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EDITORIAL COMMENT

Statin Therapy for Subclinical Atherosclerosis in Primary Prevention

Time to Prove It?*

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Coronary artery calcium (CAC) scanning, as a measure of coronary artery disease (CAD) burden (1), has been shown to significantly improve coronary heart disease (CHD) risk prediction in screening populations when compared with the Framingham Risk Score (2) and high-sensitivity C-reactive protein testing (3,4). On the basis of the consistent demonstration of its prognostic value in studies involving more than 30,000 patients, CAC scanning was recently endorsed by American College of Cardiology Guidelines as a screening test in

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patients at intermediate risk (10-year CHD risk: 10% to 20%) (5), and is considered an appropriate test in low-risk patients (10-year CHD risk: <10%) with a family history of premature CHD (6). The premise for these recommendations is that screening for subclinical coronary atherosclerosis and refinement of individual cardiovascular risk will lead to more appropriate use of preventative medications, where patients reclassified to a high-risk strata receive more intensive preventative therapies proven to reduce cardiovascular events in secondary prevention cohorts, whereas patients at very low risk (e.g., Agatston score of zero) are managed conservatively.

Prospective evaluations of the downstream impact of CAC scanning are limited but suggest that compared with usual care, CAC scanning is associated with increases in statin and aspirin utilization among patients with manifest CAC and improvements in cardiovascular risk factors, without increasing costs (7,8). However, remarkably and unfortunately, only 1 study has prospectively evaluated the effect of statin treatment on clinical outcomes in patients with significantly elevated CAC scores (3). The St. Francis Heart study (randomized treatment portion) was a population-based, randomized, double-blind, placebo-controlled trial that evaluated the effect of atorvastatin 20 mg daily (in addition to vitamins C and E) on a combined cardiovascular endpoint (coronary death, myocardial infarction, coronary revascularization, peripheral arterial procedures, and nonhemorrhagic stroke) among approximately 1,000 asymptomatic subjects 50 to 70 years of age with significantly elevated Agatston CAC scores, defined as above the 80th percentile for age and gender according to an institutional database (median Agatston score approximately 370). All subjects were treated with aspirin. The study population is noteworthy because persons with Agatston scores >300 have been shown to be at relatively high CHD risk, with an annualized event rate of 2.8% (9). The authors found that active treatment involving atorvastatin for a median of 4.3 years did not significantly reduce the primary endpoint (6.9% treated vs. 9.9% placebo; $p = 0.08$); however, in an unplanned subgroup analysis, subjects with Agatston scores >400 treated with atorvastatin experienced significantly fewer events (8.7% vs. 15.0%; $p = 0.046$). In this trial, lower-than-expected annualized event rates in the placebo arm (2% for the combined endpoint and <1% for hard CHD events) served as a warning that future trials examining an asymptomatic screening cohort of similar ages may require increased

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sample sizes and longer follow-up. Unfortunately, subsequent trials have not been performed, likely for cost reasons, and perhaps, as some have suggested, due to perceived ethical concerns in randomizing subjects with significantly elevated Agatston scores at increased CHD risk, to long-term placebo therapy.

In this issue of *iJACC*, Mulders et al. (10) present an important post hoc analysis of the St. Francis Heart study assessing whether a family history of premature CAD influenced the effect of statin treatment on the combined cardiovascular endpoint. In a time-to-first event, intention-to-treat analysis, among patients with a positive family history (n = 543), atorvastatin-treated subjects experienced significantly fewer cardiovascular events as compared with those treated with placebo (7.2% vs. 12.5%; p = 0.039). Interestingly, there was no effect of statin treatment in subjects without a family history of premature CAD (n = 462). A closer look at the results again reveals the relatively low event rates in this particular population. This may be due to the relatively modest risk factor burden (mean Framingham Risk Score: 11%), the use of age- and gender-defined 80th percentile for inclusion rather than absolute CAC scores (e.g., >400), a relatively low, static statin dose, the unknown impact of aspirin use in all subjects, and possible unmeasured changes in patient lifestyle following identification of elevated CAC. Subsequently, statistical significance of statin treatment in patients with a positive family history was only achieved by the inclusion of "soft" endpoints, such as coronary revascularization and peripheral arterial surgery, which accounted for more than one-half of all events. Lastly, the percentage of patients with a positive family history in this post hoc analysis (54%) was higher than that commonly seen in primary prevention populations (typically <35%), and higher than reported in the original trial (approximately 30%) (3). This difference prompted an audit of the primary study that, reassuringly, confirmed the accuracy of the rates of family history in the current post hoc study. The reason for the increased rate of family history, an independent risk factor for hard CHD events, is likely a result of the study design, which included only patients with significantly elevated Agatston scores at a relatively young age. It is known that among patients who have suffered a premature coronary event, up to 72% will have a family history of early CHD (11). This fact and the findings of the current study reinforces the potential of this unique, heterogeneous risk factor to select patients for CAD screening using CAC scanning or, as suggested by the authors, statin treatment in the setting of advanced subclinical coronary atherosclerosis.

So how are we to manage patients with varying degrees of subclinical CAD in patients who undergo CAC scanning according to current guidelines? Does the presence of family history now influence our decision making? In the absence of large-scale outcomes studies, we are left to make an informed decision based on the limited, available data. Recent meta-analyses have questioned the use of statins for primary prevention by narrowly focusing on the relatively small absolute reduction in all-cause mortality over relatively short treatment durations, despite clear reductions in hard CHD events (coronary death and nonfatal myocardial infarction) (12,13). However, within these analyses, it is clear that the impact of statins is most significant among patients with increased cardiovascular risk. Therefore, while we await much-needed large-scale outcomes trials to better define the role of medical treatment(s) differentially applied according to cardiac computed tomography measures of risk, in patients with advanced subclinical coronary atherosclerosis, many of us will continue to reach for statins and aspirin. If unsure, then perhaps take a good family history to help you and your patient decide.

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