The prevalence of atrial fibrillation (AF) in the entire US population is \( \approx 1\% \). The prevalence of AF increases substantially with age, with \( \leq 9\% \) of patients over the age of 80 years 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\%.

Mechanisms for AF initiation and maintenance are multiple but are widely accepted to be a result of triggered initiation by atrial premature beats, and maintenance within the atrial substrate on the basis of multiple wavelets of reentry and rotors that depend on inhomogeneous atrial refractory periods and atrial conduction velocities. Atrial pacing may prevent both AF triggers and atrial substrate changes by suppressing atrial premature beats 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. This treatment effect has been postulated to be the result of atrial premature beat suppression and changes in atrial refractory periods and atrial conduction velocities as a result of atrial stretch attributed 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 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 patients with pacemakers 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 Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial did not demonstrate any efficacy with overdrive atrial pacing in the prevention of persistent AF in patients with sick sinus syndrome and paroxysmal AF. The investigators randomly assigned 385 patients with known AF and sick sinus syndrome to right atrial (RA) septum pacing and RA appendage (RAA) pacing. In addition, patients were randomly assigned 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 end point 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 lasting >6 minutes was compared across the randomly assigned groups. Importantly, there were no crossovers 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 among the 4 randomized groups was, with a mean of 3.1 years of follow-up, 20.0\%, 26.3\%, 30.3\%, and 23.0\% for patients randomly assigned 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 atrial high-rate episodes lasting >6 minutes and the percentage of AF burden were not statistically different among the 4 groups at 6 months. The quality-of-life score with the Short Form 36 was not statistically different among the 4 groups at 12 months. There were 51 deaths reported, with 14 deemed attributable to cardiovascular events, of 385 patients over a mean of 3.1 years of follow-up. Stroke or transient ischemic attack was reported in 19 patients. Of note, the use of antiplatelet agents or anticoagulants was low, with only 35\% of patients on aspirin and 12\% of patients on warfarin despite an average age of >70 years and >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 with RAA pacing.

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

So, where does the Septal Pacing for Atrial Fibrillation Suppression Evaluation (SAFE) trial fit in context of what we
know about cardiac pacing and AF? There are several points to consider on the basis of the knowledge gained from careful pacing trials such as SAFE:

1. Atrial pacing is superior to ventricular pacing in the 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.5

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 AF in patients with symptomatic bradycardia and paroxysmal AF is unacceptably high. Although 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 AF.

7. The mortality rate of individuals with paroxysmal AF and sinus node dysfunction requiring pacing is not low. Given the frequency of paroxysmal AF 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 multisite RA pacing or biatrial pacing for primary prevention of AF or the secondary prevention of progression to persistent AF, need further clinical investigation before widespread adoption.

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

On the basis of current clinical knowledge, for patients with bradycardia, paroxysmal AF, 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.

Disclosures
None.

References

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SAFE Combinations Fail to Open the Door to Atrial Fibrillation Prevention
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