SAFE Combinations Fail to Open Door to Atrial Fibrillation Prevention

Running title: Lin et al.; SAFE combinations fail

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Journal Subject Codes: Treatment:[120] Pacemaker, Treatment:[122] Secondary prevention

Key words: Editorial, atrial fibrillation, prevention, pacing
The prevalence of atrial fibrillation (AF) in the entire US population is approximately 1\%\textsuperscript{1} The prevalence of AF increases substantially with age, with up to 9\% of patients over the age of 80 developing AF. The population presenting with permanent pacing requirements also increases with age and the cumulative lifetime risk of developing paroxysmal AF in pacemaker patients may be as high as 40\%.\textsuperscript{2}

Mechanisms for AF initiation and maintenance are multiple, but are widely accepted to be a result of triggered initiation, by atrial premature beats (APB), and maintenance within the atrial substrate based on multiple wavelets of reentry and rotors that depend on inhomogeneous atrial refractory periods (ARP) and atrial conduction velocities (ACV). Atrial pacing may prevent both AF triggers and atrial substrate changes by suppressing APB and inducing a more homogenous atrial landscape of refractory periods and conduction velocities. Atrial based pacing is clearly superior to ventricular pacing alone in preventing atrial fibrillation with an 18\% relative risk reduction with atrial based pacing over a 3 year follow up.\textsuperscript{3} This treatment effect has been postulated to be the result of APB suppression and changes in ARP and ACV as a result of atrial stretch due to higher atrial pressure from AV dyssynchronous pacing. The atrial changes associated with atrial based pacing could possibly be enhanced by atrial overdrive pacing algorithms and/or by alternative site atrial pacing such as the atrial septum. The role of alternative site atrial pacing in the primary prevention of AF in pacemaker patients and the progression of AF (secondary prevention) is also not well established. In addition, despite the initial enthusiasm for overdrive atrial pacing algorithms, the recent ASSERT trial did not demonstrate any efficacy with overdrive atrial pacing in the primary prevention of AF.\textsuperscript{4}

Tse et al present a randomized trial comparing both sites of atrial pacing and the effects of atrial overdrive pacing algorithms in the prevention of persistent atrial fibrillation in patients
with sick sinus syndrome (SSS) and paroxysmal AF. The investigators randomized 385 patients with known AF and SSS to right atrial (RA) septum pacing and RA appendage (RAA) pacing. In addition, patients were randomized at both sites to an atrial overdrive pacing algorithm ON mode or just standard demand atrial based pacing. The primary endpoint was a “secondary prevention” endpoint of AF progression (in this patient population with known AF) to persistent AF defined as AF lasting for 7 days or the need for a cardioversion. In addition, the number of atrial high rate episodes (AHRE) lasting >6 minutes were compared across the randomized groups. Importantly, there was no cross-overs in the overdrive pacing ON and OFF groups and only 1% (4 patients total) did not have an atrial lead implanted in the randomized location.

The main findings of the study are that persistent AF-free survival was not statistically different between RA septal pacing and RAA and between overdrive atrial pacing algorithm ON and OFF. The progression to persistent AF amongst the 4 randomized groups was, with a mean of 3.1 years follow-up, 20.0%, 26.3%, 30.3% and 23.0% for patients randomized to RA appendage-ON, RA appendage-OFF, RA septum-ON, and RA septum-OFF, respectively. The annual rate of persistent AF was quite high at 8.3%. In addition, the number of AHRE lasting >6 minutes and the percentage AF burden were not statistically different amongst the 4 groups at 6 months. The quality of life score with the SF-36 survey was not statistically different amongst the 4 groups at 12 months. There were 51 deaths reported, with 14 deemed due to CV events, out of 385 patients over a mean of 3.1 years follow-up. Stoke or TIA was reported in 19 patients. Of note, the use of anti-platelet agents or anti-coagulants was low with only 35% of patients on aspirin and 12% of patients on warfarin despite an average age of >70 and more than 50% having hypertension. The lack of benefit with RA septal pacing is particularly disappointing given the significantly shorter P wave duration and the reduced percentage of ventricular pacing
with RA septal pacing compared to RAA pacing.

Although small and as yet undetected differences in progression to persistent AF between the 4 groups cannot be excluded based on the persistent AF free survival analysis of this trial (comparing RAA/RA septal pacing and overdrive atrial pacing ON/OFF independently), the lack of statistical difference between AHRE, AF burden, or of any sub-group makes any meaningful difference very unlikely.

So, where does the SAFE trial fit in context of what we know about cardiac pacing and AF? There are several points to consider based on the knowledge gained from careful pacing trials such as SAFE:

1. Atrial pacing is superior to ventricular pacing in primary prevention of AF in patients with sinus node dysfunction or AV block. Patients in sinus rhythm requiring a pacemaker for bradycardia should receive a device capable of atrial pacing.

2. Minimizing right ventricular pacing will decrease the risk of AF in patients with sinus node dysfunction.6

3. There are no compelling trial data at this time, including data from the SAFE trial, to support alternative single-site RA pacing over standard RAA pacing for either the primary prevention of AF or secondary prevention of persistent AF.

4. There are no compelling trial data at this time, including data from the SAFE trial, to support overdrive atrial pacing algorithms for the primary prevention of AF or secondary prevention of persistent AF.

5. Although overdrive atrial pacing algorithms are successful in increasing the percentage of atrial pacing, the lack of benefit in the primary prevention of AF and secondary prevention of persistent AF make the “cost” in terms of battery life unfavorable.
6. The progression to persistent atrial fibrillation in patients with symptomatic bradycardia and PAF is unacceptably high. While alternative single-site RA pacing and overdrive atrial pacing are not likely to impact this progression, other treatment modalities such as pharmacologic therapies and catheter ablation should be considered for secondary prevention of persistent atrial fibrillation.

7. The mortality rate of individuals with PAF and sinus node dysfunction requiring pacing is not low. Given the frequency of PAF and rate of progression to persistent AF, careful consideration of the clinical and demographic risk factors for stroke and systemic embolism and the need for anticoagulation, regardless of the type of AF treatment, is paramount.

8. Other forms of atrial pacing such as multi-site RA pacing or biatrial pacing for primary prevention of AF or the secondary prevention of progression to persistent AF need further clinical investigation before wide spread adoption.

9. There continues to be no role for permanent pacing, in the absence of a bradycardia indication, to prevent AF.

Based on current clinical knowledge, for patients with bradycardia, PAF, and sinus rhythm, atrial based pacing with an RA lead placed in a stable position with good electrical performance, minimization of unnecessary RV pacing, and careful consideration of anticoagulation are far more important than placement of the atrial lead at any specific location for single-site RA pacing and any currently available overdrive atrial pacing algorithm.

**Conflict of Interest Disclosures:** None.
References:


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_Circulation_. published online July 18, 2013;
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2013 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

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