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Left atrial thrombus resolution in atrial fibrillation or flutter: Results of a prospective study with rivaroxaban (X-TRA) and a retrospective observational registry providing baseline data (CLOT-AF)

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Background  Data on left atrial/left atrial appendage (LA/LAA) thrombus resolution after non–vitamin K antagonist (VKA) oral anticoagulant treatment are scarce. The primary objective of X-TRA was to explore the use of rivaroxaban for the resolution of LA/LAA thrombi in patients with nonvalvular atrial fibrillation (AF) or atrial flutter, with the CLOT-AF registry providing retrospective data after standard-of-care therapy in this setting.

Methods  X-TRA was a prospective, single-arm, open-label, multicenter study that investigated rivaroxaban treatment for 6 weeks for LA/LAA thrombus resolution in patients with nonvalvular AF or atrial flutter and LA/LAA thrombus confirmed at baseline on a transesophageal echocardiogram (TEE). CLOT-AF retrospectively collected thrombus-related patient outcome data after standard-of-care anticoagulant treatment for 3 to 12 weeks in patients with nonvalvular AF or atrial flutter who had LA/LAA thrombi on TEE recorded in their medical file.

Results  In X-TRA, patients were predominantly (95.0%) from Eastern European countries. The adjudicated thrombus resolution rate was 41.5% (22/53 modified intention-to-treat [mITT] patients, 95% CI 28.1%-55.9%) based on central TEE assessments. Resolved or reduced thrombus was evident in 60.4% (32/53 mITT patients, 95% CI 46.0%-73.6%) of patients. In CLOT-AF, the reported thrombus resolution rate was 62.5% (60/96 mITT patients, 95% CI 52.0%-72.2%) and appeared better in Western European countries (34/50; 68.0%) than in Eastern European countries (26/46; 56.5%).

Conclusion  X-TRA is the first prospective, multicenter study examining LA/LAA thrombus resolution with a non-VKA oral anticoagulant in VKA-naïve patients or in patients with suboptimal VKA therapy. Rivaroxaban could be a potential option for the treatment of LA/LAA thrombi. (Am Heart J 2016;178:126-34.)

Atrial fibrillation (AF) predisposes patients to the development of atrial thrombi, most often in the left atrial (LA) appendage (LAA). Left atrial appendage thrombi are the dominant source of embolism (>90%) in patients with nonvalvular AF,1,2 and LA/LAA thrombi are identified in ~10% of patients with AF.3 The use of a transesophageal echocardiogram (TEE) is an established standard for detecting the presence of LA/LAA thrombi.4-6 If an LA/LAA thrombus is detected on a TEE, current guidelines1,7 recommend vitamin K antagonist (VKA) treatment with a therapeutic international normalized ratio (INR) of 2.0 to 3.0 for at least 3 weeks and a follow-up TEE to ensure thrombus resolution prior to interventions such as cardioversion. However, reported thrombus resolution rates with VKAs vary between
approximately 50% and 90% after a median of 4 weeks’ treatment. Reasons for this wide range of resolution rates include differences in patient populations (eg, with or without the inclusion of valvular AF; first diagnosed or persistent AF) and anticoagulation strategies/treatment durations, or the use of imaging strategies evaluated in relatively small observational studies. Data on LA/LAA thrombus resolution after non-VKA oral anticoagulant (NOAC) treatment are scarce and largely comprise case reports, which generally indicate favorable outcomes.

The primary objective of the prospective X-TRA study was to explore the use of the NOAC rivaroxaban for the resolution of LA/LAA thrombi in patients with nonvalvular AF or atrial flutter who had a TEE-confirmed LA/LAA thrombus. The objective of the CLOT-AF registry was to provide retrospective thrombus-related patient outcome data after standard-of-care anticoagulant treatment in patients with nonvalvular AF or atrial flutter who had TEE-documented LA/LAA thrombi.

Methods
Study design and patient population
X-TRA study. In brief, the X-TRA study (ClinicalTrials.gov identifier NCT01839357) was a prospective, interventional, single-arm, open-label, multicenter study, as described previously. X-TRA was designed to explore once-daily (od) rivaroxaban (20 mg od, or 15 mg od in patients with creatinine clearance 15–49 mL/min) for the resolution of LA/LAA thrombi in patients with nonvalvular AF or atrial flutter and LA/LAA thrombus confirmed using a TEE at baseline. Eligible patients had to be VKA/NOAC naïve or untreated within 1 month prior to signing the informed consent form (treatment of up to 72 hours with VKA, heparin, or a low-molecular-weight heparin was allowed before the start of rivaroxaban), or, following an amendment, VKA pretreated but with suboptimal or ineffective INR levels (ie, <2.0, documented with at least 2 consecutive measurements that were at least 24 hours apart) within the last 6 weeks. The primary end point was the complete LA/LAA thrombus resolution rate on the centrally adjudicated end-of-treatment (EOT) TEE after 6 weeks’ treatment with rivaroxaban. The secondary objectives were centrally adjudicated categories of thrombus outcome (resolved, reduced, unchanged, larger, or new) confirmed on TEE at EOT, incidence of the composite of stroke and noncentral nervous system systemic embolism at EOT and during follow-up, and incidence of all bleeding events (major bleeding according to International Society on Thrombosis and Haemostasis criteria and nonmajor, unknown severity).

Thrombus assessment
X-TRA study. To ensure an objective assessment, TEE images were assessed centrally by independent adjudicators in a blinded fashion without knowledge of whether an image was pretreatment or posttreatment. The adjudicators were specialists in cardiology with a specific interest in TEE who were not otherwise involved in the study.

Each TEE was reviewed by 2 adjudicators. Both had to agree in their assessment, that is, absence of a thrombus or degree of thrombus burden. A third adjudicator performed the final judgment if their assessment differed by >1 mm for thrombi with an average thrombus diameter ≤10 mm, by >2 mm for thrombi with an average diameter >10 to ≤20 mm, or by >3 mm for thrombi with an average diameter >20 mm.

Predefined thrombus outcome criteria were as follows: “resolved” if no thrombus was detectable on the EOT TEE and “reduced”/“larger” if the thrombus was smaller/larger than at baseline (dependent on thrombus size). To qualify as a reduction or an increase compared with baseline, the thrombus size had to be reduced/enlarged by >1 mm for thrombi <10 mm in diameter at baseline, by >2 mm for thrombi of 10 to ≤20 mm in diameter at baseline, and by >3 mm for thrombi >20 mm in diameter at baseline. If the change was <1 mm, the thrombus outcome was assessed as “unchanged.” A “new” thrombus was one that had not been present on the baseline TEE. Patients were categorized according to the most severe category into which any thrombus fell.

CLOT-AF registry. The image assessment was used as recorded in the patients’ medical file without adjudication, in contrast to X-TRA.

Ethical considerations
For both studies, approval from the appropriate independent ethics committee/institutional review board was obtained for all participating centers before the start of the study, in accordance with the ethical principles of the Declaration of Helsinki, Good Clinical Practice and local laws, regulations, and organizations, as applicable. Informed consent was obtained from all patients; for the CLOT-AF registry, informed consent
from a primary relative was also accepted if allowed by local regulations.

Statistical evaluation

In both studies, statistical analyses were of an explorative and descriptive nature. Mean values were calculated based on the number of available data. Frequency distributions include a category for missing data, if applicable. The studies did not aim to confirm or refute any predefined hypotheses. Statistical evaluations were performed using the software package SAS release 9.4 (SAS Institute Inc, Cary, NC).

**X-TRA study.** The sample size was estimated based on the expected presence of LA/LAA thrombi detected on a TEE in the participating study sites and aimed to enroll 60 patients. Enrolled patients were analyzed on an intention-to-treat (ITT) basis. Patients with complete data on baseline and EOT TEEs were included in the modified ITT (mITT) population. The primary analysis evaluated the thrombus outcome in the mITT population. Exact (Clopper-Pearson) 95% CIs for the probability of complete thrombus resolution in the LA/LAA were calculated. As a sensitivity analysis (worst-case scenario applied), thrombus resolution was calculated based on the ITT population, considering patients without an evaluable EOT TEE as having resolved a thrombus. In addition, exact (Clopper-Pearson) 95% CIs were calculated for the combined category of resolved/reduced.

**CLOT-AF registry.** No sample size was calculated, but at the planned 15 to 20 study sites, the inclusion of ~150 patients was expected. The ITT population was the number of eligible and enrolled patients, and the mITT population was the number of patients with baseline and EOT TEEs. The primary analysis evaluated the thrombus resolution rate using exact (Clopper-Pearson) 95% CIs in the mITT patient population.

As best-/worst-case analyses, thrombus resolution was calculated based on the ITT population, considering patients without an evaluable EOT TEE as having resolved thrombus/still having a thrombus.

The studies were funded by Bayer Pharma AG. The authors are responsible for the design and conduct of the studies and all study analyses, the drafting of the manuscript, and its final contents.

**Results**

Disposition of patients, demographics, and baseline characteristics

**X-TRA study.** The X-TRA study was conducted at 17 study centers in 7 countries between August 2013 and December 2014. A total of 60 patients were included in the ITT population. The mITT population with complete TEE data encompassed 53 patients: 7 patients were excluded from the mITT population, of these, 4 patients had no thrombus at baseline TEE as adjudicated (1 patient withdrew from the study because of an adverse event), and 3 patients had no EOT TEE (1 patient died of acute heart failure, 1 patient emigrated to another country because of a war, and 1 patient was hospitalized for heart transplantation). The patient disposition is summarized in Figure. No patients were lost to follow-up.

Almost all patients (95.0%) were from Eastern European countries, half were male, and mean patient age was 70 years, with most patients (61.7%) being 65 years or older. Mean body weight was 85 kg, and 48.3% of patients had a body mass index of ≥30 kg/m².

Approximately three-quarters of patients (76.6%) presented with persistent, long-standing persistent, or permanent AF. The median CHADS2 and CHA2DS2-VASc scores were 2 and 4, respectively; most patients were in the high-risk category—66.7% of patients had a CHADS2 score of ≥2.0 and 83.3% had a CHA2DS2-VASc score of ≥2.0. The most common risk factors were hypertension (81.7%), heart failure (55.0%), prior stroke/transient ischemic attack (18.3%), and diabetes (15.0%). Approximately three-quarters of the patients (76.7%) had no prior VKA or NOAC treatment (Table I, ITT). These patients were VKA/NOAC naïve or untreated according to the original study design before the last amendment of the protocol. Results of the TEE analysis are summarized in online Supplementary Table I. According to the central TEE assessment, a total of 55 LA thrombi (mean values ± SD: diameter 15 ± 7.5 mm, area 130.8 ± 108.6 mm²) and 3 LA thrombi (mean values ± SD: diameter 18.7 ± 3.8 mm, area 162.7 ± 72.6 mm²) were detected on TEE in 53 patients (mITT population), in which 5 patients had 2 thrombi (all in the LAA except for 1 LA thrombus).

**CLOT-AF registry.** Medical records at the study sites encompassed the period from January 2010 to February 2013. Only the extension of the originally planned screening period from January 2011 to January 2010 allowed us to meet the target number of ~150 patients. The retrospective CLOT-AF registry included 156 patients in the ITT population at 23 centers of the same 7 countries as in X-TRA. The mITT population with complete TEE data encompassed 96 patients (Figure).

In contrast to the X-TRA study, patient numbers were balanced between Eastern (52.6%) and Western (47.4%) European countries. In total, 66.0% of the patients were male, and mean patient age was 68 years; 62.0% were 65 years or older. Mean body weight was 82 kg, and 25.0% of patients had a body mass index of ≥30 kg/m².

The number of patients with persistent, long-standing persistent, or permanent AF was 56.4%; information on the type of AF was missing for 22.4% of patients. The median CHADS2 and CHA2DS2-VASc scores were 2.0 and 3.0, respectively. The most common risk factors were hypertension (81.4%), heart failure (48.1%), diabetes (22.4%), and myocardial infarction (16.7%); prior stroke/transient ischemic attack was recorded in 10.3% of patients (Table I, ITT).
Before the start of the observation period, 55.8% of patients were VKA naïve. Owing to the retrospective nature of this registry, only limited information on prior VKA use and INR monitoring was available.

Treatment in X-TRA and observation in CLOT-AF

**X-TRA study.** Most (81.7%) of the ITT patients received oral rivaroxaban 20 mg od; 18.3% with moderate-to-severe renal impairment received the lower dose of 15 mg od. Mean compliance calculated by tablet accountability was almost 100%. The mean treatment duration was 46 days (ITT, mITT). Most patients had their EOT TEE performed within the recommended time frame, after 6 to 8 weeks of rivaroxaban treatment (85.0% ITT, 90.6% mITT).

**CLOT-AF registry.** A total of 148 (94.9%) of 156 patients had a record of any anticoagulation treatment. In most patients, the anticoagulant treatment was a VKA (127/156 patients; 81.4%), either prescribed alone or in combination with another treatment (most often low molecular weight heparin or unfractionated heparin). For those treated with a VKA, the types of VKA used included acenocoumarin in 45 patients (28.8%), warfarin in 29 patients (18.6%), phenprocoumon in 27 patients (17.3%), fluindione in 25 patients (16.0%), and 1 patient with dicoumarol (0.6%).

The observation period started with the diagnosis of an LA/LAA thrombus on the baseline TEE. In the mITT population, 83.3% of patients had the protocol-defined observation period of 3 to 12 weeks; for 5 patients (5.2%), this period was <3 weeks or unknown, and for 11 patients (11.5%), it was >12 weeks (up to 6 months).

**Thrombus resolution rates**

**X-TRA study.** In the X-TRA study, the thrombus resolution rate was 41.5% by patient (22/53 mITT patients, 95% CI 28.1%-55.9%) based on central TEE assessments (Table II). Resolved or reduced thrombus was evident in 60.4% (32/53 mITT patients, 95% CI 46.0%-73.6%) of patients (Table II). Thrombus resolution rates in subgroups are presented in online Supplementary Table II. Patients with thrombus resolution tended to have lower thromboembolic risk scores (CHADS2/CHA2DS2-VASc) and to be older (aged >75 years).

The resolution rate by individual thrombus outcome was 46.6% (27/58, mITT). With regard to the 5 patients with 2 thrombi each at baseline, at EOT 2 patients had both their LAA thrombi resolved, 2 patients had 1 LAA...
thrombus resolved and 1 thrombus unchanged (LAA in 1 patient and LA in 1 patient), and 1 patient had 1 LAA thrombus resolved and 1 enlarged (maximum area 50–51 mm², maximum diameter 6–10 mm). Of the 2 patients with a single LA thrombus at baseline, in 1 patient the LA thrombus was resolved and in the other there was no LA thrombus at EOT, but an LAA thrombus appeared.
In the CLOT-AF registry, the recorded thrombus resolution rate was 62.5% (60/96 mITT patients, 95% CI 52.0%-72.2%) (Table II). The thrombus resolution rate was better in patients from Western European countries (68.0%; 34/50 patients) than from Eastern European countries (56.5%; 26/46 patients) (Table II). The thrombus resolution rate for the 80 patients who had both TEEs performed within the range of 3 to 12 weeks was 61.2% (95% CI 50.0%-71.9%), that is, similar to the 62.5% reported for the 96 patients who had 2 TEEs.

**Secondary outcome measures**

**X-TRA study.** There were no reports of stroke or noncentral nervous system systemic embolism during the treatment period and the 30-day follow-up. In addition, no patients experienced a major bleeding event. Nonmajor bleeding events were recorded in 5 patients (Table III).

All patients took at least one tablet of study medication. Treatment-emergent adverse events (TEAEs) occurred in 36.7% of patients. Treatment-emergent adverse events reported in more than a single patient were bradycardia, cardiac failure, hyperthyroidism, nausea, peripheral edema, thyroid neoplasm, headache, and chronic renal failure. Overall, 3 patients experienced TEAEs that were assessed by the investigator as related to the study drug (ear hemorrhage, gingival bleeding, and petechia). The drug-related treatment-emergent serious adverse event rate was 1.7%.

**CLOT-AF registry.** Stroke/noncentral nervous system systemic embolism after baseline TEE or with unknown start date was recorded for 4 of the 156 patients. A major bleeding event was recorded for 1 patient who had spontaneous nonhemorrhoidal bleeding in the gastrointestinal tract (with INR <2.0) (Table III).

**Discussion**

Current guidelines recommend VKA therapy for 3 weeks upon detection of an LA/LAA thrombus in patients with AF and long-term treatment for those with a residual thrombus, but existing clinical evidence supporting the use of NOACs for LA/LAA thrombus resolution is limited to isolated case reports or small case series (usually from single-center studies). The X-TRA study is the first prospective, multicenter, interventional study examining thrombus resolution with a NOAC (rivaroxaban) in VKA-naïve patients or patients receiving suboptimal or ineffective VKA therapy (INR <2.0). The results showed that resolved or reduced thrombus (as assessed centrally by blinded, independent adjudicators) was evident in 60.4% of the mITT patient population including 2 patients with 2 thrombi resolved in each case, demonstrating the potential of rivaroxaban in this setting.

In X-TRA, patients were predominantly from Eastern European countries; approximately three-quarters were treatment naïve or untreated, and most had persistent or permanent AF. This particularly reflects the gap between guideline recommendation and local practice in reality, which means those patients with diagnosed AF were not adequately treated with an oral anticoagulant as recommended. Owing to the limitations of TEE and other imaging modalities, it could not be confirmed whether

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**Table II. Resolution rates of LA/LAA thrombi**

<table>
<thead>
<tr>
<th>Evaluation set</th>
<th>Total n</th>
<th>Thrombus resolved</th>
<th>%</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prospective X-TRA study</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete thrombus resolution</td>
<td>mITT 53</td>
<td>22</td>
<td>41.5</td>
<td>28.1-55.9</td>
</tr>
<tr>
<td>assessed by blinded adjudicators</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete thrombus resolution</td>
<td>ITT 60</td>
<td>22</td>
<td>36.7</td>
<td>24.6-50.1</td>
</tr>
<tr>
<td>assessed by blinded adjudicators, worst-case scenario considering subjects without EOT TEE as nonresolved</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resolved or reduced thrombus</td>
<td>mITT 53</td>
<td>32</td>
<td>60.4</td>
<td>46.0-73.6</td>
</tr>
<tr>
<td>assessed by blinded adjudicators</td>
<td></td>
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<tr>
<td>Retrospective CLOT-AF registry</td>
<td></td>
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</tr>
<tr>
<td>Complete thrombus resolution</td>
<td>mITT 96</td>
<td>60</td>
<td>62.5</td>
<td>52.0-72.2</td>
</tr>
<tr>
<td>Complete thrombus resolution by region</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eastern Europe</td>
<td>mITT 46</td>
<td>26</td>
<td>56.5</td>
<td>41.1-71.1</td>
</tr>
<tr>
<td>Western Europe</td>
<td>mITT 50</td>
<td>34</td>
<td>68.0</td>
<td>53.3-80.5</td>
</tr>
<tr>
<td>Complete thrombus resolution, worst-case scenario considering subjects without EOT TEE as nonresolved</td>
<td>ITT 156</td>
<td>60</td>
<td>38.5</td>
<td>30.8-46.6</td>
</tr>
<tr>
<td>Complete thrombus resolution, best-case scenario considering subjects without EOT TEE as resolved</td>
<td>ITT 156</td>
<td>120</td>
<td>76.9</td>
<td>69.5-83.3</td>
</tr>
</tbody>
</table>

* This includes 2 patients who had 2 thrombi each. Both thrombi were resolved in each case.
† In 12 patients (22.6%), thrombi were larger, and in another 9 patients (17.0%), thrombi were found unchanged (blinded central assessment); no patients had a new thrombus.
patients had recently formed a thrombus in their LA/LAA or if they had an “old” thrombus at screening.

Based on the rate of resolved/reduced thrombi after rivaroxaban treatment, and the fact that there were no stroke or thromboembolic events during treatment and follow-up and favorable safety data, rivaroxaban seems to be a treatment option for patients with nonvalvular AF or atrial flutter and an LA/LAA thrombus. Data from prospective studies of the other NOACs in this setting are currently lacking, although one prospective study with dabigatran is ongoing. In this context, the X-TRA study provides important insights into a challenging clinical problem and the potential of NOACs for this subgroup of AF patients.

It should be noted that in X-TRA, the duration of AF or atrial flutter was not recorded. It might be the case that the longer patients had AF for, the higher the possibility that they had “old” LA/LAA thrombi (especially if that they were not treated with an oral anticoagulant as recommended). In the X-TRA study, 76.6% of patients had persistent or permanent AF and 76.7% had no prior use of an oral anticoagulant. Therefore, some patients might have had “old” LA/LAA thrombi instead of a newly formed thrombus. These may be part of the reasons for the relatively lower than expected resolution rate observed in X-TRA (eg, >80%). However, in one prospective and serial study, the LAA thrombus resolution rates were 16% at 1 month, 42% at 3 months, and 56% at 12 months. This finding provides encouragement that residual thrombi might be resolved with continuous long-term anticoagulation treatment, which is in line with guideline recommendations.

Published data on LA/LAA thrombus resolution rates after VKA therapy vary, and the reported resolution rate in a prospective study was relatively low. To further understand how patients with nonvalvular AF or atrial flutter who had LA/LAA thrombi on a TEE were treated in routine practice and their outcomes, the retrospective CLOT-AF registry collected data between 2010 and 2013 from the same 7 countries as X-TRA to reflect standard-of-care in those health care settings. The reported thrombus resolution rates were also lower than expected (eg, >80%) but still within the expected range after VKA treatment; however, approximately one-third of the data were missing in this retrospective registry, which limits the generalization of the data.

Furthermore, a direct comparison of the results of X-TRA and CLOT-AF cannot be made because of the nature of the studies (prospective adjudicated study vs retrospective nonadjudicated registry), differences in patient demographics and disease severity, as well as data quality (ie, centrally adjudicated data vs hospital medical records). Thus, our results report descriptive observations, and no causality is implied.

What is most important for the patients from a clinical perspective? Ultimately it is about whether the patients are safe from major clinical events. In the X-TRA study, no stroke or peripheral embolism or major bleeding was reported during the 6-week treatment period and the 30-day follow-up period. The overall reported rate for TEAEs and bleeding events was in the expected range observed in other phase III/IV studies of rivaroxaban and the drug-related treatment-emergent serious adverse event rate was also low (1.7%). Thus, no safety concerns were raised in X-TRA.

In conclusion, the X-TRA study showed that resolved or reduced thrombus after rivaroxaban treatment was evident and consistent with LA/LAA thrombus resolution with VKA therapy from prior retrospective observational case series and the retrospective CLOT-AF registry. The results suggest that rivaroxaban seems to be a potential option for the treatment of TEE-detected LA/LAA thrombi in patients with AF or atrial flutter.

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Disclosures

G.Y.H.L. wrote the first draft and finalized the submission draft. All other authors contributed significantly to the development of this manuscript and approved the final draft for submission.

G.Y.H.L. is a member of various guideline and position statement committees (including ECS, EHRA, NICE); is a member of steering committees for various phase II and phase III, and health economics & outcomes research studies; is an investigator in various clinical trials in cardiovascular disease, including those on antithrombotic therapies in AF, acute coronary syndrome, and lipids; has been a consultant for Bayer/Janssen, Astellas, Merck, Sanofi, BMS/Pfizer, Biotronik, Medtronic, Portola, Boehringer Ingelheim, Microlife, Roche, and Daiichi-Sankyo; and has been a speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Microlife, Roche, and Daiichi-Sankyo.

C.H. has received research grants from Sanofi-Aventis and has received speaker’s honoraria from Bayer, Boehringer Ingelheim, and Pfizer. F.M. has received funding for research and acted as a consultant for and lecturing on behalf of Abbott, Boston Scientific, Bayer, AstraZeneca, Daiichi Sankyo, Bristol-Myers Squibb/Pfizer, and Boehringer Ingelheim. R.C. has received consultancy fees or research funding from Boston Scientific, Medtronic, St. Jude, Biosense Webster, Boehringer Ingelheim, Bayer, Abbott, ELA Sorin, Pfizer, and BARD medical, and has equity and intellectual property rights in Cameron. I.L.M., B.K., and M.V.E. are employees of Bayer Pharma AG. A.C. has received a research grant for research nurses (RESICARD) and consultant and lecture fees from AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, GlaxoSmithKline, and Sanofi-Aventis.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ahj.2016.05.007.

Appendix B. List of investigators

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