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AHA/ACC Guidelines for Secondary Prevention for Patients With Coronary and Other Atherosclerotic Vascular Disease: 2006 Update

Sidney C. Smith Jr.

Jerilyn Allen

Steven N. Blair

University of South Carolina - Columbia, sblair@mailbox.sc.edu

Robert O. Bonow

Lawrence M. Brass

See next page for additional authors

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Author(s)

Sidney C. Smith Jr., Jerilyn Allen, Steven N. Blair, Robert O. Bonow, Lawrence M. Brass, Gregg C. Fonarow, Scott M. Grundy, Loren Hiratzka, Daniel Jones, Harlan M. Krumholz, Lori Mosca, Richard C. Pasternak, Thomas A. Pearson, Marc A. Pfeffer, and Kathryn A. Taubert

AHA/ACC Guidelines for Secondary Prevention for Patients With Coronary and Other Atherosclerotic Vascular Disease: 2006 Update

Endorsed by the National Heart, Lung, and Blood Institute

Sidney C. Smith, Jr, MD; Jerilyn Allen, RN, ScD; Steven N. Blair, PED; Robert O. Bonow, MD; Lawrence M. Brass, MD†; Gregg C. Fonarow, MD; Scott M. Grundy, MD, PhD; Loren Hiratzka, MD; Daniel Jones, MD; Harlan M. Krumholz, MD; Lori Mosca, MD, PhD, MPH; Richard C. Pasternak, MD*; Thomas Pearson, MD, MPH, PhD; Marc A. Pfeffer, MD, PhD; Kathryn A. Taubert, PhD

Since the 2001 update of the American Heart Association (AHA)/American College of Cardiology (ACC) consensus statement on secondary prevention,¹ important evidence from clinical trials has emerged that further supports and broadens the merits of aggressive risk-reduction therapies for patients with established coronary and other atherosclerotic vascular disease, including peripheral arterial disease, atherosclerotic aortic disease, and carotid artery disease. This growing body of evidence confirms that aggressive comprehensive risk factor management improves survival, reduces recurrent events and the need for interventional procedures, and improves quality of life for these patients.

Compelling evidence from recent clinical trials and revised practice guidelines provided the impetus for this update of the 2001 recommendations with evidence-based results (Table 1). Classification of Recommendations and Level of Evidence are expressed in ACC/AHA format, as detailed in Tables 2 and 3. Recommendations made herein are based largely on major practice guidelines from the National Institutes of Health and ACC/AHA. In many cases, these practice guidelines were supplemented by research findings published

after the publication of the primary reference(s). Thus, the development of the present statement involved a process of partial adaptation of other guideline statements and reports and supplemental literature searches.^{2–32} (For specific search criteria, see the Appendix.) The findings from additional lipid reduction trials^{33–37} involving more than 50 000 patients 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.⁶ 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^{8,9} demonstrated cardiovascular benefit for lipid lowering significantly below current cholesterol goal levels for those with chronic CHD. These new trials allow for alterations in guidelines, 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 such patients. When the

*Dr Pasternak withdrew from the Writing Group on June 22, 2004, when he accepted an offer of employment as Vice President, Clinical Research, Cardiovascular and Atherosclerosis, at Merck Research Laboratories. The remaining members of the Writing Group were advised of his change in status before this Scientific Statement was finalized, and they affirmed their support of the Statement with subsequent revisions after his departure.

†Deceased.

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TABLE 1. AHA/ACC Secondary Prevention for Patients With Coronary and Other Vascular Disease*: 2006 Update

	Intervention Recommendations With Class of Recommendation and Level of Evidence
SMOKING: <u>Goal</u> Complete cessation. No exposure to environmental tobacco smoke.	<ul style="list-style-type: none"> • Ask about tobacco use status at every visit. I (B) • Advise every tobacco user to quit. I (B) • Assess the tobacco user's willingness to quit. I (B) • Assist by counseling and developing a plan for quitting. I (B) • Arrange follow-up, referral to special programs, or pharmacotherapy (including nicotine replacement and bupropion). I (B) • Urge avoidance of exposure to environmental tobacco smoke at work and home. I (B)
BLOOD PRESSURE CONTROL: <u>Goal</u> <140/90 mm Hg or <130/80 mm Hg if patient has diabetes or chronic kidney disease	<p>For all patients:</p> <ul style="list-style-type: none"> • Initiate or maintain 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. I (B) <p>For patients with blood pressure \geq140/90 mm Hg (or \geq130/80 mm Hg for individuals with chronic kidney disease or diabetes):</p> <ul style="list-style-type: none"> • As tolerated, add blood pressure medication, treating initially with β-blockers and/or ACE inhibitors, with addition of other drugs such as thiazides as needed to achieve goal blood pressure. I (A) <p>[For compelling indications for individual drug classes in specific vascular diseases, see Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7).]⁴</p>
LIPID MANAGEMENT: <u>Goal</u> LDL-C <100 mg/dL If triglycerides are \geq 200 mg/dL, non-HDL-C should be <130 mg/dL†	<p>For all patients:</p> <ul style="list-style-type: none"> • Start dietary therapy. Reduce intake of saturated fats (to <7% of total calories), <i>trans</i>-fatty acids, and cholesterol (to <200 mg/d). I (B) • Adding plant stanol/sterols (2 g/d) and viscous fiber (>10 g/d) will further lower LDL-C. • Promote daily physical activity and weight management. I (B) • Encourage increased consumption of omega-3 fatty acids in the form of fish‡ or in capsule form (1 g/d) for risk reduction. For treatment of elevated triglycerides, higher doses are usually necessary for risk reduction. Iib (B) <p>For lipid management:</p> <p>Assess fasting lipid profile in all patients, and within 24 hours of hospitalization for those with an acute cardiovascular or coronary event. For hospitalized patients, initiate lipid-lowering medication as recommended below before discharge according to the following schedule:</p> <ul style="list-style-type: none"> • LDL-C should be <100 mg/dL I (A), and • Further reduction of LDL-C to <70 mg/dL is reasonable. Iia (B) • If baseline LDL-C is \geq100 mg/dL, initiate LDL-lowering drug therapy.§ I (A) • If on-treatment LDL-C is \geq100 mg/dL, intensify LDL-lowering drug therapy (may require LDL-lowering drug combination). I (A) • If baseline LDL-C is 70 to 100 mg/dL, it is reasonable to treat to LDL-C <70 mg/dL. Iia (B) • If triglycerides are 200 to 499 mg/dL, non-HDL-C should be <130 mg/dL. I (B), and • Further reduction of non-HDL-C to <100 mg/dL is reasonable. Iia (B) • Therapeutic options to reduce non-HDL-C are: <ul style="list-style-type: none"> ⇒ More intense LDL-C-lowering therapy I (B), or ⇒ Niacin¶ (after LDL-C-lowering therapy) Iia (B), or ⇒ Fibrate therapy# (after LDL-C-lowering therapy) Iia (B) • If triglycerides are \geq500 mg/dL#, therapeutic options to prevent pancreatitis are fibrate¶ or niacin¶ before LDL-lowering therapy; and treat LDL-C to goal after triglyceride-lowering therapy. Achieve non-HDL-C <130 mg/dL if possible. I (C)
PHYSICAL ACTIVITY: <u>Goal</u> 30 minutes, 7 days per week (minimum 5 days per week)	<ul style="list-style-type: none"> • For all patients, assess risk with a physical activity history and/or an exercise test, to guide prescription. I (B) • For all patients, encourage 30 to 60 minutes of moderate-intensity aerobic activity, such as brisk walking, on most, preferably all, days of the week, supplemented by an increase in daily lifestyle activities (eg, walking breaks at work, gardening, household work). I (B) • Encourage resistance training 2 days per week. Iib (C) • Advise medically supervised programs for high-risk patients (eg, recent acute coronary syndrome or revascularization, heart failure). I (B)
WEIGHT MANAGEMENT: <u>Goal</u> Body mass index: 18.5 to 24.9 kg/m ² Waist circumference: men <40 inches, women <35 inches	<ul style="list-style-type: none"> • Assess body mass index and/or waist circumference on each visit and consistently encourage weight maintenance/reduction through an appropriate balance of physical activity, caloric intake, and formal behavioral programs when indicated to maintain/achieve a body mass index between 18.5 and 24.9 kg/m². I (B) • If waist circumference (measured horizontally at the iliac crest) is \geq35 inches in women and \geq40 inches in men, initiate lifestyle changes and consider treatment strategies for metabolic syndrome as indicated. I (B) • The initial goal of weight loss therapy should be to reduce body weight by approximately 10% from baseline. With success, further weight loss can be attempted if indicated through further assessment. I (B)

TABLE 1. Continued

	Intervention Recommendations With Class of Recommendation and Level of Evidence
DIABETES MANAGEMENT: Goal HbA _{1c} <7%	<ul style="list-style-type: none"> • Initiate lifestyle and pharmacotherapy to achieve near-normal HbA_{1c}. I (B) • Begin vigorous modification of other risk factors (eg, physical activity, weight management, blood pressure control, and cholesterol management as recommended above). I (B) • Coordinate diabetic care with patient's primary care physician or endocrinologist. I (C)
ANTIPLATELET AGENTS/ ANTICOAGULANTS:	<ul style="list-style-type: none"> • Start aspirin 75 to 162 mg/d and continue indefinitely in all patients unless contraindicated. I (A) ⇒ For patients undergoing coronary artery bypass grafting, aspirin should be started within 48 hours after surgery to reduce saphenous vein graft closure. Dosing regimens ranging from 100 to 325 mg/d appear to be efficacious. Doses higher than 162 mg/d can be continued for up to 1 year. I (B) • Start and continue clopidogrel 75 mg/d in combination with aspirin for up to 12 months in patients after acute coronary syndrome or percutaneous coronary intervention with stent placement (≥1 month for bare metal stent, ≥3 months for sirolimus-eluting stent, and ≥6 months for paclitaxel-eluting stent). I (B) ⇒ Patients who have undergone percutaneous coronary intervention with stent placement should initially receive higher-dose aspirin at 325 mg/d for 1 month for bare metal stent, 3 months for sirolimus-eluting stent, and 6 months for paclitaxel-eluting stent. I (B) • Manage warfarin to international normalized ratio=2.0 to 3.0 for paroxysmal or chronic atrial fibrillation or flutter, and in post–myocardial infarction patients when clinically indicated (eg, atrial fibrillation, left ventricular thrombus). I (A) • Use of warfarin in conjunction with aspirin and/or clopidogrel is associated with increased risk of bleeding and should be monitored closely. I (B)
RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM BLOCKERS:	<p>ACE inhibitors:</p> <ul style="list-style-type: none"> • Start and continue indefinitely in all patients with left ventricular ejection fraction ≤40% and in those with hypertension, diabetes, or chronic kidney disease, unless contraindicated. I (A) • Consider for all other patients. I (B) • Among lower-risk patients with normal left ventricular ejection fraction in whom cardiovascular risk factors are well controlled and revascularization has been performed, use of ACE inhibitors may be considered optional. IIa (B) <p>Angiotensin receptor blockers:</p> <ul style="list-style-type: none"> • Use in patients who are intolerant of ACE inhibitors and have heart failure or have had a myocardial infarction with left ventricular ejection fraction ≤40%. I (A) • Consider in other patients who are ACE inhibitor intolerant. I (B) • Consider use in combination with ACE inhibitors in systolic-dysfunction heart failure. IIb (B) <p>Aldosterone blockade:</p> <ul style="list-style-type: none"> • Use in post–myocardial infarction patients, without significant renal dysfunction** or hyperkalemia††, who are already receiving therapeutic doses of an ACE inhibitor and β-blocker, have a left ventricular ejection fraction ≤40%, and have either diabetes or heart failure. I (A)
β-BLOCKERS:	<ul style="list-style-type: none"> • Start and continue indefinitely in all patients who have had myocardial infarction, acute coronary syndrome, or left ventricular dysfunction with or without heart failure symptoms, unless contraindicated. I (A) Consider chronic therapy for all other patients with coronary or other vascular disease or diabetes unless contraindicated. IIa (C)
INFLUENZA VACCINATION:	Patients with cardiovascular disease should have an influenza vaccination. I (B)

*Patients covered by these guidelines include those with established coronary and other atherosclerotic vascular disease, including peripheral arterial disease, atherosclerotic aortic disease, and carotid artery disease. Treatment of patients whose only manifestation of cardiovascular risk is diabetes will be the topic of a separate AHA scientific statement. ACE indicates angiotensin-converting enzyme.

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

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

§When LDL-lowering medications are used, obtain at least a 30% to 40% reduction in LDL-C levels. If LDL-C <70 mg/dL is the chosen target, consider drug titration to achieve this level to minimize side effects and cost. When LDL-C <70 mg/dL is not achievable because of high baseline LDL-C levels, it generally is possible to achieve reductions of >50% in LDL-C levels by either statins or LDL-C-lowering drug combinations.

||Standard dose of statin with ezetimibe, bile acid sequestrant, or niacin.

¶The combination of high-dose statin+fibrate can increase risk for severe myopathy. Statin doses should be kept relatively low with this combination. Dietary supplement niacin must not be used as a substitute for prescription niacin.

#Patients with very high triglycerides should not consume alcohol. The use of bile acid sequestrant is relatively contraindicated when triglycerides are >200 mg/dL.

**Creatinine should be <2.5 mg/dL in men and <2.0 mg/dL in women.

††Potassium should be <5.0 mEq/L.

<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. Moreover, this guideline for patients with atherosclerotic disease does not modify the recommendations of the 2004 ATP III update for patients without atherosclerotic disease who have diabetes or multiple risk factors and a

TABLE 2. Classification of Recommendations and Level of Evidence***Classification of Recommendations**

- Class I: Conditions for which there is evidence and/or general agreement that a given procedure or treatment is beneficial, useful, and effective.
- Class II: Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment.
- Class IIa: Weight of evidence/opinion is in favor of usefulness/efficacy.
- Class IIb: Usefulness/efficacy is less well established by evidence/opinion.
- Class III: Conditions for which there is evidence and/or general agreement that a procedure/treatment is not useful/effective and in some cases may be harmful.

Level of Evidence

- Level of Evidence A: Data derived from multiple randomized clinical trials or meta-analyses.
- Level of Evidence B: Data derived from a single randomized trial or nonrandomized studies.
- Level of Evidence C: Only consensus opinion of experts, case studies, or standard-of-care.

*Classification of Recommendations and Level of Evidence are expressed in the ACC/AHA format and described in more detail in Table 3.

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.

Trials involving other secondary prevention therapies also have influenced major practice guidelines used to formulate the recommendations in this update. Thus, specific recommendations for clopidogrel use in post-acute coronary syndrome or post-percutaneous coronary intervention-stented patients are now included in this 2006 update. The present update also recommends 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. Finally, recently published findings of a trial involving angiotensin-converting enzyme inhibitor therapy among patients at relatively low risk with stable coronary disease and normal left ventricular function influenced the recommendations.²⁶

The writing group has for the first time added a recommendation 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.³⁸

The writing group emphasizes the importance of giving consideration to the use of cardiovascular medications that have been proved 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 11 years since the 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 13 million for coronary heart disease alone) 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 ACC recommend the use of programs such as the AHA's Get With The Guidelines³⁹ or the ACC's Guidelines Applied to Practice⁴⁰ to identify appropriate patients for therapy, provide practitioners with useful reminders based on the guidelines, and continuously assess the success achieved in providing these therapies to the patients who can benefit from them.

TABLE 3. Applying Classification of Recommendations and Level of Evidence

“Size of Treatment Effect”	
<p>Class I <i>Benefit >>>> Risk</i></p> <p>Procedure/Treatment SHOULD be performed/administered</p> <ul style="list-style-type: none"> • Recommendation that procedure or treatment is useful/effective • Sufficient evidence from multiple randomized trials or meta-analyses 	<p>Class IIa <i>Benefit >>> Risk</i> <i>Additional studies with focused objectives needed</i></p> <p>IT IS REASONABLE to perform procedure/administer treatment</p> <ul style="list-style-type: none"> • Recommendation in favor of treatment or procedure being useful/effective • Some conflicting evidence from multiple randomized trials or meta-analyses
<p>Class IIb <i>Benefit ≥ Risk</i> <i>Additional studies with broad objectives needed; Additional registry data would be helpful</i></p> <p>Procedure/Treatment MAY BE CONSIDERED</p> <ul style="list-style-type: none"> • Recommendation’s usefulness/efficacy less well established • Greater conflicting evidence from multiple randomized trials or meta-analyses 	<p>Class III <i>Risk ≥ Benefit</i> <i>No additional studies needed</i></p> <p>Procedure/Treatment should NOT be performed/administered SINCE IT IS NOT HELPFUL AND MAY BE HARMFUL</p> <ul style="list-style-type: none"> • Recommendation that procedure or treatment not useful/effective and may be harmful • Sufficient evidence from multiple randomized trials or meta-analyses
<p>Level A <i>Multiple (3-5) population risk strata evaluated*</i> <i>General consistency of direction and magnitude of effect</i></p>	<p>Level B <i>Limited (2-3) population risk strata evaluated*</i></p>
<p>Level C <i>Very limited (1-2) population risk strata evaluated*</i></p>	<p>Suggested phrases for writing recommendations †</p> <p>should be recommended</p> <p>is indicated</p> <p>is useful/effective/beneficial</p>

is not recommended
is not indicated
should not be useful/effective/beneficial
may/might be considered
may/might be reasonable
usefulness/efficacy is unknown /unclear/uncertain or not well established

*Data available from clinical trials or registries about the usefulness/efficacy in different sub-populations, such as gender, age, history of diabetes, history of prior MI, history of heart failure, and prior aspirin use. 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. Even though randomized trials are not available, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

†In 2003, the ACC/AHA Task Force on Practice Guidelines developed a list of suggested phrases to use when writing recommendations. All recommendations in this guideline have been written in full sentences that express a complete thought, such that a recommendation, even if separated and presented apart from the rest of the document (including headings above sets of recommendations), would still convey the full intent of the recommendation. It is hoped that this will increase readers’ comprehension of the guidelines and will allow queries at the individual recommendation level.

Appendix

Appendix: References and Supplemental Search Criteria Used to Support Each Recommendation and Level of Evidence

Recommendation	References and Supplemental Search Criteria
SMOKING:	Primary reference(s) used: 2, 3, 21, 22 Supplemental search done? No
BLOOD PRESSURE:	Primary reference(s) used: 2, 4 Supplemental search done? Yes Database(s) used: PubMed and EMBASE for all English-language human studies Key words: PubMed: <i>blood pressure</i> OR <i>hypertension</i> AND <i>practice guidelines</i> and/or <i>prevention</i> and/or <i>clinical trial</i> and/or <i>pharmacology</i> EMBASE: <i>secondary prevention</i> OR <i>guidelines</i> AND <i>blood pressure</i> AND <i>Cochrane review</i> OR <i>controlled clinical trial</i> OR <i>randomized controlled trial</i> AND <i>pharmacology</i> OR <i>hypertension</i> AND <i>Cochrane review</i> OR <i>controlled clinical trial</i> OR <i>randomized controlled trial</i> AND <i>pharmacology</i> Years searched: 2003–March 2005 Supplemental search did not alter recommendations.
LIPID MANAGEMENT:	Primary reference(s) used: 2, 5, 7 Supplemental search done? Yes Database used: PubMed for all English-language human studies Key words: <i>cholesterol/lipids/lipoproteins</i> AND <i>clinical trials</i> and/or <i>meta-analysis</i> and/or <i>practice guidelines</i> Years searched: 2002–November 2005 Supplemental search added references 6, 8–12, and 33–37 and altered the recommendations.
PHYSICAL ACTIVITY:	Primary reference(s) used: 2, 13–16, 21, 22 Supplemental search done? No
WEIGHT MANAGEMENT:	Primary reference(s) used: 2, 17–19, 21, 22 Supplemental search done? No
DIABETES MANAGEMENT:	Primary reference(s) used: 2, 20–22 Supplemental search done? No
ANTIPLATELET AGENTS/ ANTICOAGULANTS:	Primary reference(s) used: 2, 21–25, 27, 29 Supplemental search done? Yes, for use of ASA after CABG Database(s) used: PubMed for all English-language studies Key words: <i>antiplatelet agents</i> , <i>coronary artery bypass graft patency</i> Years searched: 2000–March 2005 Supplemental search did not alter the recommendations.
RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM BLOCKERS:	Primary reference(s) used: 2, 21, 22, 27, 28 Supplemental search done? Yes Database used: PubMed for all English-language studies Key words: <i>ACE inhibitor</i> or <i>angiotensin receptor antagonist</i> or <i>aldosterone antagonist</i> AND <i>clinical trials</i> and/or <i>meta-analysis</i> and/or <i>practice guidelines</i> Years searched: 2003–March 2005 Supplemental search added references 25 and 30–32 and altered the recommendations.
β-BLOCKERS:	Primary reference(s) used: 2, 21, 22, 27, 28 Supplemental search done? Yes Database used: PubMed for all English-language studies Key words: <i>beta blockers</i> AND <i>clinical trials</i> and/or <i>meta-analysis</i> and/or <i>practice guidelines</i> Years searched: 2002–March 2005 Supplemental search did not alter recommendations.
INFLUENZA VACCINATION:	Primary reference(s) used: 38 Supplemental search done? No

Disclosures

Writing Group Disclosures

Writing Group Member	Employment	Research Grant	Other Research Support	Speakers Bureau/Honoraria	Ownership Interest	Consultant/Advisory Board	Other
Sidney C. Smith Jr, MD	University of North Carolina, Chapel Hill	None	None	Honoraria: *Bayer, *BMS, *Sanofi-Aventis	None	*Sanofi-Aventis, *GlaxoSmithKline, *Eli Lilly, *Pfizer, *Merck	*Astra-Zeneca (Data Safety Monitoring Board)
Jerilyn Allen, RN, ScD	Johns Hopkins University, School of Nursing	None	None	None	None	*Board of Directors, Preventive Cardiovascular Nurses Association; Board of Directors, Southeast Lipid Association	None
Steven N. Blair, PED	Cooper Institute	†HealthTech, †Jenny Craig	None	Donates all honoraria to The Cooper Institute	None	†Miavita, †Life Fitness, †Jenny Craig	All items listed pertain to the Cooper Institute. Does not personally receive money from any of these.
Robert O. Bonow, MD	Northwestern University, School of Medicine	None	None	*Bristol-Myers Squibb Medical Imaging	None	*Bristol-Myers Squibb Medical Imaging, King Pharmaceuticals	These are no relationship to current writing committee; they are included for completeness.
Lawrence M. Brass, MD	Yale University	Bristol-Myers Squibb, Sanofi/Synthelabo*	None	Bristol-Myers Squibb, Sanofi/Synthelabo, Solvay Pharmaceuticals, Wyeth	None	AstraZeneca, Bristol-Myers Squibb, Johnson&Johnson, Merck, ONO Pharmaceuticals, Sanofi/Synthelabo, Solvay Pharmaceuticals, Wyeth	None
Gregg C. Fonarow, MD	University of California, Los Angeles	†GlaxoSmithKline, †Pfizer, †Medtronic	None	†GlaxoSmithKline, †Pfizer, †Merck-Schering Plough, †Bristol-Myers Squibb-Sanofi, *AstraZeneca, *Wyeth	None	†GlaxoSmithKline, †Pfizer, †Merck-Schering Plough, †Bristol-Myers Squibb-Sanofi, *AstraZeneca, *Wyeth	None
Scott M. Grundy, MD, PhD	University of Texas Southwestern	†Abbott, †GlaxoSmithKline	†Donald W. Reynolds Foundation, †VA Hospital	*Merck, Schering-Plough, *GlaxoSmithKline, *Pfizer, *Kos, *Bristol-Myers Squibb, *Lilly	*None	*Pfizer, *Sanofi-Aventis, *Abbott, *AstraZeneca, *GlaxoSmithKline	None
Loren Hiratzka, MD	TriHealth, Inc	None	None	None	None	None	None
Daniel Jones, MD	University of Mississippi Medical Center	None	None	None	None	None	None
Harlan M. Krumholz, MD	Yale University	†CV Therapeutics	None	None	None	*CV Therapeutics, †VHA Inc (Consultant), †United Healthcare (Advisory), †CFMC (Clin Coordinator), †MMS (Editorial Board)	
Lori Mosca, MD, PhD, MPH	New York Presbyterian	†NIH	*Pfizer	*Kos, *Abbott, *AstraZeneca, *Pfizer, *Sanofi-Aventis	None	*Kos, *Pfizer, *Sanofi-Aventis, *Schering-Plough	None
Thomas Pearson, MD, MPH, PhD	University of Rochester	†World Heart Federation, *Schering-Plough, *Pfizer, *Merck, *Sanofi-Aventis	None	*Kos, *Abbott, *AstraZeneca, *Pfizer, *Schering-Plough, *Bayer, *Merck	None	†Mediatech, *Johnson&Johnson, Merck, *Bayer, *Sanofi-Aventis	None
Marc A. Pfeffer, MD, PhD	Brigham & Women's Hospital	Amgen, Atherogenics, Novartis, Bristol-Myers Squibb, Sanofi-Synthelabo†	None	None	The Brigham & Women's Hospital has been awarded patents related to the use of inhibitors of the renin-angiotensin system in selected survivors. He is co-inventor. However, the licensing agreement is not linked to sales.†	†AstraZeneca, †Genzyme, †Guidant, †Mitsubishi, *Abbott, *Amgen, *Bristol-Myers Squibb, *CSL, *Novartis, *Sankyo, *Pfizer	None
Kathryn A. Taubert, PhD	American Heart Association	None	None	None	None	None	None

*Modest.

†Significant.

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 (a) the person receives \$10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) 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.

Reviewers' Disclosures

Reviewer	Employment	Research Grant	Other Research Support	Speakers Bureau/Honoraria	Ownership Interest	Consultant/Advisory Board	Other
Jonathan Abrams, MD	University of New Mexico Health Science Center	None	None	None	None	None	None
Joseph Alpert, MD	University of Arizona Department of Medicine	None	None	None	None	None	None
Jeffrey L. Anderson, MD	LDS Hospital Cardiology	Bristol-Myers Squibb (grant pending)	None	Bristol-Myers Squibb, Dia Dexus, Guilford, Merck, Johnson&Johnson/Merck, Merck-Schering, Sanofi-Aventis	None	Bristol-Myers Squibb, Guilford, Merck, Johnson&Johnson/Merck, Merck-Schering	None
Eric R. Bates, MD	University of Michigan Medical Center	None	None	None	None	None	None
Vera Bittner, MD	University of Alabama at Birmingham	NHLBI, Pfizer, AtheroGenics	None	Pfizer, Merck, Kos, Reliant	None	CV Therapeutics, Reliant	None
Ann Bolger, MD	University of California San Francisco	None	None	None	None	None	None
Roger S. Blumenthal, MD	Johns Hopkins Hospital	Merck, Pfizer	None	Pfizer, Merck, AstraZeneca, Kos, Schering-Plough	None	None	None
Prakash Deedwania, MD	University of California San Francisco	Pfizer, AstraZeneca	None	None	None	Pfizer, AstraZeneca, Novartis	None
Mark J. Eisenberg, MD	McGill University	None	None	None	None	None	None
Gerald Fletcher, MD	Mayo Clinic	None	None	None	None	None	None
Alan D. Forker, MD	St. Lukes Hospital	Pfizer, Merck, Kos, Novartis, Sankyo, Bristol-Myers Squibb	None	Pfizer, Merck, Takeda	None	None	None
Timothy Gardner, MD	Clinical Practices of the University of Pennsylvania	None	None	None	None	None	None
Cindy L. Grines, MD	William Beaumont Hospital	Berlex, Pfizer, GlaxoSmithKline, Aventis, Guidant Eli Lilly, SCIMED, Johnson&Johnson, Amersham Health, Otsuka, Esperion Therapeutics, Innercool Therapies, AstraZeneca	None	None	None	Innercool Therapies, Pfizer, Sanofi-Synthelabo, Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership, GlaxoSmithKline Global Cardiovascular Advisory Board	None
Suzanne Hughes, MSN, RN	None	None	Kos Pharmaceuticals	None	Guidant Corporation, Johnson&Johnson Merck	Freelance writer—honoraria paid by the ACCF; Associate Editor, <i>Cardiosource</i>	None
Edgar J. Kenton, MD	Lankenau Hospital	None	None	None	None	None	None
Marian Limacher, MD	University of Florida	Boehringer Ingelheim	NIH, NHLBI	Kos Pharmaceuticals	None	NIH Advisory Committee on Research on Women's Health	None
Jonathan R. Lindner, MD	University of Virginia	None	None	None	None	None	None
Janet B. Long, MSN, ACNP	University Cardiology Foundation	None	None	AstraZeneca	None	None	None
Patrick McBride, MD	University of Wisconsin Medical School	None	None	Kos, Merck, Pfizer, Sanyko, Schering Plough	None	Merck	None
Dale Owen, MD	None	None	None	None	None	None	None
Rita F. Redberg, MD, MSc	None	None	None	None	None	None	None
Samuel J. Shubrooks, Jr, MD	Harvard Medical School	None	None	None	None	None	None
Robert A. Vogel, MD	University of Maryland Hospital	Pfizer, Novartis, Schering-Plough	None	Pfizer, Merck	None	None	None

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