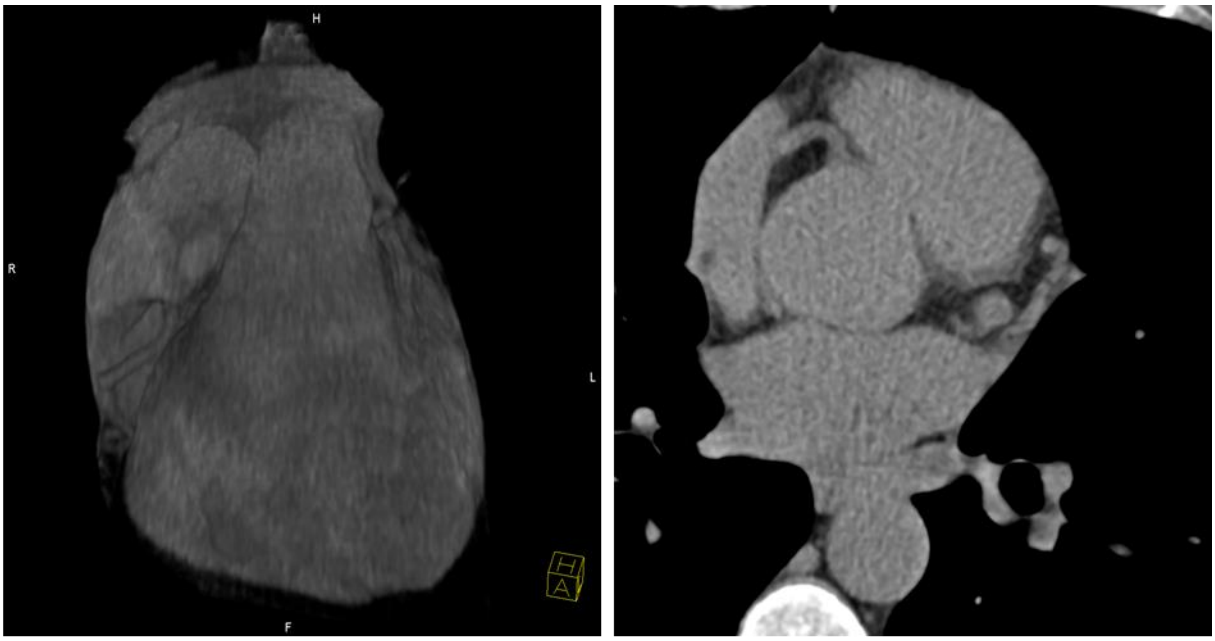
Coronary Artery Calcium:
Absence Makes the Heart…Younger?



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This is to acknowledge that Parag H. Joshi, M.D. has disclosed that he does not have any financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Joshi will not be discussing off-label uses in his presentation.

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Biography:

Dr. Joshi earned his medical degree at Texas Tech University School of Medicine. He completed an internal medicine residency at Emory University School of Medicine in 2009. He served as a Prevention Fellow at the Piedmont Heart Institute in Atlanta until 2011 before joining the Johns Hopkins School of Medicine where he completed a combined clinical and research fellowship in cardiovascular medicine. He was an inaugural Pollin Fellow in Cardiovascular Prevention which supported a Masters in Health Science in Clinical Investigation from the Johns Hopkins Bloomberg School of Public Health.

Dr. Joshi joined the UT Southwestern faculty in 2015. He is a preventive cardiologist with special expertise atherosclerotic cardiovascular disease risk assessment and in noninvasive imaging. Dr. Joshi is certified by the American Board of Internal Medicine in both internal medicine and cardiovascular diseases and he also holds subspecialty certifications in cardiovascular computed tomography and adult echocardiography.

Dr. Joshi is active in both research and patient care. His research focuses on cardiovascular disease, risk assessment, non-invasive coronary artery imaging, and lipids. He is a member of professional organizations that include the American Heart Association and the American College of Cardiology.

Purpose and Overview: The purpose of this presentation is to discuss the utility of coronary artery calcium scoring in cardiovascular risk assessment and its potential role in shared-decision making between clinicians and patients in the primary prevention of atherosclerotic cardiovascular disease.

Objectives: At the conclusion of this lecture, the listener should be able to a) Describe the association of coronary artery calcification with atherosclerotic cardiovascular disease; b) Recognize the importance of the absence of coronary artery calcium; c) Understand the potential role of coronary artery calcium in primary prevention and shared decision making under the current paradigm of the 2013 ACC/AHA guidelines; and d) Identify areas for future investigation of coronary artery calcium scoring as it relates to cardiovascular disease risk.

Current Paradigm of Primary Prevention

In 2013, the American College of Cardiology/American Heart Association (ACC/AHA) released their paradigm shifting guidelines focusing on prioritizing statin treatment over other lipid lowering therapies for primary and secondary prevention. The guidelines for cardiovascular risk assessment introduced the pooled cohort equations (PCE) for estimating the 10-year risk of developing a first atherosclerotic cardiovascular disease (ASCVD) event.[1] Simultaneously, the ACC/AHA published guidelines addressing the treatment of blood cholesterol to reduce ASCVD.[2] The two guidelines shifted the field in several ways, and though there was some controversy, there were also several strengths.

First, an emphasis was placed on weighing the absolute risk and benefits of statin therapy and other lipid lowering therapies were relegated to second line agents given a paucity of data supporting their use above statins at the time. The guidelines recommended 4 statin benefit groups, with the fourth group being the most controversial (Figure 1). Second, there was an expansion to a combined endpoint of ASCVD, comprised of fatal and non-fatal strokes, non-fatal myocardial infarctions (MI) and fatal coronary heart disease (CHD) events rather than only CHD events. Third, the risk assessment group developed a new ASCVD risk estimator from more contemporary cardiovascular cohort data, specifically including separate terms for Caucasian and African American populations, as well as for men and women. The prior approach relied on the Framingham risk estimate, mainly to predict CHD events, though this approach notably may have missed the majority of first heart attacks in younger adults.[3] Finally, and perhaps most importantly, the guidelines placed a heavy emphasis on shared decision making in the primary prevention group, highlighted by the clinician-patient discussion (Figure 1, yellow box).

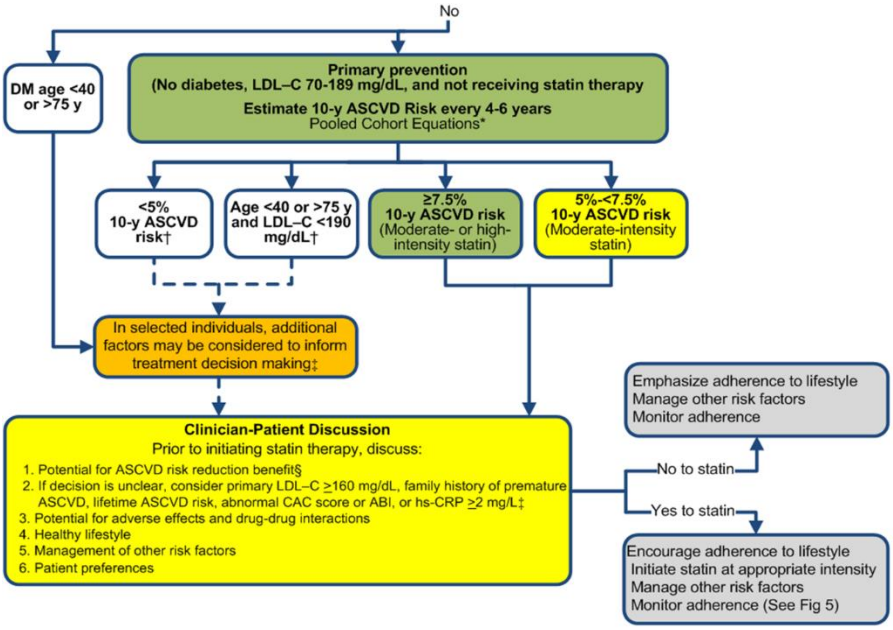

Figure 1: Primary Prevention Statin Recommendations by 2013 ACC/AHA Guidelines

While the new risk estimator represented an advance on several fronts, there were concerns about its implications. Pencina, et al applied the ACC/AHA cholesterol guidelines to the National Health and Nutrition Examination Surveys and found that 56 million U.S. adults (nearly 50%) would be classified under the four statin benefit groups.[4] This increased the statin eligible population by 12.8 million compared with prior guidelines, with the majority (10.4 million) belonging to the primary prevention group. Importantly, this was almost entirely driven by age as the dominant risk factor in the new risk estimator (Figure 2, red circle).

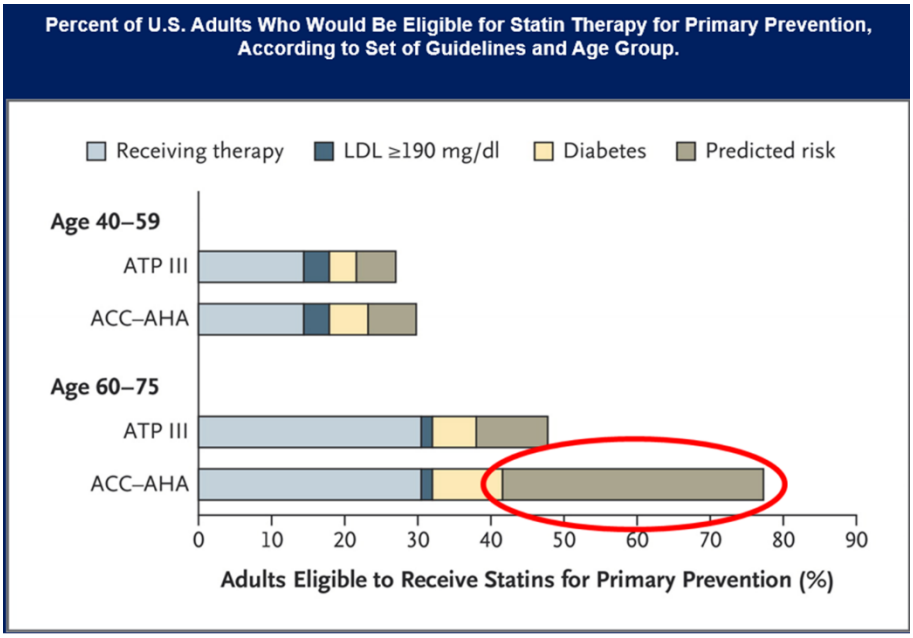

Figure 2: Increase in statin eligibility is largely driven by age (red circle)

The current guideline-based approach results in a higher sensitivity (statins recommended for adults who would develop ASCVD in the future) at the expense of lower specificity (statins recommended for adults who would not develop ASCVD in the future) compared to prior guidelines.[5] The increased eligibility for statin use per the ACC/AHA guidelines highlights an unmet need to refine cardiovascular risk assessment techniques, particularly to identify patients who are at lower risk for developing ASCVD events but are recommended statins. Non-traditional risk markers might be a solution to this problem as they can improve cardiovascular risk assessment and can guide preventive treatment decision making. Among non-traditional markers, coronary artery calcium (CAC) scoring has consistently improved risk-discrimination and correctly re-classified individuals to appropriate risk categories as reviewed below.

Significance of Coronary Arterial Calcification

Coronary artery calcification (CAC) is limited to the subintimal space of the arterial wall. It can begin as early as the second decade of life and is nearly pathognomonic for atherosclerosis. It is an active process with similarities to bone formation involving bone-

morphogenic proteins, osteoblasts, and calcium phosphate hydroxyapatite. Calcification occurs adjacent to inflammatory cells in the lipid core and is probably initiated by apoptosis of smooth muscles cells along a framework of extracellular matrix deposited by macrophages.[6] There is a direct relationship between coronary calcium burden and overall plaque burden such that calcified plaque represents approximately 20% of overall plaque burden.[7]

On the causal pathway to ASCVD events, CAC is a marker of subclinical atherosclerosis which integrates exposure to both measured and unmeasured risk factors (Figure 3). Importantly, CAC is highly specific for some coronary atherosclerosis, and highly sensitive for clinically important coronary artery disease in that there is a high negative predictive value for obstructive CAD when CAC=0. A high CAC score is more likely to reflect obstructive disease, but overall, CAC is a poor marker for obstructive CAD (i.e. >70% coronary artery stenosis).[7]

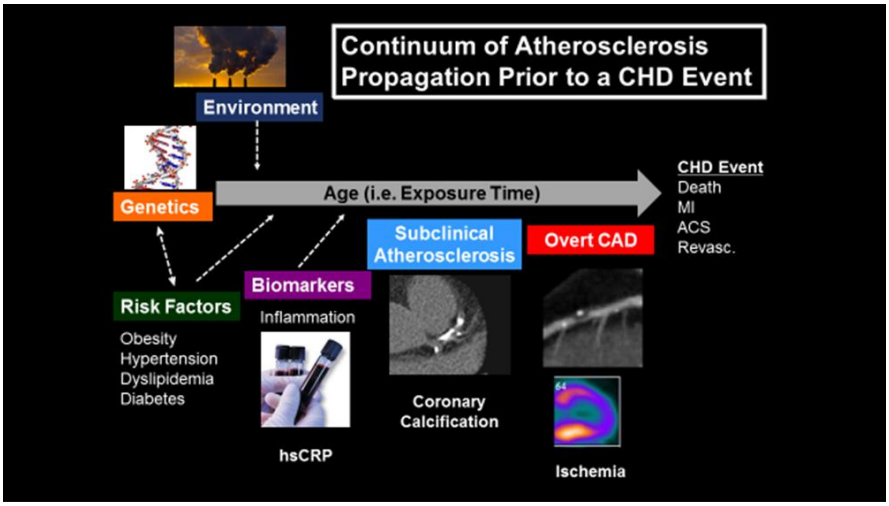

Figure 3: Schematic of progression to coronary heart disease (CHD) events

Association of CAC with ASCVD Risk

Several studies have highlighted the ability of CAC to independently predict ASCVD events. The landmark cohort Multi-Ethnic Study of Atherosclerosis (MESA) demonstrated an independent association of CAC with incident CHD among four ethnic groups across 6 cities in the US.[8] The Dallas Heart Study provided important confirmation of this association in a younger multi-ethnic population recruited from Dallas County.[9] Most importantly, CAC consistently improves discrimination and reclassification above and beyond traditional risk factor assessment (Figure 4).[9]

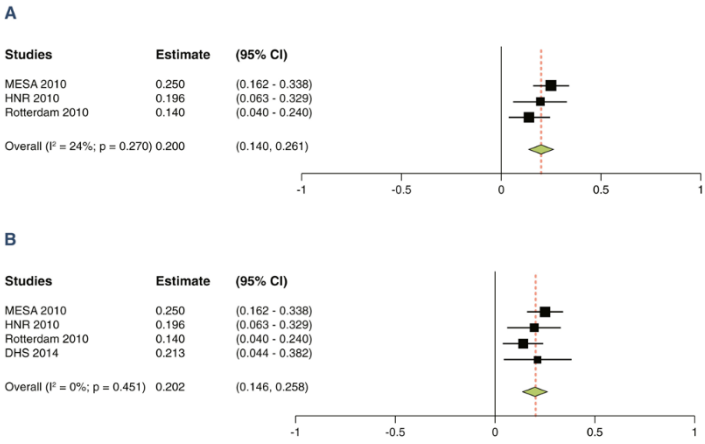

Figure 4: Meta-analysis (A) of net reclassification index (NRI) of CAC added to risk factors for major cohort studies with CAC; (B) including DHS

While prior studies focused on *CHD* risk, Yeboah et al evaluated the performance of CAC to predict *ASCVD* in MESA above and beyond both the Framingham risk score and the Pooled Cohort Equations calibrated to the MESA population.[10] CAC was compared to other non-traditional risk markers including high-sensitivity CRP, ankle-brachial index, as well as family history. CAC was the only marker to significantly improve discrimination above pooled cohort equation risk factors with a modest increase in the C-statistic from 0.74 to 0.76 (p 0.04). Similarly, in an analysis from the Heinz Nixdorf Recall study of CAC, carotid intima-media thickness, and ankle-brachial index added to traditional risk factors to discriminate ASCVD events, CAC led to the highest improvement in category-free net reclassification index (~55%).[11]

The Role of CAC=0

CAC scoring is unique in that its absence is a strong indicator of low risk, especially over the short term. A series of studies showed that event rates over 4-5 years when CAC=0 are less than 1% (Table 1).[12]

Prognostic value of CAC=0 over 4-5 years

Study Type	Participants	CAC=0 (%)	Events	Follow-up (years)	Number of Events in CAC=0 (%)
Meta-analysis Sarwar. JACC Imaging 2009;2:675-688	71,595	29,312 (41%)	CVD events**	4.3	154 (0.47%)
Retrospective Blaha. JACC Imaging 2009;2:692-700	44,052	19,898 (45%)	All Deaths	5.6	104 (0.52%)
Prospective Budoff. Am Heart J. 2009;158:554-561	6,809	3,415 (50%)	CHD events***	4.1	17 (0.52%)

CAC = Coronary artery calcium score
**CVD events varied across studies with all death, CV death, MI, revascularizations, stroke, and peripheral disease
***CHD events were CV death, MI, angina, and resuscitated cardiac arrest

Recently, the longer-term implications of CAC=0 have become evident. Shaw, et al examined the national death index for all-cause mortality in an observational single-center study of over 9,500 patients who underwent clinically-indicated CAC scoring with nearly 15 years of follow-up.[13] Exactly half of the sample had CAC=0 with an all-cause mortality rate of 3% over 15 years compared with mortality rates of 14% or higher for those with CAC>100.

These prior studies looked at short term events or long-term mortality when CAC=0. With the inclusion of stroke in the 2013 ACC/AHA guidelines, our group examined ASCVD events among MESA participants with CAC=0 using those with minimal CAC (1-10) as a

comparison over a median follow-up of 10 years, a benchmark in risk prediction.[14] We sought to examine event rates when CAC=0 across risk factor subgroups and across PCE risk categories. We also sought to understand the types of events that occur over 10 year follow-up and the risk factors that may predict these events when CAC=0.

Among 6,814 MESA participants aged 45-84 years old and without prior cardiovascular disease, there were 3,415 with CAC=0 and 508 with CAC 1-10 for comparisons. Over median follow-up of 10.3 years, among the group with CAC 0-10, there were 123 ASCVD events including 41 non-fatal MIs, 64 strokes, and 18 CHD deaths. The proportion of incident ASCVD events was similar between the CAC=0 and CAC 1-10 groups, highlighted by the finding that ~50% of these events were strokes. This is a significantly higher proportion of strokes among incident ASCVD than expected: strokes made up only 40% of the overall ASCVD events in the entire MESA study population. Upon further breakdown of the stroke data, a significant proportion (>40%) in which an etiology could be established were either hemorrhagic or cardio embolic, events that are not known to have a putative benefit from statins.

The overall ASCVD event rates were 2.9/1,000 person years (~2.9% 10 year risk) among the CAC=0 group compared to 5.5/1,000 person years in the CAC 1-10 group, reflecting a nearly 2-fold increased hazard for ASCVD with even minimal CAC (Figure 5).[14]

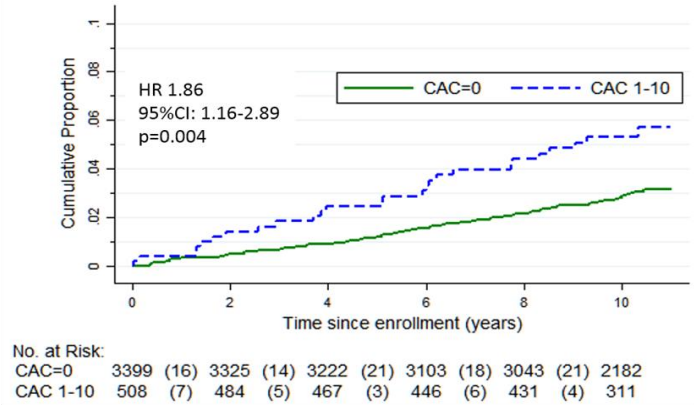

Figure 5: Cumulative proportion with ASCVD events

Across categories of risk factors and ASCVD risk categories, a CAC=0 heralded the lowest event rates (Figure 6), and none of the event rates exceeded the 7.5% 10-year risk established

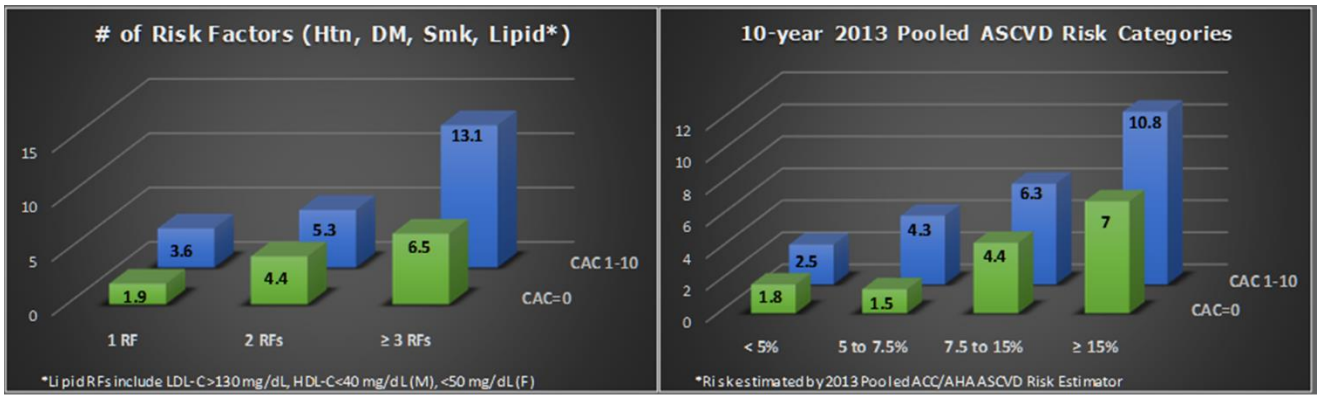

Figure 6: Event rates (per 1,000 person years) across risk categories by CAC score category

by the 2013 ACC/AHA guidelines. Notably, even in those with PCE ASCVD risk up to 15%, the event rates were 4.4/1,000 person years (~4.4% 10 year risk).

We also examined predictors of ASCVD among those with CAC=0 and minimal CAC. In multivariable models among CAC=0, only age (HR 1.5, 95%CI 1.2-1.9), current smoking (HR 3.0; 95%CI 1.8-5.1), and hypertension (HR 2.0; 95%CI 1.3-3.3) significantly predict ASCVD. Similarly, among those with CAC 1-10, age and smoking remain significant predictors, but hypertension is a much stronger predictor (HR 9.9; 95%CI 2.7-36.2) than for CAC=0 (p for interaction 0.02). We concluded that with ASCVD rates generally much lower than 7.5% when CAC=0, lifestyle modifications, smoking-cessation and hypertension-control should be top priorities.

Among non-traditional markers, Blaha et al showed that CAC scoring is the strongest for "de-risking" an individual.[15] In this MESA analysis, multivariable adjusted diagnostic likelihood ratios (DLR) were used to assess the change from pretest risk to posttest risk in the presence of a negative risk marker (e.g. no family history of CHD, normal hsCRP, CAC=0, etc…). Among all negative risk markers, CAC=0 was the strongest modifier of posttest risk with a mean DLR of 0.54 for CVD and 0.41 for CHD events (Figure 7). This suggests that on average, the posttest risk is 50% lower than the pretest risk when CAC=0; however, older participants and those with higher pre-test risk had lower average DLR. A zero CAC score resulted in the largest downward classification of risk with an NRI of approximately 14%.

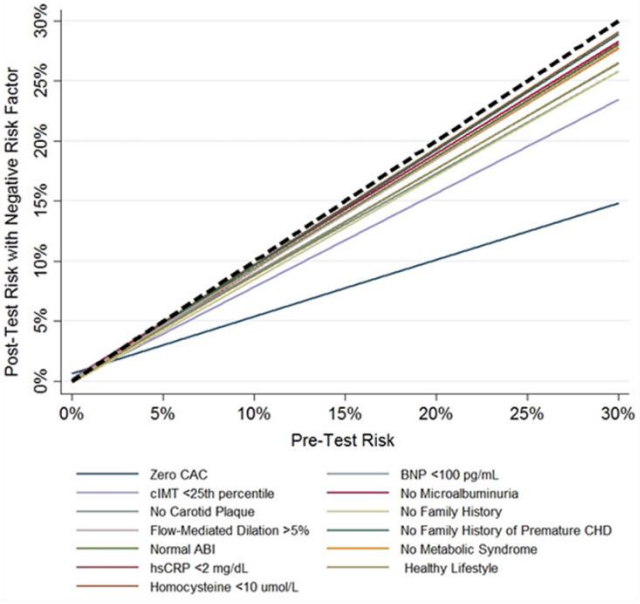

Figure 7: When non-traditional risk factors are absent, CAC=0 provides the most downward risk reclassification

Finally, Nasir et al analyzed the ACC/AHA guidelines in a systematic fashion among the statin eligible MESA population in the context of CAC scoring.[16] Nearly half of the MESA study population would be recommended statins based on either LDL-C>190 mg/dl (4%), diabetes (19%) or a 10-year ASCVD risk ≥ 7.5%. Per the ACC/AHA guidelines, statins would be considered in another 12% of the study population because of a 10-year ASCVD risk between 5 and 7.5% and 38% of the population would not be recommended statins based on <5% 10 year ASCVD risk. The event rate among all MESA participants recommended for statins but with

CAC=0 was 5.2/1,000 person years.[16] When examining this within estimated 10-year ACC/AHA pooled cohorts equation risk categories (Figure 8), those with 7.5 to 20% ASCVD risk and CAC=0 experienced only 4.6 ASCVD events per 1,000 person years (~4.6% 10 year risk).

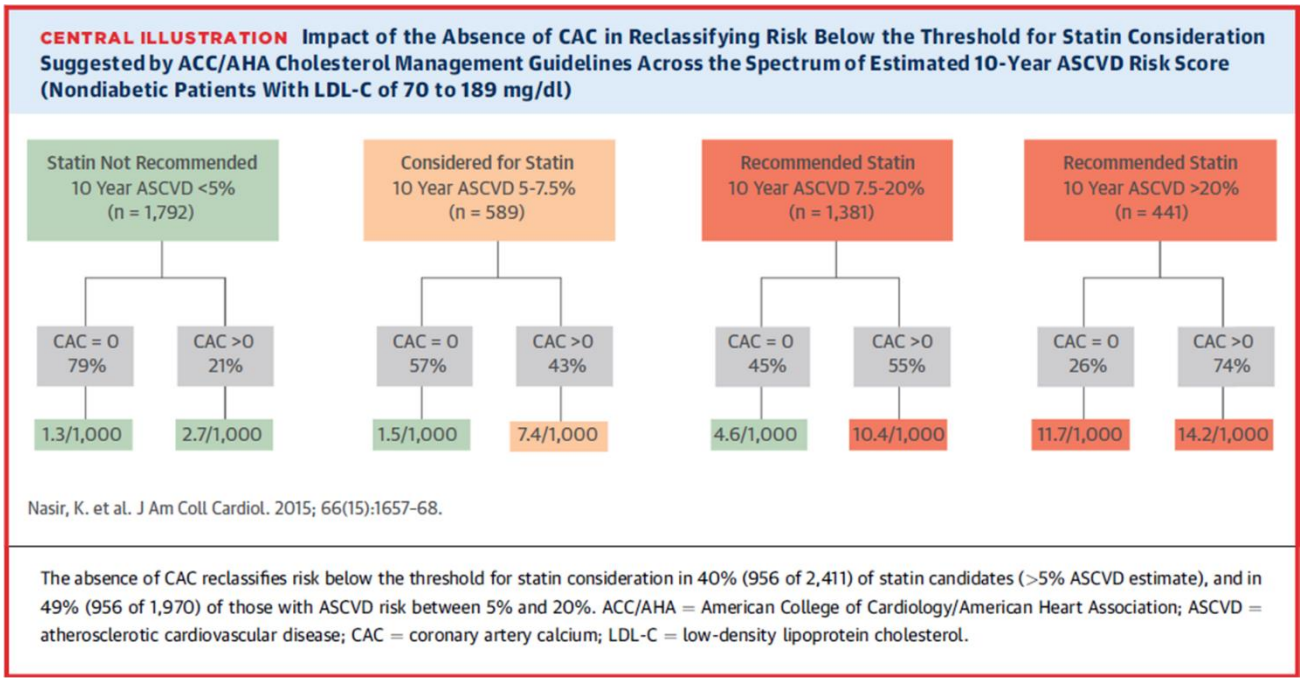

Figure 8: CAC=0 is common in the MESA participants with 2013 ACC/AHA ASCVD risk estimates between 5% and 20% and reclassifies risk below the 7.5% threshold for statin recommendation in this group.

These studies show that there is significant heterogeneity between risk factors, risk estimates and burden of subclinical atherosclerosis. In a review of prospective and retrospective studies we examined the prevalence and event rates of both extremes:

- Presence of high risk factors with CAC=0 (Table 2)
- Presence of low risk factors with CAC>100 (Table 3).[17]

We found that even in the presence of a high burden of traditional risk factors, the absence of CAC marked a low risk of events. On the other hand, among participants with normal values for traditional risk factors, a high CAC score (>100) marked a high risk of events. For example, Martin et al examined MESA participants by their burden of lipid abnormalities: high LDL-C, low HDL-C, or high triglycerides.[18] Approximately 20% of participants with no lipid abnormalities had CAC >100 and an ASCVD event rate of more than 20/1,000 person years over 7 years of follow-up. Conversely, approximately 50% of participants with 3 lipid abnormalities had CAC=0 and an ASCVD event rate of 5.9/1,000 person years. Similar findings are seen when examining extremes of age and burden of traditional risk factors (Tables 2 & 3).[17]

Table 2. Studies showing low event rates with high risk factors, but CAC =0

Study	Risk Factor	# With High Risk Factor (%)	# With CAC=0 (%)	Event Type and Follow-up Time	Event Rate (per 1000 person-years) [a]
Tota-Maharaj (29) (*n* = 43,909) retrospective	Age ≥ 75 years	1663 (4%)	266 (16%)	All-cause mortality Mean 5.6 years	2.8
MESA (30) age (*n* = 6809) prospective	Age 75–84 years	965 (14%)	180 (19%)	CHD events Median 8.5 years	1.5
MESA Lipids (33) (*n* = 5534) prospective	3 lipid abnormalities [b]	330 (6%)	165 (50%)	CVD events Median 7.6 years	5.9
Graham (34) (*n* = 44,052) retrospective	Hypertension	10,566 (34%)	3381 (32%)	All-cause mortality Mean 5.6 years	1.7
MESA Diabetes (36) (*n* = 6603) prospective	Diabetes or metabolic syndrome	2567 (39%)	1094 (43%)	CVD events Median 6.4 years	~5.2
McEvoy (37) (*n* = 44,042) retrospective	Current smokers	6020 (14%)	2288 (38%)	All-cause mortality Mean 5.6 years	3.3
MESA Smoking (38) (*n* = 6796) prospective	Current smokers	971 (14%)	494 (51%)	CVD events Median 10.2 years	7.4
MESA JUPITER (42) (*n* = 2083) prospective	hsCRP ≥ 2 mg/L	950 (46%)	444 (47%)	CVD events Median 5.8 years	3.7
Nasir (43) (*n* = 44,052) retrospective	≥ 3 risk factors [c]	6386 (14%)	2123 (33%)	All-cause mortality Mean 5.6 years	2.7
MESA Risk Factors (44) (*n* = 6698) prospective	≥ 3 risk factors [d]	1205 (18%)	422 (35%)	CHD events Mean 7.1 years	3.1

Table 3. Studies showing high event rates with low burden of risk factors, but CAC >100

Study	Risk Factor	# With Low Risk Factor (%)	# With CAC > 100 among Low Risk (%)	Event Type and Follow-up Time	Event Rate (per 1000 Person-Years) [a]
Tota-Maharaj (29) (*n* = 43,909) retrospective	Age <45 years	8143 (19%)	326 (4%)	All-cause mortality Mean 5.6 years	~12.0
MESA Age (30) (*n* = 6809) Prospective	Age 45–54 years	1947 (29%)	116 (6%)	CHD events Median 8.5 years	21.1
MESA Lipids (33) (*n* = 5534) prospective	No lipid abnormalities [b]	1975 (36%)	395 (20%)	CVD events Median 7.6 years	22.7
Graham (34) (*n* = 44,052) retrospective	No hypertension	33,486 (66%)	6362 (19%)	All-cause mortality Mean 5.6 years	~9.3
MESA Diabetes (36) (*n* = 6603) prospective	No diabetes or metabolic syndrome	4036 (61%)	807 (20%)	CVD events Median 6.4 years	~20.6
McEvoy (37) (*n* = 44,042) retrospective	No current smoking	38,022 (86%)	7985 (21%)	All-cause mortality Mean 5.6 years	~10.0
MESA Smoking (38) (*n* = 6796) prospective	Never smoker	3218 (47%)	615 (19%)	CVD events Median 10.2 years	27.5
MESA hsCRP (42) (*n* = 2083) prospective	hsCRP < 2 mg/L	1133 (54%)	317 (28%)	CVD events Median 5.8 years	24.0
Nasir (43) (*n* = 44,052) retrospective	No risk factors [c]	18,819 (43%)	2930 (16%)	All-cause mortality Mean 5.6 years	16.9
MESA Risk Factors (44) (*n* = 6698) prospective	No risk factors [d]	1067 (16%)	128 (12%)	CHD events Mean 7.1 years	~9.2

In a novel competing risks analysis from MESA, Handy et al examined the association of CAC with non-CVD outcomes over median 10.2 years follow-up.[19] In multi-variable adjusted analysis accounting for competing CVD events, those with CAC=0 had a decreased risk of incident cancer (0.76, 0.63-0.92), CKD (0.77, 0.60-0.98), COPD (0.61, 0.40- 0.91) and hip fracture (0.31, 0.14 - 0.70) compared to those with CAC>0 (Figure 9). In summary, these studies suggest CAC=0 is a marker of "health aging".

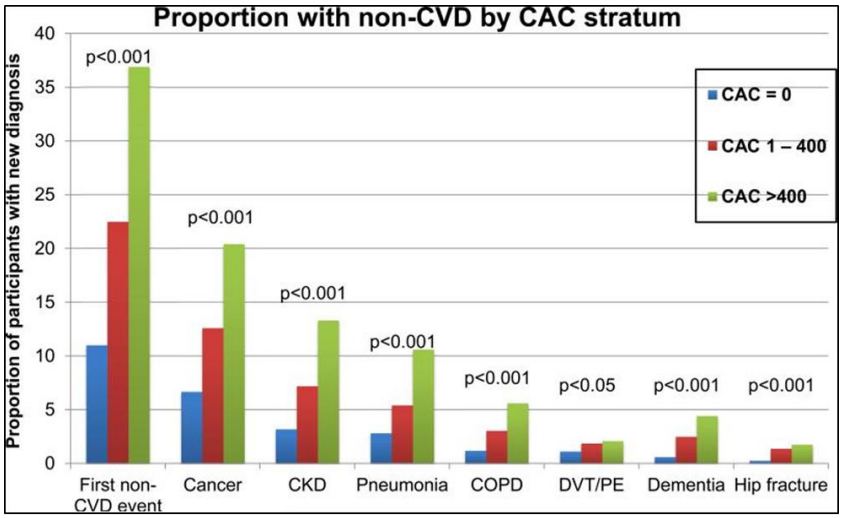

Figure 9: CAC=0 predicts the lowest risk for non cardiovascular diseases

Integrating CAC Scoring into Clinical Practice

As stated previously, one of the major advances of the 2013 ACC/AHA guidelines was the codification of the clinician-patient discussion as an emphasis of shared decision making. There are several tools available from the MESA study to help integrate CAC scoring and results into the discussion with the patient (www.mesa-nhlbi.org/CAC-Tools.aspx). One tool provides a reference percentile for the calcium score result in the context of the patient's age, gender, and ethnicity. Another provides an estimated "arterial age" calculator for the patient based on the calcium score result. The most useful tool provides a 10-year CHD risk estimate based off a combination of CAC score with traditional risk factors from MESA.[20] The score was validated in the Dallas Heart Study and the Heinz Nixdorf Recall Study and showed excellent discrimination in both validation populations (c-statistic 0.78 to 0.82). However, one key limitation is the inclusion of only CHD risk; a CVD risk estimator incorporating CAC scoring from MESA is currently in development.

The 2013 ACC/AHA guidelines significantly increased the number of statin-eligible individuals; however, many patients may have an aversion to starting statins as a lifelong therapy in primary prevention.[4,21] With the large increase in statin-eligible patients, several studies have explored the role of CAC=0 to "de-risk" statin eligible patients. In general, these studies have assessed whether the ASCVD event rates in statin-indicated patients based on the guidelines are lower than the threshold for statin initiation when CAC=0.

In addition to the study by Nasir et al from MESA, Pursnani et al. also examined statin eligible participants from the Framingham offspring study who underwent CAC scoring and were followed for ASCVD events over 9.4 years.[22] They found the ACC/AHA guidelines were more accurate than the previous ATP III guidelines in discriminating those with incident ASCVD and those with prevalent subclinical atherosclerosis as measured by CAC (Figure 10). Across all CAC categories, the ACC/AHA guidelines increased statin eligibility. However, participants who were deemed eligible for statins by ACC/AHA criteria, but with CAC=0, had an ASCVD event rate of only 1.6%. Importantly, the event rate among statin ineligible participants did not increase significantly (1% to 1.1%) when reclassifying statin eligible participants with CAC=0 to statin ineligible.

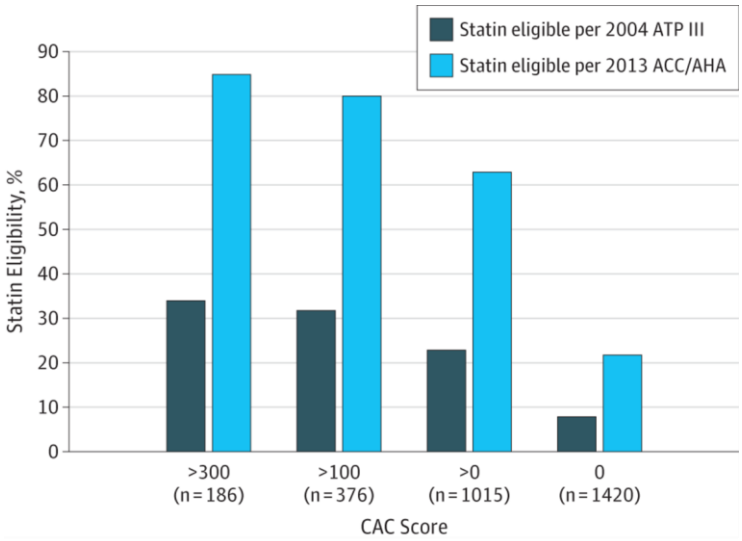

Figure 10: Framingham offspring study comparing statin allocation from previous ATP III guidelines to ACC/AHA guidelines across CAC categories

As opposed to a guideline based approach to statin eligibility, investigators applied trial eligibility criteria from 7 primary prevention statin trials to MESA participants.[23] The majority of MESA participants (73%) were eligible for statin therapy based on primary prevention statin RCT enrollment criteria. Approximately 45% of statin eligible MESA participants had CAC=0 and overall ASCVD event rates of 3.9/1,000 person years. Assuming a relative risk reduction of 30% from statin therapy, the number needed to treat to prevent one ASCVD event over 10 years among CAC=0 participants was 87. In contrast, among those with CAC>100, the number needed to treat was 19 (Figure 11).

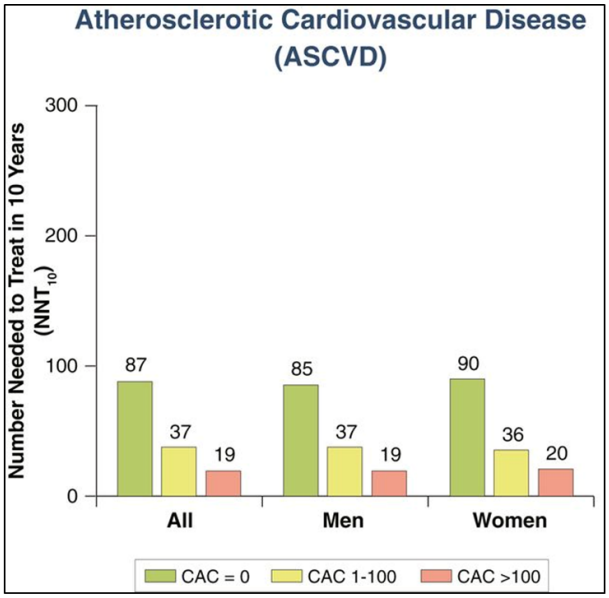

Figure 11: NNT to prevent one ASCVD event over 10 years with statin assuming 30% risk reduction among MESA participants who met eligibility criteria from at least one of 7 primary prevention statin trials

In using an atherosclerosis based approach to statin eligibility, Mortensen et al evaluated the utility of "de-risking" participants from the BioImage study with CAC=0.[24] Most of the study participants (86%) were eligible for statin therapy by ACC/AHA guidelines and 32% had CAC=0. The event rate among those with CAC=0 was 3.2/1,000 person years, well below the ACC/AHA 7.5% threshold. This imaging-based approach resulted in a binary NRI of 0.14 driven by down-classifying the 32% of the population with CAC=0 (Figure 12).

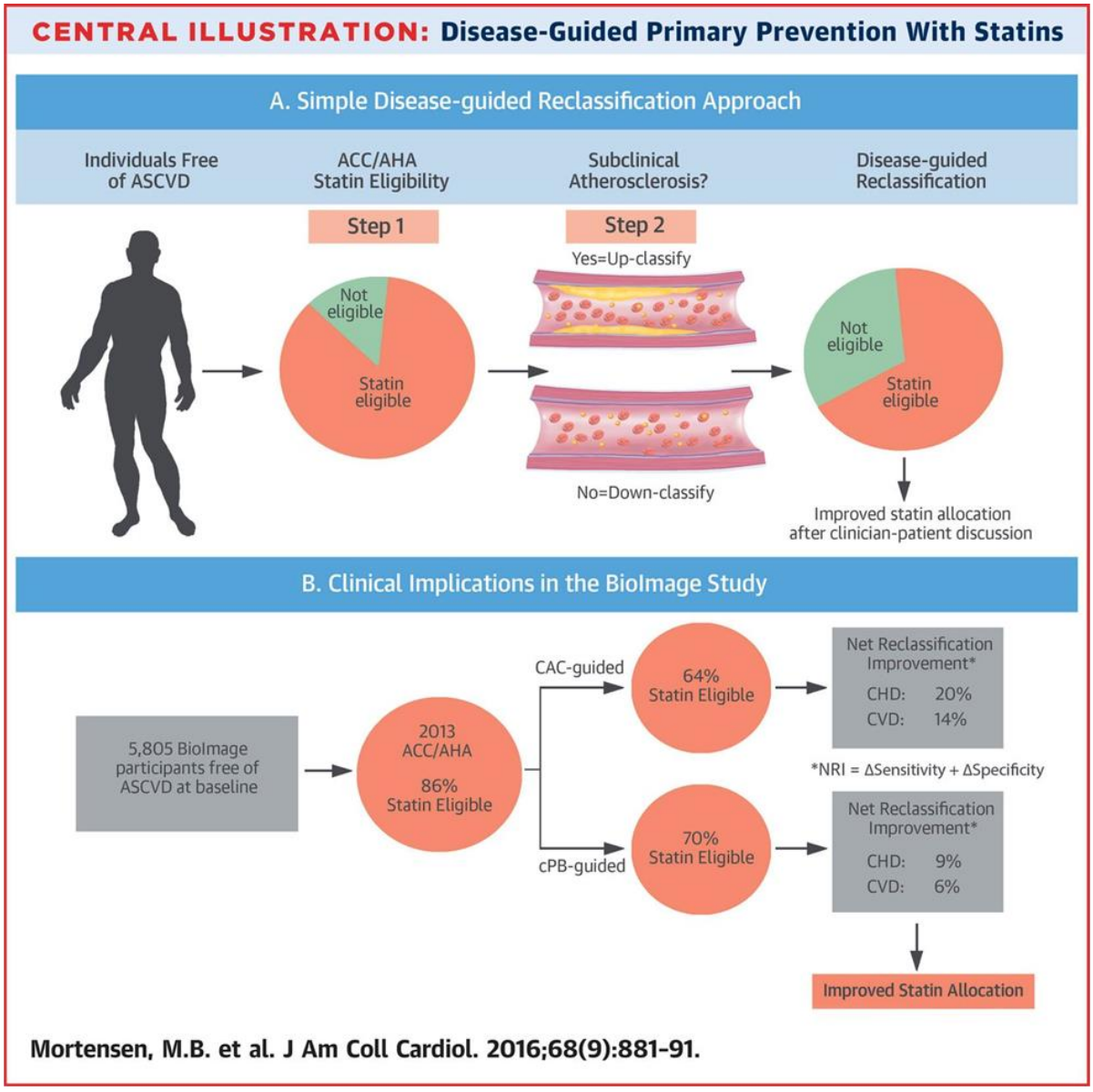

Figure 12: Driven by reclassifying participants with CAC=0 to statin ineligible, an imaging-based approach led to significant improvement in NRI from the BioImage Study.

Lastly, investigators from the Heinz Nixdorf Recall study analyzed European guidelines and ACC/AHA guidelines in the context of CAC=0.[25] They found an event rate for ASCVD of 2.7/1,000 person years among participants who were eligible for statins but with CAC=0. This resulted in a NNT over 10 years to prevent an ASCVD event of 62 among those with CAC=0 and deemed eligible for statins by the ACC/AHA criteria, assuming a 30% relative risk reduction with statins. Similarly, the NNT was 59 among those deemed eligible for statins by European guidelines but with CAC=0.

These studies strongly support the absence of CAC as a marker of low 10-year ASCVD risk despite statin eligibility by 2013 ACC/AHA pooled cohort risk estimation. They also show that CAC=0 is quite common among statin-eligible patients. In patients with CAC=0 and consequently low 10-year ASCVD event rate, statin therapy should be viewed as a means to reduce long term, or even lifelong risk, rather than 10 year benefit. The clinician-patient risk discussion over benefits and risks in such a scenario should encompass these considerations.

Prevention encompasses more than just decisions over statin therapy. Recent work has evaluated the utility of CAC scoring to guide decisions for aspirin therapy and for systolic blood pressure targets.[26,27] In both cases, CAC=0 provides strong rationale to be less aggressive given the low absolute event rates for a fixed exposure to risk of therapy.

Challenges to CAC Testing

Coronary calcium scanning is available in most major cities and is typically not covered by insurance (with rare exception in Texas). The cost is approximately $100 in most major cities. Concerns over radiation exposure are valid given overall principles for limiting medical radiation exposure. With modern technology and approaches to CT imaging, the average radiation dose is approaching ~1 mSv, or the equivalent of 2 mammograms. Finally, lung nodules or other incidental findings are present in up to 10% of studies which may stimulate further downstream testing and anxiety. Pre-scan counseling of patients about the possibility of incidental findings may be helpful in preventing anxiety and planning follow-up appropriately.

There are justified criticisms of CAC scoring in that there has not been a screening trial to show that CAC scanning changes outcomes. This is partly due to ethical concerns over potentially randomizing patients with high CAC scores to placebo. Further, there are significant cost considerations as a randomized “screening” CAC trial has been estimated to require up to 30,000 patients and cost up to $100 million.[28] Creative solutions to approach this conundrum exist, and should be considered going forward (Figure 13).[29]

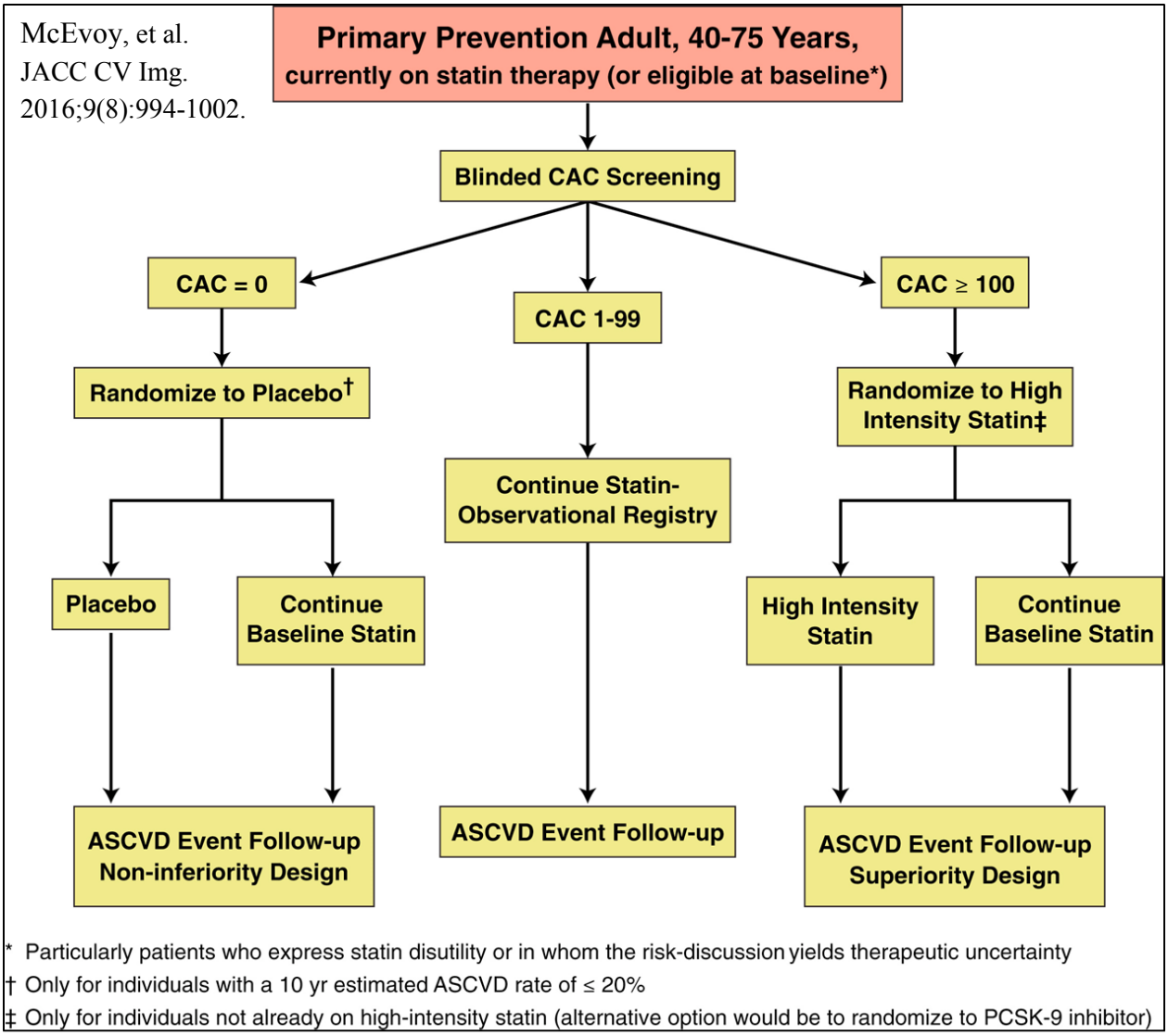

Figure 13: Potential approach to a randomized clinical trial testing the utility of CAC screening in primary prevention on clinical outcomes

A CAC-based Approach to Primary Prevention

Lifelong statin therapy in primary prevention can be intimidating for patients. In those patients who are reluctant to start a statin, but are otherwise eligible for statin therapy, CAC scoring can be particularly helpful. The absence of CAC can help reassure the patient and provider (for a few years at least) that the overall risk is low. While the absence of CAC does not indicate "no-risk", it does reclassify many patients to ASCVD risk estimates below thresholds for statin initiation and suggests low 10-year risk. Based on the above evidence, one approach to

CAC scoring in the primary prevention of ASCVD is presented (Figure 14). CAC scanning should only be pursued if the result will impact decision making. If a patient is agreeable to starting a statin, then a CAC scan is not likely to help. It is mainly in the statin-reluctant patient that CAC scanning can be useful.

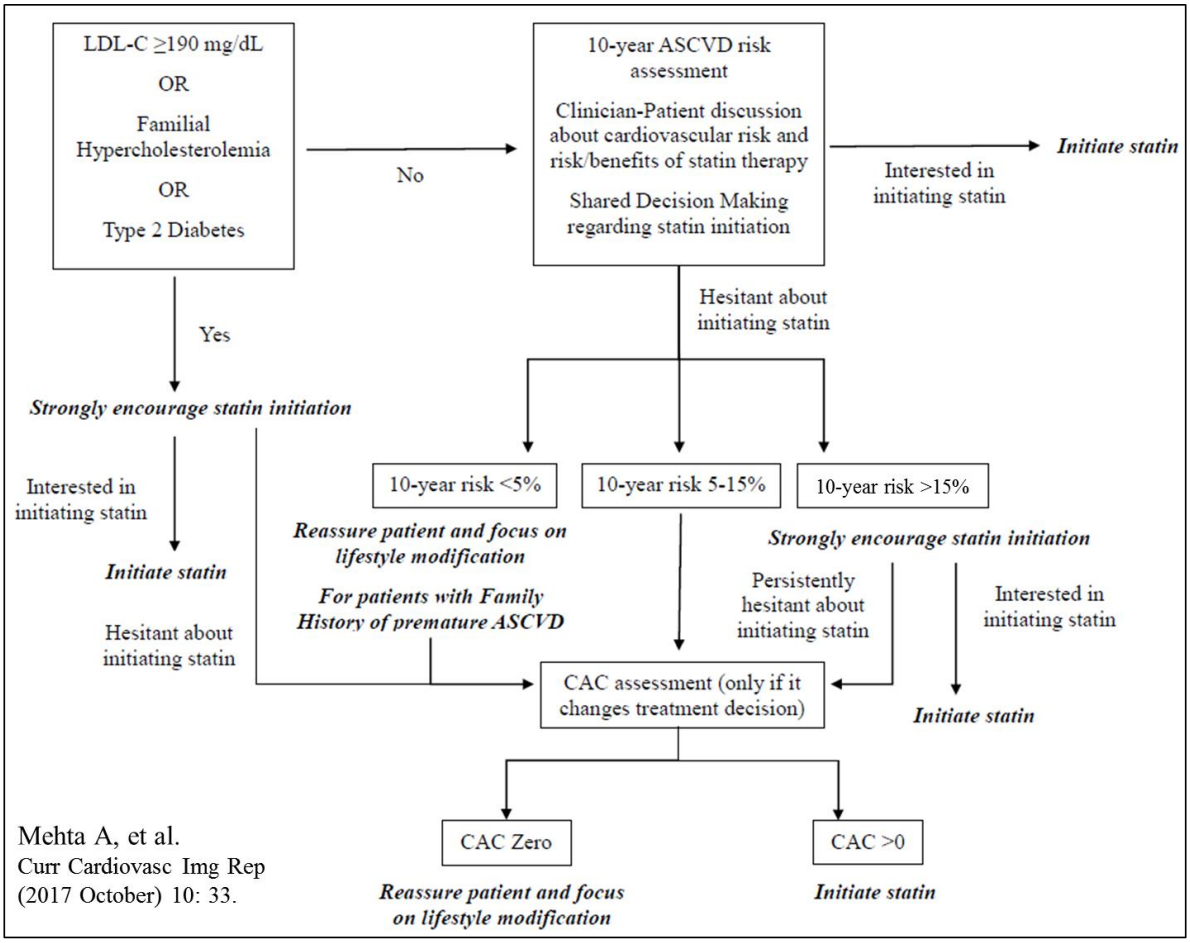

Figure 14: Algorithm for CAC assessment to improve cardiovascular risk assessment in primary prevention patients; CAC 0 vs >0 is shown here, but threshold for initiation may be patient dependent

Conclusion

CAC is a well-validated marker of cardiovascular risk, but also a strong marker of low risk when absent. In the current approach to primary prevention of ASCVD there has been a large increase in the population deemed eligible for statins. Considering patient preferences and possible reluctance for starting lifelong therapies, CAC scoring is a highly valuable aid in shared decision making between the clinician and patient, particularly when CAC=0 in the statin-reluctant patient.

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