Atherosclerosis Imaging for Primary Prevention of Coronary Heart Disease
Special Emphasis on Calcium Scoring Using Multislice Computed Tomography

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Abstract
The perception of coronary artery disease has changed significantly during the past decade. While it was thought that obstructive disease of the coronary vessels is the real danger, 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 to 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 multi slice 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 the industrialized part of the world. 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. Importantly, about 70% of acute coronary events show a deadly course within the first few hours. The sensitivity of conventional risk factors to detect people at increased risk for cardiac death is 45-50%. It is mainly therefore, that new imaging modalities are being tested worldwide to aid in risk stratification for unheralded acute coronary syndromes.

Coronary Heart Disease: an ongoing challenge
Giuseppe Sinopoli conducted Aida, the most famous opera composed by Giuseppe Verdi, but he didn’t make it to the end last April in Berlin. At the age of 54 years he suffered a sudden cardiac death during that concert. Cardiovascular disease kills 77000 people each year in Germany who often are not even aware of having coronary artery disease (CAD). Because of the threat of coronary heart disease (CHD), many people seek for medical attention frequently alarmed by unspecific chest pain. The assessment for the presence of CAD in these patients is straightforward; left heart catheterization was performed 644'100 times in Germany in the year 2000 (194'000 in 1990), of which 72% were for diagnostic purposes only (e.g. no further intervention like balloon angioplasty or stent placement was necessary). The cost to treat CHD has reached 55000 billion German marks in the year 2000. Despite efforts to prevent heart attacks, they are unheralded by cardiac symptoms in about 60% and show a deadly course in about 70%. Keeping in mind that cardiovascular disease is still the main cause of death in the industrialized world, it can readily be understood, that the prevention of cardiovascular death has prime importance for public health.

It appears as great medical progress, that new medications such as lipid-lowering statins and ACE-inhibitors are able to reduce the incidence of cardiovascular death and morbidity by 30-40% both in the field of primary and secondary cardiovascular prevention. The guidelines for the treatment of asymptomatic subjects with statins are published and have been recently expanded in the U.S. 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 adult U.S. population will need lipid lowering drugs based on these new guidelines.

But are we treating the right people with these drugs in primary prevention? This question is important, because the costs for health care in the industrialized countries is rapidly increasing. E.g., 3240 millions Swiss francs (20.9% of the total of health care expenditures) were payed for medications in Switzerland in the year 2000 with a rapid trend upward when compared to 1999 (+11.5%). This increase in cost for medications is mainly due to the increased use of statins and modern antirheumatic medications. However, more than 50% of the hard coronary events remain unpredictable with conventional risk assessment and occur in patients at intermediate or low risk. Thus, many patients who will suffer cardiac death go undetected by risk factor screening. On the other hand, many patients deemed at high risk for cardiovascular events based on conventional risk assessment (defined as risk of ≥ 20% for cardiac death or myocardial infarction in 10 years) will not suffer any events as was shown by Menotti in this study with a long-term follow up in 1712 Italian men. Framingham risk charts (FRC) produced an expected event rate for cardiac death and myocardial infarction of 37%, while these events occurred in only 3% in
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reality. Thus, especially in lower risk cohorts as the Italian, the French, the Greek or the Swiss etc, FRC are far from being a reliable tool for risk assessment and may be compared to a dog that barks at wrong occasions. Atherosclerosis imaging using carotid intimal thickness and carotid plaque formation as well as coronary calcifications are now widely available and thought to refine the risk assessment based on FRC. They introduce the idea, that plaque visualization identifies more directly the individual at increased risk for hard cardiovascular events, e.g., those individuals with vulnerable plaques.

The vulnerable coronary plaque: what is that?
While formerly it was thought that severity of CAD defined by invasive coronary angiography is dependent on the degree of a luminal stenosis, it has been shown, that these lesions are the „culprit lesions“ for 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. The presence of any plaque type in the coronary artery is, by definition, coronary artery disease, 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 for disruption and subsequent coronary occlusion, while calcific or fibrous plaques are the stable ones, that 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, hemodynamic, and biomechanical stresses. One of the intrinsic factors that has received a great deal of attention recently is the inflammatory process. Several factors have been shown to stimulate interleukin-8 secretion of intracellular 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.

However, other mechanisms for the occurrence of acute coronary syndromes should be kept in mind: a study having 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 epi-intimal thrombus formation) poorly identified either by FRC nor 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.

Imaging techniques of plaque composition are a very promising research tool increasingly used throughout the world.

The vulnerable coronary plaque: which method for assessment?
There are several methods, both invasive and non-invasive, that allow for the assessment of plaque composition. Intravascular ultrasound (IVUS) is currently one of the most promising tools in that field. As recently published by Dr Birgelen, who works with the group of Prof. Erbel at the university of Essen, Germany, ruptured plaques were more excentric, had a larger arc of disease free vessel wall and showed a higher degree of compensatory vessel enlargement when compared to non-ruptured plaques.

Another promising but yet invasive tool is intracoronary angioscopy. A recent work showed that lipid laden plaques appear yellow at angioscopy and are much more prone to rupture (and hence causing unstable coronary syndromes) in comparison with white appearing plaques (which are rich of fibrous tissue and thus stable).心血管造影术 (CMR) is thought to have good potential for plaque imaging in the human coronary arteries. The problems with imaging such small structures like the coronary arteries are however manyfold. E.g. it is not straightforward to image coronary calcifications on T1 images, since they may appear bright as fat (Image 1). Intravascular CMR was used in the work by Dr Walter Rogers. He imaged carotid specimens with different sequences. Per specimen imaging time was however 3 hours. There is probably a long way to go until non invasive (surface coil based) imaging of coronary plaques prone to rupture may be identified by CMR. A far more practical non-invasive tool to visualize coronary plaque formation is fast computed tomography. It allows for visualization of the whole coronary tree within a single breath hold, gives good images and reproducible results. There has been a lot of debate about the clinical significance of the finding of calcium deposits in human coronary arteries. It is important to emphasize the fact, that although the presence of...
calcifications assessed by fast CT is specific for calcifications when compared to histology, the likelihood for the
presence of lipid rich plaques increases with the presence and the amount of coronary calcifications. This labora-
tory finding was corroborated by a clinical study, where culprit arteries of myocardial infarction contained signifi-
cantly 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: how and what to measure.**

Risk assessment for hard events is best performed for a subject using FRC as modified by Grundy allowing 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 used to be 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
for premature CHD (+2 points).

Based on current guidelines, low risk is defined as the occurrence of hard cardiovascular events beeing expected
to be below 10% at ten years, intermediate risk is beeing 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: the time has come for refined discussions**

There has been a lot of debate about the clinical significance of the finding of calcium deposits in human coronary
arteries, as summarized in the American Heart Association Expert Consensus Document published in Circulation
2000. The authors summarized, that the review of the small number of reports in the literature reveals that
electron beam computed tomography (EBCT) calcium score can predict CAD risk. Current data, however, include
relatively small samples (fewer than 3000 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 with respect to risk prediction in the asympto-
matic 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 for determining 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 when performed in the context of a medical assessment only after the more
standard cardiac risk assessment is considered insufficient by the physician to direct further therapy plans."

This careful review of calcium score in primary prevention was essentially based on three outcome studies. The first
study by Detrano in mainly male patients with a mean age of 66 years and highest risk for cardiovascular disease based on
FRC had an unexpectedly low prevalence of coronary calcifications of 67%, which may be due to an outdated
measurement of coronary calcifications, in that a 3 mm slice thickness was used. Moreover, in all three
studies, absolute Agatston scores were used instead of percentile values based on gender- and age-matched normal
data bases.

As shown by Raggi et al., the use of percentile values had a very high power for the prediction of future hard coronary
events (Table 1), even over the presence of conventional cardiovascular risk factors, since only CS% were predictive for
events in a multiple logistic regression analysis.

Another recent study underscores the importance of using
It can therefore be expected, that future studies on CS% measured in appropriately selected subjects may save lives. However, most EBCT data were collected in mainly self referred study subjects in the past. The potential role of selection bias was tested in our institution on 84 subjects randomly selected and 84 subjects with self referral. Accuracy to detect high risk individuals as defined by a CS% of ≥75% was 75% in unselected and 64% in selected patients (p = 0.07), while the accuracy to detect low risk individuals as defined by a CS% of <25% was 77% in unselected and 55% in selected subjects (p < 0.01). Thus, future studies testing the value of CS% in primary prevention of CHF have to be performed using randomly selected population based cohorts.

Finally, the Agatston technique introduces a weighing towards more heavily calcified plaques, which are known to be more stable. A volumetric score has been shown to be more reproducible and may substitute Agatston scores for risk prognostication of cardiovascular events in asymptomatic subjects in the future.

Electron Beam CT or Multislice CT?
Based on available data, the correlation coefficients for the measurement of Agatston scores using either EBCT or MSCT show excellent agreement. Image quality is however better using MSCT because of a higher signal to noise ratio, whereas radiation burden is higher with MSCT (1.4 mSv) than with EBCT (0.7 mSv).

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

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

Risk assessment strategies with atherosclerosis imaging: two ways to do it!
In strategy 1 findings of atherosclerosis imaging may be weighted based on suggestions by Grundy, where the presence of different degrees of coronary calcifications may be used to replace the variable age in the FRC by a "biologic" factor, e.g. - 2 points for the absence of coronary calcifications. Similarly, risk assignment for Ankle Arm Index (AAI), carotid intimal thickening and presence of plaque formation (IMT), findings of family history (FA) and 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 the present knowledge, it appears important to incorporate in this model measurements of C-reactive protein and physical activity, which both have been shown to have an independent value for cardiovascular risk stratification irrespective of the presence or absence of elevated cholesterol values.

In strategy 2 the findings of atherosclerosis imaging (IMT and CS%) may be used as independent markers of risk and compared to the risk estimates bases on FRC. The problem with this approach is the substitution of FRC by a new gold standard for outcome studies based on atherosclerosis imaging. It is clear, that treatment decisions in primary prevention should not be based on atherosclerosis imaging solely at that point of time. Atherosclerosis imaging with whatever modality is not a surrogate for outcome studies, but helps to study the natural course of atherosclerosis in men and women and opens an important research field.

Conclusions
New imaging modalities allow for new strategies in primary prevention of coronary heart disease. The main players in that field are either of limited value because of the invasive nature of the procedure (intravascular ultrasound and angioscopy) or still fighting with considerable technical difficulties like cardiovascular magnetic resonance.

Readily performed techniques such as ankle arm index and carotid intimal thickening and 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.

The role of coronary calcium scoring is still controversial. This is mainly due to a poor 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. Since low cost scanning is now available with multi row computed tomography, the time for testing using this modality in primary prevention on behalf of appropriately designed epidemiological studies in randomly selected patients has come.

Because of the high impact of cardiovascular disease on mortality and major disability in the industrialized countries on one hand and the rather poor performance of conventional cardiovascular risk factors especially in lower cardiovascular risk than the Framingham cohort on the other hand, there is an urgent need to perform studies as outlined in this article.

It is thought, that the "spiralist" community should play an important role in primary prevention of premature cardiovascular events.

The best way to define the coronary plaque that kills people not even aware of having coronary artery disease is still to be defined. In the U.S., the NHLB has set up the MESA (multiethnic study on atherosclerosis) trial, that is recruiting 6500 subjects. These subjects will be submitted to various and extensive measures of atherosclerosis (http://140.142.220.3/mesa/). Radiologists, cardiologists and any interested medical doctors are called for action also in Europe and one way of „how to do“ is outlined freely available on the Internet (www.scopri.ch).
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