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REVIEW

Pleiotropic Effects of Antiarrhythmic Agents: Dronedarone in the Treatment of Atrial Fibrillation

Jordi Heijman[1], Gerd Heusch[2] and Dobromir Dobrev[1]

[1]Institute of Pharmacology, Faculty of Medicine, University Duisburg-Essen, Essen, Germany.
[2]Institute for Pathophysiology, Faculty of Medicine, University Duisburg-Essen, Essen, Germany.
Corresponding author email: dobromir.dobrev@uk-essen.de

Abstract: Atrial fibrillation remains the most common arrhythmia in clinical practice. Dronedarone is an antiarrhythmic drug for the maintenance of sinus rhythm in patients with atrial fibrillation. Dronedarone is an amiodarone derivative developed to reduce the number of extracardiovascular side effects. Dronedarone has undergone extensive experimental and clinical testing during the last decade. On the aggregate, these studies have highlighted a complex set of pleiotropic actions that may contribute to dronedarone's antiarrhythmic effects. In this review, we summarize the clinical studies that have evaluated dronedarone and provide an overview of dronedarone's electrophysiological and nonelectrophysiological pleiotropic actions.

Keywords: antiarrhythmic drugs, atrial fibrillation, dronedarone, pleiotropic effects

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Introduction

Atrial fibrillation (AF) is the most common arrhythmia encountered in clinical practice and has serious prognostic implications for morbidity and mortality, notably as a major risk factor for embolic stroke and progressive heart failure.[1] Therapeutic strategies for AF include rhythm control, aiming to achieve normal sinus rhythm (SR), and rate control, in which only the ventricular response is controlled.[2] It remains a topic of debate whether SR maintenance is superior to rate control. AF is classified as paroxysmal or persistent depending on whether the arrhythmia terminates spontaneously or is sustained for more than 7 days.[3] AF is considered permanent when no further attempts are made to achieve rhythm control.

Despite advances in ablation and surgical therapies for AF, antiarrhythmic drugs remain the mainstay therapy for the majority of AF patients.[4,5] However, current antiarrhythmic drugs for AF have major limitations, including limited efficacy, ventricular proarrhythmic side effects, and extracardiovascular toxicity.[4,6] Amiodarone is the most commonly prescribed drug for rhythm control in patients with AF and is considered one of the most successful antiarrhythmic drugs, achieving SR in 55% to 78% of patients.[7] Despite mild QT-prolonging effects, amiodarone is generally associated with less ventricular proarrhythmia than other antiarrhythmic drugs, although several cases of amiodarone-induced torsade de pointes arrhythmias have been reported.[8,9] However, amiodarone's lipophilic character and iodine moieties (Fig. 1A) are associated with pronounced extracardiovascular side effects, notably pulmonary and hepatic toxicity. These limit the use of amiodarone, particularly in younger patients who face many years of therapy.[8]

The amiodarone analog dronedarone was developed with the aim to reduce the extracardiovascular toxicity, particularly by removing the iodine

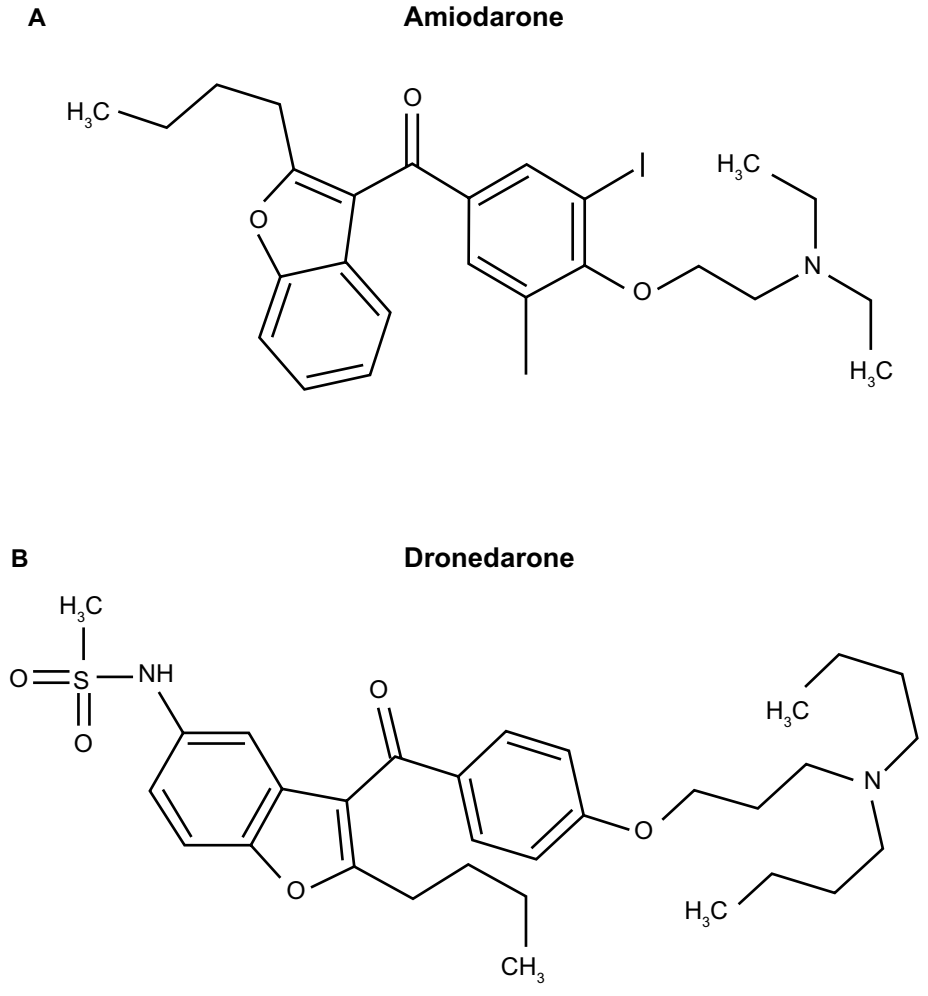

Figure 1. Chemical structures. (**A**) Amiodarone (**B**) Dronedarone. Note the absence of iodine moieties in dronedarone.

moieties (Fig. 1B).[10] Dronedarone is a benzofuran derivative with 4% to 15% absorption after oral intake with food. It undergoes extensive first-pass metabolism by cytochrome P4503A4 (CYP3A4) resulting in 15% bioavailability.[10] The metabolite N-desbutyl-dronedarone is active but less potent than dronedarone. Steady state plasma concentrations of dronedarone are between 84 and 167 ng/mL (150–300 nmol/L) with a terminal half-life of 24 to 30 hours, predominantly (94%) through nonrenal clearance.[11] This half-life is significantly shorter than that of amiodarone due to dronedarone's less lipophilic nature.[10] Inhibitors of CYP3A4 can increase dronedarone plasma concentrations. During the last decade, dronedarone has been studied extensively in a wide range of experimental and clinical settings. These studies have revealed that dronedarone has many pleiotropic effects. In this review article, we provide an overview of the clinical studies evaluating the safety and efficacy of dronedarone and discuss the various pleiotropic actions of dronedarone that may contribute to its overall antiarrhythmic properties.

Clinical Studies Evaluating Dronedarone

An overview of the clinical trials that investigated dronedarone, their inclusion and exclusion criteria, as well as their main outcomes are presented in Table 1 and summarized below. (For a more extensive discussion, see Patel et al,[10] Naccarelli,[12] Camm and Savelieva,[13] and Podda et al.[14]) The Dronedarone Atrial Fibrillation Study after Electrical Cardioversion (DAFNE) trial[15] compared 400, 600, or 800 mg dronedarone twice a day with placebo in patients with persistent AF. Dronedarone showed a dose-dependent conversion to SR. The onset of AF recurrence was delayed at the lowest dose only, with no significant improvement and increased adverse gastrointestinal effects at higher doses.[15] All subsequent trials have, therefore, used 400 mg dronedarone twice a day. The time to AF recurrence, AF recurrence rate, and ventricular rate during AF recurrence with dronedarone were evaluated in patients with paroxysmal and persistent AF in the twin studies EURIDIS (European Trial in Atrial Fibrillation or Flutter Patients Receiving Dronedarone for the Maintenance of Sinus Rhythm) and ADONIS (American-Australian-African Trial with Dronedarone for the Maintenance of Sinus Rhythm).[16] Compared with placebo, dronedarone significantly delayed the time to AF recurrence (53 vs. 116 days), reduced AF-recurrence rate (75.2% vs. 64.1%) and lowered ventricular rate during AF (117 ± 30 vs. 103 ± 26 beats per minute [bpm]).[16] In addition, a post hoc analysis revealed a significant reduction in hospitalizations and deaths in AF patients treated with dronedarone.[16]

The use of dronedarone for ventricular rate control in patients with permanent AF was evaluated in the Efficacy and Safety of Dronedarone for Control of Ventricular Rate study (ERATO).[17] When given on top of standard rate-control therapy, dronedarone reduced the mean ventricular rate by 11.7 bpm at 14-days and by 8.8 bpm at the 4-month follow-up. This effect was even more pronounced during exercise, with a ventricular rate reduction of 27.4 bpm.

The DAFNE, EURIDIS/ADONIS, and ERATO trials excluded patients with heart failure (New York Heart Association class III–IV or left-ventricular ejection fraction <35%). In the ANDROMEDA trial, the safety of dronedarone was evaluated in patients with heart failure.[18] However, the study was halted prematurely due to a higher mortality in patients receiving dronedarone, predominantly due to worsening heart failure, indicating that dronedarone should not be used in these patients.[18]

One of the major studies contributing to the approval of dronedarone for rhythm control of paroxysmal and persistent AF in patients without structural heart disease was the ATHENA trial, which included patients with paroxysmal or persistent AF or atrial flutter and at least one additional cardiovascular risk factor.[19] Dronedarone significantly reduced the primary end point of all-cause mortality and cardiovascular hospitalization. In addition, sequential analysis suggested that dronedarone may also reduce deaths due to cardiac arrhythmias.[19] Interestingly, a post hoc analysis of the ATHENA trial showed that dronedarone also significantly reduced the risk of stroke, even in patients that already received antithrombotic therapy.[20]

The efficacy and safety of dronedarone were compared with those of amiodarone in the DIONYSOS trial.[21] Dronedarone was significantly less successful than amiodarone in maintaining SR (63% vs. 42% recurrence rate, $P < 0.001$) but resulted in slightly fewer adverse events that required discontinuation of

Table 1. Clinical studies of dronedarone (Dro.).

Trial (year)	# patients (Dro./Ctrl)	Inclusion criteria	Exclusion criteria	Follow-up	Main outcomes
DAFNE (2003)[15]	102 (54/48)	Persistent AF	Permanent AF; NYHA III–IV CHF; QTc > 500 ms; LVEF < 35%; other AADs; ICD	6 months	• Dose-dependent conversion to SR with Dro. • Delayed time to first AF recurrence with 400 mg Dro. bid
EURIDIS/ ADONIS (2007)[16]	1237 (828/409)	Paroxysmal/ persistent AF	Permanent AF; NYHA III–IV CHF; renal insufficiency; HR < 50 bpm; class I–III AADs	12 months	• Dro. delayed time to AF ecurrence (116 vs. 53 days) and reduced its incidence (64.1% vs. 75.2%) • Dro. reduced ventricular rate in AF (~14 bpm)
ERATO (2008)[17]	174 (85/89)	Permanent AF (>6 months)	NYHA III–IV CHF	6 months	• Dro. reduced mean ventricular rate by 11.7 bpm (27.4 bpm during exercise) at 14 days and by 8.8 bpm at 4 months follow-up
ANDROMEDA (2008)[18]	627 (310/317)	NYHA III–IV CHF or paroxysmal nocturnal dyspnea + LVEF < 35%	Recent acute MI; Acute pulmonary edema	2 months	• Stopped prematurely due to higher mortality in the Dro. treated group
ATHENA (2009)[19]	4628 (2301/2327)	Paroxysmal/persistent AF + one cardiovascular risk factor	Permanent AF; HR < 50 bpm; NYHA IV; GFR < 10 mL/min	21 months	• Reduction in all-cause mortality or cardiovascular hospitalization with Dro. (hazard ratio 0.76) • No difference in thyroid, pulmonary or hepatic toxicity between Dro. and placebo • Reduced stroke risk with Dro. in post-hoc analysis[20]
DIONYSOS (2010)[21]	504 (249/255)	Persistent or permanent (>72 h) AF	Paroxysmal AF; NYHA III–IV; HR < 50 bpm; class I–III AADs; previous amiodarone treatment	6 months	• More frequent AF recurrence in Dro. compared to amiodarone (65.5% vs. 42.0%) • Fewer drug discontinuations in Dro. compared to amiodarone (10.4% vs. 13.3%) • Fewer side effects with Dro. compared to amiodarone (39.3% vs. 44.5%)
PALLAS (2011)[22]	3236 (1619/1617)	Permanent AF (>6 months); age >65 years; additional cardiovascular risk factors	Paroxysmal/persistent AF; HR < 50 bpm; QTc > 500 ms; NYHA IV or unstable NYHA III	3.5 months	• Prematurely halted due to increase in primary cardiovascular endpoint (stroke, MI, systemic embolism, cardiovascular death) in Dro. treated group

HESTIA (2012)[24]	112 (57/55)	Paroxysmal AF; AF burden >1%; dual-chamber pacemaker with AF detection	Persistent/permanent AF; cardiovascular risk factors; recent ablation; NYHA IV or NYHA II–III with recent decompensation; antiarrhythmics; previous amiodarone treatment; QTc > 500 ms	12 weeks	• Dro. reduced AF burden by 59%
HARMONY (exp. 2013)	150 (est.)	Paroxysmal AF; dual-chamber pacemaker with AF detection	Persistent/permanent AF; NYHA III–IV; LVEF < 40%; recent/planned ablation; QTc > 500 ms	12 weeks	• Will assess whether the combination of low dose ranolazine on top of Dro. is superior to individual drug therapy in lowering AF incidence

Abbreviations: AADs, antiarrhythmic drugs; AF, atrial fibrillation; bid, twice a day; CHF, congestive heart failure; HR, heart rate; LVEF, left-ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; QTc, rate-corrected QT-interval; SR, sinus rhythm.

drug treatment (10.4% vs. 13.3%) and slightly fewer overall side effects (39.3% vs. 44.5% occurrence of the main safety endpoint which included thyroid, hepatic, pulmonary, neurologic, skin, eye, or gastrointestinal effects with dronedarone and amiodarone, respectively, $P = 0.13$).[21] When gastrointestinal effects were excluded (a prespecified endpoint) dronedarone resulted in a significant (39%) reduction in relative risk of adverse effects.[21] The study had a power of 80% with a 2-sided type I error of 5% to detect a relative reduction in risk of 30%. Taken together, the DIONYSOS trial clearly showed that dronedarone is less efficacious than amiodarone.

Retrospective analysis suggested that several of the benefits of dronedarone observed in the ATHENA trial might also hold true for patients with permanent AF.[12,20] This led to the Permanent Atrial Fibrillation Outcome Study Using Dronedarone on Top of Standard Therapy (PALLAS) trial.[22] However, the PALLAS study was halted prematurely due to a 2.29-fold increase in the combined primary endpoint of stroke, myocardial infarction, systemic embolism, or cardiovascular death resulting from dronedarone therapy,[22] indicating that dronedarone treatment is not appropriate for this group of patients.

Many of the investigations assessing the efficacy of antiarrhythmic drugs in maintaining SR that have been performed so far employ electrocardiogram (ECG) analysis at scheduled follow-up visits. This approach may not be able to detect the exact AF burden in every patient.[23] Therefore, the Effects of Dronedarone on Atrial Fibrillation Burden in Subjects With Permanent Pacemakers (HESTIA) trial investigated the efficacy of dronedarone (400 mg twice a day) in patients with permanent dual-chamber pacemakers able to detect AF. The preliminary results of this study confirmed earlier findings that dronedarone is an effective antiarrhythmic in patients with paroxysmal AF, able to reduce the total time spent in AF ("AF burden") by 59% compared with placebo.[24] Finally, the HARMONY trial (A Study to Evaluate the Effect of Ranolazine and Dronedarone When Given Alone and in Combination in Patients With Paroxysmal Atrial Fibrillation; ClinicalTrials.gov identifier NCT01522651) is currently ongoing in patients with permanent dual-chamber pacemakers able to detect AF to assess whether a combination therapy of low-dose dronedarone and ranolazine

is superior to individual drug therapy, as suggested based on animal studies.[25,26]

Pleiotropic Actions of Dronedarone

Direct-antiarrhythmic effects

Inhibition of atrial reentrant activity by dronedarone

Similar to amiodarone,[27,28] dronedarone has a wide range of pleiotropic electrophysiological effects, either by directly inhibiting atrial ion channels or indirectly by inhibiting G-protein-coupled receptors (Fig. 2 and Table 2). Dronedarone inhibits rapid and slow delayed-rectifier K^+ currents as well as two-pore K^+ currents.[10,29] Inhibition of these repolarizing K^+ currents is the main mode of action of class III antiarrhythmic drugs. Dronedarone delays repolarization and increases atrial action-potential duration, thereby destabilizing AF-maintaining reentry, since this requires all myocardium in the reentrant path to regain excitability (and therefore repolarize) before the arrival of the next impulse.[27,30] However, inhibition of K^+ currents is also associated with prolongation of ventricular repolarization, which increases the risk of secondary depolarizations occurring before full repolarization of the ventricular action potential (termed early afterdepolarizations [EADs]) that can cause ventricular ectopic beats and may trigger torsade de pointes arrhythmias.[6] Indeed, dronedarone has been shown to cause EADs and torsade de pointes arrhythmias in dogs with chronic complete atrioventricular-block.[31] In this study, the torsadogenic potential of dronedarone was higher than that of amiodarone.[31]

In contrast to pure class III drugs, dronedarone also inhibits the depolarizing L-type Ca^{2+} current[10] ($I_{Ca,L}$, the main target of class IV antiarrhythmic drugs), which plays a major role in the development of EADs. This action may offset the effects of K^+-current inhibition and may prevent excessive repolarization prolongation. Although it is not traditionally considered torsadogenic in patients, recent observations suggest that dronedarone-induced torsade de pointes arrhythmias may be more common than originally considered, particularly in patients with multiple risk factors.[32] In vivo, the combined effects of dronedarone on QT-prolongation depend on concentration, duration of treatment, and species that receives the treatment.[10] Moreover, the effects of dronedarone on repolarization duration also differ between cell types.[33] It is likely that these heterogeneous effects, combined with patient-to-patient variations in baseline vulnerability, contribute to the discordant reports on dronedarone-induced proarrhythmia.

The acetylcholine-dependent inward-rectifier K^+ current ($I_{K,ACh}$) is activated during parasympathetic stimulation via muscarinic receptors and may promote atrial reentry by shortening repolarization duration. In patients with chronic AF, $I_{K,ACh}$ develops constitutive activity, providing repolarizing current even in the absence of muscarinic receptor agonists.[34] In addition, augmentation of inward-rectifier currents causes a hyperpolarization of the resting membrane potential,[34] an effect that has been suggested to stabilize reentrant rotors by reducing inactivation of I_{Na} and increasing excitability.[35] Since $I_{K,ACh}$ channels are selectively expressed in the atria, they are an interesting target for AF antiarrhythmics that aim to avoid ventricular proarrhythmia.[6] Dronedarone potently inhibits $I_{K,ACh}$ (Table 2), an effect that may potentially contribute to its antiarrhythmic action during vagally mediated AF.[10,36] Although there is currently no clinical evidence that selective $I_{K,ACh}$ inhibition can suppress AF in patients, some compounds have shown promise in large-animal models of vagal AF and are currently being investigated in phase 2 clinical trials.[37]

Inhibition of atrial ectopic (triggered) activity by dronedarone

Ectopic (triggered) activity, for example from the pulmonary veins, can initiate reentry in a vulnerable substrate or, when recurring repetitively, can maintain AF as a so-called driver.[6,27] Recent research has identified a major role for Ca^{2+}-handling abnormalities in both recurrent ventricular tachyarrhythmias[38] and chronic AF.[39] Notably, spontaneous sarcoplasmic reticulum Ca^{2+}-release events were more common in atrial myocytes from patients with chronic AF. In addition, Na^+/Ca^{2+} exchanger (NCX) activity was increased in AF. Since NCX is electrogenic, with 3 Na^+ entering for every Ca^{2+} extruded, this increase resulted in larger depolarizing transient inward currents for each Ca^{2+}-release event.[40] Together, these Ca^{2+}-handling abnormalities resulted in more frequent and larger delayed afterdepolarizations and triggered activity.[40] Moreover, Ca^{2+}-handling abnormalities also play

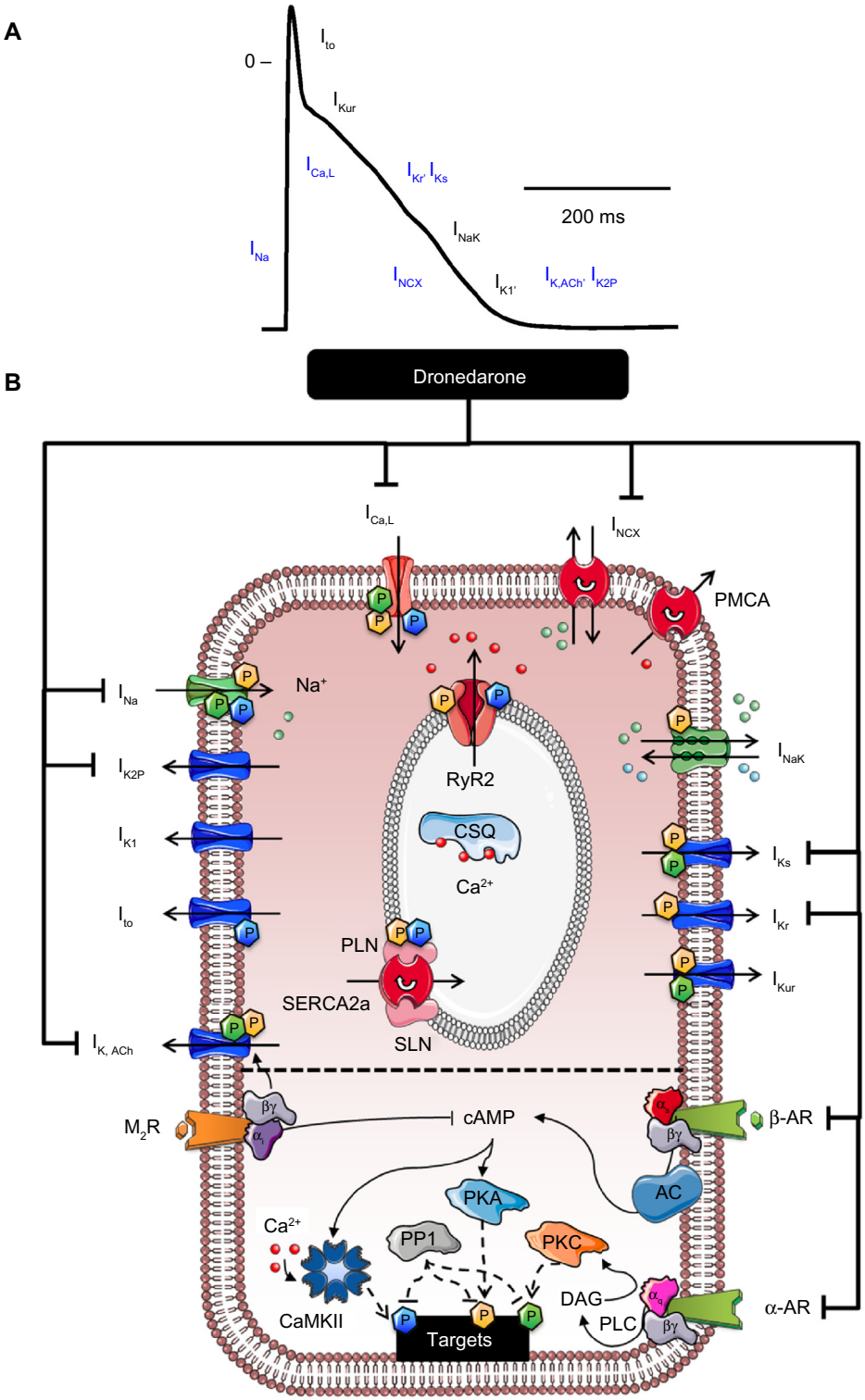

Figure 2. Atrial electrophysiological effects of dronedarone. (**A**) Atrial action potential and underlying ion currents. Placement of current labels corresponds approximately to the time point at which the current has its maximal effect on the action potential. Currents in bold/blue are those inhibited by dronedarone. (**B**) Schematic representation of the atrial myocyte and the targets of dronedarone. Elements from Servier Medical Art were used in the design of this figure.

Abbreviations: α-AR, α-adrenoceptor; AC, adenylyl cyclase; β-AR, β-adrenoceptor; CaMKII, Ca^{2+}/calmodulin-dependent protein kinase type II; cAMP, cyclic-AMP; CSQ, calsequestrin; DAG, diacylglycerol; $I_{Ca,L}$, L-type Ca^{2+} current; I_{K1}, inward-rectifier K^+ current; I_{K2P}, two-pore K^+ current; $I_{K,ACh}$, achetylcholine-dependent inward-rectifier K^+ current; I_{Kr}, rapid delayed-rectifier K^+ current; I_{Ks}, slow delayed-rectifier K^+ current; I_{Kur}, ultra-rapid delayed-rectifier K^+ current; I_{Na}, Na^+ current; I_{NaK}, Na^+-K^+-ATPase current; I_{NCX}, Na^+-Ca^{2+} exchange current; I_{to}, transient outward K^+ current; M_2R, muscarinic receptor type-2; PKA, protein kinase-A; PKC, protein kinase-C; PLC, phospholipase-C; PLN, phospholamban; PMCA, plasmalemmal Ca^{2+} ATPase; PP1, protein phosphatase-1; RyR2, ryanodine receptor type-2 channel; SERCA2a, sarcoplasmic reticulum Ca^{2+} ATPase 2a; SLN, sarcolipin.

Table 2. Electrophysiological effects of dronedarone and amiodarone.

Target	IC_{50} dronedarone	IC_{50} amiodarone
α-AR	Reduced pressor response to phenylephrine in vivo at 80 nmol/L plasma levels	
β-AR	1.8 μmol/L	8.7 μmol/L
$I_{Ca,L}$	0.2 μmol/L	0.4–5.8 μmol/L (state dependent)
I_f	1.0 μmol/L (mammalian expression system)	0.8 μmol/L (mammalian expression system)
$I_{K,ACh}$	0.05 μmol/L	1.0 μmol/L
I_{K1}	30 μmol/L	30 μmol/L
I_{Kr}	<3.0 μmol/L (myocytes)/59 nmol/L (mammalian expression system)	10 μmol/L (myocytes)/70 nmol/L (mammalian expression system)
I_{Ks}	10 μmol/L	>30 μmol/L
I_{K2P}	5.0–6.0 μmol/L (mammalian expression system)	0.4 μmol/L (xenopus oocytes)
I_{Na}	0.7 μmol/L, 97% inhibition at 3.0 μmol/L	41% inhibition at 3.0 μmol/L
I_{NCX}	33 μmol/L	3.3–3.6 μmol/L
I_{to}	No inhibition at 10 μmol/L	4.9 μmol/L

Notes: IC_{50} values for inhibition of targets measured in cardiac myocytes are given, unless noted otherwise. Data are compiled from several sources.[10,27,29,33,52] Therapeutic blood plasma concentrations of dronedarone range between 0.15 and 0.3 μmol/L.

a role in repolarization abnormalities[41] and in AF-related electrical and structural remodeling.[42] These remodeling processes promote AF maintenance, facilitating the transition from paroxysmal to persistent AF and making AF more difficult to treat.[43,44] As such, $I_{Ca,L}$ inhibition by dronedarone may also reduce triggered activity and other Ca^{2+}-handling abnormalities by limiting Ca^{2+} entry. In addition, dronedarone can partly inhibit NCX,[27] further reducing the likelihood of triggered activity. Finally, the family of transient receptor potential (TRP) channels has emerged as an important pathway for Ca^{2+} entry in cardiac myocytes and fibroblasts.[45] The expression of several TRP channels is increased in AF[45] and inhibition of TRP may prevent AF-related remodeling,[46] although it is at present unclear whether dronedarone inhibits TRP channels. Nonetheless, inhibition of Ca^{2+} entry may also have proarrhythmic effects. Indeed, $I_{Ca,L}$ downregulation is a hallmark of electrical remodeling in chronic AF[43] and promotes atrial reentry by shortening effective refractory period. Finally, inhibition of $I_{Ca,L}$ may also have negative inotropic effects, which may promote worsening heart failure and may contribute to the adverse outcome of patients with heart failure taking dronedarone, as observed in the ANDROMEDA trial. Taken together, these data suggest that the pleiotropic actions of dronedarone on I_{Kr} and $I_{Ca,L}$ may create a delicate balance that contributes to its antiarrhythmic effects, at least in the structurally normal heart.

Dronedarone is a powerful inhibitor of the peak Na^+ current (I_{Na}), being approximately 10 times more potent than amiodarone (Table 2).[10] Inhibition of I_{Na} reduces atrial excitability and limits ectopic/triggered activity. However, class Ic antiarrhythmic drugs such as flecainide and propafenone, which predominantly inhibit I_{Na}, have been associated with increased mortality in patients with heart failure.[7] This is likely because the proarrhythmic effects of ventricular conduction slowing due to I_{Na} inhibition offset the antiarrhythmic effects of reduced atrial excitability. As such, there is considerable interest in atrial-specific inhibition of I_{Na}.[47] Dronedarone preferentially inhibits I_{Na} at depolarized potentials, thereby showing an atrial-predominant effect.[47] Nonetheless, inhibition of ventricular I_{Na} may partially contribute to the negative outcomes with dronedarone in patients with heart failure in the ANDROMEDA trial.[18]

Taken together, dronedarone inhibits a wide range of atrial ion channels that modify the propensity for both reentrant and triggered activity. Compared with amiodarone, dronedarone is a more potent inhibitor of peak I_{Na} and $I_{K,ACh}$ and also inhibits NCX. The exact combination of these pleiotropic electrophysiological effects likely determines the antiarrhythmic profile of dronedarone.

Additional (non-electrophysiological) effects of dronedarone

Effects of dronedarone on acute coronary syndrome

In a post hoc subgroup analysis of the ATHENA trial, a reduced incidence of hospitalizations for acute coronary syndromes was observed with dronedarone.[19] There are a number of pleiotropic actions that may contribute to this result.[48] First of all, dronedarone reduces heart rate, thereby reducing myocardial oxygen consumption and increasing diastolic duration.[49]

Increased heart rate can contribute to (or in some cases even initiate) acute myocardial ischemia in the presence of coronary atherosclerosis by impairing collateral blood flow and/or promoting a transmural redistribution of blood and increasing turbulence.[50,51] Recent work has shown that at clinically relevant concentrations in a large-animal model, direct inhibition of the hyperpolarization-activated "funny" current (I_f) by dronedarone, and not inhibition of $I_{Ca,L}$ or β-adrenoceptors, is the predominant mechanism underlying the dronedarone-induced reduction in heart rate.[52] Interestingly, the heart rate reduction observed with dronedarone in the ERATO trial was similar to that in the Morbidity-Mortality Evaluation of the I_f Inhibitor Ivabradine in Patients With Coronary Artery Disease and Left Ventricular Dysfunction (BEAUTIFUL) trial, where ivabradine was associated with reduced hospitalization for myocardial infarction and coronary revascularization in patients with heart rates over 70 bpm.[53,54] On the other hand, the dronedarone-induced heart rate reduction may, in combination with its prolongation of repolarization duration, favor ventricular arrhythmogenesis, since bradycardia and sinus rhythm "pauses" promote development of torsade de pointes.[31] This may be one factor contributing to the negative results with dronedarone in patients with heart failure.[32]

In dogs and pigs, dronedarone was able to inhibit α-adrenoceptors at clinically relevant concentrations and consequently lowered mean arterial blood pressure by inhibiting α-adrenoceptor-mediated vasoconstriction.[52,55] Therefore, a reduction in vasoconstriction by dronedarone could be an alternative mechanism that could contribute to its reduction in hospitalizations for acute coronary syndrome. Indeed, α-adrenergic coronary vasoconstriction during exercise and stress, in particular in the presence of β-blockade, precipitates acute myocardial ischemia.[56,57] Amiodarone and its active metabolite N-desethylamiodarone have been shown to elevate cytosolic Ca^{2+} in endothelial cells and promote endothelin-dependent vasodilation,[58,59] suggesting that similar mechanisms could also be part of the pleiotropic effects of dronedarone that promote vasodilation, although this still requires experimental validation.

A third mechanism contributing to the beneficial effects of dronedarone in acute coronary syndrome is a direct cardioprotective effect. It was recently shown that dronedarone resulted in a significant reduction in infarct size following an ischemia/reperfusion protocol in a pig model with controlled heart rate and blood pressure, strongly suggesting a direct cardioprotective effect.[60] Consistent with this idea, dronedarone also prevented ventricular microcirculatory flow abnormalities and oxidative stress in a pig model of rapid atrial pacing, an effect that was associated with a reduction in oxidative stress- and ischemia-related gene expression.[61] In addition, dronedarone reduced the phosphorylation (activation) of protein kinase-C In HL-1 cells exposed to oxidative stress,[61] suggesting that it may act, at least partly, directly on cardiomyocytes, downstream of oxidative stress. Interestingly, these protective effects were not observed with amiodarone.[61] The exact mechanisms contributing to this cardioprotection remain incompletely understood. Limiting potential cardiotoxic Ca^{2+} overload by inhibition of $I_{Ca,L}$, NCX and/or I_f has been suggested as one potential mechanism. In addition, it has been shown that the active metabolite of dronedarone (N-desbutyl-dronedarone) inhibits myocardial thyroid hormone receptors.[62] Hypothyroidism can be protective against acute ischemic injury,[63] whereas hyperthyroidism has been shown to promote AF through downregulation of $I_{Ca,L}$, facilitating atrial reentry.[64] However, Mourouzis et al have shown recently that N-desbutyl-dronedarone worsens the progression of heart failure following acute myocardial infarction in mice.[62] These findings are consistent with the observation that hypothyroid patients had smaller infarcts but worse prognosis following myocardial infarction[63] and emphasize the importance of assessing both short- and long-term pleiotropic effects of dronedarone. Chronic atrial ischemia/infarction has been shown to create a vulnerable atrial substrate for both reentry and ectopic activity (through abnormal Ca^{2+}-handling and increased NCX),[65] suggesting that dronedarone may affect both the cause (ischemia) and the electrophysiological consequences that promote AF in this setting.

Reduction of stroke by dronedarone

A post hoc analysis of the ATHENA trial suggested that dronedarone could potentially reduce the incidence of stroke, independent of the use of oral anticoagulants,[20] in line with a meta-analysis of the ATHENA, DAFNE, EURIDIS, and ADONIS trials (although the results were dominated by the ATHENA trial),[66] but

not with the ANDROMEDA and PALLAS trials.[18,22] The potential reduction in stroke incidence has not been observed with other antiarrhythmic drugs[67] and constitutes an interesting and clinically relevant pleiotropic effect of dronedarone.

The mechanisms contributing to the reduced incidence of stroke with dronedarone remain incompletely understood.[48,66] A reduction in AF burden per se, as well as several of the factors contributing to the beneficial effects of dronedarone in acute coronary syndrome (notably reduced blood pressure and ventricular rate) may play a role in preventing stroke.[20,66] In addition, Breitenstein et al showed that dronedarone inhibits arterial thrombus formation in a mouse photochemical injury model through inhibition of platelet aggregation and plasminogen activator inhibitor-1, mechanisms that could also play a role in the reduced stroke incidence.[68] Finally, dronedarone, which easily passes the blood-brain barrier, may have direct cerebroprotective effects, consistent with its cardioprotective effects in acute coronary syndrome. Indeed, preischemic and postischemic treatment with dronedarone reduced the cerebral infarct size in a rat model of cerebral ischemia/reperfusion injury, independent of heart rate or blood pressure.[69]

Other pleiotropic effects

Dronedarone, like amiodarone, is an inhibitor of CYP2D6 and a substrate and inhibitor of CYP3A4, which are enzymes involved in drug metabolism. As such, dronedarone may increase the bioavailability of other cardiovascular drugs including digoxin, simvastatin, and metropolol in some patients,[10] and the pleiotropic effects of dronedarone may partly be due to effects on other drugs. Dosing of these drugs may need to be adjusted to prevent unwanted side effects.[70] For example, it has been suggested that concomitant digoxin therapy contributed to the adverse outcomes with dronedarone in the PALLAS trial,[22] and the combined use of both drugs is discouraged in the current guidelines.[71]

Another interesting pleiotropic effect of amiodarone and dronedarone is their use in Chagas disease. Chagas disease is due to infiltration of the disease-causing parasite *Trypanosoma cruzi* in various tissues, including the heart, and is associated with cardiomyopathic manifestations and associated arrhythmias.[72] Amiodarone has been shown as one of the most promising treatment modalities, likely due to its combined antiarrhythmic and antiparasitic effects. This latter pleiotropic action is due to amiodarone-induced Ca^{2+}-handling abnormalities and blockade of sterol synthesis in *Trypanosoma cruzi*.[72] There are experimental data suggesting that dronedarone has similar pleiotropic antiparasitic effects,[73] although it is currently not used clinically for Chagas disease and may not be appropriate in these patients with reduced ejection fractions.[72]

Unwanted side effects of dronedarone

Compared with amiodarone, dronedarone is generally considered to have fewer severe side effects (but see Said et al[74] and Chatterjee et al[75]).[21,76] The most common side effects with dronedarone include gastrointestinal effects (diarrhea, nausea, and vomiting) and rash.[76] Cardiovascular side effects include bradycardia and QT-interval prolongation, which may promote potential life-threatening arrhythmias in susceptible patients.[76] Finally, dronedarone has also been associated with a few cases of severe hepatotoxicity, which has prompted more extensive monitoring of liver function in patients on long-term dronedarone therapy.[71]

Place in Therapy

Relation between pleiotropic effects of dronedarone and its clinical efficacy

Several preclinical studies have highlighted a wide range of pleiotropic actions of dronedarone that could potentially be antiarrhythmic. However, these actions can also be proarrhythmic in vulnerable patients. For example, dronedarone-induced inhibition of I_{Na} is expected to reduce the likelihood of ectopic activity but may also promote reentry, notably in heart failure. Similarly, inhibition of repolarizing currents and subsequent prolongation of action-potential duration may destabilize reentrant circuits but may also promote torsade de pointes arrhythmias. Accordingly, dronedarone can have diverse effects on repolarization depending on dose, treatment duration, and so on.[10] Whether the effects of dronedarone are antiarrhythmic or proarrhythmic is, therefore, likely determined by many patient-to-patient variations. This may at least partly explain the divergent results of the various clinical trials of dronedarone, with the

ATHENA trial suggesting dronedarone as a relatively safe and efficacious antiarrhythmic drug, whereas the ANDROMEDA and PALLAS trials have highlighted important concerns about the use of dronedarone. In addition, these data highlight the need for better animal models of AF that reflect the complexity of the clinical phenotype. Future translational research will be necessary to further explain the relation between dronedarone's pleiotropic effects and the divergent clinical outcomes.

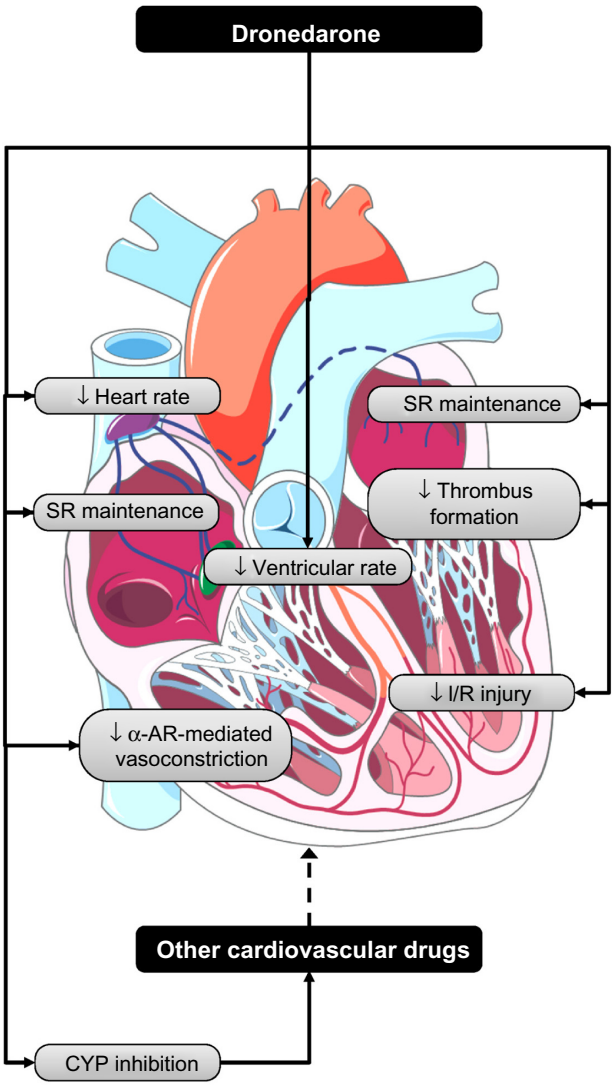

Figure 3. Pleiotropic actions of dronedarone. In addition to its electrophysiological properties, promoting sinus rhythm (SR) maintenance by antagonizing reentry and ectopic activity in the atria, dronedarone reduces heart rate (through β-AR, $I_{Ca,L}$ and I_f inhibition), decreases ventricular rate, inhibits atrial thrombus formation, attenuates α-AR-mediated coronary vasoconstriction, and prevents ischemia/reperfusion (I/R injury). In addition, it can affect the actions of other cardiovascular drugs through inhibition of cytochrome-P 450 enzymes. Elements from Servier Medical Art were used in the design of this figure.

Therapeutic value of dronedarone

The therapeutic value of dronedarone has been extensively discussed, particularly after the PALLAS trial was halted, and is reviewed in several excellent articles.[12,14,67,77,78] In line with the latest European and American guidelines,[71,79] the general consensus appears to be that, despite its limitations, dronedarone still has its place in therapy. Dronedarone has several advantages, including its relatively limited number of (severe) side effects and relative ease of administration, but should be targeted to the right subpopulation of patients. As such, dronedarone is listed as a first-line therapeutic option for a number of patient subpopulations in the current guidelines, notably those with coronary heart disease or hypertensive heart disease.[71] However, it should not be used in patients with symptomatic heart failure or permanent AF.

Conclusions

Dronedarone is an interesting antiarrhythmic agent for the treatment of AF in selected groups of patients. In addition to its pleiotropic direct antiarrhythmic effects, reducing the likelihood of both reentry and triggered activity, dronedarone has several other pleiotropic effects that may potentially be beneficial in clinical practice (Fig. 3). These include lowering heart rate, as well as reducing the risk of stroke and acute coronary syndromes. Nonetheless, the PALLAS and ANDROMEDA trials have made it clear that dronedarone is not useful for everyone and may even be harmful. In addition, dronedarone is still associated with substantial extracardiovascular side effects that may further limit is applicability. The recent observation that the response to antiarrhythmic drug therapy in patients with AF is modulated by a common polymorphism on chromosome 4q25 near the *PITX2* gene[80] and that the risk of drug-induced QT interval prolongation and ventricular arrhythmias is modulated by common variants in *NOS1AP*,[81] suggest that genetic information may also play a role in the identification of patients that may benefit from dronedarone therapy. In addition, combination therapies such as those with dronedarone and ranolazine, currently being investigated in the HARMONY trial, may provide another interesting approach to increase the antiarrhythmic efficacy and further reduce the number of side effects.[78] Finally, a better understanding of the mechanisms underlying dronedarone's pleio-

tropic actions is expected to facilitate the selection of patients benefiting from dronedarone, as well as the development of novel antiarrhythmic drugs for AF.

Author Contributions

Analyzed the data: JH, GH, DD. Wrote the first draft of the manuscript: JH. Contributed to the writing of the manuscript: JH, GH, DD. Agree with manuscript results and conclusions: JH, GH, DD. Jointly developed the structure and arguments for the paper: JH, GH, DD. Made critical revisions and approved final version: JH, GH, DD. All authors reviewed and approved of the final manuscript.

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Competing Interests

DD held educational lectures for Sanofi, Merck-Sharp-Dohme, and Boston Scientific. GH has received financial support for experimental studies from, and held educational lectures for, Sanofi. JH discloses no competing interests.

Disclosures and Ethics

As a requirement of publication the authors have provided signed confirmation of their compliance with ethical and legal obligations including but not limited to compliance with ICMJE authorship and competing interests guidelines, that the article is neither under consideration for publication nor published elsewhere, of their compliance with legal and ethical guidelines concerning human and animal research participants (if applicable), and that permission has been obtained for reproduction of any copyrighted material. This article was subject to blind, independent, expert peer review. The reviewers reported no competing interests. Provenance: the authors were invited to submit this paper.

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