Web Supplement

to the

2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines

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Preamble (Full Version)

Since 1980, the American College of Cardiology (ACC) and American Heart Association (AHA) have translated scientific evidence into clinical practice guidelines with recommendations to improve cardiovascular health. These guidelines, which are based on systematic methods to evaluate and classify evidence, provide a foundation for the delivery of quality cardiovascular care. The ACC and AHA sponsor the development and publication of clinical practice guidelines without commercial support, and members volunteer their time to the writing and review efforts. Guidelines are official policy of the ACC and AHA. For some guidelines, the ACC and AHA partner with other organizations. The present guideline is a collaboration of the ACC and AHA with 10 other organizations.

Intended Use

Clinical practice guidelines provide recommendations applicable to patients with or at risk of developing cardiovascular disease. The focus is on medical practice in the United States, but these guidelines are relevant to patients throughout the world. Although guidelines may be used to inform regulatory or payer decisions, the intent is to improve quality of care and align with patients' interests. Guidelines are intended to define practices meeting the needs of patients in most, but not all, circumstances, and should not replace clinical judgment.

Clinical Implementation

Management, in accordance with guideline recommendations, is effective only when followed by both practitioners and patients. Adherence to recommendations can be enhanced by shared decision-making between clinicians and patients, with patient engagement in selecting interventions on the basis of individual values, preferences, and associated conditions and comorbidities.

Methodology and Modernization

The ACC/AHA Task Force on Clinical Practice Guidelines (Task Force) continuously reviews, updates, and modifies guideline methodology on the basis of published standards from organizations, including the Institute of Medicine (1, 2) and on the basis of internal reevaluation. Similarly, presentation and delivery of guidelines are reevaluated and modified in response to evolving technologies and other factors to optimally facilitate dissemination of information to healthcare professionals at the point of care.

Beginning in 2017, numerous modifications to the guidelines have been and continue to be implemented to make guidelines shorter and enhance "user friendliness." Guidelines are written and presented in a modular knowledge chunk format, in which each chunk includes a table of recommendations, a brief synopsis, recommendation-specific supportive text and, when appropriate, flow diagrams or additional tables. Hyperlinked references are provided for each modular knowledge chunk to facilitate quick access and review. More structured guidelines—including word limits ("targets") and a web guideline supplement for useful but noncritical tables and figures—are 2 such changes. Furthermore, the Preamble is presented in abbreviated form in the executive summary and full-text guideline documents to promote conciseness.

In recognition of the importance of cost–value considerations in certain guidelines, when appropriate and feasible, an analysis of value for a drug, device, or intervention may be performed in accordance with the ACC/AHA methodology (3).

Numerical values for triglycerides, total cholesterol (TC), LDL-C, HDL-C and non-HDL-C are given are in both mg/dL and mmol/L. To convert to SI units, the values for TC, LDL-C, HDL-C, and non-HDL-C were divided by 38.6 and for triglycerides, by 88.6.

To ensure that guideline recommendations remain current, new data are reviewed on an ongoing basis, with full guideline revisions commissioned ideally in approximate 6-year cycles. Publication of potentially practice-changing new study results relevant to an existing or new drug, device, or management strategy prompts evaluation by the Task Force, in consultation with the relevant guideline writing committee, to determine whether a focused update should be commissioned. For additional information and policies on guideline development, we encourage readers to consult the ACC/AHA guideline methodology manual (4) and other methodology articles (5-8).

Selection of Writing Committee Members

The Task Force strives to ensure that the guideline writing committee both contains requisite expertise and is representative of the broader medical community by selecting experts from a broad array of backgrounds, representing different geographic regions, sexes, races, ethnicities, intellectual perspectives/biases, scopes of clinical practice, and by inviting organizations and professional societies with related interests and expertise to participate as partners or collaborators.

Relationships With Industry and Other Entities

The ACC and AHA have rigorous policies and methods to ensure that documents are developed without bias or improper influence. The complete policy on relationships with industry and other entities (RWI) can be found at http://www.acc.org/guidelines/about-guidelines-and-clinical-documents/relationships-with-industry-policy. Appendix 1 of the guideline lists writing committee members' relevant RWI; for the purposes of full transparency, their comprehensive disclosure information is available online (●●●●●●●●●●). Comprehensive disclosure information for the Task Force is also available at http://www.acc.org/guidelines/about-guidelines-and-clinical-documents/guidelines-and-documents-task-forces.

Evidence Review and Evidence Review Committees

In developing recommendations, the writing committee uses evidence-based methodologies that are based on all available data (4, 6, 7). Literature searches focus on randomized controlled trials (RCTs) but also include registries, nonrandomized comparative and descriptive studies, case series, cohort studies, systematic reviews, and expert opinion. Only key references are cited.

An independent evidence review committee is commissioned when there are one or more questions deemed of utmost clinical importance that merit formal systematic review to determine which patients are most likely to benefit from a drug, device, or treatment strategy, and to what degree. Criteria for commissioning an evidence review committee and formal systematic review include absence of a current authoritative systematic review, feasibility of defining the benefit and risk in a timeframe consistent with the writing of a guideline, relevance to a substantial number of patients, and likelihood that the findings can be translated into actionable recommendations. Evidence review committee members may include methodologists, epidemiologists, clinicians, and biostatisticians. Recommendations developed by the writing committee on the basis of the systematic review are marked "SR".

Guideline-Directed Management and Therapy

The term *guideline-directed management and therapy* encompasses clinical evaluation, diagnostic testing, and both pharmacological and procedural treatments. For these and all recommended drug treatment regimens, the reader should confirm dosage with product insert material and evaluate for contraindications and interactions. Recommendations are limited to drugs, devices, and treatments approved for clinical use in the United States.

Class of Recommendation and Level of Evidence

The Class of Recommendation (COR) indicates the strength of recommendation, encompassing the estimated magnitude and certainty of benefit in proportion to risk. The Level of Evidence (LOE) rates the quality of scientific evidence supporting the intervention on the basis of the type, quantity, and consistency of data from clinical trials and other sources (see Table 1 in the guideline) (6).

Glenn N. Levine, MD, FACC, FAHA

Chair, ACC/AHA Task Force on Clinical Practice Guidelines

Supplemental Tables

Table S1. Associated Guidelines and Statements

Title	Organization	Publication Year (Reference)
Guidelines		
Lower-extremity peripheral artery disease	ACC/AHA	2016 (9)
Management of patients with peripheral artery disease	ACCF/AHA	2013 (10)
Management of patients with extracranial carotid and vertebral artery disease	ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS	2011 (11)
Diagnosis and management of patients with thoracic aortic disease	ACC/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM	2010 (12)
Stable ischemic heart disease	ACC/AHA/AATS/PCNA/SCAI/STS	2014(13), 2012 (14)
ST-elevation myocardial infarction	ACC/AHA	2013 (15)
Non–ST-elevation acute coronary syndromes	ACC/AHA	2014 (16)
Percutaneous coronary intervention	ACCF/AHA/SCA	2011 (17)
Coronary artery bypass graft surgery	ACCF/AHA	2011 (18)
Early management of patients with acute ischemic stroke	AHA/ASA	2018 (19)
Prevention of stroke in patients with stroke and transient ischemic attack	AHA/ASA	2014 (20)
Secondary prevention and risk-reduction therapy for patients with coronary and other atherosclerotic vascular disease	AHA/ACC	2011 (21)
Perioperative cardiovascular evaluation and management	ACC/AHA	2014 (22)

of patients undergoing noncardiac surgery		
Assessment of cardiovascular risk	ACC/AHA	2013 (23)
Heart failure	ACC/AHA	2013 (24)
Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults	ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA	2017 (25)
Management of overweight and obesity in adults	AHA/ACC/TOS	2013 (26)
Lifestyle management to reduce cardiovascular risk	AHA/ACC	2013 (27)
Treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults	ACC/AHA	2013 (28)
Assessment of cardiovascular risk	ACC/AHA	2013 (23)
Effectiveness-based guidelines for the prevention of cardiovascular disease in women	AHA	2011 (29)
Scientific statements		
Cardiovascular team-based care and the role of advanced practice providers	ACC	2015 (30)
Secondary prevention after coronary bypass graft surgery	AHA	2015 (31)
Secondary prevention of atherosclerotic cardiovascular disease in older adults	AHA	2013 (32)
Pharmacotherapy in chronic kidney disease patients presenting with acute coronary syndrome	AHA	2015 (33)

Eligibility and disqualification recommendations for competitive athletes with cardiovascular abnormalities: Task Force 8: coronary artery disease	ACC/AHA	2015 (34)
Prevention of cardiovascular disease in diabetes mellitus in light of recent evidence	AHA/ADA	2015 (35)
The agenda for familial hypercholesterolemia	AHA	2015 (36)
Triglycerides and cardiovascular disease	AHA	2011 (37)
Recommendations for management of clinically significant drug–drug interactions with statins and select agents used in patients with cardiovascular disease	AHA	2016 (38)
Clinical advisory on the use and safety of statins	ACC/AHA/NHLBI	2002 (39)
Spontaneous coronary artery dissection: current state of the science	AHA	2018 (40)
Childhood and adolescent adversity and cardiometabolic outcomes	AHA	2018 (41)
Principles on the accessibility and affordability of drugs and biologics	AHA	2017 (42)
Secondary prevention lipid performance measures	ACC/AHA	2015 (43)
Clinical performance measures and quality measures for adults with ST-elevation and non–ST-elevation myocardial infarction	ACCF/AHA	2017 (44)
Performance measures for adults undergoing percutaneous coronary intervention	ACC/AHA/SCAI/AMA	2014 (45)

Medication errors in acute cardiovascular and stroke patients	AHA	2010 (46)
Basic concepts and potential applications of genetics and genomics for cardiovascular and stroke clinicians	AHA	2015 (47)
Clinical guideline implementation strategies	ACC/AHA	2017 (48)
Clinical practice guidelines in patients with cardiovascular disease and comorbid conditions	ACC/AHA/HHS	2014 (5)
Cost/value methodology in clinical practice guidelines and performance measures	ACC/AHA	2014 (3)
Knowledge gaps in cardiovascular care of the older adult population	ACC/AHA/AGS	2016 (49)

AANN indicates American Association of Neuroscience Nurses; AANS, American Association of Neurological Surgeons; AAPA, American Academy of Physician Assistants; AATS, American Association for Thoracic Surgery; ABC, Association of Black Cardiologists; ACC, American College of Cardiology; ACCF, American College of Cardiology Foundation; ACPM, American College of Preventive Medicine; ACR, American College of Rheumatology; ADA, American Diabetes Association; AGS, American Geriatrics Society; AHA, American Heart Association; AMA, American Medical Association; APhA, American Pharmacists Association; ASA, American Stroke Association; ASH, American Society of Hematology; ASNR, American Society of Neuroradiology; ASPC, Association of Surgeons in Primary Care; CNS, Congress of Neurological Surgeons; HHS, U.S. Department of Health and Human Services; NMA, National Medical Association; NHLBI, National Heart, Lung, and Blood Institute; PCNA, Preventive Cardiovascular Nurses Association; SAIP, Society of Atherosclerosis Imaging and Prevention; SCA, Society of Cardiovascular Anesthesiologists; SCAI, Society for Cardiovascular Angiography and Interventions; SIR, Society of Interventional Radiology; SNIS, Society of NeuroInterventional Surgery; STS, Society of Thoracic Surgeons; SVM, Society for Vascular Medicine; SVS, Society for Vascular Surgery; and TOS, The Obesity Society.

Table S2. Criteria for Clinical Diagnosis of the Metabolic Syndrome

Measure	Categorical Cut Points
Elevated waist circumference*	≥102 cm (40.1 in) (or 90 cm (35.4 in)) in males ≥88 cm (34.6 in) (or 80 cm (31.4 in)) in females
Elevated triglycerides (drug treatment for elevated triglycerides is an alternative indicator) †	≥175 mg/dL (2.0 mmol/L§)
Reduced HDL-C (drug treatment for reduced HDL-C is an alternative indicator) †	<40 mg/dL (1.0 mmol/L) in males <50 mg/dL (1.3 mmol/L) in females
Hypertension (antihypertensive drug treatment in a patient with a history of hypertension is an alternative indicator)	Systolic ≥130 and/or diastolic ≥85 mm Hg
Elevated fasting glucose (drug treatment of elevated glucose is an alternative indicator) ¶	≥100 mg/dL

HDL-C indicates high-density lipoprotein cholesterol.

* Waist circumference cut points generally recommended for the United States are ≥102 cm in males and ≥88 cm in females, but lower cut points (≥90 cm in males and ≥80 cm in females) are commonly recommended for other populations.

† The most commonly used drugs for elevated triglycerides and reduced HDL-C are fibrates and nicotinic acid. A patient taking one of these drugs can be presumed to have high triglycerides and low HDL-C. High-dose n-3 fatty acids presume high triglycerides.

§Categorical cut point for triglycerides incorporates both fasting and nonfasting triglycerides.

¶Most patients with type 2 diabetes mellitus will have the metabolic syndrome by the current criteria.

Table S3. Characteristics of Common Lipid-Lowering Medications That Are Used to Lower LDL-C*

Medication Class	Mechanism of Action	Drugs	Total Daily Dose Range (mg/d)†	Dosing Frequency	Comments
HMG-CoA reductase inhibitors (also known as statins)	Competitively inhibit HMG-CoA reductase (rate-limiting step of endogenous cholesterol production); increase the number of LDL receptors	Atorvastatin	10-80	Once daily	• First-line therapy for nearly all patients, as based on extensive evidence demonstrating reductions in cardiovascular events over wide range of LDL-C and overall safety • Potential LDL-C reduction‡ is 18%–55% • LDL-C reductions vary according to dose of the specific statin • Fluvastatin, lovastatin, pravastatin, and simvastatin have short half-lives. They should be administered in the evening to achieve maximum LDL-C reduction. Atorvastatin, fluvastatin XL, pitavastatin, and rosuvastatin can be dosed anytime of the day.
		Fluvastatin	20-80	Once or twice daily	
		Lovastatin	10-80	Once or twice daily	
		Pitavastatin	1-4	Once daily	
		Pravastatin	10-80	Once daily	
		Rosuvastatin	5-40	Once daily	
		Simvastatin	5-40	Once daily	
Bile acid sequestrants	Bind bile acids in the gut, interrupt enterohepatic recirculation of bile acids and impede their reabsorption, decrease bile acid pooling in the liver, increase conversion of cholesterol to bile acids, increase the number of LDL receptors	Cholestyramine	4,000-24,000	Once or twice daily	• Nonsystemic add-ons to statin therapy, or used in patients with statin-associated side effects, including statin-associated muscle symptoms • Potential LDL-C reduction‡ is 15%–30% • Available as tablets or powder for suspension • Gastrointestinal side effects may limit use • May increase serum TG levels; avoid if TG >300 mg/dL • Colesevelam is approved for use in type 2 diabetes mellitus to reduce hemoglobin A1C • Can bind absorption of other medications (less
		Colesevelam	3,750	Once or twice daily	
		Colestipol	5,000-30,000	Once to 6 times daily	

					with colesevelam); should be administered at least 1 h before or 4 h after other medications to minimize potential drug–drug interaction
Cholesterol absorption inhibitors	Block the cholesterol transport Nieman Pick C1–like 1 protein to inhibit intestinal and biliary cholesterol absorption; increase the number of LDL receptors	Ezetimibe	10	Once daily	• Evidence-based add-on to statin therapy in very high-risk patients or in patients with statin-associated side effects, including statin-associated muscle symptoms • Potential LDL-C reduction‡ is 13% to 20% • Approved for use in homozygous sitosterolemia to reduce elevated sitosterol and campesterol
PCSK9 inhibitors	Fully human monoclonal antibodies that bind to PCSK9 and decrease degradation of the LDL receptor	Alirocumab	75-150	Every 2 wks	• Evidence-based add-on to statin therapy in very high-risk patients • Potential LDL-C reduction‡ is 43%–64% • Lower LDL-C reduction in heterozygous FH when added to tolerated statin/ezetimibe therapy • Mean LDL-C reduction is 30% with evolocumab in homozygous FH (50) • Requires subcutaneous injection
			300	Every 4 wks	
		Evolocumab	140	Every 2 wks	
			420	Every 4 wks	

FDA indicates U.S. Food and Drug Administration; FH, familial hypercholesterolemia; HMG-CoA, 3-hydroxy-3-methylglutaryl-coenzyme; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9; TG, triglycerides; and XL, extended release.

*Lomitapide and mipomersen sodium are other medications that are used to lower LDL-C in patients with homozygous familial hypercholesterolemia. Though rarely prescribed, these medications are usually prescribed by a clinical lipidologist because of restricted access through a Risk Evaluation and Mitigation Strategy program to assure safe use.

†Dosages and administration from FDA-approved labeling (available at: http://dailymed.nlm.nih.gov/dailymed/index.cfm (51))

‡Potential LDL-C lowering based on estimations from the National Lipid Association (52), or product labeling.

Table S4. Pharmacokinetic Properties of Statin Medications

	Absorption		Distribution		Metabolism			Elimination	
	Bio-availability (%)	T_{max} (h)	Protein Binding (%)	Lipophilicity (log *p*)	CYP Hepatic Enzyme	Pro-drug	Active Metabolite	Renal Excretion (%)	$t_{1/2}$ (h)
Atorvastatin	14	1–2	≥98	4.1	3A4	No	Yes	<2	14
Fluvastatin	24	<1	98	3.2	2C9 (2C8, 3A4 minor)	No	No	5	3
Lovastatin	<5	2–4	>95	4.3	3A4	Yes	Yes	10	2–3
Pitavastatin	43–51	1	99	1.5	2C9 (2C8 minor)	No	No	15	12
Pravastatin	17	1–1.5	50	-0.2	None	No	No	20	1.8
Rosuvastatin	20	3–5	88	-0.3	2C9	No	Minimal	10	19
Simvastatin	<5	4	95	4.7	3A4	Yes	Yes	13	2

CYP indicates cytochrome P450; T_{max}, time until maximum serum concentration achieved; and $t_{1/2}$, drug half-life.

Table S5. Common Medications That May Potentially Interact With Statins

Can Be Used With a Statin Using a Risk-Mitigation Strategy*		Do Not Use With Any Statin
• Amiodarone • Amlodipine • Atazanavir plus ritonavir • Boceprevir • Clarithromycin • Cobicistat-containing products • Colchicine • Cyclosporine • Danazol • Darunavir plus ritonavir • Diltiazem • Dronedarone • Erythromycin • Fenofibrate • Fenofibric acid • Fluconazole • Fosamprenavir (with or without ritonavir)	• Itraconazole • Ketoconazole • Lomitapide • Lopinavir plus ritonavir • Nefazodone • Nelfinavir • Niacin (≥1 g/d) • Posaconazole • Ranolazine • Rifampin • Saquinavir plus ritonavir • Telaprevir • Telithromycin • Tipranavir plus ritonavir • Verapamil • Voriconazole • Warfarin	Gemfibrozil

*Risk-mitigation strategies include avoiding use of the co-administered interacting medication; using an alternative statin that does not have the drug–drug interaction; and limiting the statin dose, depending on the statin and the nature of the drug–drug interaction.

Table S6. Relative Risk Association between Risk-Enhancing Factors and ASCVD

Risk-Modifying Factor	Risks for ASCVD – Illustrative Examples	References
Parental Cardiovascular Disease	Multivariable adjustment gave odds ratios for premature CVD: Men: 2.0 (95% CI: 1.2–3.1) Women; 1.7 (95% CI: 0.9–3.1) Comments: In the Framingham Offspring study, those participants with no parental cardiovascular disease were compared to those with at least 1 parent with premature cardiovascular disease (CVD) with onset age <55 years in father and <65 years in mother.	(53)
Family history of stroke	Comments: For family history of stroke: Multivariable adjustment gave odds ratios of All stroke: odds ratio, 2.79 (95% CI: 1.68–4.66; P<0.001) Ischemic stroke: hazard ratio, 3.15 (95% CI: 1.69–5.88; P<0.001) This was true for both maternal and paternal stroke.	(54)
Metabolic syndrome with and without DM	RR for patients with MS including DM: RR For CVD: 2.35 (95% CI: 2.02-2.73) – Men: 2.14 (95% CI: 1.62-2.83) – Women: 2.87 (95% CI: 2.40-3.43) – CVD mortality: 2.40 (95% CI: 1.87-3.08) RR for patients with MS but not with DM: ⁻ CVD mortality: 1.75 (95% CI 1.19-2.58) RR for CV events and death: 1.78 RR for patients including DM vs. those without DM: 1.51 vs. 1.69 RR for patients with CHD vs. those without CHD: 2.68 vs. 1.94	(55) (56)
Chronic Kidney Disease (CKD)	HR for cardiovascular mortality (if dipstick proteinuria ≥ ++) eGFR 45-59. 1.38 (2.67) eGFR 30-44: 2.42. (3.06) eGFR 15-29: 3.29	(57)
Inflammatory disorders	RR of cardiometabolic diseases (CHD, stroke, type 2 DM, venous thromboembolism and peripheral artery disease) Comment: Magnitude of association with inflammatory disease and cardiometabolic disease was higher among those	(58)

	prescribed nonsteroidal anti-inflammatory or corticosteroid drugs. RR by specific inflammatory conditions	
Rheumatoid arthritis	1.70 (95% CI: 1.59-1.83)	
Ankylosing spondylitis	1.28 (95% CI: 1.09-1.52)	
Psoriasis (most common)	1.25 (95% CI: 1.16-1.35)	
Systematic lupus erythematosus (least common)	6.36 (95% CI: 4.37-9.25)	
Vasculitis	1.64 (95% CI 1.42-1.90)	
HIV Hepatitis C virus Both HIV/HCV coinfection	MI rates per 1,000 person-y – Black men: 6.9 – Black women: 7.2 – White men: 4.4 – White women: 3.3 HR:2.91 (95% CI: 1.19-7.12) Comments: Note higher RR in black vs. white and black women especially. Also, HIV/HCV-coinfected patients had a higher incidence of CVD events and/or death than did HIV-monoinfected adults (59)(12) (4% vs. 1.2%, *p*=0.004).	(60) (59)

Conditions Specific to Women: Early menopause and Pre-Eclampsia	Early age at menopause (age <40 compared to age 50-<55 years) associated with higher multivariable-adjusted CVD risk: 1.32 (95% CI 1.16-1.51), *P* trend<0.0001, with excess risk for both natural and surgical menopause In women with a history of pre-eclampsia or eclampsia, a) an increased risk of CVD (leading to either a clinical diagnosis or a fatal outcome) was demonstrated (HR: 2.28; 95% CI: 1.87 to 2.78), b) cerebrovascular disease (HR: 1.76; 95% CI: 1.43 to 2.21) c) developing hypertension (HR: 3.13; 95% CI: 2.51 to 3.89) Comments: 1. Prospective cohort study data from Nurses health Study Also Furthermore, a shorter reproductive life span was associated with higher risk of incident CVD after multivariable adjustment (RR, 1.32 [95% CI, 1.16-1.49] comparing duration in years <30 with ≥42; *P* trend<0.0001). 2. Outcomes for menopausal women younger than 45 years relative to women older than 45 years. For overall CHD, relative risks were 1.50 (95% CI 1.28-1.76). 1.11 (95% CI: 1.03-1.20) for fatal CHD, 1.23 (95% CI: 0.98-1.53) for overall stroke, 0.99 (95% CI: 0.92-1.07) for stroke mortality, 1.19 (95% CI: 1.08-1.31) for CVD mortality, and 1.12 (95% CI: 1.03-1.21) for all-cause mortality. 3. A meta-analysis of 43 studies of women with a history of pre-eclampsia or eclampsia demonstrated increased risk of CVD (leading to either a clinical diagnosis or a fatal outcome) (HR: 2.28; 95% CI: 1.87 to 2.78), cerebrovascular disease (HR: 1.76; 95% CI: 1.43 to 2.21) and of developing hypertension (HR: 3.13; 95% CI: 2.51 to 3.89)	(61) (62) (63) (64)

High risk ethnicities: e.g. South Asian	Proportionate mortality ratios highest in Asian Indian men (1.43) & women (1.12), followed by Filipino men (1.15) Comments: Examined 10,442,034 U.S. records from 2003 to 2010 using U.S. Census and death records from the National Center for Health Statistics (NCHS) by Asian subgroup While non-Hispanic men and women had the highest overall mortality rates, Asian Indian men and women and Filipino men had greater proportionate mortality burden from ischemic heart disease. The proportionate mortality burden of hypertensive heart disease and cerebrovascular disease, especially haemorrhagic stroke, was higher in every Asian-American subgroup compared to non-Hispanic whites.	(65) (66)
Ankle-brachial index	ABI <0.9 supports revising risk assessment by Pooled Cohort Equations (PCE) upwards. Comments: The ABI is to be used when risk-based decisions about initiation of LDL-C lowering therapy remain uncertain after quantitative risk assessment by PCE. Same analysis also noted this to be true of family history of premature ASCVD and hs-CRP (see above)	(23)
Biomarkers		
Hypertriglyceridemia	HR: 1.37 (95% CI: 0.99) Comments: HRs were at least as strong in those who did not fast as in those who were fasting. HR for CHD after adjustment for nonlipid risk factors was 1.37 but only 0.99 (95% CI: 0.91-1.03) after further adjustment for HDL-C and non-HDL-C. 2. For Incident fatal and non-fatal cardiovascular relative risks: Men: Univariate RR for TG: 1.32 (95% CI: 1.26-1.39, p<0.05) Adjustment for HDL-C: 1.14 (95% CI: 1.05-1.28; p <0.05)	(67) (68)

	Women: Univariate RR for TG: 1.76 (95% CI: 1.50-2.07, p<0.05) Adjustment for HDL-C: Univariate RR for TG 1.37 (95% CI: 1.13 -1.66, p <0.05)	
hsCRP	HR: 1.63 (95% CI: 1.37) Comments: When adjusted for age and sex, HR was 1.63, but HR was only 1.37 when adjusted further for CHD risk factors.	(69)
Lipoprotein(a)	1.Lp(a) and CHD relationships In 24 cohort studies: RR : 1.16 (95% CI: 1.11-1.22) adjusted for age and sex only RR 1.13 (95% CI, 1.09-1.18) further adjustment for lipids, & conventional risk factors) RR: 1.10 for ischemic stroke (95% CI 0.98-1.05) 2. Individuals with Lp(a) ≥ 80th percentile show increased CVD risk with higher LDL-C values than those with LDL-C <96.8 mg/dL (2.5 mmol/L) 3. Quintile analyses showed that risk for incident CVD was graded but statistically significant only for the highest compared with the lowest quintile for Lp(a) HR 1.35 (95% CI: 1.06-1.74) for African Americans; HR 1.27 [95% CI: 1.10–1.47] for Caucasians). 4. In Women's Healthy Study, a curvilinear association with increased CVD risk reported, if Lp(a) >50 mg/dL but only among women with total cholesterol>220 mg/dL. In contrast, authors reported strong association of Lp(a) with CHD among men with low total cholesterol levels in the JUPITER randomized controlled trial.	(70) (71) (72) (73)

Apolipoprotein B. (apo B)	In large multi-center prospective follow up of patients without CVD: a) Total cholesterol (TC)/ HDL-C ratio or apoprotein ratios illustrated no improved risk prediction over TC and HDL-C. b) Adding apo B to TC and HDL-C was associated with slight improvement in CVD risk prediction. Meta-analysis prospective observational studies show apo B>Non-HDL-C >LDL-C: Apo B: RRR 1.43 (95% CI: 1.35-1.51) Non-HDL-C: RRR 1.34 (95% CI: 1.24-1.44) LDL-C: RRR 1.25 (95% CI: 1.18-1.33) In frequentist meta-analyses, the mean CHD risk reduction (95% CI) per standard deviation decrease in LDL-C, non-HDL-C and apo B across 7 placebo-controlled statin trials were: LDL-C: 20.1% (95% CI: 15.6-24.3%) Non-HDL-C: 20.0% (95% CI: 15.2-24.7%) Apo B: 24.4% (95% CI: 19.2-29.2%)	(74) (75) (76)

ASCVD indicates atherosclerotic cardiovascular disease; CHD, coronary heart disease; CI, confidence interval; CRP, C-reactive protein; CV, cardiovascular; CVD, cardiovascular disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; FHPCAD, family history of premature ASCVD; HCV, hepatitis C virus; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; MI, myocardial infarction; MS, metabolic syndrome; PCE, pooled cohort equations; RR, risk ratio; SDS, social deprivation status; and TG, triglycerides.

*Family history age-adjusted odds ratio for CVD: 2.6 for men and 2.3 for women. Multivariable adjusted odds ratio: 2.0 for men and 1.7 for women. Family history of premature CVD was defined as CVD event in first-degree relative <55 years of age in men and <65 years of age in women (53)(4).

Table S7. Strategies to Improve Guideline Implementation by Setting and Target Audience (23, 77-79)

Patient	Clinician	Office/Health System	Health Plan	Retail Pharmacy
• Simplify medication regimens • Provide clear instructions (what the medications is for, how to take it, what to expect) • Encourage the use of telephone alarms, prompts, and other tools to help patient remember to take medication • Encourage support of family and peers • Lower barriers to getting medication (cost, delivery method) • Provide consistent messaging • Remind patients about appointments and follow up on missed appointments • Ask patients to bring prescription and nonprescription medication bottles to each office visit • Provide education with behavior support,	• Initiate clinician–patient risk discussions • Provide brief, simple messages • Assess adherence at every encounter • Maintain contact with patient (follow-up laboratory tests and follow-up visits) • Use shared decision-making aids, motivational interviewing, decision coaching, and question prompt lists (81) • Incorporate discussion about lifestyle into every encounter • Provide prescriptions for diet and exercise recommendations • Teach clinicians to implement ASCVD risk reduction guidelines (48, 82) • Use apps (e.g., ASCVD Risk Estimator Plus (83), CardioSmart Explorer (84), LDL-C Manager (85), Statin Intolerance (86), Mayo Clinic Statin	• Leverage decision-support tools imbedded in electronic medical records to promote formulary-based prescribing, minimal out-of-pocket expenses, and implementation of guidelines (92) • Use technology to identify high-risk patients who are not receiving GDMT • Collaborate with other team members to provide patient care (pharmacists, including retail-based; nurses; NP; PA) (30, 93, 94) • Structure care by developing standard treatment plans and pathways • Use peer-to-peer feedback from past performance with guideline implementation to promote change in future care • Participate in registries to improve care	• Reduce the out-of-pocket cost of GDMT/prescriptions (92, 95-97) • Provide greater transparency to allow the patient and clinician determine which medications are included in the patient's drug formulary, the tier level, and the out-of-pocket cost to the patient • Increase access to care • Promote and reimburse for team-based collaborative care (pharmacists, including retail based; nurses, NP, PA) (30, 93, 94)	• Encourage enrollment in automatic refill programs (98) • Encourage 90-d refills vs. 30-d refills (99, 100) • Encourage packaging that promotes adherence (101-103) • Encourage use of medication synchronization programs (104, 105)

case management, or telehealth counseling • Increase empowerment through peer-to-peer and social support moderated by clinician • Consider clinician–patient shared accountability for performance measures (43, 80)	Choice Decision Aid) (87)and other resources (American Heart Association Life's Simple 7 (88), National Lipid Association Patient Tear Sheets (89), Clinicians' Lifestyle Modification Toolbox (90), Preventive Cardiovascular Nurses Association Heart Healthy Toolbox (91), cholesterol tear sheets, and patient education booklets)	• Use academic detailing (48, 82) • Identify stakeholders and make use of audit and feedback on clinical performance (48, 82)		

ASCVD indicates atherosclerotic cardiovascular disease; GDMT, guideline-directed management and therapy; LDL, low-density lipoprotein; NP, nurse practitioner; and PA, physician assistant.

Table S8. Clinician–Patient Risk Discussion: Useful Checklist

Individualize decision for patient regarding prevention of ASCVD

1. **Importance of addressing other risk factors**
   - Cigarette smoking
   - Hypertension
   - DM
   - Metabolic syndrome, obesity, sedentary behaviors
   - Other risk-modifying factors (Table 10 in Section 4.5)
2. **Importance of adherence to optimal lifestyle**
   - Lifestyle improves all metabolic risk factors
   - Lifestyle still important even if genetic disease or on statin therapy
3. **Understand current risk status with PCE risk estimation**
   - If age 20–39 y, estimate lifetime ASCVD risk
   - If age 40–75 y, use 10-y ASCVD risk estimator (83)
     - Risk estimator estimates to age 79 y if of interest
     - Reliability of PCEs; need to adjust for ethnic and other factors (use ACC/AHA risk estimator (106); see Section 7
   - Understand risk estimates not precise; they start the risk discussion
4. **Resolving uncertainty regarding risk estimation**
   - If uncertain, consider benefit of CAC scoring (see section 4.4.1) as a CAC score of zero may indicate that benefits of statin therapy do not outweigh risks.
   - Understand that, especially in younger patients, a CAC score of zero does not provide information on noncalcified plaques
5. **Potential benefit of statin therapy**
   - Multiple meta-analyses show them effective and safe. In those at risk, shown to reduce all-cause and cardiovascular mortality in primary and as well as in secondary prevention
   - Concept of reversal of unstable plaques for high risk
   - Concept of “the lower, the better” for LDL-C, especially in those at highest risk (favors higher intensity)
   - Expected risk reduction from prescribed dose (see section on pharmacotherapy)
6. **Potential for adverse effects of statins (See Section 5)**
   - Lack of specificity of common musculoskeletal symptoms and other symptoms falsely attributed to statin therapy.
   - Consider genetic reasons (SLC01B1) for side effects on simvastatin
   - Dose versus side effect relationship (See Section 5)
   - Potential for drug–drug interaction (see section on pharmacotherapy)
   - Guidelines encourage pharmacist input to check for drug–drug interactions
   - In those with DM risk factors, progression to DM more likely with statins, but this is not seen in those with 0–1 DM risk factors. Another reason to stick with heart-healthy lifestyle if placed on a statin.
7. **Potential adherence issues of lifetime statin therapy (See Section 6)**
   - Studies show increased risk in those assigned to statin therapy who did not persist in finding a tolerated statin or dose
   - Discuss that benefits from statin therapy are greater in year 3 than in year 1; benefits increase with duration of therapy
   - Discuss several studies with long-term follow-up showing benefit
8. **Patient preference and expectations**
   - Patients values, goals, and attitudes toward using medication should be shared so a joint decision can be made

- Important to inquire about prior experiences with drugs and/or statins
- Communicate the essential nature of a risk decision involving the evidence, patient characteristics, clinician judgment and after hearing about benefits, risks, and options, the inclusion of patient preference in shared decision-making
- Use best practices for discussing numeric risk, including teaching aides
- Ongoing reassessment of patient status and measurements of adherence and percent lowering of LDL-C on statin therapy, along with patient preference, which may change
- Special considerations for women, various racial/ethnic groups, and those >75 y of age, including cessation of statin therapy in the elderly (see Section 4.4.4.1, 4.4.5.1, and 4.4.5.4)

9. **Consider knowledgeable staff and consider materials for patients who wish to think about this decision (see Section 6). The decision may, in some cases, require a repeat visit to review issues important to the patient.**

ACC indicates American College of Cardiology; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; DM, diabetes mellitus; LDL-C, low-density lipoprotein cholesterol; and PCE, pooled cohort equations.

References

1. Editors: IoMUCoSfDTCPG. Clinical Practice Guidelines We Can Trust. Washington (DC): The National Academies Press, 2011.
2. Research IoMUCoSfSRoCE. Finding What Works in Health Care: Standards for Systematic Reviews. Washington (DC): The National Academies Press, 2011.
3. Anderson JL, Heidenreich PA, Barnett PG, et al. ACC/AHA statement on cost/value methodology in clinical practice guidelines and performance measures: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures and Task Force on Practice Guidelines. Circulation. 2014;129:2329-45.
4. Guidelines. AATFoP. Methodology Manual and Policies From the ACCF/AHA Task Force on Practice Guidelines. American College of Cardiology and American Heart Association. 2010;
5. Arnett DK, Goodman RA, Halperin JL, et al. AHA/ACC/HHS strategies to enhance application of clinical practice guidelines in patients with cardiovascular disease and comorbid conditions: from the American Heart Association, American College of Cardiology, and US Department of Health and Human Services. Circulation. 2014;130:1662-7.
6. Halperin JL, Levine GN, Al-Khatib SM, et al. Further Evolution of the ACC/AHA Clinical Practice Guideline Recommendation Classification System: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2016;133:1426-8.
7. Jacobs AK, Anderson JL, Halperin JL, et al. The evolution and future of ACC/AHA clinical practice guidelines: a 30-year journey: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. Circulation. 2014;130:1208-17.
8. Jacobs AK, Kushner FG, Ettinger SM, et al. ACCF/AHA clinical practice guideline methodology summit report: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013;127:268-310.
9. Pang X-H, Han J, Ye W-L, et al. Lower extremity peripheral arterial disease is an independent predictor of coronary heart disease and stroke risks in patients with type 2 diabetes mellitus in China. Int J Endocrinol. 2017;2017:9620513.
10. Rooke TWH, A.T.; Misra, S.; Sidawy, A.N.; Beckman, J.A.; Findeiss, L.; Golzarian, J.; Gornik, H.L.; Jaff, M.R.; Moneta, G.L.; Olin, J.W.; Stanley, J.C.; White, C.J.; White, J.V.; Zierler, R.E.; American College of Cardiology Foundation Task Force; American Heart Association Task Force. Management of patients with peripheral artery disease (compilation of 2005 and 2011 ACCF/AHA Guideline Recommendations): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013;62:1555-70.
11. Brott TG, Halperin JL, Abbara S, et al. 2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS guideline on the management of patients with extracranial carotid and vertebral artery disease. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American Stroke Association, American Association of Neuroscience Nurses, American Association of Neurological Surgeons, American College of Radiology, American Society of Neuroradiology, Congress of Neurological Surgeons, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of NeuroInterventional Surgery, Society for Vascular Medicine, and Society for Vascular Surgery. Circulation. 2011;124:e54-130.
12. Hiratzka LF, Bakris GL, Beckman JA, et al. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with Thoracic Aortic Disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology, American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons, and Society for Vascular Medicine. Circulation. 2010;121:e266-369.
13. Fihn SDB, J.C.; Alexander, K.P.; Bittl, J.A.; Byrne, J.G.; Fletcher, B.J.; Fonarow, G.C.; Lange, R.A.; Levine, G.N.; Maddox, T.M.; Naidu, S.S,; Ohman, E.M.; Smith, P.K. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the

guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. Circulation. 2014;130:1749-67.

14. Fihn SDG, J.M.; Abrams, J.; Berra, K.; Blankenship, J.C.; Dallas, A.P.; Douglas, P.S.; Foody, J.M.; Gerber, T.C.; Hinderliter, A.L.; King, S.B. 3rd; Kligfield, P.D.; Krumholz, H.M.; Kwong, R.Y.; Lim, M.J.; Linderbaum, J.A.; Mack, M.J.; Munger, M.A.; Prager, R.L.; Sabik, J.F.; Shaw, L.J.; Sikkema, J.D.; Smith, C.R. Jr; Smith, S.C. Jr; Spertus, J.A.; Williams, S.V.; Anderson, J.L.; American College of Cardiology Foundation/American Heart Association Task Force. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. Circulation. 2012;126:e354-471.

15. O'Gara PTK, F.G.; Ascheim, D.D.; Casey, D.E. Jr; Chung, M.K.; de Lemos, J.A.; Ettinger, S.M.; Fang, J.C.; Fesmire, F.M.; Franklin, B.A.; Granger, C.B.; Krumholz, H.M.; Linderbaum, J.A.; Morrow, D.A.; Newby, L.K.; Ornato, J.P.; Ou, N.; Radford, M.J.; Tamis-Holland, J.E.; Tommaso, J.E.; Tracy, C.M.; Woo, Y.J.; Zhao, D.X.; CF/AHA Task Force. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013;127:529-55.

16. Amsterdam EAW, N.K.; Brindis, R.G.; Casey, D.E. Jr; Ganiats, T.G.; Holmes, D.R. Jr; Jaffe, A.S.; Jneid, H.; Kelly, R.F.; Kontos, M.C.; Levine, G.N.; Liebson, P.R.; Mukherjee, D.; Peterson, E.D.; Sabatine, M.S.; Smalling, R.W.; Zieman, S.J.; ACC/AHA Task Force Members. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;130:e344-426.

17. Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. Circulation. 2011;124:e574-651.

18. Hillis LDS, P.K.; Anderson, J.L.; Bittl, J.A.; Bridges, C.R.; Byrne, J.G.; Cigarroa, J.E.; Disesa, V.J.; Hiratzka, L.F.; Hutter, A.M. Jr; Jessen, M.E.; Keeley, E.C.; Lahey, S.J.; Lange, R.A.; London, M.J.; Mack, M.J.; Patel, M.R.; Puskas, J.D.; Sabik, J.F.; Selnes, O.; Shahian, D.M.; Trost, J.C.; Winniford, M.D. 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2011;124:e652-735.

19. Powers WJR, A.A.; Ackerson, T.; Adeoye, O.M.; Bambakidis, N.C.; Becker, K.; Biller, J.; Brown, M.; Demaerschalk, B.M.; Hoh, B.; Jauch, E.C.; Kidwell, C.S.; Leslie-Mazwi, T.M.; Ovbiagele, B.; Scott, P.A.; Sheth, K.N.; Southerland, A.M.; Summers, D.V.; Tirschwell, D.L.; American Heart Association Stroke Council. 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2018;49:e46-e110.

20. Kernan WNO, B.; Black, H.R.; Bravata, D.M.; Chimowitz, M.I.; Ezekowitz, M.D.; Fang, M.C.; Fisher, M.; Furie, K.L.; Heck, D.V.; Johnston, S.C.; Kasner, S.E.; Kittner, S.J.; Mitchell, P.H.; Rich, M.W.; Richardson, D.; Schwamm, L.H.; Wilson, J.A.; American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Peripheral Vascular Disease. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2014;45:2160-236.

21. Smith SCJB, E.J.; Bonow, R.O.; Braun, L.T.; Creager, M.A.; Franklin, B.A.; Gibbons, R.J.; Grundy, S.M.; Hiratzka, L.F.; Jones, D.W.; Lloyd-Jones, D.M.; Minissian, M.; Mosca, L.; Peterson, E.D.; Sacco, R.L.; Spertus, J.; Stein, J.H.; Taubert, K.A. AHA/ACCF secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation. J Am Coll Cardiol. 2011;58:2432-46.

22. Fleisher LAF, K.E.; Auerbach, A.D.; Barnason, S.A.; Beckman, J.A.; Bozkurt, B.; Davila-Roman, V.G.; Gerhard-Herman, M.D.; Holly, T.A.; Kane, G.C.; Marine, J.E.; Nelson, M.T.; Spencer, C.C.; Thompson, A.; Ting, H.H.; Uretsky, B.F.; Wijeysundera, D.N. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of

patients undergoing noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;130:e278-333.
23. Goff DC, Jr., Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129:S49-73.
24. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation. 2013;128:e240-327.
25. Whelton PKC, R.M.; Aronow, W.S.; Casey, D.E. Jr; Collins, K.J.; Dennison Himmelfarb, C.; DePalma, S.M.; Gidding, S.; Jamerson, K.A.; Jones, D.W.; MacLaughlin, E.J.; Muntner, P.; Ovbiagele, B.; Smith, S.C. Jr; Spencer, C.C.; Stafford, R.S.; Taler, S.J.; Thomas, R.J.; Williams, K.A. Sr; Williamson, J.D.; Wright, J.T. Jr. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2017;71:e127-e248.
26. Jensen MD, Ryan DH, Apovian CM, et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. Circulation. 2014;129:S102-38.
27. Eckel RH, Jakicic JM, Ard JD, et al. 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129:S76-99.
28. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129:S1-45.
29. Mosca LB, E.J.; Berra, K.; Bezanson, J.L.; Dolor, R.J.; Lloyd-Jones, D.M.; Newby, L.K.; Piña, I.L.; Roger, V.L.; Shaw, L.J.; Zhao, D.; Beckie, T.M.; Bushnell, C.; D'Armiento, J.; Kris-Etherton, P.M.; Fang. J.; Ganiats, T.G.; Gomes, A.S.; Gracia, C.R.; Haan, C.K.; Jackson, E.A.; Judelson, D.R.; Kelepouris, E.; Lavie, C.J.; Moore, A.; Nussmeier, N.A.; Ofili, E.; Oparil, S.; Ouyang, P.; Pinn, V.W.; Sherif, K.; Smith, S.C, Jr; Sopko, G.; Chandra-Strobos, N.; Urbina, E.M.; Vaccarino, V.; Wenger, N.K.; American Heart Association. Effectiveness-based guidelines for the prevention of cardiovascular disease in women--2011 update: a guideline from the American Heart Association. Circulation. 2011;123:1243-62.
30. Brush JE, Jr., Handberg EM, Biga C, et al. 2015 ACC Health Policy Statement on Cardiovascular Team-Based Care and the Role of Advanced Practice Providers. J Am Coll Cardiol. 2015;65:2118-36.
31. Kulik AR, M.; Jneid, H.; Ferguson, T.B.; Hiratzka, L.F.; Ikonomidis, J.S.; Lopez-Jimenez, F.; McNallan, S.M.; Patel, M.; Roger, V.L.; Sellke, F.W.; Sica, D.A.; Zimmerman, L.; American Heart Association Council on Cardiovascular Surgery and Anesthesia. Secondary prevention after coronary artery bypass graft surgery: a scientific statement from the American Heart Association. Circulation. 2015;131:927-64.
32. Fleg JL, Forman DE, Berra K, et al. Secondary prevention of atherosclerotic cardiovascular disease in older adults: a scientific statement from the American Heart Association. Circulation. 2013;128:2422-46.
33. Washam JBH, C.A.; Beitelshees, A.L.; Cohen, M.G.; Henry, T.D.; Kapur, N.K.; Mega, J.L.; Menon, V.; Page, R.L. 2nd; Newby, L.K.; American Heart Association Clinical Pharmacology Committee of the Council on Clinical Cardiology; Council on Cardiovascular Surgery and Anesthesia; Council on Functional Genomics and Translational Biology; Council on the Kidney in Cardiovascular Disease; Council on Quality of Care and Outcomes Research. Pharmacotherapy in chronic kidney disease patients presenting with acute coronary syndrome: a scientific statement from the American Heart Association. Circulation. 2015;131:1123-49.
34. Thompson PDM, R.J.; Levine, B.D.; Udelson, J.E.; Kovacs, R.J.; American Heart Association Electrocardiography and Arrhythmias Committee of Council on Clinical Cardiology; Council on Cardiovascular Disease in Young; Council on Cardiovascular and Stroke Nursing; Council on Functional Genomics and Translational Biology; American College of Cardiology. Eligibility and Disqualification Recommendations for Competitive Athletes with Cardiovascular Abnormalities: Task Force 8: Coronary Artery Disease: A Scientific Statement from the American Heart Association and American College of Cardiology. Circulation. 2015;132:e310-4.
35. Fox CSG, S.H.; Anderson, C.; Bray, G.A.; Burke, L.E.; de Boer, I.H.; Deedwania, P.; Eckel, R.H.; Ershow, A.G.; Fradkin, J.; Inzucchi, S.E.; Kosiborod, M.; Nelson, R.G.; Patel, M.J.; Pignone, M.; Quinn, L.; Schauer, P.R.; Selvin, E.; Vafiadis, D.K.; American Heart Association Diabetes Committee of the Council on Lifestyle and Cardiometabolic Health; Council on Clinical Cardiology; Council on Cardiovascular and Stroke Nursing; Council on Cardiovascular

Surgery and Anesthesia; Council on Quality of Care and Outcomes Research; the American Diabetes Association. Update on Prevention of Cardiovascular Disease in Adults With Type 2 Diabetes Mellitus in Light of Recent Evidence: A Scientific Statement From the American Heart Association and the American Diabetes Association. Circulation. 2015;132:691-718.
36. Gidding SS, Champagne MA, de Ferranti SD, et al. The agenda for familial hypercholesterolemia: a scientific statement from the American Heart Association. Circulation. 2015;132:2167-92.
37. Miller M, Stone NJ, Ballantyne C, et al. Triglycerides and cardiovascular disease: a scientific statement from the American Heart Association. Circulation. 2011;123:2292-333.
38. Wiggins BS, Saseen JJ, Page RL, 2nd, et al. Recommendations for management of clinically significant drug-drug interactions with statins and select agents used in patients with cardiovascular disease: a scientific statement from the American Heart Association. Circulation. 2016;134:e468-e95.
39. Pasternak RCS, S.C. Jr; Bairey-Merz, C.N.; Grundy, S.M.; Cleeman, J.I.; Lenfant, C.; American College of Cardiology; American Heart Association; National Heart, Lung and Blood Institute. ACC/AHA/NHLBI clinical advisory on the use and safety of statins. J Am Coll Cardiol. 2002;40:567-72.
40. Hayes SNK, E.S.H.; Saw, J.; Adlam, D.; Arslanian-Engoren, C.; Economy, K.E.; Ganesh, S.K.; Gulati, R.; Lindsay, M.E.; Mieres, J.H.; Naderi, S.; Shah, S.; Thaler, D.E.; Tweet, M.S.; Wood, M.J.; American Heart Association Council on Peripheral Vascular Disease; Council on Clinical Cardiology; Council on Cardiovascular and Stroke Nursing; Council on Genomic and Precision Medicine; Stroke Council. Spontaneous Coronary Artery Dissection: Current State of the Science: A Scientific Statement From the American Heart Association. Circulation. 2018;137:e523-e57.
41. Suglia SFK, K.C.; Boynton-Jarrett, R.; Chan, P.S.; Clark, C.J.; Danese, A.; Faith, M.S.; Goldstein, B.I.; Hayman, L.L.; Isasi, C.R.; Pratt, C.A.; Slopen, N.; Sumner, J.A.; Turer, A.; Turer, C.B.; Zachariah, J.P.; American Heart Association Council on Epidemiology and Prevention; Council on Cardiovascular Disease in the Young; Council on Functional Genomics and Translational Biology; Council on Cardiovascular and Stroke Nursing; Council on Quality of Care and Outcomes Research. Childhood and Adolescent Adversity and Cardiometabolic Outcomes: A Scientific Statement From the American Heart Association. Circulation. 2018;137:e15-e28.
42. Antman EMC, M.A.; Houser, S.R.; Warner, J.J.; Konig, M.; American Heart Association. American Heart Association Principles on the Accessibility and Affordability of Drugs and Biologics: A Presidential Advisory From the American Heart Association. Circulation. 2017;136:e441-e7.
43. Drozda JP, Jr., Ferguson TB, Jr., Jneid H, et al. 2015 ACC/AHA focused update of secondary prevention lipid performance measures: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures. J Am Coll Cardiol. 2016;67:558-87.
44. Jneid HA, D.; Bhatt, D.L.; Fonarow, G.C.; Gokak, S.; Grady, K.L.; Green, L.A.; Heidenreich, P.A.; Ho, P.M.; Jurgens, C.Y.; King, M.L.; Kumbhani, D.J.; Pancholy, S. 2017 AHA/ACC Clinical Performance and Quality Measures for Adults With ST-Elevation and Non-ST-Elevation Myocardial Infarction: A Report of the American College of Cardiology/American Heart Association Task Force on Performance Measures. Circ Cardiovasc Qual Outcomes. 2017;10:
45. Nallamothu BKT, C.L.; Anderson, H.V.; Anderson, J.L.; Cleveland, J.C. Jr; Dudley, R.A.; Duffy, P.L.; Faxon, D.P.; Gurm, H.S.; Hamilton, L.A.; Jensen, N.C.; Josephson, R.A.; Malenka, D.J.; Maniu, C.V.; McCabe, K.W.; Mortimer, J.D.; Patel, M.R.; Persell, S.D.; Rumsfeld, J.S.; Shunk, K.A.; Smith, S.C. Jr; Stanko, S,J,; Watts, B. ACC/AHA/SCAI/AMA-Convened PCPI/NCQA 2013 Performance Measures for Adults Undergoing Percutaneous Coronary Intervention: A Report of the American College of Cardiology/American Heart Association Task Force on Performance Measures, the Society for Cardiovascular Angiography and Interventions, the American Medical Association-Convened Physician Consortium for Performance Improvement, and the National Committee for Quality Assurance. Circulation. 2014;129:926-49.
46. Michaels ADS, S.A.; Leeper, B.; Ohman, E.M.; Alexander, K.P.; Newby, L.K.; Ay, H.; Gibler, W.B.; American Heart Association Acute Cardiac Care Committee of the Council on Clinical Cardiology; Council on Quality of Care and Outcomes Research; Council on Cardiopulmonary, Critical Care, Perioperative, and Resuscitation; Council on Cardiovascular Nursing; Stroke Council. Medication errors in acute cardiovascular and stroke patients: a scientific statement from the American Heart Association. Circulation. 2010;121:1664-82.
47. Musunuru KH, K.T.; Al-Khatib, S.M.; Delles, C.; Fornage, M.; Fox, C.S.; Frazier, L.; Gelb, B.D.; Herrington, D.M.; Lanfear, D.E.; Rosand, J.; American Heart Association Council on Functional Genomics and Translational Biology; Council on Clinical Cardiology; Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; Council on Epidemiology and Prevention; Council on Hypertension; Council on Lifestyle and

Cardiometabolic Health; Council on Quality of Care and Outcomes Research; Stroke Council. Basic concepts and potential applications of genetics and genomics for cardiovascular and stroke clinicians: a scientific statement from the American Heart Association. Circ Cardiovasc Genet. 2015;8:216-42.
48. Chan WV, Pearson TA, Bennett GC, et al. ACC/AHA special report: clinical practice guideline implementation strategies: a summary of systematic reviews by the NHLBI Implementation Science Work Group: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2017;135:e122-37.
49. Rich MWC, D.A.; Skolnick, A.H.; Alexander, K.P.; Forman, D.E.; Kitzman, D.W.; Maurer, M.S.; McClurken, J.B.; Resnick, B.M.; Shen, W.K.; Tirschwell, D.L.; American Heart Association Older Populations Committee of the Council on Clinical Cardiology; Council on Cardiovascular and Stroke Nursing; Council on Cardiovascular Surgery and Anesthesia; and Stroke Council; American College of Cardiology; and American Geriatrics Society. Knowledge Gaps in Cardiovascular Care of the Older Adult Population: A Scientific Statement From the American Heart Association, American College of Cardiology, and American Geriatrics Society. J Am Coll Cardiol. 2016;67:2419-40.
50. Raal FJ, Honarpour N, Blom DJ, et al. Inhibition of PCSK9 with evolocumab in homozygous familial hypercholesterolaemia (TESLA Part B): a randomised, double-blind, placebo-controlled trial. Lancet. 2015;385:341-50.
51. DailyMed. Available at: https://dailymed.nlm.nih.gov/dailymed/index.cfm. Accessed: January 8.
52. Jacobson TA, Ito MK, Maki KC, et al. National lipid association recommendations for patient-centered management of dyslipidemia: part 1 - executive summary. J Clin Lipidol. 2014;8:473-88.
53. Lloyd-Jones DM, Nam BH, D'Agostino RB, Sr., et al. Parental cardiovascular disease as a risk factor for cardiovascular disease in middle-aged adults: a prospective study of parents and offspring. Jama. 2004;291:2204-11.
54. Seshadri S, Beiser A, Pikula A, et al. Parental occurrence of stroke and risk of stroke in their children: the Framingham study. Circulation. 2010;121:1304-12.
55. Mottillo S, Filion KB, Genest J, et al. The metabolic syndrome and cardiovascular risk a systematic review and meta-analysis. J Am Coll Cardiol. 2010;56:1113-32.
56. Gami AS, Witt BJ, Howard DE, et al. Metabolic syndrome and risk of incident cardiovascular events and death: a systematic review and meta-analysis of longitudinal studies. J Am Coll Cardiol. 2007;49:403-14.
57. Chronic Kidney Disease Prognosis C, Matsushita K, van der Velde M, et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. Lancet. 2010;375:2073-81.
58. Dregan A, Chowienczyk P, Molokhia M. Cardiovascular and type 2 diabetes morbidity and all-cause mortality among diverse chronic inflammatory disorders. Heart. 2017;103:1867-73.
59. Fernández-Montero JV, Barreiro P, de Mendoza C, et al. Hepatitis C virus coinfection independently increases the risk of cardiovascular disease in HIV-positive patients. J Viral Hepat. 2016;23:47-52.
60. Feinstein MJ, Nance RM, Drozd DR, et al. Assessing and refining myocardial infarction risk estimation among patients with human immunodeficiency virus: a study by the Centers for AIDS Research Network of Integrated Clinical Systems. JAMA Cardiol. 2017;2:155-62.
61. Ley SH, Li Y, Tobias DK, et al. Duration of reproductive life span, age at menarche, and age at menopause are associated with risk of cardiovascular disease in women. J Am Heart Assoc. 2017;6:e006713.
62. Muka T, Oliver-Williams C, Kunutsor S, et al. Association of age at onset of menopause and time since onset of menopause with cardiovascular outcomes, intermediate vascular traits, and all-cause mortality: a systematic review and meta-analysis. JAMA Cardiol. 2016;1:767-76.
63. Brown MCB, K.E.; Pearce, M.S.; Waugh, J.; Robson, S.C.; Bell, R. Cardiovascular disease risk in women with pre-eclampsia: systematic review and meta-analysis. Eur J Epidemiol. 2013;28:1-19.
64. Ahmed R, Dunford J, Mehran R, et al. Pre-eclampsia and future cardiovascular risk among women: a review. J Am Coll Cardiol. 2014;63:1815-22.
65. Jose POF, A.T.; Kapphahn, K.I.; Goldstein, B.A.; Eggleston, K.; Hastings, K.G.; Cullen, M.R.; Palaniappan, L.P. Cardiovascular disease mortality in Asian Americans. J Am Coll Cardiol. 2014;64:2486-94.
66. Volgman AS, Palaniappan LS, Aggarwal NT, et al. Atherosclerotic cardiovascular disease in South Asians in the United States: epidemiology, risk factors, and treatments: a scientific statement from the American Heart Association. Circulation. 2018;138:e1-34.
67. Emerging Risk Factors Collaboration, Di Angelantonio E, Sarwar N, et al. Major lipids, apolipoproteins, and risk of vascular disease. JAMA. 2009;302:1993-2000.

68. Hokanson JE, Austin MA. Plasma triglyceride level is a risk factor for cardiovascular disease independent of high-density lipoprotein cholesterol level: a meta-analysis of population-based prospective studies. J Cardiovasc Risk. 1996;3:213-9.
69. Emerging Risk Factors C, Kaptoge S, Di Angelantonio E, et al. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. Lancet. 2010;375:132-40.
70. Collaboration ERF, Erqou S, Kaptoge S, et al. Lipoprotein(a) concentration and the risk of coronary heart disease, stroke, and nonvascular mortality. JAMA. 2009;302:412-23.
71. Verbeek RH, R.M.; Langsted, A.; Stiekema, L.C.A.; Verweij, S.L.;, Hovingh, G.K.; Wareham, N.J.; Khaw, K.T.; Boekholdt, S.M.; Nordestgaard, B.G.; Stroes, E.S.G. Cardiovascular disease risk associated with elevated lipoprotein(a) attenuates at low low-density lipoprotein cholesterol levels in a primary prevention setting. Eur Heart J. 2018;39:2589-96.
72. Virani SS, Brautbar A, Davis BC, et al. Associations between lipoprotein(a) levels and cardiovascular outcomes in black and white subjects: the Atherosclerosis Risk in Communities (ARIC) Study. Circulation. 2012;125:241-9.
73. Cook NR, Mora S, Ridker PM. Lipoprotein(a) and cardiovascular risk prediction among women. J Am Coll Cardiol. 2018;72:287-96.
74. Emerging Risk Factors C, Di Angelantonio E, Gao P, et al. Lipid-related markers and cardiovascular disease prediction. JAMA. 2012;307:2499-506.
75. Sniderman AD, Williams K, Contois JH, et al. A meta-analysis of low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, and apolipoprotein B as markers of cardiovascular risk. Circ Cardiovasc Qual Outcomes. 2011;4:337-45.
76. Thanassoulis G, Williams K, Ye K, et al. Relations of change in plasma levels of LDL-C, non-HDL-C and apoB with risk reduction from statin therapy: a meta-analysis of randomized trials. J Am Heart Assoc. 2014;3:e000759.
77. Identifying Strategies to Address Gaps in Cholesterol Management in the U.S. Cholesterol Summit Report. Available at: https://www.heart.org/idc/groups/heart-public/@wcm/@hcm/documents/downloadable/ucm_494491.pdf. Accessed: October 13.
78. Jacobson TA, Maki KC, Orringer CE, et al. National Lipid Association Recommendations for Patient-Centered Management of Dyslipidemia: Part 2. J Clin Lipidol. 2015;9:S1-122.e1.
79. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). Jama. 2001;285:2486-97.
80. Peterson ED, Ho PM, Barton M, et al. ACC/AHA/AACVPR/AAFP/ANA concepts for clinician-patient shared accountability in performance measures: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures. Circulation. 2014;130:1984-94.
81. Stacey D, Hill S, McCaffery K, et al. Shared decision making interventions: theoretical and empirical evidence with implications for health literacy. Stud Health Technol Inform. 2017;240:263-83.
82. Fischer F, Lange K, Klose K, et al. Barriers and strategies in guideline implementation—a scoping review. Healthcare (Basel). 2016;4:
83. American College of Cardiology. ASCVD Risk Estimator Plus. Available at: http://tools.acc.org/ASCVD-Risk-Estimator-Plus/#!/calculate/estimate/. Accessed: Accessed August 24, 2018.
84. American College of Cardiology Mc. CardioSmart Heart Explorer. 2013:Requires iOS 9.3 or later, Android 4.3 or later.
85. American College of Cardiology. LDL-C Manager. Available at: http://tools.acc.org/ldl. Accessed: August 24, 2018.
86. Cardiology ACo. The ACC Statin Intolerance App. In: Amgen, editor, 2017:iOS 8.4 or later.
87. Research MFfMEa. Statin Choice Decision Aid. Available at: https://statindecisionaid.mayoclinic.org/. Accessed:
88. Association AH. Life's Simple 7.
89. Association NL. Patient Tear Sheets. Available at: https://www.lipid.org/practicetools/tools/tearsheets. Accessed: 16/09.
90. Association NL. Clinician's Lifestyle Modification Toolbox. Available at: https://www.lipid.org/CLMT. Accessed: 16/09.

91. Association PCN. THE HEART HEALTHY TOOLBOX. Available at: http://pcna.net/clinical-tools/tools-for-healthcare-providers/heart-healthy-toolbox. Accessed: 09/16.
92. Michelis KC, Hassouna B, Owlia M, et al. Effect of electronic prescription on attainment of cholesterol goals. Clin Cardiol. 2011;34:254-60.
93. Merenich JA, Olson KL, Delate T, et al. Mortality reduction benefits of a comprehensive cardiac care program for patients with occlusive coronary artery disease. Pharmacotherapy. 2007;27:1370-8.
94. Sandhoff BG, Nies LK, Olson KL, et al. Clinical pharmacy cardiac risk service for managing patients with coronary artery disease in a health maintenance organization. Am J Health Syst Pharm. 2007;64:77-84.
95. Choudhry NK, Avorn J, Glynn RJ, et al. Full coverage for preventive medications after myocardial infarction. N Engl J Med. 2011;365:2088-97.
96. Navar AM, Taylor B, Mulder H, et al. Association of Prior Authorization and Out-of-pocket Costs With Patient Access to PCSK9 Inhibitor Therapy. JAMA Cardiol. 2017;2:1217-25.
97. Watanabe JH, Kazerooni R, Bounthavong M. Association of copayment with likelihood and level of adherence in new users of statins: a retrospective cohort study. J Manag Care Pharm. 2014;20:43-50.
98. Lester CA, Mott DA, Chui MA. The Influence of a Community Pharmacy Automatic Prescription Refill Program on Medicare Part D Adherence Metrics. J Manag Care Spec Pharm. 2016;22:801-7.
99. Leslie RS, Gilmer T, Natarajan L, et al. A Multichannel Medication Adherence Intervention Influences Patient and Prescriber Behavior. J Manag Care Spec Pharm. 2016;22:526-38.
100. Taitel M, Fensterheim L, Kirkham H, et al. Medication days' supply, adherence, wastage, and cost among chronic patients in Medicaid. Medicare Medicaid Res Rev. 2012;2:
101. Conn VS, Ruppar TM, Chan KC, et al. Packaging interventions to increase medication adherence: systematic review and meta-analysis. Curr Med Res Opin. 2015;31:145-60.
102. Zedler BK, Kakad P, Colilla S, et al. Does packaging with a calendar feature improve adherence to self-administered medication for long-term use? A systematic review. Clin Ther. 2011;33:62-73.
103. Zullig LL, Pathman J, Melnyk SD, et al. A protocol to evaluate the efficacy, perceptions, and cost of a cholesterol packaging approach to improve medication adherence. Contemp Clin Trials. 2014;39:106-12.
104. Doshi JA, Lim R, Li P, et al. Synchronized prescription refills and medication adherence: a retrospective claims analysis. Am J Manag Care. 2017;23:98-104.
105. Holdford D, Saxena K. Impact of Appointment-Based Medication Synchronization on Existing Users of Chronic Medications. J Manag Care Spec Pharm. 2015;21:662-9.
106. American Heart Association. ASCVD-Risk-Calculator. Available at: https://professional.heart.org/professional/GuidelinesStatements/PreventionGuidelines/UCM_457698_ASCVD-Risk-Calculator.jsp. Accessed: