Comparative effectiveness of catheter ablation for atrial fibrillation: moving with the rhythm

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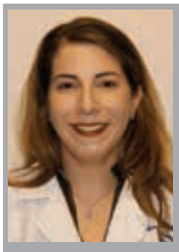

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"All scientific work is incomplete – whether it be observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge. That does not confer upon us the freedom to ignore the knowledge we already have or postpone the action that it appears to demand at a given time."

– Austin Bradford Hill (1897–1991)

On February 17, 2009, President Obama signed into law the American Recovery and Reinvestment Act. Notably, US$1.1 billion was allotted for comparative effectiveness research (CER). On June 30, 2009, in response to the Congressional directive, the Institute of Medicine released a list of 100 initial priority topics for CER [1]. Within the first quartile, the Institute recommended an initiative "to compare the effectiveness of treatment strategies for atrial fibrillation including surgery, catheter ablation, and pharmacologic treatment". Since atrial fibrillation (AF) is the most common arrhythmia in clinical practice, affecting 2.2 million people in the USA [2], has an estimated prevalence of up to 1% in the general population and up to 8% in those older than 80 years of age [3] and is associated with decreased survival [4], it is not a surprise that the wheels were already in motion. A systematic review of the literature, supported by the Agency for Healthcare Research and Quality (AHRQ), US Department of Health and Human Services, was well underway, and a manuscript based on the results was published on August 4, 2009 in the *Annals of Internal Medicine* [5] (the original full report is available at [101]). In summary, the systematic review found that radiofrequency ablation (RFA) of AF via a catheter-based approach after a failed drug course maintained sinus rhythm more often than continuation of drug therapy alone for up to 1 year of follow-up. In a subsequent publication of two systematic reviews (which used different study selection criteria from the AHRQ review) of RFA and antiarrhythmic drug therapy, Calkins *et al.* also concluded that studies of RFA for AF reported higher efficacy rates than studies of antiarrhythmic drug therapy [6].

These reviews contribute to our understanding of the effectiveness of treatment modalities for AF. However, the contribution lies not only in what was found but also in what was not found about the effectiveness of treatment strategies for AF. The conclusion, if isolated, is an oversimplification of an extraordinarily complicated issue. The conclusion, if understood in its greater context, is very useful. In order to understand the advantages and disadvantages of CER, the patient, the physician, healthcare professionals, and administrators and policy makers alike must delve further into the data – the devil is in the details, as we say. Who was enrolled in the studies? As importantly, if not more so, who was excluded from the studies? What were the patient characteristics? What procedure was performed? Where and by whom was it performed? What was considered the end point, and how was it defined and ascertained? In asking and then answering these questions, it is clear that CER is important, but it is only as robust and revealing as the primary data. The conclusions apply to the patient population in the studies, which may or may not mimic 'the real world'.

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In 'the real world', RFA is one of the tools in the armamentarium of the cardiac electrophysiologist for the treatment of AF. At present, the indications for catheter ablation include symptomatic AF refractory or intolerant to at least one antiarrhythmic agent, first-line

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therapy in rare clinical situations and selected symptomatic AF with heart failure and/or reduced ejection fraction [7,8]. The procedure is performed in patients with paroxysmal, persistent or longstanding persistent AF. Patients may have lone AF, or they may have structural heart disease and comorbidities including ischemic heart disease, valvular heart disease, congenital heart disease, diabetes mellitus, hypertension, obesity and sleep apnea, to name a few. In other words, the patient characteristics are extremely heterogeneous. Terasawa *et al.* acknowledge that the majority of patients in the analysis had a preserved left ventricular ejection fraction, only mildly dilated atria and a mean age of 55 years, reflecting a homogeneous rather than a heterogeneous patient population [5]. Since AF is more prevalent in older patients and is more frequent in patients with mitral valve disease, heart failure, ischemia, hypertension [9] and who are likely to have reduced ejection fractions and dilated atria, there is a substantial portion of the afflicted population in whom RFA of AF has not been rigorously studied. If the primary data is not available, then CER cannot address the issue either.

> *"The heterogeneity of the patient population is paralleled by the heterogeneity of the procedure itself. Although there is consensus that the foundation of AF ablation involves pulmonary vein isolation, there is more than one way to skin a cat."*

The heterogeneity of the patient population is paralleled by the heterogeneity of the procedure itself. Although there is consensus that the foundation of AF ablation involves pulmonary vein isolation, there is more than one way to skin a cat. The procedure has evolved from ostial pulmonary vein isolation to wide area circumferential ablation to hybrid techniques, which may include additional lesion sets at the roof, the mitral isthmus, the cavotricuspid isthmus, the superior vena cava and in the coronary sinus, particularly in the case of persistent or longstanding persistent AF. Thus, it is challenging to control for all of these variations in technique, and a head-to-head comparison of antiarrhythmic drug therapy to RFA is not as simple as it may seem.

As such, while registry data may not be as methodologically rigorous as a randomized controlled trial, and despite the inherent introduction of uncontrolled variables, this may supplement our knowledge base. In a worldwide survey of practices of RFA of AF, the rate of a major complication was 6% [10], which was relatively consistent with a major complication rate of less than 5% in most of the 84 studies in the analysis published in the *Annals of Internal Medicine* [5]. Observational data that reflects the population of patients who are actively being treated may also be hypothesis-generating and help guide the next randomized controlled trial.

> *"Different energy sources, energy delivery systems, imaging modalities and percutaneous epicardial approaches are not on the horizon, they are here, and their effectiveness needs to be addressed."*

The medical community has seen the technique of catheter ablation of AF change quickly over little more than a decade with advancements in the understanding of the pathophysiology of AF, from triggers to substrate. At even greater speed, technological innovations in the field of cardiac electrophysiology have changed the way in which the procedure is performed. Different energy sources, energy delivery systems, imaging modalities and percutaneous epicardial approaches are not on the horizon, they are here, and their effectiveness needs to be addressed. These advances are outpacing the available data at lightning speed. In order to have high-quality CER for AF, the medical community must strive to continue to gather information systematically and to perform high-quality randomized clinical trials of catheter-based ablation of AF in a wide variety of patients with long-term, well-defined end points and follow-up.

Financial & competing interests disclosure

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