is the most recent meta-analysis of this topic. Although this meta-analysis reports % reduction in alcohol intake, most trials aimed at reducing the number of alcoholic drinks consumed achieved a reduction of about 3 drinks/d. The intervention results were consistent with the

	normotensives (269 pts with a mean age ranging from 26.5–45.5 y). Average consumption of alcohol at baseline was not reported. Follow-up varied from 1–18 wk			-2.41 (95% CI: -3.25– -1.57). • In the subgroup of 6 RCTs in normotensives the corresponding changes in SBP and DBP were -3.5 (95% CI: -4.61– -2.51) and -1.80 (95% CI: -3.03– -0.58). • In a meta-regression analysis, a dose-response was noted between % reduction in alcohol consumption and mean reduction in BP. 1 **Safety endpoint:** N/A	relationship alcohol and BP in observational epidemiology – about a 1 mm Hg higher SBP per alcoholic drink consumed. In observational studies, type of alcohol does not seem to matter and at lower levels of alcohol consumption (<1 standard size alcoholic drink per day in women and <2 in men) there does not seem to be an important biological effect of alcohol on BP. • The relationship between alcohol consumption and BP is predictable and consistent in observational and RCT studies. However, the relationship between alcohol consumption and CVD is more complex as alcohol is associated with an apparently beneficial effect on CVD risk, possibly mediated by an increase in HDL-cholesterol. • Pregnant women,

					pts with HTN and those at risk of a drinking problem should not drink alcohol. Established light drinkers (<2 standard drinks/d in men and <1/d in women) who are • normotensive are in a favorable risk category for CVD.
Stewart SH, et al., 2008 18821872	**Aim:** Study the effect of reduced alcohol intake on BP. **Study type:** Randomized, controlled factorial trial. **Size:** 1,383 pts.	**Inclusion criteria:** • Alcohol dependence. • 4—21 d of abstinence. • Men: >21 drinks/wk; Women >14 drinks/wk. • At least 2 heavy drinking days within a consecutive 30-d period during 90 d prior to baseline. **Exclusion criteria:** • Other substance abuse. • Psychiatric disorder requiring medication. Unstable medical condition	**Intervention:** Pharmacotherapy (naltrexone, acamprosate, or both) and counseling strategies (behavioral and/or medical management). **Comparator:** Placebo.	**Change in BP:** • Based on up to 5 repeated measures of BP over 16 wk. Data modeled to estimate change in BP over time. • For pts with higher than average baseline SBP (>132 mm Hg), SBP declined by an average of 12 mm Hg (149—137) in the intervention arm compared to placebo, with a corresponding decline in DBP of 8 mm Hg. For those with a baseline SBP ≤132 mm Hg there was no change in SBP (120—121 mm Hg) or DBP.	• This trial was designed to evaluate interventions for treatment of alcohol dependence. • BP measurements were not standardized. • About 20% of the observations were missing and assumed to be random.
Dickenson HO, et al., 2006 16508562	**Aim:** Study effectiveness of lifestyle interventions, including reduced	**Inclusion criteria:** • Only parallel trials • SBP ≥140 mm Hg and/or DBP ≥85 mm Hg • ≥8 wk duration	**Intervention:** Lifestyle change aimed at reduced consumption of alcohol	**1 endpoint:** -Net reduction (95% CI): SBP -3.8 (-6.1— -1.4) DBP -3.2 (-5.0— -1.4)	• Relatively small number of trials • Limited details provided

	alcohol intake, for treatment of HTN. **Study type:** 1 of 10 meta-analyses. **Size:** 4 trials which collectively studied 305 pts	• BP outcome **Exclusion criteria:** • 2º HTN or renal disease • Pregnant women Change in BP meds during trial	**Comparator:** Usual care	**Safety endpoint:** N/A	
Wallace P, et al., 1988 3052668	**Aim:** Study effectiveness of general practitioner advice to reduce heavy drinking. **Study type:** • RCT **Size:** 909 adults (641 men and 268 women)	**Inclusion criteria:** Heavy drinking during wk prior to screening interview. **Exclusion criteria:** None mentioned	**Intervention:** Physician counselling aimed at reduced consumption of alcohol. **Comparator:** Usual care	**Endpoints:** • 1° outcome was reduction in percent with heavy consumption of alcohol (mean net change=46%). Liver enzymes and BP also measured at 6 and 12 mo. • Pretreatment SBP/DBP=133.5/79.9 mm Hg. Net reduction SBP=-2.12 (95% CI: -4.19– -0.00) **Safety endpoint:** N/A	• The goal was to blind those conducting the outcome assessment to treatment assignment but by 6 mo assignment was known in 20-30% of the participants. • A reduction in SBP was noted despite use of a modest intervention.
Lang T, et al., 1995 8596098	**Aim**: Worksite study of reduced alcohol intake effect on BP in heavy drinkers with HTN. **Study type:** RCT **Size:** 14 site physicians; 129 adults (95% men)	**Inclusion criteria:** • Heavy drinking (documented by history and liver enzyme elevation). • HTN (SBP/DBP >140/90 mm Hg) **Exclusion criteria:** • 2º HTN • Severe liver disease Planned move/retirement.	**Intervention:** Physician and worker counselling aimed at reduced consumption of alcohol. **Comparator:** Usual care. **Duration**: Follow-up visits at 1, 3, 6, and 18 mo.	**Endpoints:** • Baseline SBP/DBP=162.5/98.0. Although all of the workers had HTN, only about 20% were being treated with antihypertensive medications at baseline. • At 1 y, the net change in SBP=-5.5 ($p<0.05$). When 5 sites with <5 workers/site were excluded, the net	• Behavioral intervention state of the art for its time • Careful measurements of BP using Hawksley RZ sphygmomanometer. • Main analyses do not seem to have accounted for cluster design.

				change in SBP=-7.3 mm Hg (p<0.01). At 2 y, the net change in SBP=-6.6 (p<0.05). **Safety endpoint:** N/A	
Thompson AM, et al., 2011 21364140	**Aim:** To evaluate the effect of antihypertensive treatment on 2º prevention of CVD events and all-cause mortality among pts without clinically defined HTN. **Study type**: Meta- analysis including 25 RCTs **Size**: 64,162 pts without HTN.	**Inclusion criteria:** RCTs of antihypertensive treatment among pts with BP <140/90 mm Hg for the prevention of CVD events. **Exclusion criteria**: CVD events were not reported by HTN status that included participants with and without HTN; study population did not include persons with BP in the normal or prehypertensive ranges; study population did not include persons with preexisting CVD or CVD equivalents, such as DM; antihypertensive medication was not a part of the intervention; treatment allocation was not random; measure of variance not reported; participants were <18 y; there were differences between intervention and control groups other than antihypertensive treatment. Preexisting CVD included PAD.	**Interventions**: Any antihypertensive agent compared with placebo or no treatment.	**Results**: Compared with controls, pts receiving antihypertensive medications had a pooled RR of 0.77 (95% CI: 0.61, 0.77) for stroke: 0.80 (95% CI: 0.69, 0.93) for MI: 0.71 (95% CI: 0.65, 0.77) for CHF: 0.85 (95% CI: 0.80, 0.90) for composite CVD events: 0.83 (95% CI: 0.69, 0.99) for CVD mortality and 0.87 (95% CI: 0.80, 0.95) for all-cause mortality from random effect models. Results did not differ according to trial characteristics or subgroups defined by clinical history, although no specific PAD subgroup was defined. **Summary**: Among pts with clinical history of CVD, including PAD, but without HTN, antihypertensive treatment was associated with reduced risk of stroke, CHF, composite CVD events and all-cause mortality.	**Study limitations and adverse events:** • PAD not specifically collected at baseline, thus cannot detect actual incidence (however, randomization • presumably resulted in equal number of baseline PAD cases in each group) • Asymptomatic PAD likely missed (definition used in this study based on hospitalization, likely only capturing very severe cases)

Thomopoulos C, et al., 2014 25259547	**Aim:** Investigating whether all grades of HTN benefit from BP-lowering treatment and which are the target BP levels to maximize outcome reduction. **Study type:** Meta- analysis of RCTs **Size:** 32 RCTs with 104,359 pts	**Inclusion criteria:** Intentional BP-lowering comparing active drug treatment with placebo, or less active treatment (intentional BP-lowering trials), or comparison of an active drug with placebo over baseline antihypertensive treatment, resulting in a BP difference of at least 2 mm Hg in either SBP or DBP (nonintentional BP-lowering trials); enrolling of hypertensive individuals only or a high proportion (at least 40%) of them. **Exclusion criteria:** N/A	**Intervention/Comparator:** Criteria of eligibility were intentional BP-lowering comparing active drug treatment with placebo, or less active treatment (intentional BP-lowering trials), or comparison of an active drug with placebo over baseline antihypertensive treatment, resulting in a BP difference of at least 2 mm Hg in either SBP or DBP (nonintentional BP-lowering trials); enrolling of hypertensive individuals only or a high proportion (at least 40%) of them. Other inclusion criteria can be found in the preceding paper. 51 trials were found eligible either for assessing BP-lowering effects in different HTN grades or for assessing the effects of achieving different BP levels	**1 endpoint:** • As some trials were done on low- risk pts, others on higher risk pts, no evaluation of absolute risk-reduction was made. However, a 2º analysis was done including trials or trial subgroups with mean baseline SBP/DBP values in grade 1 range and a low-to-moderate risk (<5% CV deaths in 10 y in controls): FEVER stratum with baseline SBP below the median (<153 mm Hg) (e7); HTN Detection and Follow-up Program stratum with baseline DBP 90–94 mm Hg and no CVD (e9); OSLO (e17); TOMHS (e28) and USPHS (e29). Risks of stroke, CHD, the composite of stroke and CHD, and all-cause death were significantly reduced by BP-lowering in these low-to-moderate risk pts (control group: average CV mortality 4.5% in10 y) with a moderate BP elevation (average SBP/DBP 145.5/91 mm Hg) at randomization. Standardized risk ratio associated with 10/5 reduction in BP: stroke 0.33 (95% CI: 0.11–0.98)	**Summary**: Meta-analyses favor BP-lowering treatment even in grade 1 HTN at low-to- moderate risk, and lowering SBP/DBP to <140/90 mm Hg. Achieving <130/80 mm Hg appears safe, but only adds further reduction in stroke.

				CHD 0.68 (95% CI: 0.48–0.95) CVD death 0.57 (95% CI: 0.32– 1.02) total death 0.53 (95% 0.35– 0.80) • Compared outcomes of achieved on study SBP <130 vs. ≥130 Standardized Risk ratio associated with 10/5 reduction in BP: stroke 0.68 (95% CI: 0.57, 0.83) CHD 0.87 (95% CI: 0.76, 1.00) HF 0.92 (95% CI: 0.47, 1.77) CVD 0.81 (95% CI: 0.67, 1.00) CVD death 0.88 (95% CI: 0.77, 1.01) total death 0.88 (95% CI: 0.77, 0.99) Outcomes of achieved on study SBP 130–139 vs. ≥140 Standardized Risk ratio associated with 10/5 reduction in BP: stroke 0.63 (95% CI: 0.52–0.77) CHD 0.77 (95% CI: 0.70–0.86) HF 0.76 (95% CI: 0.47–1.25) CVD 0.74 (95% CI: 0.62–0.88) CVD death 0.81 (95% CI: 0.67– 0.97) total death 0.87 (95% CI:	

				0.75–1.00) • Similar pattern of results for on treatment DBP	
MDRD Klahr S, et al., 1994 8114857	**Aim:** To determine whether restricted protein intake or tighter HTN control would delay progression of CKD **Study type**: Randomized management to low or usual BP goal and usual, low or very low protein intake **Size:** • Total n=840 Study 1 n=585 Study 2 n=255 • Mean follow-up 2.2 y • Mean MAP, mm Hg (SD): Study 1: 98 (11) Study 2: 98 (11) • Mean SBP, mm Hg (SD): Study 1: 131 (18) Study 2: 133 (18) • Mean DBP, mm Hg (SD): Study 1: 81 (10) Study 2: 81 (10)	**Inclusion criteria:** Adults 18–70 y, with renal insufficiency (serum Cr 1.2–7.0 mg/dL in women and 1.4–7.0 mg/dL in men or CrCl <70 mL/min per 1.73 m²) and MAP≤125 mm Hg (normotensives included) **Exclusion criteria:** Pregnancy, body weight <80% or >160% of standard, DM requiring insulin, urine protein >10 g/d, history of renal transplant, chronic medical conditions, doubts regarding compliance.	**Intervention:** • Study 1 included subjects with GFR 25–55 mL/min 1.73 m² (n=585); • Study 2 included subjects with GFR 13–24 mL/min 1.73 m² (n=255) • Low MAP goal ≤92 mm Hg for those 18–60 y; ≤98 for those ≥61 y • Usual: MAP goal ≤107 mm Hg for those 18–60; MAP ≤113 for subjects ≥61 • 2 studies: Study 1: above BP goals plus usual or low protein diet (1.3 or 0.58 g protein per kg of body weight/d) Study 2: above BP goals plus low or very low protein diet (0.58 or 0.28 g per kg/d) Between group difference in MAP, mm Hg 4.7; p<0.001 **Comparator:** By BP and protein intake goals	**1° endpoint:** Rate of decline in GFR, mL/min (95% CI) • Study 1 From baseline to 4 mo Low: 3.4; 95% CI: 2.6–4.1 Usual: 1.9; 95% CI: 1.1–2.7 p=0.010 4 mo to study end, Low: 2.8; 95% CI: 2.2–3.3 Usual: 3.9; 95% CI: 3.3–4.5 p=0.006 Baseline to 3 y, Low: 10.7; 95% CI: 9.1–12.4 Usual: 12.3; 95% CI: 10.6–14.0 p=0.18 • Study 2 From baseline to end of study, Low: 3.7; 95% CI: 3.1–4.3 Usual: 4.2; 95% CI: 3.6–4.9 p=0.28 ESRD or death:	**Limitations**: • Drug therapy was not randomized. Recommended ACEI ± diuretic then CCB and others. More subjects in the low BP goal groups received ACEIs (48%, 51% also reported elsewhere) compared to the usual BP goal group (28%, 32% also reported e/w) (not noted in 1° manuscript but reported in Peterson JC, et al., 1995 (170)). 1.9% study 1, 1.2% study 2 lost to follow-up. • Rate of GFR decline was slower than expected in the control groups and was not constant. **Summary:** No significant benefits overall from either low protein or lower BP target. There was a significant interaction between baseline urinary protein excretion and BP interventions (p=0.01) indicating that low BP was of benefit to subjects with >1 g proteinuria with slower progression of loss

				• Study 2 RR for low vs. usual: 0.85; 95% CI: 0.60–1.22 p=NR	of GFR
Soliman EZ et al., 2015 26459421	**Aim:** To compare effects of combinations of standard and intensive control of BP on the risk of LVH in the ACCORD trial. **Study type**: RCT **Size**: 4,331 pts, 4.7 y follow-up	**Inclusion criteria**: DM- 2 with HgbA1c 7.5%; 40 y with CVD or 55 y with anatomical evidence of atherosclerosis, albuminuria, LVH, or at least 2 additional risk factors for CVD. **Exclusion criteria**: BMI 45, serum creatinine >1.5, and other serious illness.	Pts were randomly assigned to intensive therapy SBP<120 mm Hg or standard therapy SBP<140 mm Hg.	1 **outcomes**: Nonfatal MI, nonfatal stroke, or CV death. **Results**: The outcome measures were electrocardiographic LVH defined by Cornell voltage (binary variable) and mean Cornell index (continuous variable). The baseline prevalence of LVH (5.3% vs. 5.4%; p=0.91) and the mean Cornell index (1,456 vs. 1,470 µV; p=0.45) were similar in the intensive (n=2,154) and standard (n=2,177) BP- lowering arms, respectively. However, after median follow-up of 4.4 y, intensive, compared with standard, BP lowering was associated with a 39% lower risk of LVH (OR: 0.61; 95% CI: 0.43–0.88; p=0.008) and a significantly lower adjusted mean Cornell index (1,352 vs. 1,447 µV; p<0.001). The lower risk of LVH associated with intensive BP lowering	**Limitations:** 2º analysis; open-label design; LVH defined by EKG and not by echo or cardiac MRI; results may not apply to younger, healthier diabetics. **Conclusions**: Targeting a SBP of <120 mm Hg when compared with <140 mm Hg in pts with HTN and DM produces a greater reduction in LVH

				during follow-up was because of more regression of baseline LVH and lower rate of developing new LVH, compared with standard BP lowering. No interactions by age, sex, or race were observed.	
ACCORD Cushman WC, et al., 2010 20228401	**Aim**: To assess whether therapy targeting normal SBP (<120 mm Hg) reduces major CV events in DM-2 at high risk for CV events. **Study type**: RCT **Size**: 4,733 pts, 4.7 y follow-up	**Inclusion criteria**: DM- 2 with HgbA1c 7.5%; 40 y with CVD or 55 y with anatomical evidence of atherosclerosis, albuminuria, LVH, or ≥2 additional risk factors for CVD. **Exclusion criteria**: BMI 45, serum creatinine >1.5, and other serious illness.	Pts were randomly assigned to intensive therapy SBP <120 mm Hg or standard therapy SBP <140 mm Hg.	**1 outcomes**: Nonfatal MI, nonfatal stroke, or CV death. **Results**: Mean SBP in the intensive therapy group was 119.3 mm Hg and in the standard therapy group was 133.5 mm Hg. The annual 1° outcome 1.87% in the intensive therapy group and 2.09% in the standard therapy group HR: 0.88; 95% CI: 0.073–1.06; p=0.20. The annual rates of death from any cause were 1.28% and 1.19% in the 2 groups, respectively (HR: 0.59; 95% CI: 0.39–0.89; p=0.01). Serious adverse events attributed to antihypertensive treatment occurred in 3.3% of the intensive therapy group and 1.3% of the standard therapy group (p<0.001).	**Limitations**: This trial had an open label design. The rate of adverse events in the standard therapy group was less than expected. Pts younger than 40 y or older than 79 y were not included. **Summary**: In pts with DM-2 and high risk for CV events, targeting SBP of <120 as compared with <140 mm Hg did not reduce the rate of composite outcome of fatal and nonfatal major CV events and was associated with greater risk for adverse events.

Van Dieren S, et al., 2012 22677192	**Aim:** To assess differences in treatment effects of a fixed combination of perindopril–indapamide on major clinical outcomes in pts with type 2 DM across subgroups of CV risk. **Study type:** RCT **Size:** 11,140 pts with DM-2, from the ADVANCE trial	**Inclusion criteria:** DM-2, aged ≥55 y, with a history of major macrovascular or microvascular disease, or at least 1 other risk factor for vascular disease **Exclusion criteria:** A definite indication for, or contraindication to, any of the study treatments, a definite indication for long-term insulin treatment or were participating in any other clinical trial.	**Intervention:** Perindopril–indapamide or matching placebo	**1 endpoint:** • The Framingham equation was used to calculate 5-y CVD risk and to divide participants into 2 risk groups, moderate-to-high risk (<25% and no history of macrovascular disease), very high risk (>25% and/or history of macrovascular disease). Endpoints were macrovascular and microvascular events.	**Summary**: Relative effects of BP-lowering with perindopril–indapamide on CV outcomes were similar across risk groups whilst absolute effects trended to be greater in the high-risk group.
Montgomery AA, et al., 2003 12923409	**Aim:** To estimate the effectiveness and cost-effectiveness of BP-lowering treatment over a lifetime. **Study type:** Markov decision analysis model comparing treatment and nontreatment of HTN. **Size:** Hypothetical cohorts for 20 different strata of sex, age (30– 79 y, in 10-y bands), and CV risk (low and high)	**Inclusion criteria:** We created models for 20 different strata of sex, age (age 30–70 y in 10-y bands), and 2 risk profiles (designated as 'low' and 'high' risk). These example risk profiles represent the extremes of absolute CV risk, based on data from the Health Survey for England and using a Framingham risk function. We recognize that the risk of most individuals seen in primary care will be somewhere between the examples presented here. The data included were as follows: age- and sex-specific mean SBP of untreated individuals with SBP>0.160 mm Hg were used for both high-risk and low-risk profiles. In addition, low-risk profile was defined as nonsmoker, 10th percentile total cholesterol 90th percentile HDL cholesterol, no DM, and no LVH, and high-risk profile was defined as smoker, 90th percentile total	**Intervention:** Treatment and nontreatment of HTN.	**1 endpoint:** Life expectancy, and incremental cost: effectiveness ratios for treatment and nontreatment strategies	• Probabilities of clinical events were obtained from published literature. **Summary**: • Incremental cost per quality- adjusted life y among low-risk groups ranged from £1,030 to £3,304. Cost-effectiveness results for low-risk pts were sensitive to the utility of receiving antihypertensive treatment. Treatment of high- risk individuals was highly cost- effective, such that it was the dominant strategy in the oldest age group, and resulted in incremental costs per quality-

		cholesterol, 10th percentile HDL cholesterol, DM, and LVH. **Exclusion criteria:** N/A			adjusted life y ranging from £34–£265 in younger age groups. Policy decisions about which pts to treat depend on whether a life-expectancy or cost-effectiveness perspective is taken. Treatment increases life expectancy in all strata of age, sex, and CV risk. However, younger individuals stand to gain proportionately more from BP treatment than do the elderly. In terms of cost- effectiveness, pts at high risk of CVD are a highly cost-effective group to treat. In pts at lower risk of CVD, consideration should be given to issues of pt preference and cost.

Julius S, et al., 2006 16537662	**Study type**: RCT in pre-HTN16 mg candesartan vs. placebo **Size**: 809 pts	58% men	N/A	During the first 2 y, HTN developed in 154 (40.4%) pts in the placebo group compared with only 53 (13.6%) of those in the candesartan group, for a RR of 66.3% (p<0.0001). After 4 y, HTN developed in 240 (63.0%) in the placebo group vs. only 208 (53.2%) in the candesartan group RR 15.6% (p<0.0069).	• 2/3 of those with pre-HTN develop HTN within 4 y. Candesartan interrupts the onset and reduced by 15.6%
Lawes CMM, et al., 2002 16222626	**Study type**: Review of observational reports and randomized controlled trials	N/A	N/A	• The relative benefits of BP lowering for CHD prevention likely to be consistent across a wide range of different populations • Likely to be considerable benefit for BP lowering beyond traditional thresholds, especially in those at high risk for CVD • BP lowering is likely to be more important than choice of initial agent • A large majority of patients being treated for hypertension have suboptimal BPs. Initiatives to lower their BP further are essential	• Strongly supports lower BPs during BP treatment, especially in those at high risk of CVD

Data Supplement 14. Nonrandomized Trials, Observational Studies, and/or Registries of High Blood Pressure or Hypertension (Section 4.4.)

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Bress et al, 2017 29171809	Aim To determine the lifetime health benefits and health care costs associated with intensive control versus standard control Study type Microsimulation model N=Hypothetical population of 10,000 patients based on characteristics of Systolic Blood Pressure Intervention Trial (SPRINT) population	Inclusion criteria SPRINT trial inclusion criteria: • age ≥50 years • systolic blood pressure 130-180 mmHg on 0 or 1 antihypertensive medication class, 130-170 mmHg on up to 2 classes, 130-160 mmHg on up to 3 classes, 130-150 mmHg on up to 4 classes; • presence of one or more high CVD risk conditions (including history of clinical or subclinical cardiovascular disease other than stroke, estimated glomerular filtration rate of 20-59 ml/min/1.73m2, 10-year risk for CVD ≥15% calculated using the Framingham risk score for general clinical practice, and age ≥75 years. SPRINT trial exclusion criteria: • Diabetes • a history of stroke • more than 1 gram/day of proteinuria • heart failure • on dialysis eGFR <20 ml/min/1.73m2	1° endpoint *CVD events (acute MI, acute coronary syndrome not resulting in MI, stroke, heart failure)* 2° endpoints *all cause mortality* *CVD mortality'* *serious AEs* *Cost (total direct medical costs over remaining lifetime) and QALY* CVD Events: Simulated incidence rates were 17.3 events per 1000 person years in intensive control group and 22.2 per 1000 person years in standard control group (compared to 16.4 and 21.9 events in actual trial). Predicted hazard ratio was 0.78 (95% CI 0.70-0.87) and observed HR=0.75 (95% CI 0.64-0.89). Model predicted that intensive control would prevent 170 incident events and 190 deaths from CVD over remaining lifetime of 10,000 patients compared with standard treatment Intensive control cost $47,000 more per QALY gained than standard control. In 1000 probabilistic simulations, 54% probabitliyt that intensive control was cost effective at willingness-to-pay threshold of $50,000 per QALY and a 79% at a threshold of $100,000 per QALY	Summary: Intensive systolic blood-pressure control in adults at high risk for cardiovascular disease was cost-effective and below common U.S. willingness-to-pay thresholds in most simulations regardless of whether the benefits were reduced after 5 years or persisted for the remaining lifetime of the patient

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			Cost effectiveness of intensive control was maximized at approximately 20 years in the lifetime best-case scenario and at 10 years in the persistence-of-treatment-effect scenarios Patients 75 and older had a more favorable ICER ($26,000 per QALY gained). Women had less favorable ICERs ($77,000 per QALY gained) Patients with previous cardiovascular disease had less favorable ICERs ($72,000 per QALY gained) The model was most sensitive to the HR for cardiovascular disease events with intensive control, the risk of CVD events with standard control, the risk of end-stage renal disease after chronic kidney disease, the hazard ratio for death from causes other than CVD with intensive control during the first 5 years, and the risk of chronic kidney disease with standard control, each of which potentially increased the ICER above $50,000 per QALY	
Upadhyay A, et al., 2011 21403055	Aim: To summarize trials comparing lower vs. higher BP targets in pts with CKD; focus on proteinuria as an effect modifier	Inclusion criteria: >50 pts/group, 1 y follow-up, outcomes of death, kidney failure, CV events, change in kidney function, number of antihypertensive agents, adverse events. 3 trials (MDRD, AASK, REIN-2; 8	Results: Overall trials did not show that BP target of <125/75–130/80 is more beneficial than a target of <140/90. Lower quality evidence suggests a low target may be beneficial in subgroups with proteinuria	Limitations: No pts with DM-1 included. Duration (mean follow- up 2–4 y) may be too short to detect differences in clinically important outcomes. Reporting of adverse events not uniform. Summary: Available evidence is inconclusive but does not prove a BP target <130/80 improves clinical outcomes more than a target of <140/90 in adults with CKD.

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
	Study type: Systematic review Size: 2,272	reports)	>300–1,000/d	
Jafar TH, et al., 2003 12965979	Aim: To determine the levels of BP and urine protein excretion associated with lowest risk for progression of CKD during antihypertensive therapy with and without ACEIs. Study type: 11 RCTs in pts with predominantly nondiabetic kidney disease Size: 1,860 pooled in pt level meta-analysis; mean duration of follow-up 2.2 y	Inclusion criteria: • Pt-level meta-analysis using data from the AIPRD Study Group database to assess relationships among pts with nondiabetic kidney disease across a wide range of urine protein excretion values during antihypertensive therapy with and without ACEIs. • The AIPRD Study Group database included 1,860 pts with nondiabetic kidney disease enrolled in 11 RCTs of ACEIs to slow the progression of kidney disease. The database contained information on BP, urine protein excretion, serum creatinine, and onset of kidney failure during 22,610 visits. • Included only randomized trials (with a minimum 1 y follow-up) that compared the effects of antihypertensive regimens that included ACEIs with the effects of regimens that did not include ACEIs. HTN or decreased kidney function was required for entry into all studies. Exclusion criteria: Common to all studies: acute kidney failure, treatment with immunosuppressive meds, clinically significant chronic HF,	1° endpoint: Progression of CKD defined as doubling of serum creatinine or onset of kidney failure Results: Kidney disease progression documented in 311 pts, 124 (13.2%) in the ACEI group and 187 (20.5%) in the control group (p=0.001). 176 (9.5%) developed kidney failure: 70 (7.4%) in the ACEI group and 106 (11.6%) in the control group (p=0.002). SBP of 110–129 mm Hg and urine protein excretion <2.0 g/d were associated with lowest risk for kidney disease progression. ACEI beneficial after adjustment for BP and urine protein excretion (RR: 0.67; 95% CI: 0.53–0.84). The increased risk for kidney progression at higher SBP levels was greater in pts with urine protein excretion >1.0 g/d (p<0.006).	Limitations: Studies included were not designed to assess the effect of lowering BP and urine protein excretion on kidney disease progression. Conclusions: Although reverse causation cannot be excluded with certainty, SBP goal between 110 and 129 mm Hg may be beneficial in pts with urine protein excretion >1.0 g/d. SBP <110 mm Hg may be associated with higher risk for kidney disease progression.

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
		obstructive uropathy, renal artery stenosis, active systemic disease, DM-1, history of transplantation, history of allergy to		
Emdin C, et al., 2015 25668264	Aim: Determine associations between BP-lowering treatment and presence of vascular disease in DM-2 Study type: Large meta-analysis of 40 high quality RCTs (1/1966–10/2014) judged low risk of bias Size: 100,354 pts with DM; all trials >1,000 pt-y of follow-up BP-lowering drug vs. placebo: 26 RCTs • More intensive vs. less intensive BP lowering: 7 RCTs BP-lowering vs. another drug: 17 RCTs	Inclusion criteria: All RCTs of BP-lowering treatment in which entire trial population had DM-2 or in which the results of a DM subgroup were obtained. Studies were included regardless of the presence or absence of defined HTN. Exclusion criteria: Trials conducted predominantly in pts with type 1 DM were excluded.	• BP-lowering drug vs. placebo: 26 RCTs • More intensive vs. less intensive BP lowering: 7 RCTs • BP-lowering vs. another drug: 17 RCTs Results: Baseline BP: A 10-mm Hg SBP reduction was associated with a significantly lower risk of all-cause mortality RR: 0.87 (95% CI: 0.78–0.96), CVD events RR: 0.89 (95% CI: 0.80–0.98), and stroke events RR: 0.73 (95% CI: 0.64–0.83). The associations for HF and renal failure were not significant. For microvascular events, a 10-mm reduction in SBP was associated with a lower risk of retinopathy RR: 0.87 (95% CI: 0.76–0.99) and albuminuria RR: 0.83 (95% CI: 0.79–0.87). Stratified by initial SBP: Trials stratified by SBP >140 to <140 mm Hg showed significant interactions for all-cause mortality RR: 0.73 (95% CI: 0.64–0.84) vs. 1.07 (95% CI: 0.92–1.26), CVD RR: 0.74 (95% CI: 0.65–0.85) vs. RR: 0.96 (95% CI: 0.88–1.05), CHD RR: 0.73 (95% CI:	Limitations: Reliability of this meta-analysis is limited by the scarcity of large trials with achieved SBP levels in the 120–130 mm Hg range. The relatively short follow-up of included trails may have prevented associations of BP-lowering treatment with vascular outcomes from being observed, particularly for outcomes such as HF and renal failure, which are often a consequence of MI or albuminuria, respectively. Summary: • This large meta-analysis of 40 RCTs provides evidence that BP lowering is associated with lower risks of outcomes in pts with initial mean SBP 140 mm Hg compared with those <140 mm Hg with the exception of stroke, albuminuria and retinopathy. When trials were stratified by achieved SBP treatment was associated with lower risks only in the <130 mm Hg stratum for stroke and albuminuria. • This meta-analysis shows that although BP lowering was not associated with a lower risk of CVD or CHD events at a baseline SBP <140 mm Hg, it does observe lower risks of stroke, retinopathy and progression of albuminuria. This study provides evidence that for individuals at high risk for these outcomes (history of cerebrovascular disease or mild nonproliferative retinopathy), commencement of therapy below an initial SBP of 140 mm Hg and treatment to SBP <130 may be indicated.

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			0.61– 0.87) vs. RR: 0.97 (95% CI: 0.86–1.10), HF RR: 0.75 (95% CI: 0.59–0.94) vs. RR: 0.97 (95% CI: 0.79–1.19) and albuminuria RR: 0.71 (95% CI: 0.63–0.79) vs. RR: 0.86 (95% CI: 0.81–0.99). Stratified by achieved SBP: Trials stratified by SBP achieved in the treatment group ≥130 or <130 mm Hg and the associations of a 10-mm Hg SBP reduction compared between the strata showed significant interactions for all-cause mortality RR: 0.75 (95% CI: 0.65–0.86) vs. RR: 1.06 (95% CI: 0.90–1.265), CVD RR: 0.74 (95% CI: 0.64–0.85) vs. RR: 0.96 (95% CI: 0.88–1.05), CHD RR: 0.70 (95% CI: 0.58– 0.83) vs. RR: 0.97 (95% CI: 0.85–1.10), HF RR: 0.75 (95% CI: 0.59–0.95) vs. RR: 1.00 (95% CI: 0.81–1.23) and albuminuria RR: 0.71 (95% CI: 0.64–0.79) vs. RR: 0.86 (95% CI: 0.81–0.90) with higher risk in the ≥130 mm Hg group. Stratified by class of medications: Few	

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			differences were observed in the association between BP-lowering treatment and outcomes for regimens based on different classes of medications, except HF, in which diuretics were associated with lower RR: 0.83 (95% CI: 0.72–0.95) than all other classes. This was driven largely by the results of ALLHAT.	

Data Supplement 15. RCTs of Tobacco Use (Section 4.5.)

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 value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
Carson et al 2012 (24) 22592671	Aim of Study: To determine the effectiveness of training health care professionals in the delivery of smoking cessation interventions to their patients, and to assess the additional effects of training characteristics such as intervention content, delivery method and intensity Meta analysis of RCTs	Inclusion criteria • RCTs • Unit of randomization was a healthcare practitioner or practice • Reported effects on patients who were smokers • Compared a trained group to an untrained group and those that examined the effectiveness of adding prompts and reminders to training Exclusion criteria • Studies that used a historical control		1° endpoint Abstinence from smoking 6+ months after the start of the intervention (point prevalence and continuous abstinence) Results: 13/17 included studies found no evidence of an effect for continuous smoking abstinence following the intervention. Meta-analysis of 14 studies for point prevalence of smoking (OR 1.36, 95% CI 1.20 to 1.55). Meta-analysis of eight studies that reported continuous abstinence was statistically significant (OR 1.60, 95% CI 1.26 to 2.03).	2° endpoints Process measures at patient level Number of referrals made (physician level outcome) Results Healthcare professionals who had received training were more likely to perform tasks of smoking cessation than untrained controls, including: asking patients to set a quit date ((random effects OR 4.98, 95% CI 2.29 to 10.86), make follow-up appointments (random effects OR 3.34, 95% CI 1.51 to 7.37), counselling of smokers (OR 2.28, 95% CI 1.58 to 3.27),

	N=17 studies (28.531 patients at baseline; 1,434 health professionals at baseline)				provision of self-help material (OR 3.52, 95% CI 1.90 to 6.52) and prescription of a quit date (OR 14.18, 95% CI 6.57 to 30.61). No evidence of an effect was observed for the provision of nicotine gum/replacement therapy (OR 1.57, 95% CI 0.87 to 2.84).
Patnode, 2015 26491759	Aim of Study: To determine the effectiveness and safety of pharmacotherapy and behavioral tobacco cessation interventions in adults. Electronic nicotine delivery systems also included. Review of systematic reviews 54 SRs: Pharmacotherapy: 9 SRs Behavioral: 33 SRs			1° endpoint Quit rates One SR included one RCT that reported effect of an intensive behavioral intervention on health outcomes in males at high risk for CV disease. No effect on total mortality, CV mortality, lung cancer incidence and mortality at 20 years but at 33 years of follow-up there were fewer deaths from respiratory illness in intervention group. No other behavioral SR included a study that reported CV health outcomes. No SR of pharmacotherapy for smoking cessation reported CV health outcomes. Effect of NRT versus placebo or no NRT for smoking cessation: 117 trials, n=51,265, RR 1.60, 95% CI 1.53 to 1.68, I2=30%; 17.3% quit in intervention group versus 10.3% in control group at 6 months Effect of bupropion versus placebo or no pharmacotherapy: 44 trials, n=13,728, RR 1.62, 95% CI 1.49 to 1.76, I2-18%; 19.7% quit versus 11.5% at 6 to 12 months Effect of varenicline versus placebo or no varenicline: 14 trials, n=6,166, RR 2.27, 95% CI 2.02 to 2.55, I2=63% at 6 months	NRT: Any CV event (minor or major) of NRT versus placebo: 21 trials, n=11,647, RR 1.81, 95% CI 1.35 to 2.43, I2=0% (285 events total) Any major CV event (CV death, nonfatal MI, nonfatal stroke) of NRT versus placebo:21 trials, n=11,647, RR 1.38, 95% CI 0.58 to 3.26, I2=0 (19 events total) All cause mortality: NRT versus placebo or usual care: 8 trials, N=2,765, OR 0.74, 95% CI 0.33 to 1.67, I2=0% (27 events total) Bupropion: All CV adverse events bupropion SR versus placebo: 27 trials, n=10,402, RR 1.03, 95% CI 0.71 to 1.50, I2=0%, (92 events total) Major CV adverse events bupropion SR versus placebo: 27 trials, n=10,402, RR 0.57, 95% CI 0.31 to 1.04, I2=0 (40 events total) Varenicline: All CV adverse events varenicline versus placebo: 18 trials, n=9,072, RR 1.24, 95% CI 0.85 to 1.81, I2=0% (104 events total)

				Effect of physician advice versus no advice or usual care: 28 trials, n=22, 239, RR 1.76, 95% CI 1.58 to 1.96, I2=40%; 8.0% quit in the intervention group versus 4.8% in the control group at 6 months Effect of self-help material with or without advice versus no self-help material with or without advice: 33 trials, n=29,495, RR 1.06, 95% CI 0.98 to 1.16, I2=23% Effect of multisession helpline counseling versus single session or self-help materials: 12 trials, n=30,182, RR 1.41, 95% CI 1.20 to 1.66, I2=71% Effect of nonhelpline, proactive telephone counseling versus a control: 52 trials, n=30,246, RR 1.27, 95% CI 1.20 to 1.36, I2=42% at 6 months	Major CV events varenicline versus placebo: 18 trials, n=9,072, RR 1.44, 95% CI 0.73 to 2.83, I2=o% (35 events total) In reviews of behavioral interventions reporting of adverse events was infrequent and limited to trials of ear-acupuncture, ear-acupressure, and auriculotherapy
Stead LF, Lancaster T, 2016 23076944	Study Aims To assess the effect of combining behavioral support and medication to aid smoking cessation, compared to using neither, and to identify whether there are different effects depending on characteristics of the treatment setting, intervention, population treated, or take-up of treatment Study Type	Inclusion criteria Randomized or quasi-randomized controlled trials Trials that recruited people who smoke in any setting except those of pregnant women or adolescents Interventions for increasing smoking cessation that included behavioral support and the availability of pharmacotherapy, regardless of type Control group not systematically offered pharmacotherapy Control group offered usual care, self-help materials or brief advice	Intervention interventions for increasing smoking cessation that included behavioral support and the availability of pharmacotherapy, regardless of type of pharmacotherapy Comparison Not systematically offered pharmacotherapy, Could be offered usual care, self-help materials or brief advice on quitting, but support had to	1° endpoint: Smoking cessation at the longest follow-up using the strictest definition of abstinence Results *Smoking cessation at the longest follow-up using the strictest definition of abstinence* NB: Lung Health Study Excluded from analyses due to added heterogeneity RR=1.83 (95% CI 1.68-1.98), I^2=36%. Possibility of publication or other bias High quality evidence (GRADE)	2° endpoints: Any other abstinence outcomes reported Subgroup Analyses: *Setting* Healthcare setting RR=1.97 (95% CI 1.79-2.18) vs. other settings RR=1.53, 95% CI 1.33-1.75 *Motivation to quit* Selected for motivation RR=1.90 (95% CI 1.68-2.15) vs. “not selected” subgroup RR=1.60 (95% CI 1.42-1.80). Motivation to quit was not an effect modifier in meta regression (p=0.09) *Provider* Speciality care RR=1.81, 95% CI 1.64-1.99 vs. counseling linked to usual care

	Systematic review and meta-analysis N=53 studies	on quitting (lower intensity than intervention) Exclusion criteria Trials of interventions in pregnant women and adolescents Fewer than 20% of participants were eligible for or used pharmacotherapy Trials less than six months follow up from start of intervention	have been of a lower intensity than that given to intervention participants.		RR=2.03 (95% CI 1.70-2.43). In meta regression, type of provider was not significant effect modifier (p=0.37) *Intensity* Eight or more sessions RR=2.10 (95% CI 1.65-2.68)

Data Supplement 16. Nonrandomized Trials, Observational Studies, and/or Registries of Tobacco Use (Section 4.5.)

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Lv et al, 2015 26188829	Study type: SR and meta analysis of observational studies N=40 studies	Inclusion • prospective cohort studies or case–control studies • humans aged ≥18 year • exposure was secondhand smoke (SHS) or passive smoking in never smokers, • For self-reported SHS, detailed questionnaire-based descriptions confirming the regular exposure to another person's tobacco smoke at home or out of home should be available; • Collected outcomes of all-cause mortality or CVD (including CHD and stroke); • unexposed subjects were used as the reference group • quantitative estimates such as RR, hazard ratio, or odds ratio and	1° endpoint All cause mortality CVD CHD Stroke *Self-reported SHS exposure and all cause mortality* (n=12 studies) RR=1.18, 95% CI 1.10-1.27, with significant between study heterogeneity (p=0.001) and with some evidence of publication bias RR females=1.16, 95% CI 1.06-1.27 RR males=1.20, 95% CI 1.10-1.31 RR <65 years of age=1.28, 95% CI 1.00-1.64	Summary: never smokers exposed to SHS, compared with those unexposed, had a significantly increased risk of 18% for all-cause mortality, 23% for CVD, 23% for CHD,and 29% for stroke. The findings did not change after stratification by gender or age.

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
		corresponding variance (or information to calculate these measures) were reported • published in English	RR 65+ years of age=1.34, 95% CI 1.12-1.61 *Self-reported SHS exposure and CVD* (n=38 studies) RR=1.23, 95% CI 1.16-1.31, with significant between study heterogeneity (p-0.0001). There was evidence suggesting publication bias; trim-and-fill method used to impute 12 hypothetical studies resulting in RR=1.16, 95% CI 1.09-1.23 RR females=1.24, 95% CI 1.14-1.35 RR males=1.20, 95% CI 1.11-1.30 RR <65 years of age=1.30, 95% CI 1.18-1.43 RR 65+ years of age=1.21, 95% CI 1.01-1.44 *Objectively measured SHS exposure and CVD* (n=4 studies) RR lowest cotinine vs. cotining <15 ng/ml=1.41, 95% CI 1.05-1.88 (after exclusion of an outlier study RR=1.65, 95% CI 1.32-2.05) *Self-reported SHS exposure and CHD* (n=30 studies) RR=1.23, 95% CI 1.14-1.32, with significant between study heterogeneity (p=0.0001). There was evidence suggesting publication bias; trim-and-fill method used to impute 9 hypothetical studies resulting in RR=1.17, 95% CI 1.08-1.25	

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			RR females=1.24, 95% CI 1.12-1.38 RR males=1.16, 95% CI 1.08-1.26 RR <65 years of age=1.29, 95% CI 1.15-1.44 RR 65+ years of age=1.37, 95% CI 0.99-1.89 *Self-reported SHS exposure and stroke* (n=15 studies) RR=1.29, 95% CI 1.15-1.45, with significant between study heterogeneity (p=0.02) and no publication bias detected RR females=1.21, 95% CI 1.08-1.37 RR males=1.44, 95% CI 1.14-1.82 RR <65 years of age=1.33, 95% CI 1.06-1.68 RR 65+ years of age=1.43, 95% CI 1.03-1.99	
Pan, et al., 2015 26311724	Systematic review and meta-analyses of prospective studies in diabetic patients 89 cohorts; most studies conducted in Europe and the US	Inclusion criteria • DM1 or DM2; prospective study • Mean age NR (mean study range 25.4 to 79 years) • Mean % female NR (mean study range 0% to 100%) • Mean % current smokers not reported (mean study range 8.0% to 59.3%)	Cardiovascular death Current smokers vs. never smokers RR 1.43 (95% CI 1.18 to 1.73, I2=32%, 8 studies) All-cause mortality: RR 1.62 (95% CI 1.49 to 1.76, I2=51%, 13 studies) Cardiovascular death Former smokers vs. current smokers RR 0.66 (95% CI 0.48 to 0.91, I2=47%, 6 studies)	

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
	Total N not reported but N for all-cause mortality = 1,132,700 Follow-up duration: Overall NR (range 1 to 20 years)		All-cause mortality: RR 0.65 (95% CI 0.61 to 0.70, I2=66%, 30 studies) Acute coronary events Current smokers vs. never smokers Risk of coronary heart disease: RR 1.47 (95% CI 1.29 to 1.69, I2=61%, 13 studies) Acute coronary events Former smokers vs. current smokers Risk of coronary heart disease: RR 0.65 (95% CI 0.61 to 0.71, I2=66%, 10 studies) Stroke events Current smokers vs. never smokers RR 1.54 (95% CI 1.26 to 1.88, I2=40%, 9 studies) Stroke events Former smokers vs. current smokers RR 1.04 (95% CI 0.87 to 1.23, I2=25%, 9 studies	
Mons, et al., 2015 CHANCES Consortium 25896935	Meta-analyses of prospective studies 25 cohorts from 23 countries N=50,3905 Follow-up duration: Overall NR (range	Inclusion Criteria: • Aged 60 and above; no history of stroke or coronary events • Age: 60-69: 86.6% • 70 and above: 13.4% • % female: 0.44 • % never smoked: 190,688 (40.2%)	Cardiovascular death: Current smokers vs. never smokers All: HR 2.07 (95% CI 1.82 to 2.36) Men: HR 1.95 (95% CI 1.69 to 2.25) Women: HR 2.22 (95% CI 1.86 to 2.65) Age 60-69: HR 2.45 (95% CI 2.22 to 2.69) Age 70+: HR 1.70 (95% CI 1.42 to 2.04) Smoking < 10 cigs/day: HR 1.87 (95% CI 1.63 to 2.15)	

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
	1.6 years to 15.4 years)	• % former smokers: 255,158 (47.4%) • % current smokers: 588,737 (12.4%)	Smoking 10-19 cigs/day: HR 1.94 (95% CI 1.65 to 2.28) Smoking 20+ cigs/day: HR 2.63 (95% CI 2.28 to 3.04) Cardiovascular death: Former smokers vs. never smokers All: HR 1.37 (95% CI 1.25 to 1.49) Men: HR 1.33 (95% CI 1.20 to 1.48) Women: HR 1.40 (95% CI 1.25 to 1.57) Age 60-69: HR 1.57 (95% CI 1.43 to 1.72) Age 70+: HR 1.21 (95% CI 1.08 to 1.36) Acute coronary events: Current smokers vs. never smokers All: HR 1.18 (95% CI 1.06 to 1.32) Men: HR 1.18 (95% CI 1.00 to 1.38) Women: HR 1.24 (95% CI 1.07 to 1.41) Age 60-69: HR 1.25 (95% CI 1.10 to 1.43) Age 70+: HR 1.12 (95% CI 0.95 to 1.32) Acute coronary events: Former smokers vs. current smokers Quit < 5 years ago: HR 0.84 (95% CI 0.72 to 0.98) Quit 5 to 9 years ago: HR 0.86 (95% CI 0.72 to 1.02) Quit 10 to 19 years ago: HR 0.69 (95% CI 0.58 to 0.82) Quit 20+ years ago: HR 0.58 (95% CI 0.46 to 0.72) Stroke events: Current smokers vs. never smokers All: HR 1.58 (95% CI 1.40 to 1.78) Men: HR 1.44 (95% CI 1.23 to 1.68) Women: HR 1.78 (95% CI 1.46 to 2.17) Age 60-69: HR 1.68 (95% CI 1.46 to 1.94)	

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			Age 70+: HR 1.49 (95% CI 1.22 to 1.82) Smoking < 10 cigs/day: HR 1.43 (95% CI 1.24 to 1.64) Smoking 10 to 19 cigs/day: HR 1.60 (95% CI 1.41 to 1.82) Smoking 20+ cigs/day: HR 1.91 (95% CI 1.66 to 2.21) Stroke events: Former smokers vs. never smokers All: HR 1.17 (95% CI 1.07 to 1.26) Men: HR 1.08 (95% CI 0.97 to 1.21) Women: HR 1.20 (95% CI 1.06 to 1.36) Age 60-69: HR 1.22 (95% CI 1.10 to 1.35) Age 70+: HR 1.10 (95% CI 0.95 to 1.28) Stroke events: Former smokers vs. current smokers Quit < 5 years ago: HR 0.97 (95% CI 0.79 to 1.19) Quit 5 to 9 years ago: HR 0.98 (95% CI 0.74 to 1.31) Quit 10 to 19 years ago: HR 0.79 (95% CI 0.69 to 0.92) Quit 20+ years ago: HR 0.67 (95% CI 0.60 to 0.76)	

Data Supplement 17. RCTs of Aspirin Use (Section 4.6.)

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 value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
Guirguis-Blake, 2016 and Whitlock, 2016 USPSTF 27064410	**Aim:** Aspirin for primary prevention of cardiovascular events **Study Type:** 11 RCTs N=118,445 Also included 4 cohort studies on major bleeding risk	***Guirguis-Blake:*** **Inclusion criteria** randomized, controlled trials (RCTs) and controlled clinical trials examined the primary prevention of CVD with oral aspirin (a minimum of 75 mg every other day for 1 year or more) compared with placebo or no treatment adults aged 40 years or older **Exclusion criteria** excluded interventions that included nonaspirin antithrombotic medications or aspirin as cotreatment with another active intervention ***Whitlock:*** **Inclusion criteria** trials and large longitudinal cohort studies adults with a mean age of 40 years or older evaluated regular oral aspirin use (≥75 mg at least every other day)	**Intervention** oral aspirin (a minimum of 75 mg every other day for 1 year or more) **Comparator** placebo or no treatment	**Results:** Aspirin (any dose) vs. placebo or no aspirin Nonfatal MI: 10 trials, RR 0.78 (95% CI 0.71 to 0.87), I2=62% Nonfatal stroke: 10 trials, RR 0.95 (95% CI 0.85 to 1.06), I2=25% CVD mortality: 11 trials, RR 0.94 (95% CI 0.86 to 1.03), I2=8.8% All-cause mortality: 11 trials, RR 0.94 (95% CI 0.89 to 0.99) Aspirin <=100 mg/day vs. placebo or no aspirin Nonfatal MI: 8 trials, RR 0.83 (95% CI 0.74 to 0.94), I2=54% Nonfatal stroke: 7 trials, RR 0.86 (95% CI 0.76 to 0.98), I2=0% CVD mortality: 8 trials, RR 0.97 (95% CI 0.85 to 1.10), I2=30% All-cause mortality: 8 trials, RR 0.95 (95% CI 0.89 to 1.01), I2=0% Effects of duration: Benefits appear to begin within first 1 to 5 years; no clear upper limit Formulation: No conclusions possible Subgroups Age: 3 trials found greater RR reduction for MI with older age; no clear difference for stroke by age; inconsistent data for differences for composite CV outcomes by age	N/A

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
		for 1 year or longer for any indication compared with no treatment or placebo. reported major GI or intracranial bleeding.		Sex: No strong evidence for treatment modification for aspirin by sex or outcome Diabetes: Evidence does not clearly support heterogeneity of aspirin treatment effect based on diabetes status	
Lotrionte, 2016 26851562	**Aim:** Aspirin for primary prevention of cardiovascular events, focus on dose and preparation **Study Type:** 11 RCTs N=104,101	**Inclusion criteria** Randomized trials in primary prevention as recently reported by the updated U.S. Preventive Services Task Force reports (not otherwise specified)	**Intervention** Aspirin with average daily doses of <100 mg, 100 mg, and >100 mg. Preparations in coated, controlled release, non-coated, or otherwise unspecified **Comparator** placebo	**Results**: Aspirin vs. placebo, OR (95% CI) All-cause mortality <100 mg/day: 0.95 (0.87 to 1.03) 100 mg/day: 0.92 (0.80 to 1.05) >100 mg/day: 0.93 (0.84-1.02) Coated: 0.91 (0.77-1.07) Controlled release: 1.03 (0.80-1.32) Non-coated: 0.94 (0.87-1.02) Unspecified formulation: 0.93 (0.84-1.03) Major adverse cardiovascular events <100 mg/day: 0.86 (0.76-0.97) 100 mg/day: 1.02 (0.85-1.24) >100 mg/day: 0.80 (0.72-0.89) Coated: 0.96 (0.75-1.25) Controlled release: 0.78 (0.59-1.03) Non-coated: 0.94 (0.84-1.05) Unspecified formulation: 0.75 (0.66-0.85)	N/A
Raju, 2016 and 2011 27126466	**Aim:** Updated Meta-Analysis of Aspirin in Primary Prevention of Cardiovascular Disease (random effects)	**Inclusion criteria** randomized controlled trial included adults without a history of symptomatic cardiovascular disease (>95% of enrolled participants compared aspirin (any dose) with placebo or no aspirin treatment for the prevention of cardiovascular disease	**Intervention** Aspirin **Comparator** Placebo or non-aspirin	**Results:** Aspirin vs. placebo or no aspirin All-cause mortality (9 trials): RR 0.94 (95% CI 0.89 to 1.00) CV mortality (9 trials): RR 0.95 (95% CI 0.84 to 1.07) Major CV events (8 trials): RR 0.89 (95% CI 0.82 to 0.97) MI (9 trials): RR 0.78 (95% CI 0.65 to 0.94)	N/A

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
		reported at least one of the following outcomes: all-cause mortality, cardiovascular mortality, myocardial infarction, stroke, and bleeding. **Exclusion criteria** Studies in which aspirin was combined with a second antithrombotic agent unless there were separate placebo and aspirin-only treatment groups, in which case only the data from these groups were included •		Stroke (9 trials): RR 0.94 (95% CI 0.84-1.06)	
Prevention of Progression of Arterial and Diabetes trial Belch, 2008 18927173	**Study Type:** 2 x 2 RCT (antioxidants) N=1,276 Country: UK	• **Inclusion Criteria:** Men and women >=40 years of age, type 1 or type 2 diabetes and asymptomatic peripheral vascular disease (ankle brachial index <=0.99)	**Intervention** daily aspirin 100 mg, plus antioxidant or placebo capsule (factorial design) **Comparator** **Placebo plus** antioxidant or placebo capsule	**1° endpoint:** CV death, nonfatal MI, nonfatal stroke, or above ankle amputation for critical limb ischemia CV Death: Aspirin: 6.7% (43/638) Placebo: 5.5% (35/638) HR: 1.23 (95% CI 0.79 to 1.93) Nonfatal MI: Aspirin: 14.1% (90/638) Placebo: 12.9% (82/638) RR: 1.10 (95% CI 0.83 to 1.45) Nonfatal Stroke: Aspirin: 5.8% (37/638) Placebo: 7.8% (50/638) RR: 0.74 (95% CI 0.49 to 1.12)	N/A
Aspirin for Asymptomatic Atherosclerosis trial	**Study Type:** RCT N=3,350 Country:UK	• **Inclusion Criteria:** Men and women 50 to 75 years of age with asymptomatic peripheral vascular disease (ankle brachial index <=0.95	**Intervention** Once daily 100 mg aspirin (enteric coated)	**1° endpoint:** CV death, nonfatal MI, nonfatal stroke, or revascularization CV Death: Aspirin: 2.1% (35/1,675) Placebo: 1.8% (30/1,675)	N/A

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
Fowkes, 2010 20197530			**Comparator** placebo	RR: 1.17 (95% CI 0.72 to 1.89) Nonfatal MI: Aspirin: 5.4% (90/1,675) Placebo: 5.1% (86/1,675) RR: 1.05 (95% CI 0.78 to 1.40) Nonfatal stroke: Aspirin: 2.6% (44/1675) Placebo: 3.0% (50/1675) RR: 0.88 (95% CI 0.59 to 1.31)	
Japanese Primary Prevention Project Ikeda, 2014 25401325	**Study Type:** RCT N=14,464 Country:Japan	• **Inclusion Criteria:** Men and women 60 to 85 years of age with hypertension, dyslipidemia, or diabetes mellitus	**Intervention** 100-mg tablet of enteric-coated aspirin once daily **Comparator** No aspirin (not placebo – participants were not blinded)	**1° endpoint:** CV death, nonfatal MI, or nonfatal stroke CV Death: Aspirin: 0.8% (58/7,220) No aspirin: 0.8% (57/7,244) HR: 1.03 (95% CI 0.71 to 1.48 Nonfatal MI: Aspirin: 0.4% (27/7,220) No aspirin: 0.6% (47/7,244) RR: 0.58 (95% CI 0.36 to 0.92) Fatal Stroke: Aspirin: 0.1% (7/7,220) No aspirin: 0.2% (12/7,244) RR: 0.59 (95% CI 0.23 to 1.49)	N/A
Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes Ogawa, 2008 18997198	RCT N=2,539	**Inclusion Criteria:** • Men and women 30 to 85 years of age with type 2 diabetes mellitus	Aspirin dose & formulation: 81 or 100 mg once daily, not enteric coated Comparator: No aspirin	**Primary Endpoint:** Sudden death; death from coronary, cerebrovascular, and aortic causes; nonfatal MI; unstable angina; new exertional angina; nonfatal stroke; TIA; or nonfatal aortic and peripheral vascular disease Major CV Events: Sudden death; death from coronary, cerebrovascular, and aortic causes;	**Adverse Events:** Any GI Bleeding Aspirin: 1.0% (12/1,262) No aspirin: 0.3% (4/1,277) RR: 3.04 (95% CI 0.98 to 9.39) Serious GI Bleeding Aspirin: 0.3% (4/1,262) No aspirin: 0% (0/1,277) RR: 9.11 (95% CI 0.49 to 169)

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
				nonfatal MI; unstable angina; new exertional angina; nonfatal stroke; TIA; or nonfatal aortic and peripheral vascular disease Aspirin: 5.4% (68/1,262) No aspirin: 6.7% (86/1,277) HR: 0.80 (95% CI 0.58 to 1.10) CV Death: Aspirin: 0.08% (1/1,262) No aspirin: 0.8% (10/1,277) HR: 0.10 (95% CI 0.01 to 0.79) Stroke Aspirin: 2.2% (28/1,262) No aspirin: 2.5% (32/1,277) HR: 0.84 (95% CI 0.53 to 1.32) **Secondary Endpoints:** Adherence By end of study 10% in aspirin group had stopped aspirin and 0.5% in no aspirin group had taken aspirin All-Cause Mortality Aspirin: 2.7% (34/1,262) No aspirin: 3.0% (38/1,277) HR: 0.90 (95% CI 0.57 to 1.14) Fatal or non-fatal MI Aspirin: 1.0% (12/1,262) No aspirin: 0.7% (9/1,277) RR: 1.35 (95% CI 0.57 to 3.19) Fatal MI	

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
				Aspirin: 0% (0/1,262) No aspirin: 0.4% (5/1,277) RR: 0.09 (95% CI 0.005 to 1.66) Fatal Stroke Aspirin: 0.08% (1/1,262) No aspirin: 0.4% (5/1,277) HR: 0.20 (95% CI 0.024 to 1.74) Hemorrhagic Stroke Aspirin: 0.5% (6/1,262) No aspirin: 0.5% (7/1,277) RR: 0.87 (95% CI 0.29 to 2.57) Ischemic Stroke Aspirin: 1.7% (22/1,262) No aspirin: 2.0% (25/1,277) RR: 0.89 (95% CI 0.50 to 1.57)	
Aspirin in Reducing Events in the Elderly (ASPREE) McNeil 2018 30221597	**Study Aim** effect of aspirin on the prespecified secondary end points of cardiovascular disease and major hemorrhage **Study Type** RCT **N=19,114**	**Inclusion criteria** community-dwelling adults living in Australia and the United States 70 years of age or older (or ≥65 years of age among blacks and Hispanics in the United States). Free from overt coronary heart disease, overt cerebrovascular disease, atrial fibrillation, a clinical diagnosis of dementia, clinically significant physical disability, a high risk of bleeding, anemia, and a known	**Intervention** 100 mg of enteric-coated aspirin (n=9525) **Comparator** Placebo (n=9589)	**Primary Endpoint:** reported separately **Secondary Endpoints:** Composite of fatal coronary heart disease (myocardial infarction, sudden cardiac death, or any other death in which the underlying cause was considered to be coronary heart disease), nonfatal myocardial infarction, fatal or nonfatal stroke, or hospitalization for heart failure. Nonprespecified end point: major adverse cardiovascular events was a composite of fatal coronary heart disease (excluding death from heart	**Conclusions** The use of low-dose aspirin as a primary prevention strategy in older adults resulted in a significantly higher risk of major hemorrhage and did not result in a significantly lower risk of cardiovascular disease than placebo

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
		contraindication to or inability to take aspirin. **Exclusion criteria** Current regular use of an anticoagulant or antiplatelet medication other than aspirin systolic blood pressure of 180 mm Hg or more or a diastolic blood pressure of 105 mm Hg or more medical indication for or contraindication to regular aspirin therapy • presence of a condition that, in the opinion of the primary care physician was likely to result in death within 5 years		failure), nonfatal myocardial infarction, or fatal or nonfatal ischemic stroke Composite major hemorrhage (hemorrhagic stroke, symptomatic intracranial bleeding, clinically significant extracranial bleeding) **Results** *Cardiovascular disease Aspirin vs. Placebo* 10.7/1000 person years aspirin vs. 11.3/1000 person years placebo, HR=0.95 (95% CI 0.83-1.08) *Major adverse cardiovascular event* 7.8/1000 person years aspirin vs. 8.8/1000 person years placebo. HR=0.89 (95% CI 0.77-1.03) *Fatal cardiovascular disease* 1.8/1000 person years aspirin vs. 1.9/1000 person years placebo. HR=0.97 (95% CI 0.71-1.33) *Hospitalization for heart failure* 2.1/1000 person years aspirin vs. 1.9 per 1000 person years for placebo. HR=1.07 (95% CI 0.79-1.44) *Fatal or nonfatal myocardial infarction* 4.0/1000 person years aspirin vs. 4.3/1000 person years placebo. HR=0.93 (95% CI 0.76-1.15) *Fatal or nonfatal ischemic stroke*	

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
				3.5/1000 perso years aspirin vs. 3.9/1000 person years placebo. HR=0.89 (95% CI 0.71-1.11) *Major hemorrhage* 8.6/1000 person year aspirin vs. 6.2/1000 per years placebo. HR=1.38 (95% CI 1.18-1.62) p<0.001 *Intracranial bleeding* Any 2.5/1000 person years aspirin vs. 1.7/1000 person years placebo. HR=1.50 (95% CI 1.11-2.02) *Hemorrhagic stroke* 1.0/1000 person years aspirin vs. 0.8/1000 person years placebo. HR=1.27 (95% CI 0.81-2.00) *Subdural or extradural hemorrhage* 0.9/1000 person years aspirin vs. 0.5/1000 person years placebo. HR=1.79 (95% CI 1.06-3.02) *Subarachnoid hemorrhage* 0.4/1000 person years aspirin vs. 0.3/1000 person years placebo. HR=1.30 (95% CI 0.64-2.60) *Upper gastrointestinal bleeding* 2.1/1000 person years aspirin vs. 1.1/1000 person years placebo. HR=1.87 (95% CI 1.32-2.66) *Lower gastrointestinal bleeding*	

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
				1.7/1000 person years aspirin vs. 1.3/1000 person years placebo. HR=1.36 (95% CI 0.96-1.94) *Bleeding at another site* 2.4/1000 person years aspirin vs. 2.1/1000 person years placebo. HR=1.16 (95% CI 0.87-1.54) *Fatal major hemorrhage* 0.7/1000 person years aspirin vs. 0.6/1000 person years placebo. HR=1.18 (95% CI 0.68-2.03) *Fatal hemorrhagic stroke* 0.3/1000 person years aspirin vs. 0.3/1000 person years placebo. HR=1.01 (95% CI 0.47-2.17)	

Data Supplement 18. Nonrandomized Trials, Observational Studies, and/or Registries of Aspirin Use (Section 4.6)

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
García Rodríguez et al, 2016. 27490468	**Aim**: To determine the risks of the most clinically relevant adverse effect, GI bleeding, and the serious but rare event, ICH, in patients taking low-dose aspirin in real-world settings	**Inclusion criteria:** • Men and women age 50–75 y • Published between 1946 and March 2015 • Humans • Published in English **Exclusion criteria:** • Reviews, editorials, comments, clinical trials and pediatric studies	**1° endpoint**: incidences of GI bleeding and ICH and measures of their association (OR, RR, HR, IRR, SIR) with low-dose aspirin (75–325 mg per day) Overall incidence (as cases per 1000 person-years) of GI bleeding with low-dose aspirin were reported in two cohort studies, one of which involved only men (1.39 events per 1000 person-years) and	Limitations: Significant heterogeneity for most outcomes.

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
	Study type: Systematic review of observational studies N=39 studies	• studies using only aspirin doses higher than 325 mg per day.	the other of which involved only women (1.67 events per 1000 person-years) *Upper GI Bleeding*: Overall pooled estimate of the RR 2.3 (95% CI: 2.0–2.6), with significant heterogeneity (I^2 = 80.5%). One study compared the RR for UGIB in the primary and secondary prevention of CVD: (adjusted RR [95% CI]: 1.90 [1.59–2.26] and 1.40 [1.14–1.72], respectively), though the absolute increase in risk of UGIB with low-dose aspirin was higher in the secondary prevention cohort than in the primary prevention cohort. Range of incidence of UGIB with low-dose aspirin (n=4 studies)= 0.70–3.64 cases per 1000 person-years *Lower GI bleeding*: n=6 studies. Pooled RR=1.8 (95% CI: 1.1–3.0), with significant heterogeneity between studies (I^2 = 81.1%). Three studies reported overall incidence of LGIB (range:(0.48–0.74 cases per 1000 person-years). *Intracranial hemorrhage*: Pooled RR= 1.4 (95% CI 1.2–1.7), with significant heterogeneity between studies (I^2 = 92.0%)	

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			N=1 study reported the overall incidence of ICH with low dose aspirin (8.0 cases per 1000 person-years) in a cohort of patients with non-valvular atrial fibrillation *Age* There was no clear evidence that the RR of bleeding with low-dose aspirin increases with increasing age (n=8 studies)	

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