

SOCIETAL OVERVIEW

2015 ACC/HRS/SCAI Left Atrial Appendage Occlusion Device Societal Overview



A Professional Societal Overview from the American College of Cardiology, Heart Rhythm Society, and Society for Cardiovascular Angiography and Interventions

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Occlusion Device Societal Overview** 1511**PREAMBLE**

Left atrial appendage (LAA) occlusion devices have the potential to influence the clinical approach to stroke prevention in patients with atrial fibrillation (AF). A number of percutaneous techniques have been proposed, including intracardiac plugs and external ligation. Several devices have been adopted to various degrees in the United States and internationally. Only 1 (WATCHMAN, Boston Scientific, Marlborough, Massachusetts) has been evaluated in randomized controlled trials compared with the current standard of care. This device was recently approved for use in the United States by the Food and Drug Administration (FDA) as an alternative to warfarin for stroke prevention. Others are less well studied: the Amplatzer Cardiac Plug (St. Jude Medical, St. Paul, Minnesota), like the WATCHMAN, has been used widely outside of the United States under the Conformité Européenne (CE) mark, despite little published data to support its use; and the LARIAT (Sentreheart, Redwood City, California) is also CE marked, has received FDA 510(k) approval as a method of soft tissue approximation but not stroke prevention, and is being used off-label in clinical practice for LAA occlusion in the United States and internationally, although the evidence of its efficacy or safety is also lacking. Other percutaneous and surgical approaches to LAA occlusion are in use outside of the United States or are in development. It is anticipated that the use of LAA occlusion technologies in clinical practice will expand. The dissemination of this technology should proceed thoughtfully, guided by a coalition of stakeholders dedicated to delivering high-quality, patient-centered care while collecting the data necessary to determine optimal patient selection, effectiveness, and safety. This document seeks to highlight the critical issues surrounding LAA occlusion therapies and to facilitate the alignment of multiple interests, including those of patients and their families, primary care physicians,

general and geriatric cardiologists, other heart team members, procedural specialists* (i.e., electrophysiologists and interventional cardiologists), regulators, payers, professional societies, and industry.

The American College of Cardiology (ACC), the Heart Rhythm Society (HRS), and the Society for Cardiovascular Angiography and Interventions have collaborated in writing this overview as the first of a series of documents to address issues critical to the appropriate integration of new technologies into the care of patients with AF. In accordance with the ACC's policy on relationships with industry and other entities (RWI), relevant author disclosures are included in [Appendix 1](#) of this document. In the spirit of full disclosure, authors' comprehensive RWI information, which includes RWI not relevant to this document, is available online as a [data supplement](#) to this document. To ensure that a variety of constituencies/perspectives inform the final paper, RWI restrictions are not applied to participation in the external peer review process for clinical documents; however, for the purposes of full disclosure, all relevant RWI for reviewers, as well as their individual affiliations, are published in [Appendix 2](#). Final review and approval of the document were provided by the respective boards of the 3 professional societies. The writing group also includes a nonmedical representative with AF to provide a patient perspective during document development.

1. INTRODUCTION

Percutaneous LAA occlusion has the potential to change the clinical approach to stroke prevention in selected patients with AF. On the basis of data from large, prospective, randomized controlled trials, oral anticoagulants such as warfarin, factor Xa inhibitors, and direct thrombin inhibitors have become the current standard of care to reduce the risk of stroke in patients with risk factors, albeit at the expense of an increase in bleeding risk (1-3). Some patients with AF whose stroke risk profiles would favor anticoagulation have relative or absolute contraindications to anticoagulation. Others are unable or unwilling to adhere to long-term anticoagulation therapy. Thus, alternatives to pharmacological therapy to reduce the risk of stroke have been pursued.

In contrast to many technologies, percutaneous approaches to LAA occlusion have been developed simultaneously through multiple pathways, including the off-label use of FDA-approved devices (e.g., LARIAT,

*Procedures using LAA occlusion devices are typically performed either by electrophysiologists or interventional cardiologists. This document will use the term "procedural specialist" to apply to members of either subspecialty who implant LAA occlusion devices.

atrial and ventricular septal defect occlusion devices), use of devices intended for LAA occlusion available in other countries through local regulatory pathways, and the FDA Pivotal Trial Pathway for class III medical devices. To promote the diffusion of this technology in a manner that will optimize patient outcomes, it will be necessary to develop and implement new guidelines, expert consensus statements, requirements for training, operator credentialing, and institutional policies.

1.1. Key Questions

Several questions are relevant to the diffusion of percutaneous LAA occlusion device technologies into clinical practice:

1. Will the technology be available in all centers, or will it be restricted to specialized centers? If the latter, how will these centers be specified? What constitutes an LAA occlusion device center of excellence?
2. What training will be required for procedural specialists, and how will it be provided? What criteria will be utilized for the granting and maintenance of procedural privileges?
3. What clinical, procedural, administrative, and follow-up data should be collected, and by what mechanism, to ensure rigorous assessment of outcomes across centers and provide a framework for comparative effectiveness research, safety surveillance, and cost-effectiveness assessment?
4. How will the patient cohorts who are most and least likely to benefit from this technology be identified, particularly with respect to their risk of stroke, risk of bleeding with anticoagulant therapy, and risk of procedural complications?
5. What mechanisms will allow for the purposeful extension of this technology to the treatment of other groups of patients not included or studied in the initial clinical studies (both randomized and observational)?
6. How will this technology be reimbursed? Will there be a national coverage determination?
7. Among devices that are approved by the FDA, is the evidence sufficient to support unrestricted use, or is it appropriate to require systematic data on the selection and outcomes of patients who are treated with these technologies in practice?

Answers to these questions are complex and are partly influenced by the number of interested stakeholders. Percutaneous LAA occlusion is technically challenging and may be achieved through different approaches (e.g., internal occlusion, external ligation) that may vary in efficacy and safety. As these technologies become available as potential alternatives to anticoagulation for stroke prevention in AF, it will be important for experienced centers and cohesive teams to guide deployment into

clinical practice. Furthermore, mechanisms to rigorously evaluate the short- and long-term safety, comparative effectiveness, and cost effectiveness of these approaches that are supported by relevant stakeholders must be developed.

2. STROKE PREVENTION IN AF: CURRENT EVIDENCE AND GUIDELINES

AF affects as many as 6.1 million individuals in the United States and may account for as many as 1 in 5 strokes in persons over 80 years of age (4). Evidence supports the hypothesis that, for patients with nonvalvular AF, the LAA is the most common source of thrombus resulting in stroke (5-7). On the basis of numerous randomized clinical trials, chronic anticoagulation—traditionally with warfarin and more recently with direct thrombin and factor Xa inhibitors—has been established as the standard of care for stroke prevention in patients with AF who have an elevated stroke risk profile, provided that the risk of bleeding is not prohibitive (3).

The individualized assessment of the risk-benefit balance is central to decision making around pharmacotherapy for stroke reduction in AF. To estimate stroke risk, the ACC/American Heart Association/HRS Guideline for the Management of Patients with Atrial Fibrillation recommends the use of the CHA₂DS₂-VASc point score (Congestive heart failure, Hypertension, Age \geq 75 years [doubled], Diabetes mellitus, prior Stroke, transient ischemic attack, or thromboembolism [doubled], Vascular disease, Age 65 to 74 years, Sex category), which provides an estimate of the potential benefits of therapy (3). The potential risks of therapy can similarly be estimated with risk scores such as HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or disposition, Labile INR [international normalized ratio], Elderly, Drugs/alcohol concomitantly). However, the guideline does not formally include such bleeding risk scores in its recommendations, perhaps in part because the risk scores primarily identify patients at risk for extracranial bleeding, whereas intracranial bleeding is among the most important complications of anticoagulation therapy. The guideline includes a Class Ia recommendation for oral anticoagulation for patients with prior stroke or a CHA₂DS₂-VASc score \geq 2 (estimated annual stroke risk of 2.2%) in the context of shared decision making, including a discussion of risks of stroke and bleeding and the patient's preferences.

Guideline recommendations for LAA occlusion for stroke prevention are substantially more limited due to the lack of clinical trials data for any these devices aside from WATCHMAN. The 2012 Focused Update to the European Society of Cardiology Guidelines for the Management of Atrial Fibrillation (8) calls for "LAA

closure/occlusion/excision” using percutaneous technologies in patients who are at high stroke risk and have contraindications for long-term oral anticoagulation (Class IIb, Level of Evidence: B); however, the references that are cited as evidence for the recommendation are the PROTECT AF (WATCHMAN Left Atrial Appendage Closure Device for Embolic Protection in Patients with Atrial Fibrillation) study (6) and the WATCHMAN Continued Access Registry (9). Importantly, neither of these studies included patients who had contraindications to long-term anticoagulation, and both enrolled a majority of patients with relatively low estimated stroke risk (i.e., CHADS₂ scores of 1 and 2 in 67% and 59% of patients, respectively). The evidence base for patients who meet the European Society of Cardiology criteria is, in fact, scant, but it is discussed later in this paper. The current ACC/American Heart Association/HRS Guideline for the Management of Patients with Atrial Fibrillation does not include recommendations for the use of LAA occlusion devices because of the lack of adequate data and the absence of an FDA-approved LAA closure device labeled for the indication of stroke prevention at the time of their development (3). Given the developments in LAA occlusion since the publication of the existing guidelines, in particular the FDA approval of the WATCHMAN device, the recommendations may evolve with subsequent revisions.

3. LITERATURE REVIEW

3.1. Background

Mechanical approaches to LAA occlusion have been used for more than one-half century in cardiac surgery. Initial surgical techniques, typically performed concomitantly with mitral valve surgery or surgical maze procedures, were challenging due to fragility of the LAA, with mechanical complications resulting in hemorrhage during surgical suturing or stapling (5,10-13). Also, surgical closure of the LAA was often incomplete, raising concerns about the safety of discontinuation of pharmacological anticoagulation (12,14). These issues contributed to the premature abandonment of the only randomized surgical trial undertaken to objectively evaluate the effectiveness and safety of surgical LAA ligation (15). A larger study with a target enrollment of 4,700 patients (LAAOS [Left Atrial Appendage Occlusion Study] III) is in progress (16). More recently, percutaneous LAA occlusion has been proposed as an alternative approach to stroke prevention in patients with nonvalvular AF.

On the basis of the lessons from surgical closure and a continued belief that elimination of the LAA as a source of systemic thromboembolism could be an effective alternative to pharmacological anticoagulation for patients with AF, a Nitinol plug with a fabric component, termed the PLAATO (Percutaneous Left Atrial Appendage

Transcatheter Occlusion) device, was designed for percutaneous insertion via femoral venous access and atrial septal puncture (17). Small case series, primarily from Europe but also from North America, were reported before the WATCHMAN supplanted this device. The WATCHMAN, also a Nitinol plug with fabric (in this case fenestrated), was, in turn, assessed in a small pilot study (18). Despite considerable barriers to conducting randomized trials comparing a device with standard pharmacotherapy, and marked evolution in the agents available for thromboembolic prophylaxis for AF, 2 randomized studies were performed. Simultaneously, other technologies have been developed that, along with the WATCHMAN, have been available outside of the United States for several years.

This brief literature review will focus on the published evidence, including the PROTECT AF and PREVAIL (Prospective Randomized Evaluation of the Watchman LAA Closure Device In Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy) trials of the WATCHMAN device, and briefly describes other LAA percutaneous occlusion and suture devices for which data are being accumulated.

3.2. WATCHMAN

Two randomized controlled trials and several observational studies comprise data from more than 2,400 patients with nonvalvular AF in whom the WATCHMAN device has been implanted for stroke risk reduction (6,9,19,20). The first and largest randomized controlled trial to evaluate the noninferiority of an LAA occlusion therapy for stroke risk reduction (PROTECT AF) enrolled 707 patients between February 2005 and June 2008 at 59 sites in the United States and Europe. Warfarin-eligible patients (CHADS₂ score ≥ 1) with nonvalvular AF were randomized in a 2:1 ratio to receive WATCHMAN or control (warfarin) therapy (6). Exclusion criteria included contraindications to warfarin, any comorbidity requiring ongoing warfarin, or pre-existing left atrial thrombus. Patients who were treated with the WATCHMAN device received warfarin for at least 45 days following device implantation. A transesophageal echocardiogram was performed at 45 days, 6 months, and 12 months to evaluate for residual peridevice flow. Warfarin was discontinued if the LAA closure was complete or the width of the flow jet was < 5 mm. Once warfarin was stopped, clopidogrel 75 mg daily plus aspirin (81 or 325 mg) daily were prescribed until completion of 6-month follow-up. Following 6-month follow-up, aspirin alone was prescribed. Control group patients received warfarin for the duration of the study (international normalized ratio goal 2.0 to 3.0) and may also have received aspirin.

PROTECT AF was designed to assess the noninferiority of WATCHMAN compared with warfarin for the composite endpoint of ischemic or hemorrhagic stroke,

cardiovascular or unexplained death, or systemic embolus. The primary safety endpoint included events related to bleeding (e.g., intracranial or gastrointestinal) or procedural-related complications (e.g., serious pericardial effusion, device embolization, or procedure-related stroke). Event rates were calculated as the number of events per 100 patient-years of follow-up. The study was designed to utilize a Bayesian sequential model to limit the study size, with analysis planned once follow-up of 600 patient-years was reached, and then every 150 patient-years, until follow-up of 1,500 patient-years was achieved. Investigators selected a 1-sided probability criterion of noninferiority for the intervention of at least 97.5%, using a 2-fold noninferiority margin.

Published results from the fourth planned interim analysis of PROTECT AF were presented to the FDA Circulatory Advisory Panel on April 23, 2009 (6). The WATCHMAN was successfully implanted in 88% (408 of 463) of patients assigned to the intervention, and 86% (349 of 408) of these patients met criteria for discontinuation of warfarin at 45 days (the minimum duration of warfarin therapy in the intervention arm). By 6 months, 92% (355 of 385) of patients who had successfully undergone implantation met criteria to discontinue warfarin. For the control group, international normalized ratio values were within therapeutic range (2.0 to 3.0) 66% of the time. The efficacy of percutaneous closure of the LAA with the device met the prespecified criteria for noninferiority to therapy with warfarin (the primary efficacy endpoint being reached for 3.0% of device implant patients and 4.9% of control subjects), but the rate of adverse safety events in the intervention group was 4.4% (22 patients). These events were primarily periprocedural complications (pericardial effusion and procedure-related ischemic stroke). There were no deaths attributed to device implantation. A “learning curve” was noted, with a decline in acute complications with increasing procedural experience. In an analysis of 542 patients, including the nonrandomized group, serious pericardial effusions (requiring drainage) were observed in 7.1% (11 of 154) of the first 3 implant patients at each site compared with 4.4% (17 of 388) of subsequent patients.

At that time, the FDA Circulatory System Devices Panel concluded that the short-term effectiveness of WATCHMAN was demonstrated, but that the evidence to demonstrate long-term effectiveness was inadequate. The panel voted 7 to 5 in favor of approval with conditions; however, the FDA deemed the device not approvable, largely because of the high rate of periprocedural complications. The FDA subsequently requested that the sponsor conduct a new prospective trial, citing concerns regarding the trial design of PROTECT AF, including: difficulty interpreting the composite safety endpoint, which included ischemic as well as hemorrhagic strokes;

the inclusion of patients with a CHADS₂ score of 1 who, according to the 2006 ACC/American Heart Association/European Society of Cardiology Guidelines for the Management of Patients with Atrial Fibrillation (21), could be appropriately treated with aspirin alone; concomitant antiplatelet therapy in a significant portion of the control group (aspirin and/or clopidogrel); and the selection of a noninferiority event rate ratio for a primary effectiveness endpoint of 2.0 (meaning that the WATCHMAN arm could be found noninferior to warfarin with an event rate up to twice that observed in the control arm) (19,21). It was also recognized that acute procedure-related safety events, which comprised 56% (27 of 48) of safety events in the trial, should be considered separately from long-term events to understand the effectiveness of the device in preventing thromboembolic strokes versus procedural learning curves (9,22).

The CAP (Continued Access Protocol) Registry allowed 26 enrolling sites from the PROTECT AF trial to access the WATCHMAN device after completion of the enrollment in the trial during the FDA evaluation of the premarket approval application (9). An additional 460 patients received the device as part of this prospective, non-randomized, single-arm, continued access registry. Results from the CAP Registry demonstrated an increase in implant success rate to 95% and a lower rate of safety events. The periprocedural device-related complication rate of 3.7% (17 of 460) was similar to that observed in experienced PROTECT AF sites (>3 implants) and significantly lower than the rate of 7.7% observed in the entire PROTECT AF trial. Pericardial effusions requiring drainage occurred in 2.2% (10 of 460) of the continued access group compared with 5.0% (10 of 460) of patients in PROTECT AF. There were no procedure-related strokes identified. Ninety-five percent of patients were able to discontinue warfarin by 45 days after the procedure.

Long-term follow-up data from PROTECT AF with mean follow-up of 45 months (2,621 patient-years) demonstrated that WATCHMAN was superior to anticoagulation with respect to the primary efficacy endpoint; patients in the device group had significantly lower rates of hemorrhagic stroke and cardiovascular death than did patients receiving anticoagulation therapy (hemorrhagic stroke event rate in WATCHMAN arm: 0.2 per 100 patient-years, 95% CI: 0.0 to 0.4 vs. warfarin arm: 1.1 per 100 patient-years, 95% CI: 0.5 to 1.8; cardiovascular or unexplained death 1.0 per 100 patient-years, 95% CI: 0.6 to 1.5 vs. warfarin arm 2.4 per 100 patient-years, 95% CI: 1.4 to 3.4) (23).

The PREVAIL trial (20) was designed by the sponsor in conjunction with the FDA in response to the FDA's concerns regarding the PROTECT AF trial (24). Patients studied in PREVAIL were required to have a CHADS₂ score \geq 2.0 (or CHADS₂ = 1 with additional stroke risk

factors) to evaluate the effectiveness of WATCHMAN in a population at relatively high risk for thromboembolic events (3,21). Patients requiring chronic antiplatelet therapy with clopidogrel were excluded. To further evaluate the relationship between procedural volume and safety, the PREVAIL protocol required at least 20% of enrolling sites and operators to have no prior experience placing the WATCHMAN device. Study endpoints were the following:

- **First primary endpoint (“primary efficacy”):** the occurrence of stroke (ischemic or hemorrhagic), cardiovascular or unexplained death, and systemic embolism over 18 months.
- **Second primary endpoint (“late ischemic efficacy”):** the occurrence of ischemic stroke and systemic embolism from 8 days after randomization and onward, excluding periprocedural events to evaluate the mechanism of action of stroke prevention over 18 months.
- **Third primary endpoint (mechanistic endpoint):** the occurrence of all-cause death, ischemic stroke, systemic embolism, or device- or procedure-related events requiring open cardiac surgery or major endovascular intervention such as pseudo-aneurysm repair, arteriovenous fistula repair, or other major endovascular repair occurring between the time of randomization and within 7 days of the procedure or by hospital discharge, whichever was later.

A noninferiority hypothesis for the first and second primary endpoints was specified in terms of the 18-month risk ratio (1.75 for the first primary endpoint; 2.0 for the second primary endpoint). Noninferiority for the WATCHMAN device versus warfarin would be achieved if the noninferiority criteria for both the first and second primary endpoints were met. The safety of the device implant procedure was to be deemed acceptable if the third primary endpoint was reached in <2.67% of subjects receiving WATCHMAN, an estimated complication rate derived from literature review and agreed upon by sponsor and FDA.

The PREVAIL study was designed with a noninferiority Bayesian statistical analysis and incorporated data from PROTECT AF, which was discounted 50% for the first and second primary endpoint analysis, and was not discounted for the third primary endpoint analysis (20). Because PREVAIL used a more restrictive CHADS₂ inclusion criterion (i.e., higher estimated stroke risk profile) than did PROTECT AF, the prior data borrowed from PROTECT AF included only subjects who would have met the CHADS₂ inclusion criterion used for PREVAIL. PREVAIL enrolled 461 subjects, including 269 randomized to WATCHMAN, 138 to control (2:1 randomization), and 54 “roll-in” subjects. The study was performed at 50 U.S. sites. The protocol specified that at

least 20% of randomized patients would be enrolled in institutions that had not participated in previous WATCHMAN studies, and at least 25% of the randomized patients were to be treated by new operators.

The second FDA panel to review the WATCHMAN device was convened in December 2013 (20). The data presented at this time included only the early results of PREVAIL. The rates of the first coprimary outcome at 18 months (the composite of stroke, systemic embolism, and cardiovascular/unexplained death) were 6.4% in those treated with the WATCHMAN device versus 6.3% in the warfarin-treated arm, not meeting the criteria for noninferiority. The second coprimary outcome (stroke or systemic embolism after 7 days of randomization) occurred in 2.5% versus 2.0% in the WATCHMAN and warfarin-treated arms, respectively, which met criteria for noninferiority. Because the design specified that both of these endpoints meet noninferiority, the trial did not meet overall criteria for noninferiority. There were no procedure-related deaths; the primary safety endpoint (a composite of all-cause death, ischemic stroke, systemic embolism, or device-/procedure-related events requiring open cardiovascular surgery or major endovascular intervention) occurred in 2.2% of patients in the WATCHMAN arm, a lower rate than in the PROTECT trial, meeting the prespecified noninferiority criteria, albeit with only 18-month follow-up completed. The risk of pericardial effusion requiring drainage was 1.5% in the WATCHMAN arm, also lower than in the PROTECT trial.

Additional data from PREVAIL that became available after the second FDA panel review led to an unprecedented third Circulatory Systems Advisory Panel review on October 8, 2014 (25). Eight additional ischemic strokes occurred in the additional follow-up period, all of which occurred in the WATCHMAN group; thus, there were 13 ischemic strokes in the WATCHMAN arm versus 1 in the control arm (rate ratio: 0.15, $p = 0.044$). Hemorrhagic strokes were rare in both arms (rate ratio: 1.92, $p = 0.61$). Systemic embolism occurred in 1 patient (WATCHMAN arm) and death (cardiovascular or unexplained) was evenly distributed between the groups (rate ratio: 1.45, $p = 0.575$). With these additional data, PREVAIL failed to meet either the first or second primary efficacy endpoints, and WATCHMAN failed to demonstrate noninferiority to warfarin. The risk of ischemic strokes was statistically significantly higher in the WATCHMAN group. Of the 14 WATCHMAN subjects who suffered an ischemic stroke or systemic embolism, only 1 had an event related to the implant procedure. The remaining 12 ischemic strokes and 1 systemic embolism event occurred at a mean of 15 ± 8 months postimplant (range: 2 to 26 months). Of note, the ischemic stroke rate in the warfarin control group was unexpectedly low (1 subject with 140.1 total patient-years of follow-up).

Notably, data on the use of the WATCHMAN device in patients for whom anticoagulation therapy is considered contraindicated are limited. In a single case series, 150 patients with nonvalvular AF and CHADS₂ scores ≥ 1 who were deemed unsuitable for anticoagulation were followed for a mean duration of 14.4 months. Procedure- or device-related safety events occurred in 13 patients (8.7%). Stroke or systemic embolism occurred in 4 (2.3%), which was lower than the 7.3% that was expected given the CHADS₂ scores (26).

On March 13, 2015, the FDA issued an approval for the WATCHMAN device. The approval specified indications for use in patients with nonvalvular AF who are: 1) at increased risk of stroke and systemic embolism on the basis of CHADS₂ or CHA₂DS₂-VASc scores; 2) deemed by their physicians to be suitable for warfarin therapy; and 3) have an appropriate rationale to seek a non-pharmacological alternative to warfarin, taking into account the safety and efficacy of the device compared with warfarin (27).

3.3. Amplatzer Cardiac Plug

At least 4 Amplatzer devices (St. Jude Medical) have been utilized for LAA occlusion: the atrial septal occluder, the ventricular septal defect occluder, the Amplatzer Cardiac Plug, and the Amulet. The atrial septal occluder, designed for closure of atrial septal defects, was initially used off label when the first reports of percutaneous LAA device closure were published (28); however, there was a high risk of device embolization, which was attributed to the lack of active fixation anchoring struts (28,29). The atrial septal occluder design was modified for LAA occlusion, maintaining the self-expandable Nitinol platform with a distal lobe and proximal disk to occlude the LAA ostium with expansion (30). Clinical feasibility trials have been performed, and an investigational device exemption was issued by the FDA, which led to a U.S. pilot study. A pivotal trial in the United States, similar to PROTECT AF and PREVAIL, was designed to randomize patients to Amplatzer Cardiac Plug or optimal medical therapy with either warfarin or dabigatran; this study is on hold at the time of this publication. To date, the only published reports of these devices in the context of LAA occlusion are retrospective, nonrandomized case series (31-35). In the 2 larger series, procedure-related complications occurred in $\sim 5\%$ (33,35), although the definitions of complications vary by study. The duration of follow-up and rates of adverse outcomes, including stroke and systemic embolism, also varied; the lack of a control group in these studies precludes inferences about the comparability of these rates with contemporary treatment. Feasibility reports of a second-generation cardiac plug—the Amulet—have been published. This device is

available outside of the United States (29,36,37). The Amplatzer Cardiac Plug has been marketed for use with antiplatelet therapy only, albeit with little supportive evidence; many implantations in Europe have been performed without oral anticoagulation.

3.4. LARIAT

The LARIAT device is deployed by means of a trans-pericardial approach using an epicardial snare with a pretied suture to lasso and occlude the LAA (38,39). Both intracardiac trans-septal access to the LAA and direct pericardial access are required. Magnetically tipped guide wires are positioned to form a rail at the LAA tip. The suture is then positioned over a pericardial wire and tightened to occlude the LAA. In the United States, the LARIAT was approved for tissue approximation via the 510(k) FDA regulatory pathway “for use in surgical applications where soft tissue are [sic] being approximated and/or ligated with a pre-tied polyester suture” (40). The device is also CE marked. Because the predicate devices—designed to create preformed sutures for laparoscopic surgery—had pre-existing FDA approval, no investigational device exemption was deemed necessary; the approval does not specify the use of the device as a tool to ligate the LAA to decrease the risk of stroke. A substantial number of cases have been performed in the United States in addition to ongoing international experience. Despite the lack of evidence for effectiveness, clinicians have considered using the device for patients deemed at high risk for thromboembolic stroke who are also at high risk for the adverse consequences of anticoagulation.

The outcomes of patients undergoing LAA occlusion with the LARIAT are only reported in the context of uncontrolled case series. One single-site study evaluated 89 patients, in whom the mean CHA₂DS₂-VASc score was 2.8 (16.8% had scores >4) (39). LARIAT ligation was attempted in 92 patients; implantation was aborted in 3 because the snare could not be advanced around the LAA (1 of these patients had right ventricular puncture and required pericardial drainage). In 85 of the 89 remaining patients, the procedure was technically successful. There were access-related complications in 3 (3.3%) patients. Despite enrollment criteria specifying that patients should be high risk or ineligible for anticoagulation, more than one-half (55%) were receiving warfarin 1 year after the procedure. A retrospective, multicenter study of consecutive patients undergoing LARIAT LAA ligation at 8 U.S. centers reported data on 154 patients (mean CHADS₂ score of 3) (41). The primary endpoint was procedural success defined as suture deployment with <5 mm leak by postprocedure transesophageal echocardiogram and no major complications at the time of discharge. The device was implanted in 94% of patients successfully, with a

procedural success rate of 86%. Major complications (primarily bleeding) occurred in 9.7% of cases ($n = 15$); significant pericardial effusion occurred in 16 patients (10.4%); and emergency surgery was required for 3 patients (2%) who experienced either right ventricular or LAA perforation. An additional multicenter analysis assessed the feasibility and short-term procedural success of the LARIAT (42). None of the published literature includes longitudinal assessments of outcomes beyond the assessment of functional left atrial occlusion, or comparisons—randomized or otherwise—with other therapies (or no therapy). Thus, the existing literature provides no insight into the effectiveness of the LARIAT with respect to reducing stroke or its safety relative to other approaches.

3.5. Other Percutaneous Devices and Surgical Approaches

Other percutaneous approaches to LAA occlusion have been proposed. The WaveCrest occluder device (Coherex Medical, Salt Lake City, Utah), a polytetrafluoroethylene-based platform, is CE marked. There are no peer-reviewed reports of outcomes with this device; an unpublished 155-patient observational study of the device has been registered and has reportedly completed enrollment (43). The LAMBRE device (Lifetech, Shenzhen, China), a self-expanding Nitinol and polyester device, has also been developed. No peer-reviewed reports of experience with this device are available; 2 small studies of this device have been registered (44,45).

Surgical techniques to occlude the LAA also continue to evolve, with efforts being made to overcome the inconsistent closure, tissue tearing, and intrathoracic bleeding associated with suturing or stapling techniques (46). As previously mentioned, a large randomized trial of left atrial ligation in patients undergoing cardiac surgery (LAAOS III) is underway, and device-facilitated surgical approaches have also been developed (16). The most widely used device, the AtriClip (Atricure, West Chester, Ohio), consists of a parallel titanium crossbar clip covered with woven polyester fabric (47). The clip is available in 4 sizes and is deployed via a low-profile articulated applicator to the base of the appendage. The fabric cover promotes tissue ingrowth to encapsulate the appendage. The device has received a CE mark and is approved by the FDA for closure of the LAA under direct visualization in conjunction with other open cardiac surgical procedures. Deployment of the clip via a minimally invasive thoracoscopic approach has been reported (48). A phase 2 multicenter nonrandomized study is now underway to evaluate the safety of this technique for patients deemed at too high of a risk to receive long-term oral anticoagulation (49). The efficacy of the device to reduce the risk of thromboembolic stroke has not been evaluated.

4. CARE TEAM AND FACILITIES

4.1. Multidisciplinary Heart Team

The multidisciplinary heart team model has been widely embraced in the area of percutaneous valve replacement therapy (50) and serves as a template for care around other complex percutaneous cardiovascular procedures. The multidisciplinary heart team extends well beyond collaboration between individual clinicians; depending on the type of procedure, it may include collaboration among a wide variety of physician and nonphysician specialties. A multidisciplinary approach is applicable to LAA occlusion, although the specific composition of the team will likely differ from that employed for valve procedures. The initial evaluation should be performed by both an individual with the expertise to characterize the specific risks and benefits of medical therapy and a procedural specialist, who can estimate the risks and benefits of a proposed procedure. The procedural specialist should also have expertise related to medical therapy for stroke prevention in AF. Beyond the initial evaluation, any input and/or participation in evaluating and managing this procedure should include expertise in echocardiography, x-ray imaging modalities (primarily computed tomography [CT]), and in anesthesiology when general anesthesia is planned. A cardiac surgeon should be available for surgical backup in case of emergency. The multidisciplinary heart team must work together, particularly with respect to patient evaluation and selection, preprocedural evaluation, intraprocedural management, postprocedural management, postdischarge follow-up, and outcome analysis.

4.2. General Requirements

One of the cornerstones of a structural heart disease and/or electrophysiology program is a well-formulated, collaborative effort among all members of the care team. Depending on the type of procedure and device used, close collaboration may be required between procedural specialists, physician echocardiographers, sonographers, radiologists, hematologists, neurologists, and cardiac surgeons to ensure proper patient selection, evaluation, and execution of LAA occlusion. In some cases, expertise in other areas may be required to inform decision making (e.g., geriatric medicine and/or gastroenterology or urology for patients with a history of significant gastrointestinal or genitourinary bleeding, respectively).

Irrespective of specialty, physicians performing these procedures should possess the appropriate cognitive and technical skillsets. They should have an understanding of stroke and stroke syndromes, AF, the pharmacology of anticoagulants, and the regional anatomy of the left atrium and LAA. They should also possess the requisite technical procedural skills. LAA occlusion procedures are

complex and should be performed in institutions with experience in advanced structural heart disease procedures and/or electrophysiology procedures that require access to the left atrium. The ability to interpret echocardiographic, CT, and/or magnetic resonance imaging data preprocedurally, intraprocedurally, and postprocedurally is essential. Procedural echocardiographic guidance is also necessary; the physician echocardiographer must be familiar with the procedure and committed to being available throughout the case. Both randomized and nonrandomized studies of LAA occlusion suggest a relationship between operator procedural experience and both successful device delivery and the avoidance of complications such as cardiac perforation and cardiac tamponade. Collectively, members of the multidisciplinary heart team must be skilled in imaging of the LAA, trans-septal techniques, percutaneous pericardial puncture, advanced retrieval techniques, and large vessel access. An understanding of the interplay among wires, catheters, and left atrial regional anatomy is also required. All procedural team members should maintain an understanding of the procedures and technologies involved. Although the minimum training for these procedures may initially be prescribed by FDA approval requirements, competence in atrial septal puncture and proper handling of devices inside of the left atrium to prevent air embolization and clot formation are prerequisites. A detailed review of all skillsets necessary for these procedures as well as the means of acquiring them is beyond the scope of this document.

The team should be structured to permit the consideration of all of the available therapeutic options to the patient individualized to the risks and benefits of these approaches on the basis of available data. A tailored approach, with input from all relevant clinicians, may be facilitated by multidisciplinary conferences designed for case discussion and the development of consensus treatment recommendations.

4.3. Facilities

The institution should have an established structural heart disease and/or electrophysiology program with an individual capable of performing the procedure as well as cardiac surgical backup. The full range of facilities for diagnostic imaging as well as electrophysiology, interventional, or cardiac surgical suites should be available on site and should include the following personnel and equipment:

1. A cardiac procedure laboratory (electrophysiology or cardiac catheterization) or hybrid operating room equipped with a radiographic imaging system with fluoroscopy offering catheterization-quality imaging. A biplane unit may be useful in LAA occlusion

- procedures but is not required. Continuous hemodynamic monitoring is required during the procedure.
2. An echocardiographic laboratory with the full array of transthoracic and transesophageal capabilities. Three-dimensional and intracardiac echocardiography or intracardiac echocardiography may be useful but are not required. A transesophageal echocardiogram-capable machine should be utilized during the case. Appropriate staff should be present, including a physician echocardiographer skilled in the subtleties of the procedure and available throughout the case.
 3. A CT laboratory with CT technologists and specialists skilled in obtaining high-quality cardiac studies of the heart for procedures where CT imaging is necessary as part of the evaluation (e.g., LARIAT). Preferably CT studies would be gated to optimize image resolution.
 4. A cardiac surgeon and anesthesiologist on site available for surgical backup.
 5. Cardiac surgery operating rooms in reasonable proximity to the room in which the procedure is being performed and readily accessible.
 6. A room of sufficient size to accommodate all of the necessary equipment and personnel.
 7. The full array of equipment necessary to conduct structural heart disease interventions and device retrieval within the procedural suite.
 8. An intensive care facility with staff trained to provide postprocedural observation and management.

5. OPERATOR TRAINING

Device manufacturers often provide training for the use of advanced technologies. However, it is incumbent on professional societies to set minimal performance standards for LAA procedures, develop the training curriculum, and establish the metrics for evaluation. Challenges to this paradigm include accessing a required minimum of cases, striking the appropriate balance between simulation and/or large animal laboratory experience, and limitations on the number of experienced centers and operators. The ACC, HRS, and Society for Cardiovascular Angiography and Interventions have published recommendations for training in electrophysiology or interventional techniques (51-53), but these recommendations do not provide specific guidance for LAA occlusion devices. Thus, specific recommendations for training in LAA occlusion need to be developed. Unanswered questions concern the requisite prior training and experience (e.g., in trans-septal puncture), the type and duration of training for LAA occlusion, the number of cases needed for initial training, maintenance of competence, funding, team-based training needs, and the expectations for procedural specialists who might be interested in performing these procedures as well as for surgeons. The

establishment of such training criteria, procedural volumes, and performance and evaluation metrics is beyond the scope of this document.

6. PROTOCOLS FOR CARE

Specific protocols for preprocedural, intraprocedural, and postprocedural patient assessment and care should be in place, with clear delineation of the roles of heart team members and the specific collaborative process for shared decision making with the patient. Although protocols may vary to reflect institutional preferences, certain components should be considered fundamental. Protocols should involve assessment of the following: the patient's stroke risk (preferably using the CHA₂DS₂-VASc score), bleeding risk (using a bleeding risk score), any contraindications to anticoagulation, patient adherence to and history of adequacy of anticoagulation, cardiac structural factors (left ventricular ejection fraction and the presence of structural abnormalities such as patent foramen ovale, interatrial septal aneurysm, and LAA thrombus), and patient preferences. Documentation should include the decision making involved, including the consideration of pharmacotherapy as an alternative. Forms for obtaining informed consent should be individualized to the device and, where possible, the patient, including statements regarding procedural safety and long-term efficacy when these data are available; the absence of published data to support the efficacy and safety of the device should be noted when relevant. Protocols are also needed to standardize preprocedural evaluation, including a complete assessment of medical comorbidities, preprocedural and intraprocedural imaging, and surgical backup. All patients referred for consideration of LAA occlusion should undergo a standardized evaluation to promote consistency, reduce variability, and eliminate redundant testing. The process should help prevent inappropriate use of the technology as well as post-hoc assessment of the data needed for optimal device utilization. Finally, protocols are also needed to standardize postprocedure evaluation and follow-up. These protocols should make specific recommendations concerning the timing and frequency of follow-up transesophageal echocardiogram to assess the degree of appendage closure as well as postprocedure anticoagulation management.

7. ASSESSMENT OF PATIENT SELECTION AND OUTCOMES

Clinical, procedural, device, and administrative data collection, analysis, and reporting are vital aspects of the process whereby the patient selection for and outcomes of any new technology can be established. Although randomized clinical trials remain the standard for assessing comparative efficacy and safety, observational data,

including those collected through registries, are important complements to trials and provide a perspective on the adoption and outcomes of technologies in contemporary clinical practice. As noted previously, the evidence base for many LAA occlusion devices is limited and, for most devices, does not include evidence of efficacy in preventing stroke. In these cases, randomized trials constructed to address the risks and benefits of technologies compared with anticoagulation or other technologies are warranted.

The value of registries has been demonstrated most convincingly by the Society of Thoracic Surgeons National Database and the ACC National Cardiovascular Data Registry (54). A national clinical registry program for new transcatheter valve therapy (TVT) devices was created in December 2011, following FDA approval of the SAPIEN Transcatheter Aortic Valve (Edwards Lifesciences, Irvine, California) (55). The Society of Thoracic Surgeons/ACC TVT registry (NCT01737528) was developed in close collaboration with the FDA, Centers for Medicare and Medicaid Services (CMS), and Duke Clinical Research Institute (56). Its purpose is to provide an objective, comprehensive, and scientifically based resource to improve the quality of patient care, monitor the safety and effectiveness of novel transcatheter valve technologies, serve as a platform for TVT research, and enhance communication among multiple stakeholders. Importantly, the TVT registry fulfills the CMS national coverage determination (May 2012) (55) requirement for national registry participation for all transcatheter aortic valve replacement centers.

The Society of Thoracic Surgeons/ACC TVT registry enables device and procedure surveillance, quality improvement, and the performance of device-labeling studies to speed access to new devices and support expansion of labeling with evidence development. The registry process has included the detailed specification of the critical data elements that must be captured in a standardized manner with harmonization with pivotal clinical trials to inform regulatory approval, promote best practices, and ensure high-quality, patient-centered care. Participating centers collect information regarding patient demographics, comorbidities, functional status, patient-reported quality of life, procedural details, and postprocedure 30-day and 1-year outcomes.

The addition of LAA occlusion to an existing registry or creation of a new registry similar to the TVT registry would greatly benefit the still-nascent field of LAA occlusion technologies, in which the use of only 1 of multiple technologies is supported by randomized control trial data and significant learning curve effects exist. Such a registry would ideally include all devices used for LAA occlusion, whether they are used on or off label. This approach is consistent with the recently announced FDA strategy to enhance postmarket medical device

surveillance, which identifies registries as a central component (57). This strategy is evolving through the FDA's Medical Device Epidemiology Network initiative, which is working with industry and other stakeholders on critical issues related to registry structure and processes along with analytical methodologies for both surveillance and research (58).

Understanding patient selection for percutaneous LAA occlusion would be an important role of a registry. Data to characterize patients considered for the procedure would include estimates of risks for stroke (using CHA₂DS₂-VaSC scores) and of bleeding (using an accepted score such as HAS-BLED); previous experience with antiplatelet and anticoagulant therapy, including agents used and the contraindications—both absolute and relative—specific to each agent; cardiac structure and function, including LAA anatomy; and structural/anatomic factors pertinent to the percutaneous approach. Patient preferences should also be characterized. The estimated risks and benefits of the use of an occlusion device compared with pharmacological alternatives or no therapy should be provided, with the acknowledgment that in many cases, the benefits of the technologies have not been well characterized. The collection of these data would permit an ascertainment of the extent to which the adoption of LAA occlusion technologies compares with the enrollment criteria of randomized trials, the parameters of FDA approval, and guideline recommendations.

An LAA occlusion device registry would also collect follow-up data of patient outcomes, including immediate procedural success; procedural complications; longitudinal rates of death, stroke (including type of stroke), bleeding, and hospitalization; and longer-term device complications. The use of antiplatelet and anticoagulant therapy should also be collected during follow-up. The follow-up time should be of adequate duration to provide meaningful estimates of long-term risks, such as that proposed by the FDA for postapproval studies of the WATCHMAN device (clinical assessment at 45 days, 6 months, 1 year, and 2 years and additional follow-up with claims data through 5 years) (27).

An LAA occlusion registry would facilitate the development of standard data definitions and consistent methodologies for assessing all of the technologies and approaches being employed. This would, in turn, enable assessment of procedural effectiveness and safety in “the real world.” Important outcomes such as assessment of complete appendage occlusion rates and freedom from stroke could be ascertained along with important adverse events such as pericardial effusions and device dislodgement. A critical element that should be included in the registry is an assessment of learning curve effects, which have been identified with WATCHMAN.

The FDA approval for the WATCHMAN device included requirements for 3 postapproval studies, including: 1) a continued follow-up of the cohorts in the PREVAIL, CAP, and CAP2 investigational device exemption studies; 2) a new enrollment study of 1,000 patients with 2-year clinical follow-up and 5-year claims follow-up through linkage with CMS claims data; and 3) a novel surveillance study of an additional 1,000 patients enrolled in a registry with 12 months of clinical follow-up and 5 years of claims follow-up through linkage with CMS claims data (27). The latter 2 registry-based studies are patterned after the TVT registry, reflecting the success of the registry in providing meaningful insights into procedural safety and outcomes. By definition, these studies are limited to the WATCHMAN device. A registry would optimally be “device agnostic,” designed to capture data for all patients undergoing percutaneous left atrial closure regardless of the technology employed.

In the case of the TVT registry, the CMS national coverage determination has stimulated registry participation. In the absence of a national coverage determination for LAA occlusion devices, other mechanisms would be necessary to produce the data required for evaluating the safety and effectiveness of these technologies in clinical practice. A national registry would also provide the platform for postmarket surveillance studies requested by the FDA during approval processes and would provide payers with a mechanism to collect robust, consistent data in this patient population. It is acknowledged that registry participation requires resources for both potential subscription fees and data abstraction personnel. The integration of an LAA appendage occlusion device registry within existing programs and streamlining to the extent possible would facilitate program participation.

The ACC, HRS, and Society for Cardiovascular Angiography and Interventions are committed to the principle of working collaboratively as professional societies and in partnership with the FDA, CMS, and industry partners to bring promising, innovative LAA technologies into clinical practice as validated by the evidence and in the best interests of patients.

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KEY WORDS ACC/HRS/SCAI Societal Overview, atrial fibrillation, left atrial appendage, prevention, stroke

**APPENDIX 1. RELEVANT AUTHOR RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES—
ACC/HRS/SCAI LEFT ATRIAL APPENDAGE OCCLUSION DEVICE SOCIETAL OVERVIEW**

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Frederick A. Masoudi (<i>Chair</i>)	University of Colorado Anschutz Medical Campus, Division of Cardiology—Professor of Medicine	None	None	None	None	None	None
Hugh Calkins (<i>Vice-Chair</i>)	Johns Hopkins Hospital—Professor of Medicine, Director of Electrophysiology	<ul style="list-style-type: none"> • Atricure • Boehringer-Ingelheim • Daiichi Sankyo 	None	None	<ul style="list-style-type: none"> • St. Jude Medical* 	None	None
Clifford J. Kavinsky (<i>Vice-Chair</i>)	Rush University Medical Center—Professor of Medicine and Pediatrics	None	None	None	None	None	None
Joseph P. Drozda, Jr.	Mercy Health—Director of Outcomes Research	None	None	None	None	None	None
Phillip Gainsley	Patient Advocate	None	None	None	None	None	None
David J. Slotwiner	North Shore-Long Island Jewish Medical Center—Associate Director, Cardiac Electrophysiology Laboratory	None	None	None	None	<ul style="list-style-type: none"> • Boston Scientific 	None
Zoltan G. Turi	Rutgers Robert Wood Johnson Medical School—Director, Structural Heart Program	<ul style="list-style-type: none"> • Mitralign 	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 $\geq 5\%$ of the voting stock or share of the business entity, or ownership of $\geq \$5,000$ 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. Relationships that exist with no financial benefit are also included for the purpose of transparency. Relationships in this table are modest unless otherwise noted. According to the American College of Cardiology, a person has a *relevant* relationship if: a) the *relationship or interest* relates to the same or similar subject matter, intellectual property or asset, topic, or issue addressed in the *document*; b) the *company/entity* (with whom the relationship exists) makes a drug, drug class, or device addressed in the *document*, or makes a competing drug or device addressed in the *document*; or c) the *person or a member of the person's household*, has a reasonable potential for financial, professional, or other personal gain or loss as a result of the issues/content addressed in the *document*.

*Significant ($> \$5,000$) relationship.

**APPENDIX 2. REVIEWER RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES—
 2015 ACC/HRS/SCAI LEFT ATRIAL APPENDAGE OCCLUSION DEVICE SOCIETAL OVERVIEW**

Peer Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Zahid Amin	Official Reviewer—SCAI	Georgia Regents University—William B. Strong Endowed Chair, Professor and Chief	<ul style="list-style-type: none"> • AGA Medical* 	None	None	None	None	None
Steven R. Bailey	Official Reviewer—SCAI	University of Texas Health Science Center at San Antonio, Department of Medicine/ Cardiology—Professor of Medicine and Radiology	None	None	None	None	None	None
Richard Ira Fogel	Official Reviewer—HRS	Saint Vincent Medical Group—Chief Executive Officer; Saint Vincent Heart Center—cardiologist and electrophysiologist	None	None	None	None	None	None
Dharam J. Kumbhani	Official Reviewer—ACC Task Force on Clinical Expert Consensus Documents	UT Southwestern Medical Center—Assistant Professor of Medicine	None	None	None	None	None	None
Dhanunjaya R. Lakkireddy	Official Reviewer—HRS	University of Kansas Hospital—Professor of Medicine	<ul style="list-style-type: none"> • St. Jude Medical 	<ul style="list-style-type: none"> • Boehringer Ingelheim • Bristol-Myers Squibb • Janssen • Pfizer 	None	None	None	None
Simone Musco	Official Reviewer—ACC Board of Governors	Saint Patrick Hospital—Clinical Cardiac Electrophysiologist	None	<ul style="list-style-type: none"> • Bristol-Myers Squibb 	None	None	None	None
E. Murat Tuzcu	Official Reviewer—ACC Board of Trustees	Cleveland Clinic, Department of Cardiovascular Medicine—Professor of Medicine	None	None	None	None	None	None
Anita W. Asgar	Content Reviewer—SCAI	Montréal Heart Institute—Director, Transcatheter Valve Therapy Program; University of Montreal—Assistant Professor	<ul style="list-style-type: none"> • Gore Medical 	None	None	None	None	None
Joaquin E. Cigarroa	Content Reviewer—ACC Interventional Council	Oregon Health & Science University—Clinical Professor of Medicine	None	None	None	None	None	None
George H. Crossley, III	Content Reviewer—ACC Electrophysiology Council	Vanderbilt University—Associate Professor of Medicine	<ul style="list-style-type: none"> • Boston Scientific • Medtronic* 	<ul style="list-style-type: none"> • Medtronic 	None	None	None	None
Edward T. A. Fry	Content Reviewer—ACC Interventional Council	St. Vincent Medical Group—Chair, Cardiology Division	None	None	<ul style="list-style-type: none"> • Pfizer* • St. Jude Medical* 	None	None	None

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APPENDIX 2. CONTINUED

Peer Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Bulent Gorenk	Content Reviewer—ACC Electrophysiology Council	Eskisehir Osmangazi University, Cardiology Department—Professor of Cardiology	None	None	None	None	None	None
Rick A. Nishimura	Content Reviewer—ACC Valvular Heart Disease Guideline	Mayo Clinic, Division of Cardiovascular Disease—Judd and Mary Morris Leighton Professor of Medicine	None	None	None	None	None	None
Robert N. Piana	Content Reviewer—ACC Interventional Council	Vanderbilt University Medical Center—Professor of Medicine (Cardiology)	• W. L. Gore & Associates	None	None	None	None	None
Marwan Refaat	Content Reviewer—ACC Electrophysiology Council and ACC International Governor	American University of Beirut Faculty of Medicine and Medical Center, Department of Internal Medicine—Assistant Professor of Medicine, Cardiovascular Medicine/Cardiac Electrophysiology, Department of Biochemistry and Molecular Genetics	None	None	None	None	None	None
John Rickard	Content Reviewer—HRS	Johns Hopkins Bayview Medical Center—Assistant Professor of Medicine, Electrophysiology and Assistant Professor of Medicine	None	None	None	None	None	None
Joseph S. Rossi	Content Reviewer—ACC Individual	St. Vincent Heart Center of Indiana	None	None	None	None	None	None
John Lewis Sapp, Jr.	Content Reviewer—HRS	QEII Health Sciences Centre—Director Heart Rhythm Service; Dalhousie University—Professor of Medicine	None	None	None	• St. Jude Medical*	None	None
Christian Spies	Content Reviewer—SCAI	The Queen's Medical Center, Honolulu—Director, Structural Heart Interventions; University of Hawaii Honolulu—Associate Professor of Medicine	None	None	None	None	None	None
Dimitris Tsiachris	Content Reviewer—ACC International Governor	University of Athens Medical School—Electrophysiology Lab Director, Athens Medical Center	• Boston Scientific • Medtronic*	None	None	None	None	None

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APPENDIX 2. CONTINUED

Peer Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
L. Samuel Wann	Content Reviewer—ACC Atrial Fibrillation Guideline	Columbia St. Mary's Healthcare, Milwaukee—Clinical Cardiologist	None	None	None	None	None	None
Jacqueline E. Tamis-Holland	Content Reviewer—ACC Interventional Council	Mount Sinai, Saint Luke's Hospital—Director, Interventional Cardiology Fellowship; Women's Heart NY—Director; Icahn School of Medicine at Mount Sinai Hospital—Assistant Professor of Medicine	None	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 to this document. 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% of the voting stock or share of the business entity, or ownership of ≥\$5,000 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 that exist with no financial benefit are also included for the purpose of transparency. Relationships in this table are modest unless otherwise noted. Names are listed in alphabetical order within each category of review. According to the ACC, a person has a *relevant* relationship if: a) the *relationship or interest* relates to the same or similar subject matter, intellectual property or asset, topic, or issue addressed in the *document*; b) the *company/entity* (with whom the relationship exists) makes a drug, drug class, or device addressed in the *document*, or makes a competing drug or device addressed in the *document*; or c) the *person or a member of the person's household*, has a reasonable potential for financial, professional, or other personal gain or loss as a result of the issues/content addressed in the *document*.

*Significant (>\$5,000) relationship.

ACC = American College of Cardiology; HRS = Heart Rhythm Society; SCAI = Society for Cardiovascular Angiography and Interventions.