

Kardio News

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Primary prevention: A glance at the future

Zero tolerance with respect to sudden cardiac death calls for new strategies in primary prevention as exemplified by the Heart Protection Study and non-invasive atherosclerosis imaging in humans.

People want to become old and die healthy. What they fear the most is a debilitating brain infarct but also heart attacks. Heart attacks in asymptomatic people are fatal in 35% of cases with all its socioeconomic and disastrous consequences.

To recognize individuals who will suffer a heart or brain attack, medical visits and screening procedures are frequently used. In a population based questionnaire performed by the Swiss Academy of Medical Sciences, people named primary prevention as the main goal for medical activity in Switzerland.

The number of deaths attributable to cardiovascular disease in asymptomatic high risk patients is high. However, the absolute number of cardiovascular deaths is higher in non-high risk subjects. Therefore, the sensitivity to detect people who will die of a heart attack using Framingham Risk Charts, is 50% at its best. These charts are however recommended by European guidelines and no better alternative is offered.

In view of the fact, that atherosclerosis frequently causes severe organ damage without even preceding symptoms, we need early warning systems, which are appropriate risk stratifiers. Moreover, we are disposing of a very efficient risk lowering therapy with statins, able to reduce risk both for heart and brain attacks even independently of baseline cholesterol values¹.

The risk estimates based on blood pressure, cholesterol, smoking habits and other cardiovascular risk factors show, that about 20% of the Swiss German middle aged population is at high risk for cardiovascular events.

In about 80% of this population, risk is estimated to be below 20% hard coronary events in 10 years, and therefore, intensive and costly primary preventive activities are not recom-

mended. However, in certain cases, this rather rough approach may be quite misleading.

I give you an example: this 48 year old man is on diet for mild diabetes. He is non smoker and has a total cholesterol of 3.1 mmol/l (about 130 mg/dl). HDL is very low and triglycerides are above the normal. He is not physically active and has mildly elevated blood pressure values. The clinical investigation showed no abnormality. The electrocardiogram and the exercise – stress test were normal. His ankle-arm-index is within the normal range. The intima of the far wall of his common carotid arteries is very normal (0.450 mm, figure 1).

Fig 1: Measurement of carotid intima².



Based on Framingham Risk Charts, the sum of risk points imply a risk for fatal and non fatal myocardial infarction of 9% in 10 years. Based on Swiss (AGLA criteria) and European guidelines, this patient does not qualify for a lipid lowering drug.

This patient participated in our primary prevention pilot study and therefore an ECG-gated multislice computed tomography was performed to look for coronary calcifications. The scan showed multiple calcifications in the three coronaries, mainly located in the left anterior descending artery (figure 2).

The scan was quantified using also percentile values of Agatston Scores based on > 10'000 persons. In this subject, a percentile value of 97 was found, which puts this patient into the highest risk category (fig. 5)²².

Such measurements, when applied in an intelligent manner to further risk stratify subjects will yield good results, especially with respect to the aggressivity of primary preventive mea-

tures in subjects at intermediate risk for heart and cerebral attacks.

Figure 2: quantification of coronary scan



Example: in a subject with a Framingham risk of 13% in 10 years (=intermediate risk), the posttest probability for events is lowered to 2% in the absence of coronary calcifications. This number is based on the known sensitivity of 94% and the specificity of 56% of the coronary calcium percentile values to detect heart attacks.

The most appropriate way to select subjects for atherosclerosis imaging makes part of our scientific work and will matter for the implementation of our findings into national guidelines.

In summary: It appears evident, that atherosclerosis imaging in men and women using the combination of IMT and coronary calcium percentiles will serve as an important tool in early primary prevention of cardiovascular disease.

In case of the absence of atherosclerosis, unnecessary and frequently costly therapies and scaring will be avoided in populations with all over lower risk than the one found for the Framingham Risk Population. On the other hand, the presence of definite atherosclerosis will allow to treat individuals with increased cardiovascular risk earlier than so far for the issue of primary or better „post-primary“ prevention. Once atherosclerosis imaging is available, people will not hesitate to use it. We then have to define those subjects, for whom atherosclerosis imaging is most appropriate, and women might benefit most !

Atherosclerosis imaging

Atherosclerosis imaging is experiencing a boom in contemporary radiology and cardiology. All over the world, many centers perform intensive research to find the best imaging modalities for the identification of the dangerous atherosclerotic plaque. Moreover, atherosclerosis imaging has the potential to replace hard outcomes: it measures the reduction of atherosclerosis in intervention studies.

The culprit lesions for heart and brain attacks are not found in stenotic segments (defined as vessel narrowing of $\geq 70\%$) in over 80% of cases³.

The dangerous or vulnerable plaque is defined by the plaque composition containing large lipid pools protected by a thin fibrous cap. Plaque rupture may then lead to the catastrophic cardiovascular event, which may be triggered by extrinsic and intrinsic factors. Extrinsic factors are of biochemical or hemodynamic nature. Intrinsic factors have gained a lot of attention recently, especially atherosclerosis as an inflammatory disease. It is thought that different mechanisms stimulate Interleukin-8 secretion of intracellular foam cells, which in turn reduce the inhibition of metalloproteinase activity, which implies increased risk for fibrous matrix destruction and plaque rupture⁴. However, other mechanisms causing acute coronary syndromes should be kept in mind: a work having appeared in *Circulation* recently, examined the histological appearance of coronary lesions in 79 sudden death victims. They found, that the Framingham Risk Charts (FRC) and the histological quantification of calcifications in the culprit lesions had a complementary power for the prediction of sudden coronary death⁵. However, in this study, 22 out of 79 of the lesions having caused sudden death were in fact plaque erosions defined by epi-intimal thrombi built on top of an intact fibrous cap neither identified by FRC nor calcium deposits. Other work comes from Dr Virmani and points to the important finding, that the histological classification of culprit lesions in men aged 50 years or more is plaque rupture in only 23% of cases, while fibrocalcific plaques were found in culprit arteries of sudden coronary death victims in 31%.

Therefore, there is a need for intensified research to detect the causes of acute coronary syndromes with more precision.

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 osteopontin⁶. Osteopontin is a bone matrix

protein, which in turn leads to the formation of hydroxy apatite mineral^{7,8}. This explains the association of lipid pools with coronary calcifications, pointed out to also by Prof Valentin Fuster⁹. Therefore, the likelihood for the presence of a vulnerable plaque increases in an almost linear fashion with the degree of coronary calcification percentiles²². A recent overview on the problem of plaque instability is found in an excellent contribution by Dr Libby¹⁰.

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, but also quantify the „global plaque burden“.

The vulnerable carotid plaque e.g., is identified using magnetic resonance with a time of flight (TOF) sequence, which allows to quantify the thickness of fibrous caps (fig. 3¹¹). The prognostic impact of thin fibrous caps identified in the carotid artery using the TOF technique has also been published very recently¹².

Abb. 3: Carotid artery in vivo using MRI (TOF-sequence): at 8-9 o'clock a virtually absent fibrous cap is noted with cap rupture and intraplaque hemorrhage¹²



Other magnetic resonance sequences used to visualize atherosclerosis and plaque components in the carotid arteries include T1 and T2 black blood imaging as well as proton density imaging. Slice thickness is usually set at 2 mm and inplane resolution at 350x350 microns. A new imaging modality is 3D volume acquisition of the carotid artery and it's plaque components (fig. 4, own work), with the advantage of higher signal to noise ratios and the disadvantage of higher susceptibility to motion artifacts, especially due to swallowing.

Fig. 4: Left carotid artery in patient with thick fibrous cap¹³.



The importance of the global plaque burden for risk stratification is however much better documented than the presence of vulnerable plaques identified by atherosclerosis imaging.

The tools used for the assessment of global plaque burden are the carotid intimal thickness and eventual presence of plaque^{14,15,16,17} and the quantification of coronary calcifications in the whole coronary tree^{18,19,20,21}. Both methods are not applied widely, first, 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 over 6500 population based subjects²²), second, there are problems with reproducibility.

In our institution, interscan variability for the far wall of the common carotid IMT is 8±4% (mean IMT over 2 cm) using a caliper method.

Although there are semiautomatic IMT detection programs, they are far less practicle than the caliper method and principally indicated in intervention studies only.

The interscan variability for the quantification of coronary calcium is dependent on the way of quantification: the frequently used Agatston score is, in my opinion, the worst and should not be used for research purposes: electron Beam CT *Agatston Score* interscan variability ±17%. Based on our own preliminary experience with multislice CT, the *Agatston Score* interscan variability is ±18%, is ±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 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 rotati-

on 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 will also allow to introduce this method into interventional studies as a surrogate marker for outcome (myocardial infarction and coronary death).

In our pilot study in 100 population based, randomly selected subjects, we compared the percentile value of coronary calcifications with FRC and calculated the sensitivities and specificities to detect high risk coronary calcifications (defined as expected rate for hard events of $\geq 2\%$ /year). Figure 5 shows the expected risk in relation to percentile values of calcium scores, that we used in our pilot study.

Fig. 5: Calcium Score percentile value and yearly risk for fatal and nonfatal myocardial infarction²²

CS%	Annual absolute risk (%)	Odds ratio (95% CI)
0	0.36	1.0 (1.0-1.0)
10	0.51	1.4 (1.2-1.6)
20	0.71	2.0 (1.6-2.5)
30	0.99	2.8 (1.9-4.0)
40	1.38	3.9 (2.4-6.4)
50	1.92	5.5 (3.0-10.1)
60	2.64	7.8 (3.8-16.0)
70	3.62	10.9 (4.7-25.4)
80	4.90	15.4 (5.8-40.4)
90	6.54	21.6 (7.3-64.1)

Based on the results of our pilot study, we may extrapolate, that atherosclerosis imaging may be indicated in subjects at intermediate cardiovascular risk, in which it remains unclear, whether an intensive primary prevention therapy is warranted.

In summary, there is a need for atherosclerosis imaging.

Although the search for the vulnerable plaque is performed with more and more refined tools, the approach to use global risk assessment using Framingham Risk Charts is far more practicle. In the grey zone of intermediate risk we expect, that the modern imaging modalities of the „culprit arteries“ (coronary and carotid) will gain a central role: improving the sensitivity and specificity for the detection of cardiovascular high risk subjects in the primary prevention of heart and brain attacks.

It is already certain, that the modern imaging modalities will leave individuals impressed and thus be helpful to change a harmful life style in case of visualized atherosclerosis.

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