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Intermediate Coronary Artery Disease Risk Patients: Reclassification With Coronary Calcium Scoring or Statin Therapy?

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INTRODUCTION

Cardiovascular disease (CVD) which includes coronary artery disease (CAD), stroke and peripheral vascular disease, is the leading cause of death in developed and in most developing countries¹. The last decades have shown an impressive reduction in the rate of death from cardiac disease, both due to disease-specific therapies but mainly due to the widespread implementation of primary and secondary prevention strategies, that target modifiable risk factors²⁻⁴. The increasing prevalence of type 2 diabetes mellitus and obesity will probably have a negative impact on CVD prevention and treatment.

The Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program (NCEP) has provided clinicians with recommendations regarding primary and secondary prevention of cardiovascular disease⁵, based on Framingham risk score. Nevertheless, such a risk factor assessment would only predict 60-65% of cardiovascular events, and a substantial number of episodes occur in patients categorized in the low or moderate risk categories⁶, who would not be considered candidates for the most aggressive prevention strategies. Such an observation has led investigators to search for novel risk factors, as well as new means of diagnosing subclinical coronary artery disease in order to identify more subjects that could benefit from intensive risk factor modification.

High-sensitivity C-reactive protein (hsCRP) is an inflammatory biomarker which has been shown to be a significant contributor to the prediction of CAD⁷. The recently published JUPITER study⁸, has renewed interest on the importance of hsCRP, since the results showed an impressive reduction of cardiovascular risk with the use of a statin not for hyperlipidemia but for elevated hsCRP levels. On the other hand, coronary artery calcium (CAC) is a sensitive indicator of atherosclerosis and has also been studied in risk stratification⁹. The present review will focus on the value of the above indices as a means to better identify individuals at high risk in order to offer them appropriate prevention measures.

ATP III GUIDELINES

ATP III guidelines have been the most widely used tool for individual risk assessment. They are based on the Framingham risk score, which takes into account age,

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gender, family history of premature CAD, smoking status, blood pressure levels, as well as total and HDL cholesterol. According to these criteria, patients are categorized into low risk, if their calculated 10-year risk is less than 10%, and high risk, if they have known CAD or a CAD-equivalent such as diabetes mellitus, symptomatic carotid disease, abdominal aortic aneurysm, peripheral vascular disease or if their calculated 10-year risk exceeds 20%. The intermediate risk category has been further divided into moderate risk, for those that have two or more of the above risk factors and a 10-year risk less than 10%, and moderately high risk, if the 10-year risk is 10-20%.⁵ Only the high risk patients would be offered aggressive preventive measures and yet a great number of cardiovascular events happen in the intermediate risk patients. In particular, a study which included previously asymptomatic young adults, hospitalized for a first myocardial infarction, showed that 75% would not have been candidates for statin therapy, according to ATP III guidelines¹⁰. There is also evidence that the Framingham risk score does not perform well in women¹¹. As the treatment of all intermediate risk patients would not be cost-efficient, the need for further risk stratification in order to improve patient selection is evident.

One of the innate drawbacks of the Framingham and other risk models is that they estimate a patient's risk based on population studies, without taking into account the actual presence of atherosclerotic disease in a particular patient. Only an imaging technique with adequate sensitivity and specificity could assist in this matter by providing direct evidence of the absence or presence, as well the extent of atherosclerosis.

CORONARY ARTERY CALCIUM (CAC) SCORE

Atherosclerotic plaques are known to acquire calcium via a process that resembles normal bone formation. The lipid core is the first to be calcified and although the whole mechanism is not known, it seems that the apoptotic cells play the role of nuclei in order to start the accumulation of calcium¹². The correlation between calcification and vascular disease has been known for many years and the first report to demonstrate the diagnostic and prognostic significance of CAC was published in 1980¹³. Since then, the development of Electron-Beam Computed Tomography (EBCT) and more recently of Multi-Detector Computed Tomography (MDCT), has permitted a quantitative assessment of coronary artery calcium, providing accurate and reproducible data^{9,14}.

The most widely used tool for quantification of coronary calcium is the Agatston score¹⁵. EBCT was the first CT technique to be used and although modern technology has allowed improved visualization of the beating heart, with little or no motion artifact through MDCT, most of the data regarding CAC has been from studies utilizing EBCT.

Due to the important technical differences between the two modes, there is some debate whether the results of one can be compared to those of the other¹⁶. Although a direct head-to-head comparison between the two methods would not be feasible, there is evidence showing that their scores have a similar significance¹⁷.

Calcium is not present in normal coronary arteries. Therefore, coronary calcification with very rare exceptions is a marker of underlying atherosclerosis. The close association of CAC and atherosclerotic burden was studied with histopathology and intravascular ultrasound^{18,19}. Although the presence of calcium denotes atherosclerosis, it does not necessarily mean obstructive lesions. In the aforementioned autopsy study, the authors found that the burden of non-calcified plaques was five times higher than the calcified ones. There lies the main difference between CAC scoring and the various forms of stress testing, as the latter aim to identify flow-limiting disease. The prognosis of coronary artery disease, however, is more closely related to the extent of atherosclerosis than to a particular stenosis severity^{20,21}.

Coronary artery calcium scores tend to be higher in older patients, which correlates with advanced CAD, and also in men, compared to women²². The most commonly used classification for CAC score is as follows^{23,24}:

- 0: no identifiable disease
- <100: mild disease
- 100-400: moderate disease
- >400: severe disease

A large cohort study of more than 6000 initially asymptomatic adults who were followed up for a median of 3.8 years²⁵, showed that a higher CAC score is associated with higher events rate, although, even with the high scores the event rate was only 1% per year. The predictive role of CAC score in this Multi-Ethnic Study of Atherosclerosis (MESA) was demonstrated for whites as well as for blacks, Hispanics and Chinese. Despite a higher prevalence of CAC and higher scores in white patients, it appears that CAC is an important marker of risk in all races.

With respect to age, it should be noted that younger adults may have atherosclerotic plaques with no calcification with the obvious risk of rupture, to create an acute coronary event. Yet, any degree of calcification, even a mild score, would place them in a high risk percentile, compared to age- and sex-matched controls. Framingham risk calculation has the same limitations, since the 10-year risk in a younger adult would not be high even in the existence of multiple risk factors, and some have proposed that calculating the life-time risk in this age group would be more appropriate²⁶.

Although, as already mentioned, the purpose of CAC scoring is not the identification of obstructive disease, there are data showing that a low CAC score is associated with a low probability of abnormal SPECT²⁷. The above study also showed that CAC score may be raised even in the absence

of perfusion abnormalities. Another study of asymptomatic individuals undergoing both SPECT and EBCT, showed that CAC predicted an abnormal SPECT regardless of age or sex, and the higher the CAC score the more likely it was to have a perfusion abnormality²⁸.

CAC scoring was also shown to help in the prognostic evaluation of asymptomatic individuals and the risk of death increased proportionally to the baseline calcium scores²⁹. Moreover, data analysis utilizing both traditional risk factors and CAC score showed that coronary calcium provides independent incremental information in addition to traditional risk factors in the prediction of all-cause mortality. A meta-analysis of four trials²⁴ concluded that despite the observed variability in the relative risk estimate between studies, CAC score is an independent predictor of coronary heart disease events.

CAC score has been proven to be predictive of adverse CV events in the elderly. The prospective Rotterdam study which included CAC scoring and traditional risk factor measurement showed an improved cardiovascular risk prediction in the older age group³⁰. Moreover, a more recent study, which included a large number of patients over 70 years, showed that increasing CAC score was predictive of decreased survival rates in all age groups, even in the elderly³¹. Of equal importance was the observation that more than 40% of the elderly patients were reclassified to a lower or higher risk category using the CAC score, compared to their original classification based on the Framingham risk score.

An increased degree of calcification of the coronary arteries has been demonstrated in subjects with type 1 and type 2 diabetes mellitus and insulin resistance^{32,33}. A study comparing diabetic and non-diabetic patients, undergoing CAC scoring, showed a higher mortality rate in the former patients, for any given degree of CAC score³⁴.

Several studies have also examined the utility of CAC in women. Raggi et al showed that CAC scores were lower in women compared to men, but its addition to traditional risk calculation offered incremental prognostic value³⁵. A meta-analysis, comparing the usefulness of coronary artery calcium in men and women, concluded that CAC is equally accurate in estimating all-cause mortality and CAD death in both genders³⁶.

CAC SCREENING AND FRAMINGHAM RISK SCORE (FRS)

Taking into consideration all of the above data, the question is who should be screened using the CAC score. The Bayesian theorem provides a useful start point, as the post-test probability of events depends also on the pre-test likelihood of the patient's risk. In other words, if a patient has an initially low probability of having CAD, the addition of CAC would obviously increase the risk but even so, the resulting post-test

risk would still be low. Similarly, patients classified as high risk according to ATP III, would still merit preventive measures even if their CAC score was low.

There are reports, showing that CAC scoring in low risk subjects is not useful in modifying risk prediction^{37,38}. The study by Greenland et al³⁷, concluded that a high CAC score can significantly modify risk prediction in patients with an intermediate traditional FRS of 10-20%. In other words, the absence of coronary calcium might shift these patients to a low-risk category, while a high CAC would indicate a high level of risk. On the contrary, CAC was not useful in patients with FRS less than 10% or more than 20%, and the clinical approach to those patients would not be modified.

Therefore it appears prudent to use CAC scoring selectively, in those patients with an intermediate FRS. The authors of the ACCF/AHA expert consensus document on coronary artery calcium scoring, stated that intermediate-risk FRS patients with a CAC score greater than or equal to 400 would have an increased risk of adverse CV events, enough to place them in the high-risk category of CAD- equivalent, thus warranting aggressive preventive measures¹⁴.

IS CAC TESTING SAFE?

Obviously, there is a radiation burden associated with the use of both EBCT scanning (0.6 to 1 mSv) and MDCT (0.9 to 2 mSv) that needs to be taken into account, especially if serial testing is considered to monitor CAD progression⁹. In comparison, a chest radiograph has a dose of 0.01 to 0.02 mSv. It has been reported that a dose of 2.3 mSv can increase the probability of cancer³⁹. Thus, the use of CAC scoring in a widespread population would need to take radiation safety into account.

Therefore, the question arises whether a novel marker of CAD such as high-sensitivity C-reactive protein (hs-CRP) might be a cheaper, safer and easier way to reclassify intermediate-risk patients and thus modify their risk factor modification.

HIGH-SENSITIVITY CRP (HS-CRP) AND THE JUPITER TRIAL

There are sufficient data both from experimental and population based studies, to show that atherosclerosis has an inflammatory component⁴⁰. Inflammation not only participates in atheroma formation but also contributes to the vulnerability and plaque rupture or erosion⁴¹. CRP is an acute phase protein, secreted by the liver, in response to systemic cytokines such as interleukin 1 β and 6 and tumor necrosis factor α . Whether CRP has a pathogenetic role in the development of cardiovascular disease, or is a non specific marker of the acute phase response to inflammation, is an unresolved question^{42,43}.

Traditional assays, used for patients with infectious or inflammatory disorders, have a detection limit of 3 to 5 mg/L which is above the levels of most healthy subjects. High-sensitivity methods have been developed that detect levels as low as 0.3mg/L and these have been used for cardiovascular risk stratification. A statement from the Centers for Disease Control and Prevention and the American Heart Association (CDC/AHA) concluded that the average of two measurements, two weeks apart, rather than a single one should be used and the cutoff values for low, average and high levels should be less than 1 mg/L, 1 to 3 mg/L and above 3 mg/L respectively. There is definitely variability in hsCRP levels over time, which reflects the change in the systemic inflammatory status. This was demonstrated in a study of stable ischemic heart disease patients, where the second measurement resulted in 40% of the patients changing risk category⁴⁴.

High-sensitivity CRP has been proposed as a useful biomarker for the prediction of CVD risk stratification. A useful biomarker is one that is easy to obtain, accurate, reproducible, internationally standardized, adds to clinical knowledge, provides risk information, on top of other known predictors and helps in risk classification and patients' therapy⁴⁵. Many studies have shown that increased levels of hs-CRP are associated with an increased risk of cardiovascular events even after adjustment for traditional risk factors⁴⁶. The multivariate analysis of hsCRP and traditional risk factors, to assess their predictive value on CV risk has revealed that the strength of hs-CRP is similar to the one of LDL, systolic blood pressure and cigarette smoking. Moreover, several trials have shown that the addition of hs-CRP to other risk factors, results in reclassification of a significant number of patients to a different risk category⁴⁷. Similar trials have shown the association of hsCRP with the development of type 2 diabetes mellitus and metabolic syndrome as well as an increased risk of stroke⁴⁶.

The JUPITER trial was designed to investigate the effect of statin treatment in a population with only average LDL levels but with elevated hsCRP⁴⁸. Patients with an LDL level below 130 mg/dl and a CRP of at least 2 mg/dl were randomly assigned to treatment with rosuvastatin 20mg or placebo. Although the trial was estimated to last 4 years, it was terminated early, after approximately 2 years of follow-up due to the beneficial effect of rosuvastatin on the primary endpoint (cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina or arterial revascularization) and all cause mortality. The cumulative incidence of cardiovascular events was reduced by 44% and all cause mortality was reduced by approximately 20%. The benefit of statin treatment was seen in various subgroups such as women, patients with metabolic syndrome and the elderly. Although rosuvastatin demonstrated an excellent safety profile, similar to other statins currently used, an increased incidence of physician reported diabetes was shown on the JUPITER trial. This finding has also been observed in other statin trials^{49,50}.

Other studies such as the CARE trial have shown that statins lower hsCRP levels⁵¹. This is believed to be part of the multiple antiatherogenic effects of statins which have been shown to have an anti-inflammatory action. Moreover, statins reduce CRP levels in a manner similar to LDL, i.e. the more potent drugs have the greatest effects on hsCRP lowering.

The JUPITER trial was the first to demonstrate that a much larger subset of patients may be eligible for statin therapy in primary prevention. A simple and reproducible marker such as hsCRP can be utilized to discriminate a higher risk category than the one estimated by the Framingham risk score. These patients might also benefit not only from statin treatment but also from low-dose aspirin as has already been shown in the Physicians Health Study⁵². The number needed to treat to prevent a CV event in the JUPITER trial was calculated to be 25, which is acceptable and cost effective for primary prevention. Moreover, many studies have shown that the best results are reached in high-risk patients on statin treatment who achieve both LDL and hsCRP reductions^{53,54}. Thus, hsCRP could also serve as a follow-up marker of cardiovascular risk reduction, and potentially as an important therapeutic goal beyond LDL.

CONCLUSION

Cardiovascular diseases continue to be the leading cause of death in the developed world. A better risk prediction is definitely needed to lower morbidity and mortality by primary prevention measures. The effects of Framingham risk score calculation can be improved by both hsCRP measurement and coronary artery calcium scoring. More trials are needed in order to further estimate and compare their relative efficacy in improving risk estimation especially in the intermediate risk patients who need it more.

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