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Lessons from the trials

# CTS Trials Network: Surgical ablation of atrial fibrillation during mitral valve surgery - many questions unanswered

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## ABSTRACT

A disease that is associated with stroke and mortality, atrial fibrillation (AF) complicates 30 to 50% of mitral valve disease patients admitted for surgery.<sup>1</sup> Since the introduction of the Cox maze III procedure in 1992 many efforts have been made to come up with modified lesion sets and/or energy sources to surgically treat AF. This led to the recently published American Heart Association (AHA) – American College of Cardiology (ACC) – Heart Rhythm Society (HRS) guidelines<sup>2</sup> stating that it is reasonable to perform atrial fibrillation ablation in selected patients undergoing other types of cardiac surgery. The effectiveness of different techniques in conversion to sinus rhythm and the clinical impact of freedom from AF remain a question. The CTS Trials Network have undertaken a trial to answer these questions. The first year results of their randomized trial comparing AF ablation at the time of mitral valve surgery with mitral valve surgery alone were published recently in *The New England Journal of Medicine*.<sup>3</sup>

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## TRIAL DESIGN AND RESULTS

The *primary end point* was freedom from AF at both 6 and 12 months on 3-day continuous Holter monitoring. *Secondary end-points* were mortality, a composite of major cardiac or cerebrovascular adverse events (MACCEs) - including death, stroke, hospitalization for heart failure and mitral valve reintervention, quality of life, rehospitalization including the need for rhythm related interventions. The *primary safety end point* was a composite of death, stroke, heart failure, myocardial infarction, rehospitalization for cardiac causes, transient ischemic attack, pulmonary embolism, peripheral embolism, excessive bleeding, deep sternal-wound infection or mediastinitis, damage to the specialized conduction system necessitating implantation of a permanent pacemaker, or damage to peripheral structures such as the esophagus, within 30 days after the procedure or hospital discharge (whichever was later). *Follow-up assessments* were conducted by telephone interview at 3, 6, and 9 months and in person at 12 months.

After screening 3502 patients, the investigators enrolled 260 adult patients with persistent, or long-standing persistent AF, and requiring surgical intervention for the mitral valve. They randomized the patients, in a 1:1 ratio, to 133 receiving mitral valve surgery with ablation and 127 with mitral valve surgery without AF ablation. They further randomized the ablation arm to 67 undergoing pulmonary vein isolation and 66 having a bi-atrial maze procedure.

56% of patients underwent mitral valve repair while 44% had mitral replacement. Additional procedures were performed in 61.4% of patients. All patients underwent closure of the left atrial appendage. There was approximately 15 minutes longer operative time was in the ablation group. In both types of ablation procedures unipolar, bipolar radiofrequency and cryoablation were used interchangeably or in conjunction according to the operating surgeon.

Significantly more patients of the ablation group (63.2%) were free from atrial fibrillation at both 6 and 12 months vs. 29.4% in the control group,  $P < 0.001$  with a relative success rate of 2.15 (95% confidence interval) and no significant differences between biatrial maze and pulmonary vein isolation. There was no significant difference in the 30-day mortality (2.3% vs. 3.9%,  $P = 0.49$ ) or the one-year mortality (6.8% vs. 8.7%,  $P = 0.57$ ). There was also no difference in MACCEs at one year (23.3% vs. 20.5%,  $P = 0.58$ ) or any of its individual components. There was no difference in the duration of the index hospital length of stay or the number of hospitalizations at one year. More patients in the control group got at least daily attacks of AF than the ablation group (45.5% vs. 19.8%,  $P = 0.001$ ) apart from that there were no differences in the quality of life measure between groups.

There was a significantly higher rate of pacemaker implantation in the ablation group than in the controls most of which occurring during the index hospitalization (21.5 vs. 8.1 pacemakers per 100 patient years)

## DISCUSSION

The authors are to be congratulated for the well-constructed statistical study. It has been successful in meeting its primary end-point of freedom from AF. All of secondary end-points, although more clinically relevant, have not been met. The substantial difference in rate of sinus rhythm conversion at 12 months did not translate into improved clinical outcomes. Both groups had similar rates for mortality, MACCEs, hospitalization and use of antiarrhythmic medication. This might be because the numbers and follow-up period were not sufficient to detect differences or that obliteration of the left atrial appendage in all cases as well as treatment of the structural heart disease has made a marked impact by decreasing risk of stroke and improving heart failure symptoms. Hopefully further follow-up of the groups can provide insight to how the treatment can have a clinical bearing in the longer term.

The rate of return to sinus rhythm at one year confirms the results of similar smaller and single-center studies of AF ablation. It is, however, inferior to many other reports quoting freedom from AF of 70–80%.<sup>4</sup> This can be due to the complexity of a sicker patient cohort of which 61.4% underwent additional procedures like coronary artery bypass grafting and other valve surgery. It can also be explained by a more rigorous follow-up using 3-day Holter monitoring yielding results similar to studies, of more rigour, using implantable loop recorders.<sup>5</sup> Interestingly, the investigators have found no significant difference between PVI and biatrial maze in their cohort, which contradicts other reports of decreased effectiveness of the PVI in especially in long-standing AF.<sup>6</sup>

The rate of permanent pacemaker implantation in the trial was significantly higher in the ablation group and also higher than previous studies (17% at 30 days versus 5-10% in other studies<sup>7</sup>) which can be attributable to old age, multi-valve surgery and lower implantation thresholds.

The authors have incorporated too many variables in the recruitment of patients. In their surgical cohort, 62% of the patients had additional procedures; other valve surgery, coronary artery bypass or both. It may have served to make the patient cohort more similar to “real world” patients. It may also have added to the complexity of the patients making them generally sicker and less liable to benefit from AF ablation. The authors have not differentiated between patients having mitral valve repair and replacement and, importantly, they have not made the distinction between organic and functional - ischemic and non-ischemic- mitral valve regurgitation. They have also combined those with persistent and long-standing AF. Perhaps some of these subgroups might have shown differences in the clinical endpoints after AF ablation.

### WHAT HAVE WE LEARNED?

AF ablation is successful at conversion to sinus rhythm. The question of which patients will derive clinical benefit is still unanswered. Although it seems that, in the first year, AF ablation is not clinically beneficial, at least not for all patients. We await the follow-up results to help in understanding how to treat AF at the time of cardiac surgery.

The left atrial appendage, clearly a beneficial operative step during mitral valve surgery, was obliterated in all patients. Could this have been the reason for the similarity in clinical outcomes?<sup>8</sup>

The choice of lesion set in AF surgery remains to be an area of debate. The finding of similarity in freedom from AF between LA isolation and bi-atrial maze can lead to change in practice if studied further but would it compare with the success rate of the Cox maze III where the transmural of the lesions is guaranteed?

The first year results of the study leave many questions unanswered. Until we reach a more sound understanding of the best techniques for AF ablation, in terms of lesion sets and energy source, and the clinical benefits of sinus rhythm conversion in those patients it is advisable to tailor the procedure to the patients who will be more likely to benefit with the least possible complications.

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