

## Redefining the Standard for Atrial Fibrillation: A Patient-centric Report

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## Redefining the Standard for Atrial Fibrillation: A Patient-centric Report

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### Abstract

A roundtable discussion with three European clinical experts in AF and one expert patient diagnosed and treated for AF was conducted in London in October 2019. The panel discussed the implications of AF for patients, current patient pathways, what treatment outcomes were relevant for patients and how the recommendations for the management of AF may change in the future, based on the outcomes of recently published and on-going clinical trials. This article summarises the discussion, and draws upon wider sources to detail best practice and optimal patient treatment pathways.

### Keywords

Ablation, AF, cost, guidelines, patient pathways, quality of life, symptoms

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A roundtable was convened with three clinical experts and one patient expert to discuss the importance of a patient-centric approach in the management of AF, addressing the need for timely and optimised therapeutic approaches to improve clinical outcomes.

### Burden of Disease

The cumulative risk of developing AF is higher in men than women over most of their lifespan, but becomes similar in older age with a comparable lifetime risk.<sup>1</sup> AF is an independent risk factor of all-cause mortality in patients with AF.<sup>1–5</sup>

In addition to the association between increased mortality and AF, AF is also associated with an increased risk of cardiovascular disease, with the highest absolute risk increase identified for patients with heart failure (HF).<sup>6</sup> The risk of stroke for patients with AF also increases significantly with age, rising from 1.5% for those aged 50–59 years to 23.5% for those aged 80–89 years, suggesting that the elderly are particularly vulnerable to stroke when AF is present.<sup>7</sup> The increased incidence of cardiovascular events as a result of AF results in an increased risk of hospitalisation and mortality.<sup>4,8,9</sup> Decreased health-related quality of life (HRQoL) in patients with symptomatic AF is also associated with a higher risk of hospitalisation.<sup>10</sup>

The expert panel raised the important issue of the insidious nature of AF and how this can impact on everyday life and relationships for patients. Friends and family can often find it difficult to perceive the true burden of living with AF and how it can affect HRQoL, the stress of which can trigger more symptoms, resulting in a negative spiralling effect. Most patients with AF are symptomatic, and this has a direct

impact on HRQoL, with 30–50% suffering from psychological distress (anxiety and depression).<sup>11</sup> The most common symptoms of AF are fatigue or weakness, and breathlessness during activities; the most pronounced negative impacts on HRQoL are physically related.<sup>12</sup>

Despite these observations, only a minority of AF patients are offered rhythm control strategies, and <5% undergo catheter ablation (CA), notwithstanding the recognition for the need of more aggressive approaches to AF treatment (~80% of patients who have AF recurrence after cardioversion go on to have AF progression).<sup>13</sup> Time constraints have been identified as a key issue in underrecognising the influence of AF on patient lifestyle, leading to the underutilisation of treatments that could improve HRQoL.<sup>11</sup>

### Guidelines

In 2016, the European Society of Cardiology (ESC) guidelines emphasised the importance of integrated care and patient-reported outcomes.<sup>14</sup> The European Heart Rhythm Association (EHRA) has also highlighted the need for all stakeholders in healthcare systems, especially those in closest contact with patients, to ensure increased awareness and education of AF, recognise the risks of untreated AF and to increase auto-surveillance, so that these patients can be effectively managed as soon as AF is confirmed.<sup>15</sup>

A delay in diagnosis, or a misdiagnosis, can not only lead to patient frustration but also the lack of a timely referral for expert evaluation.<sup>11</sup> This has been evidenced by patients who are diagnosed with the condition only when they have been admitted to hospital for acute cardiac decompensation or stroke.<sup>16</sup>

It was noted that smartphone technology is increasingly used in establishing an earlier diagnosis, but that the accuracy and utility of this technology still need to be validated.<sup>17</sup> The recent AppleWatch study demonstrated how advances in technology are providing the public with self-screening devices that are increasingly affordable and accessible.<sup>18</sup> As a result, healthcare professionals (HCPs) need to be more aware of the implications of these emerging data for diagnostic pathways and the treatment of AF.<sup>19</sup>

Once AF is diagnosed, effective management requires a multidimensional management approach, including acute management, treatment of underlying and concomitant cardiovascular conditions, stroke prevention therapy, and rate and rhythm control.<sup>16</sup> However, this can often be challenging to achieve in all patients, despite recent improvements in the organisation of care, and knowledge about AF and treatment options.<sup>16</sup>

Currently, the ESC recommends that rhythm control therapy should be used to improve symptoms in AF patients who remain symptomatic on adequate rate control therapy.<sup>14</sup> These recommendations are based on outcomes from published randomised controlled trials (RCTs) and registry data. Since the ESC guidelines were published, data have been published from new RCTs, e.g. Catheter Ablation vs. Standard Conventional Treatment in Patients With LV Dysfunction and AF (CASTLE-AF), Catheter Ablation vs Antiarrhythmic Drug Therapy for AF (CABANA), Catheter Ablation Compared With Pharmacological Therapy for AF (CAPTAF) and Cryoballoon Ablation for Early Persistent AF (CRYO4PERSISTENT).<sup>20–24</sup> These trials have shown a reduction in the hospitalisation rate, increased survival, and improvements in HRQoL for patients undergoing CA versus antiarrhythmic drug (AAD) therapy, which will necessitate a review of these recommendations.

The clinical experts discussed what they would consider to be optimal first-line therapy for patients with AF. They felt there was limited evidence to support AAD therapy as a first-line choice. The 2020 ESC guidelines state that AF CA for pulmonary vein isolation should be considered as first-line rhythm control therapy to improve symptoms in selected patients with symptomatic paroxysmal AF, or persistent AF without major risk factors for AF recurrence as an alternative to class I or III AADs, considering patient choice, benefit and risk.<sup>25</sup> Many patients experience a suboptimal response to AAD, and inadequate treatment is associated with a high cost of hospital admissions and increased treatment burden. The clinical experts recommended a need for an open discussion about treatment options with patients and the importance of establishing symptom burden at the start of therapy. They also highlighted the need to talk to patients about success rates with AADs and CA and the associated risks, as well as lifestyle modifications, while meeting patient expectations.

The experts concluded that, although there is a high degree of acceptance of current guideline recommendations, disparities in resources across Europe can limit the ability of HCPs to deliver guideline-recommended treatment in a number of countries.

### Overview of CA and AAD Therapy

AAD therapy has been the primary treatment for AF for decades, but limited effectiveness combined with incompletely assessed risks have led to the development of other strategies to maintain sinus rhythm.<sup>21</sup> One explanation for the lack of benefit of AADs is their poor efficacy in maintaining normal sinus rhythm and the high rate of discontinuation, given their side-effects.<sup>26</sup> Multiple RCTs have shown that CA of AF has

a good safety profile and is clearly superior to AAD therapy in maintaining sinus rhythm and preventing the recurrence of AF.<sup>27–33</sup>

More recently, the impact of CA versus AADs on mortality or hospitalisation in patients with AF has been investigated.<sup>20,21</sup> A meta-analysis of 18 RCTs comprising 4,464 patients, concluded that CA was associated with an all-cause mortality benefit that was driven by patients with AF and HF with reduced ejection fraction.<sup>34</sup> It was also concluded that CA reduced cardiovascular hospitalisations compared with AADs.<sup>34</sup>

The expert patient explained that his expectations of CA were curative, and that the decision to undergo the procedure was not taken lightly and took some time to consider. The clinical experts highlighted that patients play an important role in the decision-making process regarding CA, and that it was important that they were aware of the potential complications associated with the procedure, even though it is considered routine and is associated with low complication rates in experienced centres. It was pointed out that, in contrast, the risks of AADs are rarely discussed with patients before treatment initiation.

Among patients with symptomatic AF, CA has been shown to lead to clinically important and significant improvements in patient HRQoL compared with AADs.<sup>22,23</sup> Cryoballoon ablation, in particular, has demonstrated successful outcomes after a single procedure in >60% of patients, which was associated with a significant improvement in the 36-Item Short Form Health Survey composite score and EHRA score at 12 months ( $p < 0.0001$  and  $p = 0.008$ , respectively).<sup>24</sup> Real-world evidence has indicated that CA for AF may be associated with reductions in stroke, transient ischaemic attack and HF.<sup>35,36</sup>

AF is generally considered a progressive disease, and medical treatment has yet to demonstrate clinical efficacy in preventing progression.<sup>37</sup> Early results from the AF Progression trial (ATTEST; NCT01570361) suggest that CA may be up to 10 times more effective than drug therapy alone in delaying AF progression.<sup>38</sup> This supports earlier long-term observations of low rates of progression (0.3%/year) after CA of paroxysmal AF.<sup>39</sup> More recently, the Catheter Cryoablation Versus Antiarrhythmic Drug as First-Line Therapy of Paroxysmal Atrial Fibrillation (Cryo-FIRST) trial reported that CA was associated with a >50% relative risk reduction in atrial arrhythmia recurrence versus AAD therapy over 12 months.<sup>40,41</sup>

Safety, efficacy, HRQoL and cost-effectiveness data for CA in drug-naïve paroxysmal AF are expected in late 2020 from the Cryoballoon Catheter Ablation in an Antiarrhythmic Drug Naive Paroxysmal AF (STOP AF First; NCT03118518) and Early Aggressive Invasive Intervention for AF (EARLY-AF; NCT02825979) trials.<sup>42</sup> In addition, the Early treatment of AF for Stroke prevention Trial (EAST) is investigating the benefits of early intervention using CA.<sup>43</sup> The outcomes of these trials will further inform treatment decision-making for patients with AF.

### Measuring Outcomes that Matter to Patients

The most important impact of AF on patients is the degree of symptoms experienced, and the subsequent effect on their HRQoL. However, these are not the main primary endpoints in clinical studies. CAPTAF was the first study with HRQoL as a primary endpoint.<sup>23</sup> This trial was able to demonstrate a direct correlation between increased HRQoL and a reduction in AF burden in patients who had undergone CA. This was also seen in the control group that received AAD, but the improvements were less pronounced compared with CA.



The clinical experts noted that, in terms of hard endpoints, freedom from AF, reduction in mortality, risk of stroke and cardiovascular-related hospitalisation would also be relevant for HCPs. From the patient perspective, the outcomes that were considered important were the resolution of symptoms, improvement in HRQoL and the ability to resume normal levels of work and exercise.

The clinical experts discussed what would be considered acceptable levels of risk and complications with CA. Tamponade, which can be a serious but effectively managed complication of CA, is considered acceptable in up to 5% of patients.<sup>44</sup> Atrio-oesophageal fistula is an extremely rare but often fatal late complication of AF ablation.<sup>45</sup> An acceptable rate for this is 1 in 10,000 patients. Cryoballoon ablation has a lower risk for atrio-oesophageal fistula versus radiofrequency ablation for pulmonary vein isolation.<sup>46</sup> Stroke risk should be <1%. The experience of the treatment centre is key to minimising risk, and data show that the more procedures that are performed, the better the outcomes for patients.<sup>44</sup>

In all cases, patients need to be better informed about treatment options, including their pros and cons, before considering CA. This can be in the form of data from registries, which provide the most up-to-date information.

### The Typical Patient Pathway

The typical patient pathway for managing AF incorporates an assessment of stroke and thromboembolic risk; discussions about anticoagulation (including education and support to enhance concordance), optimisation of rate control and rate versus rhythm control; and onward management for cardioversion or CA, when required.<sup>47</sup> However, a number of unmet needs still need to be addressed, including the need to address modifiable risk factors; a re-evaluation of what is considered to be a meaningful clinical endpoint in RCTs, such as maintained symptom relief and improvements in HRQoL; as well as a reduction in the time from diagnosis to treatment in order to improve clinical outcomes.

The expert patient explained that he initially managed his AF with medication for 5 years, but then found that these became less effective over time, with his symptoms becoming more frequent. He considered CA at this stage because he felt there was no alternative. He was not comfortable increasing his medication dose, partly because of his relatively young age, and he did not welcome the prospect of needing to continue medication over the longer term without the complete resolution of symptoms. In addition, he stated that he was an active person, but found the biggest impact of AF on his day-to-day lifestyle remained the limitation on the amount of exercise he could undertake. He also experienced anxiety about the health consequences of not optimally managing his AF.

The expert patient explained that he might have made the decision to consider CA sooner in the course of his disease if he had been better informed about the procedure. He subsequently underwent a cryoballoon ablation procedure, and reported that his experience has been positive.

The clinical experts discussed the typical timing for AF ablation, which they explained would primarily depend on who initially refers the patient. Five years on medical therapy before consideration for CA was not considered atypical in clinical practice, and they concurred that CA is often seen as a last resort, rather than being considered an early intervention in this progressive disease. The expert panel also compared CA timings in the UK and other healthcare systems in Europe. This varied depending on the social healthcare system and access to private healthcare. In the UK, patients can wait up to 1 year, but in other countries this can be as little as 3 months. It was agreed that a wait of  $\geq 6$  months was not considered acceptable. It was highlighted that registry studies, which reflect real-world data, have shown that early CA can make a difference to patients' outcomes and prognoses.<sup>48</sup>

### The Ideal AF Treatment Pathway

The European Patient Survey in Atrial Fibrillation (EUPS-AF) assessed patient satisfaction with AF management in France, Germany, Italy, Spain and the UK. It reported that the majority of patients were satisfied with their treatment for AF over the previous 12 months, but there were key areas of unmet need.<sup>51</sup> These included the need for better coordination between primary and secondary care, and a lack of patient engagement and support, especially for patients likely to have extensive contact with their healthcare system.<sup>49</sup> In addition, patients with AF indicated the need for relevant individual training and counselling so that they could lead more satisfactory lives, with appropriate health appointment and monitoring systems to address the problems associated with frequent follow-up.<sup>50</sup> Patients who have a good understanding of their AF report greater acceptance of their AF, fewer symptoms and less negative emotions related to their AF.<sup>51</sup>

Utilising an integrated care approach in a holistic manner that takes into account both AF-specific and non-specific clinical factors, as well as shared decision-making between patients and multidisciplinary teams of HCPs, can improve outcomes for patients with AF.<sup>52,53</sup> This includes the need for the early and effective control of irregular heart rhythm, improving symptoms and reducing complications to increase patient life expectancy and enhance HRQoL.<sup>53</sup>

Developing a treatment pathway that addresses both patient and HCP needs is important. The expert patient commented that his ideal journey would have included an earlier diagnosis, better awareness of treatment options and the offer of CA at an earlier stage of his disease. This would have meant emergency room visits could have potentially been avoided.

### Conclusion

There is a clear requirement for increased patient awareness of treatment options, and improvements in earlier diagnosis and effective treatment of AF that address the needs of the patient. The design of future RCTs should take into consideration patient-centred outcome measures, including symptom control and HRQoL. Further RCTs are needed to determine the optimal timing for ablation in AF. ■

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