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EDITORIAL

Run baby run … but not too fast! Rate control management in atrial fibrillation: a claim for personalization

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This editorial refers to 'Ventricular rate in atrial fibrillation and the risk of heart failure and death' by L.M. Westergaard *et al.*, https://doi.org/10.1093/europace/euad088.

Atrial fibrillation (AF) is the most common sustained arrhythmia, with a major impact on patients' outcome and burden for healthcare systems. Epidemiological studies have shown a progressive increase in its prevalence and incidence that will make AF similar to a silent but progressive pandemic.[1] Current clinical research in this topic is more focused on rhythm control, especially by catheter ablation, and on the best approach for AF screening to prevent thrombo-embolic events, especially in asymptomatic patients.[2] However, AF is a progressive disease that in most patients shows progression to a persistent form, requiring appropriate treatment for rate control.[3]

The paper by Westergaard *et al.*[4] raises some important concerns on which are the target for rate-control management. The authors provide the results of an interesting analysis based on more than 7000 patients, from the years 2001 to 2015, presenting with a first-time electrocardiogram (ECG) with AF or atrial flutter, who were dispensed with rate-control drugs at the time of ECG recording. Through an elegant matching of two other databases, the authors were able to show that a heart rate ≥100 b.p.m. was independently associated with 1-year mortality and with the risk of developing new heart failure in a dose–response manner (i.e. a higher ventricular rate was associated with a greater heart failure risk). Despite the limitations of the study design, the authors should be congratulated for these results obtained in a large cohort of unselected AF patients, providing new insights on a debated topic: how strict/lenient should be the management of heart rate in AF patients?

The evidence on rate control in AF management is clearly conflicting, since on one side the pooled data from The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) and RAte Control versus Electrical cardioversion for persistent atrial fibrillation (RACE) trials found no difference in major clinical events among patients assigned to strict rate-control strategy (≤80 b.p.m., in the AFFIRM trial) and lenient rate control (<100 b.p.m., RACE trial).[5] These findings were later confirmed by the Rate Control Efficacy in Permanent Atrial Fibrillation: a Comparison between Lenient versus Strict Rate Control II (RACE II) trial, showing that a lenient rate-control treatment strategy (<110 b.p.m.) was non-inferior to a strict rate-control treatment strategy (<80 b.p.m.) in terms of symptoms control and mortality.[6] This was translated into the official guidelines from the European Society of Cardiology, which included a Class II recommendation for lenient rate control (<110 b.p.m.) in asymptomatic patients with AF.[7] On the other hand, the same guidelines underlined the limited and conflicting evidence, claiming for personalization of the treatment in view of the known risk of tachycardia-induced cardiomyopathy and its sequelae. This is also underlined by the results of the already cited *post hoc* analysis of the AFFIRM and RACE trials showing that AF patients achieving lower ventricular rates in the two studies had better outcomes compared with AF patients with ventricular rates ≥100 b.p.m.[4,5] However, when focusing on the RACE II trial, we have to make some additional considerations. The particular design of the study requiring the patients to perform exercise testing inevitably led to enrol a more selected population, when compared with the general population of AF patients requiring rate control,[8] since these patients were relatively young (68 ± 8 years), had a preserved left ventricular ejection fraction (i.e. 52 ± 12% overall, with a prevalence of 15.1% of values ≤40%), and a relatively low $CHADS_2$ score (1.4 ± 1.1), with ventricular rates corresponding, on average, to a 'lenient' rate control already at baseline (96 ± 13 b.p.m.). More interestingly, the strengthening in rate-control pharmacological regimen in the 'strict' arm was obtained by the association of beta-blockers and digoxin in most of the patients (37.3%), or by the addition of rather high verapamil doses (in 105/303 patients vs. only 46/311 patients in the lenient rate control) and with a wider use of the association between verapamil and a beta-blocker (in ~62 vs. 32% in the lenient rate-control arm). Unfortunately, we do not have an agent-specific sub-analysis, which in any case would present several limitations, to gather if these choices could have affected the final results. This could be relevant since the rate-control effect of beta-blockers is less pronounced when compared with non-dihydropyridine calcium-channel blockers,[9] and specific calcium-channel blockers may express a different level of negative inotropic effect, the latter being more pronounced with verapamil when

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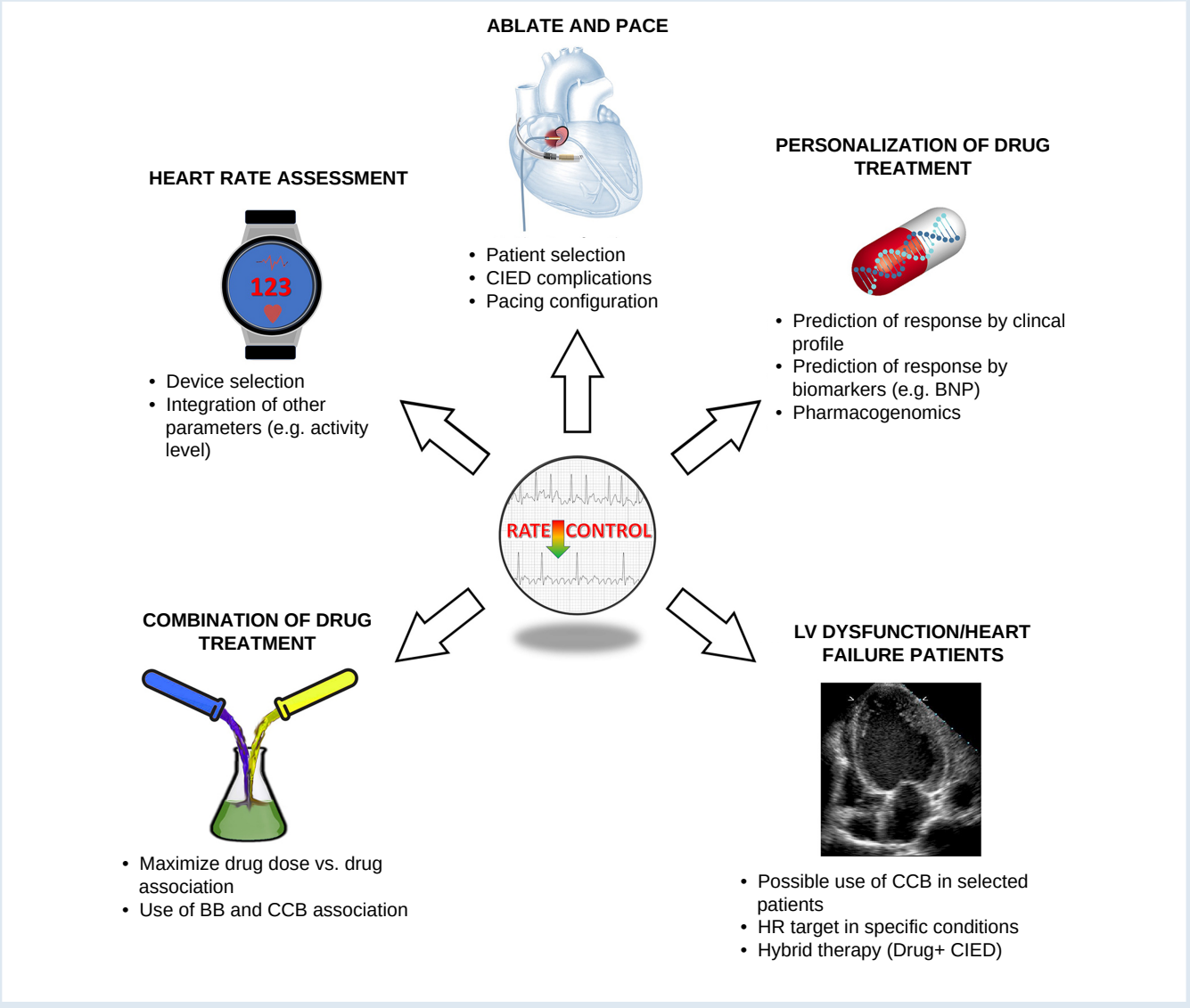

Figure 1 Open issues and area for future research in rate control for AF. AF, atrial fibrillation; BB, beta-blockers; CCB, calcium-channel blockers; CIED, cardiac implantable electrical devices.

compared with diltiazem.[10] Of note, we recently published the results of an analysis based on a cohort of AF patients showing that among the 1112 patients under rate-control treatment the group of 125 subjects treated with oral diltiazem presented good outcomes at long term, especially in selected patients with heart failure symptoms or with reduced left ventricular ejection fraction in the absence of haemodynamic compromise. Obviously, these findings are only observational and will require additional support from a randomized study. However, these data are in line with the suggestion to reconsider the role of non-dihydropyridine calcium-channel drugs for rate control of AF,[11] in view of their positive effects on exercise capacity and NT-pro BNP compared with beta-blockers[12] and taking into account that the strict contraindication to calcium-channel blockers for rate control in AF patients with heart failure patients and/or reduced ejection fraction was derived from outdated studies, not primarily designed to address the efficacy and safety of rate control in AF patients with heart failure.[13]

Moreover, as reported in current guidelines, the carefully tailoring of rate-control therapy cannot be limited to the addition of digoxin to a beta-blocker or to a calcium-channel blocker, but should also consider the association of a beta-blocker with a calcium-channel blocker, with/without the use of digoxin.[7] This is an important issue from the clinical point of view, since may actually increase the possibilities to achieve an effective rate control, pending the risk of negative inotropic effects and bradyarrhythmias. Noteworthy, the latter risk was not confirmed by the RACE II trial, where the implantation rate of pacemakers was 1.4% at 3 years in the strict rate-control arm (similar to the 0.8% observed in the lenient rate-control arm), despite the use of beta-blockers plus calcium-channel blockers, in association in more than one-fifth of the patients, as well as despite the concerns already reported regarding this specific combinations.[6] The only alternative to drugs to achieve an adequate rate control is the ablate and pace strategy, which could be an attractive option in appropriately selected patients, especially after the development of the His-bundle or conduction system pacing.[14] However, this approach is still explorative since specific trials are still ongoing (e.g. NCT02805465). Notably, the pacemaker-dependency induced by ablation of the atrioventricular node should be carefully

considered in view of the possible infective and non-infective complications associated with long-term pacing that especially in case of pacemaker-related infection will increase the complexity of patient management for a reimplantation strategy after transvenous lead extraction.[15,16]

Another clinical consideration, also analysed in the discussion by Westergaard *et al.*,[4] regards the methods to assess rate control in everyday life. The current improvement in remote management of arrhythmic patients could take advantage of wearables also for personalizing the rate-control strategy,[17] but there are still some limitations linked to technical issues (the use of photoplethysmographic signal is less reliable at high heart rates), as well as linked to the limited digital competence that may characterize many of the typical AF patients candidates to rate control.[18] Finally, there are explorative studies to adopt gene-guided drug therapy also in AF patients, albeit current results are still very preliminary. In conclusion, rate-control strategy is a part of the main treatment strategy for almost all AF patients in view of the tendency to AF progression, and for this reason, future studies aimed at improving AF therapy should consider all these debated aspects (*Figure 1*), in the perspective of improved personalization of AF management.

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