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iFORUM

NEWS AND VIEWS

Coronary Artery Calcium Scanning Should be Used for Primary Prevention

Pros and Cons

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CORONARY ARTERY CALCIUM (CAC) SCANNING HAS BEEN PERFORMED for the better part of 2 decades. Initially, many in the cardiology community viewed it skeptically because there was no evidence base, and it had appearances of a marketing/money-making ploy. Once the data began to be generated that a high Agatson score, >300 or so, was associated with elevated risk beyond the patient's Framingham risk score, it began to gain greater acceptance as a test with potential benefit for risk stratification. The absolute event rate, even in patients with higher scores, remains modest, so exactly how to use the score in an individual patient remains somewhat unclear. That being said, in the most recent guidelines for screening asymptomatic individuals, it received a Class IIa recommendation, level of evidence B, for screening those at intermediate risk and a class IIb, level of evidence B, for those at low-intermediate risk (1).

In this installment of iForum in *iJACC*, we present to our readers opposing views of the role of CAC in primary prevention. Dr. Nasir and colleagues present a cogent argument for the use of CAC in screening. They present compelling evidence of the association of higher scores with higher risk, and of the CAC score of 0 with extremely low risk. They discuss the recent studies (MESA [Multi-Ethnic Study of Atherosclerosis] and HNR [Heinz Nixdorf Recall]) that show how frequently CAC can reclassify patients. They also discuss relative benefits of screening CAC versus high-sensitivity C-reactive protein (hsCRP) in relation to the JUPITER (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin) trial. They point out that patients with low hsCRP were excluded from JUPITER, and thus it cannot be viewed as a screening trial involving all comers. They point out that patients in JUPITER with a CAC of 0 would receive therapy with little benefit, given their extremely low event rate.

Presenting the opposing view, Drs. Ridker and Pena explain that since there is strong evidence based on the JUPITER trial that one can treat with statin therapy based on hsCRP >2 and that no such evidence base exists for CAC, that hsCRP is the appropriate biomarker to use for primary prevention decision making. They present the potential downsides of CAC including radiation (albeit quite low) and the issue of noncardiac findings that generate additional testing. They make a case for the need for

"screen and treat" intervention data for CAC. They propose a concept for a trial of CAC in patients with low levels of low-density lipoprotein (LDL), high levels of high-density lipoprotein cholesterol (HDLC), and low hsCRP with randomized statin therapy, with examination of the results based on high or low CAC scores. This would indeed be an interesting study and just the kind of dialogue that iForum is designed to create.

CAC Scanning for Primary Prevention: Pros

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CLINICAL DECISION MAKING FOR PRIMARY PREVENTION OF CARDIOVASCULAR DISEASE (CVD) in asymptomatic individuals is traditionally guided by an initial estimate of the impact of single or clustered laboratory and risk factors as they relate to the risk of a coronary event. Extensive evidence demonstrates that current traditional approaches lack precision and accuracy in predicting future CVD risk among asymptomatic individuals. Considering the fact that CVD not only is associated with a high morbidity and mortality, but is also responsible for the large share of the healthcare budget, there is an urgent need for improved risk assessment methods to accurately identify not only those "at higher risk," but also those at "very low risk," for appropriate allocation of finite resources to reduce the CVD burden in a cost-effective manner.

Since atherosclerosis appears to be the main culprit for the development of a majority of these events, screening for subclinical atherosclerosis, such as CAC, may aid in supplementing current global risk assessment approaches. In order to establish the role of CAC testing in primary preventive settings, the evidence needs to be critically assessed as to whether the information gained is additive to assessments made by less expensive office-based measures.

Association of elevated CAC scores with cardiovascular risk. Over the last decade, multiple studies have shown the strong prognostic value of CAC in predicting CVD events. However, it is important to keep in mind study generalizability of these retrospective cohorts, validity of risk factor and resultant multivariable models, and risk of test-induced bias. These concerns were addressed with recent prospective registries such as MESA (2) and the HNR study (3) showing 9- to 16-fold higher hazard ratios for individuals with severe CAC compared with those with no CAC. To date, a plethora of available data consistently shows that at least two-thirds of all events are concentrated among one-fourth of the population with CAC >100 (2–5), a predictive value not seen with any other known risk factor or biomarker.

Discrimination and reclassification with CAC testing. Although the extent of CAC has been shown to predict cardiac events in asymptomatic patients with hazard ratios up to 10-fold, decisions about the predictive utility of new tests, however, should be made based on a particular test's discrimination and reclassification ability above and beyond the standard traditional risk factors. CAC scanning has been shown to result in substantial improvement in risk discrimination, as well as significantly high-risk reclassification in the MESA and HNR studies (Table 1). Notably, among intermediate-risk patients, the use of CAC is associated with a net reclassification improvement of 55%. In comparison, studies comparing conventional and newer biomarkers for predicting cardiovascular events have consistently demonstrated that adding a number of newer biomarkers (such as

Table 1. Predictive Value of CAC Testing

	Multi-Ethnic Study of Atherosclerosis (N = 6,722)	Heinz Nixdorf Recall Study (N = 4,129)
Measures of association Hazard ratios (95% CI)	CAC = 0 (reference group) CAC 1–100 = 3.6 (1.9–6.6) CAC 101–300 = 7.7 (4.1–14.5) CAC >300 = 9.7 (5.2–17.9)	CAC = 0 (reference group) CAC 1–99 = 1.7 (0.8–3.5) CAC 100–399 = 4.0 (2.0–8.1) CAC 400–999 = 5.4 (2.4–12.3) CAC ≥1,000 = 16.1 (8.0–32.2)
Measure of discrimination AUC	AUC risk factors = 0.77 AUC risk factors + CAC = 0.82*	AUC FRS = 0.681 AUC CAC = 0.741, p = 0.046 vs. FRS AUC FRS + CAC = 0.749, p = 0.003 vs. FRS
Measure of reclassification Net reclassification improvement	Total population = 25% Intermediate risk = 54.4%	Total population = 22.4% Intermediate risk = 65.6%

Risk factors include age, sex, ethnic group, cigarette smoking, presence or absence of diabetes, total cholesterol level, high-density lipoprotein cholesterol level, systolic and diastolic blood pressure, and use or nonuse of lipid-lowering or antihypertensive medication. *p < 0.001 vs. risk factors.
AUC = area under the receiver-operating characteristic curve; CAC = coronary artery calcium; CI = confidence interval; FRS = Framingham Risk Score.

hsCRP) only results in minimal improvement in risk discrimination and reclassification.

Negative likelihood of absence of CAC. Apart from the ability to identify those "high-risk" individuals, among whom the majority of events occur, absence of CAC confers a very low risk for future CVD events and mortality. In a series of studies including a meta-analysis, we have shown that among 29,312 individuals without evidence of CAC, only 0.56% of subjects without CAC experienced a CVD event during a mean follow-up period of 51 months (5) (Table 2). These findings were confirmed in a large retrospective study (6) and a multiethnic prospective study (7) demonstrating a very low risk with CAC = 0. A finding of CAC = 0 confers such low risk that clinicians may elect to focus on lifestyle therapies without need for further cardiac testing or medications. On the other hand, none of the traditional risk factors and novel serum biomarkers has sufficient sensitivity to exclude clinically important coronary events.

Based on the preceding evidence, there is little doubt of the superiority of the CAC test as far as prediction and reclassification of CVD risk is concerned. However several "criticisms" have been raised in regard to the role of CAC testing within the current primary CVD preventive efforts. In the following section, we would like to address a few of these concerns.

- **CAC testing is associated with significant radiation:** The mean effective radiation dose of a CAC scan when using appropriate protocols is ~1 mSv, a dose that is comparable to a mammogram. This radiation burden is sizably less than the average annual exposure from ionizing radiation in the United States, which is ~3 mSv. If the radiation associated with mammography for breast cancer screening performed annually in women older than 45 years of age is acceptable, we believe it should be less of a concern to screen for CAD (once in a lifetime and thus far less cumulative radiation exposure than yearly mammography), considering its mortality burden is 10-fold higher than breast cancer.
- **CAC testing leads to increase downstream testing and costs:** This myth was recently debunked by the EISNER (Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research) trial, which showed that overall rates of downstream medical testing and procedures, including stress tests as well as revascularizations, did not differ among the scan and no-scan groups, resulting in comparable costs during follow-up of 4 years (8) (Table 3). Most importantly among patients with CAC = 0, there was a 37% and 25% greater reduction in downstream procedure and medications costs, respectively, compared with those not undergoing any CAC testing.
- **CAC testing does not change patient and physician behavior:** Emerging evidence indicates that those with higher CAC scores are more likely to stimulate improved lifestyle changes and cause adherence/initiation to cardioprotective medications, which is the cornerstone of reducing future CVD events (8). In comparison, we do not know of any study providing similar data with novel biomarkers such as hsCRP.
- **CAC versus CRP: Why assess CAC when hsCRP screening identifies those who will benefit with lipid-lowering pharmacotherapy where no such evidence exists for CAC testing?** In the recent JUPITER trial, a 44% reduction was noted among men >50 years of age and women >60 years of age with no prior history of CVD with LDL levels <130 mg/dl and hsCRP >2.0 mg/l with rosuvastatin 20 mg daily. Many critics used this study finding to demand similar studies with CAC testing, as well as

Table 3. Comparison of Downstream Testing and Costs Among Those Undergoing No CAC vs. CAC Testing in 4-Year Follow-Up

	No CAC Testing (n = 623)	CAC Testing (n = 1,311)	p Value
Downstream tests			
Stress test	33.9%	34.6%	0.74
Cardiac CT	7.1%	7.7%	0.62
Cardiac catheterization	2.9%	3.3%	0.71
Coronary revascularization	1.8%	2.3%	0.46
Downstream costs			
Median procedure costs*	$721	$904	0.56
Median medication costs	$2,937	$3,149	0.09

Adapted from Rozanski et al. (8). *Includes $150 for coronary artery calcium (CAC) testing.
CT = computed tomography.

Table 2. Prognostic Value of CAC = 0 Among Asymptomatic Individuals

Study Type, Ref. #	Total Population, N	CAC = 0, n (%)	Follow-Up, Yrs	Number of Events, %
Meta-analysis (4)	71,595	29,312 (41%)	4.3	154 (0.47%) CVD events
Retrospective study (5)	44,052	19,898 (45%)	5.6	104 (0.52%) deaths
Prospective study (6)	6,809	3,414 (50%)	4.1	17 (0.52%) CHD events

CAC = coronary artery calcium; CHD = coronary heart disease; CVD = cardiovascular disease.

using these data to justify hsCRP screening in asymptomatic individuals to identify those who will benefit from lipid-lowering pharmacotherapy.

In response, the following should be considered.

1. JUPITER was not a "screening trial"; those with lower hsCRP levels were specifically excluded. In the absence of a "low-LDL/low-hsCRP" arm, it is impossible to determine whether the benefit seen with rosuvastatin was based at all upon the presence of elevated hsCRP.
2. A post hoc analysis of JUPITER found the benefit of lipid-lowering management was greater in those with hsCRP levels lower than the median (4.2 mg/l), suggesting that the effect of pharmacotherapy, if not better, would be the same among those with lower CRP (<2 mg/l) who were excluded from the trial. In that scenario, the role of "CRP screening" is highly questionable.
3. On the other hand, the St. Francis Heart Study demonstrated that atorvastatin 20 mg significantly lowered events in patients with CAC >400 (8.7% vs. 15.0%, p = 0.046 [42% reduction]), whereas a nonsignificant 30% reduction was noted among those with lower CAC scores (9). This is consistent with the hypothesis that individuals with higher risk (as accurately identified by CAC) will confer greater benefit, whereas lesser event reductions will be noted among those at relatively lower risk (lower CAC scores).
4. Further evidence to the preceding hypothesis was provided by our recent study demonstrating that among participants meeting JUPTER criteria, CAC was absent in nearly one-half of the individuals' CAC scores and during a 6-year follow-up (almost 3-fold more than the JUPITER trial), rates of coronary events were 0.8/1,000 person-years (5). The majority (74%) of all coronary events occurred in only one-fourth of participants with CAC >100 (20.2 per 1,000 person-years). Applying the effect of rosuvastatin from the JUPITER trial to this population, the number needed to treat (NNT) to prevent 1 coronary event was inappropriately high (n = 549) for CAC = 0. On the other hand, the NNT for any CAC was 42 and as low as 24 for CAC >100. In addition, among those with LDL <130 mg/dl, CAC >0 was associated with a 4-fold higher risk of coronary heart disease events and as high as 9-fold for CAC >100. In comparison, the respective HR for hsCRP >2 versus <2 mg/l was 0.90 (0.54 to 1.50). As shown in Figure 1, clearly CAC has been significantly superior to hsCRP in predicting events among those with LDL <130 mg/dl.
5. One must acknowledge that it is difficult to prevent events if they rarely occur. We demonstrated that nearly 50% of patients fitting JUPITER criteria have no CAC, and experience an extremely low event rate of ~1 per 1,000 patient-years (~1% 10-year event rate). Within this specific cohort (n = 444), no one suffered a myocardial infarction or cardiovascular death (hard event), and only 2 had soft coronary heart disease events in 6 years of follow-up (4).
6. In our estimate, even if statins could prevent every event in this population, the 5-year NNT would still be over 200 (4). Based on this undeniably strong evidence of excellent prognosis for those with CAC = 0, would the critics still argue that the majority of the event reductions in JUPITER would occur in those with CAC = 0 rather than the higher-risk individuals with detectable CAC, among whom the majority of events occur?

Conclusions. Detection of CAC as a measure of subclinical coronary atherosclerosis provides an integrated view of the cumulative exposure to exposure over an individual's lifetime, explaining its superior performance to individual risk factors/biomarkers measured at single time points. The unique role of CAC testing is in its "power of zero" (3–6). Since all nonspecific biomarkers, including hsCRP, cannot really rule out

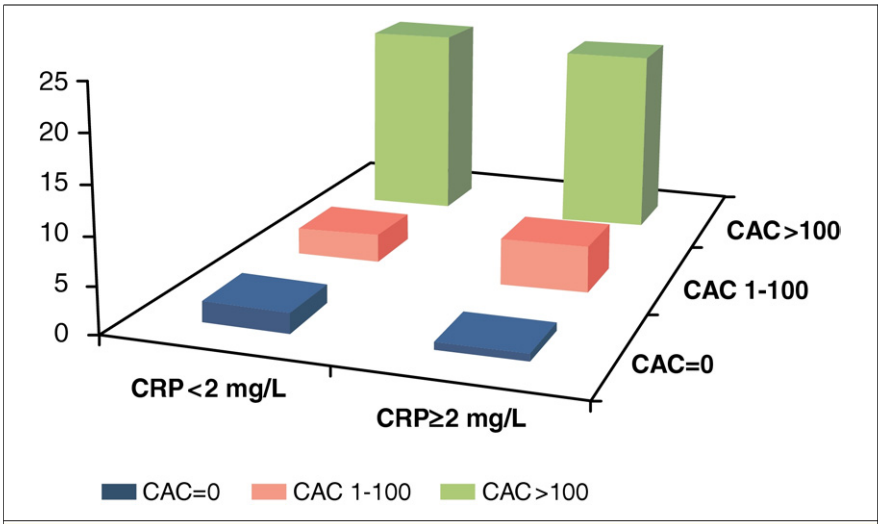

Figure 1. CHD Event Rates (Per 1,000 Person-Years)

Event rates are according to C-reactive protein (CRP) and coronary artery calcium (CAC) levels among those with low-density lipoprotein <130 mg/dl. Adapted, with permission, from Blaha et al. (4). CHD = coronary heart disease.

disease, they can only be used to raise risk estimates, and thus are inextricably tied to more treatment and downstream cost. In the current environment of rising healthcare costs and shrinking resources, we cannot afford to treat a large number of individuals to prevent few events and are obligated to prioritize how best to allocate our limited resources to reduce the overall economic healthcare cost burden. Based on clinical equipoise, current treatment strategies should be based to match one's clinical risk to limit both under- and overtreatment by using CAC to guide therapy intensity. Finally, we would like to end this debate with a question, "Would you be more reassured about a patient's prognosis if the hsCRP was below 2 mg/l or if CAC = 0?" Based on emerging data, the choice is clear.

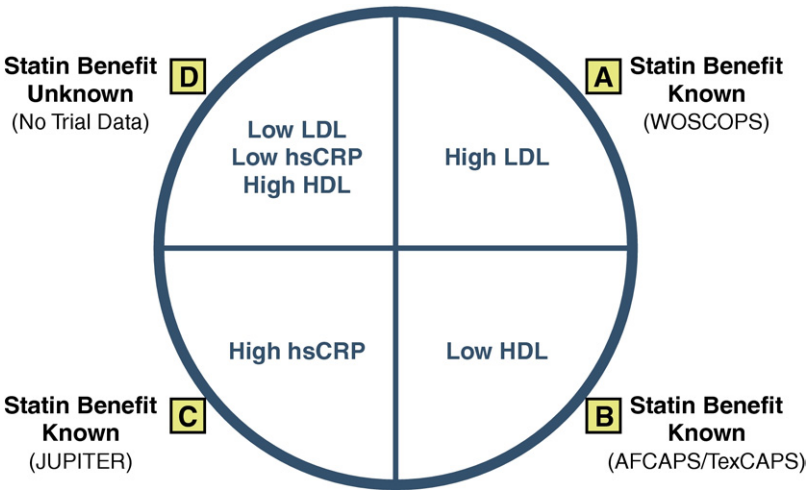

Figure 2. Evidence-Based "Screen and Treat" Strategies in the Primary Prevention of CVD

AFCAPS/TexCAPS = Airforce Texas Coronary Atherosclerosis Prevention Study; CVD = cardiovascular disease; HDL = high-density lipoprotein; JUPITER = Justification for Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin; LDL = low-density lipoprotein; WOSCOPS = West of Scotland Coronary Prevention Study.

CAC Scanning for Primary Prevention: Cons

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IN PRIMARY PREVENTION, IT IS NOT SUFFICIENT TO ORDER A SCREENING TEST simply because it improves risk prediction. The screening test must also lead to a specific risk-lowering intervention that the patient would otherwise not receive. Since all patients should receive advice on exercise, smoking cessation, and dietary discretion, the main reason to order a screening test for cardiovascular risk assessment in primary prevention is to ascertain who will benefit from statin therapy.

What is known from randomized trials for "screen and treat" statin strategies based on simple blood biomarkers such as LDL cholesterol, HDL cholesterol, and hsCRP? And for comparison, what is known for "screen and treat" statin strategies based on CAC in the setting of primary prevention?

First, if LDL cholesterol is high (Fig. 2, Quadrant A), physicians can reliably prescribe statin therapy to reduce cardiovascular risk. As demonstrated in the randomized, double-blind, placebo-controlled WOSCOPS (West of Scotland Coronary Prevention Study) trial (10), random allocation to pravastatin among those with elevated LDL cholesterol reduced rates of first coronary events by 31% (95% confidence interval [CI]: 17 to 43).

Second, if HDL cholesterol is low (Fig. 2, Quadrant B), physicians can also reliably prescribe statin therapy to reduce cardiovascular risk. This finding was demonstrated clearly in the AFCAPS/TexCAPS (Airforce Texas Coronary Atherosclerosis Prevention Study) trial (11) in which random allocation to lovastatin among those with low HDL cholesterol reduced rates of first coronary events by 37% (95% CI: 21 to 50).

Third, if hsCRP is high (Fig. 2, Quadrant C), physicians can further reliably prescribe statin therapy to reduce cardiovascular risk even if the patient already has a low LDL cholesterol level. This is the fundamental finding of the JUPITER trial (12), where rosuvastatin reduced the risk of vascular events by 44% (95% CI: 31 to 54) among men and women with hsCRP >2 mg/l who had levels of LDL cholesterol <130 mg/dl.

Thus, among primary prevention patients screened for elevated LDL cholesterol (Quadrant A), low HDL (Quadrant B), or elevated hsCRP (Quadrant C), the clinical community already has hard trial evidence that providing statin therapy (an intervention the patient otherwise would not receive) significantly reduces cardiovascular event rates. As statins are both cost effective and low risk, there is no reason to withhold treatment from patients where a "screen and treat" strategy has proven effective,

unless a clinical contraindication is present. Further, for patients in Quadrants A, B, or C of Figure 2 who already have an indication for statin therapy, there is no current reason to obtain a CAC scan, particularly as knowledge of the CAC score does not improve statin compliance nor do statins reduce CAC. It is possible that CAC scanning might provide a mechanism to reduce the NNT for those in Quadrants A, B, and C, but this has never been formally tested.

What about patients in Quadrant D of Figure 2 who have low LDL cholesterol, high HDL cholesterol, and low hsCRP? This group includes apparently healthy men and women at low absolute cardiovascular risk, almost all of whom have 10-year Framingham or Reynolds estimated risks well below 10%.

Is there any evidence that individuals in Quadrant D benefit from statin therapy? Regrettably, there is not.

Does CAC identify higher-risk individuals in this group? Perhaps, but most studies to date have not focused here and include instead the many primary prevention patients in Quadrants A, B, and C, who already have an indication for therapy. But even if we knew with clarity that CAC does identify higher risk among those with low LDL cholesterol, high HDL cholesterol, and low hsCRP, we still would not know without randomized trial evidence that this group preferentially benefits from statin treatment.

In fact, as clinical trials have repeatedly shown, physicians cannot assume efficacy for statins in any unstudied patient group. Consider, for example, that 4 major trials of statin therapy—AURORA (A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events), CORONA (Controlled Rosuvastatin in Multinational Trial in Heart Failure), 4D (Deutsche Diabetes Dialyse Studie), and GISSI-HF (GISSI-HF–Effects of n-3 PUFA and Rosuvastatin on Mortality-Morbidity of Patients With Symptomatic CHF) (13–16)—all failed to demonstrate benefits of treatment when compared with placebo. Data from these trials are particularly relevant to the imaging community since each enrolled high-risk patients with considerable underlying atherosclerosis, and thus represent patient groups likely to have high CAC scores. So at least for now, it is impossible to make an argument that the presence of CAC guarantees a benefit from statin therapy.

Critics of CAC note that the technique requires considerable infrastructure investment, is expensive compared with simple blood biomarkers, is associated with radiation exposure, and leads to incidental radiographic findings that often necessitate further expense and repeat radiation. All of these issues are substantive, and creative work is being done by many investigators to reduce hazards through optimized imaging protocols and improved clinical decision algorithms. However, even if these other shortcomings were absent, we should not endorse CAC scanning in primary prevention without clear "screen and treat" intervention data.

It is a paradox of prevention that most individuals destined to suffer a cardiovascular event have low-to-moderate absolute risk and cholesterol levels that do not meet current thresholds for treatment. A further complexity of the prevention paradox for statins is that discordance exists between relative risk reduction and absolute risk reduction associated with these drugs. U.S. and European guidelines typically assume that as an individual's risk of a cardiovascular event increases, the relative risk reduction derived from statin therapy either increases or remains stable. However, as shown in Figure 3, there is an inverse relationship between absolute risk of a major coronary event and the relative risk reduction achieved with statin therapy. Namely, as the absolute risk of a major coronary event decreases in the trial population, the observed relative risk reduction increases.

This latter observation raises the possibility that early use of statins may be the most effective way to eliminate cardiovascular disease. Slowing the initial steps of atherogenesis and early lesion progression appears to be a major mechanism by which statins ultimately reduce event rates. However, early statin use from a biological perspective is likely to imply a time frame for initiation well before calcified plaques are present. As documented by many investigators, noncalcified and partially calcified plaques are more likely to rupture than heavily calcified plaques, and vulnerability is not easily detected by CAC alone. Thus, there is considerable controversy as to whether or not targeting statin therapy to those with CAC is a correct biological strategy. This is exactly the kind of equipoise that can be resolved in an appropriately designed clinical trial.

Geoffrey Rose noted more than 2 decades ago that treatment of a large number of people at small risk can lead to greater population benefit than an approach targeting high-risk individuals alone (17). A screening paradigm predicated on the estimation of an individual's absolute risk and treating only those who reach certain risk thresholds could overlook the potential public health impact of treating the more numerous lower-risk indi-

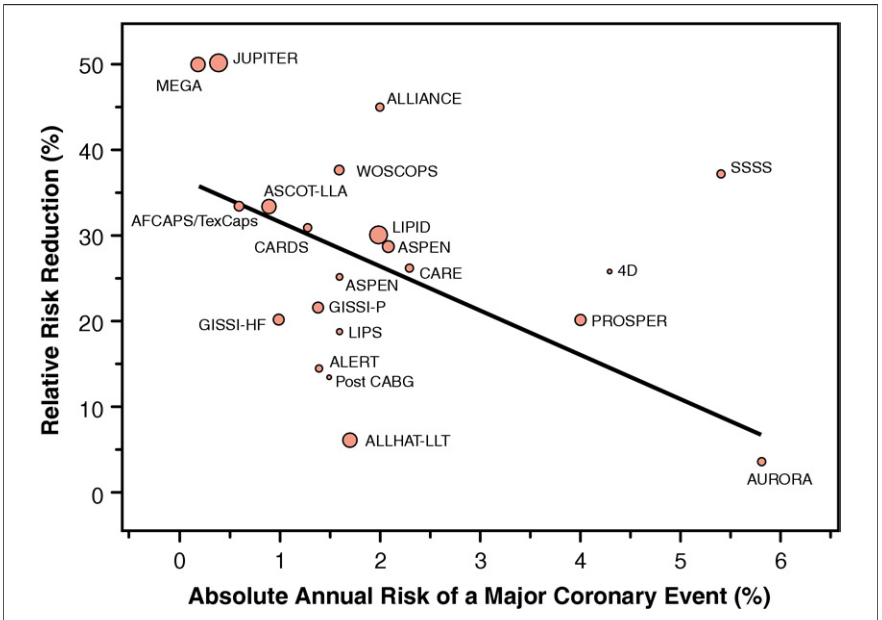

Figure 3. Observed Relative Risk Reductions in Placebo-Controlled Statin Trials as a Function of Absolute Cardiovascular Risk

The annual risk of a major coronary event in the placebo group was used to approximate the absolute risk of the trial population. Data obtained from Cholesterol Treatment Trialists Collaboration (CTT [19]). The **solid line** represents a regression fit through the data points. 4D = Deutsche Diabetes Dialyse Studie; ALERT = Assessment of Lescol in Renal Transplant; ALLHAT-LLT = Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial—Lipid-Lowering Trial; ALLIANCE = Aggressive Lipid Lowering to Alleviate New Cardiovascular Endpoints; ASCOT-LLA = Anglo-Scandinavian Cardiac Outcomes Trial—Lipid-Lowering Arm; ASPEN = Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus; AURORA = A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events; CARDS = Collaborative Atorvastatin Diabetes Study; CARE = Cholesterol and Recurrent Events; GISSI-HF = GISSI-HF–Effects of n-3 PUFA and Rosuvastatin on Mortality-Morbidity of Patients With Symptomatic CHF; GISSI-P = GISSI-Prevenzione; LIPID = Long-Term Intervention with Pravastatin in Ischaemic Disease; LIPS = Lescol Intervention Prevention Study; MEGA = Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese; Post CABG = Post Coronary Artery Bypass Graft; PROSPER = Prospective Study of Pravastatin in the Elderly at Risk; SSSS = Scandinavian Simvastatin Survival Study; other abbreviations as in Figure 2.

viduals who contribute a significant burden of disease. If, as described in Figure 3, the relationship between absolute risk and relative risk reduction is inverse for statins, the potential public health impact of an approach targeting lower-risk individuals may be even greater than Rose might have conceived in the classic "prevention paradox."

What then might an appropriate randomized trial designed to objectively evaluate the potential for CAC scanning in primary prevention look like? First, we would start with those in Quadrant D of Figure 2. Individuals with low LDL cholesterol, high HDL cholesterol, and low hsCRP do not have a current indication for statin therapy, and no trial being conducted at this time includes such individuals. Thus, there would be no threat of "drop in" in the placebo group if this group were enrolled.

Second, we would randomize all participants in a 1:1 manner between statin and placebo, preferably using a potent generic statin at a fixed dose. All participants would then be followed over an approximate 5-year period for major incident cardiovascular events.

Third, all participants would undergo a blind baseline CAC scan prior to randomization. The data from this baseline scan would only come into play after the trial was complete and would be used in a set of pre-specified analyses to address formally whether any effects of statin therapy overall are modified by the underlying extent of calcification at study entry. Such a simple trial design avoids the pitfalls associated with using the baseline CAC score to dictate subsequent therapy, a problematic clinical trial strategy that can introduce investigator bias and has the potential to deliver a self-fulfilling outcome.

There are several possible results from such a trial, all of which would be informative for patient care. One possible outcome is that statin therapy proves to be highly effective for all participants, in which case the trial would demonstrate little need for any screening test at all. Such an outcome would be important for public health and move the field closer to a "simply treat" strategy that would obviate the need for LDL, HDL, hsCRP, and CAC testing altogether.

A second potential outcome is that statin therapy proves effective, but has far greater efficacy among those with high as compared with low CAC scores. In this case, there would be much smaller NNT values for those with high CAC values, and CAC would be seen as a potentially important method to cost-effectively target statin therapy in the general population.

A third potential outcome is that among those with low LDL, high HDL, and low hsCRP, statin therapy proves to be ineffective. This is not an impossible outcome; in the AFCAPS/TexCAPS trial, those with low LDL cholesterol and low hsCRP did not achieve any benefit from statin ther-

apy in terms of clinical event reduction despite large reductions in LDL cholesterol (18). Such a result would provide a clear demonstration that Quadrant D individuals should not be treated with statin therapy, again a major finding of considerable public health importance.

A critical issue in the design of this proposed trial is that it is unbiased for or against imaging and thus, after a 5-year period, we would finally know whether the correct answer to Geoffrey Rose's paradox is to treat all patients without screening or to treat a few patients with screening. Such a trial could be coordinated by the National Heart, Lung, and Blood Institute, with costs borne by the imaging industry, the stakeholder who stands to benefit the most financially from a positive outcome.

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