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COMMENTARIES

Statin Drugs Protect From Atrial Fibrillation In Patients With Stable Coronary Artery Disease. Is Atrial Fibrillation A Preventable Atherosclerotic Process?

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Atrial fibrillation (AF) is a common cardiac arrhythmia of nearly epidemic proportions. Currently AF affects an estimated 2.3 million adults in the United States, and this number is expected to double in the next 30 years [1]. Approximately 4% of persons older than 60 years and 9% of persons older than 80 years suffer from AF; an estimated 50% of all AF patients are older than 75 years, which is the fastest growing segment of the population [2]. Atrial fibrillation is associated with substantial health consequences and resource utilization. The number of hospitalizations for AF in the United States has increased 2-3 fold between 1985 and 1999 [3]. The risk of stroke is increased 4-5 fold in AF patients, and AF is responsible for about 16% of all ischemic (and frequently disabling) strokes in the elderly [4]. Besides anticoagulation with warfarin for stroke prevention, the mainstay of AF management is rate or rhythm control to prevent tachycardia-mediated cardiomyopathy and alleviation of symptoms, both of which are accomplished either by AV nodal blocking agents, anti-arrhythmic drugs or non-pharmacological techniques. Therapies for treating AF, though effective in reducing the morbidity burden, have significant drawbacks including therapeutic failures, drug side effects, inconvenience, and financial costs. Frequently patients are not managed optimally and occasionally AF is "silent," which undermines the potential to prevent complications [5].

Previous studies have focused on various treatment options for AF after it has already developed, but none has focused on preventing the condition altogether, partially because of the limited understanding of the pathogenesis of AF. In the long term, however, developing effective and safe therapies to prevent AF represents the best hope to mitigate a problem of such magnitude and to reduce the number of new AF cases.

Major risk factors associated with non-valvular AF include aging, hypertension, diabetes mellitus, coronary artery disease (CAD), and male gender. These factors are also associated with increased risk for atherogenesis in general, which suggests that AF, especially in older and hypertensive patients, might be part of the spectrum of atherosclerotic cardiovascular diseases (ASCVD) and therefore could be prevented by measures employed for primary and secondary prevention of ASCVD. Several recent studies support this notion.

Aviles et al. [6] analyzed the role of inflammation and elevated C-reactive protein (CRP) as a risk factor for developing AF in 5,806 persons age 65 years and older enrolled in the cardiovascular health study. At baseline 315 patients (5%) had AF,

and during 7 years of follow up 897 patients of the remaining 5,491 patients had new onset of AF. Compared with subjects in the first CRP quartile (< 0.97mg/L), patients in the fourth CRP quartile (> 3.41mg/L) had significantly higher prevalence of AF at baseline and were more likely to develop AF during follow up suggesting that inflammation is playing a role in the pathogenesis of AF. Furthermore, recent data from the Women's Health Study linked elevated CRP and inflammation with higher risk for developing hypertension [7], a major risk factor for AF. CRP has been reported to reduce nitric oxide (NO) production in endothelial cells [8] and induce plasminogen activator inhibitor (PAI-1) [9], both of which promote atherothrombosis. Similarly, an animal model of AF revealed down-regulation of left atrial endothelial NO synthase and an increase of PAI-1, which might predispose patients to left atrial thrombosis and again links AF to atherogenesis [10].

Along this line of thinking we investigated whether statin therapy, which poses anti-inflammatory properties and reduces CRP levels [11], protects patients with CAD from developing AF [12]. Among 449 CAD patients, mean age 68 years, who were either on statin drugs or on no lipid lowering therapy and followed for a mean of 5 years, a total of 52 patients (12%) developed AF. Among statin users, 24 of 263 patients (9%) developed AF compared with 28 of 186 patients (15%) not on lipid lowering therapy. The corresponding incidence per 1,000 person years was 18 and 37 among statin users and non-users, respectively. The adjusted OR for developing AF among statin users was 0.37 (95% CI 0.18-0.76). The protection benefit did not correlate with baseline cholesterol or with the magnitude of cholesterol lowering and might be related to statins' anti-inflammatory effects and to their role in slowing progression of ASCVD.

Angiotensin converting enzyme inhibitors (ACEI) were shown to reduce cardiovascular complications in patients at risk for or with established CAD, presumably by attenuating atherosclerosis progression [13]. Among patients enrolled in the SOLVED study of enalapril in left ventricular (LV) dysfunction, with or without heart failure followed for 3 years, only 5.4% of the patients on enalapril experienced AF compared with 24% in the placebo arm [14]. In multivariate analysis enalapril was the strongest predictor of reduced AF incidence. Furthermore, in a cohort of 10,722 hypertensive patients identified from a database of 8 million patients in the United States followed for 5 years, the risk for AF was significantly reduced in the ACEI group [15]. These reports [14,15] again link AF prevention with an intervention known to attenuate or slow the progression of ASCVD as well.

Integrating the findings from recent clinical studies with the molecular and experimental models of thrombosis and AF suggest that the pathogenesis of AF might be another facet in the spectrum of ASCVD. Furthermore it underscores the likelihood that therapies recommended for treatment of conditions that predispose patients to AF (such as hypertension, diabetes, CAD, and LV dysfunction) are also effective in reducing the incidence of AF. Until the exact causes for non-valvular AF in the aging population are clarified and specific preventive interventions are identified, aggressive management of known risk factors, strict adherence to current guidelines, and liberal use of statins and ACEI among patients at risk for AF is strongly urged. Such practices have the potential to attenuate substantially the epidemic of new AF cases and the subsequent health and fiscal toll.

Continued analysis of previous large randomized trials and future research involving populations at risk for AF are necessary and may help identify other associations with AF and develop regimens that might reduce the risk for this condition even further.

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