7 Thomas JD, Popovic ZB. Assessment of left ventricular function by cardiac ultrasound. *J Am Coll Cardiol* 2006; **48:** 2012–25.

8 Felker GM, Benza RL, Chandler AB, et al. Heart failure etiology and response to milrinone in decompensated heart failure: results from the OPTIME-CHF study. *J Am Coll Cardiol* 2003; **41:** 997–1003.

9 McMurray JJV. Systolic heart failure. *N Engl J Med* 2010; **362:** 228–38.

10 O'Connor CM, Starling RC, Hernandez AF, et al. Effect of nesiritide in patients with acute decompensated heart failure. *N Engl J Med* 2011; **365:** 32–43.

11 Konstam MA, Gheorghiade M, Burnett JC Jr, et al. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST outcome trial. *JAMA* 2007; **297:** 1319–31.

12 Dickstein K, Cohen-Solal A, Filippatos G, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. *Eur J Heart Fail* 2008; **10:** 933–89.

Predictive ability of coronary artery calcium and CRP

See **Articles** page 684

In the general population, less than 10% of healthy adults aged 25–74 years have no modifiable cardiovascular risk factors;[1] therefore, risk of cardiovascular disease can potentially be improved in most people. Statin therapy for lowering cholesterol is an important cornerstone of risk reduction. The absolute benefit of statin treatment increases with increasing patient risk; thus, risk stratification of asymptomatic patients is mandatory in clinical practice. Although accurate identification of future cardiovascular disease risk is difficult when overall risk is low, the Framingham risk score and other global risk scores offer a meaningful approximation.[2] Such algorithms now allow for a practical approach towards risk stratification, translating statistical data into quantification of an individual's global risk. However, many uncertainties remain: because more than 40% of individuals have an intermediate risk of 10–20% in 10 years, treatment options are restricted; the scores are best at predicting long-term risk even though substantial risk factor changes can occur over time; and levels of absolute risk differ across cultural and ethnic groups. Thus, individual risk stratification needs further improvement in asymptomatic adults.

C-reactive protein (CRP) and coronary artery calcium (CAC) are among the most thoroughly examined measures available for expanded risk stratification. CRP is an acute-phase reactant synthesised mainly in the liver. From an evolutionary perspective, the teleological function of CRP might have been as part of the innate immune system, promoting complement activation and antigen presentation.[3] Within the range of normal values, easily available and highly sensitive assays detect even small amounts of CRP, thus rendering it an attractive and sensitive biomarker of subclinical inflammation. Because atherosclerosis is an inflammatory disease, CRP has been associated with imminent activation of the disease and increased patient vulnerability (ie, the patient is at increased risk of a cardiovascular event). Therefore, a logical option was to investigate the practical applicability of this biomarker. The JUPITER trial[4] examined the effects of statin therapy in patients with no clinical cardiovascular disease, and with LDL in the normal range, but higher than average concentrations of CRP. Reduction of clinical events was of such a magnitude in this group (44% reduction in relative risk) that the trial was ended after only 1·9 years instead of 5 years as first planned. JUPITER did not include a control group of patients with low CRP. Was the beneficial effect of the statin therapy in JUPITER due to optimum patient selection by use of CRP?

In *The Lancet*, the well-designed substudy of the MESA trial by Michael Blaha and colleagues[5] presents data that indicate a different conclusion. MESA recruited 6814 unselected participants free of known cardiovascular disease from six centres throughout the USA. The investigators' main objective was to analyse

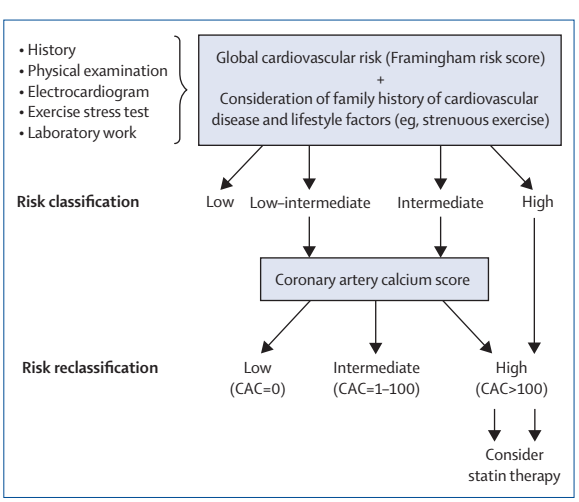

Figure: **The preferred algorithm for risk stratification in our practice**
Percentile values of the coronary artery calcium (CAC) scores are consulted, with scores >75th age-specific and sex-specific percentile signifying an increased risk. For example, in men older than 65 years, a cutoff point of 400 indicates high risk. Other measures of preclinical atherosclerosis are also factored in, if available.

the predictive ability of CAC in asymptomatic patients. 2083 MESA participants were identified who met JUPITER inclusion criteria and whose high-sensitivity CRP (hsCRP) values were 2 mg/L or more. After full adjustment for Framingham risk scores, high CRP did not seem to affect future coronary heart disease events (hazard ratio 0·90, 95% CI 0·54–1·50), whereas the presence of CAC, and particularly CAC scores of more than 100, were strongly predictive of both coronary heart disease (9·35, 4·15–21·1) and overall cardiovascular disease events (4·41, 2·42–8·04).[5] Blaha and colleagues used the event reductions noted in JUPITER to estimate that treatment with a potent statin in patients with raised CAC would be highly efficient (numbers needed to treat [NNT] to prevent an event of coronary heart disease: 5-year NNT when any CAC was present was 42, and for CAC scores >100 5-year NNT was 24), whereas treatment of patients with CAC scores of 0 would be unfavourable (5-year NNT was 549). How can this be explained and what are the practical implications?

CAC is a specific expression of coronary atherosclerotic plaque disease, with a linear relation between the extent of CAC and the overall extent of coronary atherosclerosis.[6] Although exceptions in patients aged less than 50 years are possible, to find someone with extensive coronary atherosclerosis who has no CAC is highly unlikely.[7] Despite the difficulties that have been unresolved for prospective classification of plaques as stable or unstable, CAC does not allow such distinctions.[8] Clinical studies[8–10] support the conclusion that increased CAC signifies increased amounts of plaque, and thus an increased risk. Conversely, with no CAC, plaque is absent or scarce, and risk is low.

Neither CAC nor CRP have a significant causal role in cardiovascular events.[8,11] Unlike CAC, the association of CRP with cardiovascular events seems to vary between different patient subgroups defined by level of risk and ethnicity.[12] Various inflammatory and other stimuli and components of the metabolic syndrome might increase CRP. Accordingly, in some patients with low CAC scores, CRP could be a general marker of poor health.[13] However, CAC is a much more specific expression of atherosclerosis, the immediate precursor of cardiovascular events, which probably explains the better predictive ability of CAC than of CRP for both coronary heart disease and cardiovascular disease.[5,13]

We cannot be content with statistical significance, and a practical approach towards expanded risk stratification should be established. This scenario has been achieved for high CRP in the JUPITER trial for the benefits of statin therapy. Except for one preliminary trial,[14] such data are unavailable for CAC. Nevertheless, practical application should be reserved for a measure whose statistics are clearly predictive, and as Blaha and colleagues show, this case is much stronger for CAC than for CRP. Although definitive proof of treatment effects is scarce, CAC identifies high cardiovascular risk, and statin therapy is most effective in high-risk patients. In our practice, we therefore focus on CAC and use the algorithm shown in the figure for expanded risk stratification in asymptomatic patients.

Axel Schmermund, Thomas Voigtländer
Cardioangiologisches Centrum Bethanien, CCB, Im Prüfling 23, D-60389 Frankfurt am Main, Germany
a.schmermund@ccb.de

We declare that we have no conflicts of interest.

1 Ford ES, Li C, Zhao G, Pearson WS, Capewell S. Trends in the prevalence of low risk factor burden for cardiovascular disease among United States adults. *Circulation* 2009; **120:** 1181–88.
2 Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation* 1998; **97:** 1837–47.
3 Chang MK, Binder CJ, Torzewski M, Witztum JL. C-reactive protein binds to both oxidized LDL and apoptotic cells through recognition of a common ligand: phosphorylcholine of oxidized phospholipids. *Proc Natl Acad Sci USA* 2002; **99:** 13043–48.
4 Ridker PM, Danielson E, Fonseca FA, et al, for the JUPITER Study Group. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med* 2008; **359:** 2195–207.
5 Blaha MJ, Budoff MJ, DeFilippis AP, et al. Association between C-reactive protein, coronary artery calcium, and cardiovascular events: implications for the JUPITER population from MESA, a population-based cohort study. *Lancet* 2011; **378:** 684–92.
6 Rumberger JA, Simons DB, Fitzpatrick LA, Sheedy PF, Schwartz RS. Coronary artery calcium area by electron-beam computed tomography and coronary atherosclerotic plaque area. A histopathologic correlative study. *Circulation* 1995; **92:** 2157–62.
7 Schmermund A, Baumgart D, Görge G, et al. Coronary artery calcium in acute coronary syndromes: a comparative study of electron-beam computed tomography, coronary angiography, and intracoronary ultrasound in survivors of acute myocardial infarction and unstable angina. *Circulation* 1997; **96:** 1461–69.
8 Greenland P, Bonow RO, Brundage BH, et al. ACCF/AHA 2007 clinical expert consensus document on coronary artery calcium scoring by computed tomography in global cardiovascular risk assessment and in evaluation of patients with chest pain: a report of the American College of Cardiology Foundation Clinical Expert Consensus Task Force (ACCF/AHA Writing Committee to Update the 2000 Expert Consensus Document on Electron Beam Computed Tomography). *J Am Coll Cardiol* 2007; **49:** 378–402.
9 Detrano R, Guerci AD, Carr JJ, et al. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. *N Engl J Med* 2008; **358:** 1336–45.
10 Erbel R, Möhlenkamp S, Moebus S, et al. Coronary risk stratification, discrimination, and reclassification improvement based on quantification of subclinical coronary atherosclerosis: the Heinz Nixdorf Recall study. *J Am Coll Cardiol* 2010; **56:** 1397–406.

11 Wensley F, Gao P, Burgess S, et al, for the C Reactive Protein Coronary Heart Disease Genetics Collaboration (CCGC). Association between C reactive protein and coronary heart disease: mendelian randomisation analysis based on individual participant data. *BMJ* 2011; **342:** d548.

12 Kaptoge S, Di Angelantonio E, Lowe G, et al, for the Emerging Risk Factors Collaboration. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. *Lancet* 2010; **375:** 132–40.

13 Möhlenkamp S, Lehmann N, Moebus S, et al, for the Heinz Nixdorf Recall Study Investigators. Quantification of coronary atherosclerosis and inflammation to predict coronary events and all-cause mortality. *J Am Coll Cardiol* 2011; **57:** 1455–64.

14 Arad Y, Spadaro LA, Roth M, Newstein D, Guerci AD. Treatment of asymptomatic adults with elevated coronary calcium scores with atorvastatin, vitamin C, and vitamin E: the St Francis Heart Study randomized clinical trial. *J Am Coll Cardiol* 2005; **46:** 166–72.

Antithrombin alternatives in STEMI

See **Articles** page 693

Restoration of effective myocardial perfusion by percutaneous coronary intervention (PCI) in ST-segment elevation myocardial infarction (STEMI) is a life-saving therapy. Selection of the optimum anticoagulation regimen to support primary PCI is essential. Unfractionated heparin, low molecular weight heparins, the factor Xa inhibitor fondaparinux, and the direct thrombin (factor IIa) inhibitor bivalirudin have all been studied in this setting. These agents have different mechanisms of action, binding specificity, pharmacokinetic and pharmacodynamic consistency, risks of heparin-induced thrombocytopenia, and half-lives (table). Paradoxically, unfractionated heparin, low molecular weight heparins, and fondaparinux activate platelets by binding to the platelet glycoprotein IIb/IIIa integrin receptor.[1] By inhibiting the aggregation of activated platelets, glycoprotein IIb/IIIa inhibitors reduce the rate of ischaemic complications when primary PCI is done with unfractionated heparin, at the cost of increased bleeding.[2] Fondaparinux as a stand-alone agent during primary PCI results in an unacceptably high rate of catheter thrombosis,[3] and is not recommended. Conversely, bivalirudin reduces thrombin generation and both thrombin-dependent and collagen-dependent platelet activation.[4] In the HORIZONS-AMI trial,[5] bivalirudin during primary PCI substantially decreased bleeding and thrombocytopenia while suppressing ischaemic complications compared with unfractionated heparin plus glycoprotein IIb/IIIa inhibitors, thereby reducing all-cause and cardiac mortality. These findings were replicated in a registry of more than 100 000 people.[6] These data emphasise the importance of both platelet and thrombin inhibition during PCI, and the delicate balance between safety and efficacy that has to be achieved for optimum outcomes.

Low molecular weight heparin has been increasingly studied as an anticoagulant during PCI. The most widely used low molecular weight heparin is enoxaparin, which has shown varying safety and efficacy compared with unfractionated heparin in previous trials, depending on the clinical setting and mode of administration. In the ExTRACT-TIMI-25 trial,[7] intravenous followed by subcutaneous enoxaparin reduced the 30-day composite rate of death or reinfarction, but increased major bleeding in patients with STEMI receiving fibrinolysis. In the SYNERGY trial,[8] subcutaneous enoxaparin compared with unfractionated heparin did not reduce the 48-h

	Unfractionated heparin	Enoxaparin	Fondaparinux	Bivalirudin
Factor Xa:IIa inhibition	1:1	3–4:1	100% Xa	100% IIa
Action independent of antithrombin	No	No	No	Yes
Non-specific binding	Yes	Partial	No	No
Variable PK/PD measures	Yes	Less	No	No
Inhibits fibrin-bound thrombin	No	No	No	Yes
Activates or aggregates platelets	Yes	Yes	Yes	Inhibits
Half-life	Variable with dose, about 60 min IV	300 min SC; 90–120 min IV (0·5 mg/kg)	17 h SC	25 min IV
PF-4 complexing and risk of HIT	Yes	Reduced	Low	No

PK/PD=pharmacokinetic and pharmacodynamic. PF-4=platelet factor 4. HIT=heparin-induced thrombocytopenia. SC=subcutaneous. IV=intravenous.

Table: **Comparative properties of unfractionated heparin, enoxaparin, fondaparinux, and bivalirudin**