Atrial fibrillation and heart failure- results of the CASTLE-AF trial

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ABSTRACT
Congestive Heart Failure (HF) and Atrial Fibrillation (AFIB) often coexist. Catheter ablation is a well-established option for symptomatic AFIB that is resistant to drug therapy in patients with otherwise normal cardiac function. This has been seen in various studies where catheter ablation was associated with positive outcomes in patients with HF. Recently, the study results from the Catheter Ablation versus Standard Conventional Therapy in Patients with Left Ventricular Dysfunction and Atrial Fibrillation (CASTLE-AF) trial were published. After a median follow-up of more than 3 years, patients getting catheter ablation for AFIB had significantly fewer hospital admissions as well as death from worsening HF. In addition, 63% of patients in the ablation group were in sinus rhythm, as compared with 22% of those in the medical-therapy group (P < 0.001). This trial may represent a significant additional therapeutic tool in the clinical prevention and management of cardiovascular mortality and morbidity. While catheter ablation does not eliminate the AFIB per se, it can limit the ventricular rate by eliminating triggers and altering electrophysiological connections in the heart in a similar fashion to rate control anti-arrhythmic drugs. Longer-duration normal sinus rhythm may improve outcomes by means of a number of mechanisms, including greater atrial emptying, all of which translate into improved cardiac output. A better understanding is needed as to why a decrease in density, but not complete elimination of atrial fibrillation, is sufficient for reverse remodelling. It is anticipated that the results of the CASTLE-AF trial will soon be implemented in international guidelines.

Atrial Fibrillation (AFIB) is recognized as the most common cardiac arrhythmia in the world [1]. With the ever increasing population, the incidence rate of AFIB is thought to double in 2050 [2–4]. Some data suggests that the projected incidence may be as high as 8 million by 2050 [5]. Known as the ‘disease of the old’, AFIB has age as the major determinant in calculating prevalence. Similarly, congestive heart failure (HF) is a multidisciplinary disease with vast majority of patients being elderly [6–8]. Since the incidence of HF increases with age, most of the deaths in HF patients is within the elderly population [6,7]. HF and AFIB often coexist. Hence, HF is a complex disorder requiring constant clinical research into updated evidence based therapeutic options in patients with multiple co-morbidities including atrial fibrillation. It is difficult to sort out which is cause and which is effect, yet it would seem logical that being in AFIB is not ideal for patients with HF and that maintenance of normal sinus rhythm would probably improve functional status and possibly reduce mortality in this population.

Catheter ablation is a well-established option for symptomatic AFIB that is resistant to drug therapy in patients with otherwise normal cardiac function. This has been seen in various studies where catheter ablation was associated with positive outcomes in patients with HF [9–11]. Nevertheless, the clinical efficacy of catheter ablation in improving death or hospitalization rates has not yet been established in HF patients. Furthermore, no particular guidelines regarding the best management approach exist in the current literature [12–14]. In the past few years, smaller randomized controlled trials have shown superiority of catheter ablation over medical therapy in improving quality of life [12,13]. However, no large, randomized controlled trials were available for comparison.

Recently, the study results from the Catheter Ablation versus Standard Conventional Therapy in Patients with Left Ventricular Dysfunction and Atrial Fibrillation (CASTLE-AF) trial were published [15]. Inclusion criteria included patients with AFIB, New York Heart Association (NYHA) class II, III, or IV heart failure, and a left ventricular ejection fraction
(LVEF) of 35% or less were randomly assigned to catheter ablation for AFIB (N = 179) or medical therapy (N = 184) [15]. In this trial, in contrast to previous trials, the authors evaluated the hard primary end point of death or hospitalization for heart failure. After a median follow-up of more than 3 years, patients getting catheter ablation for AFIB had significantly fewer hospital admissions as well as death from worsening HF. In addition, 63% of patients in the ablation group were in sinus rhythm, as compared with 22% of those in the medical-therapy group (P < 0.001) [15]. Furthermore, the LVEF in the catheter ablation group had increased by 8% as compared with no increase in the medical-therapy group (P = 0.005) [15].

These results from the CASTLE-AF trial are encouraging. The study benefits from the large size of the combined trials, the long duration of the trials, the randomized design, the breadth of included participants, and the high standard to which the conduct of the trials was held. This trial may represent a significant additional therapeutic tool in the clinical prevention and management of cardiovascular mortality and morbidity. In addition, the end points of death and admission for heart failure are both objective and clinically relevant. Finally, the relatively long follow-up period allowed for the detection of the benefit related to mortality, a finding that was not apparent until year three.

On the contrary, the results may still be in their infancy phase and follow-up studies regarding long-term side effects are still awaited. Specifically, this trial had a very discrete set of criteria for patient selection, hence, studies involving outcome from patients with an inclusion criteria of LVEF> 35% and NYHA class I would be interesting. Also the fact that the procedures were performed by experienced operators in high-volume medical centres, a circumstance that probably reduced complication rates. Despite these limitations, this trial builds on and adds to the accumulating evidence that the use of ablation to maintain normal sinus rhythm in patients with AFIB and HF not only results in fewer admissions for heart failure and decreased mortality but also leads to reverse remodelling, as indicated by an improvement in the left ventricular function [15–17].

More recently it has become accepted that separate mechanisms may be responsible for triggering and sustaining AFIB [17]. Focal discharges can initiate AFIB. However, AFIB maintenance probably involves some form of re-entrant activity caused by ‘wavebreak’ of the main re-entrant wavefront into multiple chaotic daughter wavelets as a consequence of inhomogeneity in atrial structure, refractoriness and conduction velocity. Additionally, the mechanisms that sustain AFIB may evolve over time as the atria electrically and structurally remodel. However, confirming whether or not these AFIB drivers are various forms of re-entry will require carefully executed high-resolution ablation studies. This may at least partially explain why targeting one specific mechanism, such as catheter ablation, is often initially successful but then fails over time. Understanding the electrophysiological mechanisms by which AFIB is initiated and sustained will be critical for developing safer and more effective therapies in the treatment of AFIB.

The CASTLE-AF trial showed that a cure of atrial fibrillation is not necessary to improve outcomes in heart failure. A reduction in the amount of time in atrial fibrillation may be sufficient for clinical benefit: catheter ablation merely decreased the time in AFIB [15]. While catheter ablation does not eliminate the AFIB per se, it can limit the ventricular rate by eliminating triggers and altering electrophysiological connections in the heart in a similar fashion to rate control anti-arrhythmic drugs. Longer-duration normal sinus rhythm may improve outcomes by means of a number of mechanisms, including greater atrial emptying, all of which translate into improved cardiac output. For years, the first-line treatment for AFIB has been rate control (along with rhythm control). However, with the advent of technology and many new drugs/devices proving efficacy, like the CASTLE-AF trial, this might change in the future. However, while advances in technologies have helped elucidate many aspects of these diseases, many mysteries still remain. A better understanding is needed as to why a decrease in density, but not complete elimination of atrial fibrillation, is sufficient for reverse remodelling. Such an understanding may lead to additional therapeutic measures in these patients. With continued research, we can expect more cost-effective and patient-friendly drug therapies to be developed in the near future. For the present, however, it seems reasonable to be more aggressive in offering catheter ablation for AFIB in patients who also have HF. It is anticipated that the results of the CASTLE-AF trial will soon be implemented in international guidelines.

Acknowledgments
None Declared

Declaration of interest
The authors declare that they have no competing interests

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