Atherosclerosis Imaging for Primary Prevention of Coronary Heart Disease

Abstract
During the past decade our perception of coronary artery disease has changed significantly. It had been thought that obstructive disease in coronary vessels was the real danger, but current research has revealed that non-obstructive coronary artery disease is the real threat and responsible for the occurrence of cardiac death and myocardial infarction in the vast majority of cases. Early detection of clinically silent, but unstable, lipid-rich coronary plaques is of utmost importance. The method currently available to detect the risk inherent in unstable plaques is based on the assessment of conventional risk factors such as total cholesterol. Because of a problem both in sensitivity and specificity of conventional risk testing, atherosclerosis imaging may increase the capability to detect high-risk individuals. This article discusses the possible role of multislice computed tomography for risk stratification in comparison to other available modalities and calls for action in primary prevention of coronary heart disease using atherosclerosis imaging.

Introduction
Coronary artery disease is the leading cause of mortality in industrialised nations. About 60% of the manifestations of coronary artery disease, in terms of cardiac death, acute myocardial infarction and unstable angina, are not heralded by cardiac symptoms. Significantly, about 30% of acute coronary events show a deadly course within the first few hours. The sensitivity of conventional risk factors to detect those with increased risk of cardiac death is 45-50%. Thus, new imaging modalities are being tested worldwide to aid in risk stratification.

Coronary heart disease: an ongoing challenge
Giuseppe Sinopoli conducted Aida, the most famous opera composed by Giuseppe Verdi, but last April, in Berlin, he didn’t make it to the end. At just 54 years of age, he suffered sudden cardiac death during the concert.

In Germany, cardiovascular disease annually kills 77,000 people - many of whom are unaware that they have coronary artery disease (CAD).

The threat of coronary heart disease (CHD) prompts many people to seek medical attention when alarmed by non-specific chest pain. Assessment for the presence of CAD in these patients is straightforward: left heart catheterisation was performed 644,100 times in this country in 2000 (and 194,000 in 1990). 72% of these were solely for diagnostic purposes (e.g. no further intervention, such as balloon angioplasty or stent placement, was necessary). The cost of CHD treatment reached € 28,000 billion in 2000. Despite prevention efforts, about 60% of heart attacks are unheralded by cardiac symptoms, and they run a deadly course in about 30% of cases. Bearing in mind that cardiovascular disease is still the leading cause of death in the industrialised world, it is readily understood that cardiovascular death prevention is of prime importance in public health.

New medications such as lipid-lowering statins and ACE inhibitors offer considerable progress, for these reduce cardiovascular deaths and morbidity by 30-40%, in both primary and secondary cardiovascular prevention. Treatment guidelines for statins for asymptomatic subjects have been published1 and recently have been expanded in the US with the recommendation to lower low-density lipoprotein (LDL) levels below 3.4 mmol/l in patients with low to medium risk and two or more cardiovascular risk factors (NCEP III guidelines 2001). It is expected that > 50% of the US adult population will need lipid-lowering drugs based on these new guidelines.

But are the right people being treated with these drugs in primary prevention? This question is important, because healthcare costs in industrialised countries are rapidly increasing. € 2,202 million (20.9% of total healthcare expenditure) were spent on medications in Switzerland in 2000, and compared with 1999 the trend upward is rapid (+11.5%). This increase is mainly due to the growing use of statins and modern anti-rheumatic medications5. However, conventional risk assessments do not predict over 50% of severe coronary events - and indeed these occur in patients with intermediate or low risks6.

Thus many patients who will suffer cardiac death go undetected by risk-factor screening. On the other hand, many patients considered to be at high risk of cardiovascular events - based on conventional risk assessment (defined as > 20% at risk of cardiac death or myocardial infarction in 10 years) – will not suffer any events. This
was demonstrated by Menotti in a study with a long-term follow-up of 1,712 Italian men. Framingham risk charts (FRC) predicted 37% would suffer cardiac death and myocardial infarction. In reality only 3% of the men suffered such events. Thus – particularly in lower-risk cohorts such as Italian, French, Greek or Swiss people, etc – the FRC is a far from reliable tool for risk assessment (it may be compared to a dog that barks at inappropriate times).

Atherosclerosis imaging techniques, using carotid intimal thickness and carotid plaque formation, as well as coronary calcifications, are now available and thought to refine risk assessment based on FRC. They introduce the idea that plaque visualisation can more directly identify a person at increased risk of hard cardiovascular events, e.g. those individuals with vulnerable plaques.

**A vulnerable coronary plaque: what is that?**

Whilst it was formerly thought that the severity of CAD by invasive coronary angiography depends on the degree of luminal stenosis, it has been shown that these lesions are the ‘culprits’ in myocardial infarction in less than 15% of cases, and that 65% of myocardial infarctions occur in coronary segments with no, or minimal (< 50%), coronary luminal narrowing. By definition, the presence of any plaque type in the coronary artery is coronary artery disease (CAD), and it is amenable to medical treatment and may improve cardiovascular prognosis when treated at earlier stages.

Plaque stability is currently defined by the plaque composition, where large lipid pools covered by a thin fibrous cap are thought to be at high risk of disruption and subsequent coronary occlusion, whilst calcific or fibrous plaques are stable and may cause anginal chest pain but rarely myocardial infarction. Rupture of the vulnerable plaque seems to stem from both extrinsic and intrinsic factors. Extrinsic factors include biochemical, haemodynamic and biomechanical stresses. Recently, one of the intrinsic factors receiving considerable attention is the inflammatory process. Several factors have been shown to stimulate interleukin-8 secretion of intra-cellular vascular foam cells, which in turn may down-regulate tissue inhibitors of metalloproteinases (TIMP) with the possible consequence of fibrous cap matrix destruction and plaque rupture. The view that coronary calcifications as imaged by computed tomography are merely an expression of stable coronary plaques is not correct. Vascular foam cells express mRNA for osteopontin. Osteopontin is a bone matrix protein which leads to the formation of hydroxyapatite mineral. This explains the association of lipid pools with coronary calcifications (see www.kardiolab.ch/newlengb0102.pdf).

Other mechanisms for the occurrence of acute coronary syndromes should be kept in mind. A study that appeared in Circulation looked at the histology of culprit lesions in 79 consecutive cardiac death (CD) victims and identified Framingham-based risk and histologically quantified culprit lesion calcifications as complementary predictors of CD. In that study, however, 22 of 79 culprit lesions were in fact plaque erosions (defined as intact fibrous cap and epimural thrombus formation) poorly identified either by FRC or by a histologic calcium score.

Thus, further research is clearly needed to address the question of plaque stability. A more comprehensive statement about the pathophysiology of plaques leading to unstable coronary syndromes is given elsewhere.

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**Glossary**

**Primary Prevention**
prevention of brain infarcts and heart attacks in asymptomatic subjects without known cardiovascular disease.

**Secondary Prevention**
prevention of brain infarcts and heart attacks in subjects with known cardiovascular disease.

**CAD**
Coronary artery disease is defined by the presence of luminal narrowing in luminograms obtained by coronary catheterisation. A new and modern paradigm further defines the presence of coronary artery disease in subjects with coronary calcifications on a computer-tomogram or fluoroscopy.

**CHD**
Coronary heart disease is the consequence of coronary artery disease. A subject with CAD may suffer CHD in terms of sudden coronary death, and myocardial infarction. Only exceptionally do subjects without CAD develop CHD (massive intraluminal thrombosis, e.g. in heavy smokers or coronary spasm in cocaine abusers).
Table 1: Calcium Score percentile value and annual risk for fatal and nonfatal myocardial infarction

<table>
<thead>
<tr>
<th>CS%</th>
<th>Annual absolute risk (%)</th>
<th>Odds ratio (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>0.36</td>
<td>1.0 (1.0 - 1.0)</td>
</tr>
<tr>
<td>10</td>
<td>0.51</td>
<td>1.4 (1.2 - 1.6)</td>
</tr>
<tr>
<td>20</td>
<td>0.71</td>
<td>2.0 (1.6 - 2.5)</td>
</tr>
<tr>
<td>30</td>
<td>0.99</td>
<td>2.8 (1.9 - 4.0)</td>
</tr>
<tr>
<td>40</td>
<td>1.38</td>
<td>3.9 (2.4 - 6.4)</td>
</tr>
<tr>
<td>50</td>
<td>1.92</td>
<td>5.5 (3.0 - 10.1)</td>
</tr>
<tr>
<td>60</td>
<td>2.64</td>
<td>7.8 (3.8 - 16.0)</td>
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<tr>
<td>70</td>
<td>3.62</td>
<td>10.9 (4.7 - 25.4)</td>
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<tr>
<td>80</td>
<td>4.90</td>
<td>15.4 (5.8 - 40.4)</td>
</tr>
<tr>
<td>90</td>
<td>6.54</td>
<td>21.6 (7.3 - 64.1)</td>
</tr>
</tbody>
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Imaging techniques of plaque composition are a very promising research tool, one that is being increasingly used throughout the world.

The vulnerable coronary plaque

Several methods, both invasive and non-invasive, enable plaque composition assessment. Currently, intravascular ultrasound (IVUS) is one of the most promising tools for this. As recently published by Dr Birgelen (working with Professor Erbel’s team at Essen University, Germany), intracoronary plaque rupture plaques were more eccentric, had a larger arc of disease-free vessel wall and showed a higher degree of compensatory vessel enlargement when compared with non-ruptured plaques.

Another promising (albeit invasive tool) is intracoronary angiography. Recent work showed that lipid-laden plaques appear yellow in angiography and are much more prone to rupture (and hence cause unstable coronary syndromes) in comparison with white-ish plaques (that are rich in fibrous tissue) and thus stable.

Techniques that allow for imaging of plaque components are very promising in the area of plaque research. The accepted non-invasive means for the visualization of atherosclerosis in men are ultrasound, magnetic resonance imaging and computed tomography.

These tools can be used to identify the vulnerable plaque prone to rupture, and to quantify the "global plaque burden".

The vulnerable carotid plaque, e.g., is identified using magnetic resonance with a time-of-flight (TOF) sequence, which makes it possible to quantify the thickness of fibrous caps (Fig. 1, Ref 16). The prognostic impact of thin fibrous caps identified in the carotid artery using the TOF technique has also been published very recently.

In risk stratification, the importance of the global plaque burden has been much better documented than has the importance of the presence of vulnerable plaques as identified by atherosclerosis imaging. Measurements of global plaque burden in the coronary arteries enables, within a single breath hold, visualisation of the whole coronary tree and produces good images.

There has been a lot of debate about the clinical significance of finding calcium deposits in human coronary arteries. It is important to emphasise the fact that, although the presence of calcifications assessed by fast CT is specific for calcifications when compared to histology, the likelihood of the presence of lipid-rich plaques increases with the presence and the amount of coronary calcifications. This laboratory finding was corroborated by a clinical study in which culprit arteries of myocardial infarction contained significantly more calcium than non-culprit arteries in 120 patients with acute myocardial infarction. Thus, coronary calcification assessed by fast CT appears actually as the only non-invasive and feasible method to accurately measure clinically significant plaque burden in a short period of time.

Conventional risk assessment strategies for coronary heart disease

Risk assessment for hard events, is best performed for individual patients using Framingham Risk Charts (FRC), as modified by Grundy, which allow for long-term (e.g. 10-year) estimates of hard cardiovascular events (cardiac death and myocardial infarction). Risk calculation is performed on behalf of age and gender-related FRC. The Framingham technique grades the major risk factors and sums these gradations to obtain risk estimates. Risk points are then assigned according to the severity of the risk factor: e.g. a total cholesterol value of 6.3 mmol/l would give 2 points in both men and women. The total number of points defines absolute risk. Risk projections denote the 10-year likelihood of developing hard coronary heart disease. Further, a modification of risk points may be done if there is a history of premature CHD in family members (+2 points).

Based on current guidelines, low risk is defined as the occurrence of hard cardiovascular events predictably falling below 10% at ten years. Intermediate risk is being defined as risk of hard endpoint occurrence between 10 -19% in ten years, and high risk as an event rate of ± 20% in ten years. One weakness of that method is the lack of implementation of physical activity. Regular physical activity is important for the prevention of CHD and may be even more important than the effect of total cholesterol on cardiac event rates.

The controversy about coronary calcium scoring

There has been a lot of debate about the clinical significance of the finding of calcium deposits in human coronary arteries, as summarised in the American Heart Association Expert Consensus Document published in
The authors summarised that the review of the small number of reports in literature reveals that an electron beam computed tomography (EBCT) calcium score can predict CAD risk. Current data, however, include relatively small samples (fewer than 3,000 asymptomatic subjects) with rare occurrences of hard coronary events (death or myocardial infarction). Prediction of all types of hard CAD events has not been demonstrated in patient samples. Importantly, the incremental value of EBCT over ‘traditional’ multivariate risk-assessment models has not yet been established. Although preliminary data are intriguing in terms of risk prediction in the asymptomatic patient, available data are insufficient to support recommending EBCT to asymptomatic members of the general public, or for routine clinical use. Further studies are enthusiastically recommended to determine the additive predictive effect of the calcium score in patients with intermediate risk, particularly in the elderly. The use of CT in selected asymptomatic patients can be justified for a medical assessment only after a physician decides that a more standard cardiac risk assessment is insufficient for therapy planning.

This careful review of calcium score in primary prevention was essentially based on three outcome studies. The first study, by Detrano, involving mainly male patients, averaging 66 years of age and at highest risk of cardiovascular disease based on FRC, had an unexpectedly low prevalence of coronary calcifications of 67%. This may be due to an outdated measurement of coronary calcifications, in that a 6-mm instead of 3-mm slice thickness was used. Moreover, in all three studies, absolute Agatston scores were used instead of percentile values based on patient age and gender, are better predictors than absolute CS and categorical risk factors. Since these physicians were unaware of calcium score results, there was no treatment bias. The high rate for hard events of 15.6% (e.g. 40/1,000/year of follow-up) proves that the cohort under investigation was at high risk.

However, atherosclerosis imaging using calcium scores and carotid intima-to-media thickness is not applied widely in Europe, firstly, because there is no definite epidemiological proof that atherosclerosis imaging has a prognostic impact above conventional cardiovascular risk testing (definite proof will come from the ongoing MESA trial recruiting and following of over 6500 population-based subjects); secondly, there are problems with reproducibility.

In our institution, interscan variability for the far wall of the common carotid IMT is 8 ±4% (mean IMT-thickness over 2 cm) using a caliper method. Although there are semiautomatic IMT detection programs, they are far less practical than the caliper method and principally indicated in intervention studies only.

The interscan variability for the quantification of coronary calcium depends on how quantification is carried out; Agatston scoring, the most frequently used method, is the worst, in my opinion, and should not be used for research purposes: Based on our own preliminary experience with multislice CT, the Agatston Score interscan variability is ±18%, ±11% for the volumetric method (in mm3) and is ±4% for the percentile values of Agatston Scores based on > 10’000 EBCT scans. From these numbers it becomes apparent that the future of coronary calcium quantification will lie in own-population-based normal databases of percentile values of volumetric scores with an expected interscan variability of ±2% (the interobserver variability we found for the Agaston derived calcium score percentile value is 0.2 (1.3%).

The reproducibility of this method may be further enhanced by a second scan in subjects...
with coronary calcifications. For this, in most cases only a few slices have to be acquired again, since most coronary calcifications are located in the proximal segments and roughly 70% of the asymptomatic middle-aged population has no documentable calcium in the first scan. The mean overall radiation burden may then be estimated at 1.0-1.5 mSv based on the number of acquired slices, the speed of rotation time (320-700 ms), kV of 120 and mA of 300.

The advantage of optimized reproducibility of coronary calcifications lies first in the high importance for the individual patients. Secondly, it also makes it possible to introduce this method into interventional studies as a surrogate marker for outcome (myocardial infarction and coronary death).

**Electron beam CT or multislice CT?**

Based on available data, the correlation coefficients for measuring Agatston scores using either EBCT or MSCT show excellent agreement. However, image quality is better using MSCT, due to a higher signal-to-noise ratio, whereas the radiation burden is higher with MSCT (1.4 mSv) than with EBCT (0.7 mSv).

Therefore, motion artefacts due to the longer imaging window with MSCT (340 ms) vs. EBCT (100 ms) do not degrade the accuracy of measuring calcium scores. Due to the lack of prognostic data using multi-row computed tomography in primary prevention of CHD, such studies are urgently needed and must be carried out before any recommendations can be made about using this imaging tool.

Instrumentation and acquisition techniques for calcium scoring, measures of carotid intimal thickening and of ankle-arm indices are outlined in greater detail on the Internet (www.scopri.ch).

### Risk assessment strategies with atherosclerosis imaging

Cardiovascular risk is well evaluated based on FRC tables suggested by Dr Grundy, who, by the way, is the chairman of the new American NCEP III guidelines. As stated by Dr Grundy himself, the presence of different degrees of coronary calcifications may be used to replace the variable “age” in the FRC by a “biologic” factor. Similarly, risk assignment for ankle arm index (AAI), carotid intimal thickening and the presence of plaque formation (IMT), findings of family history (FA) and the presence of previous myocardial infarction or left bundle branch block in the surface electrocardiogram (ECG) may be incorporated in a stepwise model on top of FRC. As to current knowledge, in this model it appears to be important to incorporate measurements of C-reactive protein and physical activity, which have both been shown to have an independent value for cardiovascular risk stratification irrespective of the presence or absence of elevated cholesterol values.

Based on these clinical tools, a first risk estimate is taken. If the subject under investigation is at high risk (risk estimate gives a result of > 20% risk for myocardial infarction in 10 years), intensive medical care to reduce cardiovascular risk is warranted, including the use of statins irrespective of cholesterol values. A cardiac scan under these circumstances will normally not add further elucidation of the problem at present, although this statement will have to be questioned based on the poor specificity of FRC in relatively low risk populations.

If however, the subject is at intermediate risk, it is difficult to know, whether intensive and certainly costly risk lowering strategies are warranted. This problem will occur in about 30% of middle aged men and women in central and southern Europe. In these cases it is certainly helpful to obtain a calcium score of the coronary arteries. It permits calculation of the probability for a hard coronary event based on post-test probabilities using the Bayes theorem (the theorem is available under www.kardiolab.ch/bayes.xls).

This sounds complicated but is readily understood. Based on published work on calcium score percentile values (which have far better reproducibility than Agatston Scores and should therefore be favored), a percentile value above 50 is able to detect risk of ±2% for the occurrence of a myocardial infarction within one year with a sensitivity of 93% and a specificity of 56%. If a subject has a 13% probability of suffering a myocardial infarction in 10 years based on FRC as the pretest value, but has no coronary calcifications (Calcium score zero), the probability for myocardial infarction will be lowered from 13% to 2% in 10 years. However, if the percentile value is found to be above 50 (see example in figure 2), the likelihood for a poten-
ially catastrophic myocardial infarction increases from 13% to 23% in ten years, in which case intensive primary prevention activities have to be prescribed. Based on our pilot study, this strategy helps to clean up the middle field of risk and reduces significantly the uncertainty about the need for intensive risk prevention by leaving only 1% of the population at intermediate risk and reduces uncertainty for the need for intensive risk lowering strategies.

Conclusions

Framingham Risk Charts have a rather low sensitivity and specificity for the detection of heart attacks in Europe. New imaging modalities enable new strategies in primary prevention of coronary heart disease. The main imaging modalities in that field are either of limited value, due to invasiveness (intravascular ultrasound and angioscopy) or they are still fighting with considerable technical difficulties, such as cardiovascular magnetic resonance.

Rapidly performed investigations, such as the ankle arm index and the quantification of the carotid intima and coronary plaque formation, have been tested in a sufficiently large number of patients and were convincingly shown to add incremental value on top of conventional measures of cardiovascular risk. They should be used for clinical decision-making in selected intermediate risk subjects.

The role of coronary calcium scoring as a mass screening tool to prevent coronary heart disease is still controversial – mainly due to a poor epidemiological database provided by the EBCT people during the past 15 years: too few patients, selection bias, self-reported conventional risk factors, use of absolute Agatston scores instead of percentile values, use of Agatston scores instead of volumetric scores.

It is thought that the ‘spiralist’ community should play an important role in primary prevention of premature cardiovascular events. Since low-cost scanning is now available with multi-row computed tomography, the time has come to use this tool in appropriately designed epidemiological studies that include randomly selected subjects in the field of primary care. Similar work is already performed in the U.S.: the NHLB has set up the MESA (multi-ethnic study on atherosclerosis) trial in the US, which is recruiting 6,500 subjects, who will be subjected to various and extensive measures of atherosclerosis (http://140.142.220.3/mesa/). One way of “how to do it” is freely available on the Internet (www.scopri.ch).

Radiology has to become a main definer of risk in primary prevention of cerebral infarctions using carotid far-wall ILM imaging and primary prevention of heart attacks using coronary calcium quantification based on European normal databases derived from multislice computed tomography scans and carotid ultrasound in the near future. People will ask for it.

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