Associations between C-reactive protein, coronary artery calcium, and cardiovascular events: implications for the JUPITER population from MESA, a population-based cohort study

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Summary

Background The JUPITER trial showed that some patients with LDL-cholesterol concentrations less than 3·37 mmol/L (<130 mg/dL) and high-sensitivity C-reactive protein (hsCRP) concentrations of 2 mg/L or more benefit from treatment with rosuvastatin, although absolute rates of cardiovascular events were low. In a population eligible for JUPITER, we established whether coronary artery calcium (CAC) might further stratify risk; additionally we compared hsCRP with CAC for risk prediction across the range of low and high hsCRP values.

Methods 950 participants from the Multi-Ethnic Study of Atheroslcerosis (MESA) met all criteria for JUPITER entry. We compared coronary heart disease and cardiovascular disease event rates and multivariable-adjusted hazard ratios after stratifying by burden of CAC (scores of 0, 1–100, or >100). We calculated 5-year number needed to treat (NNT) by applying the benefit recorded in JUPITER to the event rates within each CAC strata.

Findings Median follow-up was 5·8 years (IQR 5·7–5·9). 444 (47%) patients in the MESA JUPITER population had CAC scores of 0 and, in this group, rates of coronary heart disease events were 0·8 per 1000 person-years. 74% of all coronary events were in the 239 (25%) of participants with CAC scores of more than 100 (20·2 per 1000 person-years). For coronary heart disease, the predicted 5-year NNT was 549 for CAC score 0, 94 for scores 1–100, and 24 for scores greater than 100. For cardiovascular disease, the NNT was 124, 54, and 19. In the total study population, presence of CAC was associated with a hazard ratio of 4·29 (95% CI 1·99–9·25) for coronary heart disease, and of 2·57 (1·48–4·48) for cardiovascular disease. hsCRP was not associated with either disease after multivariable adjustment.

Interpretation CAC seems to further stratify risk in patients eligible for JUPITER, and could be used to target subgroups of patients who are expected to derive the most, and the least, absolute benefit from statin treatment. Focusing of treatment on the subset of individuals with measurable atherosclerosis could allow for more appropriate allocation of resources.

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Introduction

Findings from landmark clinical trials[1–3] have led to progressive liberalisation of statin use for primary prevention of cardiovascular disease. The JUPITER trial[4] led to further liberalisation by showing that some patients with normal concentrations of LDL cholesterol (ie, <3·37 mmol/L) and high-sensitivity C-reactive protein (hsCRP) (≥2 mg/L) benefit from treatment with rosuvastatin. Unfortunately, because modern statin trials enrol low-risk populations, even large reductions in relative risk result in only small reductions in absolute risk. Thus, many patients who are newly eligible for statins will not accrue a net benefit from treatment. Personalised assessment of cardiovascular risk is still needed.

Coronary artery calcium (CAC) detected by cardiac CT estimates the burden of coronary atherosclerosis and is effective for further stratification of risk in patients who are asymptomatic.[5] The absence of CAC in an asymptomatic adult nearly excludes clinically important coronary atherosclerosis, and is associated with a mortality rate of about 1% in 10 years.[6,7] By contrast, substantially increased CAC is associated with a rise of almost ten times in risk of adverse coronary events after multivariable adjustment.[8] Furthermore, CAC can improve the classification of patients into appropriate risk groups for clinical decision making.[9]

We sought to establish whether tests for CAC could identify a subgroup of patients eligible for JUPITER who would be expected to derive the most or the least benefit from statin treatment. In view of estimates based on findings from JUPITER that 6·5 million individuals in the USA would be newly eligible for statins,[10] these results have important implications for guidelines and public health discussions aimed at improving the efficiency and cost-effectiveness of statin use in primary prevention.

Furthermore, we aimed to directly compare CAC with hsCRP as additional markers to identify risk in individuals eligible for JUPITER, independent of hsCRP inclusion criteria. Such comparative-effectiveness analyses examining the incremental predictive value of tests in their intended target populations are crucial for their appropriate use.

Methods

Study design and patients

The Multi-Ethnic Study of Atherosclerosis (MESA)—a population-based, prospective cohort study—describes the prevalence, progression, and clinical significance of subclinical atherosclerosis. Full details of the MESA study design have been previously published.[11] Between July, 2000, and September, 2002, MESA enrolled 6814 individuals at six field centres in the USA (Baltimore; Chicago; Forsyth County, North Carolina; Los Angeles; New York; and St Paul, Minnesota). Participants had to be aged between 45 and 84 years, and have no known clinical cardiovascular disease at enrolment. Participants were recruited at each site from lists of residents, dwellings, and telephone companies, with emphasis on neighbourhoods that show the ethnic diversity of the USA. From baseline data[11] we identified 2083 (31%) participants in MESA who fit specific inclusion criteria for JUPITER: aged 50 years and older for men and 60 years and older for women, LDL cholesterol less than 3·37 mmol/L, not on lipid-lowering therapy, free of diabetes, triglycerides less than 5·65 mmol/L, and creatinine less than 176·8 μmol/L (figure 1). Of these participants, 950 (46%) had high hsCRP (≥2 mg/L) and were thus eligible for JUPITER (MESA JUPITER population, figure 1).

Procedures

Cardiac CT was done at three centres with a cardiac-gated electron-beam CT scanner, and at three centres with four-slice multidetector CT. Patients were scanned twice, with CAC (Agatston) scores averaged. Images were interpreted at the MESA CT reading centre (Harbor-University of California, Los Angeles, CA, USA). Carr and colleagues[12] have reported details of the methods used by MESA for CT scanning and interpretation. The K statistic for agreement of presence of CAC was 0·92, and the percentage for mean rescan absolute difference in CAC was 20·1% in those with a CAC score greater than 0.

As part of the baseline examination, clinical teams at each of the six centres collected information about cardiovascular risk factors. A central laboratory (University of Vermont, Burlington, VT, USA) measured concentrations of total and HDL cholesterol, triglycerides, plasma glucose, and hsCRP after a 12-h fast. hsCRP was determined by Behring nephelometer-2 (N High Sensitivity CRP; Dade Behring Inc, Deerfield, IL, USA). The lower limit of detection was 0·17 mg/L.

New occurrences of coronary heart disease and cardiovascular disease were recorded over a median follow-up of 5·8 years (IQR 5·7–5·9). At intervals of 9–12 months, an interviewer contacted each participant or a family member about interim hospital admissions, outpatient diagnoses of coronary heart disease and cardiovascular diseases, and deaths. MESA successfully obtained medical records for about 98% of hospitalised events and information about 95% of outpatient cardiovascular diagnoses. Follow-up telephone interviews were completed in 92% of living participants. Two physicians from the MESA mortality and morbidity review committee independently classified events; in the event of disagreement, the full committee adjudicated. Events of coronary heart disease were myocardial infarction, death from coronary heart disease, definite angina, probable angina resulting in revascularisation, or resuscitated cardiac arrest. Cardiovascular events were coronary heart disease events plus stroke (not transient ischaemic attack), stroke death, other atherosclerotic death, or other cardiovascular death. Full details of the MESA follow-up methods, investigators, and institutions are available at the MESA website.

Statistical analysis

Baseline characteristics of the 2083 study participants were analysed in accordance with hsCRP status (low [<2 mg/L] or high [≥2 mg/L]). Frequencies and
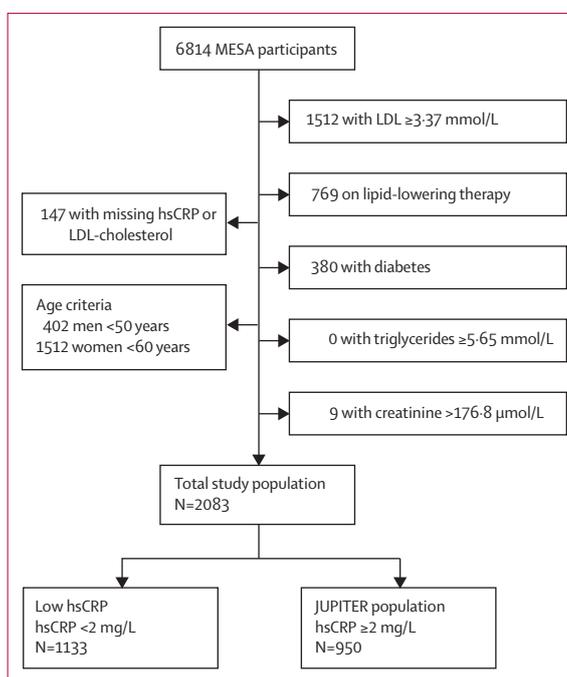
Figure 1: Trial profile
The MESA JUPITER population was used to test the ability of coronary artery calcium (CAC) to stratify risk in the population eligible for JUPITER. The total study population was used to test the relative predictive value of CAC and high-sensitivity C-reactive protein (hsCRP).

proportions were calculated for categorical variables, and either means with SDs or medians with IQRs were calculated for continuous variables. We used Kaplan-Meier estimates of cumulative event-free survival to describe the occurrence of events of coronary heart disease and cardiovascular disease over time. To establish whether CAC could further stratify risk in the JUPITER population, we compared absolute event rates of both diseases, and Cox multivariable-adjusted hazard

ratios, after stratification by presence and burden of CAC. Models were adjusted for age, sex, race and ethnic origin, hypertension, whether the patient smoked, body-mass index, HDL cholesterol, use of an antihypertensive drug, family history of myocardial infarction, level of education (a measure of socioeconomic status), and MESA centre. To assess the relative predictive power of hsCRP versus CAC, we compared absolute event rates of coronary heart disease and cardiovascular disease stratified by hsCRP and CAC status in the total study population. We also tested for interaction and effect modification between hsCRP and CAC.

We calculated 5-year number needed to treat (NNT) for both coronary heart disease and cardiovascular disease by applying the hazard ratio (HR) associated with rosuvastatin treatment in the JUPITER trial (HR 0·56, 95% CI 0·46–0·69, p<0·0001) to the event rates within each CAC strata. For this analysis, NNT were directly calculated as the reciprocal of the difference in absolute risk at median follow-up (5·8 years), on the basis of Kaplan-Meier estimates, and then adjusted to a 5-year NNT with the Altman and Anderson method.[13] Sensitivity analyses were done with the upper and lower limits of the HR from JUPITER.

Role of the funding source

National Institutes of Health (NIH) funded the overall MESA project. A group of individual investigators proposed and undertook the present study. NIH-sponsored MESA committees reviewed and approved the proposal, abstract, and manuscript from the present study. All authors had full access to the data and jointly decided to submit for publication.

Results

Median age of the total study population (N=2083) was 67 years (IQR 61–73). Overall, 835 (40%) were women, with mean calculated 10-year Framingham risk of 9·7% (SD 7). Median hsCRP of the total study population was 1·8 mg/L (IQR 0·78–4·0). 1133 (54%) participants had hsCRP less than 2 mg/L, and 950 (46%) had hsCRP 2 mg/L or more (MESA JUPITER population). Individuals in the MESA JUPITER subgroup were more likely to be women and either African-American or Hispanic, with

	Total population (N=2083)	hsCRP <2 mg/L (N=1133)	JUPITER population hsCRP ≥2 mg/L (N=950)	p value
Age (years)	66·5 (9)	66·3 (9)	66·7 (8)	0·30
Sex				<0·0001
Female	835 (40%)	349 (31%)	486 (51%)	
Race				0·0001
White	853 (41%)	465 (41%)	388 (31%)	
Chinese	276 (13%)	229 (20%)	47 (5%)	
African-American	552 (27%)	257 (23%)	295 (31%)	
Hispanic	402 (19%)	182 (16%)	220 (23%)	
BMI (kg/m²)	27·4 (5)	26·0 (4)	29·1 (5)	<0·0001
Systolic blood pressure (mm Hg)	129 (22)	127 (22)	130 (21)	0·005
Diastolic blood pressure (mm Hg)	72 (10)	73·0 (10)	71·6 (11)	0·004
Hypertension	972 (47%)	469 (41%)	503 (53%)	<0·0001
Fasting glucose (mmol/L)	5·4 (10)	5·3 (9)	5·4 (10)	0·005
Creatinine (μmol/L)	74·7 (0·2)	74·7 (0·2)	74·0 (0·2)	0·17
Smoking				0·0001
Former	(41%)	(40%)	(43%)	
Current	(12%)	(9%)	(14%)	
LDL cholesterol (mmol/L)	2·64 (19)	2·67 (19)	2·64 (20)	0·48
HDL cholesterol (mmol/L)	1·35 (16)	1·35 (16)	1·35 (17)	0·77
Triglycerides (mmol/L)	1·15 (72–151)	1·20 (69–141)	1·23 (77–160)	<0·0001
Family history of heart attack	(40%)	(38%)	(43%)	0·03
Drugs for hypertension	(37%)	(32%)	(42%)	<0·0001
Education, completed HS or GED	(83%)	(86%)	(80%)	0·0004
hsCRP (mg/L)	1·77 (0·78–3·99)	0·85 (0·52–1·32)	4·26 (2·96–7·77)	<0·0001
10-year FRS (%)	9·7 (7)	10·1 (7)	9·2 (7)	0·003

Data are mean (SD), number (%), or median (IQR). hsCRP=high-sensitivity C-reactive protein. BMI=body-mass index. HS=high school. GED=general educational development. FRS=Framingham risk score.

Table 1: Baseline characteristics

	N (%)	CHD events			CVD events		
		CHD events (%)	Event rate (per 1000 person-years)	Hazard ratio (95% CI)	CVD events (%)	Event rate (per 1000 person-years)	Hazard ratio (95% CI)
CAC 0	444 (47%)	2 (0·5%)	0·8	1* (ref)	9 (2·0%)	3·7	1* (ref)
CAC 1–100	267 (28%)	7 (2·6%)	4·8	4·91 (0·97–24·9)	12 (4·5%)	8·4	1·86 (0·73–4·76)
CAC >100	239 (25%)	25 (10·6%)	20·2	27·8 (5·97–129·8)	32 (13·4%)	26·4	6·16 (2·51–15·1)
Any CAC present	506 (53%)	32 (6·3%)	11·0	11·0 (2·51–48·5)	44 (8·7%)	16·6	3·20 (1·41–7·24)

Adjusted for age, sex, race, hypertension, cigarette smoking, body-mass index, HDL cholesterol, use of antihypertensive drug, family history of CHD, socioeconomic status, and MESA site. CHD=coronary heart disease. CVD=cardiovascular disease. CAC=coronary artery calcium. *Hazard ratios of 1 were used as a reference.

Table 2: CHD and CVD events by CAC status in the MESA population eligible for JUPITER

more features of the metabolic syndrome than those with hsCRP less than 2 mg/L (table 1).

The MESA JUPITER population closely resembled the placebo group in the JUPITER trial (webappendix p 2). Median age of patients in the JUPITER placebo group was 66 years (IQR 60–71), mean calculated 10-year Framingham risk of 10%, and median hsCRP was 4·3 mg/L (IQR 3·0–7·8). The MESA JUPITER population had more women than the JUPITER population (51% *vs* 38%) because of its population-based recruitment with similar initial enrolment by gender, coupled with the higher concentrations of hsCRP in women.

444 (47%) patients in the MESA JUPITER population had a CAC score of 0. Of those with CAC, 267 (28%) had scores 1–100, and 239 (25%) had scores more than 100. The number needed to scan to identify one individual with a CAC score of 0 was 2, and to identify one individual with a CAC score more than 100 was 4. The frequency of increased CAC burden was similar in the low hsCRP group (p=0·09, webappendix pp 3–6). Prevalence of CAC differed according to sex. 259 (53%) women had a CAC score of 0 compared with 185 (40%) men, and 97 (20%) of women had a score of more than 100 compared with 142 (31%) men.

Table 2 shows the frequency of cardiovascular disease events and coronary heart disease events, the corresponding event rates per 1000 person-years, and the multivariable-adjusted HRs associated with prevalence and burden of CAC in MESA JUPITER participants. Event rates for coronary heart disease and cardiovascular disease were low when CAC scores were 0 and high when CAC scores were more than 100 (table 2). Only 6% of all coronary heart disease events and 17% of all cardiovascular disease events were in the individuals with scores of 0 (table 2). Almost 75% of all coronary heart disease events, and about 60% of all events of cardiovascular disease, were in the 25% of participants with scores more than 100 (table 2).

The presence of CAC was associated with an HR of 11·0 (95% CI 2·51–48·5) for coronary heart disease, and 3·20 (1·41–7·24) for cardiovascular disease in the MESA JUPITER population in the fully adjusted model. We noted a graded increase in events for both diseases with increasing burden of CAC (table 2).

Figure 2 shows Kaplan-Meier estimates of event-free survival for coronary heart disease and cardiovascular disease for the MESA JUPITER population by CAC burden. Table 3 shows the Kaplan-Meier failure (event) function. From these estimates, the 5-year NNT to prevent an event of coronary heart disease was 549 for CAC score 0, 94 for scores 1–100, and 24 for scores more than 100. The corresponding 5-year NNT to prevent an event of cardiovascular disease was 124, 54, and 19, respectively (table 3). Webappendix p 1 shows the results of the sensitivity analysis.

In the total study population, overall event rates were similar in the low (<2 mg/L) and high (≥2 mg/L) hsCRP

groups for coronary heart disease (7·6 *vs* 6·4 per 1000 person-years, p=0·47) as were event rates for cardiovascular disease (10·1 *vs* 10·4 per 1000 person-years, p=0·87). Figure 3 shows Kaplan-Meier plots stratified by hsCRP status. hsCRP status did not predict coronary heart disease events (HR 0·98, 95% CI 0·62–1·57) or cardiovascular disease events (1·15, 0·78–1·68) after adjustments for age, sex, and race. By contrast, presence of CAC was a strong predictor of both coronary heart disease (6·65, 2·99–14·78) and cardiovascular disease (3·06, 1·82–5·13) in similarly adjusted models. CAC prevalence and increased CAC burden were significant predictors of events after full multivariable adjustment (table 4).
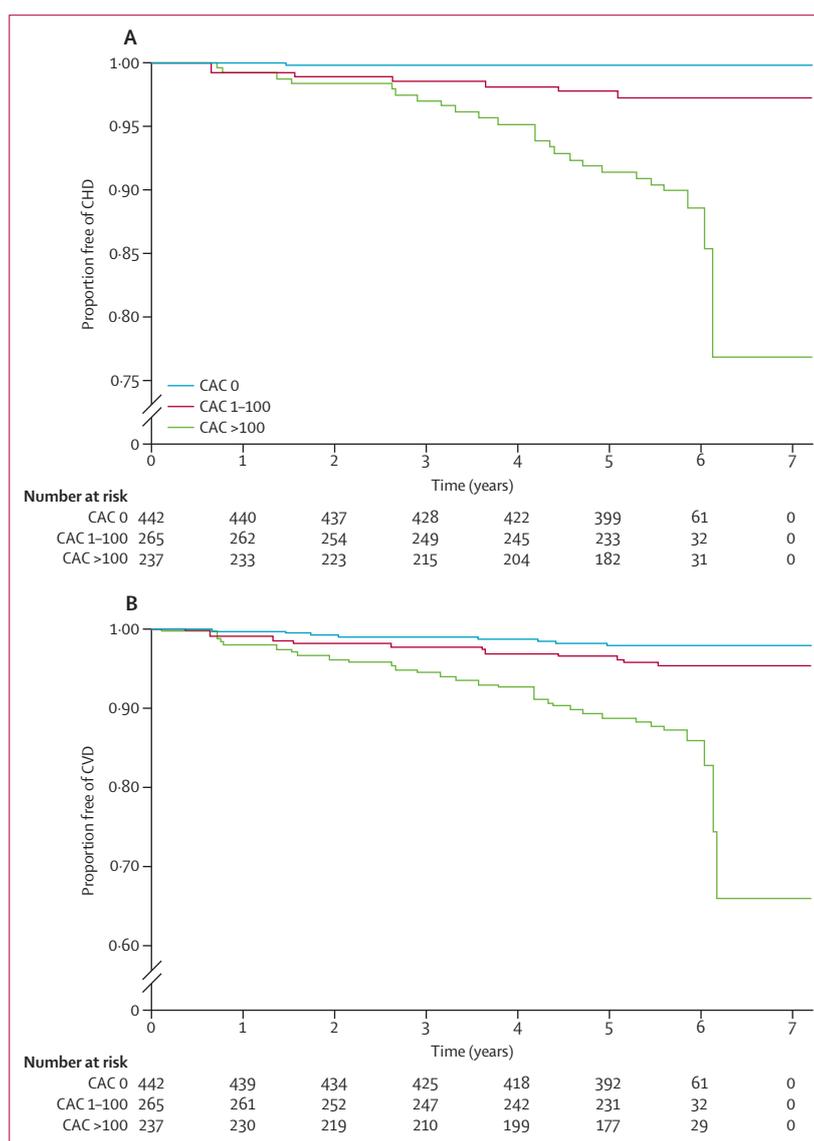
***Figure 2*: Kaplan-Meier estimates of CHD (A) and CVD (B) event-free survival by CAC burden in the MESA JUPITER population**
CHD=coronary heart disease. CAC=coronary artery calcium. CVD=cardiovascular disease.

	Estimated rate of CHD events at 5·8 years	Estimated rate of CVD events at 5·8 years	5-year NNT for CHD	5-year NNT for CVD
CAC 0	0·48%	2·12%	549	124
CAC 1–100	2·79%	4·86%	94	54
CAC >100	10·76%	13·65%	24	19
Any CAC present	6·22%	8·87%	42	30

NNT were calculated directly as the reciprocal of the absolute risk difference at median follow-up of the cohort (5·8 years), based on Kaplan-Meier estimates, and then adjusted to a 5-year NNT with the Altman-Anderson method.[13] Webappendix p 1 shows results of the sensitivity analysis using the hazard ratio CIs from JUPITER. CHD=coronary heart disease. CVD=cardiovascular disease. NNT=number needed to treat. CAC=coronary artery calcium.

Table 3: **Estimated 5-year NNT to prevent an event of CHD or CVD, by CAC burden in population eligible for JUPITER**

	CHD events		CVD events	
	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
hsCRP <2 mg/L	1*	..	1*	..
hsCRP ≥2 mg/L	0·90 (0·54–1·50)	0·69	1·08 (0·71–1·64)	0·73
CAC 0	1*	..	1*	..
CAC 1–100	1·66 (0·65–4·25)	0·29	1·46 (0·75–2·81)	0·26
CAC >100	9·35 (4·15–21·1)	<0·0001	4·41 (2·42–8·04)	<0·0001
Any CAC present	4·29 (1·99–9·25)	<0·0001	2·57 (1·48–4·48)	0·001

We noted no evidence of interaction between hsCRP status and CAC burden (p=0·71). Adjusted for age, sex, race, hypertension, cigarette smoking, body-mass index, HDL cholesterol, use of antihypertensive drug, family history of CHD, socioeconomic status, and MESA site. No change in the model was noted (ie, no residual confounding) with adjustments for LDL cholesterol. CHD=coronary heart disease. CVD=cardiovascular disease. hsCRP=high-sensitivity C-reactive protein. CAC=coronary artery calcium. *Hazard ratios of 1 were used as a reference level.

Table 4: **CAC versus hsCRP for risk prediction in patients eligible for JUPITER**

A

Number at risk
Low hsCRP	1128	1113	1077	1050	1027	965	137	0
High hsCRP	944	935	914	892	871	814	124	0

B

Number at risk
Low hsCRP	1128	1110	1071	1043	1020	959	137	0
High hsCRP	944	930	905	882	859	800	122	0
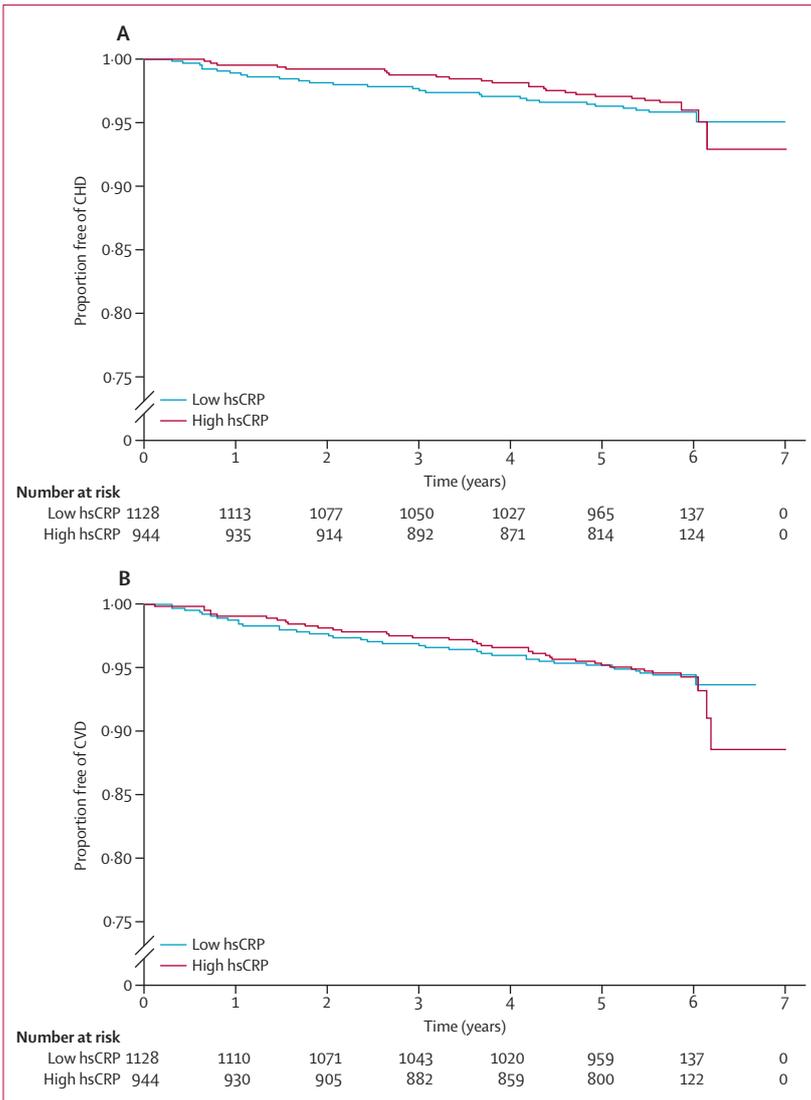
Figure 3: **Kaplan-Meier estimates of CHD (A) and CVD (B) event-free survival by hsCRP status in the total study population**
Event-free survival did not differ by hsCRP status (log-rank test, p=0·55 for CHD events; p=0·87 for CVD events). CHD=coronary heart disease. CVD=cardiovascular disease. hsCRP=high-sensitivity C-reactive protein.

Increased CAC burden led to similar increases in absolute coronary heart disease and cardiovascular disease events in both the low and high hsCRP groups (figure 4). We recorded no evidence of interaction between hsCRP status and CAC burden (p=0·71), or of residual confounding with hsCRP with use of dichotomised hsCRP status (low and high). Median hsCRP in the MESA JUPITER population was 4·54 mg/L (IQR 2·77–10·6) with cardiovascular disease events and 4·25 mg/L without (2·96–7·71, p=0·61). Median hsCRP in the total study population was 1·73 mg/L (IQR 0·84–4·15) in participants with cardiovascular disease events, and 1·78 mg/L (0·78–3·98) in those without events (p=0·67). 48 (68%) of the 71 coronary heart disease events were classed as so-called hard coronary heart disease events (myocardial infarction, resuscitated cardiac arrest, or death from coronary heart disease), and 79 (67%) of 118 cardiovascular disease events (hard coronary heart disease events plus stroke [not transient ischaemic attack] or stroke death). No differences were recorded in the predictive value of CAC or hsCRP when hard events were substituted for all coronary heart disease or cardiovascular disease events (data not shown).

Discussion

As statin use is extended to low-risk populations, accurate assessment of absolute risk becomes crucial to measure the net value of treatment. Our findings show that nearly half of the MESA JUPITER population had no CAC, had a very low event rate, and an unfavourable estimated 5-year NNT of 549 to prevent one coronary heart disease event. By contrast, most coronary heart disease events (74%) were in the small (25%) group of MESA JUPITER patients

with CAC scores greater than 100. With these scores, the estimated 5-year NNT was small at 24 for coronary heart disease and 19 for cardiovascular disease. These results have important implications for future guidelines and public health discussions aimed at improving the efficiency of statin use in primary prevention (panel).

Current guidelines for primary prevention lend support to the use of statins to treat increased cholesterol in individuals deemed high risk by traditional risk scoring. Future guidelines might incorporate the recommendation for statin treatment in patients with normal cholesterol who are at increased risk because of another risk factor or biomarker (such as hsCRP). In view of our results, CAC should be strongly considered in these patients; this supports the IIA recommendation for CAC screening in the updated American Heart Association guidelines for testing in adults who are asymptomatic.[17]

Because of the inflammatory hypothesis of athero-thrombosis, increased hsCRP might provide a mechanistic link to individuals who will receive the greatest benefit from statins.[18] Without a biomarker control group of individuals with hsCRP concentrations less than 2 mg/L in JUPITER, whether such low hsCRP patients would have similarly benefited is impossible to determine. Secondary analyses from JUPITER have shown that the reduction in relative risk with rosuvastatin was remarkably consistent, and not graded, across increased concentrations of hsCRP.[19] Secondary analysis of the Heart Protection Study showed that statins achieve a similar relative risk reduction at all concentrations of hsCRP, including in patients with low hsCRP.[20] Therefore, the benefit of hsCRP testing seems to rely solely on its generally consistent association with slightly increased absolute risk, and thus anticipated high absolute benefit from treatment.[19]

We noted that the presence of CAC identifies both absolute and relative risk of coronary heart disease over a much wider range than an hsCRP of greater than or equal to 2 mg/L. Although CAC predicts cardiovascular disease—including stroke—less strongly than it does coronary heart disease, it is still better than use of hsCRP (2·57 vs 1·08 in fully adjusted models). Our finding that hsCRP does not effectively identify risk has been noted in other studies,[21] but is in contrast to the moderate independent predictive value of hsCRP in the largest meta-analysis (relative risk 1·63, adjusted for sex and age).[14] Reasons for the failure of hsCRP to predict risk in MESA might include the various ethnic origins of patients in the cohort and the use of the fixed JUPITER cutoff of 2 mg/L, which does not account for the highly different distributions of hsCRP across sex and race in a highly diverse population.

CAC has both advantages and disadvantages compared with hsCRP. CAC is a direct measure of the burden of atherosclerosis—the precursor lesion for most coronary heart disease events—and is best regarded a measure of disease rather than a risk factor. Indeed, the progression
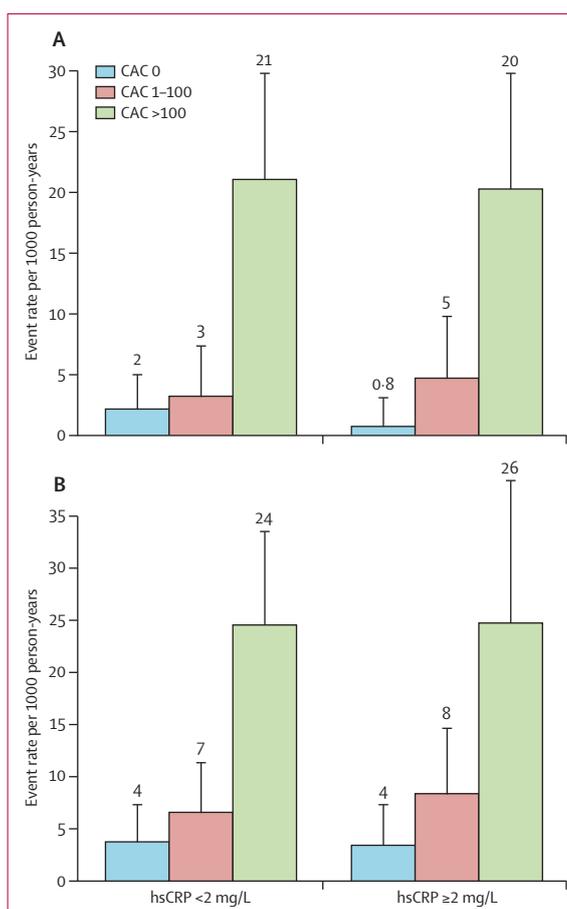
Figure 4: Absolute rates of CHD (A) and CVD (B) events CAC burden, stratified by hsCRP status
Error bars show the 95% CI for the incidence rate. CHD=coronary heart disease. hsCRP=high-sensitivity C-reactive protein. CAC=coronary artery calcium. CVD=cardiovascular disease.

of CAC is a strong predictor of mortality.[22] Another advantage is the small variability when the measurement is repeated.[23] Additionally, CAC has consistent thresholds of risk in different populations,[8] whereas hsCRP varies greatly by sex and ethnic origin, with few data for variations in risk thresholds.[24,25] Although a disadvantage of CAC is radiation exposure (the average measured dose of radiation was 0·89 mSv in MESA), the dose with modern technology is low (0·5–1·5 mSv compared with background radiation of 3 mSv per year). Furthermore, incidental non-cardiac findings, such as lung nodules more than 4–6 mm in diameter, generally lead to referral for imaging follow-up at 6–12 months, despite no proven mortality benefit for this follow-up. CAC is more expensive than hsCRP testing; however, many metropolitan areas in the USA charge less than US$100 for CAC testing. Although hsCRP has possible value in monitoring the potency of the effect of statin treatment,[26] no data or biologically plausible mechanisms are available to suggest that statins reduce CAC.[27]

Systematic review

Searches of PubMed and Google Scholar for articles published from 2000 to 2011, supplemented by hand searches of reference lists of review articles and meta-analyses, yielded high-quality summaries of the independent predictive values of coronary artery calcium (CAC) and high-sensitivity C-reactive protein (hsCRP). Methodology of these studies differs sufficiently from the present report to preclude meta-analysis.

Interpretation

The highest quality articles suggest that both CAC and hsCRP improve prediction of cardiovascular disease risk beyond global risk assessment algorithms.[8,14] Although no systematic review compares CAC with hsCRP for risk prediction, smaller studies have suggested that CAC is a stronger predictor than hsCRP.[15,16] Our study from the Multi-Ethnic Study of Atherosclerosis, which includes measurements of baseline CAC and hsCRP, and 6-year follow-up, confirms the excellent prognosis associated with CAC scores of 0, and extends this finding to the population eligible for JUPITER. Our conclusion that CAC is a stronger predictor of cardiovascular events than hsCRP is consistent with previous reports,[15,16] and we extend these findings to the population with low LDL cholesterol (<3·37 mmol/L). Our results are consistent with the hypothesis that focus of treatment on the subset of individuals who have low LDL cholesterol with measurable atherosclerosis could represent a more appropriate allocation of resources, and reduce overall health-care cost, while preventing a similar number of events.

Published work[15,16] has suggested that a combination of hsCRP and CAC might be better than use of either method alone in select patients. Park and colleagues[15] followed up 967 individuals without diabetes for a mean of 6·4 years, and showed that most risk resided with CAC, with very high hsCRP (>4·05 mg/L) providing slight improvement in incremental risk. Similarly, data from the Heinz-Nixdorf Recall study[16]—a large cohort study with a design similar to MESA—showed that improvement in prediction and discrimination of coronary risk was driven mostly by CAC, with hsCRP more than 3 mg/L (the JUPITER cutoff point of 2 mg/L was not studied) providing mild incremental improvement mainly versus hsCRP less than 1 mg/L in people with very low CAC scores. Importantly, CAC and hsCRP could identify distinct mechanisms of risk. CAC, but not hsCRP,[28] identifies overall burden of coronary atherosclerosis, although emerging data indicate that hsCRP might provide some insight into the stability of the coronary plaque.[29]

Our results have important public health implications. MESA patients with no coronary calcification who are eligible for JUPITER had a very low rate of coronary heart disease events of less than 1 per 1000 person-years, corresponding to about a 1% 10-year event rate, consistent with data showing excellent prognosis when CAC scores are 0.[6,7] Reports have suggested that asymptomatic patients with such scores can be treated to less aggressive targets, with less aggressive pharamacotherapy, emphasising low-cost lifestyle interventions.[30] The 5-year NNT to prevent one coronary heart disease event of 549 in this study when CAC is 0 seems to support a conservative strategy. Indeed, this NNT exceeds the 4-year NNT of 255 for new-onset diabetes recorded with statin use in a meta-analysis.[31]

Similar to many studies,[6,8] most events in MESA JUPITER participants were in those few with CAC scores greater than 100. The rate of 20–26 events per 1000 person-years in this group puts them within the conventional high-risk designation of more than a 20% 10-year risk. On the basis of these findings, restriction of therapy to those with scores of more than 100 (about a quarter of the JUPITER population) would result in treatment of a subgroup in whom nearly 75% of all coronary heart disease events would occur. If statin therapy were limited to those with CAC (about half the JUPITER population), treatment of a subgroup who have 95% of coronary heart disease events would occur over 6 years. Event rates in MESA (table 2) were lower than those in the JUPITER placebo group (13·6 events of cardiovascular disease per 1000 patient-years) and the ARIC JUPITER population (15·7).[32] Despite this finding, the 5-year NNT of 19 for cardiovascular disease in the MESA JUPITER population with CAC greater than 100 is lower than the overall estimate in JUPITER (5-year NNT 25, extrapolated from median follow-up of 1·9 years)[33] and in ARIC (38, adjusted from mean follow-up of 6·9 years).[32]

In the short term, a cost–benefit analysis is needed to explore the potential effect of allocation of statins guided by CAC in populations with both high (JUPITER eligible) and low hsCRP. Findings from a similar study for hsCRP[34] showed that hsCRP screening was not more cost effective than traditional risk-based allocation of statins. The EISNER study[35] suggested a potential cost saving with CAC screening, with substantially reduced downstream spending in the large group of participants with CAC scores of 0.

Many believe that a clinical trial is needed before CAC can be widely endorsed to stratify risk in adults for whom treatment decisions are unclear.[36] Such a trial could be approached in several ways. One design would aim to show overall cost savings with non-inferior clinical outcomes (increased treatment efficiency) when CAC scoring is used to allocate statin treatment. Another design would randomly assign patients to CAC screening versus traditional risk assessment, thus aiming to show a net treatment benefit when those with elevated CAC receive an additional multifaceted, dosed-intensity lifestyle and pharmacotherapy intervention. However, there are challenges to such a trial design, including cost and insufficient knowledge about key assumptions (eg, whether CAC testing would improve adherence to therapies).[37] Another potential design, analogous to the

JUPITER study design, would be to randomly assign patients with increased CAC, but with Framingham 10-year risk estimates of coronary heart disease of less than 10% to treatment or no treatment. However, this design could be regarded as unethical in view of the strong relations between raised CAC and future cardiovascular events.

The main limitation of this analysis is the uncertainty in application of the reduction in relative risk noted in JUPITER to a separate population for the estimation of NNT. For example, whether patients with increased CAC obtain an equivalent benefit with statins compared with those with low or no CAC is unknown. The only available data are from a post-hoc analysis of the St Francis Heart Study,[38] which showed that atorvastatin 20 mg significantly lowered events in patients with CAC score more than 400, with non-significant lowering of events in those with lower scores. As such, our NNT results should be regarded as hypothesis generating. How the greater prevalence of women than men in our population affects the overall results is unclear.

In conclusion, CAC seems to further stratify risk in patients who meet eligibility criteria for JUPITER, and might be used to target a subgroup of patients expected to derive the most and the least absolute benefit from treatment. Focusing of treatment on the subset of individuals with low LDL cholesterol with measurable atherosclerosis might represent a more appropriate allocation of resources, reduce overall health-care cost, and prevent the occurrence of a similar number of events.

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