Year: 2009

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Screening tools for coronary artery disease (CAD) in asymptomatic subjects: the role of stress testing

A contribution of the Taskforce on Vascular Risk Prediction

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Summary

Coronary risk assessment in asymptomatic subjects is an important issue in primary care. Global coronary risk assessment has been incorporated in recent guidelines (www.agla.ch) and clearly defines, which step should be taken in relation to risk stratification obtained from coronary risk charts. However, silent myocardial ischaemia is encountered quite frequently and such subjects probably are at higher risk than derived from coronary risk charts. Silent ischaemia can be detected by several methods: exercise electrocardiogram (ECG), stress imaging studies (stress echocardiography, stress myocardial perfusion SPECT, stress myocardial perfusion PET, stress magnetic resonance) or Holter monitoring. Increasing evidence suggests that coronary revascularisation of asymptomatic ischaemia with known CAD improves prognosis, however, in primary care subjects with silent ischaemia and under optimal medical treatment, revascularisation does not improve outcome. In the future it may prove to be important to define categories of asymptomatic patients who might nevertheless benefit from ischaemia testing. Numerous studies have shown that an aggressive medical therapy in asymptomatic subjects with high coronary risk reduces global plaque burden, myocardial ischaemia and coronary events. "Negative" ischaemia tests in the setting of high coronary risk may even deter primary care physicians from aggressive primary prevention. Therefore, at the moment, ischaemia tests are neither recommended in asymptomatic primary care patients nor in the general population; but adherence to preventive guidelines is fundamentally important to reduce the epidemic of coronary artery disease.

Grants and other sources of support: none.
Conflict of interest: none.

Key words: coronary heart disease; primary care; prevention

Introduction

Should tests that detect myocardial ischaemia be used to identify asymptomatic subjects at high cardiovascular risk? Might myocardial ischaemia tests extend or even replace conventional risk factor assessment and global risk charts? Is the risk in subjects without ischaemia low enough to defer intensive medical primary prevention therapy despite high coronary risk derived from risk charts? Will serial ischaemia tests help to guide the intensity of medical therapy in primary care?

Answers to these questions are important, since pre- and in-hospital mortality of a first myocardial infarction are as high as 23% (17–29%) and 16% (13–19%) respectively in large historical series of untreated subjects [1] with a very high subsequent all-cause and vascular mortality rate (up to 10% in the first year). Further, the epidemic of diseases caused by coronary atherosclerosis is a long way from being under control [2].

Performing ischaemia tests in the healthy, asymptomatic general population or in the setting of primary care in order to detect and treat coronary artery disease before the occurrence of myocardial ischaemia, cardiac death, or myocardial infarction, is not established. However, in certain subsets of risk subject, ischaemia testing might be useful to improve outcome.

In this review we discuss the possible value of myocardial ischaemia tests in the general population and in various subsets of the population, e.g., in subjects with a high coronary risk score, severe atherosclerosis

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defined by atherosclerosis imaging, in subjects with dyspnoea or in subjects with diabetes mellitus.

Detection of ischaemia using exercise ECG or Holter monitoring in the healthy, asymptomatic population

In an overview study including over 10 000 healthy subjects participating in prevention trials (Seattle Heart Watch study, Lipid Research Clinics Program, United States Air Force personnel, Norwegian office workers, Indiana State Police employees), a pathological exercise ECG test was documented in 5% of the subjects [3]. Coronary artery disease (CAD) was confirmed subsequently by a coronary angiography in 2.5% (specificity of the exercise ECG in this population: 50%). Therefore, the prevalence of silent CAD in this large group of subjects was low and the absence of silent CAD as measured by the exercise ECG was present in as many as 9750 subjects which makes cost-efficiency of such unrestricted testing very questionable [3]. Although the relative risk of death per year was increased 10-fold in subjects with a pathological exercise test, absolute annual mortality was relatively low in both groups (0.7% per year in subjects with ischaemia on a stress ECG vs 0.07% in those subjects without ECG defined ischaemia). However, in selected patients, untreated silent ischaemia on a stress ECG was found to be related to an all cause mortality of 1.4% per year and 0% if patients were managed with an additional intensive antiischaemic drug therapy [4].

A Holter ECG monitoring study revealed that the prevalence of silent ischaemia in a healthy, asymptomatic population may increase with age and may be associated with a >4-fold increase for coronary events [5]. However, the majority of events occurred in subjects without evidence of ischaemia in this Holter monitoring study, highlighting the problem of its low sensitivity for detecting silent ischaemia in asymptomatic subjects and thereby preventing serious cardiac events [5].

Recently, the U. S. Preventive Services Task Force published a review on exercise ECG testing as a screening tool for CAD [6]. This Task Force aimed to answer the question, whether such tests add incremental information. The Task Force concluded, that "although screening exercise tolerance testing detects severe coronary artery obstruction in a small proportion (<2.7%) of persons screened and can provide independent prognostic information about the risk of coronary heart disease events, the effect of this information on clinical management and disease outcomes in asymptomatic patients is unclear." Similar conclusions were made in a recent statement by the American Heart Association [7].

Other parameters derived from the exercise ECG, such as heart rate recovery (HRR) and exercise capacity expressed as metabolic equivalents (MET) have been proposed as additional factors for identifying high risk subjects classified as intermediate risk by the Framingham risk scores [8]. In a long-term cohort study with over 20-years observation time in which 3329 men and 2797 women, 25% of men had an intermediate Framingham risk score (FRS 10–19%) and 7% of women had a low to intermediate FRS (6–19%). In those found to have a low HRR/MET, 50% were shifted into the high risk category. The cardiovascular death rate over 10 years for these patients was 8.3% in men. In women, the observed cardiac death rate was even higher: 10.8% in women with FRS of 6–9% and 18.5% in those with a baseline of FRS of 10–19%. Therefore, a strategy of "sequential testing" could potentially identify subjects at intermediate risk based on FRS and at high risk based on the combination of FRS and HRR/MET.

In summary, exercise testing in asymptomatic subjects is not accepted or recommended in the current guidelines. More observational data are needed to clearly identify the benefit of exercise testing in asymptomatic, healthy individuals. An important role of exercise testing appears to be the stratification of intermediate risk subjects, however, further studies are needed in the absence of sufficient evidence.

Ischaemia testing with imaging techniques (ECHO, SPECT, MRI) in high-risk asymptomatic subjects

Silent myocardial ischaemia (i.e. ischaemia causing no symptoms) has a poor prognosis in patients after myocardial infarction [9, 10] or in diabetic subjects [11]. In patients without known prior coronary artery disease (CAD), the prevalence of silent CAD (defined by a coronary stenosis of >50%) is 2.5–11% in non-diabetic patients as compared to 6.4–23% in low-risk diabetic patients [12, 13]. More importantly, diabetic patients without documented CAD have the same prognosis as non-diabetic patients with manifest CAD placing diabetic patients directly in the high-risk group. The prognosis of diabetic patients worsens dramatically once they develop manifest CAD. It is therefore important to treat all diabetic patients as aggressively as patients with manifest CAD and without further risk stratification.

In CAD, chest pain or angina represent only the "tip of the iceberg" [12, 13]. Several steps precede the onset of angina. The decrease of perfusion is the first step of the cascade and perfusion is reliably visualized e.g., by nuclear cardiology methods (MPS and Positron Emission Tomography [PET]).

There are several subsets of subjects with a higher potential for silent ischaemia: e.g., subjects with a >20% risk for a heart attack based on risk charts (e.g., PROCAM or NCEP III), subjects with subclinical atherosclerosis as evidenced non-invasively by atherosclе-

rosis imaging, subjects with dyspnoea or subjects with diabetes mellitus.

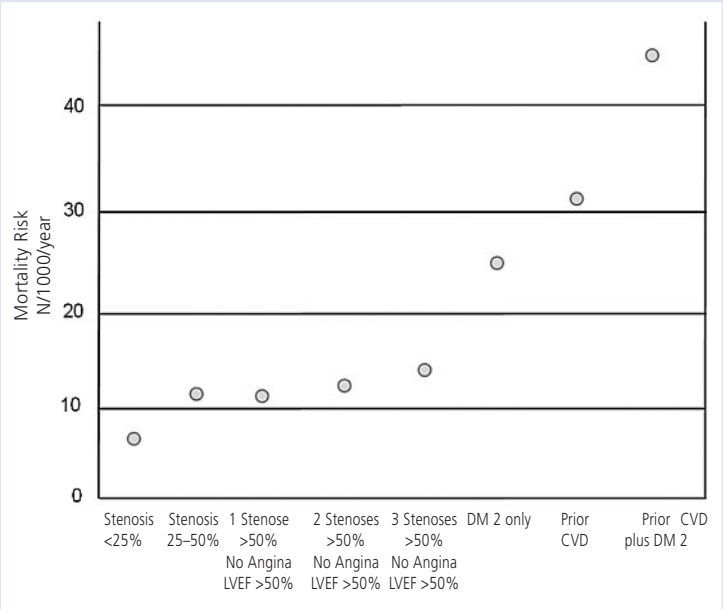
No proven benefit of ischaemia imaging testing in subjects defined at high risk by risk charts, atherosclerosis imaging or subclinical atherosclerosis by coronary angiography

Non significant coronary atherosclerosis (e.g., stenosis <50%) is viewed as a benign condition, even when untreated. Based on large historical cohorts observed in the pre-aspirin period (before 1980, fig. 1), the absence of signs of atherosclerosis on a coronary angiography was related to an excellent survival with an annual mortality of 0.6% [14]. However, in subjects with some subclinical atherosclerosis, a so called "near-normal" coronary angiogram, mortality was nearly doubled at 1.1% per year. Vascular risk of death higher than 5% in 10 years or 0.5% per year has been defined a high risk situation by the European Score guidelines [15]. Therefore, an annual mortality of 1.1% year is not a low risk situation in subjects with a "near normal" coronary angiogram. Surprisingly, in this historical pre-aspirin and pre-statin cohort of the CASS registry, subjects with angiographically documented CAD (luminal narrowing >50%), angina Class I and II and preserved left ventricular function (LVEF >50%) had an annual mortality rate of 1.0% in single vessel disease, of 1.2% in dual vessel disease and of 1.4% in triple vessel disease [16]. Therefore, "natural course" mortality risk in subjects with "near normal", non obstructive CAD is similar to subjects with preserved left ventricular function and single or dual vessel disease, if anginal symptoms are not severe (Class I and II). Further, based on another historical observation, the annual risk for fatal or non-fatal myocardial infarction was 1.2% annually in subjects with coronary luminal narrowing between 25–50% as opposed to 0.3% annually in subjects with coronary stenoses <25% [17]. Therefore, in terms of heart attack risk defined by the cardiovascular Munster (PROCAM) study [18], "near normal" angiography may infer at least an intermediate risk for myocardial infarction. Therefore, the argument, that the detection of clinically silent atherosclerosis with outward remodelling of coronary plaques and compensatory enlargement of the coronary arteries – the so-called Glagov phenomenon [19] – may be important. In fact, high risk defined by major independent cardiovascular risk factors correlates well with a non-invasively detected heavy burden of atherosclerosis in coronary and carotid arteries [20]. This lends support to the concept, that atherosclerosis imaging may yield additional and independent information above and beyond risk scores derived from Framingham, PROCAM or SCORE. Importantly, most subjects with subclinical atherosclerosis have cardiovascular risk factors and should be treated accordingly. Ischaemia imaging tests in these subjects are very likely to show normal results and result in false reassurance.

Further, there are no scientific data that have addressed the question, whether routine testing using stress echocardiography, stress myocardial perfusion studies (SPECT) or stress cardiovascular magnetic resonance (CMR) would help to reduce event rates for myocardial infarction in asymptomatic subjects with a *high risk* based on risk charts, e.g., PROCAM. The same is true for subjects with high risk findings based on atherosclerosis imaging, e.g., extensive coronary calcifications. Although subjects with a coronary calcium score (Agatston Score) over 400 were shown to have silent ischaemia on an exercise SPECT study in 40% of cases [21], there is still a lack of proof, that these 40% with ischaemia and severe and extensive coronary calcifications have a higher risk for subsequent myocardial infarction than those with severe and extensive coronary calcifications, but without ischaemia. Further, we do not know, if medical intervention following this kind of sequential testing (e.g., first coronary calcium score testing, then second, SPECT testing, only if severe and extensive coronary calcifications are present) would reduce the risk for heart attacks in these patients.

A still experimental but promising ischaemia testing tool is adenosin cardiovascular magnetic resonance (CMR). So far the largest multicentre study comparing this method with invasive coronary angiography and stress SPECT found a higher diagnostic accuracy to detect stenoses >50% for adenosin-CMR than for stress SPECT: using ROC analysis, adenosin-CMR had a value of 0.86 versus 0.67 for stress SPECT (p <0.01)

Figure 1
Total mortality: risk in relation to coronary atheromatosis and stenosis in historical patient groups (before 1980) and actual risk for clinical entities (previous vascular disease or diabetes mellitus type 2) [14–18, 32, 39, 41].



[22]. Another potential advantage of adenosin-CMR is the complete absence of irradiation. However, in view of the very low event rate of 0.6% per year with stress SPECT, the higher sensitivity of adenosin-CMR may not translate into a better outcome, if such patients with a normal stress SPECT, but an abnormal adenosin-CMR are revascularised. Further, in subjects able to exercise physically, pharmacological stress tests are neither indicated [7] nor do they in general allow detection of exercise induced endothelial vasomotor dysfunction, subclinical atherosclerosis and subsequent exercise induced coronary artery spasm [23]. Therefore, adenosin CMR is still reserved for experienced and specialised centres in symptomatic subjects with clinical suspicion of CAD who are unable to perform a regular exercise stress test.

In summary, it is generally not recommended to perform ischaemia tests in asymptomatic high-risk subjects defined by risk scores or atherosclerosis imaging. However, intensive primary prevention therapy is certainly needed in all these cases.

Is there an additive value of ischaemia imaging in subjects with diabetes mellitus or exercise induced dyspnoea?

The relatively high prevalence of silent CAD in particular in the diabetic patient stresses the fact that prognostic considerations of this problem are of potential prognostic benefit.

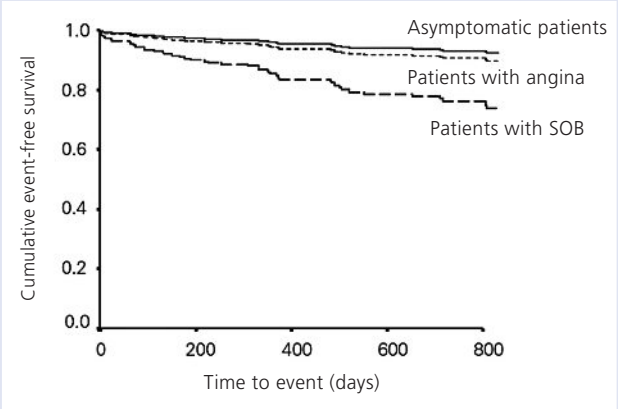
Myocardial perfusion SPECT (MPS) is a widely used cardiac imaging tool to detect CAD in symptomatic subjects. Its diagnostic and prognostic value has been demonstrated by a huge amount of evidence [12, 24–32]. MPS has excellent sensitivity and good specificity in the detection of CAD, 87% and 73%, respectively [33], as shown by a pooled analysis evaluating over 4000 patients. Patients with a normal MPS and normal left ventricular ejection fraction, in general have an excellent prognosis, with a cardiac death or myocardial infarction rate of less than 1% [34–36], even in the presence of CAD.

To date, there are several retrospective studies, but only one study that has prospectively evaluated the prevalence of silent CAD in diabetic patients. Wackers et al. conducted the Detection of silent myocardial Ischaemia in Asymptomatic Diabetic subjects (DIAD) study [37, 38]. 522 patients were screened by MPS. Of these, 22% had an abnormal stress test result. Cardiac autonomic neuropathy turned out to be the only independent predictor of abnormal MPS – none of the well-known CAD risk factors.

Rajagopalan et al. examined angiographic findings and mortality rates in 826 asymptomatic diabetic patients with respect to MPS findings [39, 40]. The mortality rate was 5.9% in high-risk patients, 5.0%, in intermediate-risk patients and patients 3.6% in low-risk ($p < 0.001$ for differences between groups). Post hoc analyses were performed to determine if a truly low-risk (annual mortality <1%) subset of patients could be identified. Annual mortality in diabetic patients without Q-wave myocardial infarction at ECG, without peripheral arterial disease, and with a completely normal SPECT imaging scan (n = 443), was only slightly lower but at 2.9%. The annual mortality rate was higher in patients with preoperative versus other indication for MPS evaluation (5.9% vs 2.7%; $p < 0.001$). The annual mortality rate for patients without a preoperative indication whose scan was normal (n = 298) amounted to 1.9%. For patients without a preoperative indication, Q-waves, or peripheral arterial disease, the annual mortality rate was 1.6% for those with a normal scan (n = 237) and 3.4% for those with a high-risk scan (n = 79). Importantly, although a normal MPS study is generally associated with a low risk (<1% annual risk of cardiac death or myocardial infarction), the challenge in a diabetic population is to define the elusive "low-risk" patient. To date, reports have consistently shown that normal MPS in diabetic populations is not associated with this low level of risk and, in direct comparisons, patients with diabetes are at significantly greater risk than non diabetics with normal MPS [11, 32, 39, 41, 42]. Similarly, in the setting of an abnormal MPS, the risk conferred by any given extent and severity of perfusion abnormality is greater in patients with diabetes than in non diabetics. Zellweger et al. assessed the incidence of MPS evidence of CAD in diabetic patients without known CAD and the impact of symptoms and scintigraphic findings on prognosis [32]. Objective evidence of CAD was found in 39% of 826 asymptomatic diabetic patients, in 51% of 151 diabetic patients with shortness of breath, and in 44% of 760 diabetic patients with angina. Overall, patients with a normal MPS had quite a good prognosis irrespective of symptomatic status, although the mortality was not <1%. Patients with an abnormal MPS had a significantly worse outcome. Of note, there was no prognostic difference in patients with abnormal MPS when asymptomatic patients and those with angina were compared.

In contrast, patients with shortness of breath had a very high event rate, reflecting in part that these patients had more often suffered a silent myocardial infarction than asymptomatic patients and those with angina. In the multivariate Cox proportional hazards model, age, hypertension, shortness of breath, extent of scarring, and extent of ischaemia were independent predictors of events. Hypercholesterolaemia and family history of CAD tended to be independent predictors of events [43]. Of note, angina was not a significant predictor of critical events in this model, but shortness of breath was. MPS added incremental information to clinical and prescan information to predict the outcome (fig. 2).

Figure 2
Kaplan-Meier survival curves in patients with abnormal MPS (n = 509; adapted from [43]). SOB = shortness of breath.



In summary, in asymptomatic *high risk* subjects as defined by high risk scores (i.e. subclinical atherosclerosis or diabetes mellitus) under optimal medical treatment, there is no proof until today, that the addition of highly technological ischaemia tests will improve outcome [44]. The worst case scenario is that high-risk subjects with a "negative" ischaemia test might not receive adequate aggressive preventive therapy. In fact, the recently published DIAD study [45] assessed the impact of myocardial perfusion SPECT in 1123 diabetic subjects (mean age 61 years, mean duration of diabetes mellitus 8 years) randomised to ischaemia screening or usual care. The 5 year rate of myocardial infarction and cardiac death (MACE) could not be positively influenced by the ischaemia screening strategy, in that both groups had a low risk for MACE at 5 years of follow up (2.7% in the screening and 3.0% in the non screening group, p not significant). However, during the course of study there was a significant and equivalent increase in primary medical prevention in both groups. This underscores again the importance of treating – and not imaging – high risk subjects in order to reduce risk.

However, subjects with exercise induced dyspnoea should be submitted to a thorough medical investigation in order to identify treatable causes.

Conclusions

Coronary risk in the asymptomatic population is best assessed and treated according to coronary risk charts (e.g., PROCAM) and guidelines even in asymptomatic subjects with proven coronary artery stenosis [9]. ACC/AHA/ASNC Guidelines for the "Clinical Use of Cardiac Radionuclide Imaging" made a clear statement about testing asymptomatic patients [33]: The relatively low prevalence of CAD and risk of future events will affect the performance of any diagnostic test in a manner predictable by Bayesian principles (e.g., positive predictive value will usually be low). It is not clear that detecting asymptomatic preclinical CAD will lead to therapeutic intervention and reduce risk beyond that indicated by risk factor profiling and currently recommended strategies in reducing risk. Persons whose occupations may affect public safety (e.g., airline pilots, truck-drivers, bus drivers) or who are professional or high-profile athletes commonly undergo periodic exercise testing for statutory reasons. Currently, there are no existing guidelines saying, that ischaemia testing may be appropriate when there is a high-risk clinical situation (e.g., diabetes mellitus or multiple risk factors).

The question of therapeutic approaches in silent CAD is an important topic for ongoing debate. The data dealing with this issue are scarce and further studies are underway.

It is also likely that rigorous primary prevention by risk factor modification and treatment (e.g., lipid lowering with statins) will lead to improvement of perfusion and thus to regression of CAD in asymptomatic patients with evidence of silent CAD.

In summary, the key message of this review is simple. High risk subjects (diabetes, several cardiovascular risk factors) should be treated maximally in primary care. This is the only proven strategy preventing organ damage due to atherosclerosis and emphasises the eminent importance of family doctors in the protection of their patients. Subjects with exercise induced dyspnoea need a medical work up in order to identify the cause of this high risk clinical condition. Ischaemia tests are not a treatment, are not infrequently normal despite a high risk situation and may detract physicians from treating their patients correctly. More studies however are needed in order to clarify the advantage of ischaemia tests to identify undetected CAD, since these subjects may benefit from coronary revascularisation in an additive way, on top of vigorous risk factor treatment.

The coexistence of diabetes and previous cardiovascular disease infers highest risk to these patients (fig. 1). These patients benefit the most from aggressive risk lowering medical intervention.

Acknowledgement

The taskforce on vascular risk prediction was created by the Swiss Working Group on Lipids and Atherosclerosis (Swiss Atherosclerosis) in 2005. As of 2009, future work will be performed under the name Taskforce Atherosclerosis Imaging of the AGLA (www.taskforce.atherosclerosisimaging.ch).

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