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REVIEW

Dronedarone and Atrial Fibrillation: A Critical Review

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Abstract: The recent approval of dronedarone by the Food and Drug Administration has expanded the list of drugs available for the treatment of atrial fibrillation (AF). Despite wide-spread attention, the future of this antiarrhythmic compound remains uncertain. The aim of this review is to examine the major clinical trials that have evaluated dronedarone in human subjects and provide a practical framework for its use among patients with AF.

Keywords: dronedarone, atrial fibrillation, AF, Food and Drug Administration

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Introduction

The recent approval of Dronedarone by the Food and Drug Administration (FDA) "to reduce the risk of cardiovascular hospitalization in patients with paroxysmal or persistent atrial fibrillation" (AF) is likely to result in a surge of prescriptions. Given the paucity of effective antiarrhythmic treatments for AF, it should come as no surprise that dronedarone's emergence has been met with a great deal of anticipation. Despite great enthusiasm, the role of dronedarone in clinical practice remains uncertain. The purpose of this review is to critically examine the evidence supporting dronedarone's use, address specific controversies that have emerged, and offer practical suggestions for the clinician regarding its role in the treatment of atrial fibrillation.

Electrophysiological Properties

Dronedarone is by all accounts, a "designer drug". Although its counterpart, amiodarone has a long-standing track record for maintaining sinus rhythm, its use, particularly in higher doses, is limited by untoward side effects. Dronedarone was specifically engineered to overcome these side effects while maintaining its antiarrhythmic efficacy. A methanesulfonyl group was added to decrease dronedarone's lipophilicty, thereby decreasing its half-life. Dronedarone blocks outward potassium currents (I_{Kr} and I_{Ks}), inward sodium (I_{Na}), and calcium (I_{Cal}) currents, inward rectifier current (I_{k1}), transient outward current (I_{to}) and possesses anti-adrenergic activity. It has also been shown to produce blockade of the Na^{+}/Ca^{++} exchanger (INCX) and the acetylcholine-activated potassium current $I_{K\text{-}Ach}$ in cardiac myocytes.[1,2]

Is Dronedarone an Effective Antiarrhythmic?

There have been seven randomized controlled trials that have investigated the impact of dronedarone in humans. Of these, only four were designed to specifically assess dronedarone's effectiveness in suppressing AF.

The DAFNE trial was a dose-ranging, randomized placebo-controlled trial, comparing three different doses of dronedarone (400 mg BID, 600 mg BID and 800 mg BID) with placebo for the maintenance of sinus rhythm following electrical cardioversion among patients with AF.[3] The 400 mg BID dose of dronedarone was found to possess the best safety and efficacy. However, recurrence rates were high in both groups–at one year 65% of patients on dronedarone versus 90% on placebo experienced AF.

The most robust evidence of Dronedarone's antiarrhythmic efficacy comes from two identical sister trials—EURIDIS and ADONIS.[4] In these trials, the effect of dronedarone (400 mg BID) was assessed with respect to maintenance of sinus rhythm after electrical, pharmacological, or spontaneous conversion of AF or atrial flutter (AFL). Dronedarone reduced the risk of arrhythmia recurrence by 22% in the EURIDIS trial ($P = 0.0138$) and by 27.5% in the ADONIS trial ($P = 0.0017$) compared with control. Pooled analysis of these two trials demonstrated that 64% of dronedarone-treated patients versus 75% of placebo-patients experienced AF/AFL recurrence at one year ($P < 0.001$).

The ATHENA trial examined dronedarone's impact on the primary endpoint of hospitalization due to cardiovascular events or death among patients with non-permanent AF/AFL.[5] Although AF/AFL recurrence was not a primary or secondary endpoint, dronedarone had only a modest effect on AF suppression as compared to placebo (45% versus 55% AF/AFL recurrence in the dronedarone and placebo groups respectively, $P < 0.001$).[6]

Only one randomized controlled trial has evaluated dronedarone compared with amiodarone so far. The DIONYSOS trial compared the efficacy and safety of dronedarone (400 mg BID) versus amiodarone (600 mg daily for 28 days, then 200 mg daily thereafter) for the maintenance of sinus rhythm patients with AF.[7] The follow up period was short with a mean duration of 6 months. The primary endpoint was defined as recurrence of AF or premature study drug discontinuation for intolerance or lack of efficacy.

The primary composite endpoint of AF recurrence or premature drug discontinuation was reached in 75% of patients taking dronedarone versus 58.8% of patients receiving amiodarone HR 1.59; 95% CI 1.28–1.98; $P < 0.0001$. Recurrences of AF were more frequent in the dronedarone group than in the amiodarone group—63% vs. 42% (RR 1.51, 95% CI 1.27–1.80). Premature study drug discontinuations due to intolerance were less frequent (but not significantly

different) in the dronedarone group—10.4% vs. 13.3% (RR 0.78, 95% CI 0.48–1.27). The results of the DIONYSOS trial therefore suggest that although dronedarone is less effective at suppression AF, it may be better tolerated than amiodarone.

A recent metanalysis performed by Piccini and colleagues compared the efficacy and safety of dronedarone versus amiodarone for prevention of recurrent AF.[8] Using a random-effects model, they analyzed four placebo-controlled trials of dronedarone, four placebo-controlled trials of amiodarone, and 1 trial of dronedarone versus amiodarone. The results suggest that for the prevention of AF recurrence at 6 months, dronedarone was modestly, but not significantly, superior to placebo (OR 0.79, 95% CI 0.33–1.87) and inferior to amiodarone (OR 0.16, 95% CI 0.06–0.42). A greater trend toward all cause mortality and adverse events requiring drug discontinuation with amiodarone-treated patients was also observed.

Taken in total, it appears that dronedarone's ability to suppress AF in patients with non-permanent AF is rather modest. Singh and colleagues recently performed analysis of relevant dronedarone trials in order to summarize its antiarrhythmic effects in AF (Table 1).[9] Pooled data from the four placebo-controlled studies in Table 1 demonstrate that 43% of dronedarone-treated patients were estimated to have experienced a first AF/AFL recurrence, compared to 54% of placebo-treated patients.[9] To put these findings in perspective, dronedarone's effectiveness in suppressing AF is only marginally better than quinidine (50% efficacy in maintaining sinus rhythm at one year).[10] Moreover, as these results reflect limited follow-up, dronedarone's long-term effectiveness (as with most antiarrhythmics) is likely to be attenuated.

Does Dronedarone Reduce Hospitalizations?

The FDA's approval of Dronedarone for the reduction of cardiovascular hospitalizations, was largely based on the results of the ATHENA trial. The ATHENA trial was the largest antiarrhythmic trial ever conducted having enrolled 4628 patients with a recent or current history of AF/AFL. Patients between the ages of 70–75 with risk factors for stroke, or patients >75 years old with or without risk factors for stroke were included. Patients with permanent AF, recently decompensated heart failure, and New York Heart Association (NYHA) class IV congestive heart failure were excluded from the trial. ATHENA assessed the impact of dronedarone 400 mg BID versus placebo on the primary endpoint of CV hospitalization or all-cause mortality. The primary outcome occurred in 734 patients (31.9%) in the dronedarone group and in 917 patients (39.4%) in the placebo group (RR 0.76, 95% CI 0.69–9.84,) over a follow-up period of 21 months. A decrease in CV hospitalization was largely responsible for the reduction in the pri-

Table 1. Antiarrhythmic Efficacy of Dronedarone (reproduced with permission).[9]*

Trial	Dronedarone	Control	Risk ratio	*P* value
DAFNE				
–Time to recurrence	60 days	5.32 days	0.45 (0.28–0.72)	0.001
–Recurrence rate	35/54 (65%)	43/48 (90%)	0.72 (0.58–0.90)	0.004
EURIDIS				
–Time to recurrence	96 days	41 days	0.78 (0.64–0.96)	0.013
–Recurrence rate	150/411 (37%)	95/201 (47%)	0.77 (0.64–0.94)	0.009
ADONIS				
–Time to recurrence	158 days	9 days	0.73 (0.59–0.89)	0.002
–Recurrence rate	154/417 (37%)	89/208 (43%)	0.86 (0.71–1.06)	0.151
ATHENA				
–Time to recurrence	498 days	737 days	0.75 (0.65–0.87)	<0.001
–Recurrence rate	779/1732 (45%)	950/1741 (55%)	0.75 (0.68–0.82)	<0.001
DIONYSOS				
–Recurrence rate	158/249 (63%)	107/255 (42%)	1.51 (1.27–1.80)	<0.001

*Dronedarone dose 400 mg bid; time to recurrence is shown in median days; the control arm in all trials was placebo except for DIONYSOS where dronedarone was compared with amiodarone.

mary endpoint (Table 2). No statistically significant difference in all-cause mortality was observed (RR 0.84, 95% CI 0.66–1.08).

Although sub-group analysis revealed a reduction in CV mortality, it should only be considered as hypothesis generating because all-cause mortality (the principal secondary endpoint) was not significantly reduced. While the reduction in CV hospitalizations with dronedarone was due largely to a decrease in AF-related hospital admissions, decreased hospitalizations for acute coronary syndrome and stroke also contributed to this finding.

The findings in ATHENA suggest that dronedarone does indeed reduce cardiovascular-related hospitalization among stable patients with non-permanent AF/AFL. Further exploration of ATHENA's results however reveals several caveats that might influence this trial's clinical importance.

One of the major limitations of the ATHENA trial concerns the quality of its hospitalization data. This data was not classified by a central adjudication committee. Rather, investigators classified each hospitalization based on data collected from case report forms (CRF's).[6] Information provided on these forms was limited and failed to capture the exact reasons for hospitalization such as hemodynamic instability, heart failure exacerbation, poor rate control, or need for anticoagulation. Thus, while an investigator may have attributed a hospital admission to "atrial fibrillation", the specific reasons for admission were not clear. Such information could yield vital insights into the mechanisms (rate-control, antiarrhythmic, or other properties) by which dronedarone reduces cardiovascular hospitalizations.

Although dronedarone's modest effect on AF recurrence in ATHENA is unlikely to fully account for its impact on cardiovascular hospitalizations, the results are nevertheless consistent with a 20% reduction in the risk of death or CV hospitalization derived from a post hoc pooled analysis of the EURIDIS and ADONIS trials (relative risk 0.80, 95% CI 0.59–1.09).[6] As in ATHENA, the 20% risk reduction observed in the pooled analysis was largely related to a reduction in the risk of CV hospitalization.

At the heart of this discussion, is whether reduced hospitalization is a clinically meaningful endpoint for an antiarrhythmic agent. Moreover, the lack of clarity regarding ATHENA's hospitalization data, makes it difficult to interpret dronedarone's role in the treatment of AF. Given dronedarone's weak antiarrhythmic efficacy, it would be a leap of faith to assume that an ATHENA-like patient would experience fewer hospitalizations on dronedarone due to a reduction in AF burden. On the other hand, a reduction in

Table 2. Study outcomes, ATHENA trial (reproduced with permission).[5]

Outcome	Dronedarone (N = 2301)	Placebo (N = 2327)	Hazard ratio for dronedarone (95% CI)	*P* value
	number (percent)			
Primary outcome	734 (31.9)	917 (39.4)	0.76 (0.69–0.84)	<0.001
First hospitalization due to cardiovascular events	675 (29.3)	859 (36.9)	0.74 (0.67–0.82)	<0.001
First hospitalization				
For atrial fibrillation	335 (14.6)	510 (21.9)	0.63 (0.55–0.72)	<0.001
For congestive heart failure	112 (4.9)	132 (5.7)	0.86 (0.67–1.10)	0.22
For acute coronary syndrome	62 (2.7)	89 (3.8)	0.70 (0.51–0.97)	0.03
For syncope	27 (1.2)	32 (1.4)	0.85 (0.51–1.42)	0.54
For ventricular arrhythmia or nonfatal cardiac arrest	13 (0.6)	12 (0.5)	1.09 (0.50–2.39)	0.83
Death from any cause	116 (5.0)	139 (6.0)	0.84 (0.66–1.08)	0.18
From noncardiovascular causes	53 (2.3)	49 (2.1)	1.10 (0.74–1.62)	0.65
From cardiovascular causes	63 (2.7)	90 (3.9)	0.71 (0.51–0.98)	0.03
From nonarrhythmic cardiac causes	17 (0.7)	18 (0.8)	0.95 (0.49–1.85)	0.89
From cardiac arrhythmia	26 (1.1)	48 (2.1)	0.55 (0.34–0.88)	0.01
From noncardiac vascular causes (including stroke)	20 (0.9)	24 (1.0)	0.84 (0.47–1.52)	0.57
Any hospitalization due to any cardiovascular event or death from any cause	1253 (54.5)	1668 (71.7)	0.76 (0.68–0.84)	<0.001

hospitalization, regardless of the underlying etiology, might have important implications for cost and quality of life issues. The true nature of dronedarone's impact on cardiovascular hospitalization, therefore warrants further clarification.

Does Dronedarone Reduce Mortality?

Evaluating dronedarone's impact on mortality requires analysis of two key trials, the ATHENA trial mentioned above, and the ANDROMEDA trial. ANDROMEDA enrolled patients with recently symptomatic or decompensated heart failure (NYHA Class II–IV) to evaluate the effect of dronedarone 400 bid on the combined endpoint of all-cause mortality or hospitalization for heart failure.[10] Eligible patients had to be hospitalized for the management of worsening heart failure at the time of randomization, had to have NYHA class II–IV heart failure with at least one episode of dyspnea or fatigue at rest or on slight exertion in the past month, and had to have a wall motion index (WMI) $\leq$1.2 (equivalent to a LVEF $\leq$ 35%). A history of AF was not required for entry into the study. In fact, at the time of randomization, AF was only present in 23.2% of the patients in the dronedarone group and 26.8% in the placebo group.

The trial was terminated prematurely by the data and safety monitoring board due to excess mortality among patients assigned to dronedarone. The excess mortality appeared to be predominantly related to worsening heart failure and was most apparent in patients with the most advanced heart failure (Table 3). While the mechanisms underlying this apparent increase in mortality have not yet been elucidated, the FDA has issued a "black box" warning against dronedarone's use in NYHA Class IV heart failure, and recently decompensated NYHA Class II–III heart failure.

The increased mortality signal in ANDROMEDA can be explained by several potential mechanisms. First, it is plausible that this was a spurious finding due to chance. Relatively small numbers of events observed over a short period of time may well have yielded imprecise results. Second, it has been argued by some that the asymptomatic increases in creatinine associated with dronedarone's use prompted more frequent discontinuation of angiotensin converting enzyme inhibitors (ACE's) and angiotensin receptor blockers (ARB's) leading to greater mortality. However this hypothesis remains implausible for several reasons.[6]

1. When the magnitude of dronedarone's mortality effect was adjusted for the use of ACE's/ARBs, the excess risk of death attributable to dronedarone was not meaningfully altered.
2. If this hypothesis were true, then one would expect that dronedarone patients who had their ARB or ACE discontinued and died, would have had their drug stopped due to increases in serum creatinine. In fact none of the dronedarone patients who died had their ACE/ARB discontinued for asymptomatic increases in creatinine.
3. Patients taking dronedarone who remained on their ACE/ARB still had increased mortality with rates similar to those patients who were not on ACE's and ARB's at the beginning of the study.

Table 3. Cause of death among patients in the ANDROMEDA trial (reproduced with permission).[10]

Cause	Dronedarone group (N = 310)	Placebo group (N = 317)
	number (percent)	
Cardiovascular	24 (7.7)	9 (2.8)
Myocardial infarction	0	2 (0.6)
Progressive heart failure	10 (3.2)	2 (0.6)
Documented arrhythmia	6 (1.9)	2 (0.6)
Other cardiovascular cause	3 (1.0)	0
Presumed cardiovascular cause	5 (1.6)	3 (0.9)
Arrhythmia or sudden death*	10 (3.2)	6 (1.9)
Noncardiovascular	1 (0.3)	3 (0.9)
Total	25 (8.1)	12 (3.8)

Finally, it is possible that the increased mortality associated with dronedarone use in ANDROMEDA may have been directly related to the deleterious effects of dronedarone itself. Keeping in mind that ANDROMEDA patients were highly symptomatic advanced heart failure patients, a drug with even mild negative ionotropic properties such as dronedarone could be potentially harmful. Alternatively, the deleterious effects of dronedarone may have yet to be characterized.

Reconciling ATHENA and ANDROMEDA

In contrast to the ANDROMEDA trial, no increase in mortality was seen among patients in the ATHENA trial (RR 0.84, 95% CI 0.66–1.08). How can these disparate results be reconciled? First, it is important to recognize that the ANDROMEDA and ATHENA populations were markedly different (Table 4). While both trials enrolled patients with low ejection fraction, the majority of patients in ATHENA had no clinical heart failure or reduced ejection fraction (EF), whereas the majority of patients in ADROMEDA met both of these criteria. Recently decompensated heart failure was a requirement for enrollment in ANDROMEDA; in ATHENA, this was an exclusion criteria.

The central question in reconciling the results of ATHENA and ANDROMEDA is how to identify patients who may benefit from dronedarone and not be harmed. In ATHENA the upper bound of the mortality confidence interval (1.08) indicates that a >8% increase in the risk of death associated with dronedarone was excluded. However, subgroup analysis of the ATHENA trial suggested that the only subgroup in whom a clinically meaningful increase in the risk of death was excluded were clinically stable patients without AF/AFL on randomization. The upper bound of the confidence interval was 1.21 in patients with EF < 35% (0.55 (0.25–1.21)), 1.34 in patients with NYHA Class III heart failure (0.66 (0.32–1.34)) and 1.47 in patients with NYHA Class I or II heart failure (0.93 (0.59–1.47)), and 1.51 in stable patients with AF/AFL on randomization, indicating that an increase in mortality ranging from up to 21% to 51% could not be excluded in these patients.

Taking this analysis into account, if a patient has non-permanent AF, no recent symptoms of heart failure, an ejection fraction greater than 35 percent, and class I–II heart failure (i.e. the majority of ATHENA-like patients) it is likely that dronedarone could be used safely. Conversely, if a patient has class IV heart failure, or recent heart failure hospitalization, dronedarone should be avoided (i.e. ANDROMEDA-like patients). The grey zone lies in the small area of overlap between the ATHENA and ANDROMEDA populations (Fig. 1). While this zone cannot be precisely defined, NYHA Class III patients with EF's ≤ 35% may well represent an area of overlap between the two trials. The most conservative approach would be classify these patients as ANDROMEDA-like patients, and avoid the use of dronedarone. However, the precise effects of dronedarone in this sub-population remain unclear.

Does Dronedarone Reduce Stroke?

Recently, a post hoc analysis of the ATHENA trial suggested that dronedarone was associated with a reduction in stroke risk (1.8% vs. 1.2% per year, hazard ratio 0.66, 95% CI 0.46–0.96).[11] This reduction was driven primarily by a decrease in ischemic stokes. While these findings are thought provoking, they should be interpreted with caution. First, given

Table 4. Comparison of ANDROMEDA and ATHENA populations.[5,10]

	ANDROMEDA	ATHENA
% NYHA Class IV	3%	0%
% NYHA Class II or III	97%	21%
% NYHA Class I	0%	79%
% with EF < 35%	100%*	3.90%
% with EF > 45%	0%*	88.00%
Recent CHF exacerbation	required for entry	excluded from entry

*Based on a wall motion index score of ≤1.2.

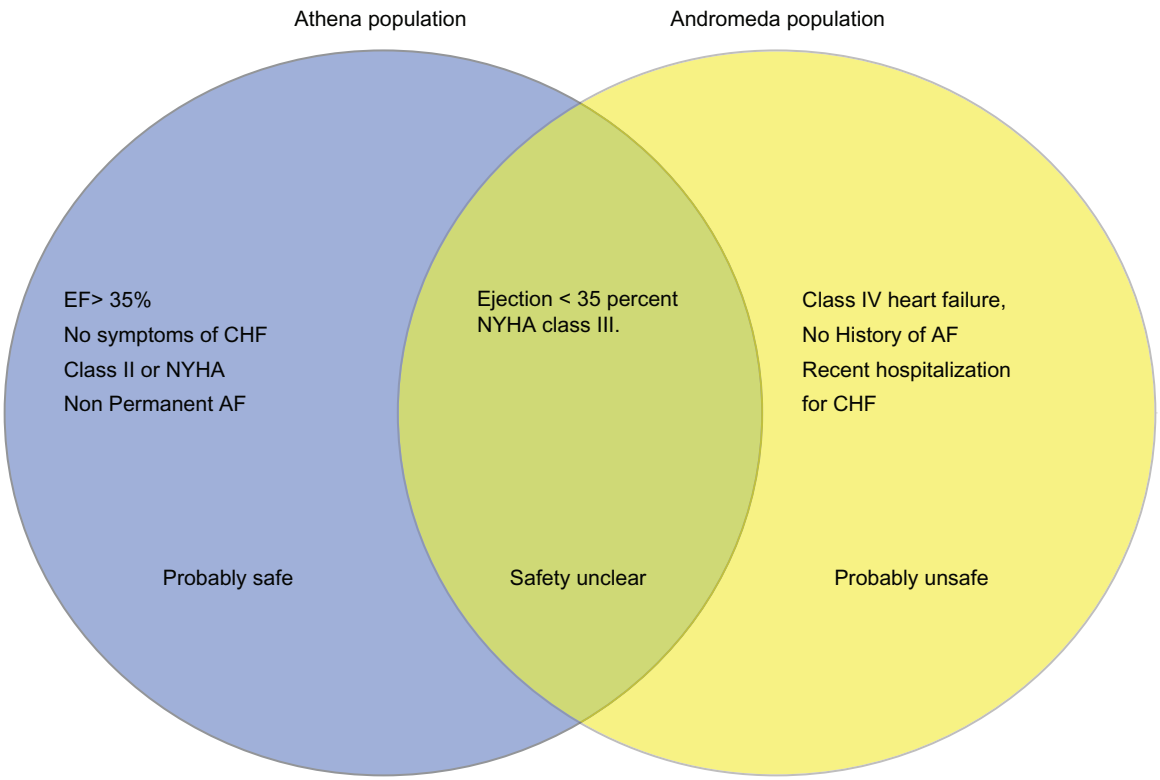

Figure 1. Safety profile of dronedarone based on comparison of ATHENA and ANDROMEDA trials.

its modest rhythm control properties, it is unlikely that AF suppression could account for the reductions in stroke observed in ATHENA. In previous trials, agents with superior rhythm-control efficacy such as amiodarone and sotalol were not associated with a stroke benefit.[12–15] It has been suggested that blood pressure reduction might account for the findings of this sub-study. This explanation remains implausible as blood pressure was not found to be an independent predictor of stroke risk in ATHENA. Finally, as stroke was not a prespecified endpoint and outcomes were not centrally adjudicated, these findings should only be considered as hypothesis generating. Further studies are required to establish whether this was a chance finding, or to clarify the mechanisms by which dronedarone reduces stroke risk.

Is Dronedarone Well Tolerated?

Clinical trials have demonstrated that dronedarone is generally well tolerated. The most common adverse events identified with dronedarone have been diarrhea, nausea or vomiting and rash. In a pooled analysis, the most common reason for discontinuation of therapy with dronedarone was GI disorders (3.2% of patients in dronedarone 400 mg BID versus 1.8% in the placebo group).[6]

Dronedarone's cardiac side effects are consistent with its pharmacological properties including bradycardia and QT prolongation. Approximately a ten millisecond (ms) increase in the corrected QT in patients has been observed in patients with baseline sinus rhythm. There has been no evidence of proarrhythmic effect observed with dronedarone. One case of torsades de pointes has been identified so far in clinical trials.[5] Accordingly, dronedarone should not be used in patients with a QTc $>$ 500 ms.

Unlike amiodarone, no change in INR dosing or monitoring is required with dronedarone. Caution should be used in patients taking digoxin as dronedarone may increase digoxin levels. It is recommend that a patient's digoxin dose be reduced by 50% with monitoring of digoxin levels if dronedarone is to be used. A benign transient increase in serum creatinine (attributed to inhibition of renal tubular secretion) has been observed with dronedarone that peaks at 7 days and returns to baseline within 1 week after treatment discontinuation. Dronedarone has not been associated with endocrinological, neurological, or pulmonary

toxicity in the pooled AF/AFL studies—although most studies have been of short duration, which might be insufficient to uncover the side effects typically associated with long-term amiodarone use.

The DIONYSOS trial is the only trial to directly compare the tolerability of dronedarone with amiodarone.[7] In this study, dronedarone was associated with a reduced risk of thyroid disorders, sleep disorders and tremor, and fewer episodes of bleeding due to less interference with oral anticoagulants. However, the risk of adverse gastrointestinal events was increased in patients taking dronedarone.

In DIONYSOS, no significant difference was observed between dronedarone and amiodarone with respect to the primary tolerability endpoint, premature drug discontinuation (10.4% vs. 13.3% respectively, RR of 0.78, 95% CI 0.48–1.27).[7] Although no pulmonary or liver toxicities were observed with dronedarone, the trial's short duration (6 months) makes it difficult to establish definitive conclusions regarding dronedarone's long-term safety. Thus, while dronedarone has been shown to be well tolerated compared with placebo, when compared with amiodarone it is only marginally better tolerated. Additional studies will need to be performed to definitively establish its superior safety and tolerability profile compared to other antiarrhythmic agents.

Conclusions/Recommendations

While great emphasis has been placed on the development of strategies to maintain sinus rhythm, the primacy of rhythm control over rate control has never been conclusively established. Accordingly, truly asymptomatic patients with AF can be comfortably managed with rate control agents and anticoagulation according to their stroke risk. However, clinicians are well aware of an important subset of patients in whom AF is poorly tolerated. In these patients, antiarrhythmics should be considered. For this reason, dronedarone is a welcome addition to the antiarrhythmic armamentarium. Its effectiveness, while modest, does not exclude the possibility that it may play a role in the treatment of AF.

In patients, without structural heart disease or with mild heart failure but with no recent decompensation, dronedarone may be considered a reasonable option for a rhythm control strategy. However the availability of relatively safe and more effective agents should relegate its use to a second or third-line agent in most instances.

In conclusion, dronedarone is a new antiarrhythmic agent that has been approved for the reduction of cardiovascular hospitalizations related to AF. Clinical trials have demonstrated modest efficacy with respect to AF suppression. In one clinical trial dronedarone decreased cardiovascular hospitalizations compared with placebo. However, the underlying mechanisms responsible for this effect remain unclear. Dronedarone may increase mortality in patients with recently decompensated or severe heart failure and should be avoided in these populations. Finally, the drug appears to be well tolerated compared with placebo and amiodarone. While dronedarone has expanded the pool of antiarrhythmics available for management of AF/AFL, its precise therapeutic role will continue to evolve in the coming years.

Disclosures

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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