

## 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

*Endorsed by the World Heart Federation and the Preventive Cardiovascular Nurses Association*

Sidney C. Smith, Jr, MD, FAHA, FACC, Chair; Emelia J. Benjamin, MD, ScM, FAHA, FACC; Robert O. Bonow, MD, FAHA, FACC; Lynne T. Braun, PhD, ANP, FAHA; Mark A. Creager, MD, FAHA, FACC; Barry A. Franklin, PhD, FAHA; Raymond J. Gibbons, MD, FAHA, FACC; Scott M. Grundy, MD, PhD, FAHA; Loren F. Hiratzka, MD, FAHA, FACC; Daniel W. Jones, MD, FAHA; Donald M. Lloyd-Jones, MD, ScM, FAHA, FACC; Margo Minissian, ACNP, AACC, FAHA; Lori Mosca, MD, PhD, MPH, FAHA; Eric D. Peterson, MD, MPH, FAHA, FACC; Ralph L. Sacco, MD, MS, FAHA; John Spertus, MD, MPH, FAHA, FACC; James H. Stein, MD, FAHA, FACC; Kathryn A. Taubert, PhD, FAHA

Since the 2006 update of the American Heart Association (AHA)/American College of Cardiology Foundation (ACCF) guidelines on secondary prevention,<sup>1</sup> important evidence from clinical trials has emerged that further supports and broadens the merits of intensive risk-reduction therapies for patients with established coronary and other atherosclerotic vascular disease, including peripheral artery disease, atherosclerotic aortic disease, and carotid artery disease. In reviewing this evidence and its clinical impact, the writing group believed it would be more appropriate to expand the title of this guideline to “Secondary Prevention and Risk Reduction Therapy for Patients With Coronary and Other Atherosclerotic Vascular Disease.” Indeed, the growing body of evidence confirms that in patients with atherosclerotic vascular disease, comprehensive risk factor management reduces risk as assessed by a variety of outcomes, including improved survival, reduced recurrent events, the need

for revascularization procedures, and improved quality of life. It is important not only that the healthcare provider implement these recommendations in appropriate patients but also that healthcare systems support this implementation to maximize the benefit to the patient.

Compelling evidence-based results from recent clinical trials and revised practice guidelines provide the impetus for this update of the 2006 recommendations with evidence-based results<sup>2–165</sup> (Table 1). Classification of recommendations and level of evidence are expressed in ACCF/AHA format, as detailed in Table 2. Recommendations made herein are largely based on major practice guidelines from the National Institutes of Health and updated ACCF/AHA practice guidelines, as well as on results from recent clinical trials. Thus, the development of the present guideline involved a process of partial adaptation of other guideline statements and reports and supplemental litera-

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

This document was approved by the American Heart Association Science Advisory and Coordinating Committee on October 5, 2011, and by the American College of Cardiology Foundation Board of Trustees on September 29, 2011.

The American Heart Association requests that this document be cited as follows: Smith SC Jr, Benjamin EJ, Bonow RO, Braun LT, Creager MA, Franklin BA, Gibbons RJ, Grundy SM, Hiratzka LF, Jones DW, Lloyd-Jones DM, Minissian M, Mosca L, Peterson ED, Sacco RL, Spertus J, Stein JH, Taubert KA. 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. *Circulation*. 2011;124:2458–2473.

Copies: This document is available on the World Wide Web site of the American Heart Association ([my.americanheart.org](http://my.americanheart.org)). A copy of the document is available at <http://my.americanheart.org/statements> by selecting either the “By Topic” link or the “By Publication Date” link. To purchase additional reprints, call 843-216-2533 or e-mail [kelle.ramsay@wolterskluwer.com](mailto:kelle.ramsay@wolterskluwer.com).

Expert peer review of AHA Scientific Statements is conducted at the AHA National Center. For more on AHA statements and guidelines development, visit <http://my.americanheart.org/statements> and select the “Policies and Development” link.

Permissions: Multiple copies, modification, alteration, enhancement, and/or distribution of this document are not permitted without the express permission of the American Heart Association. Instructions for obtaining permission are located at [http://www.heart.org/HEARTORG/General/Copyright-Permission-Guidelines\\_UCM\\_300404\\_Article.jsp](http://www.heart.org/HEARTORG/General/Copyright-Permission-Guidelines_UCM_300404_Article.jsp). A link to the “Copyright Permissions Request Form” appears on the right side of the page. (*Circulation*. 2011;124:2458–2473.)

© 2011 American Heart Association, Inc.

*Circulation* is available at <http://circ.ahajournals.org>

DOI: 10.1161/CIR.0b013e318235eb4d

**Table 1. AHA/ACCF Secondary Prevention and Risk Reduction Therapy for Patients With Coronary and Other Atherosclerotic Vascular Disease: 2011 Update: Intervention Recommendations With Class of Recommendation and Level of Evidence**

Area for Intervention	Recommendations
<b>Smoking</b> Goal: Complete cessation. No exposure to environmental tobacco smoke	<b>Class I</b> 1. Patients should be asked about tobacco use status at every office visit. <sup>2,3,4,5,7</sup> ( <b>Level of Evidence: B</b> ) 2. Every tobacco user should be advised at every visit to quit. <sup>4,5,7,9</sup> ( <b>Level of Evidence: A</b> ) 3. The tobacco user's willingness to quit should be assessed at every visit. ( <b>Level of Evidence: C</b> ) 4. Patients should be assisted by counseling and by development of a plan for quitting that may include pharmacotherapy and/or referral to a smoking cessation program. <sup>4-9</sup> ( <b>Level of Evidence: A</b> ) 5. Arrangement for follow up is recommended. ( <b>Level of Evidence: C</b> ) 6. All patients should be advised at every office visit to avoid exposure to environmental tobacco smoke at work, home, and public places. <sup>10,11</sup> ( <b>Level of Evidence: B</b> )
<b>Blood pressure control</b> Goal: <140/90 mm Hg	<b>Note: The writing committee did not think that the 2006 recommendations for blood pressure control (below) should be modified at this time. The writing committee anticipates that the recommendations will be reviewed when the updated JNC guidelines are released.</b> <b>Class I</b> 1. All patients should be counseled regarding the need for lifestyle modification: weight control; increased physical activity; alcohol moderation; sodium reduction; and emphasis on increased consumption of fresh fruits, vegetables, and low-fat dairy products. <sup>12-16</sup> ( <b>Level of Evidence: B</b> ) 2. Patients with blood pressure $\geq$ 140/90 mm Hg should be treated, as tolerated, with blood pressure medication, treating initially with $\beta$ -blockers and/or ACE inhibitors, with addition of other drugs as needed to achieve goal blood pressure. <sup>12,17,18</sup> ( <b>Level of Evidence: A</b> )
<b>Lipid management</b> Goal: Treatment with statin therapy; use statin therapy to achieve an LDL-C of <100 mg/dL; for very high risk* patients an LDL-C <70 mg/dL is reasonable; if triglycerides are $\geq$ 200 mg/dL, non-HDL-C† should be <130 mg/dL, whereas non-HDL-C <100 mg/dL for very high risk patients is reasonable	<b>Note: The writing committee anticipates that the recommendations will be reviewed when the updated ATP guidelines are released.</b> <b>Class I</b> 1. A lipid profile in all patients should be established, and for hospitalized patients, lipid-lowering therapy as recommended below should be initiated before discharge. <sup>20</sup> ( <b>Level of Evidence: B</b> ) 2. Lifestyle modifications including daily physical activity and weight management are strongly recommended for all patients. <sup>19,29</sup> ( <b>Level of Evidence: B</b> ) 3. Dietary therapy for all patients should include reduced intake of saturated fats (to <7% of total calories), <i>trans</i> fatty acids (to <1% of total calories), and cholesterol (to <200 mg/d). <sup>21-24,29</sup> ( <b>Level of Evidence: B</b> ) 4. In addition to therapeutic lifestyle changes, statin therapy should be prescribed in the absence of contraindications or documented adverse effects. <sup>25-29</sup> ( <b>Level of Evidence: A</b> ) 5. An adequate dose of statin should be used that reduces LDL-C to <100 mg/dL AND achieves at least a 30% lowering of LDL-C. <sup>25-29</sup> ( <b>Level of Evidence: C</b> ) 6. Patients who have triglycerides $\geq$ 200 mg/dL should be treated with statins to lower non-HDL-C to <130 mg/dL. <sup>25-27,30</sup> ( <b>Level of Evidence: B</b> ) 7. Patients who have triglycerides >500 mg/dL should be started on fibrate therapy in addition to statin therapy to prevent acute pancreatitis. ( <b>Level of Evidence: C</b> ) <b>Class IIa</b> 1. If treatment with a statin (including trials of higher-dose statins and higher-potency statins) does not achieve the goal selected for a patient, intensification of LDL-C-lowering drug therapy with a bile acid sequestrant‡ or niacin§ is reasonable. <sup>31-33</sup> ( <b>Level of Evidence: B</b> ) 2. For patients who do not tolerate statins, LDL-C-lowering therapy with bile acid sequestrants‡ and/or niacin§ is reasonable. <sup>35,36</sup> ( <b>Level of Evidence: B</b> ) 3. It is reasonable to treat very high-risk patients* with statin therapy to lower LDL-C to <70 mg/dL. <sup>26-28,37,38,166</sup> ( <b>Level of Evidence: C</b> ) 4. In patients who are at very high risk* and who have triglycerides $\geq$ 200 mg/dL, a non-HDL-C goal of <100 mg/dL is reasonable. <sup>25-27,30</sup> ( <b>Level of Evidence: B</b> )

(Continued)

Table 1. Continued

Area for Intervention	Recommendations
<b>Lipid management cont'd</b>	<p><b>Class IIb</b></p> <ol style="list-style-type: none"> <li>The use of ezetimibe may be considered for patients who do not tolerate or achieve target LDL-C with statins, bile acid sequestrants,† and/or niacin.§ (<b>Level of Evidence: C</b>)</li> <li>For patients who continue to have an elevated non-HDL-C while on adequate statin therapy, niacin§ or fibrate   therapy<sup>32,35,41</sup> (<b>Level of Evidence: B</b>) or fish oil (<b>Level of Evidence: C</b>) may be reasonable.</li> <li>For all patients, it may be reasonable to recommend omega-3 fatty acids from fish¶ or fish oil capsules (1 g/d) for cardiovascular disease risk reduction.<sup>44–46</sup> (<b>Level of Evidence: B</b>)</li> </ol>
<p><b>Physical activity</b></p> <p>Goal: At least 30 minutes, 7 days per week (minimum 5 days per week)</p>	<p><b>Class I</b></p> <ol style="list-style-type: none"> <li>For all patients, the clinician should encourage 30 to 60 minutes of moderate-intensity aerobic activity, such as brisk walking, at least 5 days and preferably 7 days per week, supplemented by an increase in daily lifestyle activities (eg, walking breaks at work, gardening, household work) to improve cardiorespiratory fitness and move patients out of the least fit, least active high-risk cohort (bottom 20%).<sup>54,55,58</sup> (<b>Level of Evidence: B</b>)</li> <li>For all patients, risk assessment with a physical activity history and/or an exercise test is recommended to guide prognosis and prescription.<sup>47–52,58</sup> (<b>Level of Evidence: B</b>)</li> <li>The clinician should counsel patients to report and be evaluated for symptoms related to exercise. (<b>Level of Evidence: C</b>)</li> </ol> <p><b>Class IIa</b></p> <ol style="list-style-type: none"> <li>It is reasonable for the clinician to recommend complementary resistance training at least 2 days per week.<sup>59</sup> (<b>Level of Evidence: C</b>)</li> </ol>
<p><b>Weight management</b></p> <p>Goals:</p> <p>Body mass index: 18.5 to 24.9 kg/m<sup>2</sup></p> <p>Waist circumference: women &lt;35 inches (&lt;89 cm), men &lt;40 inches (&lt;102 cm)</p>	<p><b>Class I</b></p> <ol style="list-style-type: none"> <li>Body mass index and/or waist circumference should be assessed at every visit, and the clinician should consistently encourage weight maintenance/reduction through an appropriate balance of lifestyle physical activity, structured exercise, caloric intake, and formal behavioral programs when indicated to maintain/achieve a body mass index between 18.5 and 24.9 kg/m<sup>2</sup>.<sup>60–62,65–70</sup> (<b>Level of Evidence: B</b>)</li> <li>If waist circumference (measured horizontally at the iliac crest) is ≥35 inches (≥89 cm) in women and ≥40 inches (≥102 cm) in men, therapeutic lifestyle interventions should be intensified and focused on weight management.<sup>66–70</sup> (<b>Level of Evidence: B</b>)</li> <li>The initial goal of weight loss therapy should be to reduce body weight by approximately 5% to 10% from baseline. With success, further weight loss can be attempted if indicated. (<b>Level of Evidence: C</b>)</li> </ol>
<b>Type 2 diabetes mellitus management</b>	<p><b>Note: Recommendations below are for prevention of cardiovascular complications.</b></p> <p><b>Class I</b></p> <ol style="list-style-type: none"> <li>Care for diabetes should be coordinated with the patient's primary care physician and/or endocrinologist. (<b>Level of Evidence: C</b>)</li> <li>Lifestyle modifications including daily physical activity, weight management, blood pressure control, and lipid management are recommended for all patients with diabetes.<sup>19,22–24,29,56,58,59,62,66,74,162</sup> (<b>Level of Evidence: B</b>)</li> </ol> <p><b>Class IIa</b></p> <ol style="list-style-type: none"> <li>Metformin is an effective first-line pharmacotherapy and can be useful if not contraindicated.<sup>74–76</sup> (<b>Level of Evidence: A</b>)</li> <li>It is reasonable to individualize the intensity of blood sugar-lowering interventions based on the individual patient's risk of hypoglycemia during treatment. (<b>Level of Evidence: C</b>)</li> </ol> <p><b>Class IIb</b></p> <ol style="list-style-type: none"> <li>Initiation of pharmacotherapy interventions to achieve target HbA1c may be reasonable.<sup>71,72,74–80</sup> (<b>Level of Evidence: A</b>)</li> <li>A target HbA1c of ≤7% may be considered. (<b>Level of Evidence: C</b>)</li> <li>Less stringent HbA1c goals may be considered for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, or extensive comorbidities, or those in whom the goal is difficult to attain despite intensive therapeutic interventions. (<b>Level of Evidence: C</b>)</li> </ol>
<b>Antiplatelet agents/anticoagulants</b>	<p><b>Class I</b></p> <ol style="list-style-type: none"> <li>Aspirin 75–162 mg daily is recommended in all patients with coronary artery disease unless contraindicated.<sup>64,81,82,116</sup> (<b>Level of Evidence: A</b>) <ul style="list-style-type: none"> <li>Clopidogrel 75 mg daily is recommended as an alternative for patients who are intolerant of or allergic to aspirin.<sup>117</sup> (<b>Level of Evidence: B</b>)</li> </ul> </li> <li>A P2Y12 receptor antagonist in combination with aspirin is indicated in patients after ACS or PCI with stent placement.<sup>83–85</sup> (<b>Level of Evidence: A</b>) <ul style="list-style-type: none"> <li>For patients receiving a bare-metal stent or drug-eluting stent during PCI for ACS, clopidogrel 75 mg daily, prasugrel 10 mg daily, or ticagrelor 90 mg twice daily should be given for at least 12 months.<sup>84,86,113,114</sup> (<b>Level of Evidence: A</b>)</li> </ul> </li> </ol>

(Continued)

Table 1. Continued

Area for Intervention	Recommendations
<b>Antiplatelet agents/anticoagulants cont'd</b>	<ol style="list-style-type: none"> <li>For patients undergoing coronary artery bypass grafting, aspirin should be started within 6 hours after surgery to reduce saphenous vein graft closure. Dosing regimens ranging from 100 to 325 mg daily for 1 year appear to be efficacious.<sup>87–90</sup> <b>(Level of Evidence: A)</b></li> <li>In patients with extracranial carotid or vertebral atherosclerosis who have had ischemic stroke or TIA, treatment with aspirin alone (75–325 mg daily), clopidogrel alone (75 mg daily), or the combination of aspirin plus extended-release dipyridamole (25 mg and 200 mg twice daily, respectively) should be started and continued.<sup>91,104,116</sup> <b>(Level of Evidence: A)</b></li> <li>For patients with symptomatic atherosclerotic peripheral artery disease of the lower extremity, antiplatelet therapy with aspirin (75–325 mg daily) or clopidogrel (75 mg daily) should be started and continued.<sup>92,107,116,117</sup> <b>(Level of Evidence: A)</b></li> <li>Antiplatelet therapy is recommended in preference to anticoagulant therapy with warfarin or other vitamin K antagonists to treat patients with atherosclerosis.<sup>93,94,105,110</sup> <b>(Level of Evidence: A)</b> <ul style="list-style-type: none"> <li>If there is a compelling indication for anticoagulant therapy, such as atrial fibrillation, prosthetic heart valve, left ventricular thrombus, or concomitant venous thromboembolic disease, warfarin should be administered.<sup>95,99–102</sup> <b>(Level of Evidence: A)</b> (NOTE: Patients receiving low dose aspirin for atherosclerosis should continue to receive it.)</li> <li>For patients requiring warfarin, therapy should be administered to achieve the recommended INR for the specific condition.<sup>81,96</sup> <b>(Level of Evidence: B)</b></li> <li>Use of warfarin in conjunction with aspirin and/or clopidogrel is associated with increased risk of bleeding and should be monitored closely.<sup>97,98,110</sup> <b>(Level of Evidence: A)</b></li> </ul> </li> </ol>
	<b>Class IIa</b>
	<ol style="list-style-type: none"> <li>If the risk of morbidity from bleeding outweighs the anticipated benefit afforded by thienopyridine therapy after stent implantation, earlier discontinuation (eg, &lt;12 months) is reasonable. <b>(Level of Evidence: C)</b> (Note: the risk for serious cardiovascular events because of early discontinuation of thienopyridines is greater for patients with drug-eluting stents than those with bare-metal stents.)</li> <li>After PCI, it is reasonable to use 81 mg of aspirin per day in preference to higher maintenance doses.<sup>84,85,118–122</sup> <b>(Level of Evidence: B)</b></li> <li>For patients undergoing coronary artery bypass grafting, clopidogrel (75 mg daily) is a reasonable alternative in patients who are intolerant of or allergic to aspirin. <b>(Level of Evidence: C)</b></li> </ol>
	<b>Class IIb</b>
	<ol style="list-style-type: none"> <li>The benefits of aspirin in patients with asymptomatic peripheral artery disease of the lower extremities are not well established.<sup>108,109</sup> <b>(Level of Evidence: B)</b></li> <li>Combination therapy with both aspirin 75 to 162 mg daily and clopidogrel 75 mg daily may be considered in patients with stable coronary artery disease.<sup>112</sup> <b>(Level of Evidence: B)</b></li> </ol>
<b>Renin-angiotensin-aldosterone system blockers</b>	
ACE inhibitors	<b>Class I</b>
	<ol style="list-style-type: none"> <li>ACE inhibitors should be started and continued indefinitely in all patients with left ventricular ejection fraction <math>\leq 40\%</math> and in those with hypertension, diabetes, or chronic kidney disease, unless contraindicated.<sup>124,125</sup> <b>(Level of Evidence: A)</b></li> </ol>
	<b>Class IIa</b>
	<ol style="list-style-type: none"> <li>It is reasonable to use ACE inhibitors in all other patients.<sup>126</sup> <b>(Level of Evidence: B)</b></li> </ol>
ARBs	<b>Class I</b>
	<ol style="list-style-type: none"> <li>The use of ARBs is recommended in patients who have heart failure or who have had a myocardial infarction with left ventricular ejection fraction <math>\leq 40\%</math> and who are ACE-inhibitor intolerant.<sup>130–132</sup> <b>(Level of Evidence: A)</b></li> </ol>
	<b>Class IIa</b>
	<ol style="list-style-type: none"> <li>It is reasonable to use ARBs in other patients who are ACE-inhibitor intolerant.<sup>133</sup> <b>(Level of Evidence: B)</b></li> </ol>
	<b>Class IIb</b>
	<ol style="list-style-type: none"> <li>The use of ARBs in combination with an ACE inhibitor is not well established in those with systolic heart failure.<sup>132,134</sup> <b>(Level of Evidence: A)</b></li> </ol>
Aldosterone blockade	<b>Class I</b>
	<ol style="list-style-type: none"> <li>Use of aldosterone blockade in post-myocardial infarction patients without significant renal dysfunction# or hyperkalemia** is recommended in patients who are already receiving therapeutic doses of an ACE inhibitor and <math>\beta</math>-blocker, who have a left ventricular ejection fraction <math>\leq 40\%</math>, and who have either diabetes or heart failure.<sup>136,137</sup> <b>(Level of Evidence: A)</b></li> </ol>

(Continued)

Table 1. Continued

Area for Intervention	Recommendations
<b><math>\beta</math>-Blockers</b>	<b>Class I</b> 1. $\beta$ -Blocker therapy should be used in all patients with left ventricular systolic dysfunction (ejection fraction $\leq$ 40%) with heart failure or prior myocardial infarction, unless contraindicated. (Use should be limited to carvedilol, metoprolol succinate, or bisoprolol, which have been shown to reduce mortality.) <sup>138,140,141</sup> <b>(Level of Evidence: A)</b> 2. $\beta$ -Blocker therapy should be started and continued for 3 years in all patients with normal left ventricular function who have had myocardial infarction or ACS. <sup>139,142,143</sup> <b>(Level of Evidence: B)</b>
	<b>Class IIa</b> 1. It is reasonable to continue $\beta$ -blockers beyond 3 years as chronic therapy in all patients with normal left ventricular function who have had myocardial infarction or ACS. <sup>139,142,143</sup> <b>(Level of Evidence: B)</b> 2. It is reasonable to give $\beta$ -blocker therapy in patients with left ventricular systolic dysfunction (ejection fraction $\leq$ 40%) without heart failure or prior myocardial infarction. <b>(Level of Evidence: C)</b>
	<b>Class IIb</b> 1. $\beta$ -Blockers may be considered as chronic therapy for all other patients with coronary or other vascular disease. <b>(Level of Evidence: C)</b>
<b>Influenza vaccination</b>	<b>Class I</b> 1. Patients with cardiovascular disease should have an annual influenza vaccination. <sup>144–147</sup> <b>(Level of Evidence: B)</b>
<b>Depression</b>	<b>Class IIa</b> 1. For patients with recent coronary artery bypass graft surgery or myocardial infarction, it is reasonable to screen for depression if patients have access to case management, in collaboration with their primary care physician and a mental health specialist. <sup>148–152</sup> <b>(Level of Evidence: B)</b>
	<b>Class IIb</b> 1. Treatment of depression has not been shown to improve cardiovascular disease outcomes but may be reasonable for its other clinical benefits. <b>(Level of Evidence: C)</b>
<b>Cardiac rehabilitation</b>	<b>Class I</b> 1. All eligible patients with ACS or whose status is immediately post coronary artery bypass surgery or post-PCI should be referred to a comprehensive outpatient cardiovascular rehabilitation program either prior to hospital discharge or during the first follow-up office visit. <sup>55,154,161,163</sup> <b>(Level of Evidence: A)</b> 2. All eligible outpatients with the diagnosis of ACS, coronary artery bypass surgery or PCI <b>(Level of Evidence: A)</b> , <sup>55,154,155,161</sup> chronic angina <b>(Level of Evidence: B)</b> , <sup>161,163</sup> and/or peripheral artery disease <b>(Level of Evidence: A)</b> <sup>58,164</sup> within the past year should be referred to a comprehensive outpatient cardiovascular rehabilitation program. 3. A home-based cardiac rehabilitation program can be substituted for a supervised, center-based program for low-risk patients. <sup>153,159,160</sup> <b>(Level of Evidence: A)</b>
	<b>Class IIa</b> 1. A comprehensive exercise-based outpatient cardiac rehabilitation program can be safe and beneficial for clinically stable outpatients with a history of heart failure. <sup>159,159a–159c</sup> <b>(Level of Evidence: B)</b>

JNC indicates the report of the National Heart, Lung, and Blood Institute's Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure guidelines; ACE, angiotensin-converting enzyme; ATP, Adult Treatment Panel; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; HbA1c, hemoglobin A1c; ACS, acute coronary syndrome; PCI, percutaneous coronary intervention; TIA, transient ischemic attack; INR, international normalized ratio; and ARB, angiotensin receptor blocker.

\*Presence of established CVD plus (1) multiple major risk factors (especially diabetes), (2) severe and poorly controlled risk factors (especially continued cigarette smoking), (3) multiple risk factors of the metabolic syndrome (especially high triglycerides  $\geq$ 200 mg/dL plus non-HDL-C  $\geq$ 130 mg/dL with low HDL-C  $<$ 40 mg/dL), and (4) patients with ACSs.

†Non-HDL-C=total cholesterol minus HDL-C.

‡The use of bile acid sequestrants is relatively contraindicated when triglycerides are  $\geq$ 200 mg/dL and is contraindicated when triglycerides are  $\geq$ 500 mg/dL.

§Dietary supplement niacin must not be used as a substitute for prescription niacin.

||The combination of high-dose statin plus fibrates (especially gemfibrozil) can increase risk for severe myopathy. Statin doses should be kept relatively low with this combination.

¶Pregnant and lactating women should limit their intake of fish to minimize exposure to methylmercury.

#Estimated creatinine clearance should be  $>$ 30 mL/min.

\*\*Potassium should be  $<$ 5.0 mEq/L.

ture searches. The recommendations listed in this document are, whenever possible, evidence based. Writing group members performed these relevant supplemental literature searches with key search phrases including but not limited to tobacco/smoking/smoking cessation; blood pressure control/hypertension; chole-

sterol/hypercholesterolemia/lipids/lipoproteins/dyslipidemia; physical activity/exercise/exercise training; weight management/overweight/obesity; type 2 diabetes mellitus management; antiplatelet agents/anticoagulants; renin/angiotensin/aldosterone system blockers;  $\beta$ -blockers; influenza vaccination;



Table 2. Applying Classification of Recommendation and Level of Evidence

		SIZE OF TREATMENT EFFECT				
		CLASS I <i>Benefit &gt;&gt;&gt; Risk</i> Procedure/Treatment <b>SHOULD</b> be performed/administered	CLASS IIa <i>Benefit &gt;&gt; Risk</i> <i>Additional studies with focused objectives needed</i> <b>IT IS REASONABLE</b> to perform procedure/administer treatment	CLASS IIb <i>Benefit ≥ Risk</i> <i>Additional studies with broad objectives needed; additional registry data would be helpful</i> Procedure/Treatment <b>MAY BE CONSIDERED</b>	CLASS III <i>No Benefit or CLASS III Harm</i>	
				Procedure/ Test	Treatment	
				COR III: No benefit	No Proven Benefit	
				COR III: Harm	Excess Cost w/o Benefit or Harmful to Patients	
ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT	LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	<ul style="list-style-type: none"> <li>Recommendation that procedure or treatment is useful/effective</li> <li>Sufficient evidence from multiple randomized trials or meta-analyses</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation in favor of treatment or procedure being useful/effective</li> <li>Some conflicting evidence from multiple randomized trials or meta-analyses</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation's usefulness/efficacy less well established</li> <li>Greater conflicting evidence from multiple randomized trials or meta-analyses</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation that procedure or treatment is not useful/effective and may be harmful</li> <li>Sufficient evidence from multiple randomized trials or meta-analyses</li> </ul>	
	LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	<ul style="list-style-type: none"> <li>Recommendation that procedure or treatment is useful/effective</li> <li>Evidence from single randomized trial or nonrandomized studies</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation in favor of treatment or procedure being useful/effective</li> <li>Some conflicting evidence from single randomized trial or nonrandomized studies</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation's usefulness/efficacy less well established</li> <li>Greater conflicting evidence from single randomized trial or nonrandomized studies</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation that procedure or treatment is not useful/effective and may be harmful</li> <li>Evidence from single randomized trial or nonrandomized studies</li> </ul>	
	LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	<ul style="list-style-type: none"> <li>Recommendation that procedure or treatment is useful/effective</li> <li>Only expert opinion, case studies, or standard of care</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation in favor of treatment or procedure being useful/effective</li> <li>Only diverging expert opinion, case studies, or standard of care</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation's usefulness/efficacy less well established</li> <li>Only diverging expert opinion, case studies, or standard of care</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation that procedure or treatment is not useful/effective and may be harmful</li> <li>Only expert opinion, case studies, or standard of care</li> </ul>	
Suggested phrases for writing recommendations		should is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	COR III: No Benefit is not recommended is not indicated should not be performed/administered/other is not useful/beneficial/effective	COR III: Harm potentially harmful causes harm associated with excess morbidity/mortality should not be performed/administered/other
Comparative effectiveness phrases†		treatment/strategy A is recommended/indicated in preference to treatment B treatment A should be chosen over treatment B	treatment/strategy A is probably recommended/indicated in preference to treatment B it is reasonable to choose treatment A over treatment B			

A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Although randomized trials are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

\*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as sex, age, history of diabetes, history of prior myocardial infarction, history of heart failure, and prior aspirin use.

†For comparative effectiveness recommendations (Class I and IIa; Level of Evidence A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

clinical depression/depression screening; and cardiac/cardiovascular rehabilitation. Additional searches cross-referenced these topics with the subtopics of clinical trials, secondary prevention, atherosclerosis, and coronary/cerebral/peripheral artery disease. These searches were limited to studies, reviews, and other evidence conducted in human subjects and published in English. In addition, the writing group reviewed documents related to the subject matter previously published by the AHA, the ACCF, and the National Institutes of Health.

With regard to lipids and dyslipidemias, the lipid reduction trials published between 2002 and 2006<sup>18,25,166–168</sup> included >50 000 patients and resulted in new optional therapeutic

targets, which were outlined in the 2004 update of the National Heart, Lung, and Blood Institute's Adult Treatment Panel (ATP) III report.<sup>169</sup> These changes defined optional lower target cholesterol levels for very high-risk coronary heart disease (CHD) patients, especially those with acute coronary syndromes, and expanded indications for drug treatment. Subsequent to the 2004 update of ATP III, 2 additional trials<sup>26,27</sup> demonstrated cardiovascular benefit for lipid lowering significantly below current cholesterol goal levels for those with chronic coronary heart disease. These trials allowed for alterations in the 2006 guideline, such that low-density lipoprotein cholesterol (LDL-C) should be <100 mg/dL for all patients with CHD and other clinical forms of atherosclerotic disease, but in addition, it is

reasonable to treat to LDL-C <70 mg/dL in patients at highest risk. The benefits of lipid-lowering therapy are in proportion to the reduction in LDL-C, and when LDL-C is above 100 mg/dL, an adequate dose of statin therapy should be used to achieve at least a 30% lowering of LDL-C. When the <70 mg/dL target is chosen, it may be prudent to increase statin therapy in a graded fashion to determine a patient's response and tolerance. Furthermore, if it is not possible to attain LDL-C <70 mg/dL because of a high baseline LDL-C, it generally is possible to achieve LDL-C reductions of >50% with either statins or LDL-C-lowering drug combinations. For patients with triglyceride levels  $\geq$ 200 mg/dL, non-high-density lipoprotein cholesterol values should be used as a guide to therapy. Although no studies have directly tested treatment to target strategies, the target LDL-C and non-HDL-C levels are derived from several randomized controlled trials where the LDL-C levels achieved for patients showing benefit are used to suggest targets. Thus, references for the studies from which targets are derived are listed and targets are considered as level of evidence C. Importantly, this guideline statement for patients with atherosclerotic disease does not modify the recommendations of the 2004 ATP III update for patients without atherosclerotic disease who have diabetes mellitus or multiple risk factors and a 10-year risk level for CHD >20%. In the latter 2 types of high-risk patients, the recommended LDL-C goal of <100 mg/dL has not changed. Finally, to avoid any misunderstanding about cholesterol management in general, it must be emphasized that a reasonable cholesterol level of <70 mg/dL does not apply to other types of lower-risk individuals who do not have CHD or other forms of atherosclerotic disease; in such cases, recommendations contained in the 2004 ATP III update still pertain. The writing group agreed that no further changes be made in the recommendations for treatment of dyslipidemia pending the expected publication of the National Heart, Lung, and Blood Institute's updated ATP guidelines in 2012. Similar recommendations were made for the treatment of hypertension by the writing group pending the publication of the updated report of the National Heart, Lung, and Blood Institute's Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure guidelines, expected in the spring of 2012.

Trials involving other secondary prevention therapies also have influenced major practice guidelines used to formulate the recommendations in the present update. Thus, specific recommendations for clopidogrel use in post-acute coronary syndrome or post-percutaneous coronary intervention stented patients were included in the 2006 update, and recommendations regarding prasugrel and ticagrelor are added to this guideline on the basis of the results of the TRITON-TIMI 38 trial (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel-Thrombolysis in Myocardial Infarction) and PLATO (Study of Platelet Inhibition and Patient Outcomes). The present update continues to recommend lower-dose aspirin for chronic therapy. The results of additional studies have further confirmed the benefit of aldosterone antagonist therapy among patients with impaired left ventricular function. The results of several trials involving angiotensin-converting enzyme inhibitor therapy among patients at relatively low risk with stable coronary disease and normal left ventricular function influenced the current recommendations.<sup>32</sup> Finally, the recom-

mendations for  $\beta$ -blocker therapy have been clarified to reflect the fact that evidence supporting their efficacy is greatest among patients with recent myocardial infarction (<3 years) and/or left ventricular systolic dysfunction (left ventricular ejection fraction  $\leq$ 40%). For those patients without these Class I indications,  $\beta$ -blocker therapy is optional (Class IIa or IIb).

The writing group confirms the recommendation introduced in 2006 for this guideline with regard to influenza vaccination. According to the US Centers for Disease Control and Prevention, vaccination with inactivated influenza vaccine is recommended for individuals who have chronic disorders of the cardiovascular system because they are at increased risk for complications from influenza.<sup>147</sup> Additionally, the writing group added new sections on depression and on cardiovascular rehabilitation.

The writing group continues to emphasize the importance of giving consideration to the use of cardiovascular medications that have been proven in randomized clinical trials to be of benefit. This strengthens the evidence-based foundation for therapeutic application of these guidelines. The committee acknowledges that ethnic minorities, women, and the elderly are underrepresented in many trials and urges physician and patient participation in trials that will provide additional evidence with regard to therapeutic strategies for these groups of patients.

In the 15 years since these guidelines were first published, 2 other developments have made them even more important in clinical care. First, the aging of the population continues to expand the number of patients living with a diagnosis of cardiovascular disease (now estimated at 16.3 million for CHD alone)<sup>170</sup> who might benefit from these therapies. Second, multiple studies of the use of these recommended therapies in appropriate patients, although showing slow improvement, continue to support the discouraging conclusion that many patients in whom therapies are indicated are not receiving them in actual clinical practice. The AHA and ACCF recommend the use of programs such as the AHA's Get With The Guidelines,<sup>171</sup> the American Cancer Society/American Diabetes Association/AHA's Guideline Advantage Program,<sup>172</sup> and the ACC's PINNACLE (Practice INNOvation And CLinical Excellence) program<sup>173</sup> to identify appropriate patients for therapy, provide practitioners with useful reminders based on the guidelines, and continually assess the success achieved in providing these therapies to the patients who can benefit from them. In this regard, it is important that the healthcare provider not only implement the therapies according to their class of recommendation but also assess for and assist with patient compliance with these therapies in each patient encounter. Discussion of the literature and supporting references for many of the recommendations summarized in the present guideline can be found in greater detail in the upcoming ACCF/AHA guideline for management of patients undergoing PCI,<sup>174</sup> ACCF/AHA guideline for management of patients with peripheral artery disease,<sup>175,176</sup> the AHA effectiveness-based guidelines for cardiovascular disease prevention in women,<sup>46</sup> and in the AHA/American Stroke Association guidelines for the prevention of stroke in patients with stroke or transient ischemic attack.<sup>123</sup>

Finally, the practitioner should exercise judgment in initiating the various recommendations if the patient has recently experienced an acute event.

Disclosures

Writing Group Disclosures

Writing Group Member	Employment	Research Grant	Other Research Support	Speakers' Bureau/Honoraria	Expert Witness	Ownership Interest	Consultant/Advisory Board	Other
Sidney C. Smith, Jr	University of North Carolina	None	None	None	None	None	None	None
Emelia J. Benjamin	Boston University School of Medicine	None	None	None	None	None	None	None
Robert O. Bonow	Northwestern University	None	None	None	None	None	None	None
Lynne T. Braun	Rush University Medical Center	NIH-Coinvestigator, Reducing Health Disparity in African American Women: Adherence to Physical Activity*	None	None	None	None	None	None
Mark A. Creager	Brigham and Women's Hospital	Merck†; Sanofi Aventis†	None	None	None	None	Pfizer*; Sanofi Aventis*; Merck (via TIMI group)*; AstraZeneca*	None
Barry A. Franklin	William Beaumont Hospital	None	None	I receive honoraria throughout the year for talks to hospitals (ie, medical grand rounds) and cardiac rehabilitation state associations*	None	None	Smart Balance Scientific Advisory Board*	None
Raymond J. Gibbons	Mayo Clinic	King Pharmaceuticals†; TherOx†; VeloMedix†	None	None	None	None	Cardiovascular Clinical Studies*; Medscape (heart.org)*; Molecular Insight Pharmaceuticals*; TherOx*; Lantheus Medical Imaging*	None
Scott M. Grundy	UT Southwestern Medical Center	Sankyo†	Perot Foundation†	None	None	None	AstraZeneca*; Merck*; Merck/Schering-Plough*; Pfizer* (Relationships ended 3 years ago)	None
Loren F. Hiratzka	Cardiovascular and Thoracic Surgeons/Tri-Health Inc	None	None	None	None	None	None	None
Daniel W. Jones	University of Mississippi	None	None	None	None	None	None	None
Donald M. Lloyd-Jones	Northwestern	None	None	None	None	None	None	None
Margo Minissian	Cedars Sinai Medical Center	RWise Study, Co-Investigator, Gilead Sciences†	None	None	None	None	None	None
Lori Mosca	Columbia University	NIH*	None	None	None	None	Advise & Consent, Inc.*; Gilead Science*; Rowpar Pharmaceuticals, Inc.†; Sanofi-Aventis*	None
Eric D. Peterson	Duke University Medical Center	Bristol-Myers Squibb/Sanofi†; Eli Lilly†; Merck/Schering-Plough†; Johnson & Johnson†	None	None	None	None	None	None
Ralph L. Sacco	University of Miami	NINDS-Northern Manhattan Study*	None	None	None	None	Boehringer Ingelheim* (ended March 2009); GlaxoSmithKline (ended March 2009)*; Sanofi Aventis* (ended March 2009); DSMB (Atrial Fibrillation Trial—institutionally sponsored by Population Health Research Institute at McMaster University, Hamilton, Ontario)*	None

(Continued)

Downloaded from http://circ.ahajournals.org/ by guest on March 4, 2017



Writing Group Disclosures, *Continued*

Writing Group Member	Employment	Research Grant	Other Research Support	Speakers' Bureau/Honoraria	Expert Witness	Ownership Interest	Consultant/Advisory Board	Other
John Spertus	Mid America Heart Institute	Amgen†; Bristol-Myers Squibb/Sanofi†; Eli Lilly†; Cordist†; NIH†; ACCF†; AHA†	Atherotech†; Roche Diagnostics†	None	None	Holds copyright to Kansas City Cardiomyopathy Questionnaire†; holds copyright to Peripheral Artery Questionnaire*; holds copyright to Seattle Angina Questionnaire†	St. Jude Medical*; United HealthCare*; Amgen*	None
James H. Stein	University of Wisconsin School of Medicine and Public Health	Sanofi-Aventis† (ended July 2009); Siemens Medical Solutions† (ended July 2009); SonoSite† (ended September 2009)	None	Abbott* and Takeda* (no permanent remuneration; all money to charity. Both were terminated December 2008)	None	None	Abbott*, Lilly*, and Takeda* (research trial DSMBs)	Takeda* (training grant to institution ended June 2009); Wisconsin Alumni Research Foundation* (royalties related to carotid ultrasound and cardiovascular disease risk prediction)
Kathryn A. Taubert	World Heart Federation	None	None	None	None	None	None	None

This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (1) the person receives \$10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (2) the person owns 5% or more of the voting stock or share of the entity, or owns \$10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

\*Modest.

†Significant.

## Reviewer Disclosures

Reviewer	Employment	Research Grant	Other Research Support	Speakers' Bureau/Honoraria	Expert Witness	Ownership Interest	Consultant/Advisory Board	Other
Elliott M. Antman	Brigham & Women's Hospital	None	None	None	None	None	None	None
Jeffrey L. Anderson	Intermountain Medical Center	None	None	None	None	None	AstraZeneca*	None
Gary J. Balady	Boston Medical Center	None	None	None	None	None	None	None
Eric R. Bates	University of Michigan	None	None	None	None	None	AstraZeneca*; Daiichi Sankyo*; Eli Lilly*; Merck*; Sanofi Aventis*	None
Vera Bittner	University of Alabama at Birmingham	Clinical site PI for multicenter trials funded by: Roche/Genentech†; Gilead; GSK†; NIH/Abbott†; NIH/Yale†	None	None	None	None	Roche/Genentech*; Amarin*; Pfizer*	None
Ann F. Bolger	University of California, San Francisco	None	None	None	None	None	None	None
Victor A. Ferrari	University of Pennsylvania	None	None	None	None	None	Board of Trustees, Society for Cardiovascular Magnetic Resonance (no monetary value)*; Editorial Board, <i>Journal of Cardiovascular Magnetic Resonance</i> (no monetary value)*	None
Stephan Fihn	Department of Veterans Affairs and University of Washington	None	None	None	None	None	None	None
Gregg Fonarow	UCLA	NHLBI†; AHRQ†	None	None	None	None	Novartis†; Medtronic*	None
Federico Gentile	Centro Medico diagnostic, Naples-Italy	None	None	None	None	None	None	None
Larry B. Goldstein	Duke University	None	None	None	None	None	None	None
Jonathan Halperin	Mount Sinai Medical Center, New York, NY	None	None	None	None	None	Boehringer Ingelheim†; Astellas Pharma, US*; Bristol-Meyers Squibb*; Daiichi Sankyo*; Johnson & Johnson*; Pfizer, Inc*; Sanofi-Aventis*	None

(Continued)

Reviewer Disclosures, Continued

Reviewer	Employment	Research Grant	Other Research Support	Speakers' Bureau/Honoraria	Expert Witness	Ownership Interest	Consultant/Advisory Board	Other
Courtney Jordan	University of Minnesota	None	None	None	None	None	None	None
Noel Bairey Merz	Cedars-Sinai Medical Center	Gilead†	NHLBI†	Mayo Foundation*; SCS Healthcare†; Practice Point Communications*; Inst for Professional Education*; Medical Education Speakers Network*; Minneapolis Heart Institute*; Catholic Healthcare West*; Novant Health*; HealthScience Media Inc*; Huntsworth Health*; WomenHeart Coalition*; Los Robles Medical Center*; Monterrey Community Hospital (honorarium, donated to ACC)*; Los Angeles OB-GYN Society*; Pri-Med*; North American Menopause Society*	None	Medtronic†	UCSF*; Society for Women's Health Research*; Interquest*; Dannemiller*; Navvis & Co*; Springer SBM LLC*; Duke*; NHLBI*; Italian National Institutes of Health*; Gilead*	None
L. Kristin Newby	Duke University	None	None	None	None	None	None	None
Patrick O'Gara	Brigham & Women's Hospital	None	None	None	None	None	Lantheus Medical Imaging*	None
Thomas W. Rooke	Mayo Clinic	None	None	None	None	None	Merck-Adjudication (Event) Committee*	None
Vincent Sorrell	University of Arizona	None	None	Lantheus Medical Imaging†	None	None	None	None

This table represents the relationships of reviewers that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all reviewers are required to complete and submit. A relationship is considered to be "significant" if (1) the person receives \$10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (2) the person owns 5% or more of the voting stock or share of the entity, or owns \$10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

\*Modest.  
†Significant.

References

- Smith SC Jr, Allen J, Blair SN, Bonow RO, Brass LM, Fonarow GC, Grundy SM, Hiratzka L, Jones D, Krumholz HM, Mosca L, Pasternak RC, Pearson T, Pfeffer MA, Taubert KA. AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update: [published correction appears in *Circulation*. 2006;113:e847]. *Circulation*. 2006;113:2363-2372.
- Rothemich SF, Woolf SH, Johnson RE, Burgett AE, Flores SK, Marsland DW, Ahluwalia JS. Effect on cessation counseling of documenting smoking status as a routine vital sign: an ACORN study. *Ann Fam Med*. 2008;6:60-68.
- Rosser A, McDowell I, Newvell C. Documenting smoking status: trial of three strategies. *Can Fam Physician*. 1992;38:1623-1628.
- US Department of Health and Human Services. *Systems Change: Treating Tobacco Use and Dependence*. Based on the Public Health Service (PHS) Clinical Practice Guideline—2008 Update. www.ahrq.gov/clinic/tobacco/systems.htm. Accessed September 25, 2011.
- Cummings SR, Coates TJ, Richard RJ, Hansen B, Zahnd EG, VanderMartin R, Duncan C, Gerbert B, Martin A, Stein MJ. Training physicians in counseling about smoking cessation: a randomized trial of the "Quit for Life" program. *Ann Intern Med*. 1989;110:640-647.
- Cummings SR, Richard RJ, Duncan CL, Hansen B, Vander Martin R, Gerbert B, Coates TJ. Training physicians about smoking cessation: a controlled trial in private practice. *J Gen Intern Med*. 1989;4:482-489.
- Fiore MC, Jaén CR, Baker TB, Bailey WC, Benowitz NL, Curry SJ, Dorfman SF, Froelicher ES, Goldstein MG, Heaton CG, Henderson PN, Heyman RB, Koh HK, Kottke TE, Lando HA, Mecklenburg RE, Mermelstein RJ, Mullen PD, Orleans CT, Robinson L, Stitzer ML, Tommasello AC, Villejo L, Wewers ME. *Treating Tobacco Use and Dependence: 2008 Update*. Clinical Practice Guideline. Rockville, MD: US Department of Health and Human Services, Public Health Service; May 2008. http://www.surgeongeneral.gov/tobacco/treating\_tobacco\_use08.pdf. Accessed December 9, 2010.
- Duncan C, Stein MJ, Cummings SR. Staff involvement and special follow-up time increase physicians' counseling about smoking cessation: a controlled trial. *Am J Public Health*. 1991;81:899-901.
- Anthonisen NR, Skeans MA, Wise RA, Manfreda J, Kanner RE, Connett JE; Lung Health Study Research Group. The effects of a smoking cessation intervention on 14.5-year mortality: a randomized clinical trial. *Ann Intern Med*. 2005;142:233-239.
- US Department of Health and Human Services. *The Health Consequences of Involuntary Exposure to Tobacco Smoke: A Report From the Surgeon General*. Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention, Coordinating Center for Health Promotion, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2006.
- Committee on Secondhand Smoke Exposure and Acute Coronary Events, Institute of Medicine. *Secondhand Smoke Exposure and Cardiovascular Effects: Making Sense of the Evidence*. Washington, DC: National Academies Press; 2010. http://www.nap.edu/catalog/12649.html. Accessed May 31, 2011.
- Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ; and the National High Blood Pressure Education Program Coordinating Committee. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension*. 2003;42:1206-1252.
- Appel LJ, Moore TJ, Obarzanek E, Vollmer WM, Svetkey LP, Sacks FM, Bray GA, Vogt TM, Cutler JA, Windhauser MM, Lin PH, Karanja N. A clinical trial of the effects of dietary patterns on blood pressure: DASH Collaborative Research Group. *N Engl J Med*. 1997;336:1117-1124.
- Sacks FM, Svetkey LP, Vollmer WM, Appel LJ, Bray GA, Harsha D, Obarzanek E, Conlin PR, Miller ER 3rd, Simons-Morton DG, Karanja N, Lin PH; DASH-Sodium Collaborative Research Group. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. *N Engl J Med*. 2001;344:3-10.
- Appel LJ, Frohlich ED, Hall JE, Pearson TA, Sacco RL, Seals DR, Sacks FM, Smith SC Jr, Vafiadis DK, Van Horn LV. The importance of population-wide sodium reduction as a means to prevent cardiovascular disease and stroke: a call to action from the American Heart Association. *Circulation*. 2011;123:1138-1143.
- Whelton SP, Chin A, Xin X, He J. Effect of aerobic exercise on blood pressure: a meta-analysis of randomized, controlled trials. *Ann Intern Med*. 2002;136:493-503.

Downloaded from http://circ.ahajournals.org/ by guest on March 4, 2017

17. SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension: final results of the Systolic Hypertension in the Elderly Program (SHEP). *JAMA*. 1991;265:3255–3264.
18. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) [published corrections appear in *JAMA*. 2004;291:2196 and *JAMA*. 2003;289:178]. *JAMA*. 2002;288:2981–2997.
19. Dattilo AM, Kris-Etherton PM. Effects of weight reduction on blood lipids and lipoproteins: a meta-analysis. *Am J Clin Nutr*. 1992;56:320–328.
20. Murphy SA, Cannon CP, Wiviott SD, McCabe CH, Braunwald E. Reduction in recurrent cardiovascular events with intensive lipid-lowering statin therapy compared with moderate lipid-lowering statin therapy after acute coronary syndrome: from the PROVE IT-TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction 22) trial. *J Am Coll Cardiol*. 2009;54:2358–2362.
21. Ginsberg HN, Kris-Etherton P, Dennis B, Elmer PJ, Ershow A, Lefevre M, Pearson T, Roheim P, Ramakrishnan R, Reed R, Stewart K, Stewart P, Phillips K, Anderson N. Effects of reducing dietary saturated fatty acids on plasma lipids and lipoproteins in healthy subjects: the DELTA Study, protocol 1. *Arterioscler Thromb Vasc Biol*. 1998;18:441–449.
22. Schaefer EJ, Lamon-Fava S, Ausman LM, Ordovas JM, Clevidence BA, Judd JT, Goldin BR, Woods M, Gorbach S, Lichtenstein AH. Individual variability in lipoprotein cholesterol response to National Cholesterol Education Program Step 2 diets. *Am J Clin Nutr*. 1997;65:823–830.
23. Schaefer EJ, Lichtenstein AH, Lamon-Fava S, Contois JH, Li Z, Rasmussen H, McNamara JR, Ordovas JM. Efficacy of a National Cholesterol Education Program Step 2 diet in normolipidemic and hypercholesterolemic middle-aged and elderly men and women. *Arterioscler Thromb Vasc Biol*. 1995;15:1079–1085.
24. Yu-Poth S, Zhao G, Etherton T, Naglak M, Jonnalagadda S, Kris-Etherton PM. Effects of the National Cholesterol Education Program's Step I and Step II dietary intervention programs on cardiovascular disease risk factors: a meta-analysis. *Am J Clin Nutr*. 1999;69:632–646.
25. MRC/BHF Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet*. 2002;360:7–22.
26. LaRosa JC, Grundy SM, Waters DD, Shear C, Barter P, Fruchart JC, Gotto AM, Greten H, Kastelein JJ, Shepherd J, Wenger NK; Treating to New Targets (TNT) Investigators. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med*. 2005;352:1425–1435.
27. Pedersen TR, Faergeman O, Kastelein JJ, Olsson AG, Tikkanen MJ, Holme I, Larsen ML, Bendixen FS, Lindahl C, Szarek M, Tsai J; Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) Study Group. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial [published correction appears in *JAMA*. 2005;294:3092]. *JAMA*. 2005;294:2437–2445.
28. Cholesterol Treatment Trialists' (CTT) Collaborators; Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhalra N, Peto R, Barnes EH, Keech A, Simes J, Collins R. Efficacy and safety of more intense lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet*. 2010;376:1670–1681.
29. National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). 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) final report. *Circulation*. 2002;106:3143–3421.
30. Robinson JG, Wang S, Smith BJ, Jacobson TA. Meta-analysis of the relationship between non-high-density lipoprotein cholesterol reduction and coronary heart disease risk. *J Am Coll Cardiol*. 2009;53:316–322.
31. Zhao XQ, Brown BG, Hillger L, Sacco D, Bisson B, Fisher L, Albers JJ. Effects of intensive lipid-lowering therapy on the coronary arteries of asymptomatic subjects with elevated apolipoprotein B. *Circulation*. 1993;88:2744–2753.
32. Brown BG, Zhao XQ, Chait A, Fisher LD, Cheung MC, Morse JS, Dowdy AA, Marino EK, Bolson EL, Alaupovic P, Frohlich J, Albers JJ. Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. *N Engl J Med*. 2001;345:1583–1592.
33. Campeau L, Hunnigake DB, Knatterud GL, White CW, Domanski M, Forman SA, Forrester JS, Geller NL, Gobel FL, Herd JA, Hoogwerf BJ, Rosenberg Y; and Post CABG Trial Investigators. Aggressive cholesterol lowering delays saphenous vein graft atherosclerosis in women, the elderly, and patients with associated risk factors: NHLBI post coronary artery bypass graft clinical trial. *Circulation*. 1999;99:3241–3247.
34. Rubins HB, Robins SJ, Collins D, Fye CL, Anderson JW, Elam MB, Faas FH, Linares E, Schaefer EJ, Schemman G, Wilt TJ, Wittes J; Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. *N Engl J Med*. 1999;341:410–418.
35. Canner PL, Berge KG, Wenger NK, Stamler J, Friedman L, Prineas RJ, Friedewald W. Fifteen year mortality in Coronary Drug Project patients: long-term benefit with niacin. *J Am Coll Cardiol*. 1986;8:1245–1255.
36. The Lipid Research Clinics Coronary Primary Prevention Trial results, I: reduction in incidence of coronary heart disease. *JAMA*. 1984;251:351–364.
37. Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, Joyal SV, Hill KA, Pfeffer MA, Skene AM; Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 Investigators. Intensive versus moderate lipid lowering with statins after acute coronary syndromes [published correction appears in *N Engl J Med*. 2006;354:778]. *N Engl J Med*. 2004;350:1495–1504.
38. Cannon CP, Steinberg BA, Murphy SA, Mega JL, Braunwald E. Meta-analysis of cardiovascular outcomes trials comparing intensive versus moderate statin therapy. *J Am Coll Cardiol*. 2006;48:438–445.
39. Frick MH, Elo O, Haapa K, Heinonen OP, Heinsalmi P, Helo P, Huttunen JK, Kaitaniemi P, Koskinen P, Manninen V, Mäenpää H, Mäkkönen M, Mänttari M, Norola S, Pasternack A, Pikkariainen J, Romo M, Sjöblom T, Nikkilä EA. Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia: safety of treatment, changes in risk factors, and incidence of coronary heart disease. *N Engl J Med*. 1987;317:1237–1245.
40. Keech A, Simes RJ, Barter P, Best J, Scott R, Taskinen MR, Forster P, Pillai A, Davis T, Glasziou P, Drury P, Kesäniemi YA, Sullivan D, Hunt D, Colman P, d'Emden M, Whiting M, Ehnholm C, Laakso M; FIELD Study Investigators. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial [published corrections appear in *Lancet*. 2006;368:1415 and *Lancet*. 2006;368:1420]. *Lancet*. 2005;366:1849–1861.
41. Robins SJ, Rubins HB, Faas FH, Schaefer EJ, Elam MB, Anderson JW, Collins D; Veterans Affairs HDL Intervention Trial (VA-HIT). Insulin resistance and cardiovascular events with low HDL cholesterol: the Veterans Affairs HDL Intervention Trial (VA-HIT). *Diabetes Care*. 2003;26:1513–1517.
42. LaRosa JC, Grundy SM, Kastelein JJ, Kostis JB, Greten H; Treating to New Targets (TNT) Steering Committee and Investigators. Safety and efficacy of atorvastatin-induced very low-density lipoprotein cholesterol levels in patients with coronary heart disease (a post hoc analysis of the Treating to New Targets [TNT] study). *Am J Cardiol*. 2007;100:747–752.
43. Hayward RA, Krumholz HM, Zulman DM, Timbie JW, Vijan S. Optimizing statin treatment for primary prevention of coronary artery disease [published correction appears in *Ann Intern Med*. 2011;154:848]. *Ann Intern Med*. 2010;152:69–77.
44. Kris-Etherton PM, Harris WS, Appel LJ; for the Nutrition Committee. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease [published correction appears in *Circulation*. 2003;107:512]. *Circulation*. 2002;106:2747–2757.
45. Bucher HC, Hengstler P, Schindler C, Meier G. N-3 polyunsaturated fatty acids in coronary heart disease: a meta-analysis of randomized controlled trials. *Am J Med*. 2002;112:298–304.
46. Mosca L, Benjamin EJ, Berra K, Bezanson JL, Dolor RJ, Lloyd-Jones DM, Newby LK, Piña IL, Roger VL, Shaw LJ, Zhao D, Beckie TM, Bushnell C, D'Armiento J, Kris-Etherton PM, Fang J, Ganiats TG, Gomes AS, Gracia CR, Haan CK, Jackson EA, Judelson DR, Kelepouris E, Lavie CJ, Moore A, Nussmeier NA, Ofili E, Oparil S, Ouyang P, Pinn VW, Sherif K, Smith SC Jr, Sopko G, Chandra-Strobus N, Urbina EM, Vaccarino V, Wenger NK. Effectiveness-based guidelines for the prevention of cardiovascular disease in women: 2011 update: a guideline

- from the American Heart Association [published correction appears in *Circulation*. 2011;123:e624]. *Circulation*. 2011;123:1243–1262.
47. Balady GJ, Williams MA, Ades PA, Bittner V, Comoss P, Fodym JM, Franklin B, Sanderson B, Southard D. Core components of cardiac rehabilitation/secondary prevention programs: 2007 update: a scientific statement from the American Heart Association Exercise, Cardiac Rehabilitation, and Prevention Committee, the Council on Clinical Cardiology; the Councils on Cardiovascular Nursing, Epidemiology and Prevention, and Nutrition, Physical Activity, and Metabolism; and the American Association of Cardiovascular and Pulmonary Rehabilitation. *Circulation*. 2007;115:2675–2682.
  48. Mark DB, Hlatky MA, Harrell FE Jr, Lee KL, Califf RM, Pryor DB. Exercise treadmill score for predicting prognosis in coronary artery disease. *Ann Intern Med*. 1987;106:793–800.
  49. Mark DB, Shaw L, Harrell FE Jr, Hlatky MA, Lee KL, Bengtson JR, McCants CB, Califf RM, Pryor DB. Prognostic value of a treadmill exercise score in outpatients with suspected coronary artery disease. *N Engl J Med*. 1991;325:849–853.
  50. Vanhees L, Fagard R, Thijs L, Staessen J, Amery A. Prognostic significance of peak exercise capacity in patients with coronary artery disease. *J Am Coll Cardiol*. 1994;23:358–363.
  51. Kavanagh T, Mertens DJ, Hamm LF, Beyene J, Kennedy J, Corey P, Shephard RJ. Prediction of long-term prognosis in 12 169 men referred for cardiac rehabilitation. *Circulation*. 2002;106:666–671.
  52. Kavanagh T, Mertens DJ, Hamm LF, Beyene J, Kennedy J, Corey P, Shephard RJ. Peak oxygen intake and cardiac mortality in women referred for cardiac rehabilitation. *J Am Coll Cardiol*. 2003;42:2139–2143.
  53. Lloyd-Jones DM, Hong Y, Labarthe D, Mozaffarian D, Appel LJ, Van HL, Greenlund K, Daniels S, Nichol G, Tomaselli GF, Arnett DK, Fonarow GC, Ho PM, Lauer MS, Masoudi FA, Robertson RM, Roger V, Schwamm LH, Sorlie P, Yancy CW, Rosamond WD. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's Strategic Impact Goal through 2020 and beyond. *Circulation*. 2010;121:586–613.
  54. 2008 *Physical Activity Guidelines for Americans*. Washington, DC: US Department of Health and Human Services; 2008.
  55. Taylor RS, Brown A, Ebrahim S, Jolliffe J, Noorani H, Rees K, Skidmore B, Stone JA, Thompson DR, Oldridge N. Exercise-based rehabilitation for patients with coronary heart disease: systematic review and meta-analysis of randomized controlled trials. *Am J Med*. 2004;116:682–692.
  56. Marwick TH, Hordern MD, Miller T, Chyun DA, Bertoni AG, Blumenthal RS, Philippides G, Rocchini A; on behalf of the American Heart Association Exercise, Cardiac Rehabilitation, and Prevention Committee of the Council on Clinical Cardiology; Council on Cardiovascular Disease in the Young; Council on Cardiovascular Nursing; Council on Nutrition, Physical Activity, and Metabolism; and the Interdisciplinary Council on Quality of Care and Outcomes Research. Exercise training for type 2 diabetes mellitus: impact on cardiovascular risk: a scientific statement from the American Heart Association. *Circulation*. 2009;119:3244–3262.
  57. Antman EM, Anbe DT, Armstrong PW, Bates ER, Green LA, Hand M, Hochman JS, Krumholz HM, Kushner FG, Lamas GA, Mullany CJ, Ornato JP, Pearle DL, Sloan MA, Smith SC Jr, Alpert JS, Anderson JL, Faxon DP, Fuster V, Gibbons RJ, Gregoratos G, Halperin JL, Hiratzka LF, Hunt SA, Jacobs AK. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1999 Guidelines for the Management of Patients With Acute Myocardial Infarction) [published correction appears in *Circulation*. 2005;111:2013]. *Circulation*. 2004;110:588–636.
  58. Haskell WL, Lee IM, Pate RR, Powell KE, Blair SN, Franklin BA, Macera CA, Heath GW, Thompson PD, Bauman A. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. *Circulation*. 2007;116:1081–1093.
  59. Williams MA, Haskell WL, Ades PA, Amsterdam EA, Bittner V, Franklin BA, Gulanick M, Laing ST, Stewart KJ. Resistance exercise in individuals with and without cardiovascular disease: 2007 update: a scientific statement from the American Heart Association Council on Clinical Cardiology and Council on Nutrition, Physical Activity, and Metabolism. *Circulation*. 2007;116:572–584.
  60. National Institutes of Health; National Heart, Lung, and Blood Institute. *Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults: The Evidence Report*. Bethesda, MD: National Institutes of Health, National Heart, Lung, and Blood Institute; 1998. NIH publication No. 98-4083. [http://www.nhlbi.nih.gov/guidelines/obesity/ob\\_gdlns.pdf](http://www.nhlbi.nih.gov/guidelines/obesity/ob_gdlns.pdf). Accessed October 3, 2011.
  61. Klein S, Burke LE, Bray GA, Blair S, Allison DB, Pi-Sunyer X, Hong Y, Eckel RH. Clinical implications of obesity with specific focus on cardiovascular disease: a statement for professionals from the American Heart Association Council on Nutrition, Physical Activity, and Metabolism. *Circulation*. 2004;110:2952–2967.
  62. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith SC Jr, Spertus JA, Costa F. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement [published corrections appear in *Circulation*. 2005;112:e297 and *Circulation*. 2005;112:e298]. *Circulation*. 2005;112:2735–2752.
  63. Antman EM, Anbe DT, Armstrong PW, Bates ER, Green LA, Hand M, Hochman JS, Krumholz HM, Kushner FG, Lamas GA, Mullany CJ, Ornato JP, Pearle DL, Sloan MA, Smith SC Jr, Alpert JS, Anderson JL, Faxon DP, Fuster V, Gibbons RJ, Gregoratos G, Halperin JL, Hiratzka LF, Hunt SA, Jacobs AK. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction) [published corrections appear in *Circulation*. 2005;111:2013–2014, *Circulation*. 2007;115:e411, and *Circulation*. 2010;121:e441]. *Circulation*. 2004;110:e82–e292.
  64. Gibbons RJ, Abrams J, Chatterjee K, Daley J, Deedwania PC, Douglas JS, Ferguson TB Jr, Fihn SD, Fraker TD Jr, Gardin JM, O'Rourke RA, Pasternak RC, Williams SV, Gibbons RJ, Alpert JS, Antman EM, Hiratzka LF, Fuster V, Faxon DP, Gregoratos G, Jacobs AK, Smith SC Jr. ACC/AHA 2002 guideline update for the management of patients with chronic stable angina: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Chronic Stable Angina). *Circulation*. 2003;107:149–158.
  65. Calle EE, Thun MJ, Petrelli JM, Rodriguez C, Heath CW Jr. Body-mass index and mortality in a prospective cohort of U.S. adults. *N Engl J Med*. 1999;341:1097–1105.
  66. Jensen MK, Chiuvè SE, Rimm EB, Dethlefsen C, Tjønneland A, Joensen AM, Overvad K. Obesity, behavioral lifestyle factors, and risk of acute coronary events. *Circulation*. 2008;117:3062–3069.
  67. Arnlöv J, Ingelsson E, Sundström J, Lind L. Impact of body mass index and the metabolic syndrome on the risk of cardiovascular disease and death in middle-aged men. *Circulation*. 2010;121:230–236.
  68. Lavie CJ, Milani RV, Ventura HO. Obesity and cardiovascular disease: risk factor, paradox, and impact of weight loss. *J Am Coll Cardiol*. 2009;53:1925–1932.
  69. Gruberg L, Weissman NJ, Waksman R, Fuchs S, Deible R, Pinnow EE, Ahmed LM, Kent KM, Pichard AD, Suddath WO, Satler LF, Lindsay J Jr. The impact of obesity on the short-term and long-term outcomes after percutaneous coronary intervention: the obesity paradox? *J Am Coll Cardiol*. 2002;39:578–584.
  70. Jacobs EJ, Newton CC, Wang Y, Patel AV, McCullough ML, Campbell PT, Thun MJ, Gapstur SM. Waist circumference and all-cause mortality in a large U.S. cohort. *Arch Intern Med*. 2010;170:1293–1301.
  71. Skyler JS, Bergenstal R, Bonow RO, Buse J, Deedwania P, Gale EAM, Howard BV, Kirkman MS, Kosiborod M, Reaven P, Sherwin RS. Intensive glycemic control and the prevention of cardiovascular events: implications of the ACCORD, ADVANCE, and VA Diabetes Trials: a position statement of the American Diabetes Association and a scientific statement of the American College of Cardiology Foundation and the American Heart Association [published correction appears in *Circulation*. 2009;119:e605]. *Circulation*. 2009;119:351–357.
  72. Kelly TN, Bazzano LA, Fonseca VA, Thethi TK, Reynolds K, He J. Systematic review: glucose control and cardiovascular disease in type 2 diabetes. *Ann Intern Med*. 2009;151:394–403.
  73. Kaul S, Bolger AF, Herrington D, Giugliano RP, Eckel RH. Thiazolidinedione drugs and cardiovascular risks: a science advisory from the American Heart Association and the American College of Cardiology Foundation. *Circulation*. 2010;121:1868–1877.
  74. American Diabetes Association. Standards of medical care in diabetes: 2011. *Diabetes Care*. 2011;34(suppl 1):S11–S61.



75. Selvin E, Bolen S, Yeh H-C, Wiley C, Wilson LM, Marinopoulos SS, Feldman L, Vassy J, Wilson R, Bass EB, Brancati FL. Cardiovascular outcomes in trials of oral diabetes medications: a systematic review. *Arch Intern Med*. 2008;168:2070–2080.
76. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34) [published correction appears in *Lancet*. 1998;352:1558]. *Lancet*. 1998;352:854–865.
77. Turnbull FM, Abraira C, Anderson RJ, Byington RP, Chalmers JP, Duckworth WC, Evans GW, Gerstein HC, Holman RR, Moritz TE, Neal BC, Ninomiya T, Patel AA, Paul SK, Travert F, Woodward M; Control Group. Intensive glucose control and macrovascular outcomes in type 2 diabetes [published correction appears in *Diabetologia*. 2009;52:2470]. *Diabetologia*. 2009;52:2288–2298.
78. Ray KK, Seshasai SR, Wijesuriya S, Sivakumaran R, Nethercott S, Preiss D, Erqou S, Sattar N. Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials. *Lancet*. 2009;373:1765–1772.
79. Currie CJ, Peters JP, Tynan A, Evans M, Heine RJ, Bracco OL, Zagar T, Poole CD. Survival as a function of HbA<sub>1c</sub> in people with type 2 diabetes: a retrospective cohort study. *Lancet*. 2010;375:481–489.
80. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med*. 2008;359:1577–1589.
81. Becker RC, Meade TW, Berger PB, Ezekowitz M, O'Connor CM, Vorchheimer DA, Guyatt GH, Mark DB, Harrington RA; American College of Chest Physicians. The primary and secondary prevention of coronary artery disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest*. 2008;133:776S–814S.
82. Antithrombotic Trialists' (ATT) Collaboration; Baigent C, Blackwell L, Collins R, Emberson J, Godwin J, Peto R, Buring J, Hennekens C, Kearney P, Meade T, Patrono C, Roncaglioni MC, Zanchetti A. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta analysis of individual participant data from randomised trials. *Lancet*. 2009;373:1849–1860.
83. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK; Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation [published corrections appear in *N Engl J Med*. 2001;345:1506 and *N Engl J Med*. 2001;345:1716]. *N Engl J Med*. 2001;345:494–502.
84. Mehta SR, Yusuf S, Peters RJ, Bertrand ME, Lewis BS, Natarajan MK, Malmberg K, Rupprecht H, Zhao F, Chrolavicius S, Copland I, Fox KA; Clopidogrel in Unstable angina to prevent Recurrent Events trial (CURE) Investigators. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet*. 2001;358:527–533.
85. Steinhubl SR, Berger PB, Mann JT 3rd, Fry ET, DeLago A, Wilmer C, Topol EJ; CREDO Investigators. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial [published correction appears in *JAMA*. 2003;289:987]. *JAMA*. 2002;288:2411–2420.
86. Montalescot G, Wiviott SD, Braunwald E, Murphy SA, Gibson CM, McCabe CH, Antman EM; TRITON-TIMI 38 Investigators. Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON-TIMI 38): double-blind, randomised controlled trial. *Lancet*. 2009;373:723–731.
87. Chesebro JH, Fuster V, Elveback LR, Clements IP, Smith HC, Holmes DR Jr, Bardsley WT, Pluth JR, Wallace RB, Puga FJ, Orszulak TA, Piehler JM, Danielson GK, Schaff HV, Frye RL. Effect of dipyridamole and aspirin on late vein-graft patency after coronary bypass operations. *N Engl J Med*. 1984;310:209–214.
88. Lorenz RL, Schacky CV, Weber M, Meister W, Kotzur J, Reichardt B, Theisen K, Weber PC. Improved aortocoronary bypass patency by low-dose aspirin (100 mg daily): effects on platelet aggregation and thromboxane formation. *Lancet*. 1984;1:1261–1264.
89. Sharma GV, Khuri SF, Josa M, Folland ED, Parisi AF. The effect of antiplatelet therapy on saphenous vein coronary artery bypass graft patency. *Circulation*. 1983;68(pt 2):II-218–II-221.
90. Mangano DT; Multicenter Study of Perioperative Ischemia Research Group. Aspirin and mortality from coronary bypass surgery. *N Engl J Med*. 2002;347:1309–1317.
91. The ESPRIT Study Group; Halkes PH, van Gijn J, Kappelle LJ, Koudstaal PJ, Algra A. Aspirin plus dipyridamole versus aspirin alone after cerebral ischaemia of arterial origin (ESPRIT): randomised controlled trial [published correction appears in *Lancet*. 2007;369:274]. *Lancet*. 2006;367:1665–1673.
92. Critical Leg Ischaemia Prevention Study (CLIPS) Group; Catalano M, Born G, Peto R. Prevention of serious vascular events by aspirin amongst patients with peripheral arterial disease: randomized, double-blind trial. *J Intern Med*. 2007;261:276–284.
93. Anand SS, Yusuf S. Oral anticoagulant therapy in patients with coronary artery disease: a meta-analysis [published correction appears in *JAMA*. 2000;284:45]. *JAMA*. 1999;282:2058–2067.
94. Hurlen M, Abdelnoor M, Smith P, Eriksen J, Arnesen H. Warfarin, aspirin, or both after myocardial infarction. *N Engl J Med*. 2002;347:969–974.
95. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation: analysis of pooled data from five randomized controlled trials [published correction appears in *Arch Intern Med*. 1994;154:2254]. *Arch Intern Med*. 1994;154:1449–1457.
96. Bonow RO, Carabello BA, Kanu C, de Leon AC Jr, Faxon DP, Freed MD, Gaasch WH, Lytle BW, Nishimura RA, O'Gara PT, O'Rourke RA, Otto CM, Shah PM, Shanewise JS, Smith SC Jr, Jacobs AK, Adams CD, Anderson JL, Antman EM, Faxon DP, Fuster V, Halperin JL, Hiratzka LF, Hunt SA, Lytle BW, Nishimura R, Page RL, Riegel B. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease) [published corrections appear in *Circulation*. 2010;121:e443 and *Circulation*. 2007;115:e409]. *Circulation*. 2006;114:e84–e231.
97. Fiore LD, Ezekowitz MD, Brophy MT, Lu D, Sacco J, Peduzzi P; Combination Hemotherapy and Mortality Prevention (CHAMP) Study Group. Department of Veterans Affairs Cooperative Studies Program Clinical Trial comparing combined warfarin and aspirin with aspirin alone in survivors of acute myocardial infarction: primary results of the CHAMP study. *Circulation*. 2002;105:557–563.
98. Anand SS, Yusuf S. Oral anticoagulants in patients with coronary artery disease. *J Am Coll Cardiol*. 2003;41(suppl S):62S–69S.
99. Turpie AG, Gent M, Laupacis A, Latour Y, Gunstensen J, Basile F, Klimek M, Hirsh J. A comparison of aspirin with placebo in patients treated with warfarin after heart-valve replacement. *N Engl J Med*. 1993;329:524–529.
100. Mok CK, Boey J, Wang R, Chan TK, Cheung KL, Lee PK, Chow J, Ng RP, Tse TF. Warfarin versus dipyridamole-aspirin and pentoxifylline-aspirin for the prevention of prosthetic heart valve thromboembolism: a prospective randomized clinical trial. *Circulation*. 1985;72:1059–1063.
101. Adjusted-dose warfarin versus low-intensity, fixed-dose warfarin plus aspirin for high-risk patients with atrial fibrillation: Stroke Prevention in Atrial Fibrillation III randomized clinical trial. *Lancet*. 1996;348:633–638.
102. Kearon C, Gent M, Hirsh J, Weitz J, Kovacs MJ, Anderson DR, Turpie AG, Green D, Ginsberg JS, Wells P, MacKinnon B, Julian JA. A comparison of three months of anticoagulation with extended anticoagulation for a first episode of idiopathic venous thromboembolism [published correction appears in *N Engl J Med*. 1999;341:298]. *N Engl J Med*. 1999;340:901–907.
103. Adams RJ, Albers G, Alberts MJ, Benavente O, Furie K, Goldstein LB, Gorelick P, Halperin J, Harbaugh R, Johnston SC, Katzan I, Kelly-Hayes M, Kenton EJ, Marks M, Sacco RL, Schwamm LH. Update to the AHA/ASA recommendations for the prevention of stroke in patients with stroke and transient ischemic attack [published correction appears in *Stroke*. 2010;41:e455]. *Stroke*. 2008;39:1647–1652.
104. Sacco RL, Diener HC, Yusuf S, Cotton D, Ounpuu S, Lawton WA, Palesch Y, Martin RH, Albers GW, Bath P, Bornstein N, Chan BP, Chen ST, Cunha L, Dahlöf B, De Keyser J, Donnan GA, Estol C, Gorelick P, Gu V, Hermansson K, Hilbrich L, Kaste M, Lu C, Machnig T, Pais P, Roberts R, Skvortsova V, Teal P, Toni D, Vandermaelen C, Voigt T, Weber M, Yoon BW; PROFESS Study Group. Aspirin and extended-release dipyridamole versus clopidogrel for recurrent stroke. *N Engl J Med*. 2008;359:1238–1251.



105. Mohr JP, Thompson JL, Lazar RM, Levin B, Sacco RL, Furie KL, Kistler JP, Albers GW, Pettigrew LC, Adams HP Jr, Jackson CM, Pullicino P; Warfarin-Aspirin Recurrent Stroke Study Group. A comparison of warfarin and aspirin for the prevention of recurrent ischemic stroke. *N Engl J Med*. 2001;345:1444–1451.
106. Halkes PH, van Gijn J, Kappelle LJ, Koudstaal PJ, Algra A; ESPRIT Study Group. Medium intensity oral anticoagulants versus aspirin after cerebral ischaemia of arterial origin (ESPRIT): a randomised controlled trial. *Lancet Neurol*. 2007;6:115–124.
107. Hirsch AT, Haskal ZJ, Hertzner NR, Bakal CW, Creager MA, Halperin JL, Hiratzka LF, Murphy WR, Olin JW, Puschett JB, Rosenfield KA, Sacks D, Stanley JC, Taylor LM Jr, White CJ, White J, White RA, Antman EM, Smith SC Jr, Adams CD, Anderson JL, Faxon DP, Fuster V, Gibbons RJ, Hunt SA, Jacobs AK, Nishimura R, Ornato JP, Page RL, Riegel B. ACC/AHA 2005 practice guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease). *Circulation*. 2006;113:e463–e654.
108. Berger JS, Krantz MJ, Kittelson JM, Hiatt WR. Aspirin for the prevention of cardiovascular events in patients with peripheral artery disease: a meta-analysis of randomized trials. *JAMA*. 2009;301:1909–1919.
109. Fowkes FG, Price JF, Stewart MC, Butcher I, Leng GC, Pell AC, Sandcock PA, Fox KA, Lowe GD, Murray GD; Aspirin for Asymptomatic Atherosclerosis Trialists. Aspirin for prevention of cardiovascular events in a general population screened for a low ankle brachial index: a randomized controlled trial. *JAMA*. 2010;303:841–848.
110. Anand S, Yusuf S, Xie C, Pogue J, Eikelboom J, Budaj A, Sussex B, Liu L, Guzman R, Cina C, Crowell R, Keltai M, Gosselin G; Warfarin Antiplatelet Vascular Evaluation Trial Investigators. Oral anticoagulant and antiplatelet therapy and peripheral arterial disease. *N Engl J Med*. 2007;357:217–227.
111. Bhatt DL, Fox KA, Hacke W, Berger PB, Black HR, Boden WE, Cacoub P, Cohen EA, Creager MA, Easton JD, Flather MD, Haffner SM, Hamm CW, Hankey GJ, Johnston SC, Mak KH, Mas JL, Montalescot G, Pearson TA, Steg PG, Steinhubl SR, Weber MA, Brennan DM, Fabry-Ribaud L, Booth J, Topol EJ; CHARISMA Investigators. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *N Engl J Med*. 2006;354:1706–1717.
112. Bhatt DL, Flather MD, Hacke W, Berger PB, Black HR, Boden WE, Cacoub P, Cohen EA, Creager MA, Easton JD, Hamm CW, Hankey GJ, Johnston SC, Mak KH, Mas JL, Montalescot G, Pearson TA, Steg PG, Steinhubl SR, Weber MA, Fabry-Ribaud L, Hu T, Topol EJ, Fox KA; CHARISMA Investigators. Patients with prior myocardial infarction, stroke, or symptomatic peripheral arterial disease in the CHARISMA trial. *J Am Coll Cardiol*. 2007;49:1982–1988.
113. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, Neumann FJ, Ardissino D, De Servi S, Murphy SA, Riesmeyer J, Weerakkody G, Gibson CM, Antman EM; TRITON-TIMI 38 Investigators. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2007;357:2001–2015.
114. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, Mahaffey KW, Scirica BM, Skene A, Steg PG, Storey RF, Harrington RA; PLATO Investigators. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2009;361:1045–1057.
115. Mega JL, Close SL, Wiviott SD, Shen L, Hockett RD, Brandt JT, Walker JR, Antman EM, Macias W, Braunwald E, Sabatine MS. Cytochrome p-450 polymorphisms and response to clopidogrel. *N Engl J Med*. 2009;360:354–362.
116. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients [published correction appears in *BMJ*. 2002;324:141]. *BMJ*. 2002;324:71–86.
117. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet*. 1996;348:1329–1339.
118. Chen ZM, Jiang LX, Chen YP, Xie JX, Pan HC, Peto R, Collins R, Liu LS; COMMIT (Clopidogrel and Metoprolol in Myocardial Infarction Trial) Collaborative Group. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet*. 2005;366:1607–1621.
119. Brar SS, Kim J, Brar SK, Zedegan R, Ree M, Liu IL, Mansukhani P, Aharonian V, Hyett R, Shen AY. Long-term outcomes by clopidogrel duration and stent type in a diabetic population with de novo coronary artery lesions. *J Am Coll Cardiol*. 2008;51:2220–2227.
120. Patrono C, Baigent C, Hirsh J, Roth G. Antiplatelet drugs: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest*. 2008;133(suppl):199S–233S.
121. Steinhubl SR, Bhatt DL, Brennan DM, Montalescot G, Hankey GJ, Eikelboom JW, Berger PB, Topol EJ; CHARISMA Investigators. Aspirin to prevent cardiovascular disease: the association of aspirin dose and clopidogrel with thrombosis and bleeding. *Ann Intern Med*. 2009;150:379–386.
122. Serebruany VL, Steinhubl SR, Berger PB, Malinin AI, Baggish JS, Bhatt DL, Topol EJ. Analysis of risk of bleeding complications after different doses of aspirin in 192,036 patients enrolled in 31 randomized controlled trials. *Am J Cardiol*. 2005;95:1218–1222.
123. Furie KL, Kasner SE, Adams RJ, Albers GW, Bush RL, Fagan SC, Halperin JL, Johnston SC, Katzan I, Kernan WN, Mitchell PH, Ovbiagele B, Palesch YY, Sacco RL, Schwamm LH, Wassertheil-Smoller S, Turan TN, Wentworth D; on behalf of the American Heart Association Stroke Council, Council on Cardiovascular Nursing, Council on Clinical Cardiology, and Interdisciplinary Council on Quality of Care and Outcomes Research. Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2011;42:227–276.
124. Garg R, Yusuf S; Collaborative Group on ACE Inhibitor Trials. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure [published correction appears in *JAMA*. 1995;274:462]. *JAMA*. 1995;273:1450–1456.
125. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G; Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients [published corrections appear in *N Engl J Med*. 2000;342:1376 and *N Engl J Med*. 2000;342:748]. *N Engl J Med*. 2000;342:145–153.
126. Fox KM; EUROpean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease Investigators. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). *Lancet*. 2003;362:782–788.
127. Braunwald E, Domanski MJ, Fowler SE, Geller NL, Gersh BJ, Hsia J, Pfeffer MA, Rice MM, Rosenberg YD, Rouleau JL; PEACE Trial Investigators. Angiotensin-converting-enzyme inhibition in stable coronary artery disease. *N Engl J Med*. 2004;351:2058–2068.
128. Turnbull F, Neal B, Algert C, Chalmers J, Chapman N, Cutler J, Woodward M, MacMahon S; Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different blood pressure-lowering regimens on major cardiovascular events in individuals with and without diabetes mellitus: results of prospectively designed overviews of randomized trials. *Arch Intern Med*. 2005;165:1410–1419.
129. Kunz R, Friedrich C, Wolbers M, Mann JF. Meta-analysis: effect of monotherapy and combination therapy with inhibitors of the renin-angiotensin system on proteinuria in renal disease. *Ann Intern Med*. 2008;148:30–48.
130. Pitt B, Poole-Wilson PA, Segal R, Martinez FA, Dickstein K, Camm AJ, Konstam MA, Riegger G, Klingner GH, Neaton J, Sharma D, Thyagarajan B. Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomized trial: the Losartan Heart Failure Survival Study (ELITE II). *Lancet*. 2000;355:1582–1587.
131. Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, Michelson EL, Olofsson B, Ostergren J, Yusuf S, Pocock S; CHARM Investigators and Committees. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme [published correction appears in *Lancet*. 2009;374:1744]. *Lancet*. 2003;362:759–766.
132. Pfeffer MA, McMurray JJ, Velazquez EJ, Rouleau JL, Køber L, Maggioni AP, Solomon SD, Swedberg K, Van de Werf F, White H, Leimberger JD, Henis M, Edwards S, Zelenkofske S, Sellers MA, Califf RM; Valsartan in Acute Myocardial Infarction Trial Investigators. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both [published correction

- appears in *N Engl J Med*. 2004;350:203]. *N Engl J Med*. 2003;349:1893–1906.
133. Yusuf S, Teo K, Anderson C, Pogue J, Dyal L, Copland I, Schumacher H, Dagenais G, Sleight P; Telmisartan Randomized Assessment Study in ACE Intolerant subjects with cardiovascular Disease (TRANCEND) Investigators. Effects of angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: a randomized controlled trial [published correction appears in *Lancet*. 2008;372:1384]. *Lancet*. 2008;372:1174–1183.
  134. Yusuf S, Teo KK, Pogue J, Dyal L, Copland I, Schumacher H, Dagenais G, Sleight P, Anderson C; ONTARGET Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med*. 2008;358:1547–1559.
  135. Matchar DB, McCrory DC, Orlando LA, Patel MR, Patel UD, Patwardhan MB, Powers B, Samsa GP, Gray RN. Systematic review: comparative effectiveness of angiotensin converting enzyme inhibitors or angiotensin II receptor blockers for treating essential hypertension. *Ann Intern Med*. 2008;148:16–29.
  136. Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, Bittman R, Hurlley S, Kleiman J, Gatlin M; Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction [published correction appears in *N Engl J Med*. 2003;348:2271]. *N Engl J Med*. 2003;348:1309–1321.
  137. Zannad F, McMurray JJV, Henry Krum H, Dirckx J, van Veldhuisen DJ, Swedberg K, Shi H, Vincent J, Stuart J, Pocock SJ, Pitt B; EMPHASIS-HF Study Group. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med* 2011;364:11–21.
  138. Packer M, Bristow MR, Cohn JN, Colucci WS, Fowler MB, Gilbert EM, Shusterman NH; US Carvedilol Heart Failure Study Group. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. *N Engl J Med*. 1996;334:1349–1355.
  139. Freemantle N, Cleland J, Young P, Mason J, Harrison J.  $\beta$  Blockade after myocardial infarction: systematic review and meta regression analysis. *BMJ*. 1999;318:1730–1737.
  140. Poole-Wilson PA, Swedberg K, Cleland JG, Di Lenarda A, Hanrath P, Komajda M, Lubsen J, Lutiger B, Metra M, Remme WJ, Torp-Pedersen C, Scherhag A, Skene A; COMET Investigators. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): randomised controlled trial. *Lancet*. 2003;362:7–13.
  141. Domanski MJ, Krause-Steinrauf H, Massie BM, Deedwania P, Follmann D, Kovar D, Murray D, Oren R, Rosenberg Y, Young J, Zile M, Eichhorn E. A comparative analysis of the results from 4 trials of beta-blocker therapy for heart failure: BEST, CIBIS-II, MERIT-HF, and COPERNICUS. *J Card Fail*. 2003;9:354–363.
  142. de Peuter OR, Lussana F, Peters RJG, Büller HR, Kamphuisen PW. A systematic review of selective and non-selective beta blockers for prevention of vascular events in patients with acute coronary syndrome or heart failure. *Neth J Med*. 2009;67:284–294.
  143. De Lima LG, Soares B, Saconato H, da Silva EMK, Atallah ÁN. Beta blockers for preventing stroke recurrence (Protocol). *Cochrane Database Syst Rev*. 2009;3:CD007890. doi:10.1002/14651858.CD007890. <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD007890/abstract>. Accessed September 22, 2011.
  144. Gurfinkel EP, Leon de la Fuente R, Mendiz O, Mautner B. Flu vaccination in acute coronary syndromes and planned percutaneous coronary interventions (FLUVACS) Study. *Eur Heart J*. 2004;25:25–31.
  145. Ciszewski A, Bilinska ZT, Brydak LB, Kepka C, Kruk M, Romanowska M, Ksiezyccka E, Przyluski J, Piotrowski W, Maczynska R, Ruzyllo W. Influenza vaccination in secondary prevention from coronary ischaemic events in coronary artery disease: FLUCAD study. *Eur Heart J*. 2008;29:1350–1358.
  146. Davis MM, Taubert K, Benin AL, Brown DW, Mensah GA, Baddour LM, Dunbar S, Krumholz HM. Influenza vaccination as secondary prevention for cardiovascular disease: a science advisory from the American Heart Association/American College of Cardiology [published correction appears in *Circulation*. 2006;114:e616]. *Circulation*. 2006;114:1549–1553.
  147. Centers for Disease Control and Prevention. Prevention and control of influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2010. *MMWR Morb Mortal Wkly Rep*. July 29, 2010;59(Early Release):1–62.
  148. Ziegelstein RC, Thombs BD, Coyne JC, de Jonge P. Routine screening for depression in patients with coronary heart disease: never mind. *J Am Coll Cardiol*. 2009;54:886–890.
  149. Thombs BD, de Jonge P, Coyne JC, Whooley MA, Frasure-Smith N, Mitchell AJ, Zuidersma M, Eze-Nliam C, Lima BB, Smith CG, Soderlund K, Ziegelstein RC. Depression screening and patient outcomes in cardiovascular care: a systematic review. *JAMA*. 2008;300:2161–2171.
  150. US Preventive Services Task Force. Screening for depression in adults: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2009;151:784–792.
  151. Rollman BL, Belnap BH, LeMenager MS, Mazumdar S, Houck PR, Counihan PJ, Kapoor WN, Schulberg HC, Reynolds CF 3rd. Telephone-delivered collaborative care for treating post-CABG depression: a randomized controlled trial. *JAMA*. 2009;302:2095–2103.
  152. Larsen KK, Agerbo E, Christensen B, Sondergaard J, Vestergaard M. Myocardial infarction and risk of suicide: a population-based case-control study. *Circulation*. 2010;122:2388–2393.
  153. Taylor RS, Dalal H, Jolly K, Moxham T, Zawada A. Home-based versus centre-based cardiac rehabilitation. *Cochrane Database Syst Rev*. 2010;1:CD007130. doi:1002/14651858.CD007130.pub2. <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD007130.pub2/full>. Accessed September 22, 2011.
  154. Clark AM, Hartling L, Vandermeer B, McAlister FA. Meta-analysis: secondary prevention programs for patients with coronary artery disease. *Ann Intern Med*. 2005;143:659–672.
  155. Hambrecht R, Walther C, Mobius-Winkler S, Gielen S, Linke A, Conradi K, Erbs S, Kluge R, Kendziorra K, Sabri O, Sick P, Schuler G. Percutaneous coronary angioplasty compared with exercise training in patients with stable coronary artery disease: a randomized trial. *Circulation*. 2004;109:1371–1378.
  156. Hammill BG, Curtis LH, Schulman KA, Whellan DJ. Relationship between cardiac rehabilitation and long-term risks of death and myocardial infarction among elderly Medicare beneficiaries. *Circulation*. 2010;121:63–70.
  157. Leon AS, Franklin BA, Costa F, Balady GJ, Berra KA, Stewart KJ, Thompson PD, Williams MA, Lauer MS. Cardiac rehabilitation and secondary prevention of coronary heart disease: an American Heart Association scientific statement from the Council on Clinical Cardiology (Subcommittee on Exercise, Cardiac Rehabilitation, and Prevention) and the Council on Nutrition, Physical Activity, and Metabolism (Subcommittee on Physical Activity) [published correction appears in *Circulation*. 2005;111:1717]. *Circulation*. 2005;111:369–376.
  158. McDermott M, Ades P, Guralnik JM, Dyer A, Ferrucci L, Liu K, Nelson M, Lloyd-Jones D, Van Horn L, Garside D, Kibbe M, Domanchuk K, Stein J, Liao Y, Tao H, Green D, Pearce WH, Schneider JR, McPherson D, Laing ST, McCarthy WJ, Shroff A, Criqui MH. Treadmill exercise and resistance training in patients with peripheral arterial disease with and without intermittent claudication: a randomized controlled trial. *JAMA*. 2009;301:165–174.
  159. O'Connor CM, Whellan DJ, Lee KL, Keteyian SJ, Cooper LS, Ellis SJ, Leifer ES, Kraus WE, Kitzman DW, Blumenthal JA, Rendall DS, Miller NH, Fleg JL, Schulman KA, McKelvie RS, Zannad F, Piña IL; HF-ACTION Investigators. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. *JAMA*. 2009;301:1439–1450.
  - 159a. Belardinelli R, Georgiou D, Cianci G, Purcaro A. Randomized, controlled trial of long-term moderate exercise training in chronic heart failure: effects on functional capacity, quality of life, and clinical outcome. *Circulation*. 1999;99:1173–1182.
  - 159b. ExTraMATCH Collaborative. Exercise training meta-analysis of trials in patients with chronic heart failure (ExTraMATCH). *BMJ*. doi: 10.1136/bmj.37938.645220.EE (published 16 January 2004).
  - 159c. Passino C, Severino S, Poletti R, Piepoli MF, Mammì C, Clerico A, Gabutti A, Nassi G, Emdin M. Aerobic training decreases B-type natriuretic peptide expression and adrenergic activation in patients with heart failure. *J Am Coll Cardiol*. 2006;47:1835–1839.
  160. Clark AM, Haykowsky M, Kryworuchko J, MacClure T, Scott J, DesMeules M, Luo W, Liang Y, McAlister FA. A meta-analysis of randomized control trials of home-based secondary prevention programs for coronary artery disease. *Eur J Cardiovasc Prev Rehabil*. 2010;17:261–270.
  161. Thomas RJ, King M, Lui K, Oldridge N, Piña IL, Spertus J. AACVPR/ACC/AHA 2007 performance measures on cardiac rehabilitation for

- referral to and delivery of cardiac rehabilitation/secondary prevention services. *Circulation*. 2007;116:1611–1642.
162. Thompson PD, Buchner D, Pina IL, Balady GJ, Williams MA, Marcus BH, Berra K, Blair SN, Costa F, Franklin B, Fletcher GF, Gordon NF, Pate RR, Rodriguez BL, Yancey AK, Wenger NK. Exercise and physical activity in the prevention and treatment of atherosclerotic cardiovascular disease: a statement from the Council on Clinical Cardiology (Subcommittee on Exercise, Rehabilitation, and Prevention) and the Council on Nutrition, Physical Activity, and Metabolism (Subcommittee on Physical Activity). *Circulation*. 2003;107:3109–3116.
  163. Walther C, Möbius-Winkler S, Linke A, Bruegel M, Thiery J, Schuler G, Halbrecht R. Regular exercise training compared with percutaneous intervention leads to a reduction of inflammatory markers and cardiovascular events in patients with coronary artery disease. *Eur J Cardiovasc Prev Rehabil*. 2008;15:107–112.
  164. Watson L, Ellis B, Leng GC. Exercise for intermittent claudication. *Cochrane Database Syst Rev*. 2008;4:CD000990.
  165. Wenger NK, Froelicher ES, Ades PA, Berra K, Blumenthal JA, Certo CME, Dattilo AM, Davis D, DeBusk RF, Drozda JP, Fletcher BJ, Franklin BA, Gaston H, Greenland P, McBride PE, McGregor CG, Oldridge NB, Piscatella JC, Rogers FJ. *Cardiac Rehabilitation: Clinical Practice Guideline 17*. Washington, DC: US Department of Health & Human Services; 1995. AHCPR publication No. 96-0672.
  166. Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, Joyal SV, Hill KA, Pfeffer MA, Skene AM; Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 Investigators. Intensive versus moderate lipid lowering with statins after acute coronary syndromes [published correction appears in *N Engl J Med*. 2006;354:778]. *N Engl J Med*. 2004;350:1495–1504.
  167. Shepherd J, Blauw GJ, Murphy MB, Bollen EL, Buckley BM, Cobbe SM, Ford I, Gaw A, Hyland M, Jukema JW, Kamper AM, Macfarlane PW, Meinders AE, Norrie J, Packard CJ, Perry IJ, Stott DJ, Sweeney BJ, Twomey C, Westendorp RG; PROSPER Study Group. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet*. 2002;360:1623–1630.
  168. Sever PS, Dahlöf B, Poulter NR, Wedel H, Beevers G, Caulfield M, Collins R, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, Nieminen M, O'Brien E, Ostergren J; ASCOT Investigators. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet*. 2003;361:1149–1158.
  169. Grundy SM, Cleeman JI, Merz CN, Brewer HB Jr, Clark LT, Hunninghake DB, Pasternak RC, Smith SC Jr, Stone NJ; for the Coordinating Committee of the National Cholesterol Education Program. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines [published correction appears in *Circulation*. 2004;110:763]. *Circulation*. 2004;110:227–239.
  170. Roger VL, Go AS, Lloyd-Jones DM, Adams RJ, Berry JD, Brown TM, Carnethon MR, Dai S, de Simone G, Ford ES, Fox CS, Fullerton HJ, Gillespie C, Greenlund KJ, Hailpern SM, Heit JA, Ho PM, Howard VJ, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Makuc DM, Marcus GM, Marelli A, Matchar DB, McDermott MM, Meigs JB, Moy CS, Mozaffarian D, Mussolino ME, Nichol G, Paynter NP, Rosamond WD, Sorlie PD, Stafford RS, Turan TN, Turner MB, Wong ND, Wylie-Rosett J; on behalf of the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2011 update: a report from the American Heart Association [published correction appears in *Circulation*. 2011;123:e240]. *Circulation*. 2011;123:e18–e209.
  171. American Heart Association Web site. Focus on quality. [http://www.heart.org/HEARTORG/HealthcareProfessional/GetWithTheGuidelines/HFStroke/Focus-on-Quality-Home-Page\\_UCM\\_306348\\_SubHomePage.jsp](http://www.heart.org/HEARTORG/HealthcareProfessional/GetWithTheGuidelines/HFStroke/Focus-on-Quality-Home-Page_UCM_306348_SubHomePage.jsp). Accessed July 14, 2011.
  172. AHA/ADA/ACS. The Guideline Advantage Program. <http://www.th guidelineadvantage.org>. Accessed July 14, 2011.
  173. PINNACLE Registry. <http://www.pinnacleregistry.org>. Accessed July 14, 2011.
  174. Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, Chambers CE, Ellis SG, Guyton RA, Hollenberg SM, Khot UN, Lange RA, Mauri L, Mehran R, Moussa ID, Mukherjee D, Nallamothu BK, Ting H. 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. *Circulation*. In press.
  175. Rooke TW, Hirsch AT, Misra S, Sidawy AN, Beckman JA, Findeiss L, Golzarian J, Gornik HL, Halperin JL, Jaff MR, Moneta GL, Olin JW, Stanley JC, White CJ, White JV, Zierler RE. 2011 ACCF/AHA focused update of the guideline for the management of patients with peripheral artery disease (updating the 2005 guideline): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2011;124:2020–2045.
  176. Hirsch AT, Haskal ZJ, Hertzner NR, Bakal CW, Creager MA, Halperin JL, Hiratzka LF, Murphy WRC, Olin JW, Puschett JB, Rosenfield KA, Sacks D, Stanley JC, Taylor LM Jr, White CJ, White J, White RA. ACC/AHA 2005 guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): executive summary: a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease). *Circulation*. 2006;113:1474–1547.

KEY WORDS: AHA Scientific Statements ■ secondary prevention ■ coronary disease ■ vascular disease ■ risk factors

**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**

Sidney C. Smith, Jr, Emelia J. Benjamin, Robert O. Bonow, Lynne T. Braun, Mark A. Creager, Barry A. Franklin, Raymond J. Gibbons, Scott M. Grundy, Loren F. Hiratzka, Daniel W. Jones, Donald M. Lloyd-Jones, Margo Minissian, Lori Mosca, Eric D. Peterson, Ralph L. Sacco, John Spertus, James H. Stein and Kathryn A. Taubert

*Circulation*. 2011;124:2458-2473; originally published online November 3, 2011;  
doi: 10.1161/CIR.0b013e318235eb4d

*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231  
Copyright © 2011 American Heart Association, Inc. All rights reserved.  
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://circ.ahajournals.org/content/124/22/2458>

An erratum has been published regarding this article. Please see the attached page for:  
</content/131/15/e408.full.pdf>

**Permissions:** Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the [Permissions and Rights Question and Answer](#) document.

**Reprints:** Information about reprints can be found online at:  
<http://www.lww.com/reprints>

**Subscriptions:** Information about subscribing to *Circulation* is online at:  
<http://circ.ahajournals.org/subscriptions/>



# Correction

In the article by Smith et al, “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,” which published online November 3, 2011, and appeared with the November 29, 2011, issue of the journal (*Circulation*. 2011;124:2458–2473. DOI: 10.1161/CIR.0b013e318235eb4d.), several corrections were needed.

1. In Table 1, the Antiplatelet agents/anticoagulants section on page 2461, Class I, recommendation 4, the recommendation read,

4. In patients with extracranial carotid or vertebral atherosclerosis who have had ischemic stroke or TIA, treatment with aspirin alone (75–325 mg daily), clopidogrel alone (75 mg daily), or the combination of aspirin plus extended-release dipyridamole (25 mg and 200 mg twice daily, respectively) should be started and continued.<sup>91,104,116</sup> (*Level of Evidence: B*)

The recommendation Level of Evidence has changed to “A”; the recommendation now reads,

4. In patients with extracranial carotid or vertebral atherosclerosis who have had ischemic stroke or TIA, treatment with aspirin alone (75–325 mg daily), clopidogrel alone (75 mg daily), or the combination of aspirin plus extended-release dipyridamole (25 mg and 200 mg twice daily, respectively) should be started and continued.<sup>91,104,116</sup> (*Level of Evidence: A*)

2. In Table 1, the Antiplatelet agents/anticoagulants section on page 2461, Class I, recommendation 6, first bullet, the recommendation read,

6. Antiplatelet therapy is recommended in preference to anticoagulant therapy with warfarin or other vitamin K antagonists to treat patients with atherosclerosis.<sup>93,94,105,110</sup> (*Level of Evidence: A*)
  - If there is a compelling indication for anticoagulant therapy, such as atrial fibrillation, prosthetic heart valve, left ventricular thrombus, or concomitant venous thromboembolic disease, warfarin should be administered in addition to the low-dose aspirin (75–81 mg daily).<sup>95,99–102</sup> (*Level of Evidence: A*)

The bullet now reads,

- If there is a compelling indication for anticoagulant therapy, such as atrial fibrillation, prosthetic heart valve, left ventricular thrombus, or concomitant venous thromboembolic disease, warfarin should be administered.<sup>95,99–102</sup> (*Level of Evidence: A*) (NOTE: Patients receiving low-dose aspirin for atherosclerosis should continue to receive it.)

The authors regret the errors.

These corrections have been made to the current online version of the article, which is available at <http://circ.ahajournals.org/content/124/22/2458>.