

# 2011 ACCF/AHA/HRS Focused Update on the Management of Patients With Atrial Fibrillation (Update on Dabigatran)

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

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## Preamble

A primary challenge in the development of clinical practice guidelines is keeping pace with the stream of new data on which recommendations are based. In an effort to respond promptly to new evidence, the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) Task Force on Practice Guidelines (Task Force) has created a “focused update” process to revise the existing guideline recommendations that are affected by the evolving data or opinion. Before the initiation of this focused approach, periodic updates and revisions of existing guidelines required up to 3 years to complete. Now, however, new evidence will be reviewed in an ongoing fashion to more efficiently respond to important science and treatment trends that could have a major impact on patient outcomes and quality of care. Evidence will be reviewed at least twice a year, and updates will be initiated on an as-needed basis and completed as quickly as possible while maintaining the rigorous methodology that the ACCF and AHA have developed during their partnership of more than 20 years.

These updated guideline recommendations reflect a consensus of expert opinion after a thorough review primarily of late-breaking clinical trials identified through a broad-based vetting process as being important to the relevant patient population, as well as other new data deemed to have an impact on patient care (see Section 1.1, Methodology and Evidence Review, for details). This focused update is not intended to represent an update based on a full literature

review from the date of the previous guideline publication. Specific criteria/considerations for inclusion of new data include the following:

- publication in a peer-reviewed journal;
- large, randomized, placebo-controlled trial(s);
- nonrandomized data deemed important on the basis of results affecting current safety and efficacy assumptions;
- strength/weakness of research methodology and findings;
- likelihood of additional studies influencing current findings;
- impact on current and/or likelihood of need to develop new performance measure(s);
- request(s) and requirement(s) for review and update from the practice community, key stakeholders, and other sources free of relationships with industry or other potential bias;
- number of previous trials showing consistent results; and
- need for consistency with a new guideline or guideline revisions.

In analyzing the data and developing the recommendations and supporting text, the focused update writing group used evidence-based methodologies developed by the Task Force that are described elsewhere.<sup>1</sup> The committee reviewed and ranked evidence supporting current recommendations with the weight of evidence ranked as Level A if the data were derived from multiple randomized clinical trials or meta-analyses. The committee ranked available evidence as Level B when data were derived from a single randomized trial or nonrandomized studies. Evidence was ranked as Level C when the primary source of the recommendation was consensus opinion, case studies, or standard of care. In the narrative portions of these guidelines, evidence is generally presented in chronological order of development. Studies are identified as observational, retrospective, prospective, or randomized when appropriate. For certain conditions for which inadequate data are available, recommendations are based on expert consensus and clinical experience and ranked as Level C. An example is the use of penicillin for pneumococcal pneumonia, for which there are no randomized trials and treatment is based on clinical experience. When recommendations at Level C are supported by historical clinical data, appropriate references (including clinical reviews) are cited if available. For issues where sparse

**Table 1** Applying classification of recommendations and level of evidence

|   |  | SIZE OF TREATMENT EFFECT   |   |  |   |  |
|---|--|--|---|--|---|--|
|   |  | CLASS I<br><i>Benefit &gt;&gt;&gt; Risk</i><br>Procedure/Treatment <b>SHOULD</b> be performed/administered   | CLASS IIa<br><i>Benefit &gt;&gt; Risk</i><br><i>Additional studies with focused objectives needed</i><br><b>IT IS REASONABLE</b> to perform procedure/administer treatment  | CLASS IIb<br><i>Benefit ≥ Risk</i><br><i>Additional studies with broad objectives needed; additional registry data would be helpful</i><br>Procedure/Treatment <b>MAY BE CONSIDERED</b>                  | CLASS III <i>No Benefit</i> or CLASS III <i>Harm</i>  |  |
|   |  |  |   | Procedure/ Test  | Treatment   |  |
|   |  |  |   | COR III: No benefit  | No Proven Benefit   |  |
|   |  |  |   | COR III: Harm  | Excess Cost w/o Benefit or Harmful to Patients or Harmful   |  |
| ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT | LEVEL A<br>Multiple populations evaluated*<br>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<br>Limited populations evaluated*<br>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<br>Very limited populations evaluated*<br>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<br>is recommended<br>is indicated<br>is useful/effective/beneficial   | is reasonable<br>can be useful/effective/beneficial<br>is probably recommended or indicated   | may/might be considered<br>may/might be reasonable<br>usefulness/effectiveness is unknown/unclear/uncertain or not well established  | COR III: No Benefit<br><br>is not recommended<br>is not indicated<br>should not be done<br>is not useful/beneficial/effective   | COR III: Harm<br><br>potentially harmful<br>causes harm associated with excess morbidity/mortality<br>should not be done |
| Comparative effectiveness phrases <sup>†</sup>        |  | treatment/strategy A is recommended/indicated in preference to treatment B<br>treatment A should be chosen over treatment B  | treatment/strategy A is probably recommended/indicated in preference to treatment B<br>it is reasonable to choose treatment A over treatment B  |  |   |  |

\*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. 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.

†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.

data are available, a survey of current practice among the clinicians on the writing committee was the basis for Level C recommendations and no references are cited. The schema for classification of recommendation and level of evidence is summarized in Table 1, which also illustrates how the grading system provides an estimate of the size and the certainty of the treatment effect. A new addition to the ACCF/AHA methodology is a separation of the Class III recommendations to delineate whether the recommendation is determined to be of “no benefit” or associated with “harm” to the patient. In addition, in view of the increasing number of comparative effectiveness studies, comparator verbs and suggested phrases for writing recommendations

for the comparative effectiveness of one treatment/strategy with respect to another for Class I and IIa, Level A or B only have been added.

The Task Force makes every effort to avoid actual, potential, or perceived conflicts of interest that may arise as a result of relationships with industry and other entities (RWI) among the writing group. Specifically, all members of the writing group, as well as peer reviewers of the document, are asked to disclose all current relationships and those existing 12 months before initiation of the writing effort. In response to implementation of a newly revised RWI policy approved by the ACC and AHA, it is also required that the writing group chair plus a majority of the writing group (50%) have no *relevant* RWI.

All guideline recommendations require a confidential vote by the writing group and must be approved by a consensus of the members voting. Members who were recused from voting are noted on the title page of this document and in [Appendix 1](#). Members must recuse themselves from voting on any recommendation to which their RWI apply. Any writing group member who develops a new RWI during his or her tenure is required to notify guideline staff in writing. These statements are reviewed by the Task Force and all members during each conference call and/or meeting of the writing group and are updated as changes occur. For detailed information about guideline policies and procedures, please refer to the ACCF/AHA methodology and policies manual.<sup>1</sup> Authors' and peer reviewers' RWI pertinent to this guideline are disclosed in [Appendixes 1 and 2](#), respectively. In addition, to ensure complete transparency, writing group members' *comprehensive disclosure information*—including RWI not pertinent to this document—is available online as a supplement to this document. Disclosure information for the Task Force is also available online at [www.cardiosource.org/ACC/About-ACC/Leadership/Guidelines-and-Documents-Task-Forces.aspx](http://www.cardiosource.org/ACC/About-ACC/Leadership/Guidelines-and-Documents-Task-Forces.aspx). The work of the writing group was supported exclusively by the ACCF and AHA and Heart Rhythm Society (HRS) without commercial support. Writing group members volunteered their time for this effort.

The ACCF/AHA practice guidelines address patient populations (and healthcare providers) residing in North America. As such, drugs that are currently unavailable in North America are discussed in the text without a specific classification of recommendation. For studies performed in large numbers of subjects outside of North America, each writing group reviews the potential impact of different practice patterns and patient populations on the treatment effect and the relevance to the ACCF/AHA target population to determine whether the findings should inform a specific recommendation.

The ACCF/AHA practice guidelines are intended to assist healthcare providers in clinical decision making by describing a range of generally acceptable approaches for the diagnosis, management, and prevention of specific diseases or conditions. These practice guidelines represent a consensus of expert opinion after a thorough review of the available current scientific evidence and are intended to improve patient care. The guidelines attempt to define practices that meet the needs of most patients in most circumstances. The ultimate judgment regarding care of a particular patient must be made by the healthcare provider and patient in light of all the circumstances presented by that patient. Thus, there are circumstances in which deviations from these guidelines may be appropriate. Clinical decision making should consider the quality and availability of expertise in the area where care is provided. When these guidelines are used as the basis for regulatory or payer decisions, the goal should be improvement in quality of care. The Task Force recognizes that situations arise for which additional data are needed to better inform patient

care; these areas will be identified within each respective guideline when appropriate.

Prescribed courses of treatment in accordance with these recommendations are effective only if they are followed. Because lack of patient understanding and adherence may adversely affect outcomes, physicians and other healthcare providers should make every effort to engage the patient's active participation in prescribed medical regimens and lifestyles.

The recommendations in this focused update will be considered current until they are superseded by another focused update or the full-text guideline is revised. This focused update is published in the *Journal of the American College of Cardiology*, *Circulation*, and *HeartRhythm* as an update to the full-text guideline, and it is also available on the ACC ([www.cardiosource.org](http://www.cardiosource.org)), AHA ([my.americanheart.org](http://my.americanheart.org)), and HRS ([www.hrsonline.org](http://www.hrsonline.org)) World Wide Web sites. A revised version of the full-text guideline with links to the focused update is e-published in the March 15, 2011, issues of the *Journal of the American College of Cardiology* and *Circulation*. For easy reference, this online-only version denotes sections that have been updated.

Alice K. Jacobs, MD, FACC, FAHA  
Chair, ACCF/AHA Task Force on Practice Guidelines

## 1 Introduction

### 1.1 Methodology and Evidence Review

The publication of the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) trial was considered important enough to prompt a focused update of the ACC/AHA/ESC 2006 Guidelines for the Management of Patients With Atrial Fibrillation.<sup>2</sup> To provide clinicians with a comprehensive set of data, whenever deemed appropriate or when published, the absolute risk difference and number needed to treat or harm will be provided in the guideline, along with confidence intervals (CI) and data related to the relative treatment effects such as odds ratio, relative risk (RR), hazard ratio, or incidence rate ratio.

Consult the full-text version or executive summary of the ACC/AHA/ESC 2006 Guidelines for the Management of Patients With Atrial Fibrillation for policy on clinical areas not covered by the focused update.<sup>2</sup> The individual recommendations in this focused update will be incorporated into future revisions and/or updates of the full-text guideline.

### 1.2 Organization of the Writing Committee

For this focused update, all eligible members of the 2006 Atrial Fibrillation Writing Committee were invited to participate; those who agreed (referred to as the 2011 focused update writing group) were required to disclose all RWI relevant to the data under consideration. The HRS was invited to be a partner on this update and provided 3 representatives.

### 1.3 Document Review and Approval

This document was reviewed by 2 official reviewers each nominated by the ACCF, AHA, and HRS, and 5 individual

**Table 2** Recommendation for emerging antithrombotic agents

| 2011 Focused update recommendation  | Comments           |
|---|--------------------|
| Class I   |                    |
| 1. Dabigatran is useful as an alternative to warfarin for the prevention of stroke and systemic thromboembolism in patients with paroxysmal to permanent AF and risk factors for stroke or systemic embolization who do not have a prosthetic heart valve or hemodynamically significant valve disease, severe renal failure (creatinine clearance <15 mL/min) or advanced liver disease (impaired baseline clotting function). <sup>3</sup> (Level of Evidence: B) | New recommendation |

content reviewers (including members of the ACCF Electrophysiology Committee, the ACCF/AHA Task Force on Performance Measures, and the ACCF/AHA Atrial Fibrillation Data Standards Committee). All information on reviewers' RWI was collected and distributed to the writing committee and is published in this report (Appendix 2).

This document was approved for publication by the governing bodies of the ACCF, AHA, and HRS.

## 8 Management

This guideline update will focus on the use of dabigatran, a new antithrombotic agent that was recently approved by the US Food and Drug Administration (FDA), for the management of patients with atrial fibrillation (AF).

### 8.1.4.2.5 Recommendation for Use of Oral Direct Thrombin Inhibitor Anticoagulant Agents (See Table 2).

Dabigatran etexilate is a prodrug that is rapidly converted to the active direct thrombin (factor IIa) inhibitor dabigatran. This conversion is independent of cytochrome P-450, making drug-drug and drug-diet interactions less likely. Dabigatran is predominantly excreted via a renal pathway. Dabigatran was evaluated in a large, open-label, randomized trial (RE-LY) in which it was compared with warfarin (goal international normalized ratio [INR] 2.0 to 3.0) in 18 113 patients with nonvalvular AF.<sup>3</sup> Dabigatran was administered in fixed doses without laboratory monitoring of anticoagulation intensity. Eligible participants had at least 1 risk factor for stroke (previous stroke or transient ischemic attack or systemic embolism, left ventricular ejection fraction <40% or symptomatic heart failure [New York Heart Association class II or higher in the last 6 months], hypertension, age ≥75 years, or age 65 to 74 years with either diabetes mellitus or coronary artery disease). Exclusion criteria in RE-LY included a prosthetic heart valve or hemodynamically significant valvular heart disease, disabling or recent stroke, recent or pending surgery, recent or known bleeding disorders, uncontrolled hypertension, need for anticoagulation of disorders other than AF, planned ablation or surgery for AF, reversible causes of AF, severe renal dysfunction (creatinine clearance <30 mL/min), active liver disease, or pregnancy. Two doses of dabigatran

(110 mg and 150 mg twice daily) were evaluated. The mean age of participants was 71 years, 63.6% were male, half had prior long-term therapy with vitamin K antagonists, and the mean CHADS2 (Congestive heart failure, Hypertension, Age, Diabetes, prior Stroke) risk prediction score was 2.1. The primary outcome was all stroke (ischemic or hemorrhagic) or systemic embolism; safety outcomes included bleeding, liver dysfunction, and other adverse events.

Results of the RE-LY trial were published in 2009.<sup>3</sup> Rates for the primary outcome of all stroke (ischemic or hemorrhagic) or systemic embolism were 1.71% per year in the warfarin group. Dabigatran etexilate, 150 mg twice daily, reduced the rate by 34% (to 1.11% per year;  $P<0.001$  for superiority; RR 0.65; 95% CI: 0.52 to 0.81), and at this dose there was no increase in major bleeding.<sup>3</sup> Dabigatran etexilate, 110 mg twice daily, was also associated with a rate of stroke and systemic embolism (1.54% per year) that was noninferior to warfarin ( $P<0.001$  for noninferiority; RR with dabigatran: 0.90; 95% CI: 0.74 to 1.10), and at this dose there was a 20% reduction in major bleeding risk compared with warfarin ( $P=0.003$  for superiority). Rates of major bleeding were 3.57% per year for patients taking warfarin, 2.87% per year for those on dabigatran 110 mg twice daily ( $P=0.003$ ), and 3.32% per year for those on dabigatran 150 mg twice daily ( $P=0.32$ ). In the warfarin group, INR values were within the target range 64.4% of the time.<sup>4</sup>

In addition, the results showed other secondary benefits and adverse outcomes. For safety, both doses showed a reduction in life-threatening, intracranial, and total bleeding, including lower rates of intracerebral hemorrhage with both 150 mg and 110 mg twice-daily doses (from 0.38% per year in the warfarin group to 0.12% per year with dabigatran 110 mg twice daily [ $P<0.001$ ] and 0.10% per year with dabigatran 150 mg twice daily [ $P<0.001$ ]). Dyspepsia occurred more frequently with dabigatran (11.8% and 11.3% of patients in the low-dose [110 mg] and high-dose [150 mg] groups, respectively) compared to warfarin (5.8% of patients). Also, myocardial infarction was more frequent with dabigatran and occurred at rates of 0.82% (RR: 1.29; 95% CI: 0.96 to 1.75;  $P=0.09$ ) and 0.81% (RR: 1.27; 95% CI: 0.94 to 1.71;  $P=0.12$ ) with dabigatran, 110 mg and 150 mg twice daily, respectively, and 0.64% with warfarin.<sup>3,4</sup> Increased<sup>3</sup> or decreased<sup>5</sup> rates of myocardial infarction have been reported with other oral thrombin inhibitors in different patient populations; however, the increase in myocardial infarction seen in RE-LY was not statistically significant in the dabigatran groups.<sup>4</sup> In RE-LY, dabigatran did not cause hepatotoxicity.<sup>3</sup> Drug discontinuation rates were slightly higher in the dabigatran groups compared with warfarin. There was no difference in mortality with dabigatran compared with warfarin. Both dabigatran doses appeared to be noninferior to warfarin with respect to the primary efficacy outcome of stroke or systemic embolism. In addition, the 150-mg twice-daily dose was superior to warfarin with respect to stroke or systemic embolism, and the 110-mg twice-daily dose was superior to warfarin with respect to

major bleeding. There is no specific antidote for dabigatran, which has a half-life of 12 to 17 hours. Supportive therapy for severe hemorrhage may include transfusions of fresh-frozen plasma, packed red blood cells, or surgical intervention if appropriate.

Because of the twice-daily dosing and greater risk of nonhemorrhagic side effects with dabigatran, patients already taking warfarin with excellent INR control may have little to gain by switching to dabigatran. Selection of patients with AF and at least 1 additional risk factor for stroke who could benefit from treatment with dabigatran as opposed to warfarin should consider individual clinical features, including the ability to comply with twice-daily dosing, availability of an anticoagulation management program to sustain routine monitoring of INR, patient preferences, cost, and other factors.<sup>6</sup>

Dabigatran etexilate was approved by the FDA on October 19, 2010, for marketing in the United States for the prevention of stroke and systemic embolism in patients with non-valvular AF. A dose of 150 mg twice daily was approved for patients with a creatinine clearance  $>30$  mL/min, whereas in patients with severe renal insufficiency (creatinine clearance 15 to 30 mL/min) the approved dose is 75 mg twice daily, a dose currently marketed in the European Union but not evaluated in the RE-LY trial. There are no dosing recommendations for patients with creatinine clearance  $<15$  mL/min or patients on dialysis. The 110-mg twice-daily dose used in the RE-LY trial did not receive FDA

approval. The approval requires distribution of a medication guide with each prescription that details the risk of serious bleeding in patients receiving dabigatran in this open-label (or “unblinded”) trial.<sup>7</sup> Dabigatran is the first new oral anticoagulant to become available for clinical use in  $>50$  years.

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## Appendixes

### Appendix 1 Author Relationships With Industry and Other Entities—2011 ACCF/AHA/HRS Focused Update on the Management of Patients With Atrial Fibrillation (Update on Dabigatran)

| Committee Member      | Employment   | Consultant  | Speaker's Bureau                      | Ownership/ Partnership/ Principal | Personal Research  | Institutional, Organizational, or Other Financial Benefit | Expert Witness |
|-----------------------|--|---|---------------------------------------|-----------------------------------|--|---|----------------|
| L. Samuel Wann, Chair | Wisconsin Heart and Vascular Clinics—Chairman, Department of Cardiovascular Medicine   | None  | None                                  | None                              | None   | None  | None           |
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| Craig T. January      | University of Wisconsin, Madison—Professor of Medicine, Departments of Medicine (Division of Cardiovascular Medicine) and Physiology                     | None  | None                                  | None                              | None   | None  | None           |
| James E. Lowe         | Duke University Hospital   | None  | None                                  | None                              | None   | None  | None           |
| Richard L. Page       | University of Wisconsin, Madison—Professor of Medicine and Chairman of the Department of Medicine  | None  | None                                  | None                              | None   | None  | None           |
| David J. Slotwiner‡   | North Shore, Long Island Jewish Health Care System—Associate Director, Electrophysiology Laboratory  | None  | None                                  | None                              | ● Boehringer Ingelheim*  | None  | None           |
| William G. Stevenson  | Brigham and Women's Hospital, Cardiovascular Division—Director, Clinical Cardiac Electrophysiology Program   | None  | None                                  | None                              | None   | None  | None           |
| Cynthia M. Tracy      | George Washington University Medical Center—Associate Director, Division of Cardiology; George Washington University Hospital—Director, Cardiac Services | None  | None                                  | None                              | None   | None  | None           |

This table represents the relationships of committee members with industry and other entities that were determined to be relevant to this document. These relationships were reviewed and updated in conjunction with all meetings and/or conference calls of the writing committee during the document development process. The table does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of 5% or more of the voting stock or share of the business entity, or ownership of \$10 000 or more of the fair market value of the business entity; or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. A relationship is considered to be modest if it is less than significant under the preceding definition. Relationships in this table are modest unless otherwise noted.

\*Significant (greater than \$10 000) relationship.

†Recused from voting on Section 8.1.4.2.5, Recommendation for Use of Oral Direct Thrombin Inhibitor Anticoagulant Agents.

## Appendix 2 Reviewer Relationships With Industry and Other Entities—2011 ACCF/AHA/HRS Focused Update on the Management of Patients With Atrial Fibrillation (Update on Dabigatran)

| Reviewer               | Representation   | Consultant   | Speaker's Bureau | Ownership/ Partnership/ Principal | Personal Research   | Institutional, Organizational, or Other Financial Benefit | Expert Witness                          |
|------------------------|--|--|------------------|-----------------------------------|---|---|---|
| Hugh Calkins           | Official Reviewer—HRS and ACCF/AHA Task Force on Performance Measures  | • Medtronic  | None             | None                              | • Medtronic*  | None  | None                                    |
| A. John Camm           | Official Reviewer—ACCF Board of Trustees                               | • ARYx Pharmaceuticals<br>• Boehringer Ingelheim<br>• Daiichi Sankyo<br>• Medtronic<br>• Portola Pharmaceuticals | None             | None                              | None  | None  | • 2009, Plaintiff arbitration procedure |
| Christopher B. Granger | Official Reviewer—AHA  | • AstraZeneca<br>• Boehringer Ingelheim<br>• Bristol-Myers Squibb  | None             | None                              | • AstraZeneca*<br>• Boehringer Ingelheim<br>• Bristol-Myers Squibb* | None  | None                                    |
| Jonathan L. Halperin   | Official Reviewer—AHA and ACCF/AHA Task Force on Practice Guidelines   | • Boehringer Ingelheim<br>• Daiichi Sankyo<br>• Portola Pharmaceuticals  | None             | None                              | None  | None  | None                                    |
| Bradley P. Knight      | Official Reviewer—HRS  | None   | • Medtronic*     | None                              | • Medtronic*  | None  | None                                    |
| Allen J. Solomon       | Official Reviewer—ACCF Board of Governors                              | None   | None             | None                              | None  | None  | None                                    |
| Ralph G. Brindis       | Content Reviewer   | None   | None             | None                              | None  | None  | None                                    |
| Mark S. Link           | Content Reviewer   | None   | None             | None                              | None  | None  | None                                    |
| Frederick A. Masoudi   | Content Reviewer—ACCF/AHA Task Force on Performance Measures           | None   | None             | None                              | None  | None  | None                                    |
| Robert L. McNamara     | Content Reviewer—ACCF/AHA Atrial Fibrillation Data Standards Committee | • Boehringer Ingelheim   | None             | None                              | None  | None  | • 2010, Defendant anticoagulation       |
| Paul J. Wang           | Content Reviewer—ACCF Electrophysiology Committee                      | • Medtronic  | None             | None                              | None  | None  | None                                    |

This table represents the relationships of reviewers with industry and other entities that were disclosed at the time of peer review and determined to be relevant. It does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of 5% or more of the voting stock or share of the business entity, or ownership of \$10 000 or more of the fair market value of the business entity; or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. A relationship is considered to be modest if it is less than significant under the preceding definition. Relationships in this table are modest unless otherwise noted.

\*Significant (greater than \$10 000) relationship.

ACCF indicates American College of Cardiology Foundation; AHA, American Heart Association; and HRS, Heart Rhythm Society.

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