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EDITORIAL COMMENT

The Sins of the Fathers (and Mothers) and the 2013 Guidelines*

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The Bible offers mixed messages on whether the sins of the fathers (and mothers) are to be passed on to the children. In the world of cardiovascular disease, however, the answer is unequivocally and unfortunately in the affirmative, as highlighted in the paper by Paixao et al. (1) in this issue of *iJACC*, documenting the critical importance of a family history (FH) of coronary artery disease. In the Dallas Heart Study, 2,390 primary prevention patients, mean age 44 years, underwent coronary artery calcium (CAC) scanning and were followed for a mean of 8.1 ± 1.2 years. There were 76 coronary heart disease (CHD) events: 17 deaths,

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38 nonfatal myocardial infarctions, 16 percutaneous coronary interventions, and 5 coronary artery bypass graft surgeries. After adjustment for traditional risk factors, a FH of coronary artery disease in any first-degree relative was associated with a hazard ratio (HR) of 2.6 ($p < 0.001$), which was unchanged after adjusting for CAC. The event rates were 8.8% in those with both FH and CAC, 3.3% in those with prevalent CAC alone, 1.9% with FH alone, and 0.4% in those with neither FH nor CAC. The addition of FH to CAC increased the c-statistic from 0.86 to 0.87 ($p = 0.037$). The results were unchanged when a premature FH (age <50 years in males and <55 years in females) was substituted for any FH. The greater prominence of the results in younger (age ≤45 years in males and ≤55 years in females) compared with older patients (HRs: 5.1 vs. 2.0, $p = 0.007$) is of particular importance because the younger cohort is virtually ignored by risk factor-based paradigms.

The FH arena is complicated by varying definitions. Classically, premature FH is defined as the onset of clinical disease in male first-degree relatives age <55 years and females <65 years. Alternatively, premature FH in the PROCAM (Prospective Cardiovascular Münster trial) score and Reynolds risk score is defined as onset in either males or females at age <60 years. Only rarely is the onset at any age utilized. However, data from the Physicians' Health Study and Women's Health Study suggest that FH at any age, particularly maternal history, is important. Whatever the definition, FH has been universally accepted as a risk factor, but has not been universally incorporated into risk equations; the Framingham risk score and the EuroSCORE do not include FH. The mechanism for the increased risk, other than the transmission of lipid and blood pressure abnormalities, is unclear. Inherited abnormalities of coagulation, inflammation, and endothelial function have been postulated.

SINS OF THE GUIDELINES

The 2013 American College of Cardiology (ACC)/American Heart Association (AHA) Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults (2) and the 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk (3) have been quite controversial; this discussion will be limited to the role, or lack thereof, of FH and CAC. On the basis of the assumption that the goal of guidelines is to utilize the most powerful predictors of risk to direct treatment, it is incomprehensible that the 2 most powerful risk predictors, that is, CAC and FH, have been trivialized and downgraded from earlier documents, rather than further upgraded on the basis of robust data published after the 2010 ACCF/AHA Guideline for Assessment of Cardiovascular Risk in Asymptomatic Adults (4).

FAMILY HISTORY. The 2010 report awarded FH a Class I recommendation, Level of Evidence: B (4). Since then, there have been multiple reports in populations ranging from 12,000 to almost 4 million patients (5),

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further strengthening the case for FH as a critical risk factor. The response of the 2013 guideline was to downgrade FH to a Class IIb recommendation: "If, after quantitative risk assessment, a risk based treatment decision is uncertain, assessment of…family history…may be considered" (2). The justification was the failure of FH to add significantly to the c-statistic of the new risk equation by their undocumented analysis, despite the abundant literature to the contrary (5). For example, in the intermediate-risk group in MESA (Multi-Ethnic Study of Atherosclerosis), FH increased the area under the Framingham Risk Score receiver-operating characteristic curve (from 0.623 to 0.675, $p = 0.001$), second only to CAC (from 0.623 to 0.784, $p < 0.001$), with a net reclassification index (NRI) of 16%, again second only to CAC (65.9%) (6). FH was superior to the ankle-brachial index, carotid intima-media thickness, and high-sensitivity C-reactive protein. Although the authors of the 2013 guideline (2) are to be congratulated for including FH, the downgrading to Class IIb and its application only to those few who are not in their 4 risk categories renders the inclusion of FH almost meaningless.

CORONARY ARTERY CALCIUM. A review of the rationale for downgrading CAC is instructive: "the outcomes in the studies reviewed by Peters et al. and by Greenland et al. were CHD outcomes, not hard ASCVD [atherosclerotic cardiovascular disease] events that included stroke; hence, uncertainty remains regarding the contribution of assessing CAC to estimating 10-year risk of first hard ASCVD events" (2). In other words, the outcomes were changed to include stroke, and because there was a paucity of stroke-related CAC data, the extraordinary body of coronary-related CAC data was trivialized.

The rationale continues: concerns regarding costs and radiation exposure "resulted in a decision in the current guideline to make assessment of CAC a Class IIb recommendation among individuals for whom a risk-based treatment decision is uncertain after formal risk estimation" (2). In fact, the cost of CAC scanning has dramatically decreased to the ~$100 level, and a recent analysis demonstrated that treating 7.5% of 10-year-risk patients with statins at a $1/pill cost who had CAC >0 resulted in a cost per quality-adjusted life year saved of $18,000 compared with $78,000 for risk factor assessment alone (7). The radiation issue has become less relevant because the dosage has progressively decreased to ≤1 mSv.

Reading further: "The Work Group notes that this Class IIb recommendation is consistent with the recommendations in the 2010 ACCF/AHA guideline for patients with a 10-year CHD risk of <10%" (2). However, it is totally inconsistent with the Class IIa 2010 guideline recommendation for the 10% to 20% group (4), which is now excluded from CAC evaluation because they will all receive statins by the new recommendations. It is precisely this very large group for which the NRI by CAC in 3 major population-based prospective outcome studies (MESA, Heinz Nixdorf Recall, and Rotterdam) has ranged from 52% to 66%! Moreover, as demonstrated in the Dallas Heart Study (1) and in *every* study comparing CAC with conventional risk factor-based assessment, CAC is superior to risk factors. The most persistent criticism of CAC has been the absence of randomized controlled trials (RCTs) that demonstrate its ability to improve outcomes. However, to continue from the 2013 guideline, "The Work Group acknowledges that none of the risk assessment tools…examined in the present document have been formally evaluated in randomized controlled trials" (2).

In summary, the 2013 guideline, under the rubric of dedication to RCTs, has presented a non-RCT-validated risk assessment paradigm that is erroneous in at least 50% of the 7.5% to 20.0% 10-year-risk group based on the CAC NRI in multiple prospective studies, and have downgraded CAC and FH to a Class IIb recommendation for whom only those few patients who are not in their 4 primary risk categories will be eligible. Moreover, the downgrading of CAC was rationalized by a restructuring of the outcome definition to include stroke, which conveniently excluded CAC from playing a major role, as well as by erroneous cost and radiation concerns.

ATONEMENT

As the authors state: "Periodic updating of the guidelines should address numerous issues related to risk assessment" (2). This periodic updating should take place immediately, with restoration of FH and CAC at least to the 2010 risk guideline levels of Classes I and IIa, respectively, with applicability of FH to everybody and CAC to the 7.5% to 20.0% 10-year-risk population. In the meantime, doctors and patients should take solace in, and advantage of, the most enlightened 2013 guideline statement: "These guidelines are not a replacement for clinical judgment; they are meant to guide and inform decision making." Doctors and patients should exercise their judgment, ignore the current CAC and FH recommendations, and follow the 2010 risk guideline (4).

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