Cardiac computed tomography and myocardial perfusion scintigraphy for risk stratification in asymptomatic individuals without known cardiovascular disease: a position statement of the Working Group on Nuclear Cardiology and Cardiac CT of the European Society of Cardiology

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Cardiovascular events remain one of the most frequent causes of mortality and morbidity worldwide. The majority of cardiac events occur in individuals without known coronary artery disease (CAD) and in low- to intermediate-risk subjects. Thus, the development of improved preventive strategies may substantially benefit from the identification, among apparently intermediate-risk subjects, of those who have a high probability for developing future cardiac events. Cardiac computed tomography and myocardial perfusion scintigraphy (MPS) by single photon emission computed tomography may play a role in this setting. In fact, absence of coronary calcium in cardiac computed tomography and inducible ischaemia in MPS are associated with a very low rate of major cardiac events in the next 3−5 years. Based on current evidence, the evaluation of coronary calcium in primary prevention subjects should be considered in patients classified as intermediate-risk based on traditional risk factors, since high calcium scores identify subjects at high-risk who may benefit from aggressive secondary prevention strategies. In addition, calcium scoring should be considered for asymptomatic type 2 diabetic patients without known CAD to select those in whom further functional testing by MPS or other stress imaging techniques may be considered to identify patients with significant inducible ischaemia. From available data, the use of MPS as first line testing modality for risk stratification is not recommended in any category of primary prevention subjects with the possible exception of first-degree relatives of patients with premature CAD in whom MPS may be considered. However, the Working Group recognizes that neither the use of computed tomography for calcium imaging nor of MPS have been proven to significantly improve clinical outcomes of primary prevention subjects in prospective controlled studies. This information would be crucial to adequately define the role of imaging approaches in cardiovascular preventive strategies.

Keywords   Cardiac computed tomography • Myocardial perfusion scintigraphy • Risk stratification • Coronary artery calcium

Preamble

Despite dramatic decrease in mortality over the past decades, cardiovascular diseases remain the most frequent cause of death worldwide.[1,2] To decrease the burden of cardiovascular mortality and morbidity, primary and secondary prevention strategies have been advocated by current prevention guidelines.[3] It is known that primary prevention interventions are more effective in

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terms of absolute number of prevented deaths compared with interventions in secondary prevention populations.[4] Although this may appear paradoxical considering the higher cardiovascular risk of patients experiencing prior cardiovascular events, it is easily explained by the fact that people without a previous event (primary prevention) represent the vast majority of the population. Therefore, the concept of risk stratification of asymptomatic individuals without previous cardiovascular events has been implemented in prevention guidelines to identify subjects at high cardiovascular risk in whom secondary prevention strategies, including drug therapy, are recommended. Yet, only a minority of asymptomatic individuals are classified as high risk and, consequently, the majority of events occurs in subjects at low to intermediate risk, a phenomenon known as the Rose' paradox.[5] As recently pointed out by Bonow,[6] this phenomenon holds true for all screening modalities. To overcome this limitation, several new biomarkers and imaging variables have been proposed to refine current risk calculation based on traditional risk factors and to reclassify asymptomatic subjects, reducing the proportion currently classified at intermediate risk in whom appropriate management of risk factors is often unclear.[3,7] In addition, although type 2 diabetic patients are considered at high risk by current guidelines and secondary prevention measures are recommended, some patients may in fact have silent ischaemia and severe coronary artery disease (CAD) which may benefit from even more aggressive measures, including coronary revascularization.

For the identification of asymptomatic individuals with high cardiovascular event risk who would benefit from more aggressive prevention measures, and of diabetic patients with severe CAD who might benefit from revascularization, imaging approaches may be useful. Direct visualization of the coronary arteries by computed tomography (CT) and imaging of perfusion by myocardial perfusion scintigraphy (MPS) have been investigated in this context. The purpose of this position paper is to summarize current evidence on the value of cardiac CT and MPS for risk stratification and the impact on clinical outcome of asymptomatic subjects. Special consideration is given to individuals with type 2 diabetes and other patient groups with a higher baseline risk, for example due to familial hypercholesterolaemia or in relatives of patients with premature CAD. The document represents the opinion of the Working Group on Nuclear Cardiology and Cardiac CT of the European Society of Cardiology and intends to foster future research in this field.

The anatomical and pathophysiological basis for risk evaluation with cardiac computed tomography and myocardial perfusion scintigraphy

Prevention of cardiac events in asymptomatic subjects without known CAD may follow two complementary strategies: (i) prevention of development, progression, and complications of atherosclerosis (reduction of CAD substrate), and, in a minority of subjects, (ii) identification and treatment (including revascularization) of patients with a prognostically relevant ischaemic burden.

Most available studies that evaluate the prognostic power of diagnostic tests are focused on the prediction of hard cardiac events, usually acute myocardial infarction (MI) and cardiac death. Obviously, this approach intrinsically implies that these events are precipitated by the same mechanism(s) and, hence, that an abnormality would predict the future risk for both of these events in the same way. Yet, this assumption has not been conclusively proven. While it is true that sudden death can represent an early complication of an acute MI, it can also occur in the absence of myocardial necrosis,[8] for example in the context of a transient ischaemic episode. On the other hand, although severe coronary stenoses are more prone to instability, acute MI often occurs at the site of non-haemodynamically significant plaques (which represent the majority of atherosclerotic lesions[9]) and in non-previously ischaemic myocardial regions.[10,11] In fact, it has been reported that following ischaemia detection, acute cardiac events are more likely to occur at the site of the haemodynamically significant stenosis, whereas events occurring at distance (more than 2 years) from ischaemia detection more likely develop from instabilization of coronary stenosis remote to the site of ischaemia.[12]

These considerations suggest that the two major complications of CAD might only partially share common underlying mechanisms and this needs to be taken into account when cardiac CT and MPS are considered for risk stratification. In fact, coronary morphology and atherosclerotic burden, as assessed with cardiac CT, do not accurately predict the functional/pathophysiological effects of epicardial stenosis on myocardial perfusion, which is also subject to influence by impaired endothelial function and loss of integrity of microcirculation.[13] Accordingly, a functional approach using MPS would be more useful to identify candidates for revascularization based on the quantification of ischaemia, especially in the presence of intermediate coronary stenosis and to predict cardiac events in the short term[14] (1–2 years), whereas the evaluation of the atherosclerotic burden by cardiac CT would be more useful for intervention strategies aimed at reducing the progression of atherosclerosis and lowering the long-term rate of CAD events in less selected populations.

Coronary artery calcium

In the coronary arteries, calcifications occur almost exclusively in the context of atherosclerosis.[15] The only exception are patients in renal failure, in whom medial (non-atherosclerotic) calcification of the coronary artery wall may occur in addition to atherosclerotic calcification. In fact, coronary calcium is considered to provide an estimate of the vascular biological age.[16] It has been shown that the amount of Coronary Artery Calcium (CAC) reflects the total atherosclerotic burden, including both calcified and non-calcified plaques.[17] The quantitative relationship between calcified and non-calcified plaque components is not uniform, and, in some individuals, purely non-calcified plaques may be present, which in part explains the occasional occurrence of cardiac events in subjects with no detectable coronary calcification. Coronary Artery Calcium can be detected in non-contrast cardiac CT data sets. In

order to quantify CAC, the area and density of calcified deposits are measured. Several quantification methods, including the 'Agatston Score' as well as the calcified volume or the derived calcium mass,[18] and recently a calcium coverage score, defined as the percentage of coronary arteries affected by calcified plaque,[19] have been proposed for clinical use. To date, the 'Agatston Score' remains the most commonly used measure because most previous large-scale trials and cross-sectional studies used this method, so that large reference data sets exist. 'Agatston Scores' are often classified as to their severity and meaning as listed in *Table 1*.[20] However, these categories are purely empirical. The prevalence and extent of CAC increases with age and is more severe in men compared with women.[21] A direct comparison of the prognostic value between absolute CAC scores and calcium 'percentiles' relative to age and gender has been recently reported by the Multi-Ethnic Study of Atherosclerosis (MESA) investigators.[22] In this study, although both methods yielded effective risk stratification, the absolute measurement approach performed better than the percentile approach. Therefore, reporting the absolute CAC score is currently recommended for clinical practice.

Prognostic value of coronary artery calcium in asymptomatic subjects

In asymptomatic individuals, the absence of detectable CAC is associated with a very low (<1% per year) risk of major cardiovascular events over the next 3–5 years, whereas an up to 11-fold increase of the risk for major cardiac events has been reported in asymptomatic subjects with extensive coronary calcification ('Agatston Score' >1000).[20,23,24] Not all published studies provide a realistic estimate of the relative risk for future cardiovascular events in asymptomatic individuals with detectable coronary calcification. This is due to limitations of some published studies, including self-referral of participants instead of general populations, unblinded outcomes adjudication, and self-reported instead of measured risk factors.[20] However, results of several large population-based studies have now become available and provide evidence for the incremental prognostic value of CAC as quantified by CT. In asymptomatic subjects without known CAD, CAC is predictive of future hard cardiovascular events above and beyond traditional risk factors, as determined by the significant increase in the area under the receiver operator characteristics curves.[22,25,26] The recent population-based MESA study, conducted in 6722 asymptomatic subjects belonging to four racial groups and followed for 3.8 years, demonstrated a significant difference in the prevalence of CAC among different ethnic groups (from 70% in white men to 52% for black men) but similar incremental prognostic value of CAC scores over traditional risk factors, with a seven-fold increase in the incidence of CAD events for 'Agatston Scores' >100 when compared with individuals without CAC.[23]

For clinical decision making, the additional risk of cardiac events associated with CAC in each conventional risk categories may be important to appropriately reclassify subjects. In a prospective population analysis of 1461 individuals, it was observed that cardiac event rates increased with increasing CAC scores in each Framingham risk category, including low-risk, intermediate-risk,

Table 1   Classification of coronary calcium score

Absolute value (Agatston units)	Ranking
0	Absent
>0<10	Minimal
≥10<100	Mild
≥100<400	Moderate
≥400<1000	Severe
≥1000	Extensive

Classification of coronary calcium absolute content evaluated by cardiac CT and quantified by Agatston units.
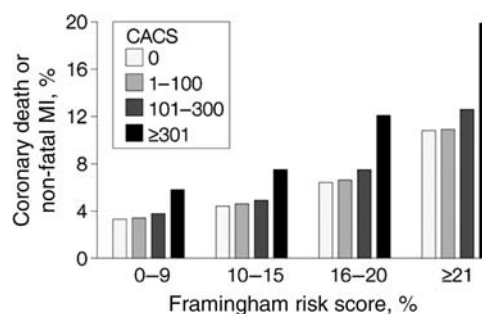

Figure 1 Predicted event rates for Coronary Artery Calcium Score in relation to Framingham risk categories. Predicted 7-year event rates from COX regression model for coronary artery disease death or non-fatal MI for categories of Framingham risk score (FRS) or coronary artery calcium score (CACS) in subjects without previous cardiovascular disease reported by Greenland *et al.* In intermediate FRS risk patients, a CACS >300 Agatston units identifies subjects at high cardiovascular risk whereas in the low FRS category subjects remain at low risk for any level of CACS. Reproduced with permission from reference 26

and high-risk individuals.[26] However, in individuals classified as low risk by the Framingham method, high CAC scores ('Agatston Score' >300) are infrequently found and the affected group of individuals despite increased risk remains, as a population, below the current risk threshold set by guidelines for implementation of aggressive risk factors modification[26] (*Figure 1*). This suggests that CAC imaging as screening modality would not be currently useful or cost-effective in this population although still relevant in selected individual subjects. Similarly, in the high-risk group (based on Framingham or other risk scores), a low CAC score does not reclassify subjects to low risk and would therefore not justify to avoid therapy for risk reduction, as currently recommended by guidelines.[3,7]

However, CAC assessment may be beneficially used in intermediate risk patients in whom the required intensity of risk factor modification is often uncertain.[3,7] In this category, a high CAC score clearly identifies a group of high-risk subjects, in whom intensive treatment of risk factors may be warranted,

while absence of relevant coronary calcification reclassifies individuals to low risk (*Figure 1*).[7]

It has been suggested that an appropriate evaluation of the clinical relevance of a new risk marker should be derived from the actual number of subjects reclassified to more appropriate categories of risk from the application of the new marker, calculated by the Net Reclassification Improvement (NRI) and by the Integrated Discrimination Improvement (IDI) indices.[27] Thus, these indices are calculated to evaluate the additional number of subjects in whom clinical events will occur, identified by the new risk marker. Preliminary data from the Heinz Nixdorf Recall Study,[28] a population-based study in 4327 randomly selected individuals from the general population without known CAD, indicate that CAC scoring of persons at intermediate risk results in an NRI of 21% ($P = 0.0003$) after 5 years of follow-up, with an IDI of 1.52% ($P < 0.0001$). These data compare favourably with other novel markers of risk.[27,29,30]

In summary, there is overwhelming evidence that coronary calcification represents a strong marker of risk for future cardiovascular events in asymptomatic individuals and has prognostic power above and beyond traditional risk factors. However, prospective outcomes data from trials in which individuals are randomized to receiving or not receiving a coronary calcium scan would be required to firmly establish whether CAC imaging in intermediate risk subjects ultimately results in reduced coronary events, provides improved clinical outcomes, and is cost-effective.

Coronary calcium in type 2 diabetic patients

Patients with type 2 diabetes experience more diffuse, calcified, and extensive CAD, more often have left ventricular dysfunction, and more frequently have silent ischaemia. Consequently, diabetic individuals have substantially higher cardiovascular event rates than non-diabetic individuals without cardiovascular disease and, even when asymptomatic, type 2 diabetics are considered at high cardiovascular risk,[31] so that secondary prevention strategies are recommended.[3,7] However, further risk stratification in diabetic patients may help identify subjects with extensive coronary atherosclerosis and with significant inducible silent myocardial ischaemia,[32,33] who would potentially benefit from even more aggressive treatment strategies, including coronary revascularization.

The presence of coronary calcium has proven predictive for future cardiovascular events in asymptomatic diabetic individuals, even though for any degree of CAC, mortality of diabetic individuals is higher than in non-diabetic subjects.[34] Assessment of CAC may also aid in identifying diabetic individuals with a higher likelihood of inducible ischaemia: in diabetic patients without prior cardiovascular events, low CAC scores ('Agatston Score' ≤10) are associated with a low prevalence of inducible myocardial ischaemia and a low event rate.[34,35] Use of CAC scoring for risk stratification in asymptomatic diabetic patients is not currently endorsed by the American Diabetes Association recommendations.[36] However, if a strategy of testing asymptomatic diabetic individuals for the presence of silent ischaemia is needed, pre-selection of individuals based on calcium scores with the intent of performing subsequent functional imaging in the presence of a substantial atherosclerotic burden should therefore be considered.

Coronary calcium in the elderly and in renal disease

Several studies have specifically addressed the prognostic value of CAC in older subjects.[37–39] These studies indicate that, like in middle-aged subjects, low CAC scores are associated with a favourable mid-term prognosis and event rates increase with increasing amounts of coronary calcium. However, more data are needed in older asymptomatic subjects to verify whether recommendations for different intensities of risk modification therapies, based on the combination of age, risk factor burden, and CAC scores, can be provided.

Impaired renal function is a major cardiovascular risk factor and risk gradually increases as the glomerular filtration rate decreases.[40] Patients with impaired renal function have elevated CAC scores and the prevalence and extent of CAC is especially high in dialysis patients. Importantly, coronary calcification may partly be due to non-atherosclerotic mechanisms in patients with renal failure and on dialysis.[41] Coronary artery calcium progresses more rapidly in dialysis patients, in whom it correlates with age, duration of dialysis, cause of chronic renal failure, diabetes mellitus, alterations in mineral metabolism as well as use and dose of calcium-based phosphate binders.[42–44] The amount of CAC in dialysis patients has been reported to be associated with cardiovascular outcome.[44] Similarly, non-coronary cardiac calcification (e.g. calcification of the mitral annulus and non-coronary vascular calcification) have also been shown to be associated with increased mortality in patients with renal failure.[45,46] However, dialysis patients are candidates for intensive risk modification even without the knowledge of calcium scores and additional data are needed to assess the potential clinical use of CAC scoring for further risk stratification of this population.

Measurement of coronary artery calcium progression

The simplicity to obtain a CAC score makes it a potentially appealing tool for monitoring atherosclerosis burden over time, and the implications of serial measurements have been recently reviewed.[42] At present, there is no consensus on the most appropriate definition of progression, i.e. whether using absolute score differences, percent changes, or square root changes. Progression of the calcium score averages 15–25% per year and is substantially dependent on the baseline amount of calcium. It is also determined by age, sex, family history of premature CAD, the ethnic background, diabetes, body mass index, elevated blood pressure, and renal insufficiency.[47–49] In some studies, rapid progression of CAC, e.g. >15% per year, was associated with an increased risk of events.[47] Even though modification of CAC scores over time has been reported under statin therapy in some trials,[50,51] others[52,53] have failed to reproduce these observations, including the randomized SALTIRE trial in patients with aortic calcific stenosis treated with atorvastatin[52] and it is unclear whether CAC progression is influenced by medications. Furthermore, the variability

of repeated calcium scans is relatively high and a recent meta-analysis from 10 prospective randomized trials in subjects with CAD (5 trials) and in subjects with chronic renal disease (5 trials) suggests that the 1 year change in CAC burden may not be a reliable endpoint for medical intervention trials[53] and may hence not be suitable to monitor the effect of preventive medications on clinical disease progression. Therefore, 'serial' or 'repeated' coronary calcium scans are currently not recommendable.

Coronary computed tomography angiography

After injection of contrast agent, coronary CT angiography allows visualization of the coronary lumen and wall. Image quality of coronary CT angiography depends on many factors and in selected patients high accuracy for stenosis detection can be achieved. In addition, coronary CT angiography allows the detection of both calcified and also non-calcified plaque components, and, to a certain extent, plaque quantification and characterization is possible. It has recently been shown that some characteristics of coronary atherosclerotic plaques detected by coronary CT angiography, such as positive remodelling and low CT attenuation of the atherosclerotic material, are associated with the occurrence of future acute coronary syndromes.[54] Several studies have been able to demonstrate a prognostic value of atherosclerotic lesions detected by coronary CT angiography.[55–57] However, all these analyses were retrospectively performed in individuals who had undergone coronary CT angiography for clinical reasons, and it must therefore be assumed that most of the included patients were symptomatic. In *asymptomatic* individuals, the prognostic role of coronary CT angiography is ill defined, as it was assessed in only one study which included 1000 Korean subjects aged 35–75 years.[58] In this study, 22% of individuals had detectable coronary atherosclerosis but only 5% showed significant stenosis. Coronary events occurred exclusively in individuals with detectable plaques but most of them were revascularizations triggered by the very fact that an atherosclerotic lesion had been detected, not necessarily demonstrating a less favourable prognosis had coronary CT angiography not been performed. Similarly, although a 26–36% prevalence of significant CAD was reported in asymptomatic type 2 diabetic patients,[59,60] lack of follow-up makes the prognostic value of these observations uncertain.

In addition, when considering current use of coronary CT angiography for risk stratification in asymptomatic individuals, it must be taken into account the required injection of contrast agent and the exposure of patients to substantially higher radiation doses compared with coronary calcium measurements. However, due to the availability of prospective and high-pitch helical scan techniques, improved detector technology and reconstruction algorithms coronary CT angiography can be optimized to reduce radiation exposure to a dose similar to CAC examination. These aspects will influence the ratio between risk and benefit, especially in low-risk individuals.

To summarize, beyond the detection of coronary artery stenosis, coronary CT angiography has the potential for the detection and characterization of coronary atherosclerosis. However, due to the lack of favourable prognostic data in asymptomatic individuals, it is currently not recommended for risk stratification in primary prevention.[61]

Myocardial perfusion scintigraphy

Myocardial perfusion scintigraphy in asymptomatic subjects

The absence of inducible ischaemia at MPS identifies subjects with very low (<1% per year) event rates during the following 2–3 years.[62,63] The prevalence of silent myocardial ischaemia in asymptomatic populations varies according to the characteristics of the patient population screened.[64,65] In non-diabetic patient populations, approximately 0.52–22% of subjects have evidence of silent ischaemia, with an increase from 2% in the fifth and sixth decades of life to 15% in the ninth decade.[64]

Only a few studies have specifically evaluated the value of MPS in asymptomatic individuals with intermediate risk. Khandaker *et al.*[65] recently showed, in 260 asymptomatic patients at moderate CAD risk, that stress MPS was effective for detection and risk stratification of CAD. Average annual mortality was 4.0% in patients with high risk vs. 1.6% in patients with normal scans. Similar to what were reported in a general patient population,[14] it has been shown in a general asymptomatic population that an extent of ischaemia of more than 7.5% of left ventricular myocardium is associated with a high risk of major cardiac events (cardiac death or non-fatal MI).[66] Of note, although in this last study, angina or ischaemic ECG changes during stress testing were observed in only 7 and 51%, respectively, these variables were predictors of high-risk ischaemia at MPS, underscoring the fact that some patients not reporting angina during daily life activities may develop symptoms during adequate exercise testing.[66] In addition, known CAD risk factors (male gender, age, diabetes, and hypertension) and an abnormal resting ECG were independently predictive of high-risk silent ischaemia suggesting that consideration of these variables may facilitate identification of individuals that may benefit from further evaluation by MPS.

Myocardial perfusion scintigraphy in asymptomatic type 2 diabetic patients

A meta-analysis of 31 studies including 69 655 diabetic and non-diabetic patients showed that the average annual hard event rate (cardiac death or MI) in diabetic patients with a normal MPS was 0.85% as opposed to 5.9% in those with a moderately to severely abnormal MPS.[62] Yet, for any degree of perfusion abnormality, the risk of diabetic patients is higher compared with non-diabetic patient populations.[67]

Although stress imaging is recommended for *symptomatic* type 2 diabetics, there is still no consensus on the best approach for screening *asymptomatic* diabetic subjects without known CAD[35] in whom the prevalence of silent ischaemia, identified as perfusion abnormalities, has been reported to be up to 59%.[68,69] Recently, Wackers *et al.*,[70] in a contemporary population of 522

asymptomatic diabetic patients with at least two risk factors enrolled in the Detection of Silent Myocardial Ischemia in Asymptomatic Diabetics (DIAD) study, reported a prevalence of 21% abnormal MPS using gated ^{99m}Tc-sestamibi. Of note, conventional risk factors did not predict perfusion abnormalities, whereas the only independent predictor of an abnormal perfusion was the presence of autonomic cardiac neuropathy.

The prognostic value and clinical implications of ischaemia detection in asymptomatic diabetic patients without known CAD have been evaluated in a limited number of studies[68,71,72] and none of these studies tested whether screening asymptomatic diabetics with MPS would alter clinical outcome. This fundamental aspect was investigated in the DIAD prospective trial[73] which evaluated a population of about 1000 asymptomatic type 2 diabetics randomized to a MPS vs. non-MPS assisted management and followed up for 4.8 years. As expected, the presence of moderately to large ischaemic defects was associated with a significantly higher event rate (2.4% per year) compared with patients with normal perfusion or small perfusion abnormalities (0.4% per year). However, moderate to large perfusion defects occurred in only 33 (6%) of 561 patients.[73] Thus, in summary, the trial showed no difference in outcomes between the two strategies and a very low (<1% per year) event rate in the whole population, due to implementation of preventive therapies in both groups of patients, thus potentially obscuring the benefit of ischaemia detection on the primary endpoint.

These data can be interpreted in the context of the recent BARI 2D trial[74] which compared medical therapy vs. revascularization in type 2 diabetic patients with chronic CAD. Although the trial failed to demonstrate a significant difference between the two treatment strategies in the whole population, a significant benefit of revascularization was observed in the pre-specified subgroup of patients randomized to coronary artery bypass grafting in whom more extensive CAD and more severe inducible ischaemia were present. These two trials put together indicate that ischaemia evaluation by MPS is not recommended as first line strategy in unselected asymptomatic type 2 diabetics without known CAD and with normal resting ECG.

In addition, the negative predictive 'warranty period' for a normal MPS study has been reported to be shorter in diabetic compared with non-diabetic patients but additional data would be warranted to recommend an optimal and cost-effective time interval between repeat evaluation in these subjects.[75]

Combination of coronary calcium or coronary computed tomography angiography with myocardial perfusion scintigraphy

Comparative studies between either CAC or coronary CT angiography and functional imaging tests such as MPS have shown that anatomical tests cannot accurately predict the haemodynamic relevance of the detected atherosclerotic lesions.[10] On the other hand, functional tests may frequently underestimate the extent of underlying atherosclerosis.[13] Accordingly, these techniques yield distinct information regarding the presence and severity of CAD and their combination may potentially provide complementary and incremental information for risk stratification. In patients without known CAD, a correlation between CAC scores and functionally significant CAD has been reported, with the negative predictive value of the calcium score for excluding coronary stenosis ranging from moderate[76] to high (>90%)[77] and a positive predictive value regarding inducible ischaemia of up to 50% for high 'Agatston Scores' (>400),[77] depending on the characteristics of the population studied.

The value of combining CAC scores and MPS (ischaemia) assessment in non-diabetic subjects is not yet clear, since available data are limited and yielded conflicting results. Schenker et al.[76] reported that a high CAC score was associated with a stepwise increase of major cardiac events (cardiac death and MI) in subjects without known CAD and without typical angina, but with two or more risk factors. This was observed both in the presence or absence of inducible ischaemia, thus suggesting an incremental role of the CAC score over perfusion abnormalities. In agreement with this study, Chang et al.[78] recently reported, in a population of 1126 asymptomatic subjects undergoing CAC imaging and MPS, that in subjects with a normal MPS, coronary calcification added incremental prognostic information, with a 3.55-fold relative increase for any cardiac event (2.75-fold for death/MI) when calcification was severe ('Agatston Score' >400) vs. minimal ('Agatston Score' <10). Interestingly, separation of the survival curves occurred at 3 years after initial testing for all cardiac events and at 5 years for death/MI, indicating an incremental mid- to long-term prognostic value of the CAC score over MPS. In contrast, Rozanski et al.,[77] in an asymptomatic population at lower cardiovascular risk, observed no increased risk in subjects without inducible ischaemia but with high CAC scores.

In diabetic patients without history of CAD, Anand et al.,[35] using a combined approach of CAC imaging and MPS, reported abnormal MPS findings in 18% of patients with an 'Agatston Score' between 10 and 100, in 48% of patients with an 'Agatston Score' between 100 and 400 and in 71% of patients with 'Agatston Scores' >1000, whereas no patients with absent or minimal CAC ('Agatston Score' 0 to 10) showed abnormal MPS. In addition, although only 20 cardiovascular events occurred in this population during a follow-up interval of 2.2 years, no event was observed in patients with absent or minimal coronary calcification.

Thus, it needs to be recognized that while in intermediate risk subjects, a two-step risk stratification strategy of an initial coronary calcium scan, followed by selective MPS imaging in subjects with high CAC scores sounds attractive and would be worth testing, there is no definitive evidence to support any clinical benefit of this approach. In contrast, based on Anand et al.'s[35] study, it seems conceivable that in asymptomatic type 2 diabetics without known CAD, a CAC score followed by selective ischaemia evaluation for subjects with significant 'Agatston Scores' (>10) should be considered to identify candidates for invasive CAD assessment.[79] Thus, MPS would be potentially useful for those with evidence of coronary atherosclerosis through a positive CAC scan or, as first line test, in those with abnormal resting ECG, in agreement with recommendations of the American Diabetes Association.[36]

Asymptomatic diabetics with evidence of moderate to severe inducible ischaemia at MPS should then undergo invasive coronary angiography as they may benefit from revascularization.

Risk assessment in subjects with familial hypercholesterolemia (FH) and with familial history of premature coronary artery disease

Subjects with familial hypercholesterolemia (FH) and relatives of patients with premature CAD represent high-risk populations in whom detection of premature CAD may be relevant for prognosis. While non-invasive imaging by cardiac CT and MPS may play a role in these individuals, currently available data are very limited.

In a group of 29 young subjects (<23 years old) with FH, Gidding *et al.*[80] reported a 24% prevalence of significant coronary calcium. Similarly, Mouratidis *et al.*[81] reported a 26% prevalence of abnormal MPS in 54 adolescents and young adults with FH (51 of them with heterozygote FH). However, no prognostic or angiographic data were available in these studies, and, therefore, the clinical and prognostic value of these findings remains uncertain.

In subjects with familial history of premature CAD, the prevalence and extent of coronary calcium was investigated in 8549 asymptomatic individuals.[82] Those without familial history, with affected parents, or affected siblings had a coronary calcium prevalence of 55, 64, and 78% ($P < 0.0001$) among men and 27, 36, and 56% ($P < 0.0001$) among women, respectively. In a MPS study which included 264 asymptomatic siblings of patients with premature CAD, abnormal ^{201}Tl scans were observed in 29% of men and 9% of women, while abnormal exercise ECGs occurred in only 12

and 5%, respectively.[83] Nineteen siblings developed clinical CAD (sudden death in 1, MI in 10, coronary revascularization in 8) over a mean of 6.2 years of follow-up. Although abnormal exercise ECGs and ^{201}Tl MPS were both predictive of future clinical CAD, an abnormal MPS was associated with a 4.7 higher relative risk after adjustment for age, sex, and exercise ECG results. Siblings with a concordant abnormal exercise ECG and ^{201}Tl scan had a relative risk of 14.5.[83]

To test the relationship between CAC and inducible ischaemia in these subjects, Blumenthal *et al.*[84] studied 260 asymptomatic siblings of patients with premature CAD. Abnormal MPS was reported in 50% of subjects with 'Agatston Scores' >100, but also in 21% of those with absent or minimal CAC (0 to 10 Agatston score), indicating that the negative prognostic power of coronary calcium for excluding significant CAD in this high-risk population is suboptimal and, therefore, a strategy of screening subjects for inducible-ischaemia based on previous coronary calcium scans is not recommended.

To summarize, more prognostic studies are definitively needed to assess the value of cardiac CT and MPS for stratification of subjects who may have a baseline risk above the general population. However, preliminary data indicate MPS may be considered in asymptomatic subjects with FH or familial history of CAD.

Conclusions and perspectives from the working group

The role of non-invasive cardiac imaging for risk stratification in primary prevention has been considerably evolving in recent years. Strong evidence indicates that coronary calcification provides effective, independent, and incremental risk stratification in intermediate-risk subjects without known cardiovascular disease.

Table 2 Applications of CCT and myocardial perfusion scintigraphy in asymptomatic subjects without previous cardiovascular events
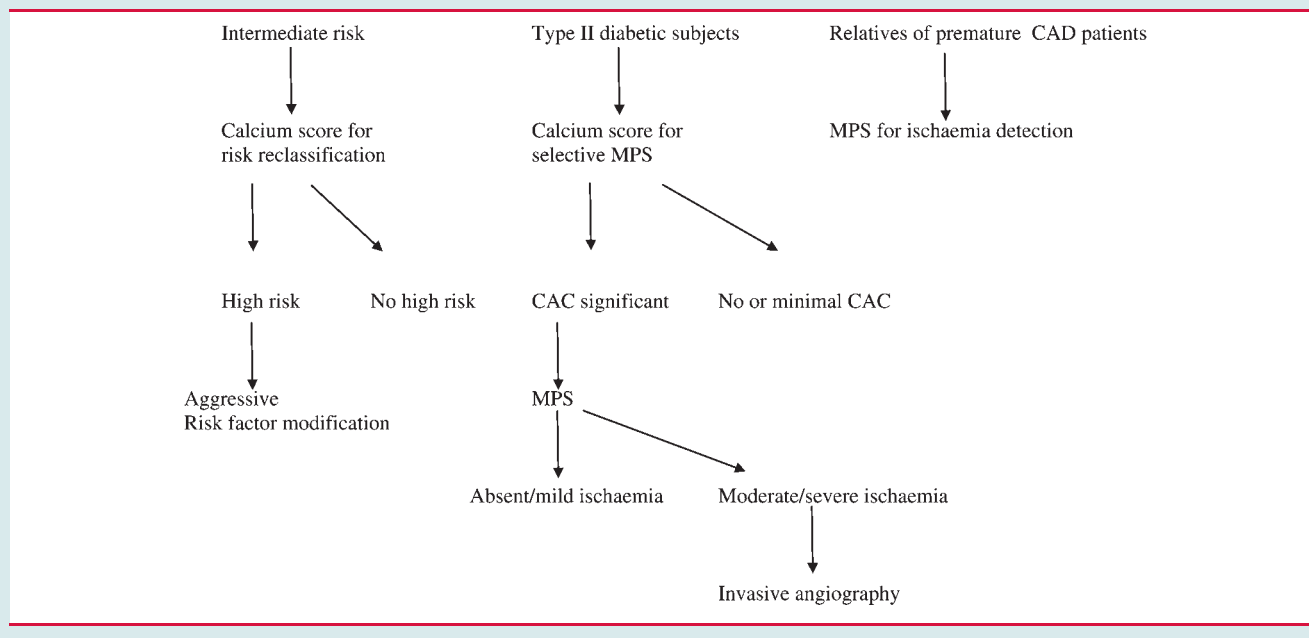
Table 3 **Recommended future research**

Prospective clinical trials to evaluate the prognostic impact and cost effectiveness of calcium score assisted management of the following subjects' categories:

    Intermediate-risk asymptomatic subjects without previous cardiovascular events, including elderly and renal disease patients

    Type II diabetic patients without previous cardiovascular events

Prospective clinical trials to evaluate the prognostic impact and cost effectiveness of ischaemia detection by MPS in:

    First-degree relatives of patients with premature CAD

    Adult patients with familial hypercholesterolemia

Prospective clinical trials to evaluate the prognostic impact and cost-effectiveness of computed tomography coronary angiography in selected high-risk subjects without previous cardiovascular events

In addition, both coronary calcium and MPS provide prognostic information in asymptomatic type 2 diabetic patients without known CAD. Yet, there is currently no evidence that the use of CAC imaging or MPS for risk stratification of asymptomatic subjects without known cardiovascular diseases will favourably impact on clinical outcome. Thus, both tests do not fully meet appropriateness criteria for routine clinical use.[85,86]

In summary, the Working Group recognizes that there are currently no prospective outcome trials which would lend evidence to primary prevention strategies which incorporate imaging studies for the detection of coronary calcium, coronary atherosclerotic plaque, or myocardial ischaemia in asymptomatic individuals. However, given strong prognostic data collected in retrospective trials and observational studies, several patient groups may potentially benefit from imaging strategies for risk stratification in primary prevention and the use of imaging may be reasonable, after consideration of patient characteristics and the specific clinical situation, in the following scenarios (with level of evidence C for all) (*Table 2*):

- Coronary calcium evaluation should be considered in selected intermediate-risk subjects. Detection of coronary calcium would reclassify patients to high risk and qualify them for according treatment (class of recommendation IIa).
- Myocardial perfusion imaging by MPS in unselected, asymptomatic diabetic individuals is not recommended (class of recommendation III). However, the presence of coronary calcium detected by cardiac CT preselects diabetic individuals with increased likelihood for myocardial ischaemia in MPS. Asymptomatic type 2 diabetic patients without known CAD should thus be considered for coronary calcium imaging followed by MPS for those with significant coronary calcium, in order to identify subjects with a moderate to severe extent of ischaemia which are likely to benefit from invasive evaluation and revascularization (class of recommendation IIa).
- MPS may be considered a first-line test for first-degree relatives of patients with premature CAD (class of recommendation IIb).

Furthermore, the Working Group concludes:

- Coronary CT angiography is currently not recommended as a screening tool in asymptomatic individuals (class of recommendation III).
- Serial measurement of coronary calcium in order to 'monitor' progression of coronary atherosclerosis is not recommended (class of recommendation III).

Finally, radiation exposure is of considerable concern in primary prevention patients[87,88] and under all circumstances imaging tests need to be performed with the lowest possible radiation exposure. The Working Group strongly supports further research (*Table 3*) regarding the use of imaging for risk stratification, and specifically encourages outcome trials to evaluate the clinical effects and cost-effectiveness of imaging-based treatment algorithms in a randomized fashion.

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