Atrial fibrillation

Smit, Marcelle D.; Van Gelder, Isabelle C.

Published in:
Europace

DOI:
10.1093/europace/eux040

ESC European Society of Cardiology

Europace (2017) **19**, 1413–1415
doi:10.1093/europace/eux040

EDITORIAL

Atrial fibrillation: a mechanism or just a bystander?

Marcelle D. Smit and Isabelle C. Van Gelder*

Department of Cardiology, Thoraxcenter, University of Groningen, University Medical Center Groningen, Hanzeplein 1, GZ 9713, Groningen, The Netherlands

Online publish-ahead-of-print 12 April 2017

This editorial refers to 'Rate vs. rhythm control and adverse outcomes among European patients with atrial fibrillation' by Y. Purmah *et al.*, doi:10.1093/europace/euw421.

Atrial fibrillation (AF) can cause symptoms and is associated with stroke, heart failure and death.[1] To this day, rate vs. rhythm control trials have shown no benefit of a strategy determined to restore and maintain sinus rhythm.[2,3] Therefore, at present the only reason to treat AF *itself* is to reduce symptoms, improve quality of life, prevent cardiovascular morbidity and mortality, and avert iatrogenic consequences of unnecessary therapy. The lack of beneficial effect of rhythm control, however, may be related to the lack of ability of rhythm control approaches to maintain sinus rhythm, but it may be more than that. In the past ten years, success of atrial catheter ablation in maintaining sinus rhythm has improved significantly. It is superior to antiarrhythmic drugs for rhythm control in paroxysmal AF,[4] but still less effective in patients with persistent or long-standing (> 1 year) persistent AF.[5]

Implementing atrial ablation in rate vs. rhythm control trials may alter outcomes in favour of rhythm control therapy but this has not yet been shown. The Early treatment of Atrial fibrillation for Stroke prevention Trial (EAST, ClinicalTrials.gov Identifier: NCT01288352)[6] and the Catheter Ablation vs. Antiarrhythmic Drug Therapy for Atrial Fibrillation Trial (CABANA, ClinicalTrials.gov Identifier: NCT00911508) randomize patients to usual care or structured rhythm control therapy including early catheter ablation (EAST) and optimal therapy with either rate control or rhythm control drugs or catheter ablation (CABANA). Outcomes in cardiovascular morbidity and mortality will be available within several years. These trials will provide contemporary data concerning whether catheter ablation of AF is indeed accompanied by a reduction of morbidity and mortality.

Meanwhile, the EURObservational Research Programme Atrial Fibrillation (EORP-AF) pilot registry Investigators report contemporary data on rate and rhythm control strategies in Europe. They investigated management of AF and assessed differences in adverse outcomes in patients treated either with rate or rhythm control during 1-year follow-up.[7] This pilot registry was conducted in 9 European countries and enrolled both in- and outpatients with AF. From February 2012 to March 2013 a total of 3119 AF patients were included. Analyses were performed according to four different regions: Eastern, Southern, Northern, and Western Europe. The majority of patients were included in Eastern and Southern Europe (42% and 34%, respectively). One finding of interest was the unexpected differences between the diverse regions in patients included in the registry and choice of therapy. In Northern Europe (Belgium and the Netherlands), more patients with paroxysmal AF (47%) were included compared to the other regions (24, 22, and 26% in Eastern, Southern, and Western European countries, respectively). There was a wide range in number of patients treated with antiarrhythmic drugs between the regions, ranging between 26% in Norway and 75% in Denmark. Except for Western Europe, amiodarone was the most common antiarrhythmic drug. Atrial ablation was performed in a minority of patients treated with rhythm control, and was conducted predominantly in Northern Europe. For rate control, all four regions most frequently instituted beta-blockers.

To assess differences in outcome between rate and rhythm control treated patients the authors analysed a subgroup of patients treated with either a pure rate control strategy ($n = 1036$, 34%) or rhythm control strategy ($n = 355$, 11%). They excluded patients treated with a mixed strategy or only managed by clinical observation. Not surprisingly, the important differences in clinical characteristics between patients included in both strategies were present. Patients treated with a pure rhythm control approach were younger, had more often paroxysmal AF and had less severe comorbidities translating into a lower CHA_2DS_2-VASc score. Interestingly, also more women were treated with pure rate control. After a follow-up of 1 year, there were more thromboembolic complications, cardiovascular and all-cause deaths in the rate control treated patients. Cox regression analysis showed that a pure rate control strategy was independently associated with higher all-cause mortality. Other characteristics associated with higher all-cause mortality included the presence of several comorbidities. Propensity score matched analysis, which accounts for comorbidities, however, showed no significant outcome rates between the groups anymore. This analysis

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

* Corresponding author. Tel: +31 50 3611327; fax: +31 50 3614391. *E-mail address*: i.c.van.gelder@umcg.nl

revealed that older age, chronic kidney disease, and diabetes mellitus were parameters associated with a higher mortality rate, but not the type of therapy. Kaplan–Meier survival analysis showed a trend that all-cause mortality in patients assigned to rate control was higher in Southern European countries.

What clinical lessons can we learn from these data? First, patients treated with pure rate control in this registry differed significantly from those treated with pure rhythm control. Patients treated with pure rate control were older, more often had persistent forms of AF, had more severe comorbidities and less severe symptoms. These differences in characteristics between the groups are not unexpected. This was not a randomized trial, and the current guidelines recommend a rate control approach in older patients with minor symptoms and a lower likelihood of successful rhythm control therapy.[1,8] In line with these differences in characteristics between the groups, all-cause mortality rates were higher in the pure rate control treated patients. Intriguingly, outcome differed across the different European regions.

Once more the present data raise the question whether AF is an underlying mechanism contributing to worse prognosis or whether AF is a bystander being a marker of increased cardiovascular risk.[9] It is generally assumed that eliminating AF may be associated with an improved outcome. So far, however, the randomized trials did not show any benefit of attempts to abolish AF, albeit those rhythm control strategies were rather unsuccessful. This registry suggests at first glance an improved outcome in rhythm control treated patients, however, propensity score matched analysis, accounting for comorbidities, showed no difference.

Will EAST and CABANA change our guidelines? On one hand, the answer may be yes. The outcome may be in favour of rhythm control, especially considering the inclusion criteria of EAST.[6] They enrolled patients with a short history of AF, diagnosed within one year prior to inclusion. This is an important difference with the earlier randomized trials. It is generally assumed that mortality, stroke, and other vascular events most frequently occur early after start of AF.[10] *Early* and aggressive rhythm control therapy in order to restore sinus rhythm may be one of the prerequisites to show a favourable outcome of a strategy intended to restore and maintain sinus rhythm.[11,12] Furthermore, recent data suggesting that duration of both clinical and subclinical AF may have prognostic consequences also favour the deleterious impact of AF itself.[13–16] On the other hand, the favourable outcome in shorter lasting AF may also be related to the fact that patients with shorter forms of AF tend to have fewer other risk factors and comorbidities, as was the case in the present registry.

Yet, it still may be questioned whether AF is a causal factor or just another associated risk marker for stroke and other vascular complications.[9,17,18] Several analyses showed that only a few patients with subclinical AF associated stroke had evidence of subclinical AF during the last months prior to their embolic event.[17,18] In the present study, patients with more persistent AF also were more likely to have other stroke risk factors, suggesting that confounding factors, other than rate or rhythm control strategy, might be responsible for the increased risk of adverse outcomes. The results of ongoing trials, such as EAST, are eagerly awaited.[6]

The 2016 European Society of Cardiology AF guidelines strongly recommend treatment of associated conditions in order to improve prognosis.[1,19] At this time, rhythm control therapy is indicated to improve symptoms in AF patients who remain symptomatic on adequate rate control therapy. In this respect, it is important to stress out that the general opinion nowadays is that the term 'lone AF' should be avoided because (subclinical) risk factors and cardiovascular diseases are likely to be present in almost every patient.[20] This implies the need for a careful identification of associated conditions and triggers. Therefore, our message when reading another analysis on rate vs. rhythm control therapy is to look for and treat associated comorbidities. Only this, together with adequate stroke prevention, may improve outcome.

References

1. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B *et al.* 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Europace* 2016;**18**:1609–78.
2. Wyse DG, Waldo AL, DiMarco JP, Domanski MJ, Rosenberg Y, Schron EB *et al.* A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med* 2002;**347**:1825–33.
3. Van Gelder IC, Hagens VE, Bosker HA, Kingma JH, Kamp O, Kingma T *et al.* A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. *N Engl J Med* 2002;**347**:1834–40.
4. Morillo CA, Verma A, Connolly SJ, Kuck KH, Nair GM, Champagne J *et al.* Radiofrequency ablation vs antiarrhythmic drugs as first-line treatment of paroxysmal atrial fibrillation (RAAFT-2): a randomized trial. *JAMA* 2014;**311**:692–700.
5. Mont L, Bisbal F, Hernandez-Madrid A, Perez-Castellano N, Vinolas X, Arenal A *et al.* Catheter ablation vs. antiarrhythmic drug treatment of persistent atrial fibrillation: a multicentre, randomized, controlled trial (SARA study). *Eur Heart J* 2014;**35**:501–7.
6. Kirchhof P, Breithardt G, Camm AJ, Crijns HJ, Kuck KH, Vardas P *et al.* Improving outcomes in patients with atrial fibrillation: rationale and design of the Early treatment of Atrial fibrillation for Stroke prevention Trial. *Am Heart J* 2013;**166**:442–8.
7. Purmah Y, Proietti M, Laroche C, Mazurek M, Tahmatzidis D, Boriani G *et al.* Rate vs. rhythm control and adverse outcomes among European patients with atrial fibrillation. *Europace* 2017. doi:10.1093/europace/euw421.
8. Van Gelder IC, Rienstra M, Crijns HJ, Olshansky B. Rate control in atrial fibrillation. *Lancet* 2016;**388**:818–28.
9. Emdin CA, Anderson SG, Salimi-Khorshidi G, Woodward M, MacMahon S, Dwyer T *et al.* Usual blood pressure, atrial fibrillation and vascular risk: evidence from 4.3 million adults. *Int J Epidemiol* 2016;doi: 10.1093/ije/dyw053.
10. Bassand JP, Accetta G, Camm AJ, Cools F, Fitzmaurice DA, Fox KA *et al.* Two-year outcomes of patients with newly diagnosed atrial fibrillation: results from GARFIELD-AF. *Eur Heart J* 2016;**37**:2882–9.
11. Cosio FG, Aliot E, Botto GL, Heidbüchel H, Geller CJ, Kirchhof P *et al.* Delayed rhythm control of atrial fibrillation may be a cause of failure to prevent recurrences: reasons for change to active antiarrhythmic treatment at the time of the first detected episode. *Europace* 2008;**10**:21–7.
12. Kirchhof P, Bax J, Blomstrom-Lundquist C, Calkins H, Camm AJ, Cappato R *et al.* Early and comprehensive management of atrial fibrillation: proceedings from the 2nd AFNET/EHRA consensus conference on atrial fibrillation entitled 'research perspectives in atrial fibrillation'. *Europace* 2009;**11**:860–85
13. Vanassche T, Lauw MN, Eikelboom JW, Healey JS, Hart RG, Alings M *et al.* Risk of ischaemic stroke according to pattern of atrial fibrillation: analysis of 6563 aspirin-treated patients in ACTIVE-A and AVERROES. *Eur Heart J* 2015;**36**:281–7a.
14. Boriani G, Laroche C, Diemberger I, Fantecchi E, Popescu MI, Rasmussen LH *et al.* 'Real-world' management and outcomes of patients with paroxysmal vs. non-paroxysmal atrial fibrillation in Europe: the EURObservational Research Programme-Atrial Fibrillation (EORP-AF) General Pilot Registry. *Europace* 2016;**18**:648–57.

15. Ganesan AN, Chew DP, Hartshorne T, Selvanayagam JB, Aylward PE, Sanders P *et al.* The impact of atrial fibrillation type on the risk of thromboembolism, mortality, and bleeding: a systematic review and meta-analysis. *Eur Heart J* 2016;**37**:1591–602.
16. Van Gelder IC, Healey J, Crijns HJ, Wang J, Hohnloser SH, Gold MR *et al.* Duration of device-detected subclinical atrial fibrillation and occurrence of stroke in ASSERT. *Eur Heart J* 2017;doi:10.1093/eurheartj/ehx042.
17. Daoud EG, Glotzer TV, Wyse DG, Ezekowitz MD, Hilker C, Koehler J *et al.* Temporal relationship of atrial tachyarrhythmias, cerebrovascular events, and systemic emboli based on stored device data: a subgroup analysis of TRENDS. *Heart Rhythm* 2011;**8**:1416–23.
18. Brambatti M, Connolly SJ, Gold MR, Morillo CA, Capucci A, Muto C *et al.* Temporal relationship between subclinical atrial fibrillation and embolic events. *Circulation* 2014;**129**:2094–9.
19. Gorenek B, Pelliccia A, Benjamin EJ, Boriani G, Crijns HJ, Fogel RI, Van Gelder IC *et al.* European Heart Rhythm Association (EHRA)/European Association of Cardiovascular Prevention and Rehabilitation (EACPR) position paper on how to prevent atrial fibrillation endorsed by the Heart Rhythm Society (HRS) and Asia Pacific Heart Rhythm Society (APHRS). *Europace* 2017;**19**:190–225.
20. Wyse DG, Van Gelder IC, Ellinor PT, Go AS, Kalman JM, Narayan SM *et al.* Lone atrial fibrillation: does it exist? *J Am Coll Cardiol* 2014;**63**:1715–23.

Corrigendum

doi:10.1093/europace/euw441
Online publish-ahead-of-print 4 February 2017

Corrigendum to: Left univentricular pacing for cardiac resynchronization therapy [*Europace* doi:10.1093/europace/euw179]

In figure 5 of this manuscript, the Adaptive LV conditions include an AP-VS interval of 250 ms or less (and not 200 ms or less as initially printed). The authors apologise for this error and the figure has been corrected online.

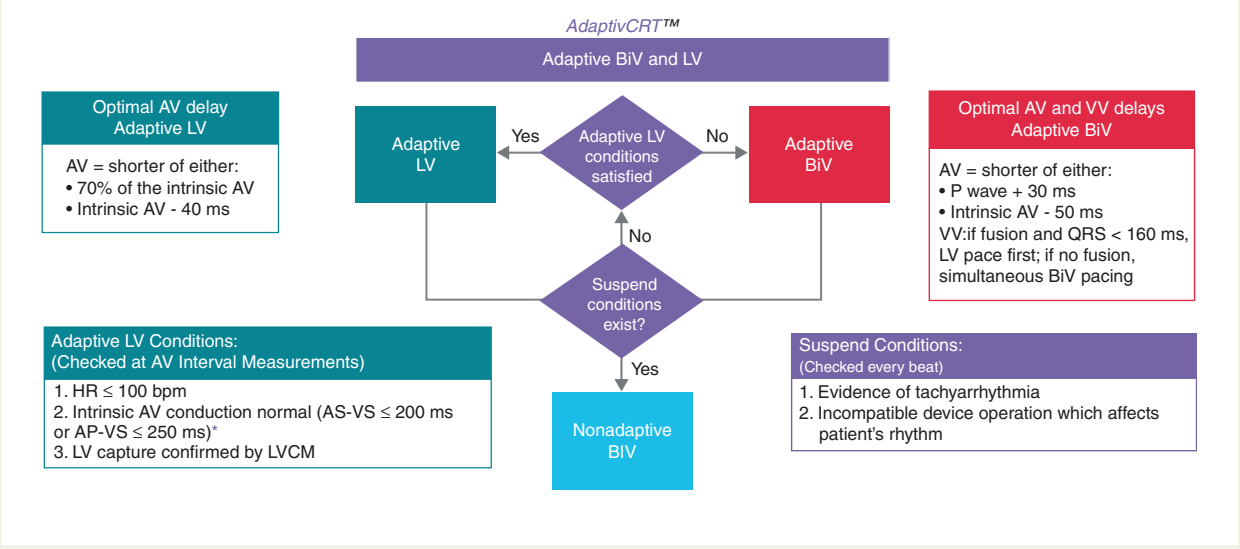

Figure 5 Description of the Medtronic AdaptivCRT™ algorithm function. *In models released as from 2016, the intrinsic AV delays that qualify for LV pacing is extended by 20 ms (i.e. from 200 to 220 ms for the sensed AV delay and from 250 to 270 ms for the paced AV delay). This should increase the percentage of LV pacing by ~20% (personal communication, data on file). Adapted and reproduced with permission from Medtronic. AV, atrioventricular; BiV, biventricular; LV, left ventricular; LVCM, left ventricular capture management.