

Kardio News

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Atherosclerosis imaging is best suited for detecting the vulnerable patient: the bet is over

Atherosclerosis imaging has proven superior to conventional cardiovascular risk factor testing – the time has come to measure the biological expression of atherosclerosis non-invasively in order to increase the performance of risk prediction in Switzerland – and save money.

Introduction

People want to age healthy. What they fear most is an early stroke or a heart attack.

Heart attacks in asymptomatic people are fatal in 15% of cases with all its socioeconomic and disastrous consequences¹.

The U.S. Hastings Center has published a consensus paper including representatives of 14 countries. The main goal of medicine in the future was and naturally is the prevention of disease (SAMW August 2001).

Fifty percent of cerebral and myocardial ischemic events are not heralded by cardiovascular symptoms and remain unpredictable by conventional cardiovascular risk factors².

The tools to define an asymptomatic person's risk in primary care are all well known. They are primarily based on age and conventional risk factors. The ability of these risk charts to detect subjects at risk for heart attacks is however limited by low sensitivity of 34%, e.g. if PROCAM databases are used³.

Age and conventional risk factors are not satisfactory risk prediction tools. They are derived from higher risk populations than the Swiss (Framingham, Münster), are likely to overestimate risk in Switzerland and lead to costly and unnecessary drug treatment in some cases⁴. Importantly, none of these risk assessment tools are validated for Switzerland.

Opinion leaders are of course quite aware of this situation, but, because of "faute de mieux", everything is left as it is.

Others, however try to look beyond the horizon and aim at identifying the vulnerable patient through imaging (the vulnerable plaque⁵) or recommend the measurement of newer risk factors such as hsCRP, homocysteine, air pollution and depression, probably at the expense of lower specificity.

Yet another approach is to look at atherosclerosis directly and non-invasively.

Carotid Imaging

New tests have emerged, e.g. the total carotid plaque area as a risk prognosticator and tool for

atherosclerosis tracking and management in 1686 men and women followed over a period of 5 years⁶. This very important study will be discussed here. It was shown, that atherosclerosis has to be quantified and tracked, in order to treat it. As Dr. Spence states, you wouldn't treat blood pressure, without measuring it. I have measured total carotid plaque area in > 300 patients since April 2002. The data await to be analyzed and I call for a student.

Let us look a case to illustrate the importance of atherosclerosis imaging. For instance, you ask yourself about the risk of your patient to suffer a heart attack, or want to know his risk for stroke ?

1. Carotid Intima: In order to answer this question, you will normally proceed as follows: the patient is found to be hypertensive and shows signs of ischemia on a surface electrocardiogram. You diagnose hypertensive heart disease, a condition with increased likelihood for stroke but not for myocardial infarction. Why ?

Hypertension is an independent risk factor for stroke, because it induces small vessel disease of the brain vasculature, a recognized cause of stroke in 25% of cases (lipohyalinosis and micro atheromata). Another 50% of strokes are caused by carotid atherosclerosis (arterio-arterial emboli). And finally, about 12% of your patients with hypertensive heart disease develop stroke due to atrial fibrillation. What is the role of atherosclerosis imaging in this case ?

Left ventricular hypertrophy is not readily depicted by surface ECG, you would need a screening echocardiogram. The cost is however quite superior than just measuring carotid IMT, which is an established risk factor for stroke⁷ and costs 35 Swiss francs at our institution measured by a semiautomatic software from France (M'ATH, Touboul).

Now, with this information, you end up to know, that your patient has a risk for stroke of around 12 cases per 1000 subjects per year, if mean maximum IMT is found to be 1.06-1.17.

Figure 1: IMT can be measured reliably with a caliper method, however I prefer the M'ATH software (metris-france.com)



This risk is, however, below the threshold for intensive medical treatment with a calculated risk of 20% or more in 10 years.

Further, such information may help to guide the aggressiveness of your medical therapy. If you are a friend of Sartans (ARB: angiotensin receptor blocker), your cost analysis will call for low numbers needed to treat. If your patient has a mean blood pressure on an ambulatory profile of around 142/98 mm Hg, has a BMI of 30.2 and does not perform physical exercise on a regular base, then would you give a sartan in this subject? The way I deal with this problem: if carotid IMT is normal, costly medication can be deferred safely. The patient has to loose weight and increase physical activity. If however carotid mean IMT measures > 0.7 mm in women or > 0.8 mm in men, that's the subject with good indication for costly medications.

2. Carotid plaques: Now you look at carotid plaque formation. If no plaques are present (defined as intimal thickening > 1 mm), I would treat hypertension with vigor, but not install lipid lowering therapy, unless LDL is > 5.0 mmol/l.

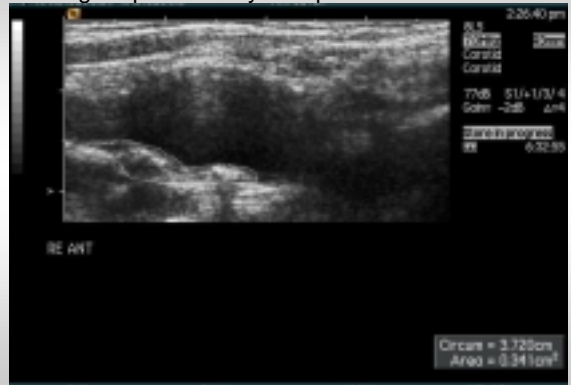
If plaques with a total plaque area of > 0.400 cm² are present indicating global risk (myocardial infarction, cardiac death, stroke) around 20% in ten years, then lipid lowering drugs seem warranted in subjects with LDL > 2.7 mmol/l and of course, aspirin might be considered as an additive risk prevention regimen.

Of note, in that same study, relative risk for hard cardiovascular events was not changed after correction for conventional cardiovascular risk factors.

Further, relative risk increased to the same extend by quartiles of the total plaque area for the prediction of stroke and myocardial infarction, however, the incidence of myocardial infarction was three times that of stroke. Thus, total plaque area is a strong predictor for coronary artery disease and coronary events.

Last, the authors could show, that patients without progression of atherosclerosis as defined by the total plaque area had significantly less events than patients with progression. Therefore, patients with plaque growth at the annual visit were treated more aggressively for atherosclerosis. Thus, atherosclerosis tracking is another tool to manage atherosclerosis.

Figure 2: Large Plaque in the carotid bulb (70 year male patient). Plaques can be measured easily and with high reproducibility. Plaque area was 0.341 cm²



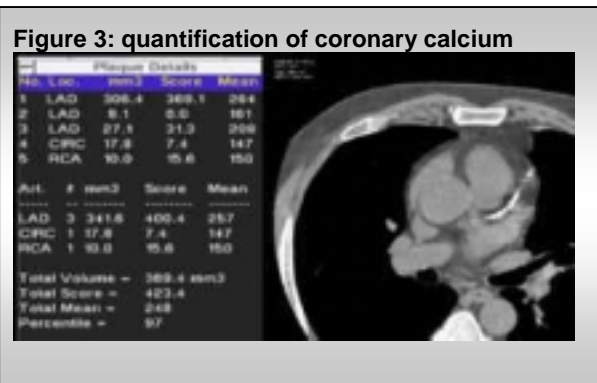
Coronary calcium imaging

When Doherty asked himself about the prognostic relevance of coronary calcium back in 1999⁶, he was uncertain whether it is good or bad. However, important news have emerged since then and were presented at the American Heart Meeting in October 2002. Summaries and my comments are given at the end of Kardiolab Newsletter. It is likely, that the measurement of coronary calcium in humans will help the clinicians in several ways.

- In the setting of primary care, absence of coronary calcium will identify low risk subjects even when having a risk factor profile indicating moderately high risk. About 10% of the middle aged population, who would need statins in Switzerland, can be safely deferred from taking these costly medications, probably for several years. Therefore, substantial cost savings can be expected.
- Symptomatic subjects with unclear chest pain indicating possible coronary obstruction can be imaged for coronary calcium. If no calcium is found, the probability to find a coronary stenosis is 0.0 % in women and 0.7% in men, and the probability to find an abnormal myocardial perfusion scan is 0.0%. Therefore, coronary calcium will become the gate keeper for costly imaging studies and coronary angiography.
- Coronary calcifications have the potential to better predict prognosis (risk for myocardial infarction) than the number of coronary stenoses as shown by invasive coronary angiography.
- Coronary calcifications are probably better to predict total and cardiovascular mortality than conventional cardiovascular risk factors (see the communication from the Rotterdam study).

There is no doubt, that this technology will soon enter medical practice in Switzerland. We will do any effort to improve the performance of this test in our institutes, population based studies included.

Figure 3 gives an example of coronary calcium. The quantification should be performed with a FDA approved software only.



**Communications about coronary calcium
American Heart Meeting 2002
My comments added**

**Long-Term Prognostic Value of
Coronary Calcification Detected by
Electron Beam Computed Tomogra-
phy in Patients with Indications for
Coronary Angiography**

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Background: Electron beam CT (EBCT) quantification of coronary artery calcification (CAC) allows non-invasive assessment of coronary atherosclerosis by generating an Agatston calcium score. We undertook a follow-up study to assess if this measure of CAC extent, determined at the time of angiography, correlated with future hard cardiac events, comprising cardiac death and non-fatal myocardial infarction (MI). We also assessed the potential of angiographic findings and recognized coronary artery disease (CAD) risk factors to predict these events.

Methods: 288 patients who underwent contemporaneous coronary angiography and EBCT scanning were contacted a mean of 6.9 years after evaluation. Vital status and history of MI during follow-up were determined. We examined the association of CAC extent with hard endpoints in these patients. We also compared the predictive ability of this measure of CAD to angiographic findings and recognized CAD risk factors.

Results: The median Agatston score was 160 [range 0-7633]. Twenty-two patients experienced hard events during follow-up. On average, these patients were older and had more extensive CAC and angiographic disease ($p < 0.05$ for both). Only one of the 87 patients in the cohort with minimal CAC on EBCT (Agatston score < 20) experienced a subsequent hard event during the 6.9-year follow-up period. Event-free survival was significantly higher for patients with Agatston scores < 100 compared to > 100 ($p < 0.01$). Using a multivariable Cox proportional hazard model, only age and CAC extent could predict event-free survival (risk ratios 1.72 and 1.88 respectively for a one standard deviation increase, $p < 0.05$ for both). Angiographic measures of CAD, including number of diseased vessels and overall disease burden, failed to reach statistical significance in this model.

Conclusions: In patients undergoing angiography, CAC extent on EBCT is highly predictive of future hard cardiac events and adds valuable prognostic information.

My comment: The risk for subsequent CD and AMI can be assessed by left ventricular function studies, by the extent score (number of vessels exhibiting a 5 to 75% stenosis in a 15 segment model of the coronary tree), by the number of coronary vessels

with stenosis $> 75\%$ (e.g. Gensini and Friesinger score = stenosis score), by nuclear imaging and by stress-echocardiography. Comparing left ventricular function, the extent score and the stenosis score in 312 patients with follow-up over a mean period of 3.4 years, Moise¹ found (using Cox multivariate analysis) that left ventricular function was the best predictor for CD (chi-square 17.78), followed by the extent score (chi-square 9.87) and the stenosis score (chi-square 6.61). The only statistically relevant predictors of the combined endpoints (CD, AMI and unstable angina) were left ventricular function (chi-square 12.02) and the extent score (chi-square 8.12), whereas the stenosis score was statistically not significant in this historical population with known CAD and without aspirin and statin medication. Thus, it is the number of minimal to moderate plaques found in the coronary tree that more precisely defines the patients risk for subsequent cardiac hard endpoints more precisely than the presence of severe coronary obstruction. Of note, left ventricular function was found to be the best predictor for subsequent cardiac events, over coronary anatomy.

The study by Keelan shows, that virtual absence of coronary calcification infers a risk for hard cardiac endpoints of 1 in 87 subjects over an observation time of 6.7 years. This equals a hard event rate of 1.7/1000/year. What test in medicine can do better? However, why did angiographic disease burden fail to show increased risk over time despite the Moise data? I believe, that in the era of risk lowering strategies (aspirin, statin, ecc), only very strong predictors of risk remain predictive. That is, left ventricular function, and coronary calcifications.

Further Readings:

¹ Moise A et al. Clinical and angiographic correlates and prognostic significance of the coronary extent score. *Am J Cardiol* 1988;61:1255

**The Extent of Coronary Calcium by
Electron Beam Computed Tomogra-
phy Discriminates the Likelihood of
Abnormal Myocardial Perfusion
SPECT**

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Publishing ID: 2640 Abstract ID: 109948

Background: A coronary calcium score (CCS) of > 400 by electron beam computed tomography (EBCT) has previously been established as a criterion for extensive atherosclerotic plaque burden (Rumberger et al, *Mayo Clin Proc* 1999;74:243-252) and as a predictor of silent ischemia by myocardial perfusion SPECT (MPS) (He et al, *Circ* 2000;101:244-251). This study independently evaluates the optimal cut point for CCS in discriminating the likelihood of abnormal MPS results.

Methods: We studied 233 consecutive patients (male = 84.7 \pm 2.4%, age = 59.7 \pm 6.8 yrs) who had both EBCT and MPS imaging at our institution. EBCT and MPS were performed within 90 days with a mean of 18.8 \pm 1.4 days between tests. CCS was calculated from EBCT by the Agatston scoring tech-

nique. Rest thallium-201/stress (86% exercise, 14% pharmacological) gated Tc-99m sestamibi MPS was interpreted by semi-quantitative visual analysis and categorized for overall interpretation as normal or abnormal.

Results: Of the 233 patients, 17(7%) had abnormal MPS. Mean CCS in the normal MPS patients was 522 ± 48 . Mean CCS in the abnormal MPS patients was 1245 ± 243 . Using ROC analysis, a CCS of 399 resulted in the optimal sensitivity (82%) and specificity (62%) for detecting an abnormal MPS with the area under the curve=0.766 (95%CI=0.66-0.87). Of 96 patients with CCS>399, 14(14.6%) had abnormal MPS.

Conclusions: CCS by EBCT can discriminate normal from abnormal MPS tests with scores>399 being associated strongly with abnormal MPS results. These findings validate the conventional criterion that a CCS>400 implies extensive coronary artery disease; however, these findings also suggest that the frequency of abnormal MPS in pts with CCS>400 may be lower than previously suggested.

My comment: The probability to find angiographically relevant stenoses on a coronary angiogram is related to the presence and extent of coronary calcifications and the presence of ischemia in a myocardial perfusion scan. Therefore, there is also an interrelationship between the presence and extent of coronary calcifications and the probability to find an abnormal myocardial perfusion scan. As published recently¹, in subjects with cardiac symptoms but with an Agatston score below 100, no subject (0/118) had ischemia on the myocardial SPECT study, while the ECG showed abnormalities suggesting ischemia in this population in 17% (20/118). In contrast to the above mentioned findings with an abnormal perfusion scan in 15% of the subjects with an Agatston score > 400, Zuo¹ found this finding in 40% of his population (42/105). Since both studies were obtained from US populations, the reason for the apparent difference remains unclear. From the point of view of health care resources it becomes readily clear that in subjects with suspicion of myocardial ischemia and an intermediate pretest-probability before performing the nuclear scan, an EBCT screen would save a lot of money also in Switzerland.

Further Readings:

¹ Zuo et al. Severity of coronary calcification on EBCT predicts silent myocardial ischemia. *Circulation* 2000;101:244

Exclusion of Coronary Calcification with EBCT is a Safe and Effective Filter for Invasive Coronary Angiography: Results of 1764 Symptomatic Patients

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Rationale: Electron beam computed tomography (EBCT) is a sensitive method to detect coronary

calcifications. This monocenter study correlated the EBCT calcium score (C150XP, Imatron, 40 slices, scan time 100 ms, Agatston score) to the results of coronary angiography in 1764 symptomatic patients (1225 men, 539 women, mean age 59 ± 11 years) with atypical or typical chest pain and/or signs of myocardial ischemia in noninvasive testing with unclear diagnosis, who were referred to our hospital for invasive evaluation.

Results: 56% of men and 47% of women revealed significant coronary stenoses (>50%). No coronary calcium at all (score=0) was found in 29.6% of the total population, and in 32% of men and 55% of women below the age of 60 years. Exclusion of coronary calcium was associated with an extremely low probability of significant stenosis (0.7% in men and 0.0% in women). With higher scores of 20, 100 or >75% percentile of age group, sensitivity decreased to 97%, 93%, and 81%, respectively in men, and 98%, 82%, and 76%, respectively in women. At the same time specificity increased to 75% in men and women. There was a significant difference in calcification between men and women in all age groups, however, receiver operating characteristic (ROC) curves indicated that the test can be performed equally accurate in all of these subgroups. The large cohort of patients allowed to calculate cut points of coronary calcium in different age groups separating patients with high versus low probability of significant coronary stenosis.

Conclusion: EBCT calcium scoring was a highly sensitive and moderately specific test to predict stenotic disease in this symptomatic study population. Exclusion of coronary calcium defines a substantial number of patients - although symptomatic - with an extremely low probability of significant stenoses, in whom invasive angiography may be omitted.

My comment: The probability to find angiographically relevant stenoses on a coronary angiogram is related to the presence and extent of coronary calcifications. In view of the tremendous amount of diagnostic coronary angiograms performed annually in Germany (with 70% of coronary angiograms having no further therapeutic impact on medical therapy¹), alternative approaches to exclude subjects with coronary stenosis is crucial. This study is important indeed. In 55% symptomatic women and 32% symptomatic men without coronary calcium detected on the screening EBCT, and who otherwise would have undergone coronary angiography in Germany, the incidence of coronary stenosis was 0.0% in women and 0.7% in men. The test performance is certainly better than ECG stress testing and probably better than a myocardial perfusion scan. For Europe, a very detailed study has shown, that in relation to age and gender, coronary stenosis can be excluded with a high probability using EBCT calcium scores².

Further Readings:

¹ Der Spiegel. 02.07.2001.

² Haberl et al. EBCT calcium score cut points and accuracy to detect significant coronary narrowing. *JACC* 2001;37:451-457.

Prognostic value of coronary calcifications for cardiovascular events in patients with diabetes mellitus

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Publishing ID: 2535 Abstract ID: 110366

Introduction: Coronary calcifications are a highly significant marker of the early stage of atherosclerosis. We determined coronary calcifications in patients with diabetes mellitus to evaluate the possibility to predict cardiovascular events. Patients: We examined 281 patients (174 men, 107 women, age 57.8 ± 9.1 years) without known cardiovascular diseases. All patients suffered from non insulin-dependent diabetes mellitus for 6.4 ± 3.7 years. Additional risk factors were arterial hypertension (n = 189) and hyperlipidemia (n=100).

Methods: For determination of coronary calcifications we acquired 40 slices with the Imatron C-150 EBCT. For calcium quantification we calculated the Agatston and the volume score. The patients were divided into group I, Agatston score below 100 and group II, score above 100. Evaluation of cardiovascular events took place 35 months after initial examination.

Results: The average score in group I was 62 ± 34 , n = 119 and 231 ± 87 in group II, n = 162. There was no significant difference in risk factor distribution between group I and II. During observation period the number of patients with unstable angina pectoris was 10 (8,4 %) in group I compared to 38 (23.4 %) in group II, 6 patients (5.0 %) underwent coronary angioplasty in group I, 25 (15.4 %) in group II. 1 patient (0.8 %) suffered from myocardial infarction in group I, 10 in group II (6.2 %). There was a highly significant difference between group I and II for all cardiovascular events (p < 0.01).

Conclusion: The number of cardiovascular events was significantly higher in patients with calcium scores above 100. The determination of coronary calcifications allows the identification of patients with a high risk for future cardiovascular events in a group of initial asymptomatic patients with diabetes mellitus.

My comment: I have awaited this study for a long time. From the data of the heart protection study, it appeared reasonable to treat every diabetic subject with statins irrespective of the lipid level. This kind of simplistic approach had to be challenged. This cohort included 281 subjects with diabetes (duration 6.4 ± 3.7 years). The cohort was divided by absence (group I) or presence (group II) of an Agatston score of 100. Cardiovascular events were censored at 3 years after initial examination. Both groups had comparable risk factor distribution. Hard cardiovascular events, which is commonly defined by fatal or nonfatal myocardial infarction occurred rarely in group I (1/119 in 3 years which equals a hard event rate of 2.8/1000/year). Therefore, diabetes with low calcium scores appears to be a benign disease, however in relatively short follow-up. Two questions arise: 1. What is the hard event rate in diabetic subjects having undergone ischemia testing (myocardial perfusion scans or stress echocardiography) ? 2. Why is the event rate so much higher for normal ischemia testing than for near normal calcium scores ?

For myocardial perfusion scans, Giri¹ found 30/1000/year fatal and nonfatal myocardial infarctions in normal myocardial perfusion SPECT (follow

up time 2.5 years) and Kamalesh² found 62/1000/year fatal and nonfatal myocardial infarctions in normal stress echocardiography (follow up time 2.1 years). Therefore, an EBCT calcium score below 100 reflects a 10 times lower hard event rate when compared to myocardial perfusion SPECT and a 20 times lower hard event rate when compared to stress echocardiography.

These findings are corroborated by a genetic study on the hepatic lipase gene promoter polymorphism (LIPC-480C>T), which may identify a subgroup of diabetic subjects, in whom early intervention to prevent coronary heart disease may be appropriate³.

So, diabetic subjects with low coronary calcium scores (Agatston score < 100), may not benefit – in general – from aggressive lipid lowering regimens. But, what is the explanation for these findings ? High risk subjects do not produce flow limiting plaques necessarily, in contradiction to believes, that coronary obstruction is dangerous, several studies have shown, that coronary obstruction reflects the stabilized fibrotic plaque, while plaque with positive remodeling (thus growing outward) are more prone to become culprit coronary lesions due to their increased content of macrophages and lipidpools⁴, but also due to their increased arch of calcification⁵. Thus summarizing these data: coronary calcification is the strongest risk predictor in high risk subjects available to contemporary medicine.

Further Readings:

¹ Giri et al. Circulation 2002;105:32. ² Kamalesh M et al. Am Heart J 2002;143:163. ³Hokanson et al. Diabetes 2002;51:1208. ⁴Varnava et al. Relationship between coronary artery remodeling and plaque vulnerability. Circulation 2002;105:939. ⁵Rioufol et al. Multiple atherosclerotic plaque rupture in acute coronary syndrome. A three vessel IVUS study. Circulation 2002;106:804.

Coronary calcification is a strong predictor of all-cause and cardiovascular mortality in the elderly

Oudkerk Matthijs , Witteman Jacqueline , Hofman Albert , Breteler Monique , Oei Hok-hay , Vliegenthart Rozemarijn , AHA 2002

Introduction: Coronary calcification is promising for the detection of subjects at high risk of cardiovascular events. Especially in elderly, in which the predictive value of risk factors decreases, coronary calcification may improve risk stratification. No data are available in elderly populations. Hypothesis: We assessed the hypothesis that coronary calcification predicts all-cause and cardiovascular mortality in elderly.

Methods: From 1997 onward, elderly were invited to participate in the Rotterdam Coronary Calcification Study and undergo electron-beam computed tomography scanning. Calcifications were quantified according to Agatston's method. Calcium scores were available for 2013 participants (mean age 71.0 ± 5.7 years) and were divided into 4 predefined categories. Cox regression analysis was used to calculate hazard ratios of death in calcium score

categories. Two models were applied: adjusted for age and sex, and multivariate adjusted.

Results: During a mean follow-up of 2.7 ± 0.7 years, 96 subjects died, 36 from a cardiovascular cause. A strong and graded association was found between coronary calcification and mortality. Age- and sex-adjusted hazard ratios of death were 1.98 (95% confidence interval, 1.11-3.53) for a calcium score of 101 to 500, 2.19 (1.13-4.25) for a calcium score of 501 to 1000, and 3.13 (1.72-5.70) for a calcium score above 1000, compared to a calcium score of 0 to 100 (reference category). Corresponding hazard ratios of cardiovascular death were 2.93 (1.00-8.54), 3.99 (1.27-12.55), and 5.32 (1.81-15.65), respectively. After additional adjustment for cardiovascular risk factors, hazard ratios of death ranged from 1.58 for a calcium score of 101 to 500 (0.86-2.90) to 2.60 for a calcium score above 1000 (1.39-4.88), compared to the reference category. For cardiovascular death, corresponding hazard ratios were 2.29 (0.76-26.91) and 3.66 (1.20-11.16), respectively. Exclusion of subjects with a history of cardiovascular disease did not materially change the estimates.

Conclusions: Coronary calcification is a strong predictor of all-cause and cardiovascular mortality in elderly.

My comment This is a landmark study. The work was derived from the population based Rotterdam cardiovascular risk survey. People did not get the EBCT scan for money. It is the first study, that looked at the relative value of cardiovascular risk factors and findings from the EBCT scanner in randomly selected subjects. This is therefore a true epidemiological study. It was found that high coronary calcium scores (> 500) remained an independent predictor of cardiac death, beyond and after adjustment for conventional cardiovascular risk factors in multivariate analysis. More studies will come from other populations (Nixdorf recall study in Germany is recruiting > 4000 subjects, and the MESA study in U.S. is recruiting > 6500 subjects). This study is challenging a paradigm in medicine, e.g. that cardiovascular risk is best predicted by cardiovascular risk factors.

It has to be anticipated, that there will be a paradigm shift towards measuring cardiovascular risk more accurately and non-invasively using atherosclerosis imaging for the following reasons

- Subjects without atherosclerosis (Carotid IMT, Carotid Plaques, Coronary Calcifications) are at extremely low risk for cardiovascular events irrespectively of their conventional cardiovascular risk status
- No visible atherosclerosis means, therefore, no substrate for cardiovascular events
- Rare exceptions are severe coronary spasm e.g. in Cocaine users or heavy smokers
- There is an increasing number of risk factors, since conventional risk factors, as used in available guidelines in Europe (PROCAM) and US (NCEP III) suffer from low sensitivity (around 30-50%), which is not a satisfying situation. To increase sensitivity (probably at the cost of specificity) you have to measure the following risk factors in your patients: total cholesterol, HDL-Cholesterol, LDL-cholesterol, small and dense HDL, Lp(a), triglycerides, ho-

mozystein, Insulin resistance, air pollution, renal function, PAI-1, F VII, VIII, IX, X, Prothrombin, vWF, F XIII and B-subunit, D-Dimers, hs-CRP (not available in the PROCAM database ...!), fasting glucose, proteinuria, hypertension, obesity, waist-hip circumference, depression, microalbuminuria, physical inactivity, alcohol consumption in men, diabetes, smoking habits, viral infection, age, Apo B, Chlamydia pneumoniae titer and so on.

Why not look at the common pathway of all cardiovascular risk factors, that *is* atherosclerosis and measure atherosclerosis first, and if plaques are present, look for modifiable risk factors? The work by Spence is here for daily medicine and cardiovascular risk assessment¹.

Further Readings:

¹ David Spence. Carotid plaque area. A tool for targeting and evaluating vascular preventive therapy. Stroke 2002;33:2916-2922.

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- ⁸ Am Heart J 1999;137:806-14

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