Dialogues in Cardiovascular Medicine

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Prevention Through Imaging

Aim s & Scope

Dialogues in Cardiovascular Medicine is a peer-reviewed, quarterly journal for cardiologists and physicians with an interest in cardiology. It seeks to present thoughtfully addressing the current body of knowledge on a specific area of cardiovascular medicine, such issues to provide a comprehensive analysis of the evidence that is available at the present time. Each issue of Dialogues in Cardiovascular Medicine is divided into different sections, including the Lead Article, the Expert Answers, the Summaries of Ten Seminal Papers, the Fascinom a Cardiologica section, and the Bibliography of One Hundred Key Papers. The journal offers unique coverage of the state of the art in clinical cardiology. The journal is indexed in medical databases and is part of the continuing medical education program of several major international cardiological societies.

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Prevention Through Imaging

2013
Prevention Through Imaging

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Cardiovascular disease (CVD) remains the first cause of mortality, morbidity, and disability worldwide. The World Health Organization Fact Sheet on CVD (No. 317, updated March 2013) states that throughout the world more people die each year from CVD than from any other cause, with 17.3 million deaths in 2008, representing 30% of all global deaths, a figure expected to rise to 23.3 million by 2030. According to SIGN (Scottish Intercollegiate Guidelines Network), Risk Estimation and the Prevention of Cardiovascular Disease. A National Clinical Guideline. 2007. Report No. 97, CVD disability-adjusted life years (DALYs) are expected to rise from a loss of 85 million DALYs in 1990 to a loss of close to 150 million DALYs globally in 2020, thereby remaining the leading somatic cause of loss of productivity. A point of note is that over recent decades there has been a marked trend for a shift in the incidence of CVD away from Europe, with more than 80% of all CVD mortality now occurring in developing countries. This trend of course has profound implications for the topic discussed in this issue of Dialogues in Cardiovascular Medicine—cardiovascular imaging—in terms of how these countries will be able to cope with the high costs attached to cardiovascular imaging.

In addressing CVD, currently available drugs such as aspirin, angiotensin-converting enzyme inhibitors, statins, and β-blockers are certainly useful: together they are estimated to account for a 30% reduction in cardiovascular mortality worldwide. This contrasts with the 5% to 10% reduction in cardiovascular mortality observed with the more sophisticated reperfusion techniques. But this is probably mainly because these techniques are applied too late or to too few patients or are too expensive.

What this says is that, in spite of dramatic advances, treatment still falls short of achieving the expected goal and still has a long way to go. Thus, the battle against cardiovascular disease still has a lot more to do with prevention than treatment. This is where the sophisticated (and, once again, costly—the reader will have to bear with our hammering this point in!) new imaging techniques come into the picture, such
as: assessment of carotid intimal-media thickness as a surrogate of atherosclerosis, determination of coronary artery calcium scores by computed tomography, CT angiography, detection of plaque vulnerability by invasive imaging modalities, or, more simply, echocardiography to detect early abnormalities in the cascade of the cardiovascular continuum.

These new techniques provide an unprecedented wealth of information previously out of reach. Obviously, the temptation to use these techniques is high if only because, contrary to biological markers, they do not produce mere numbers, but images, which usually mean much more to the cardiologist.

The temptation grows even more irresistible in light of the recent European Guidelines on Cardiovascular Disease Prevention in Clinical Practice (2012). These guidelines no longer make the distinction between primary and secondary prevention, but refer instead to a gradual increase in cardiovascular risk independently of the presence of overt cardiovascular disease. For their patients at high or very high risk, cardiologists now have the means to determine the precise level of risk and fine-tune the treatment accordingly. As for patients at low or very low risk, as usual, when precise cutoff points fade away and turn into a continuum, the decision as to when and in whom apply such costly techniques tends to become an economic issue, hence very quickly a political one (for health services, doctors, institutions, cities, nations, policymakers, politicians, etc).

These techniques are undoubtedly helpful. But a few hard questions must be asked. Just how helpful are these techniques really, in terms of specific data not obtainable otherwise? In which patients should they be applied? And, more down-to-earth, is their use sustainable considering the increasing economic belt-tightening medicine is faced with? Finally, are we not underestimating the risks of radiation associated with these techniques?

This latter point is relevant as official health regulators approve the use of such techniques not on the basis of their efficacy (as is the case for drugs), but solely of safety. No clinical trials are requested to prove the real advantages obtained by each technique, which leaves the decision to the individual cardiologist on when, how, and in whom to use them. This is the reason why the Editorial Board of Dialogues in Cardiovascular Medicine decided to produce this issue: to put the readers in the picture by reviewing the advantages and disadvantages of the new cardiovascular imaging techniques in order to help them make the right choice.
Prevention through imaging: current knowledge and perspectives

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Cardiology Department - Faculty of Medicine of Lisbon University - University Hospital Santa Maria - Lisbon - PORTUGAL

The impact of cardiovascular imaging on cardiovascular prevention and risk assessment has substantially increased over the last few years, mainly due to the amount of relevant information that imaging modalities now provide. This review discusses different aspects of cardiovascular imaging with respect to prevention and risk assessment, including: (i) the role of carotid intima-media thickness as a risk marker and surrogate marker of atherosclerosis; (ii) the relevance of quantifying coronary calcium by computed tomography and the added value of computed tomography angiography; (iii) the ability of echocardiography to detect subclinical abnormalities early in the natural history of a disease process, potentially allowing early treatment and thus interrupting the cascade of events that can lead to adverse outcomes; (iv) the use of cardiac hybrid imaging as a way to obtain the advantages of combining methods used simultaneously; and (v) the detection of vulnerable plaque and the role of some of the invasive imaging modalities such as intravascular ultrasound or optical coherence tomography. Further research is needed to document whether these approaches will prove clinically effective and have a positive cost/benefit ratio in the management and risk assessment of heart disease. This will likely represent an important step forward in the field of cardiovascular prevention.

Cardiovascular diseases, in particular, those derived from atherosclerosis (stroke and acute coronary syndromes) represent the main cause of death worldwide. Once one of these cardiovascular events occurs, there are likely to be serious consequences, ultimately death, but also major lifestyle implications. This is true both of stroke and of acute myocardial infarction with major impairment of cardiac function, which sooner or later evolves into heart failure. Thus, over the years, a clear need for prevention has emerged that is based on a better understanding of the risk factors that may be responsible for having a greater chance of developing one of these cardiovascular diseases. This has led to the development of prevention guidelines that are very much focused on preventing the development and progression of known significant risk factors such as diabetes, hypertension, dyslipidemia, smoking, and obesity, among others. However, more recently, evidence has been building regarding the added value in this regard of some of the technical tools that we use mostly for diagnosis and monitoring of disease and less with the intention of early detection of disease or even prevention. This applies, for instance, to the different imaging modalities that over the last few years have seen enormous and exciting developments, both from a technical perspective and also from a medical one.

With the development of new technologies applied to medical diagnostic pathways, cardiovascular imaging has rapidly progressed. Consequently, the clinical cardiologist has had to keep updated regarding the main characteristics, and particularly, uses and indications, of these innovative diagnostic tools. The need to understand a new language is fundamental in the selection of diagnostic and therapeutic strategies for patients with heart disease—especially heart failure, which for many cardiovascular diseases is often the final end point. Alongside standard diagnostic techniques, such as chest radiography, two-dimensional echocardiography, and cardiac Doppler, all of which are essential in

Keywords: cardiac hybrid imaging; cardiovascular prevention; coronary artery disease; CT angiography; echocardiography; heart failure; MRI; myocardial perfusion imaging

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daily practice, innovative tools have been playing an incremental role in cardiovascular imaging. Cardiac computed tomography (CT), cardiac magnetic resonance, ultrasound of intima-media thickness, speckle tracking, three-dimensional echocardiography, new applications in nuclear medicine, and more recently, “cardiac hybrid imaging” and even molecular imaging, are emerging as new tools for research and are also playing a pivotal role in risk stratification. Whether the economic impact of these emerging technologies is sustainable is a question that the cardiology community will have to answer in the near future taking into consideration the cost/benefit ratio of the particular diagnostic tool. The main uses of these different imaging modalities in relation to what could be described as “prevention through imaging” will briefly be discussed in this review.

**NONINVASIVE CARDIOVASCULAR IMAGING IN PRIMARY PREVENTION**

Over the last few years, noninvasive imaging of atherosclerosis has increasingly been used in clinical practice. In some cases, guidelines have been produced that recommend screening all healthy adults for atherosclerosis. It is appalling to realize, however, that there is a lack of data regarding the impact of such screening. In a recent systematic review by Rodondi et al, the authors assessed whether atherosclerosis screening with noninvasive imaging (e.g. carotid ultrasound, coronary calcification) improves cardiovascular risk factors, cardiovascular events, or mortality in adults without cardiovascular disease. They identified 4 randomized controlled trials (n=709) and 8 nonrandomized studies comparing participants with evidence of atherosclerosis on screening with those who showed no evidence (n=2994). In the randomized controlled trials, atherosclerosis screening did not improve cardiovascular risk factors, but in one randomized controlled trial, smoking cessation rates increased (18% versus 6%; P=0.03). In the nonrandomized studies, the authors found improvements in several intermediate outcomes, such as increased motivation to change lifestyle and increased perception of cardiovascular risk. However, the data were conflicting and were limited by the lack of a randomized control group. No studies examined the impact of screening on cardiovascular events or mortality. Heterogeneity in screening methods and studied outcomes did not permit pooling of results. The authors of the systematic review concluded that available evidence regarding atherosclerosis screening is limited, with mixed results regarding cardiovascular risk factor control: increased smoking cessation in one randomized controlled trial, and no data on cardiovascular events. Such screening should obviously be validated through large clinical trials before its widespread use.

In another study, Hackam et al analyzed 7 randomized trials that compared use of different imaging modalities (CT, magnetic resonance imaging [MRI], echocardiography, positron emission tomography [PET], arterial ultrasonography, nuclear myocardial perfusion imaging, exercise electrocardiography, and radionuclide angiography) with usual care and reported any of the following outcomes in a primary prevention setting: medication prescribing, lifestyle modification (including diet, exercise, or smoking cessation), angiography, or revascularization. In this analysis, imaging had no effect on medication prescribing overall or on provision of lipid-modifying drugs, antihypertensive drugs, or antiplatelet agents. Similarly, no effect was seen on dietary improvement, physical activity, or smoking cessation. Imaging was not associated with invasive

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**SELECTED ABBREVIATIONS AND ACRONYMS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AVC</td>
<td>aortic valve calcium</td>
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<tr>
<td>CAC</td>
<td>coronary artery calcium</td>
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<tr>
<td>CAD</td>
<td>coronary artery disease</td>
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<tr>
<td>CHD</td>
<td>coronary heart disease</td>
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<tr>
<td>CIMT</td>
<td>carotid intima-media thickness</td>
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<tr>
<td>CORI</td>
<td>cerebrovascular or retinal ischemic (events)</td>
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<tr>
<td>CT</td>
<td>computed tomography</td>
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<tr>
<td>CTCA</td>
<td>computed tomography coronary angiography</td>
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<tr>
<td>DAVES</td>
<td>Disfunzione Asintomatica VEntricolare Sinistra (trial)</td>
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<tr>
<td>ECST</td>
<td>European Carotid Surgery Trial</td>
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<tr>
<td>LA</td>
<td>left atrial</td>
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<tr>
<td>LV</td>
<td>left ventricular</td>
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<tr>
<td>MESA</td>
<td>Multi-Ethnic Study of Atherosclerosis</td>
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<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
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<tr>
<td>PALS</td>
<td>peak atrial longitudinal strain</td>
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<tr>
<td>PET</td>
<td>positron emission tomography</td>
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<tr>
<td>PROSPECT</td>
<td>Providing Regional Observations to Study Predictors of Events in the Coronary Tree (trial)</td>
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<tr>
<td>SPECT</td>
<td>single-photon emission computed tomography</td>
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angiography. The authors therefore concluded that limited evidence suggests that noninvasive cardiovascular imaging alters primary prevention efforts. However, they also concluded that given the imprecision of these results, further high-quality studies are needed. In fact, one of the conclusions that we may draw at this time concerns the lack of robust, large studies that look in a scientifically sound way at the potential advantages of using imaging to help direct prevention more efficiently and in a more cost-effective way.

**CAROTID ULTRASOUND**

**C**arotid intima-media thickness (CIMT) assessed by ultrasound has proven to be a noninvasive biomarker of early atherosclerosis, and a positive association between CIMT and the risk of subsequent cardiovascular events has been shown. Thus, it may improve global cardiovascular risk prediction. However, several recently published studies have in some instances shown contradictory results.

Elias-Smale et al in the Rotterdam Study looked at whether intima-media thickness of the common carotid artery in addition to traditional risk factors improves risk classification in a general population of older people. They studied a group of 3580 nondiabetic people aged 55-75 years who were free of cardiovascular disease at baseline and followed them for a median time of 12.2 years. They studied the ability of measurement of intima-media thickness in the common carotid artery on top of Framingham risk factors to better classify people into categories of low (<10%), intermediate (10%-20%), and high (>20%) 10-year risk of hard coronary heart disease (CHD) and stroke compared with models based only on Framingham risk factors. They found a sex difference: in older men, addition of CIMT to Framingham risk factors did not improve prediction of hard CHD or stroke. In older women, addition of CIMT to Framingham risk factors significantly improved risk classification. Reclassification was most substantial in women at intermediate risk. The authors concluded that CIMT had some additional value beyond traditional risk factors in the cardiovascular risk stratification of older women, but not of older men.

In the recently published PROG-IMT collaborative project (carotid intima-media thickness progression to predict cardiovascular events in the general population), the association between changes in CIMT and cardiovascular risk—which is frequently assumed, but has rarely been reported—was tested. The authors identified general population studies that assessed CIMT at least twice and followed up participants for myocardial infarction, stroke, or death. The association between CIMT progression and the risk of cardiovascular events (myocardial infarction, stroke, vascular death, or a combination of these) for each study was determined. Of 21 eligible studies, 16 were included with a total of 36 984 participants and a mean follow-up period of 7.0 years. An interesting finding in this study was that although no associations with CIMT progression were detected in sensitivity analyses, the mean CIMT of the 2 ultrasound scans was positively and robustly associated with cardiovascular risk. In 3 studies including 3439 participants who had 4 ultrasound scans, CIMT progression did not correlate between occasions. The variability in measurement/lack of evidence for its use in clinical risk prediction has been one of the main limitations regarding CIMT use in a clinical setting. Based on these results, the
PROG-IMT authors concluded that the association between CIMT progression, as assessed from 2 ultrasound scans, and cardiovascular risk in the general population remains unproven and, therefore, no conclusion can be derived regarding the use of CIMT progression as a surrogate in clinical trials.

In a prospective, multicenter, cohort study of patients undergoing medical intervention for vascular disease, Nicolaides et al determined the cerebrovascular risk stratification potential of baseline degree of stenosis, clinical features, and ultrasonic plaque characteristics in patients with asymptomatic internal carotid artery stenosis. Hazard ratios for internal carotid artery stenosis, clinical features, and plaque texture features associated with ipsilateral cerebrovascular or retinal ischemic (CORI) events were calculated using proportional hazards models. A total of 1121 patients with 50%-99% asymptomatic internal carotid artery stenosis in relation to the bulb (European Carotid Surgery Trial [ECST] method) were followed-up for a mean of 48 months. Severity of stenosis, age, systolic blood pressure, increased serum creatinine, smoking history of more than 10 pack-years, history of contralateral transient ischemic attacks or stroke, low gray-scale median, increased plaque area, plaque types 1, 2, and 3, and the presence of discrete white areas without acoustic shadowing were associated with increased risk. The areas under the receiver operating characteristic curves for a model of stenosis alone, a model of stenosis combined with clinical features, and a model of stenosis combined with clinical and plaque features were 0.59 (95% confidence interval [CI], 0.54-0.64), 0.66 (95% CI, 0.62-0.72), and 0.82 (95% CI, 0.78-0.86), respectively. In the last model, stenosis, history of contralateral transient ischemic attacks or stroke, gray-scale median, plaque area, and discrete white areas were independent predictors of ipsilateral CORI events. Combinations of these could stratify patients into different levels of risk for ipsilateral CORI and stroke, with predicted risk close to observed risk. The authors concluded that cerebrovascular risk stratification is possible using a combination of clinical and ultrasonic plaque features.

It seems clear that there is an independent association between CIMT and cardiovascular events. However, there are few data showing that it improves measures of predictive performance. Despite the fact that it has already been used as a surrogate end point in randomized clinical trials of new cardiovascular drugs, there is still a need for a standardized approach that will allow widespread clinical screening.

### Cardiac CT and Cardiovascular Magnetic Resonance

The detection of coronary artery calcium (CAC) by electron beam CT or multidetector CT has gained some relevance due to the documented association between coronary calcium scores and risk of cardiovascular events. An increase in CAC scores over time (CAC progression) improves prediction of CHD events. In a recent study, Okwuosa et al determined whether novel markers not involving ionizing radiation could predict CAC progression in a population of 2620 individuals classified as being at low risk of CHD events (Framingham risk score <10%) and who underwent follow-up CAC measurement. In addition to traditional risk factors, various combinations of novel marker models were selected on the basis of data-driven, clinical, or backward stepwise selection techniques. It was shown that after a mean follow-up period of 2.5 years, CAC progression occurred in 574 participants (22% overall; 214 of 1830 with baseline CAC = 0 and 360 of 790 with baseline CAC >0). Addition of various combinations of novel markers to the base model revealed improvements in discrimination of approximately only 0.005 each for the best-fit models. All three best-fit novel marker models calibrated well, but they were similar to the base model in predicting individual risk probabilities for CAC progression. The highest prevalence of CAC progression occurred in the highest compared with the lowest probability quartile groups (39.2% to 40.3% versus 6.4% to 7.1%).

The authors concluded that in individuals at low predicted risk according to the Framingham risk score, traditional risk factors predicted CAC progression in the short term with good discrimination and calibration. In addition, prediction improved minimally when various novel markers were added to the model. Figure 2 shows electron beam CT images at different scan planes illustrating extended CAC. Centile distribution (25th, 50th, 75th, 90th centiles) of men aged between 45-75 years are also illustrated based on the results of the Heinz Nixdorf Recall study.

In another study, Owens et al tested whether aortic valve calcium (AVC) is independently associated with coronary and cardiovascular events in a primary prevention population. Aortic sclerosis is associated with increased cardiovascular morbidity and mortality among the elderly, but the mechanisms underlying this association remain controversial. It is also unknown whether this association extends to younger individuals. A prospective analysis of 6685 participants in the
Multi-Ethnic Study of Atherosclerosis (MESA) was performed. All participants aged 45-84 years and free of clinical cardiovascular disease at baseline underwent CT for AVC and CAC scoring. The primary, prespecified combined end point of cardiovascular events included myocardial infarction, fatal and nonfatal strokes, resuscitated cardiac arrest, and cardiovascular death, whereas a secondary combined end point of coronary events excluded strokes. The association between AVC and clinical events was assessed using Cox proportional hazards regression with incremental adjustments for demographics, cardiovascular risk factors, inflammatory biomarkers, and subclinical coronary atherosclerosis. However, despite these results, the association between AVC and excess cardiovascular mortality beyond coronary atherosclerosis risk merits further investigation.

Another area of research has been the use of CT angiography to determine the prognostic value of absence or presence of coronary artery disease (CAD). Abdulla et al carried out a meta-analysis to determine the prognostic value of 64-slice CT angiography by quantifying the risk of major adverse cardiac events in different patient groups classified according to CT angiography findings. A systematic literature search and meta-analysis was conducted on 10 studies examining stable, symptomatic, and intermediate-risk patients (n=5675) by 64-slice CT angiography. Patients were followed up for a mean of 21 months. Patient groups with CT-angiographic nonobstructive (stenosis <50% of luminal narrowing) or obstructive (stenosis ≥50% of luminal narrowing) CAD were compared with those who had normal angiography without CAD. Numbers of major adverse cardiac events (cardiac death, nonfatal myocardial infarction, and revascularization) were used to calculate odds ratios (OR) with a 95% CI in each group. The cumulative rate of major adverse cardiac events over 21 months was 0.5% in patients with normal CT angiography, 3.5% in those with nonobstructive CAD, and 16% in those with obstructive CAD. Compared with normal CT angiography, nonobstructive CAD was associated with a significantly increased risk of major adverse cardiac events, with an OR of 6.68. Obstructive CAD was associated with further significantly increased risk of major adverse cardiac events with an OR of 41.19. The authors concluded that 64-slice CT angiography is able to differentiate low-risk from high-risk patients with suspected or known CAD. Moreover, absence of CAD predicts excellent prognosis, while obstructive CAD is associated with markedly increased risk of major adverse cardiac events.

Figure 3 (page 74) shows a three-dimensional-rendered image of the heart and multiplanar reconstruction of the coronary arteries.
In a very extensive document, Waugh et al assessed the clinical effectiveness and cost-effectiveness of CT screening for asymptomatic CAD. They also sought to establish whether CAC predicts coronary events and adds anything to risk factor scores, and whether measuring CAC changes treatment. They carried out a search using the main electronic databases for literature published up to 2005, with a MEDLINE update in February 2006, and carried out a systematic review of screening studies and economic evaluations. Studies were included in the review if screening for CHD was the principal theme of the study, and if data were provided that allowed comparison of CT screening with current practice, which was taken to be risk factor scoring. Mismatches between CAC scores and risk factor scoring were of particular interest. A review of the case for screening against the criteria used by the National Screening Committee for assessing screening programs was also undertaken. The authors found no randomized controlled trials that assessed the value of CT screening in reducing cardiac events. Seven studies including 30,599 individuals were identified that assessed the association between CAC scores and cardiac outcomes in asymptomatic people. Six of the studies used electron-beam CT. The relative risk of a cardiac event was 4.4 if CAC was present compared with no CAC being present. As the CAC score increased, so did the risk of cardiac events. The correlation between CAC and cardiac risk was consistent across studies. There was evidence that CAC scores differed among people with the same Framingham risk factor scores, and that within the same Framingham bands, people found that showed whether the addition of CAC scores to standard risk factor assessment would improve outcomes. There were reports from 2 observational studies that lowering of low-density lipoprotein cholesterol to about 3 mmol/L or below with statin treatment modestly reduced CAC scores, but this was not confirmed in 2 randomized controlled trials. In 3 studies examining whether knowledge of CAC scores would affect compliance with lifestyle measures, perception of risk was affected, but it did not improve smoking cessation rates, although it did increase anxiety. There were a few economic studies of CT screening for heart disease, which provided useful data on costs of scans, other investigations, and treatment, but they relied on a number of assumptions and were unable to provide definitive answers. One modeling study estimated that adding CT screening to risk factor scoring and only giving statins to those with a CAC score of >100 would save money, based on a cost per CT screen of US$400 and statin costs of US$1000 per annum per patient. However, the arrival of generic statins has reduced the price of this drug dramatically, and these savings no longer apply. In this important systematic review, CT examination of the coronary arteries was able to detect calcification indicative of arterial disease in asymptomatic people, many of whom would be at low risk when assessed by traditional risk factors. The higher the CAC score, the higher the risk. Treatment with statins can reduce that risk. However, CT screening would miss many of the most dangerous patches of arterial disease, because they are not yet calcified, and so there would be false-negative results: normal CT followed.
by a heart attack. There would also be false-positive results in that many calcified arteries will have normal blood flow and will not be affected by clinically apparent thrombosis: abnormal CT not followed by a heart attack. For CT screening to be cost-effective, it has to add value over risk factor scoring by producing sufficient additional information to change treatment, and hence cardiac outcomes, at an affordable cost per quality-adjusted life-year. There was insufficient evidence to support this. Most of the National Screening Committee criteria were either not met or only partially met. It would be useful to have more data on the distributions of risk scores and CAC scores in asymptomatic people, the level of concordance between risk factor and CAC scores, the risk of cardiac events per annum according to CAC score and risk factor scores, information on the acceptability of CT screening, information about the radiation doses used, and a randomized controlled trial of addition of CT screening to current risk factor–based practice. 29

**ECHOCARDIOGRAPHY**

The magnitude of age-related public health problems such as atrial fibrillation and heart failure is enormous and escalating despite the conventional strategies for clinical risk factor assessment and management. Therefore, new paradigms for risk stratification need to be considered. Of all the currently available imaging technologies, echocardiography is likely the one with a wider margin of patient safety and that is also mature enough to be used in prevention. Alongside its unique characteristics of portability, availability at the population level, and relatively low cost, echocardiography is well positioned for use in preventive strategies. The ability to detect subclinical abnormalities early in the natural history of a disease may potentially allow treatment within the window of opportunity, interrupting the cascade of events that lead to adverse outcomes. 30 The important contribution of echocardiography in prognostication and its role in risk stratification have been shown in different studies. This shows that echocardiography has evolved from being solely a tool for confirming diagnosis to one that will also guide prevention of public health problems.

Carej et al in the DAVES trial (Disfunzione Asintomatica VEntricolare Sinistra) carried out echocardiographic examination of subjects with stage A heart failure, cardiovascular risk factors, and normal electrocardiogram and clinical examination results to: (i) define whether stage A subjects with risk factors are really free of functional or structural cardiac abnormalities; and (ii) assess the impact of the presence of risk factors and the incremental value of echocardiographic parameters in the prediction of progression of heart failure or development of cardiovascular events. 30 In this study, a total of 1097 asymptomatic participants underwent echocardiographic examination as a screening evaluation in the presence of cardiovascular risk factors. Left ventricular (LV) dysfunction, both systolic (ejection fraction) and diastolic (transmitral flow velocity pattern), was evaluated according to standard criteria. The participants were divided according to different criteria: presence of 1 or more risk factors, presence or absence of LV systolic dysfunction, and presence or absence of LV diastolic dysfunction. A follow-up period of 26±11 months was undertaken, with observation of primary (cardiac death, myocardial infarction, coronary artery bypass grafting, percutaneous transluminal coronary angioplasty, acute pulmonary edema, stroke, and transient ischemic attack) and secondary (cardiologist-made diagnosis of heart failure and heart failure hospitalization) end points. The multivariate analysis for independent predictors of combined end points showed that only age, gender, obesity, and systolic dysfunction represented the significant predictors. Echocardiography showed a high incremental value in the detection of systolic LV dysfunction and the prediction of cardiovascular events during follow-up in participants with at least 2 risk factors. Importantly, this study demonstrated that preclinical functional or structural myocardial abnormalities could be detected by echocardiography in asymptomatic individuals with 2 or more cardiovascular risk factors and without electrocardiogram abnormalities (stage A of heart failure classification). Moreover, the presence or absence of LV systolic dysfunction or LV diastolic dysfunction, as demonstrated by echocardiography, has incremental value to cardiovascular risk factors in predicting both the evolution toward more severe stage C heart failure and the occurrence of cardiovascular events.

The incremental value of left atrial (LA) deformation analysis by speckle tracking echocardiography compared with LA volume or LA ejection fraction as a cardiovascular risk marker has recently been evaluated. In a recent study by Cameli et al, LA function by speckle tracking echocardiography was compared with other conventional LA parameters for prediction of adverse cardiovascular outcomes. 31 This prospective study included 312 adults (mean age 71±6 years, 56% men) in sinus rhythm who were followed for development of first atrial fibrillation, congestive heart failure, stroke, transient ischemic attack, myocardial infarction, coro-
nary revascularization, and cardiovascular death. Global peak atrial longitudinal strain (PALS) by speckle tracking echocardiography was measured in all individuals by averaging all atrial segments (see Figure 4). The left atrium was assessed using biplane LA volume, LA ejection fraction, 4-chamber LA area, and M-mode dimension. All patients were followed for development of new outcome events (eg, atrial fibrillation, stroke, transient ischemic attack, myocardial infarction, coronary revascularization, congestive heart failure, and cardiovascular death). Of the 312 participants at baseline, 43 had 61 new events during a mean follow-up period of 3.1±1.4 years. All LA parameters were independently predictive of combined outcomes (P<0.0001 for all comparisons). Overall performance for prediction of cardiovascular events was greatest for global PALS (area under receiver operator characteristic curve: global PALS, 0.83; indexed LA volume, 0.71; LA ejection fraction, 0.69; LA area, 0.64; LA diameter, 0.59).

A graded association between degree of LA enlargement and risk of cardiovascular events was evident only for global PALS and indexed LA volume. Importantly, it was found in this study that global PALS is a strong and independent predictor of cardiovascular events and appears to be superior to conventional parameters of LA analysis.

In summary, we agree with the conclusions of Tsang at the Feigenbaum lecture 2008:

The magnitude of age-related public health problems, such as atrial fibrillation and heart failure, is enormous and is expected to increase in the foreseeable future. Echocardiography is safe and effective for the early detection of subclinical abnormalities, augmenting clinical risk prediction of first cardiovascular events. At this time, relatively little is known regarding the impact of reversing LA remodeling and diastolic dysfunction on outcomes, and studies that can provide greater understanding of the cost-effectiveness of population screening and monitoring are warranted. Echocardiography continues to rapidly evolve beyond its established role as a noninvasive diagnostic tool to one that will assume an integral role in the prediction and prevention of age-related cardiovascular outcomes.

CARDIAC HYBRID IMAGING FOR RISK STRATIFICATION

CT coronary angiography (CTCA) and myocardial perfusion imaging techniques are established noninvasive modalities for the diagnosis of CAD. Cardiac hybrid imaging consists of the combination (or “fusion”) of both modalities and allows complementary morphological (coronary anatomy, stenoses) and functional (myocardial perfusion) information to be obtained in a single setting. However, hybrid cardiac imaging has also generated controversy with regard to which patients should undergo such integrated examinations in terms of clinical effectiveness and minimization of costs and radiation dose. The feasibility and clinical value of hybrid imaging has been documented in small cohort studies and selected series of patients. Hybrid imaging appears to offer superior diagnostic and prognostic information compared with stand-alone or side-by-side interpretation of data sets. Particularly in patients with multivessel disease, the hybrid approach allows identification of flow-limiting coronary lesions and thereby provides useful information for the planning of revascularization procedures. Furthermore, integration of the detailed anatomical information from CTCA with the high molecular sensitivity of single-photon emission CT (SPECT) and positron emission tomography (PET) may be useful for evaluating targeted molecular and cellular abnormalities in the future. While currently still restricted to

Figure 4. Composite figure showing measurement of peak atrial longitudinal strain using speckle tracking echocardiography from an apical two-chamber view in a representative individual. Figure is from a study comparing left atrial function by speckle tracking echocardiography with other conventional left atrial parameters for prediction of adverse cardiovascular outcomes. An average atrial longitudinal strain along the cardiac cycle is depicted (dashed curve).

Abbreviations: AVC, aortic valve closure; PALS, peak atrial longitudinal strain.
specialized cardiac centers, the ongoing efforts to reduce radiation exposure and the increasing clinical interest will further pave the way for an increasing use of cardiac hybrid imaging in clinical practice. Figure 5 shows image fusion of a myocardial perfusion SPECT bull’s-eye plot and CTCA.37

Pazhenkottil et al carried out a study aimed at assessing the impact of cardiac hybrid imaging on the choice of treatment strategy for CAD in 318 consecutive patients who underwent a 1-day stress/rest (99mTc)-tetrofosmin SPECT and a CTCA on a separate scanner for evaluation of CAD.36 Patients were divided into one of the following 3 groups according to findings in the hybrid images obtained by fusing SPECT and CTCA images: (i) matched finding of stenosis on CTCA and corresponding reversible SPECT defect; (ii) unmatched CTCA and SPECT finding; and (iii) normal finding on both CTCA and SPECT. Follow-up was confined to the first 60 days after hybrid imaging, as this best allows assessment of treatment strategy decisions, including revascularization procedures, triggered by the findings of hybrid imaging. Hybrid images revealed matched, unmatched, and normal findings in 51, 74, and 193 patients, respectively. The revascularization rate within 60 days was 41%, 11%, and 0% for matched, unmatched, and normal findings, respectively (P<0.001 for all intergroup comparisons). The authors concluded that cardiac hybrid imaging with SPECT and CTCA provides added clinical value for decision making with regard to treatment strategies for CAD.

Figure 5. Image fusion of a myocardial perfusion single-photon emission computed tomography bull’s-eye plot and computed tomography coronary angiography (CTCA).

A. Stress perfusion polar map with questionable anterior and inferior reduction in counts. B. Normal left anterior descending coronary artery from CTCA. C. 30% soft plaque in left circumflex coronary artery (yellow arrow). D. Fused myocardial perfusion image and CTCA showing normal perfusion in the questionable area. E. CTCA three-dimensional surface projection.


A recent study by Johnson et al sought to understand the physiological integration of data obtained from different imaging techniques.34 The authors proposed two-dimensional scatter plots of stress flow and coronary flow reserve with superimposed thresholds for normal flow, reduced flow without ischemia, definite ischemia, and transmural infarction to allow for automatic and objective classification. Application of this schema to 1500 studies demonstrated that flow capacity is inversely related to risk factors and atherosclerotic burden. For broad application in all patients, interpretation of stress flow for clinical decision making requires rest flow or coronary flow reserve. Although relative uptake images alone are adequate in some patients, in many individuals, they can lead to either underestimation or overestimation of flow capacity. In conclusion, a standardized framework could prompt future studies and lead to a trial of revascularization guided by absolute flow measurements.34

INVASIVE IMAGING: ASSESSING PLAQUE VULNERABILITY

Cardiovascular imaging has played a major role in the identification and characterization of the so-called “vulnerable” plaque. A major goal in particular over the past few years has been the possibility of identifying individuals at risk of plaque rupture and therefore of developing an acute coronary syndrome. This early identification of atherosclerotic plaques that are more likely to rupture could lead to the development of pharmacological and interventional strategies aimed at reducing acute coronary events and their dreadful consequences.

The morphological characteristics of atherosclerotic plaques may be targeted by noninvasive and invasive imaging modalities such as angiography, intravascular
ultrasonography, optical coherence tomography, CT, and MRI. In addition, molecular imaging offers the possibility of better discriminating the individual components of plaque. Thus, in order to globally assess vulnerable plaque, imaging modalities should target plaque morphology and structure and plaque inflammation, apoptosis, and thrombosis, and provide information regarding flow and wall stress.

Intravascular ultrasonography has been used to try to identify high-risk plaques. Plaque features shown to be related to acute coronary syndromes are positive remodeling, plaque rupture, and hypoechoic plaque. Attenuated plaques are also frequently found in patients with acute coronary syndromes. These are defined as being hypoechoic with deep ultrasound attenuation, in the absence of calcification. Histopathology studies have shown microcalcification, cholesterol crystals, and importantly, thrombus in these plaques. Moreover, the burden of attenuated plaque correlates with no-reflow phenomenon in ST-segment elevation myocardial infarction. However, recognition of the existence of nonculprit attenuated plaques that remain stable during follow-up brings into question their usefulness in predicting acute coronary syndromes.

Although in vivo coronary arterial histology is not feasible, radiofrequency intravascular ultrasonography analysis provides characterization of vessel wall components with high accuracy. The images obtained are usually color-coded to discriminate dense calcium, the necrotic core, fibrofatty tissue, and fibrotic tissue. According to the relative amounts of the components, lesions may be classified as thin-cap fibroatheroma, thick-cap fibroatheroma, pathologic intimal thickening, fibrotic plaque, and fibrocalcific plaque. Optical coherence tomography is an imaging modality that uses light instead of ultrasound for generating intravascular images. Spatial resolution is about 10 times higher than with intravascular ultrasonography, but due to the limited depth of penetration, imaging of the vessel wall and plaque burden is often problematic. However, this imaging modality may provide characterization of plaque components, particularly the differentiation of fibrous, fibrocalcific, and calcific plaques. In addition, in patients with acute coronary syndromes, optical coherence tomography identifies fibrous cap disruption, fibrous cap erosion, intracoronary thrombus, and thin-cap fibroatheroma more frequently than does intravascular ultrasonography, making it an attractive imaging method for the identification of the vulnerable plaque. New and emerging optical coherence tomography modalities like polarization sensitive optical coherence tomography, which provides assessment of plaque collagen content, may expand the future capabilities of this intravascular imaging technique. However, large prospective studies in this area are currently lacking.
Angioscopy is an intravascular imaging modality that allows direct visualization of the plaque surface and luminal thrombus. Patients with yellow plaques more frequently develop acute coronary syndromes. Yellow plaques are usually thin-capped, exhibit positive remodeling, have high lipid content, and often present intraluminal thrombi. However, there are considerable limitations that impair further use of this technique, namely, the need for blood displacement and the subjectivity of the assessment of plaque color.

Other invasive imaging modalities currently under development that show promise for the morphologic detection of vulnerable plaques include near-infrared spectroscopy and intravascular magnetic resonance. In future, these modalities may be able to provide chemical characterization of plaque components, but their relevance still needs to be prospectively tested.

There are specific advantages and hurdles associated with each modality for imaging the vulnerable atherosclerotic plaque in the coronary arteries. There are certain technical and patient-security challenges associated with molecular imaging modalities that need to be overcome in order for them to become clinical tools. These imaging techniques should therefore be tested in clinical trials to assess their utility in real-life prediction of coronary events. Although all of these imaging modalities are very promising, ultimately, their ability to identify and differentiate patients that will benefit from intense medical therapy, local intravascular therapy, or preventive coronary bypass surgery will dictate their success.

Multimodal imaging integrating coronary morphology, wall composition, and characterization, in addition to coronary wall stress assessment, may provide a highly accurate and predictive assessment of the vulnerable plaque. In providing this integrated individual risk profile, invasive imaging modalities currently present several advantages over MRI and CT. They provide higher anatomical detail, have tissue characterization capabilities, and, in the case of intravascular ultrasonography, may assess inflammation and thrombosis through molecular imaging and localize high wall stress areas.

There is ample evidence to support a strong relationship between plaque morphology and patient outcome. However, molecular imaging may add significant relevant information concerning tissue inflammation and subclinical thrombosis. Additionally, identification of arterial wall exposed to high shear stress may further identify rupture-prone arterial segments. These new modalities may thus contribute to lowering the individual, social, and economic burden of cardiovascular disease.

Thus, much of the effort in the development of the new imaging modalities has come from the basic sciences. An integrative clinical translation of this work will be crucial to the future success of vulnerable plaque imaging for prediction of individual cardiovascular risk and development of pharmacological and interventional strategies to reduce acute coronary events.

**CONCLUSIONS AND FUTURE DEVELOPMENTS**

Evaluation of myocardial perfusion and the structures of coronary arteries using advanced technologies, such as MRI, advanced echocardiography, spiral CT, and a broad spectrum of nuclear cardiology techniques, is gaining more and more importance in the diagnosis and management of CHD. Detection of coronary ath erosclerosis and evaluation of early signs of myocardial hypoperfusion may significantly impact the selection of an effective treatment modality and may also provide risk stratification value. Nuclear cardiac studies are frequently being used in this field, and importantly, outstanding results are being achieved by PET and combined acquisitions involving PET/CT and SPECT/CT hybrid systems. CTCA and myocardial perfusion imaging provide additional complementary information to these techniques regarding vascular structure and myocardial perfusion. Spiral CT, which can reveal calcium deposits in blood vessels, has an important role in the detection of the severity and extent of atherosclerotic lesions. In the near future, use of multislice CT could potentially replace use of coronary angiography, particularly for assessment of the degree of stenosis and patency of grafts.

MRI has also had noticeable success in this field. Cardiac MRI clearly has potential and has already emerged as a robust method for assessing ventricular function, myocardial mass, and myocardial viability, and this approach is increasingly being used for clinical rest and stress perfusion measurements. While cardiac MRI angiography holds great promise as a radiation-free method, further improvement is needed regarding equipment and methodological approaches involving use of novel contrast agents to achieve the accuracy of CT angiography in noninvasive coronary angiography. In patients with CAD, the ideal approach would be to embrace multimodal applications that cover both mor-
phological and functional assessment to achieve early diagnosis and allow early planning of therapeutic strategies. Moreover, in the field of ultrasonography, recent developments have enabled objective quantification of global and regional ventricular function, and real-time evaluation of coronary walls and lesions. Although more knowledge about atherosclerotic lesions is gained through use of intravascular ultrasound, tissue Doppler and strain imaging have emerged as being able to provide a more objective assessment of myocardial function. In addition, three-dimensional quantification of carotid plaque by ultrasound may be a stronger predictor of atherosclerotic cardiovascular disease than the current two-dimensional approach. However, the predictive value of this novel approach will remain unknown until further prospective outcome data are obtained. Ultrasound and other imaging techniques that measure both anatomy and function provide well-validated surrogate markers for atherosclerosis that are incremental to the Framingham heart study score. Of course, as with any diagnostic test, careful use of pretest probability assessment to determine individuals most likely to benefit from an imaging modality (ie, those at intermediate risk), and individual interpretation and treatment on the basis of test results, are imperative.

AVC has been shown to serve as a marker of subclinical atherosclerosis severity. Whether AVC adds to cardiovascular risk prediction beyond the Framingham risk categorization merits additional investigation.

These new developments in imaging represent an economical and effective method of screening for CHD risk and for informing clinical management decisions. In summary, atherosclerosis is systemic, silent, and deadly. Primary risk reduction is effective; however, cost-effective risk modification relies on accurate and individualized risk stratification. Traditional risk factor-based assessments fail to account for individual progression along the pathophysiologic continuum. The incremental use of imaging as a reliable additional tool to help in preventing the development of heart disease is a reality and will certainly be an area of intense research in the near future. This research will document whether these approaches are clinically effective and have a positive cost/benefit ratio in the management and risk assessment of heart disease.

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Prevention Through Imaging

Expert Answers to Three Key Questions

1

Ultrasonic imaging of the carotid arteries, from intima-media thickness to histological markers for plaque vulnerability: what do we know?

A. G. Fraser, Y. Kyaw, M. Kozakova, C. Palombo

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Cardiac computed tomography: is the calcium score index outweighed by noninvasive angiography?

A. Saraste, J. Knuuti

3

Is echocardiography useful in prevention?

G. A. Derumeaux
Ultrasonic imaging of the carotid arteries, from intima-media thickness to histological markers for plaque vulnerability: what do we know?

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Carotid intima-media thickness has been evaluated as a predictor of cardiovascular disease and as a surrogate end point, but it cannot be equated with early atherosclerosis simply, because it reflects aging and hemodynamic load. Meta-analyses suggest that its added value as a risk factor is small, and that changes correlate poorly with clinical events. Carotid plaque is a stronger predictor of myocardial infarction and stroke. The protocols used in trials are rarely applied in routine practice. Prospective head-to-head comparisons are needed to demonstrate which imaging tools are most useful for preclinical diagnosis — because their results can influence treatment and outcomes — before these tests are advocated for individual patients.

The accessibility of the carotid arteries to noninvasive imaging means that their structure and function can be studied in great detail, most readily using ultrasound. Few would dispute that imaging should be performed in patients who have had a transient ischemic attack or a cerebrovascular accident, but it is much less clear if — or when — imaging should be performed for preclinical diagnosis. In healthy individuals, carotid intima-media thickness (CIMT) increases with age and with the presence of cardiovascular risk factors, and the carotid arterial wall stiffens. In asymptomatic individuals, atherosclerotic plaque and positive remodeling can be detected, and aspects of the composition of a plaque can be inferred by imaging its substructure. Conduit arterial function can be studied by measuring local distensibility. It has been suggested that imaging of the carotid arteries should be used not just as an epidemiological tool and as a surrogate end point for clinical trials, but also as an early diagnostic test in men aged over 45 years or women aged over 55 years.1-3

Keywords: carotid intima-media thickness; carotid plaque; arterial stiffness; cardiovascular risk; vascular ultrasound

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SELECTED ABBREVIATIONS AND ACRONYMS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ARBITER 6-HALTS</td>
<td>Arterial Biology for the Investigation of the Treatment Effects of Reducing cholesterol 6–HDL and LDL Treatment Strategies (trial)</td>
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<td>ARIC</td>
<td>Atherosclerosis Risk in Communities (trial)</td>
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<td>CAPS</td>
<td>Carotid Atherosclerosis Progression Study</td>
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<td>CCA</td>
<td>common carotid artery</td>
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<td>CHS</td>
<td>Cardiovascular Health Study</td>
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<td>CIMT</td>
<td>carotid intima-media thickness</td>
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<tr>
<td>DCCT</td>
<td>Diabetes Control and Complications Trial</td>
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<tr>
<td>EDIC</td>
<td>Epidemiology of Diabetes Interventions and Complications (trial)</td>
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<tr>
<td>ICA</td>
<td>internal carotid artery</td>
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<tr>
<td>MESA</td>
<td>Multi-Ethnic Study of Atherosclerosis</td>
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<td>MI</td>
<td>myocardial infarction</td>
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<td>RISC</td>
<td>Relationship between Insulin Sensitivity and Cardiovascular risk (trial)</td>
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There are already many well-validated scores for predicting cardiovascular risk, and there are also many biomarkers. In some studies, the presence of increased intima-media thickness or carotid plaque has been used to reclassify individuals at low or intermediate risk and place them at a higher risk level.\(^4,5\) Subclinical changes may reflect cumulative lifelong exposure to risk factors, which is not always captured by population-based risk algorithms; however, a recent large meta-analysis showed no relationship between change in CIMT and change in risk.\(^6\) It is therefore important to critically examine the added value and clinical utility of carotid ultrasound scanning before suggesting that it should be used routinely in individual patients at intermediate risk of cardiovascular disease—whether to guide decisions about treatment or to monitor responses.

**INTIMA-MEDIA THICKNESS AND PLAQUE**

*Pathological basis for assessment*

When the carotid arteries are imaged with ultrasound, their triple-layered structure is clearly visible (Figure 1). Using standard B-mode ultrasound, the thickness of the intima cannot be measured separately from the underlying echolucent layer that corresponds to the tunica media, whereas the adventitia is a strong reflector of ultrasound. The measurement that can be made thus represents the combined thickness of the intima and media.\(^7\)

Whenever CIMT is used as a marker of preclinical atherosclerosis, it is assumed that it is related to the severity of cardiovascular risk factors, and that increased thickness represents early atherosclerotic disease. However, an increase in CIMT may also represent adaptive remodeling caused by changes in intraluminal flow and pressure that affect shear and tensile stress.\(^8-10\) The cellular mechanisms that are involved in the expansion of CIMT differ for early atherosclerotic lesions and adaptive responses to hemodynamic changes. The former are characterized by accumulation of lipids and proteoglycans (intimal xanthomas) with loss of smooth muscle cells,\(^11\) whereas in the latter, there is an increase in the amount of smooth muscle cells and extracellular matrix (proteoglycans and collagen).\(^12,13\)

Plaques develop at sites of turbulent flow and low shear stress, so carotid plaques tend to be more prominent in the bulb and at the origin of the internal carotid artery (ICA). Most often, however, CIMT is measured in the common carotid artery (CCA), where flow is usually laminar. Plaque rupture is preceded by the development of inflammation and a necrotic core within the accumulated lipid pool, but CIMT does not reflect these processes.\(^12\) On average, the sensitivity of ultrasound scans of the carotid artery for detecting plaque ulceration is 60% (with 74% specificity).\(^14\)

Intima-media thickening varies at different sites. Differences between carotid segments can be explained by interactions between local hemodynamic factors, local cellular factors, and active circulating molecules.\(^15\) There is an asymmetrical pattern of CIMT thickening, with significant variations around the circumference of each carotid segment; on average, CIMT is greatest in the anterolateral wall of the CCA and the posteromedial wall of the ICA.\(^16\) In a study of 272 subjects, the correlation of CIMT (taken as the average of automated measurements of the far walls of both CCAs obtained in anterolateral views) with total carotid plaque volume between the clavicle and the angle of the jaw measured by 3-dimensional reconstructions was only 0.59.\(^17\) In a study of 27 patients, a detailed quantitative comparison showed no correlation between CIMT measured by vascular ultrasound and coronary intima-media cross-sectional area determined by intracoronary ultrasound.\(^18\)

Ten-year follow-up results from CAPS (Carotid Atherosclerosis Progression Study) showed that the inclusion of measurement of ICA plaque as well as CIMT was more useful for predicting stroke in an in-
individual than CIMT alone—whether in the CCA or at the bifurcation. Autopsies in 112 individuals with dementia and 577 controls demonstrated a correlation between ICA plaque with stenosis and dementia, whereas mean CIMT measured and averaged around the whole circumference showed no such correlation (odds ratios: 2.55 and 0.87, respectively). Since CIMT is correlated with older age and hypertension, which do not necessarily reflect atherosclerosis, the value of CIMT for predicting acute events related to plaque rupture has been questioned. At best, the association between CIMT and acute coronary syndromes is modest and does not necessarily indicate a common disease mechanism.

**Ultrasonic imaging: methods**

Consensus recommendations for optimal imaging techniques have been published. The CCA, the carotid bulb, and the proximal portions of the external carotid artery and ICA should all be imaged, using a high-frequency (7.5-10 MHz) linear-array vascular ultrasonic transducer. There is a small reduction in CIMT from end-diastole to systole (about 6%; less in diseased arteries), so measurements should be standardized from end-diastolic frames using a single longitudinal image of the CCA and three different views of the carotid bulb and ICA. CIMT should be calculated as the mean of all measurements in each segment; by convention, in the CCA, it should be averaged over a segment of the artery ≥1 cm in length, 1 cm proximal to the carotid bulb (Figure 2). CIMT can also be reported as the maximal value anywhere within the segment that is analyzed. In formal research studies, detailed images of multiple sites can best be made and compared using the Meijer Carotid Arc. The Mannheim consensus recommended that CIMT should be measured in the far wall of the carotid artery, since in the near wall, measurement of trailing rather than leading edges may reduce resolution and introduce errors. Other authors have reported that a mean value from both near and far carotid walls ensures the best reproducibility. Measurements of the lumen should be recorded. The luminal diameter of the CCA varies between men and women and between lean and obese subjects. CCA luminal diameter and intima-media thickness are highly correlated, so an adjustment for diameter is appropriate when comparing CIMT between unmatched populations.

Bots and colleagues estimated the sample sizes needed for studies using CIMT as a surrogate end point: for example, 273 subjects per group would have 90% power to demonstrate a 50% effect within 2 years in a parallel-group trial. By common definition, a plaque is a focal thickening of the intima and media that encroaches into the arterial lumen by >0.5 mm or by >50% of the CIMT measured in adjacent segments, or it is a focal increase in CIMT that exceeds 1.5 mm (Figure 3, page 90). The severity of carotid arterial stenosis assessed by ultrasound correlates well with...
angiographic measurements. A plaque score can be calculated and used to track changes in plaque burden over time.

### Normal values and reference ranges

Intima-media thickness is about 11% greater in men than in women; sex-specific differences are probably related to the effects of sex hormones on the carotid wall. Differences between males and females are no longer significant from the sixth decade onward, because progression accelerates in women after the onset of menopause.

CIMT is about 6% greater in the left CCA than the right CCA. It is higher in black individuals than in non-Hispanic white individuals.

In the Young Finns Study, in healthy young individuals aged 24-39 years, intima-media thickness values in men and women were 0.59±0.10 mm and 0.57±0.08 mm in the CCA, and 0.77±0.13 mm and 0.74±0.12 mm in the carotid bulb. Similar results were obtained in 614 healthy subjects aged 30-60 years in the RISC study (Relationship between Insulin Sensitivity and Cardiovascular risk). Intima-media thickness values in men and women, respectively, were 0.62±0.09 mm and 0.59±0.08 mm in the CCA, 0.77±0.12 mm and 0.73±0.11 mm in the bulb, and 0.64±0.11 mm and 0.59±0.11 mm in the ICA.

An abnormal intima-media thickness is usually defined as a value above the 75th percentile of age- and sex-specific ranges obtained from large and representative populations (such as those of the ARIC [Atherosclerosis Risk in Communities] and Bogalusa trials). The upper 95th percentile for CIMT increases from about 0.8 mm at age 45 years to about 1.2 mm at 65 years. As CIMT is strongly related to age, it is inappropriate to use single cutoff points of CIMT did not correlate with established risk factors. CIMT progression has been reported to correlate with endothelial dysfunction more than with baseline risk factors, supporting the hypothesis that endothelial dysfunction integrates and mediates the effects of risk factors, genetics, and lifestyle upon the arterial wall.

### Correlation of CIMT with risk factors

The strongest correlates of increased CIMT are increasing age and blood pressure, but there may be large variations between individuals of comparable age (Figure 4). Associations with numerous other risk factors have been established, including elevated low-density lipoprotein cholesterol, low high-density lipoprotein cholesterol, smoking, and physical inactivity. CIMT is increased in type 1 and type 2 diabetes mellitus and in patients with impaired glucose tolerance. Genetic factors that influence CIMT have been described. A genome-wide analysis in 31,211 individuals identified 3 single nucleotide polymorphisms that correlated with intima-media thickness, but together they accounted for only 1.1% of variance. More unusual variables that have been identified as independently contributing to CIMT include nutrition in childhood (a diet low in vegetables), personality, low testosterone levels, subclinical hypothyroidism, osteoarthritis, elevated C-reactive protein levels, chronic obstructive pulmonary disease, and fatty liver disease.

Cardiovascular risk factors correlate more strongly with baseline CIMT than with changes in CIMT, perhaps because there is substantially higher within-subject variance...
When measuring progression, it has been suggested that a single baseline measurement of CIMT reflects long-term exposure to vascular risk factors, whereas progression may be more influenced by short-term changes. Individuals with a significant short-term increase in their risk profile (determined using the Framingham risk score) show accelerated progression of CIMT. Progression that is accelerated by diabetes may be halted by intensive glycemic control.

**Using CIMT and/or Plaque for Predicting Risk**

**Coronary artery disease**

Every 0.1-mm increase in CIMT is associated with a 10%-15% increase in the risk of myocardial infarction (MI). In 37 197 individuals followed for a mean of 5.5 years, the age- and sex-adjusted estimate of the relative risk of MI per standard deviation difference in intima-media thickness in the CCA was 1.26 (95% confidence interval [CI], 1.21-1.30).

In the Tromso Study, 6226 men and women aged 25-84 years were followed for 6 years, and cases of new, first-ever MI were documented. The adjusted relative risk with comparison of the highest tertile of plaque area and no plaque area was 1.56 in men and 3.95 in women. Comparison of the highest and lowest quartiles of CIMT produced adjusted risk ratios of 1.73 in men and 2.86 in women. If carotid bulb intima-media thickness was excluded from the analysis, intima-media thickness did not predict MI in either sex.

In a Chinese population followed for 5 years, carotid plaque similarly predicted cardiovascular ischemic events, whether it was measured as the number of segments with plaque (multivariable adjusted hazard ratio [HR], 1.45; 95% CI, 1.09-1.93), the number of plaques (HR, 1.14; 95% CI, 1.02-1.27), or their total area (HR, 1.29; 95% CI, 1.08-1.55). CIMT at baseline in the absence of plaques also predicted risk (HR, 1.59; 95% CI, 1.04-2.45).

In a study of 783 patients with type 2 diabetes mellitus who were followed for 5.4 years, addition of CIMT measurement to the Framingham risk score increased the area under the receiver-operating curve (C-statistic) for predicting cardiovascular disease by only 1% (from 0.645 to 0.656). In the MESA study (Multi-Ethnic Study of Atherosclerosis), in patients with diabetes mellitus or metabolic syndrome, CIMT did not predict coronary heart disease or cardiovascular disease, whereas coronary calcification did predict these. Moreover, in nondiabetic individuals in MESA, CIMT did not significantly enhance risk prediction, whereas coronary artery calcium did. In the Rotterdam study of 3580 nondiabetic individuals aged 55-75 years, CIMT improved prediction of cardiovascular risk, but only in women, of whom 8% were reclassified.

Inaba and colleagues conducted a meta-analysis of 11 population-based studies that included 54 336 patients. They found considerable technical variation between the studies, some of which were based on maximal, and some on mean, CIMT values. Carotid plaque predicted future MI with an area under the receiver-operating curve (C-statistic) of 0.64, compared with 0.61 for CIMT.

When examined critically, the added value of CIMT is small, but the test does have the advantages of being simple, quick, reasonably reproducible, and cheap. The consensus from large observational studies is that a high CIMT value indicates a 10%-15% 10-year risk of developing coronary disease. by comparison, carotid plaque or a high coronary calcium score on computed tomography both predict a 10-year risk of about 20%-30%. In CHS (Cardiovascular Health Study), for example, the relative risk of MI or stroke associated with a high CIMT was 3.9. In MESA, the relative risk of clinical...
coronary artery disease associated with a high coronary calcium score on computed tomography was 9.7.

**Stroke**

An absolute increase in CIMT of 0.1 mm increases the risk of a future stroke by 13%-18%.48 Per standard deviation difference in intima-media thickness in the CCA, the relative risk of stroke is 1.32 (95% CI, 1.27-1.38).48 Carotid plaque area was found to predict stroke, MI, or vascular death over a period of 5 years, with a risk ratio of >3 between the lowest and highest quartiles; the risk was doubled in individuals with progression of plaque.

In MESA, progression of CIMT in the CCA over 32 months was associated with incident stroke.59 In ARTICO (not an acronym), a study of older individuals recruited after a first-ever noncardioembolic stroke, a high CIMT was related to recurrent stroke and death.60 In the Tromsø study of 4371 stroke-free middle-aged participants, total plaque area was an independent predictor of first-ever ischemic stroke,61 as well as cognitive function after 7 years.62 Cognitive function was not related to baseline CIMT.62 In individuals with asymptomatic carotid arterial stenosis, echolucent plaques at baseline were associated with an increased risk of ipsilateral stroke over the next 2 years.63 New methods for imaging the vasa vasorum within carotid plaques, such as contrast echocardiography, have shown that plaque neovascularization is associated with a history of MI and transient ischemic attack or stroke, with an odds ratio of 4.0.64

**Meta-analyses**

Imaging and measurement of CIMT should not be recommended for screening purposes unless there is evidence that baseline values or rates of progression significantly augment the prognostic power of traditional risk factors such as the Framingham score. Recent meta-analyses have addressed these questions.

Peters and colleagues reported a meta-analysis of studies that evaluated the increase in prognostic power when imaging was added to risk scores based on traditional risk factors. The added predictive value of CIMT was examined in 12 studies that included 76 102 subjects. The authors found that the C statistic of the prediction models was unchanged or increased by up to 3%.4 The net reclassification index among individuals at intermediate risk was 8%-11%. Addition of ultrasound diagnosis of plaque to traditional risk factors led to reclassification of risk in 14%-25% of subjects.

In ARIC, for example, after a mean follow-up interval of 15.2 years, the added value of imaging was low—the area under the curve for traditional risk factors alone was 0.741, and this changed to 0.754 when CIMT in the CCA was added, and 0.753 when both CIMT and plaque were considered.65

Den Ruijter and colleagues pooled the results of 14 population-based cohort studies that included a total of 45 828 participants who had been followed for a median of 11 years. Measurement of CIMT made no difference to the risk prediction models, and even in subjects at intermediate risk, the net reclassification index was only 3.6%.66

Accelerated progression of CIMT fares little better as a prognostic tool. Although it predicts clinical events,67 a recent meta-analysis of 21 general population studies including 36 984 participants with a mean follow-up of 7 years did not prove the association between CIMT progression and cardiovascular risk.4

**CIMT as a surrogate end point for clinical trials**

Goldberger and colleagues reported a meta-analysis of 28 randomized controlled trials that compared changes in CIMT over time in 15 598 patients and controls (mean age 55 years).68 Overall, for each 0.01 mm per year smaller rate of CIMT increase, the incidence of nonfatal MI was reduced by 18%, but the effect was less strong if the initial CIMT value was high. Numerous clinical trials have confirmed the clinical benefit of statins, but in 10 trials of statins included in this meta-analysis, there was no significant relationship between mean change in CIMT and reduction in nonfatal MI.68 An informative example was ARBITER 6-HALTS (ARterial Biology for the Investigation of the Treatment Effects of Reducing cholesterol 6–HDL And LDL Treatment Strategies), a study of a statin combined with ezetimibe or niacin in which a fall in LDL cholesterol was paradoxically associated with an increase in CIMT.69 This makes no intuitive sense and suggests that CIMT was an inappropriate (or unvalidated) surrogate end point. This conclusion is supported by the finding in the aforementioned meta-analysis that the relationship between change in CIMT and impact on clinical end points was stronger in trials of antihypertensive drugs.

In DCCT (Diabetes Control and Complications Trial)/EDIC (Epidemiology of Diabetes Interventions and Complications), the first 6.5 years of intensive glycemic control slowed the progression of CIMT in type 1 diabetic patients, but event rates were too low to detect any as-
Association between change in CIMT and cardiovascular events. In the CHS study, an increase in arterial diameter (positive remodeling) was itself a predictor of new cardiovascular events.

Labreuche and colleagues identified 26 randomized studies of lipid-lowering drugs that reported changes in CIMT. A reduction in LDL cholesterol levels was associated with reduced progression of CIMT, but changes in triglyceride levels were not. In 51 studies of patients with familial hypercholesterolemia, statins reduced CIMT by an average of 0.025 mm, but the impact on clinical events was not reported.

Other meta-analyses of many studies that have used CIMT as an end point reached similar conclusions; namely, that progression or regression of CIMT did not correlate with changes in cardiovascular events.

MEASURING CAROTID ARTERIAL FUNCTION

Stiffening of conduit arteries is a different aging process to intima-media thickening. Arterial stiffness varies at different sites, and different types of large arteries may age at different rates. Measurements of the biomechanical properties of the carotid artery may be different to those of the aorta. Peterson’s pressure-strain elastic modulus (epsilon) in the CCA is moderately associated with aortic stiffness (pulse wave velocity, \( r^2 = 0.6 \)). Carotid plaques, but not intima-media thickness, are associated with increased aortic stiffness. Increased carotid stiffness is associated with reduced longitudinal function and diastolic dysfunction of the left ventricle.

Vascular ultrasonic systems can be used to estimate arterial distensibility by relating changes in diameter or area to changes in pressure. Ideally, pressure should be measured locally, but this is difficult to carry out noninvasively; arm blood pressure may be substituted, which introduces imprecision into the measurements, or local pressure can be measured using a calibrated tonometer. Changes in arterial diameter are best assessed using an automated method (Figure 5). Reproducibility is moderate, but can be improved by tracking radiofrequency signals from the arterial walls during the cardiac cycle.

There may be significant differences between results obtained with different ultrasound systems.

Parameters of local arterial stiffness that can be obtained from local measurements of diameter and pressure include the pressure-strain elastic modulus (epsilon), the stiffness parameter (beta), and arterial compliance. In a recent pooled analysis of more than 2000 individuals, age accounted for 57% of the variability in epsilon, 51% of variability in beta, and 41% in arterial compliance. On average, blood pressure accounted for a further 7% of variability. Correlates of arterial stiffness have been reported from large population studies in children and adults.

As with CIMT, measurement of carotid arterial distensibility can only be advocated if the results have prognostic or therapeutic implications. Aortic stiffness estimated from mean wave speed has a well-established prognostic value, but fewer studies of local stiffness in the carotid arteries exist. A long-term follow-up (13.8 years) of ARIC was recently published; after full adjustment for risk factors and CIMT, all arterial stiffness parameters except arterial compliance predicted incident stroke, but not coronary disease. For example, the hazard ratios were 1.19 for arterial distensibility and 1.13 for the elastic modulus.

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Cardiac computed tomography: is the calcium score index outweighed by noninvasive angiography?

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Cardiac computed tomography (CT) offers new possibilities in the diagnostic evaluation and risk stratification of coronary artery disease (CAD). Coronary calcium can be detected using nonenhanced CT scanning with low radiation doses. Coronary CT angiography due to its higher radiation dose, is mainly used to exclude obstructive CAD in symptomatic patients, but it also detects both calcified and noncalcified plaques that do not cause significant luminal obstruction, and which provide incremental prognostic information over and above the presence of obstructive lesions and information on clinical variables. Current data do not support the use of coronary CT angiography for screening for obstructive CAD in asymptomatic individuals, but characterization of coronary plaques with the use of CT may have a role to play in the future.

Coronary computed tomography (CT) imaging with a multidetector device offers the possibility of noninvasive detection and risk stratification of coronary atherosclerosis.1 CT scans performed with a relatively low radiation dose and without injection of a contrast agent can be used to detect and quantify coronary calcium. Coronary calcium has shown high predictive value for future cardiac events in asymptomatic individuals. Coronary CT angiography (CTA) performed after injection of intravenous iodinated contrast agent allows detection of obstructive coronary stenoses as well as both calcified and noncalcified plaques. Ruling out obstructive coronary artery disease (CAD) in symptomatic patients has been documented to have prognostic value, and the incremental prognostic value of detecting obstructive or nonobstructive lesions by CTA has recently been investigated. This article will give an updated overview of the cardiac CT techniques for detection and risk stratification of coronary atherosclerosis, followed by a discussion of whether the benefits of calcium scoring are outweighed by the benefits of CT angiography in this respect.

CORONARY CALCULUM

Coronary calcifications are a very specific feature of atherosclerosis.2,3 Although not every atherosclerotic plaque shows calcification, the amount of calcium present roughly correlates with the extent of the coronary atherosclerotic plaque burden.4,7 Measurement of coronary...
calcium by CT is therefore an interesting tool for the detection and quantification of atherosclerosis.

It is important to note that the amount of coronary calcium present is only weakly correlated with the presence of significant luminal stenosis, which causes the symptoms of CAD. Furthermore, coronary calcification is not an indicator of plaque stability or instability, and it does not predict the likelihood of an individual atherosclerotic lesion rupturing and causing an event.

**Detection**

Coronary calcium can be detected using a noncontrast electrocardiogram (ECG)-gated CT scan of the heart (Figure 1). With the proper technique, the radiation exposure is relatively low, approximately 1-2 mSv. Use of the Agatston score is the most common method of quantifying coronary calcium. The score accounts for both the volume and density of the calcified deposits. Coronary calcium increases with age; therefore, the score is normally reported as both an absolute value and a percentile band based on reference datasets with calcium stratified by age and gender.

**Prognostic value**

Large prospective cohort studies of different populations have shown that a coronary calcium score (CCS) provides additional prognostic information to a traditional risk factor–based assessment of mortality and other major cardiac end points in asymptomatic individuals.

Even a small amount of calcium is associated with increased risk. Of 6809 participants in MESA (Multi-Ethnic Study of Atherosclerosis), the 908 individuals with an Agatston score of between 1 and 10 had a threefold higher risk for major cardiac events compared with individuals without detectable calcium. Increasing amounts of calcium are associated with an increasing degree of risk. In MESA, compared with patients with no coronary calcium, major cardiac event rates in patients with a calcium score of between 101 and 300 were increased 7.73-fold, and 9.67-fold in those with a score of over 300.

In MESA, compared with conventional risk stratification based on the Framingham risk score, addition of CCS led to a significant improvement in classification of patient risk, with more patients placed in the low- and high-risk groups. Similar results were also obtained in a European population, as shown by a high net reclassification rate (21.7% in the intermediate risk population). Notably, CCS performed much better than the blood biomarker high sensitivity C-reactive protein, and even better than ultrasound measurement of carotid intima-media thickness.

A calcium score of 0 is associated with a very low risk of future myocardial infarction and mortality. However, it is important to note that the absence of calcium does not exclude the possibility of significant obstructive CAD in symptomatic individuals, because not all plaques are calcified. An example of such a case is shown in Figure 2. In one study, 16% of such patients showed ischemia on myocardial perfusion investigation, despite having a CCS of 0, resulting in a negative predictive value of only 84%. This is more likely to be the case in the setting of unstable angina or non-ST-segment elevation myocardial infarction (NSTEMI) than in stable chest pain, and it occurs more frequently in younger patients.

**Clinical implications**

Assessment of absolute risk of cardiovascular disease has become routine clinical practice and is recommended in multiple recent guidelines. The guidelines indicate that measurement of coronary artery calcification is reasonable to improve risk assessment in asymptomatic adults at moderate risk. The identification of established atherosclerosis in an asymptomatic patient provides important information for risk management. However, disease screening should also enable patient selection for treatments that can improve outcome, and the
process should be cost effective. Use of CCS improved adherence to lifestyle modification and medication in some, but not all studies. In addition, the cost implications of CCS remain largely unknown. Since CCS is essentially a risk prediction tool, it is not recommended for patients with established coronary artery disease, and the value of repeat follow-up testing is uncertain.

**CORONARY CT ANGIOGRAPHY**

Current multislice devices coupled with up-to-date acquisition protocols allow robust and reproducible assessment of coronary atherosclerosis with high temporal and spatial resolution as well as an acceptable radiation dose. By comparison with a calcium scan, the use of CTA involving intravenous injection of an iodinated contrast agent and a substantially higher radiation dose raises concerns, especially in asymptomatic individuals. Helical scanning with retrospective selection of the phase of the cardiac cycle used for image interpretation is associated with a high effective dose, typically in the order of 20 mSv. However, improvements in image acquisition protocols, particularly the introduction of ECG-driven tube current modulation, body mass index–adapted tube voltage modulation, and prospective ECG-triggered sequential scanning that limits radiation exposure to the selected phase of the cardiac cycle, can be associated with doses that are 5 or 10 times lower. Moreover, the most recent high-pitch scanning protocols using dual-source CT scanners have lowered doses even further into the submillisievert range. However, there is still considerable variability in the radiation doses used in multicenter studies, suggesting that in real-life clinical routine, the radiation dose may be higher than could be achieved with use of the newest techniques.

**Detection of coronary stenosis**

Many single-center studies as well as multicenter studies have demonstrated high diagnostic accuracy with CTA for the identification of significant coronary artery stenosis, and very low rates of unevaluable scans in patients with low-to-intermediate likelihood of obstructive CAD. In the ACCURACY trial (Assessment by Coronary CompUted tomogRaphic Angiography of individuals undergoing invasive Coronary angiographyY), 230 patients underwent CTA and invasive coronary angiography. In a patient-based analysis, the sensitivity, specificity, positive predictive value, and negative predictive value to detect ≥50% stenosis were 95%, 83%, 64%, and 99%, respectively. Most studies have shown that CTA has a particularly high negative predictive value—close to 100%. Positive predictive value is usually lower, mainly because there is a tendency to overestimate the degree of stenosis in the presence of artifacts, such as the blooming artifacts caused by dense calcified plaques. Furthermore, it is notable that the angio-

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Figure 2. Presence of significant obstructive coronary artery disease in the absence of any coronary calcium.

The patient is a 33-year-old male who was referred for coronary computed tomography angiography (CTA) due to a history of atypical chest pain.

A. A coronary calcium scan showed no calcium (Agatston score = 0).

B. Multiplanar reconstruction images of coronary CTA after intravenous contrast injection showed a stenosis in the distal right coronary artery, and the right posterolateral branch was missing, suggesting total occlusion (arrows).

C. Invasive coronary angiography confirmed the findings of CTA (arrows) and the patient was treated successfully with percutaneous balloon angioplasty and stenting.
graphic severity of a coronary lesion is a poor predictor of its hemodynamic relevance, and only a proportion of stenoses are associated with myocardial ischemia. Thus, combination of CTA with a functional assessment such as a myocardial perfusion study can be beneficial in evaluation of intermediate stenoses for the identification of those patients who may benefit from revascularization. Coronary CTA has become an established noninvasive method recommended in recent guidelines for the detection of — and particularly for ruling out — significant coronary stenosis in asymptomatic patients with suspected CAD.

Ruling out obstructive CAD by CTA obviously has prognostic value in symptomatic patients with suspected CAD. A meta-analysis and data from a large registry in patients with low or intermediate likelihood of CAD indicate that individuals with normal CTA findings have very low rates of major cardiac events and mortality (as low as 0.3% per year). The addition of coronary CTA information regarding the presence of obstructive CAD and extent of atherosclerosis on top of clinical variables and CCS scores resulted in a significant improvement in the prediction of cardiac events (cardiac death, myocardial infarction, unstable angina, or revascularization later than 90 days) in a population of 2223 patients.

So far, there have been few data on the prognostic value of CTA in the asymptomatic population due to the large sample size that is needed because of low event rates. Recent data from the CONFIRM registry (CORonary CT angiography evaluationN For clinical outcomes: an International Multicenter) of 27,125 patients, 7590 of whom were asymptomatic and underwent CTA, demonstrated that the presence of obstructive CAD significantly predicted all-cause mortality. However, the net improvement in reclassification that resulted from the addition of coronary CTA to a model based on standard risk factors and CCS scores was negligible, suggesting that the additional risk prediction advantage of detecting obstructive CAD by CTA is not significant enough to justify its application in asymptomatic patients.

**Imaging of atherosclerotic plaque with CTA**

Beyond detection of coronary stenosis, coronary CTA can detect both calcified and noncalcified atherosclerotic plaque (Figure 3). A large proportion of patients with suspected CAD who are referred for CTA have coronary atherosclerotic lesions that do not cause significant anatomical luminal obstruction. The presence of such nonobstructive coronary artery lesions provides incremental prognostic information over and above the presence of obstructive lesions and information about clinical variables.

Evidence is accumulating to suggest that characterization of atherosclerotic plaque is to some extent possible with CTA. Plaque characterization by coronary CTA has been validated against other imaging modalities, including intravascular ultrasound virtual histology and optical coherence tomography (reviewed in reference 35). Some features, such as large plaque size, low attenuation, spotty calcifications, and eccentric vascular remodeling, have been associated with culprit lesions in acute coronary syndromes. In clinical studies, qualitative characterization of plaques using calcified, noncalcified (so-called soft plaques with presumably high lipid content), and mixed (ie, plaques with calcified and noncalcified components) categories is the most common approach. Pandziiute and colleagues reported that the mixed plaque phenotype carries an independent prognostic value. Subsequent studies have identified noncalcified plaques with low CT plaque attenuation and positive vessel remodeling to be predictors of future acute ischemic events. One study indicated that the presence of noncalcified plaque could provide additional prognostic information to CCS.

**Figure 3. Visualization of characteristics of coronary atherosclerotic plaques in computed tomography angiography images.**

A. A multiplanar reconstructed image of a noncalcified plaque (arrow) in the ostium of the left coronary artery as well as calcified plaques (arrowheads) more distally. B. A plaque with both calcified (arrowhead) and noncalcified (arrow) areas in the proximal right coronary artery.
**CALCIUM SCORE OR ANGIOGRAPHY?**

As described, the CT techniques involving CCS and angiography have different strengths and weaknesses. Imaging of CCS is a very strong technique for detecting and quantifying the atherosclerotic process in coronary arteries directly and noninvasively and with quite a low radiation dose. This makes it a more powerful risk stratification tool than other traditional risk factors and clinical variables. However, its main limitation is that the calcium score does not provide any information about coronary stenoses, and thus it cannot exclude even significant coronary stenoses in symptomatic patients. In addition, the use of calcium score imaging in screening for CAD in asymptomatic patients has been criticized due to a lack of strong evidence that it has an impact on subsequent therapy and prognosis. Also, the cost effectiveness is incompletely understood.

Noninvasive CTA offers a new possibility of noninvasive detection of coronary artery plaques and stenoses. Its diagnostic and prognostic value in symptomatic populations, especially in patients with low to moderate likelihood of CAD, has been quite well studied. However, the technique is more expensive than other techniques and utilizes contrast agents associated with nontrivial risk. In addition, although the newest techniques allow very low radiation dose scanning, these techniques may not currently be utilized in the majority of clinical centers, and the radiation dose will therefore very likely be significantly higher than that used with calcium score imaging. Although it has been shown that CTA can better characterize coronary plaques and identify both calcified and noncalcified plaques as well as obstructive and nonobstructive lesions, it has not shown an additional risk-predictive advantage over other risk factors and calcium scoring in asymptomatic patients.

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Is echocardiography useful in prevention?

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Cardiovascular events remain major contributors to hospitalization and death. Cardiovascular risk assessment would benefit from identifying patients with silent/subclinical cardiovascular disease. Biomarker analysis and recent developments in imaging have now made this possible. Echocardiography allows quantitation of cardiac functional disturbances and evaluation of structural myocardial tissue alteration. Stress echocardiography detects coronary artery disease and can be used for risk stratification based on the myocardium’s response to stress. Combining clinical data with stress test findings confers greater prognostic power. Doppler imaging and deformation imaging have the potential to identify alterations in myocardial function too subtle for conventional echocardiography to detect. However, to avoid runaway costs, use of detailed echocardiography should be targeted to patients positive for biomarkers for subclinical myocardial dysfunction.

Primary prevention is focused on achieving target levels for longstanding risk factors such as blood pressure and cholesterol, and then awaiting symptoms of overt heart disease. Despite the benefits of primary prevention, cardiovascular events are still the most common cause of hospitalization and death, and it has been estimated that 43% of coronary events would still occur even if we achieved perfect risk factor control.

Myocardial infarction represents the first clinical manifestation of coronary artery disease in 50%-65% of previously asymptomatic patients, and approximately 35% of these events are fatal. Moreover, sudden cardiac death is unfortunately the first manifestation of cardiovascular disease in 40%-50% of previously asymptomatic individuals. Among these individuals, it is therefore crucial to identify those with silent cardiac target organ damage. Identification of subclinical disease may have implications for primary prevention.

In the assessment of cardiovascular risk, evaluation of clinical characteristics and the presence of cardiovascular disease risk factors remains the mandatory initial step that allows quick identification of high-risk individuals who might benefit from more rigorous treatment. However, additional strategies are greatly needed to further refine risk assessment and identify subclinical cardiovascular disease to ensure adequate prevention programs. To this end, the use of biomarkers and noninvasive imaging modalities has been proposed. Recent recommendations from the European Society of Cardiology acknowledge the relevance of imaging methods for cardiovascular disease risk assessment in individuals at moderate risk. The consequences of coronary atherosclerosis can be objectively assessed noninvasively using a variety of techniques such as bicycle or treadmill exercise electrocardiogram (ECG) testing, stress echocardiography, and radionuclide scintigraphy. Recent developments in measurement of cardiovascular structure and function have made the imaging of subclinical cardiovascular disease in population-based studies feasible and accurate, providing specific, detailed information that relates more directly to pathology. This review will explore more specifically the role of echocardiography in the diagnosis of subclinical cardiovascular disease.

**STRICTURAL ALTERATIONS AND MYOCARDIAL CHARACTERIZATION IN SUBCLINICAL CARDIOVASCULAR DISEASES**

In order to detect subclinical cardiac dysfunction, the underlying pathophysiology of the myocardial disease should be targeted. Aside from alterations in microcirculation that are related to decreased myocardial blood flow or capillary rarefaction and myocyte dysfunction, abnormalities in extracellular matrix remodeling and subsequent development of myocardial fibrosis have been highlighted as substrates for ventricular arrhythmias in many car-
diovascular diseases and increased myocardial stiffness, thereby promoting cardiac dysfunction. As interstitial fibrosis also involves perivascular areas, the process induces decreased vasodilator capacity in the intramyocardial segments of coronary arteries, resulting in reduced coronary flow reserve and subsequent myocardial dysfunction. Diffuse reactive interstitial fibrosis is a labile process that may be governed in the nonischemic setting by extrinsic factors such as blood glucose and blood pressure levels. The process is exemplified in diabetic cardiomyopathy, hypertensive cardiomyopathy, and metabolic syndrome characterized by diffuse myocardial fibrosis and myofibrillar hypertrophy without evidence of valvular, congenital, hypertensive, or ischemic heart disease. Affected patients may present with symptoms of cardiac failure, although often they have subclinical disease.

In patients with these pathological conditions, noninvasive assessment of the presence of myocardial fibrosis is relevant—both for screening in asymptomatic patients and monitoring in patients with cardiac dysfunction. Various imaging modalities and collagen biomarkers have been used to provide surrogate markers to assess the presence, extent, and turnover of myocardial fibrosis. The goal of this approach is to enable targeted therapy to be instituted earlier, leading to prevention of disease progression and fibrosis accumulation in the long term.

Aside from cardiac magnetic resonance imaging (delayed enhancement after gadolinium infusion and T1 mapping), techniques have been developed in echocardiography to detect and quantify myocardial fibrosis (integrated backscatter) and to assess early features of systolic and diastolic left ventricular dysfunction (myocardial Doppler imaging and deformation approaches). Findings using ultrasonic tissue characterization by calibrated integrated backscatter have been shown to be related to measures of myocardial collagen content, and fibrous tissue accumulation has previously been shown to be a major determinant of altered myocardial acoustic properties. The different amplitudes of integrated backscatter have also been correlated with circulating biomarkers, such as elevated serum concentrations of procollagen propeptides in hypertensive and diabetic patients.

Integrated backscatter offers the advantage of greater availability than contrast cardiac magnetic resonance imaging. However, despite great potential, integrated backscatter is not yet used routinely in clinical practice, and it remains a research tool. In addition, further studies are needed to standardize the integrated backscatter method among the different echocardiography machine vendors and to determine the threshold values that justify additional preventive or therapeutic interventions.

Modern echocardiography machines provide simple tools for analyzing two myocardial backscatter parameters: (i) magnitude of cyclic variation in integrated backscatter, a marker of regional function influenced by anisotropy, and (ii) calibrated integrated backscatter, calculated from tissue intensity curves derived offline (Figure 1). A greater calibrated integrated backscatter is indicative of greater myocardial interstitial fibrosis. This technique has been used to assess diffuse fibrotic pro-

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**Figure 1. Myocardial integrated backscatter.** The measurement of myocardial integrated backscatter is usually performed in the parasternal long-axis view on regions of interest in the interventricular septum and the posterior wall. The value of myocardial calibrated integrated backscatter obtained at end diastole is calculated by subtracting average pericardial integrated backscatter intensity from average myocardial integrated backscatter intensity for the septum and posterior wall. Measurements of tissue intensity are obtained from sample volumes (4 × 4 mm) placed within the posterior wall (blue), and septum wall (green). A resultant integrated backscatter curve is derived using standard commercial software (EchoPAC, General Electric Medical Systems, Milwaukee, Wisconsin).
cesses in various pathological settings such as diabetic heart disease,15 metabolic syndrome,16 and systemic hypertension.17

The link between interstitial fibrosis, as assessed by integrated backscatter, and left ventricular dysfunction has been demonstrated in recent studies performed in patients with diabetes mellitus15 and metabolic syndrome.16 In subclinical disease, conventional echocardiography may fail to identify subtle myocardial dysfunction. New ultrasound techniques aimed at assessing regional myocardial function such as tissue Doppler imaging and deformation imaging can be used to assess myocardial tissue velocity and deformation parameters (systolic strain and strain rate), and they have the potential to unmask alterations in myocardial function that may be related to myocardial fibrosis.18

Reductions in myocardial velocity and strain appear to be sensitive markers of subclinical heart disease in many conditions associated with fibrosis including diabetes and hypertension (Figures 2 and 3). A reduction in both parameters has been detected in patients with diabetes but normal ejection fraction,19 and an inverse relationship between deformation parameters and backscatter in left ventricular hypertrophy and diabetes further supports the notion that underlying fibrosis is a common pathology.20 Cine-DENSE (displacement encoding with stimulated echoes) magnetic resonance imaging, a novel technique to assess myocardial deformation, has recently been able to confirm these results in diabetic patients.21 Finally, recent studies provide support for previous findings that antifibrotic treatment such as aldosterone antagonism improves myocardial function in hypertensive patients.22
Echocardiography is therefore an interesting noninvasive imaging option that allows not only the quantitation of cardiac functional disturbances, but also the evaluation of structural alterations to myocardial tissue.

**IMAGING OF CARDIAC MORPHOLOGY AND FUNCTION**

Echocardiography may play an important role in the identification of the patient at high risk. Indeed, by virtue of it being noninvasive and without the need for radiation exposure, echocardiography is uniquely positioned to provide additional information that is so essential in managing the high-risk individual.

A worse cardiovascular prognosis has been associated with the degree of left ventricular hypertrophy, the presence of systolic or diastolic myocardial dysfunction (which may be asymptomatic), and the presence of stress-induced ischemia.

Indeed, the detection of both left ventricular hypertrophy in itself and its type help in the risk stratification of hypertensive patients.\(^{23,24}\) Left ventricular mass index was significantly associated with the cardiovascular event rate in a population with left ventricular hypertrophy.\(^{23}\) Concentric left ventricular remodeling characterized by an increase in relative wall thickness with minimal or no increase in left ventricular mass is associated with a higher event rate than normal. The worst prognosis is seen in patients with concentric hypertrophy (increase in mass with normal ventricular size), whereas an intermediate risk is seen in those with eccentric hypertrophy (increase in mass with increase in ventricular size).

Moreover, a few studies indicate that the regression of left ventricular hypertrophy under antihypertensive treatment is associated with a reduction in the risk of cardiovascular events, independent of the ambulatory blood pressure.\(^{25-27}\) Therefore, left ventricular hypertrophy might be regarded as an intermediate criterion, and its regression might be used as a surrogate end point for risk assessment in systemic hypertension.\(^{28}\) Although left ventricular hypertrophy may be a valuable criterion, there are important limitations associated with its measurement using echocardiography based on M-mode that lead to poor reproducibility. In the LIVE trial (Left ventricular hypertrophy regression: Indapamide Versus Enalapril) trial, the standard deviation of differences between one examination and another reached 50 g.\(^{29}\) It has not yet been demonstrated whether three-dimensional echocardiography can improve the evaluation of left ventricular hypertrophy and its changes with therapy, although encouraging reports have shown that it can achieve a similar degree of accuracy to magnetic resonance imaging despite there being a slight overestimation of left ventricular mass with three-dimensional echocardiography (Figure 4).\(^{30-32}\)

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Figure 4. An example of three-dimensional echocardiography. The acquisition of the left ventricular volume enables the measurement of left ventricular mass in addition to left ventricular volume, ejection fraction, and strain.
The importance of systolic and diastolic function in determining prognosis is also well documented. Although depressed left ventricular function is easy to recognize by assessment of left ventricular ejection fraction, identification of subtle myocardial dysfunction is also important to identify, as it represents a first step toward further deterioration. This is particularly crucial in hypertensive patients in whom normal ejection fraction may mask alterations in myocardial contractility. Myocardial contractility increases to match arterial load in asymptomatic hypertensive heart disease, but progression to heart failure with preserved ejection fraction may be mediated by processes that simultaneously impair myocardial contractility and increase passive myocardial stiffness.33

Furthermore, assessment of diastolic function is crucial for predicting cardiac risk. Recent recommendations from the American Society of Echocardiography/European Association of Echocardiography have described the techniques for grading the severity of diastolic dysfunction and have highlighted the role of a simple parameter, left atrial volume, as a sensitive cumulative marker of diastolic dysfunction.34 Tsang et al have also shown that left atrial enlargement and echocardiographic abnormalities like left ventricular hypertrophy, left ventricular systolic dysfunction, and left ventricular diastolic dysfunction each independently predict cardiovascular events (hazard ratios, 1.42 to 1.70).35

Stress echocardiography is a valuable technique that allows the detection of coronary artery disease and stratification of cardiovascular risk based on the response of the myocardium to stress. Data are quite limited regarding the prognostic utility of noninvasive measures of myocardial ischemia induced in apparently asymptomatic people. Very few prognostic studies have included adequate numbers of asymptomatic people, and few data exist to support the use of noninvasive testing modalities to screen asymptomatic populations for high-risk subclinical coronary artery disease. The European Association of Echocardiography recently published an expert consensus for performance, interpretation, and application of stress echocardiography.36 Stress echocardiography provides different markers of severity and prognosis, such as the ischemic threshold, the double product of heart rate and blood pressure, and the presence and extent of ischemia. Individuals who have normal wall motion and no ECG changes during exercise and who can exercise for more than 9 minutes on the treadmill have a very low cumulative risk of cardiovascular events in the ensuing 3 years (1%); by contrast, those who have a high risk score have an event rate that is close to 30%.37 In addition to the binary approach to positive and negative test results, the development of multivariate scores combining clinical data with stress test findings permits the assessment of disease probability and outcome, and these appear to have greater prognostic power than the stress data alone.37,38 Thus, the application of this composite score rather than the results of stress echocardiography alone may further streamline the allocation of low risk to individuals who do not require further investigation, while not compromising those few individuals without ischemia who are at risk and do warrant further consideration.

CONCLUSION

In current primary prevention, echocardiography has the technical capacity and potential to be used to investigate asymptomatic patients in order to identify silent and/or subclinical myocardial disease. However, the ultrasound “phenotyping” of all primary prevention patients would be prohibitively expensive. What might reduce the costs of phenotyping would be pre-screening treated primary prevention patients for a biomarker that identifies those patients with subclinical myocardial dysfunction, and then targeting only this group of patients for detailed cardiac ultrasound “phenotyping.”

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Prevention Through Imaging

Summaries of Ten Seminal Papers

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Dialogues Cardiovasc Med., 2013;18:113-123

1. Coronary artery calcium score combined with Framingham score for risk prediction in asymptomatic individuals
   P. Greenland and others. JAMA. 2004

2. Economic burden of cardiovascular diseases in the enlarged European Union
   J. Leal and others. Eur Heart J. 2006

3. Intravascular ultrasound radiofrequency analysis of coronary atherosclerosis: an emerging technology for the assessment of vulnerable plaque
   S. K. Mehta and others. Eur Heart J. 2007

4. Coronary artery calcification compared with carotid intima-media thickness in the prediction of cardiovascular disease incidence: the MESA…

5. Clinical imaging for prevention: directed strategies for improved detection of presymptomatic patients with undetected atherosclerosis—Part I
   L. J. Shaw and others. J Nucl Cardiol. 2008

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10. Aortic valve calcium independently predicts coronary and cardiovascular events in a primary prevention population
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Selection of seminal papers by Fausto J. Pinto, MD, PhD, FESC, FACC; Inês Zimbarra Cabrita, MSc, BSc (Hons)
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Highlights of the years by Ian Mudway, MD
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Coronary artery calcium score combined with Framingham score for risk prediction in asymptomatic individuals

P. Greenland, L. LaBree, S. P. Azen, T. M. Doherty, R. C. Detrano

JAMA. 2004;291:210-215

Seeking to improve the risk prediction of coronary heart disease, this study evaluated the use of a novel parameter, the coronary artery calcium score, in comparison with the traditionally used Framingham risk scoring system. An important aspect of this study is that it did not only evaluate the predictive performance of this parameter on its own, it also evaluated the predictive performance of these two approaches in concert.

The Framingham risk score is a risk scoring system that takes different relatively easily assessable parameters into account, including age, sex, blood pressure, cholesterol, smoking history, and history of diabetes to calculate an estimation for the coronary event risk among individuals without previously diagnosed coronary heart disease. The main limitation of this kind of risk estimation system is that it does not allow a clear distinction between individuals who will or will not experience coronary heart disease. As cardiovascular diseases and coronary heart disease are on a significant rise, novel approaches have to be tested and established to more clearly identify the patients who will benefit most from preventive therapy. One possible approach to improve the predictive value of the Framingham risk score could be to combine or extend this system with additional parameters. One of the currently highly promising parameters is the coronary artery calcium score, which is measured by computed tomography. This technique employs only low radiation doses and does not rely on the administration of iodinated contrast media.

The specific aim of this study was to test whether the Framingham risk score combined with coronary artery calcium scoring in asymptomatic adults improved the prognostic value of each of these techniques used alone. In addition, the authors tested whether this approach allowed a more precise guidance of primary preventive strategies in patients with coronary heart disease risk factors. This prospective study included an intermediate- to high-risk cohort of more than 1300 asymptomatic adults with coronary risk factors. After the initial computed tomography, patients were contacted each year for up to 8.5 years, with a median follow-up of 7 years.

The study showed that coronary artery calcium scoring significantly modified risk prediction in all categories of the Framingham risk score higher than 10%. It also showed that in individuals with a coronary artery calcium score of 0, the rate of coronary events was 4.4%. This result is in contrast to the observations made by several previous studies and showed that the coronary artery calcium score also has limitations and may benefit from the combination with a further parameter. An other important finding was an increase in coronary heart disease event risk in the group of patients with a coronary artery calcium score of >300, compared with the risk determined by Framingham risk score alone.

The results of this study therefore indicated that the coronary artery calcium score can add valuable independent information to the Framingham risk score and significantly modify the assessed risk profile of patients, thereby influencing clinical decision processes and therapeutic approaches.

This prospective study showed that complementing the Framingham risk score with another parameter can significantly improve this risk stratification system, as the combined assessment outperformed each of these approaches taken alone, an especially important advantage in patients belonging to the intermediate-risk category.

Cartoon characters Tintin and Popeye both turn 75; the discovery of a new (6th) form of matter, fermionic condensate, is announced; a fermionic condensate is a superfluid phase formed by fermionic particles (eg, quarks and leptons) at low temperatures ($5 \times 10^{-8}$ K); and David Bradley, creator of the “Ctrl-Alt-Del” keystroke combination, which stops a process gone awry in Windows or ends a Windows session, retires from IBM.
Cardiovascular diseases in the European Union represent the largest cause of morbidity, mortality, and reduced quality of life. This study gave a comprehensive analysis of the extent of cardiovascular diseases in the European Union and its associated economic burden on society. Cardiovascular diseases cause more than 1.5 million deaths each year, with coronary heart disease and cerebrovascular disease being the main diseases represented.

This study is unique as it is the first systematic cost-of-illness analysis to assess the economic impact of cardiovascular diseases. The data generated by the study also estimate the quantity of resources that are invested for prevention, detection, and treatment, as well as hidden costs like relatives providing care and inability to work due to disability.

The objectives of this study were to provide an estimate of the economic costs of cardiovascular disease for the European Union, including health care costs, informal care costs, and productivity loss. The costs were estimated using data on morbidity, mortality, and health care resources. Health care costs were estimated from expenditure on all fields of patient care including medication. Lost earnings due to morbidity and premature death were also included in the study.

The main result of this study was that cardiovascular diseases cost the European Union an estimated €169 billion annually. Health care accounts for 62%, productivity losses for 21%, and informal care for 17% of costs, respectively. Coronary heart disease results in 27%, and cerebrovascular diseases in 20%, of the overall costs in this group of diseases.

This study highlighted the significance of cardiovascular diseases in the European Union, regarding prevalence, mortality, and resources needed, especially in comparison with the burden of other diseases, eg, cancer. In addition, this study was designed to help to monitor the short- and long-term effects of therapeutic strategies aimed at reducing the disease burden on society.

The 90th anniversary of the Battle of the Somme is commemorated by a ceremony in Thiepval, Picardy, in France. The Thiepval Memorial bears the names of 72 194 officers and men of the United Kingdom and South African forces who died without known graves; Italy defeats France 5-3 in a penalty shoot out to win the 2006 FIFA World Cup; and an aristocratic house believed to be the birthplace of Augustus, the first emperor of ancient Rome, is discovered under the Palatine Hill.
Intravascular ultrasound radiofrequency analysis of coronary atherosclerosis: an emerging technology for the assessment of vulnerable plaque

S. K. Mehta, J. R. McCracy, A. D. Frutkin, W. J. Dolla, S. P. Marso

Eur Heart J. 2007;28:1283-1288

Current clinical risk evaluation systems and therapeutic concepts regarding coronary atherosclerosis are mainly based on systemic risk factors from which a general risk score is calculated, eg, the Framingham risk score, and the assessment of the degree of coronary stenosis by conventional x-ray angiography. However, these methods fail to distinguish between subjects who will or will not experience plaque rupture associated with an acute coronary syndrome. One potential approach to improve risk prediction is to directly characterize the morphology and composition of atherosclerotic plaques in the coronary artery.

For this, one must first define the characteristics that allow differentiation of instable atherosclerotic plaques from stable ones. Most of these characteristics are derived from postmortem studies of sudden cardiac death victims. In most cases, an intraluminal thrombus occluding the downstream artery is evidenced. Typical histological findings include plaque rupture, plaque erosion, “thin cap fibroatheroma” (thin fibrous cap <65 μm with high macrophage density, large necrotic core), and positive arterial remodeling. Most of these features can be evaluated by intravascular ultrasound (IVUS) techniques. Data can be displayed as a two-dimensional greyscale image, allowing the assessment of parameters like lumen and vessel areas. Results have, however, been variable and not highly reproducible. A more accurate and reproducible alternative is analysis of radiofrequency data from unprocessed backscattered signal.

These techniques have shown that the thin-cap fibroatheroma type of atherosclerotic plaque is more prevalent in patients who experience an acute coronary syndrome. A further feature of vulnerable plaques visualized with IVUS is positive remodeling of the arterial wall, defined as an enlargement of the external elastic membrane cross-sectional area in the presence of atheroma. Longitudinal studies have shown that vulnerable plaques are characterized by high plaque burden, positive vascular remodeling, a decreased fibrous area, and a larger percentage of lipid area. A recent landmark prospective study underlines the potential of IVUS-based methods to detect vulnerable atherosclerotic plaque (Stone et al. N Engl J Med. 2011). This study investigated the relationship between plaque burden and composition in patients with acute coronary syndromes using x-ray coronary angiography vs greyscale and radiofrequency IVUS methods. It was found that the majority of atherosclerotic plaques responsible for major cardiac events had either large plaque burden or a small luminal area or both. These findings were frequently missed by conventional x-ray angiography. Additionally, the presence of thin-cap fibroatheroma, detected by radiofrequency IVUS measurements, was also shown to be a strong predictor of subsequent cardiovascular events.

These studies demonstrate the potential of greyscale and radiofrequency IVUS methods for the detection and in vivo characterization of atherosclerotic plaque. This is of high relevance in view of the limitations of current clinical decision processes based on conventional x-ray angiography. IVUS-based methods allow the evaluation of atherosclerotic plaque composition and morphometry and may therefore yield insight into plaque biology and plaque rupture. Analysis of IVUS radiofrequency backscatter signal in particular allows simultaneous in vivo assessment of both atherosclerotic plaque composition and morphometry. This technique could significantly improve the in vivo detection of potentially vulnerable atherosclerotic plaques and therefore influence therapeutic strategies in patients.

2007

A new tribe of indigenous people, the “Metyktire” are discovered in the Amazon rainforest; American scientists identify a new strain of potentially lethal bacteria called Bartonella rochalimae, that caused high fever and anemia, in a 43-year-old woman who had traveled to Peru; and Switzerland opens the 34-kilometer Lötschberg road tunnel beneath the Alps
Coronary artery calcification compared with carotid intima-media thickness in the prediction of cardiovascular disease incidence: the Multi-Ethnic Study of Atherosclerosis (MESA)


Arch Intern Med. 2008;168:1333-1339

MESA (Multi-Ethnic Study of Atherosclerosis) was designed to directly compare the performance of two imaging biomarkers—coronary artery calcium score and carotid intima-media thickness—regarding risk stratification of a study population initially free of symptomatic cardiovascular disease. Different consensus panels have recommended these two biomarkers as possible additions to the traditional risk factor assessment for cardiovascular risk prediction. Thus, this type of study is highly relevant as it allows further determination of the most accurate biomarker for the prediction of cardiovascular risk.

In this large study, coronary artery calcium score, assessed by computed tomography, was compared prospectively with carotid intima-media thickness, assessed by carotid ultrasound, for the prediction of the risk of incident cardiovascular disease-related events. These events included coronary heart disease, stroke, and fatal cardiovascular disease. This multicenter study included six field centers from MESA. The multiethnic study population was initially free of symptomatic cardiovascular disease and was followed over more than 5 years. The study population consisted of more than 6,500 subjects aged 45 to 84 years. Although several previously performed studies had already compared coronary artery calcium score and carotid intima-media thickness in various smaller patient populations, none directly correlated results to cardiovascular disease events.

The main finding of this study was that coronary artery calcium score was a better predictor for coronary heart disease and total cardiovascular disease in the investigated study population than carotid intima-media thickness. Carotid intima-media thickness was shown to be a marginally better predictor of stroke, taking into account the fact that only a limited number of strokes occurred in this study collective. This study also confirmed that coronary artery calcium score and carotid intima-media thickness are both measures of subclinical atherosclerosis and both allow the prediction of future cardiovascular disease-related events.

The results of this study are highly relevant since several previous consensus statements had indicated that coronary artery calcium score and carotid intima-media thickness were equally effective in refining cardiovascular disease risk scores such as the Framingham risk score and in guiding the choice of atherosclerosis measures. The MESA study suggests that in asymptomatic 45-to 84-year-old adults free of cardiovascular symptoms assessment of coronary artery calcium is to be preferred as a more accurate parameter than carotid intima-media thickness. The significantly better prediction of coronary heart disease with the coronary artery calcium score and the marginally better prediction of stroke with carotid intima media thickness are very likely a direct reflection of the different vascular territories supplied by coronary and carotid arteries.

This study was important in highlighting that direct comparison of established and recommended biomarkers in a large population-based study can help to determine which parameter or risk stratification system is the most reliable for accurate risk stratification of patients and population groups free of symptoms.

The Rajasthan Royals defeat the Chennai Super Kings to win the first Indian Premier League 20/20 cricket competition; a 365 million-year-old fossil of a four-legged fish discovered in Latvia sheds new light on the evolution of land animals; and French president Nicolas Sarkozy announces that France intends to rejoin NATO, 42 years after Charles de Gaulle abruptly pulled out from the organization and expelled foreign NATO troops from French territory, infuriating the US.
Clinical imaging for prevention: directed strategies for improved detection of presymptomatic patients with undetected atherosclerosis—Part I: Clinical imaging for prevention


J Nucl Cardiol. 2008;15:e6-e19

In a context of growing questions about the validity of classic concepts for the selection of patients referred for cardiovascular imaging, mainly based on population screening, the authors of this statement look at the role of imaging modalities in disease prevention and introduce a novel concept of imaging. This statement, endorsed by the Society of Atherosclerosis Imaging and Prevention, Society of Nuclear Medicine—Advancing Molecular Imaging and Therapy, and Society of Cardiovascular Computed Tomography, provides guidance and recommendations for additional imaging tests in selected patient populations, for better and more cost-effective risk detection.

The authors suggest that the classic concept of matching treatment intensity to risk, mainly based on clinical history and angiographic data, should be extended to include a range of atherosclerotic and ischemic risk markers. They introduce the concept of presymptom risk assessment, focusing on appropriate imaging techniques in high-risk asymptomatic patients. Different high-risk asymptomatic patient cohorts liable to benefit most from cardiovascular imaging are defined and discussed: (1) patients with a family history of premature coronary heart disease and metabolic syndrome, as these risk factors are not included in the Framingham risk, (2) women with polycystic ovary syndrome or early menopause, (3) patients with rheumatoid arthritis, systemic lupus erythematosus, or other autoimmune diseases, as a higher risk of atherosclerosis exists in these groups, (4) patients with long-standing or poorly controlled diabetes, in whom imaging could serve as a guide to evaluate disease progression. Specific attention should also be directed at patient subsets with low Framingham risk scores, especially women and younger men, whose risk may be underestimated.

The statement is a direct reflection of the conflict between traditional recommendations derived from conventional risk scoring systems, eg, the Framingham risk score, and the predictive information derived using novel imaging technologies. Established and novel parameters derived from imaging technologies include assessment of myocardial perfusion, noninvasive imaging of coronary stenosis, and estimation of atherosclerotic plaque burden by computed tomography, single-photon emission computed tomography, and magnetic resonance imaging.

This statement successfully challenges current traditional risk assessment methods and guidelines. It presents valuable suggestions to improve treatment concepts and patient outcomes, based on the use of imaging modalities. It focuses on the concept of selective imaging for prevention, aimed at directly linking the use of imaging to targeted treatment strategies, to improve patient outcomes.

These suggestions highlight the potential of novel and already established imaging biomarkers to significantly influence risk assessment and therapeutic interventions in patients and asymptomatic subjects in the future.

Midnight’s Children by Salman Rushdie is recognized as the best novel to have won a Man Booker Prize in first 40 years of its existence; NASA confirms the presence of a liquid ethane lake on Saturn’s moon Titan; and John McCain selects Alaskan Governor Sarah Palin as his vice-presidential running mate for the US presidential election.
Risk stratification of patients has been shown to benefit from the combination of information from different angles, such as the combination of the Framingham risk score with the coronary artery calcium score. This study describes a different, purely imaging-based approach for the characterization of coronary artery disease, which combines structural and functional information.

In current clinical practice, functional relevance is based on the degree of the coronary stenosis. If the degree is graded as higher than 50%, the stenosis is usually considered to be hemodynamically relevant. Various studies have shown that this purely anatomical grading does not reflect hemodynamic relevance accurately. As patients do not benefit from the revascularization of a non-myocardial-flow-limiting stenosis, different modalities, including magnetic resonance and single-photon emission computed tomography myocardial perfusion imaging have been proposed as gatekeeper modalities prior to an invasive procedure.

In recent years, various hybrid imaging systems allowing the integration of morphological information from coronary computed tomography angiography and functional information from nuclear myocardial perfusion imaging have been introduced.

In this study, the prognostic value of hybrid cardiac imaging combining information from single-photon emission computed tomography myocardial perfusion imaging and coronary computed tomography angiography was evaluated. More than 300 patients were followed for a median of 2.8 years and the rate of major adverse cardiac events was recorded. The prognostic value of different groups (stenosis by angiography with matching reversible perfusion defect; unmatched angiographic and perfusion finding; normal findings on angiography and perfusion imaging) was tested. To provide clinically relevant information on hemodynamically relevant stenosis, only reversible perfusion imaging findings were considered as matched findings. It was shown that the corresponding matched finding of a coronary stenosis with a perfusion defect gave the best predictive results and was an independent predictor for major adverse cardiac events. These results therefore support the added value of functional lesion characterization with respect to the anatomical characterization of the degree of stenosis.

This is the first study to show the independent prognostic value of cardiac hybrid imaging findings. Cardiac hybrid imaging has the unique advantage of providing complete noninvasive assessment of anatomic and functional data. The combined evaluation of coronary stenosis and its functional relevance result in improved risk stratification.

Li Na of the People’s Republic of China becomes the first Asian tennis player to win a major title, by beating Italian Francesca Schiavone 6-4, 7-6 (7-0) in the 2011 French Open; Christine Lagarde is named the new head of the International Monetary Fund (IMF) following the resignation of Dominique Strauss-Kahn; and More than 1000 new animal and plant species are described following a survey conducted on Espiritu Santo island in Vanuatu in 2006, coordinated by the French Muséum National d’Histoire Naturelle (MNHN)
Combining cardiac magnetic resonance and computed tomography coronary calcium scoring: added value for the assessment of morphological coronary disease?

P. Stolzmann, H. Alkadhi, H. Scheffel, A. Plass, S. Leschka, V. Falk, S. Kozerke, C Wyss, O. F. Donati

Int J Cardiovasc Imaging. 2011;27:969-977

So far, none of the recently introduced novel biomarkers have been shown to be highly superior to already established biomarkers and risk stratification systems. The answer for an improved risk stratification of patients may therefore lie in the combination of different types of biomarkers reflecting disease development from different pathophysiological angles. This publication is an example of the combination of information concerning different disease processes in one patient, using different imaging modalities. In this study, the authors combined the information obtained from computed tomography calcium scoring with that derived from cardiovascular magnetic resonance perfusion and late gadolinium-enhancement imaging, which reflects myocardial scarring. Both modalities allow the investigation of different pathophysiologic pathways and consequences of coronary artery disease.

Myocardial perfusion imaging assessed by cardiovascular magnetic resonance is a noninvasive imaging approach for the diagnostic and prognostic evaluation of patients with suspected coronary artery disease. Cardiovascular magnetic resonance was shown to have a good diagnostic performance in the detection of coronary artery disease determined by coronary angiography. Myocardial perfusion deficits are, however, not solely attributable to luminal stenosis, and may include other causes, such as microvascular obstruction. Computed tomography allows quantification of coronary calcifications by calcium scoring. This information can be acquired without relying on administration of contrast media and by using low radiation dose techniques. Studies have shown that calcium scoring allows the diagnosis of early subclinical atherosclerosis and thereby improves risk stratification of asymptomatic individuals. Recent data confirm that calcium scoring by computed tomography is also a valuable test for improving risk stratification of patients at intermediate risk for coronary artery disease. Although arterial wall calcifications are a typical feature of coronary artery disease, they are not considered an adequate hallmark for the identification of coronary artery stenosis. In this context, several studies reported that low calcium scoring thresholds are sensitive, but not specific, for predicting coronary stenoses. The aim of this study was to prospectively investigate the value of calcium scoring as an additional parameter to cardiovascular magnetic resonance imaging for the diagnosis of coronary atherosclerosis, and particularly epicardial coronary stenosis, in patients with suspected coronary artery disease. Catheter coronary angiography was used as the standard of reference. In this study, a relatively small patient population of 60 patients was investigated and characterized.

The main finding of this study was that combining calcium scoring, assessed by computed tomography, with cardiovascular magnetic resonance, has greater sensitivity, negative predictive value, and accuracy in the detection of patients with coronary stenosis than cardiovascular magnetic resonance alone. One further important observation was that if an adequate calcium score cutoff is used, patients with coronary stenosis can be identified even if no functional deficits are found on cardiovascular magnetic resonance imaging.

This study is therefore a very interesting and relevant example that shows that the combination of two independent biomarkers can result in significant improvement in risk stratification of patients.
Assessing the role of circulating, genetic, and imaging biomarkers in cardiovascular risk prediction

T. J. Wang

*Circulation*. 2011;123:551-565

For decades one of the main thrusts of cardiovascular research has been the development of novel invasive and noninvasive biomarkers to increase the sensitivity and specificity of the detection of different types of cardiovascular disease. Genetic biomarkers hold the promise of revealing the genetic predisposition of individuals for the development of various diseases, such as atherosclerosis. Yet genetic biomarkers in the field of cardiovascular disease have failed to display the same success as in predicting the risk of development of certain kinds of tumors. In contrast, circulating biomarkers are a promising approach as they reflect ongoing pathological processes, even though they have limited sensitivity and specificity for the prediction of disease development. Anatomical, morphological, and biological markers derived from different imaging modalities, such as computed tomography, positron emission tomography, and magnetic resonance imaging have also been extensively tested. One example is the coronary calcium score, derived from computer tomography scans. This score does not rely on the administration of contrast media and employs only low radiation doses. The coronary calcium score is among the most promising novel biomarkers, as it combines biological information—calcification of atherosclerotic lesions—with spatial location.

The reason such an intense focus is placed on identifying novel biomarkers is that traditional risk factors do not allow reliable and sufficient identification of all subjects at risk for the onset and development of cardiovascular disease. Even though many highly promising biomarkers have been introduced and tested in large patient populations, only very few breakthroughs have been made in this field recently. Some of the highly promising biomarkers have already had an impact on screening recommendations. An example is the state of Texas, which passed legislation in 2009 mandating the coverage of screening coronary calcium scans in older adults.

The most important role of biomarkers is the reliable primary prevention of diseases. In the majority of cases, the newer biomarkers have demonstrated only little improvement over traditional risk scores like the Framingham risk score. Combination of different biomarkers has also failed to evidence significant improvement in the prediction of disease development. Some biomarkers have resulted in the reclassification of certain patient groups. However the true benefit of these biomarkers remains theoretical in the absence of confirmation by large randomized trials.

Even though no revolutionary novel biomarkers have yet been discovered and introduced into the field of cardiovascular diseases, some have shown great potential and are now being tested in large randomized trials. They include biomarkers from the fields of proteomics, metabolomics, and transcriptomics. However, these techniques do not allow spatial localization of the causative pathological process in the body. Several currently tested promising approaches are based on specific spatial localization. In this context, techniques combining the spatial or anatomical information derived from imaging with the biological information derived from molecular probes seem to be a particularly promising approach for improving the risk stratification of patients. Among the most promising such techniques are novel hybrid molecular imaging modalities (e.g., magnetic resonance imaging with positron emission tomography [MR-PET]) with novel in vivo molecular markers.

At least two million people gather in Tahrir Square, in Cairo, to demonstrate against the Mubarak regime; Forkhead box protein M1 (FOXM) is announced as the “The Molecule of the Year 2010”; and “The King’s Speech” wins seven awards at the 64th British Academy Film Awards, including Best Film and Best Actor for Colin Firth.
Common carotid intima-media thickness in cardiovascular risk stratification of older people: the Rotterdam Study


Even though there is a well-established association between certain novel biomarkers, such as common carotid intima-media thickness, and the risk of future cardiovascular events, controversy still exists regarding the additional value of such markers compared with traditional risk scoring systems. In clinical practice, treatment of a given disease should be adapted to its severity or degree. In the context of cardiovascular diseases, patients are increasingly stratified using risk-scoring systems. One example is the Framingham Risk Score, which classifies patients into categories of high, intermediate, and low risk for cardiovascular disease. This risk scoring system is based on 10-year absolute risk of coronary heart disease or cardiovascular disease. Risk-scoring systems, however, have been shown to have limited accuracy in certain patient populations like women and older patients. To improve risk stratification, additional tests extending predictive accuracy have been proposed. In the case of atherosclerotic disease, assessment of carotid intima-media thickness has been proposed as an additional test to improve risk stratification. Studies have shown that addition of carotid intima-media thickness measurement to established risk scoring systems can lead to a small, but significant, improvement in cardiovascular risk prediction.

In this large population-based study, the authors aimed to compare carotid intima-media thickness measurement vs the traditionally used Framingham Risk Scoring System. The authors investigated a large population of more than 3500 nondiabetic subjects aged 55 to 75 years. The ability of carotid intima-media thickness measurements to better classify people into categories of high, intermediate and low 10-year risk of hard coronary heart disease and stroke was tested.

In contrast to other larger population-based studies, this study did not evidence a comparable high additional benefit of carotid intima-media thickness measurements in predicting cardiovascular disease. Specifically, it was demonstrated that in older men, addition of carotid intima-media thickness to Framingham risk factors did not improve prediction of coronary heart disease or stroke. In older women, addition of carotid intima media thickness to Framingham risk factors significantly improved risk classification. Reclassification was most substantial in women at intermediate risk for coronary heart disease and for stroke. The discrepancy between this study and previously performed studies could at least be partially explained by the differences in included study populations.

This study is a good example that shows that even in cases in which a well-established association between a parameter (carotid intima-media thickness) and risk of future events exists, its additional predictive value within clinical risk categories based on traditional risk factors is not always clear.

South African 400-m runner Oscar Pistorius becomes the first amputee to compete at the Olympic Games;
Mount Tongariro in New Zealand erupts;
and NASA’s Mars Science Laboratory rover Curiosity lands on Mars
Aortic valve calcium independently predicts coronary and cardiovascular events in a primary prevention population


JACC Cardiovasc Imaging. 2012;5:619-625

In this prospective study, the authors tested the potential of aortic valve calcium, detected on computed tomography scans, as an independent predictor for coronary and cardiovascular events. The authors investigated the large primary prevention population of MESA (Multi-Ethnic Study of Atherosclerosis). This was a population of more than 6500 participants between the ages of 45 to 84 and free of clinical cardiovascular disease at the time the study was initiated. The primary end point was prespecified and included myocardial infarction, resuscitated cardiac arrest, cardiovascular death, and stroke. A secondary combined end point of coronary events excluded stroke.

Aortic valve calcification is a particularly interesting parameter, as it can be assessed with the standard coronary artery scan and is therefore available without the need for additional examinations or tests. It is commonly observed in older adults, with an estimated prevalence of 25% in individuals older than 65 years of age. Aortic valve calcification is now recognized as an actively regulated inflammatory process that shares many similarities with the development of coronary atherosclerosis. In older adults without known cardiovascular disease, aortic valve calcification was shown to be a strong marker for the occurrence of future cardiovascular events.

This study with its unique population of individuals free of clinical cardiac symptoms is especially important as it highlights the significance of aortic valve calcification in a large multiethnic population. This study showed that aortic valve calcification was associated with a significantly higher risk for cardiovascular events (50%) and coronary events (72%). It is important to mention that risk estimates did not change after adjustment for inflammatory biomarkers. This indicates that systemic inflammatory processes do not play a leading role in the onset and development of aortic valve calcification. A further finding of this study was the existence of a strong association between aortic valve calcification and coronary artery calcification. This suggests that the processes responsible for coronary and aortic wall calcification occur, at least to some extent, concomitantly.

In summary, this study of a large population free of clinical cardiovascular disease at the time the study was initiated showed that aortic valve calcification is a valid biomarker for the risk assessment of cardiovascular and coronary events, and that it is superior to traditionally assessed risk factors. It was also shown that, even when risk associations are adjusted for inflammatory biomarkers, aortic valve calcification remains a strong predictor of cardiovascular and coronary events. This finding suggests that aortic valve calcification may be a helpful marker for the severity of subclinical atherosclerosis. It should, however, be mentioned that the risk associations were significantly attenuated after adjustment for coronary artery calcium, suggesting that both these parameters, at least to some extent, reflect comparable biological processes that occur concomitantly in the arterial wall.

A surprising and highly important finding of the study was that, even when aortic valve calcification was adjusted for inflammation, subclinical atherosclerosis, and other risk factors, the association with excess cardiovascular mortality remained. This observation could not be fully explained by the authors, but was very interesting, as excess mortality may be unrelated to progressive heart valve disease.

The Diamond Jubilee of Elizabeth II of the United Kingdom reaches its peak with a pageant on the River Thames; Scientists decode the bonobo (pygmy chimpanzee) genome, making it the last great ape to have its DNA sequence described; and Wikileaks editor-in-chief Julian Assange takes refuge in Ecuador’s embassy in London to avoid extradition to Sweden, where he remains to this day.
Prevention Through Imaging

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selected by Fausto J. Pinto, MD, PhD, FESC, FACC; Inês Zimbarra Cabrita, MSc, BSc (Hons)
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Aim s & Scope

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