Dronedarone for the treatment of atrial fibrillation with concomitant heart failure with preserved and mildly reduced ejection fraction: a post-hoc analysis of the ATHENA trial

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Aims

Limited therapeutic options are available for the management of atrial fibrillation/flutter (AF/AFL) with concomitant heart failure (HF) with preserved (HFP EF) and mildly reduced ejection fraction (HFmrEF). Dronedarone reduces the risk of cardiovascular events in patients with AF, but sparse data are available examining its role in patients with HF complicated by HFP EF and HFmrEF.

Methods and results

ATHENA was an international, multicentre trial that randomized 4628 patients with paroxysmal or persistent AF/AFL and cardiovascular risk factors to dronedarone 400 mg twice daily versus placebo. We evaluated patients with (i) symptomatic HFP EF and HFmrEF (defined as left ventricular ejection fraction [LVEF] >40%, evidence of structural heart disease, and New York Heart Association class II/III or diuretic use), (ii) HF with reduced ejection fraction (HFrEF) or left ventricular dysfunction (LVEF ≤40%), and (iii) those without HF. We assessed effects of dronedarone versus placebo on death or cardiovascular hospitalization (primary endpoint), other key efficacy endpoints, and safety. Overall, 534 (12%) had HFP EF or HFmrEF, 422 (9%) had HFrEF or left ventricular dysfunction, and 3672 (79%) did not have HF. Patients with HFP EF and HFmrEF had a mean age of 73 ± 9 years, 37% were women, and had a mean LVEF of 57 ± 9%. Over a mean follow-up of 21 ± 5 months, dronedarone consistently reduced risk of death or cardiovascular hospitalization (hazard ratio 0.76; 95% confidence interval 0.69–0.84) with no heterogeneity based on HF status (pinteraction >0.10). This risk reduction in the primary endpoint was consistent across the range of LVEF (as a continuous function) in HF without heterogeneity (pinteraction = 0.71). Rates of death, cardiovascular hospitalization, and HF hospitalization each directionally favoured dronedarone versus placebo in HFP EF and HFmrEF, but these treatment effects were not statistically significant in this subgroup.

Conclusions

Dronedarone is associated with reduced cardiovascular events in patients with paroxysmal or persistent AF/AFL and HF across the spectrum of LVEF, including among those with HFP EF and HFmrEF. These data support a rationale for a future dedicated and powered clinical trial to affirm the net clinical benefit of dronedarone in this population.

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Dronedarone in AF and HFpEF

Graphical Abstract

Dronedarone for the treatment of atrial fibrillation with concomitant heart failure with preserved and mildly reduced ejection fraction: a post-hoc analysis of the ATHENA trial.

Keywords
Antiarhythmic drugs • Atrial fibrillation • Dronedarone • Heart failure with preserved ejection fraction

Introduction

Sustained atrial arrhythmias frequently complicate heart failure (HF) with preserved (HFpEF) and mildly reduced ejection fraction (HFmrEF), in part related to rising rates of obesity and shared cardiometabolic risk factors. One in two patients enrolled in recent HFpEF clinical trials have a history of atrial fibrillation or flutter (AF/AFL) and a substantial proportion of patients with AF with unexplained dyspnoea may in fact have occult HFpEF. Comorbid AF and HFpEF are independently associated with excess cardiovascular risks and adverse health status, and may represent a distinct phenotype distinguished by marked left atrial mechanical dysfunction, congestion, mitral annular dilatation often with atrial functional mitral regurgitation, and perturbed myocardial performance. Indeed, increasing AF burden is closely correlated with progressive left atrial remodelling, elevated filling pressures, and clinical risk, and may represent a marker of disease progression in HFpEF.

Despite this substantial clinical overlap and the recognition of AF as a potential therapeutic target in HFpEF, limited evidence-based strategies are available for its management. Designed as a non-iodinated congener of amiodarone with less tissue accumulation, dronedarone has been previously shown to increase mortality among hospitalized decompensated patients with HF and severe left ventricular dysfunction. Whether its use in patients with HFpEF and AF in more stable settings can improve outcomes remains unknown. The recent 2020 European Society of Cardiology AF guideline provides a Class IA recommendation for dronedarone for long-term rhythm control in patients with AF and HFpEF. This recommendation is based, in part, on its reassuring safety profile and effectiveness in real-world evaluation. Given the limited evidence from randomized trials evaluating dronedarone in populations of HF with higher left ventricular ejection fraction (LVEF), we examined the efficacy and safety of dronedarone among patients with paroxysmal or persistent AF/AFL and HFpEF/HFmrEF in the ATHENA (A Placebo-Controlled, Double-Blind, Parallel Arm Trial to Assess the Efficacy of Dronedarone 400 mg bid for the Prevention of Cardiovascular Hospitalization or Death from Any Cause in Patients with Atrial Fibrillation/Atrial Flutter) trial (ClinicalTrials.gov Identifier: NCT00174785).

Methods

ATHENA trial population

The design and primary results of ATHENA have been previously published. In brief, ATHENA was a randomized, double-blind, placebo-controlled trial that randomized high-risk patients with paroxysmal or persistent AF/AFL to either dronedarone 400 mg twice daily or matching placebo. The pre-specified high-risk features for enrolment included at least one of the following: age ≥70 years, hypertension requiring two or more antihypertensive therapies, diabetes mellitus, prior stroke, transient ischaemic attack, or systemic embolism, left
atrial enlargement, or LVEF ≤40%. During the trial, an amendment allowed enrollment of patients aged ≥75 years (without additional risk factors) but required those aged ≥70 years to have one other risk factor and those younger than 70 years no longer met eligibility. Exclusion criteria included permanent AF, decompensated HF within 4 weeks, New York Heart Association (NYHA) class IV functional status, or life-limiting non-cardiac illness. All participants provided written informed consent and the institutional review boards or local ethics committees at each participating site approved the study protocol.

Identifying heart failure with preserved ejection fraction in ATHENA

Within the overall ATHENA study population, we evaluated patients with AF/AFL and (i) symptomatic HFrEF or HFrEF; (ii) HF with reduced ejection fraction (HFrEF) or left ventricular dysfunction (LVEF ≤40%); and (iii) those without HF. We adapted previously employed criteria from prior clinical trials to define HFrEF/HFrEF to require (i) LVEF >40%; (ii) evidence of structural heart disease defined as left atrial enlargement (length on M-mode ≥50 mm) or investigator-reported left ventricular cardiomyopathy; and (iii) NYHA functional class II/III or diuretic use (other than spironolactone) at baseline.

Efficacy and safety outcomes

Patients were followed at day 7, day 14, months 1, 3, 6, 9, and 12, and every 3 months thereafter. The primary endpoint of ATHENA was time to first occurrence of all-cause mortality or cardiovascular hospitalization. Other endpoints of interest for this analysis included components of the primary composite endpoint (which were both pre-specified secondary endpoints in ATHENA), stroke, HF hospitalization, and first AF/AFL recurrence. We additionally evaluated adverse events, including those that led to premature drug discontinuation, as key safety measures.

Statistical analyses

All baseline characteristics were summarized as number (%) or mean (standard deviation) between study arms, stratified by HF status (HFrEF/HFrEF, HFrEF/left ventricular dysfunction, no HF). Kaplan–Meier curves were generated by study arm for the primary composite endpoint for each of the groups. Cox proportional hazards models were used to evaluate time to first events among each of these groups with interaction testing between treatment effects with dronedarone and HF status (based on these three categorical groups). In addition, among patients with HF or left ventricular dysfunction, the relationship between LVEF (as a continuous measure with restricted cubic splines) and treatment effect was evaluated. Additionally, a sensitivity analysis relaxing the criteria to define HFrEF/HFrEF to remove the requirement for structural heart disease was conducted. Two-tailed p-values <0.05 were considered statistically significant. No adjustment was made for multiple comparisons given the exploratory nature of this work.

Results

Baseline characteristics

Across 551 sites in 37 countries, a total of 4628 participants were enrolled in ATHENA. Overall, 534 (12%) had HFrEF or HFrEF, 422 (9%) had HFrEF or left ventricular dysfunction, and 3672 (79%) did not have HF. Patients with HFrEF and HFrEF had a mean age of 73 ± 9 years, 37% were women, and had a mean LVEF of 57 ± 9% (22% with LVEF 41–49%, 36% with LVEF 50–59%, and 42% with LVEF ≥60%). In those with HFrEF and HFrEF, β-blockers were used in 77%, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in 78%, spironolactone in 8%, digoxin in 18%, and oral anticoagulants in 72%. Baseline characteristics overall and in the HFrEF/HFrEF subgroup were well balanced between study arms (Table 1).

Efficacy and safety outcomes

Over a mean follow-up of 21 ± 5 months, 1651 patients in ATHENA experienced a first primary endpoint (death or cardiovascular hospitalization), including 221 patients with HFrEF/HFrEF. Placebo-treated patients with HFrEF or HFrEF faced risks of death or cardiovascular hospitalization (57 [50–64] per 100 patient-years) comparable to those in HFrEF or left ventricular dysfunction (54 [47–62] per 100 patient-years; p = 0.37) and higher than risks in those without HF (41 [39–44] per 100 patient-years; p = 0.03) (online supplementary Figure S1).

Dronedarone consistently reduced risk of death or cardiovascular hospitalization (hazard ratio [HR] 0.76, 95% confidence interval [CI] 0.69–0.84) without heterogeneity based on HF status (pinteraction >0.10) (Figures 1 and 2). In those with HFrEF and HFrEF, dronedarone was associated with a HR of 0.79 (95% CI 0.59–1.00) for the primary endpoint with an absolute risk difference of 13 per 100 patient-years. Risk reductions appeared relatively consistent across LVEF 41%–49% (HR 0.81, 95% CI 0.44–1.48), LVEF 50%–59% (HR 0.94, 95% CI 0.59–1.49), and LVEF ≥60% (HR 0.68, 95% CI 0.47–1.006). The lower hazards with dronedarone for the primary endpoint were consistent across a range of LVEF (as a continuous function) in HF without heterogeneity (pinteraction = 0.71) (Figure 3).

Rates of death, cardiovascular hospitalization, and HF hospitalization each directionally favoured dronedarone versus placebo in HFrEF/HFrEF, but these treatment effects were not statistically significant. In the HFrEF/HFrEF subgroup, there were 45 death events in follow-up and dronedarone was associated with an HR of 0.59 (95% CI 0.33–1.09). In HFrEF/HFrEF, any treatment-emergent adverse events (36% vs. 36%) or serious treatment-emergent adverse events (13% vs. 13%) were similar between arms, but dronedarone increased rates of permanent drug discontinuation due to treatment-emergent adverse events (7% vs. 4%) (Figure 4). These consisted mainly of gastrointestinal adverse effects such as nausea or diarrhea.

Sensitivity analysis with broader heart failure with preserved ejection fraction selection criteria

In a sensitivity analysis, we identified 2353 individuals meeting less stringent criteria for HFrEF or HFrEF by removing requirement for structural heart disease (online supplementary Figure S2). In this cohort, dronedarone was associated with a lower risk of
Abstract

These data support the safety and efficacy of dronedarone in paroxysmal or persistent AF/AFL and HF with higher LVEF (Graphical Abstract).

Despite recent European Society of Cardiology AF guideline Class IA recommendations for the use of dronedarone as a rhythm control strategy in AF with HFpEF, there has been limited randomized clinical trial evidence in this special population. A previous ATHENA secondary analysis focused on 209 participants with symptomatic HFrEF with NYHA class II or III symptoms. We extended this assessment to patients with any left ventricular systolic dysfunction (LVEF ≤40%) irrespective of symptoms and evaluated patients at higher LVEF. ATHENA specifically enriched enrolment of older adults and those with abnormalities of myocardial structure or function and AF/AFL, and thus it was expected that many may have HFpEF. As HFrEF diagnoses were not prospectively assessed by investigators in ATHENA, we relied on retrospective application of established criteria. To improve specificity of this retrospective approach, we employed a rigorous definition similar to ones used in contemporary HFrEF clinical trials (requiring mildly reduced or preserved left ventricular function, structural heart disease, and symptoms of HF or active diuretic use). Consistent treatment effects were observed even at higher LVEFs (so-called ‘true HFrEF’) in spline analyses without attenuation at LVEF ≥60% as has been seen with some HF therapies. Furthermore, sensitivity analyses with less stringent HFrEF diagnostic criteria yielded consistent benefits, including lower all-cause mortality in those randomized to dronedarone. While this broader selection criteria may lessen the certainty of a HFrEF diagnosis, it has been demonstrated that the majority of these patients with AF/AFL and preserved left ventricular function with dyspnoea may...

Table 1  Baseline characteristics in the ATHENA trial by heart failure status

|                  | HFpEF or HFmrEF | HFrEF or LV dysfunction | No HF       |
|------------------|-----------------|-------------------------|-------------|
|                  | Dronedarone     | Placebo                 | Dronedarone | Placebo | Dronedarone | Placebo |
| **Age, years, mean (SD)** |                 |                         |             |         |             |         |
| Women            | 71.6 (8.9)      | 72.5 (9.1)              | 71.3 (9.4)  | 72.5 (9.2) | 71.6 (8.9)  | 71.5 (9.0) |
| Women            | 110 (41.4%)     | 99 (36.9%)              | 60 (29.9%)  | 66 (29.9%) | 961 (52.4%) | 873 (47.5%) |
| Race             |                 |                         |             |         |             |         |
| White            | 240 (90.2%)     | 246 (91.8%)             | 182 (90.5%) | 200 (90.5%) | 1643 (89.6%) | 1626 (88.5%) |
| Asian            | 16 (6.0%)       | 10 (3.7%)               | 5 (2.5%)    | 8 (3.6%)   | 129 (7.0%)  | 136 (7.4%)  |
| Black            | 5 (1.9%)        | 3 (1.1%)                | 3 (1.5%)    | 6 (2.7%)   | 11 (0.6%)   | 22 (1.2%)   |
| Other            | 5 (1.9%)        | 9 (3.4%)                | 11 (5.5%)   | 7 (3.2%)   | 51 (2.8%)   | 54 (2.9%)   |
| Body mass index ≥30 kg/m² | 120 (45.1%)     | 120 (44.8%)             | 59 (29.4%)  | 64 (29.0%) | 578 (31.5%) | 549 (29.9%) |
| Coronary artery disease | 100 (37.6%)     | 108 (40.3%)             | 99 (49.3%)  | 119 (53.8%) | 462 (25.2%) | 501 (27.3%) |
| Hypertension     | 242 (91.0%)     | 237 (88.4%)             | 148 (73.6%) | 165 (74.7%) | 1609 (87.7%) | 1594 (86.7%) |
| Prior AF/AFL ablation | 17 (6.4%)       | 18 (6.7%)               | 8 (4.0%)    | 13 (5.9%)  | 65 (3.5%)   | 75 (4.1%)   |
| CHA₂DS₂-VASc score | 2.9 (1.1)       | 3.0 (1.1)               | 2.9 (1.2)   | 2.9 (1.1)  | 2.9 (1.1)   | 2.8 (1.1)   |
| LA diameter, mm, mean (SD) | 52.5 (5.5)      | 52.4 (5.8)              | 47.6 (7.1)  | 46.9 (7.7) | 42.5 (5.8)  | 42.4 (6.1)  |
| LVEF, %, mean (SD) | 57.6 (8.8)      | 57.3 (9.1)              | 33.3 (6.6)  | 33.7 (6.3) | 60.0 (7.9)  | 60.2 (8.1)  |
| Implantable cardioverter defibrillator | 5 (1.9%)        | 5 (1.9%)                | 30 (14.9%)  | 28 (12.7%) | 7 (0.4%)    | 10 (0.5%)   |
| Pacemaker        | 30 (11.3%)      | 38 (14.2%)              | 38 (18.9%)  | 39 (17.6%) | 146 (8.0%)  | 166 (9.0%)  |
| Diuretics        | 240 (90.2%)     | 246 (91.8%)             | 123 (61.2%) | 142 (64.3%) | 824 (44.9%) | 836 (45.5%) |
| β-blockers       | 196 (73.7%)     | 205 (76.5%)             | 151 (75.1%) | 174 (78.7%) | 1281 (69.8%) | 1262 (68.7%) |
| Calcium channel blockers | 39 (14.7%)      | 35 (13.1%)              | 21 (10.4%)  | 18 (8.1%)  | 271 (14.8%) | 254 (13.8%) |
| Digoxin          | 47 (17.7%)      | 47 (17.5%)              | 56 (27.9%)  | 59 (26.7%) | 218 (11.9%) | 202 (11.0%) |
| ACEi/ARB         | 209 (78.6%)     | 210 (78.4%)             | 141 (70.1%) | 157 (71.0%) | 1264 (68.9%) | 1235 (67.2%) |
| Spiropironolactone | 29 (10.9%)      | 21 (7.8%)               | 38 (18.9%)  | 44 (19.9%) | 81 (4.4%)   | 71 (3.9%)   |
| Aspirin          | 89 (33.5%)      | 104 (38.8%)             | 91 (45.3%)  | 98 (44.3%) | 838 (45.7%) | 817 (44.5%) |
| Oral anticoagulant | 202 (75.9%)     | 192 (71.6%)             | 149 (74.1%) | 159 (71.9%) | 1052 (57.4%) | 1033 (56.2%) |

ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; AFL, atrial flutter; ARB, angiotensin receptor blocker; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFrEF, heart failure with preserved ejection fraction; HFpEF, heart failure with reduced ejection fraction; LA, left atrial; LV, left ventricular; LVEF, left ventricular ejection fraction; SD, standard deviation.

Discussion

In this post-hoc analysis of the ATHENA trial, dronedarone, when compared with placebo, was consistently associated with lower rates of death or cardiovascular hospitalization (HR 0.78, 95% CI 0.68–0.89) and a number of secondary endpoints including all-cause mortality (HR 0.65, 95% CI 0.45–0.95). There was no evidence of an increase in HF hospitalizations with dronedarone (HR 1.01, 95% CI 0.74–1.39).

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We extended this assessment to patients with any left ventricular systolic dysfunction (LVEF ≤40%) irrespective of symptoms and evaluated patients at higher LVEF. ATHENA specifically enriched enrolment of older adults and those with abnormalities of myocardial structure or function and AF/AFL, and thus it was expected that many may have HFpEF. As HFrEF diagnoses were not prospectively assessed by investigators in ATHENA, we relied on retrospective application of established criteria. To improve specificity of this retrospective approach, we employed a rigorous definition similar to ones used in contemporary HFrEF clinical trials (requiring mildly reduced or preserved left ventricular function, structural heart disease, and symptoms of HF or active diuretic use). Consistent treatment effects were observed even at higher LVEFs (so-called ‘true HFrEF’) in spline analyses without attenuation at LVEF ≥60% as has been seen with some HF therapies. Furthermore, sensitivity analyses with less stringent HFrEF diagnostic criteria yielded consistent benefits, including lower all-cause mortality in those randomized to dronedarone. While this broader selection criteria may lessen the certainty of a HFrEF diagnosis, it has been demonstrated that the majority of these patients with AF/AFL and preserved left ventricular function with dyspnoea may...
**Figure 1** Kaplan–Meier analysis for death or cardiovascular hospitalization in ATHENA by heart failure (HF) status.
in fact have occult HFpEF when rigorously evaluated with invasive haemodynamics.\textsuperscript{3}

In ATHENA, 68% of patients with known onset of their first AF/AFL episode were included \textless 12 months of AF/AFL diagnosis\textsuperscript{20} and this ATHENA analysis is also consistent with a pre-specified secondary analysis of the HF subgroup of the EAST-AFNET 4 trial (Early Treatment of Atrial Fibrillation for Stroke Prevention Trial).\textsuperscript{2}

Among 798 patients with early AF (diagnosed within a year of enrolment) and HF in this trial (83% of whom had HF with mildly reduced or preserved LVEF), early rhythm control reduced cardiovascular events compared with usual care (symptom-directed rhythm control).\textsuperscript{22} Importantly, early rhythm control in HFpEF was mostly achieved with antiarrhythmic drugs (such as flecainide, amiodarone, and dronedarone) in EAST-AFNET 4, while AF ablation was selected by investigators in a minority of individuals.\textsuperscript{22}

Rhythm control was also shown to be an effective strategy in reducing cardiovascular events, extending survival, and improving health-related quality of life in 778 participants with symptomatic HF in the CABANA trial (Catheter Ablation Versus Antiarrhythmic Drug Therapy for Atrial Fibrillation), the vast majority of whom had preserved or mildly reduced LVEF.\textsuperscript{21} Observational studies too have suggested beneficial effects among those with HFpEF treated with rhythm control approaches (including dronedarone) in clinical practice,\textsuperscript{24} but these may be subject to selection bias and unmeasured confounding.

These data affirming the safety of dronedarone in AF/AFL and HF with LVEF above 40% are in contrast to evidence of increased mortality in patients recently hospitalized with decompensated HFrEF in ANDROMEDA (Antiarrhythmic Trial with Dronedarone in Moderate to Severe CHF Evaluating Morbidity Decrease).\textsuperscript{9} What might explain these differences? ANDROMEDA evaluated a distinct patient population of whom only 38% had a history of AF/AFL and thus might not fully benefit from rhythm control like a population with AF/AFL and HFpEF. The safety of dronedarone may be more favourable in a stable, ambulatory population such as those evaluated in ATHENA and EAST-AFNET 4. Use of dronedarone in a manner consistent with guideline recommendations, appropriate monitoring, and use of oral anticoagulation for stroke prevention, may be higher in these more recent studies. As dronedarone has
class II anti-adrenergic and class IV vasodilatory properties, stable patients with HF might benefit while decompensated patients with severe left ventricular dysfunction might be harmed by these effects. Additionally, as dronedarone is known to inhibit tubular transport of creatinine, thereby reducing creatinine clearance by 15%–20% (without causing kidney injury), it may be hypothesized that this could have led to alteration of use or dosing of disease-modifying therapies in recently hospitalized patients with HFrEF leading to disease progression. In contrast, transient perturbations in creatinine clearance in otherwise stable patients and resultant short-term changes in HF therapies may be less impactful in HFrEF. Furthermore, dronedarone is known to increase digoxin concentrations via a P-glycoprotein interaction, which may have partially mediated adverse safety signals in prior trials. 24 Regulatory labelling recommends digoxin discontinuation or dose reduction when initiating dronedarone. 25,26 Digoxin use was notably less common in ATHENA (18% in the HFrEF/HFmrEF subgroup) than in ANDROMEDA (31%)9 or in PALLAS (Permanent Atrial Fibrillation Outcome Study Using Dronedarone on Top of Standard Therapy; 33%).24 The efficacy of dronedarone among those with less severe forms of HF in ATHENA and early rhythm control in EAST-AFNET 4 may also be necessary to disrupt early pathways of left atrial myopathy and adverse remodelling. As anti-arrhythmic drug therapy remains limited in contemporary HFrEF clinical practice,27 these data suggest reconsideration of the role of dronedarone in current care pathways to manage AF/AFL in HF at higher LVEF.

Conclusions
Dronedarone is associated with reduced cardiovascular events in patients with paroxysmal or persistent AF/AFL and HF across the spectrum of LVEF, including among those with HFrEF and HFmrEF. These data support a rationale for a future dedicated and powered clinical trial to affirm the net clinical benefit of dronedarone in patients with AF and HFrEF.

Supplementary Information
Additional supporting information may be found online in the Supporting Information section at the end of the article.

Acknowledgements
The original analysis was performed by the sponsor. Complete individual participant-level data from the ATHENA trial were then shared with Brigham and Women’s Hospital (Boston, MA) for independent data analytic validation. The manuscript was drafted by the first author and revised with input from all coauthors. Editorial support was provided by Hanna Mourad-Agha of Fishawack Communications Ltd, and was limited to formatting and collating co-author feedback and approvals. This support was funded by Sanofi.

Funding
The original ATHENA trial and this post-hoc analysis were sponsored by Sanofi.
Conflict of interest: M.V. has received research grant support or served on advisory boards for American Regent, Amgen, AstraZeneca, Bayer AG, Baxter Healthcare, Boehringer Ingelheim, Cytokinetics, Lexicon Pharmaceuticals, Novartis, Pharmacosmos, Relypsa, Roche Diagnostics, and Sanofi, speaker engagements with Novartis and Roche Diagnostics, and participates in clinical trial committees for studies sponsored by Galmed, Novartis, Bayer AG, Occlutech, and Impulse Dynamics. J.P.P. is supported by R01HL128595 from the National Heart, Lung and Blood Institute and R01AG074185 from the National Institutes of Aging; he also receives grants for clinical research from Abbott, American Heart Association, the Association for the Advancement of Medical Instrumentation, Bayer, Boston Scientific, iRhythm, and Philips and serves as a consultant to Abbott, Abbvie, Ablocaon, Altathera, ARCA Biopharma, Biotronik, Boston Scientific, Bristol Myers Squibb, LivaNova, Medtronic, Milestone, ElectroPhysiology Frontiers, Pfizer, Sanofi, Philips, and Up-to-Date. A.J.C. reports grants and personal fees from Boehringer Ingelheim, Bayer, Pfizer/BMS, Daiichi Sankyo, personal fees from Medtronic, Boston Scientific, Menarini, and Biotronik, and support from Anthos, Sanofi, St. Jude (now Abbott), Glaxo Smith Kline, Abbott, Johnson and Johnson, The Atrial Fibrillation Association, The Arrhythmia Alliance, The European Heart Rhythm Association, and The World Society of Arrhythmia. H.J.G.M.C. reports support from the Netherlands Cardiovascular Research Initiative: an initiative with support of the Dutch Heart Foundation, CVON 2014–9 (RACE V); he also acts as consultant/advisor/speaker to Aescion, Incarda, Sanofi, Roche, Ksyos, Corsano Health, and DZH/K; support for educational activities from Medtronic, Abbott and Boston Scientific. S.D.A. reports grants and personal fees from Vifor Int. and Abbott Vascular and personal fees from AstraZeneca, Bayer, Brahms, Boehringer Ingelheim, Cardiac Dimensions, Novartis, Occlutech, Servier and Vifor Int. J.B. reports consulting fees from BI, Cardior, CVRx, Foundry, G3 Pharma, Imbria, Impulse Dynamics, Innolife, Janssen, LivaNova, Luipold, Medtronic, Merck, Novartis, NovoNordisk, Relypsa, Roche, Sanofi, Sequana Medical, V-Wave Ltd, and Vifor. J.S., R.B., A.P.A.A. and M.W. are employees of Sanofi and may hold shares and/or stock options in the company. S.H.H. reports personal fees from Bayer Healthcare, Boehringer Ingelheim, Bristol Myers Squibb, Janssen, Pfizer, and Sanofi.

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