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EDITORIAL

Towards personalized therapy for atrial fibrillation: the rhythmic climbing of dronedarone

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This editorial refers to 'Dronedarone provides effective early rhythm control: post-hoc analysis of the ATHENA trial using EAST-AFNET 4 criteria' by P. Kirchhof *et al.*, https://doi.org/10.1093/europace/euaf080.

In this issue of *Europace*, Kirchhof *et al.*[1] provided new results supporting the use of dronedarone for long-term maintenance of sinus rhythm (SR) in patients with recently diagnosed atrial fibrillation (AF) and cardiovascular risk factors, including heart failure (HF). This paper is a sort of landmark, such as *a cairn*, in the challenging mountain trail of dronedarone (see *Figure 1*), marked by steep ascents of initial promise, treacherous descents of unexpected risks, and narrow ridges requiring careful navigation. To unravel this path, we have to go back well before dronedarone authorization. At the beginning of this century, two randomized controlled trials (RCTs), the *Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM)* and *RAte Control versus Electrical cardioversion (RACE)* studies, deeply impacted on the management of AF by signalling an increased risk associated with a strategy based on maintenance of SR, driving more attention to rate control.[2] However, more careful re-analysis showed that actual SR maintenance, interruption of anticoagulation, and use of digoxin played a major role on the results of these RCTs clearing a bit the track to SR maintenance. In this scenario, dronedarone, an amiodarone derivative designed for long-term rhythm control and to reduce extracardiac amiodarone-induced toxicity (mainly thyroid and pulmonary), came as a promising guide to this new way.

Dronedarone was approved in the Europe in 2009 for rate and rhythm control following several key trials that still constitute the most comprehensive clinical assessment ever done for an antiarrhythmic agent used in AF management. The *Dronedarone Atrial FibrillatioN study after Electrical Cardioversion (DAFNE)* trial (2003) evaluated its efficacy after cardioversion, establishing dronedarone as a second-line option for rhythm control. Additionally, the pivotal *EURopean trial In AF or flutter patients receiving Dronedarone for maintenance of Sinus rhythm (EURIDIS)* and the *American-Australian-African Trial with Dronedarone in AF Patients for the Maintenance of Sinus Rhythm (ADONIS)* trials (2007) demonstrated that dronedarone significantly extended the time to first AF recurrence in patients with paroxysmal or persistent AF and reduced hospitalization rates. The *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 (ATHENA)* trial (2009),[2,3] and its *post hoc* analysis,[4] provided further pivotal evidence that dronedarone is effective in reducing all-cause and cardiovascular death, stroke, and hospitalizations due to worsening HF in patients with paroxysmal or persistent AF while offering a significantly safer profile, particularly in terms of organ toxicity and proarrhythmic effects.

The enthusiasm brought by these results drove the hope to extend the indications for dronedarone to HF (independently from AF) and rate control in permanent AF, blind to the crevasse in front. The *Antiarrhythmic Trial with Dronedarone in Moderate to Severe CHF Evaluating Morbidity Decrease (ANDROMEDA)* trial highlighted the lack of safety of dronedarone in patients with recently decompensated severe HF, and the *Permanent Atrial FibriLLAtion Outcome Study Using Dronedarone on Top of Standard Therapy (PALLAS)* trial was prematurely halted because treatment was associated with an increased risk of death. Both trials raised several concerns for the use of dronedarone in patients with HF and long-lasting AF (not limited to permanent AF) (see *Figure 1*).

A light in this hole later came from additional RCTs and real-world studies. In 2017, a meta-analysis evaluated available RCTs on dronedarone not finding any trend towards worse all-cause mortality [odds ratio (OR) 1.36, 95% confidence interval (CI) 0.79–2.33; $P = 0.732$] or cardiovascular mortality (OR 1.51, 95% CI 0.74–3.08; $P = 0.860$), with significant heterogeneity between the studies that was abolished when adjusting for co-administration of digoxin and prevalence of non-permanent AF at the meta-regression analysis. Moreover, the authors showed that the meta-analysis of the observational real-world studies evidenced a significantly lower cardiovascular mortality (effect size 0.52, 95% CI 0.36–0.69 vs. effect size 1.86, 95% CI 0.62–3.09; $P < 0.001$), compared with RCTs, underlying the importance to avoid dronedarone in patients without paroxysmal/persistent AF and/or in combination with digoxin.[5,6]

The opinions expressed in this article are not necessarily those of the Editors of *Europace* or of the European Society of Cardiology.

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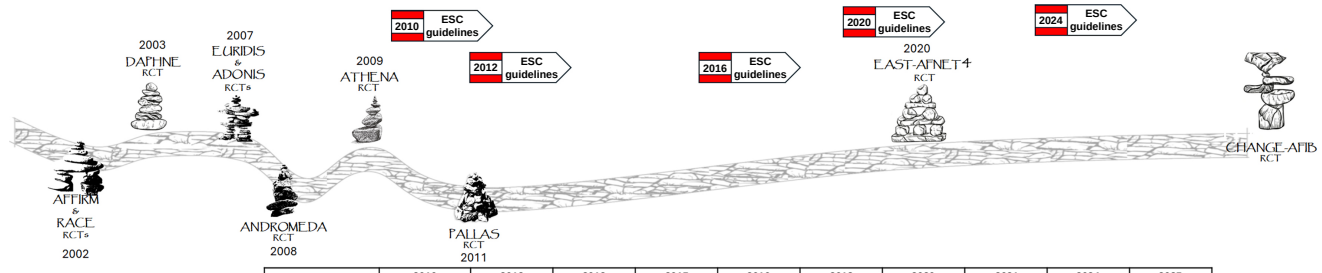

		2010	2012	2013	2015	2016	2018	2020	2021	2024	2025
		ESC guidelines	ESC guidelines	Europace 15:625–51	Europace 17:1467–1507	ESC guidelines	Eur Heart J 39:1330–1393	ESC guidelines	Europace 23:1612–1676	ESC guidelines	Europace https://doi.org/10.1093/europace/euaf076
Rhythm control		No/minimal structural HD (IA)	No/minimal structural HD (IA)			No/minimal structural HD (IA)		No/minimal structural HD (IA)		No/minimal structural HD (IA)	No/minimal structural HD
		HHD LVH (IA) (only option)	HHD LVH (IA) (only option)			HHD LVH (IA)		HHD LVH (IA)		HHD LVH (IA)	HHD LVH 1st choice
		CAD (IA)	CAD w/o HF, with caution (IA)			CAD w/o HF (IA)		CAD, VHD w/o HF (IA) and/or HFpEF (IA)		CAD, VHD (IA)	CAD, VHD 1st choice
		HF NYHA I/II (IA 1st option)	HF NYHA I/II should be avoided			Avoid with HF				HFpEF HFmrEF (IA)	HFpEF HFmrEF 1st choice
		Contraindicated in III/IV or unstable HF	Contraindicated in III/IV or unstable HF			Contraindicated in III/IV or unstable HF		Contraindicated in III/IV or unstable HF		Contraindicated in III/IV or unstable HF	Contraindicated in III/IV HF or HFrEF
Rate control		Non-perm AF w/o NYHAIII/IV or unstable HF (IIa B)	Not for perm AF (III)			AAD not to be used for rate control (III)		Not for rate control		Not for rate control	Not for rate control
Concomitant DOAC	Apixaban			No data	Caution no clinical/PK data		Caution no clinical/PK data		With caution	No contraind.	With caution
	Dabigatran			Contraind/not recom	Contraind/not recom		Contraind/not recom		Contraind/not recom	Avoid where possible	Avoid where possible
	Edoxaban			Reduce dose by 50%	Reduce dose by 50%		Reduce dose by 50%		Reduce dose by 50%	Reduce dose by 50%	Reduce dose by 50%
	Rivaroxaban			Contraind/not recom	Caution, try to avoid		Should be avoided		Should be avoided	Avoid where possible	Avoid where possible

Figure 1 Evolution of the recommendations of the European Society of Cardiology for dronedarone use in light of the mainly related randomized control trials. The upper portion depicts the temporal distribution, as a virtual path, of the randomized trials reported in this paper. Below are included the temporal trend of the recommendations regarding the use of dronedarone for rate/rhythm control and the precautions with combined use with direct oral coagulants. AAD, antiarrhythmic drugs; AF, atrial fibrillation; CAD, coronary artery disease; DOAC, direct oral anticoagulant; ESC, European Society of Cardiology; HD, heart disease; HF, heart failure; HFpEF, HF with preserved ejection fraction; HFmrEF, HF with mildly reduced ejection fraction; HFrEF, HF with reduced ejection fraction; HHD, hypertensive heart disease; LVH, left ventricular hypertrophy; NYHA, New York Heart Association; PK, pharmacokinetics; RCT, randomized controlled trial; VHD, valvular heart disease; W/O, without.

In 2020, the *Early Treatment of Atrial Fibrillation for Stroke Prevention Trial (EAST-AFNET 4)* marked a turning point in the climbing tour of AF management, carving out a new path where early rhythm control might lead to better outcomes than the long-favoured rate control approach, demonstrating that early, systematic rhythm control significantly reduced stroke and cardiovascular events in patients with newly diagnosed AF (within 12 months), challenging the assumption that rhythm control was merely a side trail, useful for symptom relief but offering no real protection against cardiovascular events.[7] The study suggested that by proactively stabilizing heart rhythm at an early stage, clinicians could prevent complications rather than just managing symptoms, akin to a more direct, strategic ascent to avoid treacherous descents.

This new path remains challenging for patients with a history of stroke, who are often frail, with multiple comorbidities, making them more susceptible to the risks of rhythm-control therapies. Recognizing this, EAST-AFNET 4 included a prespecified subgroup analysis to determine whether this early intervention was not only effective but also safe in high-risk population.[7] This careful examination ensures that the new route, while promising, needs caution, balancing the potential for improved outcomes against the dangers of adverse events.

Capitalizing all the experience gained during this long expedition, Kirchhof *et al.*[1] provide a new *cairn* with this sub-analysis of the ATHENA trial through the EAST-AFNET 4 lens. This *post hoc* analysis reveals that dronedarone improves cardiovascular outcomes in patients with early AF and concomitant cardiovascular risk factors. This finding mirrors the core results of EAST-AFNET 4 and reinforced the idea that rhythm control, when initiated early, may be a key route to safer ground. Kirchhof *et al.*[1] suggested that patients who successfully reached and maintained SR at 12 months benefited significantly from dronedarone, much like a climber securing a foothold on stable rock after a precarious stretch. This observation reinforced a crucial lesson from EAST-AFNET 4: achieving SR, rather than the specific trail used to get there, was the way to reach the peak.

Despite these promising findings, this ATHENA sub-analysis highlighted key differences in the terrain covered. Patients in ATHENA were slightly older and had higher CHA_2DS_2-VASc scores, and fewer had HF compared with those in EAST-AFNET 4. Anticoagulation strategies had also evolved—ATHENA largely relied on vitamin K antagonists, while EAST-AFNET 4 included a broader use of direct oral anticoagulants (DOACs). These differences underscored how the landscape of AF management has shifted over time, with newer tools making the climb potentially safer for actual patients.[8]

The 2024 European Society of Cardiology guidelines[9] recognized dronedarone as a key component of modern rhythm control strategies. With expanded indications for persistent AF, growing evidence of disease-modifying effects, and an improved safety profile, dronedarone holds a Class IA recommendation for long-term rhythm control in patients with

preserved to mildly impaired left ventricular function, ischaemic heart disease, or valvular disease to prevent recurrence and progression of AF (without the careful need for monitoring extracardiac toxicity required for amiodarone). However, a recent European Heart Rhythm Association (EHRA) physician survey revealed a striking discrepancy between guideline recommendations and actual prescribing patterns,[10] in line with dispensation/consumption data.[11] Despite its strong endorsement, more than half of surveyed physicians barely use dronedarone as a first-choice drug, reserving its use for cases of thyroid disorders or when other antiarrhythmic drugs fail. Several barriers may contribute to this reluctance: concerns about dronedarone efficacy relative to amiodarone, contraindications in common AF scenarios, and the burden of liver function monitoring.[3] The latest post-marketing data from US-DILI network[12] found a distinct clinical feature of liver injury with dronedarone (3 cases) as compared with amiodarone (10 cases): predominantly hepatocellular, less predictable, with a shorter latency (119 vs. 388 days), without observed chronic injury. All these factors made clinicians cautious, preferring more familiar but potentially riskier alternatives, like experienced mountaineers who, despite knowing of a newly charted route, stick to the known.

Recent real-world data[13] reassess the safety and efficacy of dronedarone, particularly in combination with DOACs. In particular, available clinical evidence and pharmacokinetic modelling showed a similar effect of dronedarone and amiodarone on rivaroxaban exposure, while the few available real-world data report similar findings for dabigatran, despite the limited use in view of the contraindication to the co-administration with dronedarone. These data, albeit non-randomized, underline the importance of a comprehensive assessment of the bleeding risk factors, since comorbidities, frailty, and additional modifiers can have a major impact on bleeding events.

Thus, while the AF treatment landscape is evolving, the climb remains uneven. The challenge is not just refining treatment strategies but ensuring that clinicians embrace them, recognizing dronedarone's role in the whole compendium of antiarrhythmic drugs.[14] The road to this summit will be made clearer through the integration of guided therapy with real-world evidence, as well as the results of new clinical trials, such as the *Early Dronedarone Versus Usual Care to Improve Outcomes in Persons With Newly Diagnosed Atrial Fibrillation (CHANGE-AFIB)* study,[15] which will test the hypothesis that early administration of dronedarone can lead to improved CV outcomes and quality of life in patients with newly diagnosed AF, adding new paving to this trail.

Conflict of interest: The authors have no conflicts of interest to declare regarding the purpose of this manuscript.

Data availability

The data underlying this article are available in the article.

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