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Blaauw, Yuri; Mulder, Bart; Rienstra, Michiel

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Is catheter ablation of atrial fibrillation as first-line treatment ready for prime time?

Yuri Blaauw , Bart Mulder , Michiel Rienstra 

Atrial fibrillation (AF) is the most common arrhythmia and is associated with increased risk of thromboembolic events, heart failure and mortality.¹ In addition, many patients have symptomatic episodes of AF and quality of life is impaired. In this group of patients, rhythm control management is the preferred therapy of choice. Anti-arrhythmic drugs (AADs) have long been the most often used treatment modality for symptomatic AF. The last decades, catheter ablation (CA) has emerged as an alternative treatment option, especially in patients with failed AAD treatment.² Studies comparing CA and AADs demonstrated superiority of CA in patients with previous failed AAD treatment.³ Recently, numerous studies comparing CA and AAD as first-line treatment for symptomatic AF have been reported.

Imberti *et al* reported a systematic review and meta-analysis of six randomised clinical trials (RCTs) comparing these two treatment arms in patients with predominantly paroxysmal AF who had no prior treatment with AADs, that is, first-line treatment with CA or AADs.⁴ Pooled data from six RCTs showed that CA is more effective than AADs in reducing AF recurrences. In addition, side effects were numerically non-significantly different between the two treatment arms. Other factors favouring CA as the preferred treatment were a reduced healthcare utilisation and a lower treatment crossover rate in the CA patients. The strength of the current meta-analysis is that it included medium-to-large-sized RCT using contemporary ablation techniques.

The authors should be congratulated for their important contribution in this rapidly evolving field of CA. The main findings further strengthen the arguments of those supporting first-line treatment of AF with CA. However, several questions are still open for debate.

University Medical Center Groningen, Groningen, The Netherlands

Correspondence to Dr Yuri Blaauw, Department of Cardiology, University Medical Center Groningen, Groningen, 9713GZ, The Netherlands; y.blaauw01@umcg.nl

First and foremost, the question remains *when* first-line CA should be initiated in patients with symptomatic AF. From clinical observations we know that AF often starts as paroxysmal self-terminating AF and without intervention, in many AF progresses over time to a persistent non-self-terminating type of AF.² AF progression is associated with increased cardiovascular morbidity and mortality.² Therefore, the concept that effective early rhythm control promotes sinus rhythm is of interest, as it thereby decelerates AF-related structural pathological atrial changes, and reduces progression to persistent AF, and reduces its associated cardiovascular morbidity and mortality. Exactly, this hypothesis was investigated and confirmed in EAST-AFNET 4.⁵ The EAST-AFNET 4 investigators demonstrated that early rhythm control management led to a (slightly) lower risk of major adverse cardiovascular outcomes, compared with a rate control strategy during more than 5 years of follow-up.⁵ These results favour more aggressive early rhythm control management, although rhythm control resulted in more treatment-related adverse effects without gain in quality of life. On the contrary, not all patients have progression of AF. Continuous rhythm monitoring studies showed that there is a wide variability in the temporal pattern of paroxysmal self-terminating AF and in the risk of AF progression.⁶ In the RACE V trial, AF progression was studied by continuous rhythm monitoring in patients with ECG-confirmed paroxysmal AF.⁶ One-third had no AF during 1-year follow-up, and in two-thirds recurrent episodes of AF were monitored. There were large differences observed in duration of episodes, number of episodes and AF burden. This suggests that paroxysmal AF is not one simple entity. With regard to AF progression, almost two-thirds had no change in AF temporal pattern, in 22% AF episodes progressed to longer duration, and in 16% AF regressed. In only 3% paroxysmal AF progressed to persistent AF. This emphasises that paroxysmal AF is not one entity, and risk of AF

progression differs. This makes that the ideal time of a first-line CA has no one-size-fits-all answer. Clinical decision-making for first-line CA still warrants careful consideration of patient-related factors, risk of AF progression, presence of AF progression risk factors or AF-associated comorbidities, and risk-benefit weighing of the different rhythm control options. Making that first-line CA in some patients means CA virtually directly after paroxysmal AF diagnosis, where in others a more conservative approach can be considered as an initial step after paroxysmal AF diagnosis.

Second, it is important to realise that superiority of AF prevention by CA was achieved in selected patient populations in highly experienced centres. Average age was 56 years old and more than 98% had paroxysmal AF. Also, the number of comorbidities was relatively low. This is different from typical real-life patients with AF offered for CA of whom many are older and have at least some comorbidities. It is well known that the outcome of CA depends on the patient characteristics.² Especially patients with non-paroxysmal AF and multiple comorbidities experience more AF recurrences following CA. In addition, the complication rate may be higher in an older population. Also, efficacy and side effects of AADs will also be different in real-life populations. Furthermore, CA results may have been impacted by operator experience. With respect to operator experience, it is important to remark an observed lower arrhythmia recurrence rate with the cryoballoon approach as compared with a radiofrequency approach.⁷ CA procedures using a cryoballoon have a short learning curve, and CA results may be less dependent on skills of the operator thus leading to a more reproducible outcome. The generalisability of present meta-analysis of RCTs to real-life populations, operators using radiofrequency and less-experienced centres is therefore limited.

Third, the primary outcome of the meta-analysis was recurrence of atrial arrhythmia. For most patients, the main objective of rhythm control treatment is to improve quality of life. This was not addressed in the current analysis. In recent years, however, numerous studies showed improved quality of life after CA. An important limitation is that in all the trials conducted, so far patients were unblinded for the intervention arm. Therefore, a so-called nocebo effect is probably present as the effect is most pronounced following invasive procedures than for those receiving medical

treatment. For a definitive answer, only a blinded randomised CA trial is needed to overcome the nocebo effect.

Fourth, the safety of CA and/or AADs is of great importance. The current meta-analysis shows that CA is as safe as AADs. Important to note is that there are distinct differences in the type of complications between the two approaches, side effects of AADs mostly reversible when stopped versus procedural-related complications of CA. Physicians should be informed about their local safety data of AADs and CA. Outweighing the benefits versus risks of CA and AADs should be part of the shared decision-making process of each individual patient, and may differ from patient to patient.

Finally, information on adequacy of treatment of comorbidities, risk factors and lifestyle management is unavailable in present meta-analysis. Treatment of underlying cardiovascular conditions and risk factors are important recommendations in the treatment of AF and may have great impact on efficacy of rhythm control treatments.²⁻⁸ Therefore, risk factor and lifestyle management should be background therapy in all patients opting for rhythm control treatments.

In conclusion, Imberti *et al* demonstrated that CA as a first-line treatment is more effective than AADs in reducing AF recurrences. However, questions remain regarding timing of CA, selection of patients, quality of life outcomes, balancing procedural complications and AAD side effects, and instituting

risk factor management as background therapy. Shared decision-making focusing on individualised timing and balancing benefits–risks is the preferred approach to assess first-line treatment with CA. As CA is rapidly evolving, with novel single-shot devices and promising energy sources (eg, pulsed field ablation), it is foreseen that CA keeps moving towards the frontline of AF management.

Twitter Bart Mulder @BA_Mulder

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ORCID iDs

Yuri Blaauw <http://orcid.org/0000-0003-2366-3686>
Bart Mulder <http://orcid.org/0000-0002-4411-3918>
Michiel Rienstra <http://orcid.org/0000-0002-2581-070X>

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