



Between risk charts and imaging: how should we stratify cardiovascular risk in clinical practice?

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Received 17 July 2012; accepted after revision 26 November 2012

Cardiovascular (CV) risk prediction has a central role in primary CV prevention. Several risk charts have been developed in the attempt to identify subjects at risk who might benefit from more aggressive interventions. However, risk charts show main limitations and they remain underutilized in general practice. The addition of novel risk markers has substantially failed to improve risk charts discrimination power. Imaging has recently gained relevance in CV risk stratification for its ability to detect subclinical atherosclerosis. Although extending non-invasive imaging to all asymptomatic middle-aged people is currently not recommended, its progressive spread may provide information on preclinical atherosclerosis and detection of *de facto* initial disease might overcome some limitations of conventional risk stratification charts.

Keywords

Risk factors • Risk markers • Biomarkers • Cardiovascular diseases • Risk prediction • Non-invasive imaging • Cardiovascular prevention

Cardiovascular risk prediction

Atherosclerotic cardiovascular disease (CVD) is the major cause of death worldwide.¹ Both time to exposure and severity of traditional risk factors (TRF) appear to be its main contributors.^{2,3} Since CVD risk is the result of the interaction of different risk factors (RF),^{2–4} risk prediction combining multiple TRF has gained a central role in CVD prevention. Thus, several risk algorithms (risk charts) have been developed in the attempt to identify subjects at high risk who might benefit from more aggressive interventions.^{2–4} Risk charts, however, are largely underutilized in clinical practice, mainly because of local health policies, low patient compliance, caregivers lack of time, or therapeutic inertia.^{5,6} The addition of novel risk markers to risk charts and/or the use of cardiovascular (CV) imaging to detect individual subclinical atherosclerosis have been proposed to improve risk assessment.

In this review, we discuss current CVD risk scores and the role of novel risk markers as well as CV imaging to stratify risk in clinical practice.

Current CVD risk scores

The main currently used risk charts estimate the absolute risk of CV events over 10 years^{2–4,7} (Table 1). According to the scientific guidelines, risk charts should be used in healthy people to guide

prevention strategies.^{8–11} All patients with CVD or asymptomatic subjects with overt atherosclerosis, those with type-1 (T1) or type-2 (T2) diabetes mellitus (DM) with one or more RF and/or subclinical organ damage (SOD), severe chronic kidney disease (CKD) (glomerular filtration rate, GFR < 30 mL/min/1.73 m²), as well as asymptomatic subjects with an estimated 10-year calculated SCORE risk ≥ 10 should be considered at very high CV risk.^{8,10} Subjects with markedly elevated single RFs, T2DM, or T1DM without adjunctive RFs or SOD, moderate CKD (GFR 30–59 mL/min/1.73 m²), or SCORE between $\geq 5\%$ and $< 10\%$ as well as those with an estimated 10-year FRS risk $\geq 20\%$ ^{4,11} are considered at high CV risk.

People are considered at moderate risk when their calculated SCORE is $\geq 1\%$ and $< 5\%$ or the estimated 10-year FRS is between 10 and 20%. Subjects at high and at very high CV risk^{4,8,10,11} are recommended for immediate interventions. Asymptomatic people with intermediate risk are recommended to undergo non-invasive testing for further risk stratification, whereas lower-risk subjects are only recommended for lifestyle modification.

Methods to assess risk prediction equations

The performance of a prediction model can be assessed by a variety of measures. The more commonly used are discrimination, calibration, and reclassification.

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Table 1 Values and limits of current CVD risk prediction scores

Study and country	Population/ sample size	Age range	Endpoints	Calculates	Variables	Advantages	Disadvantages
Framingham 1998 USA Wilson et al. <i>Circulation</i> 1998;97:1837–47.	Population cohort (original +offspring) 5345	30–74	All CHD/ Non-fatal and fatal CVD events	10-year risk of CHD events	Sex, age, T-Chol, HDL- Chol, SBP, smoking, diabetes, hypertensive treatment	<ul style="list-style-type: none"> • Most closely phenotyped cohort, therefore most complete data with high validity for risk factors • Most widely utilized and validated • Multi-generational • Can be adapted to other countries showing a good discrimination (C-statistics: 0.66–0.88) when compared with external databases. 	<ul style="list-style-type: none"> • Based on a small US largely white community • Does not take into account ethnicity, family history, or socio-economic factors • Include many years of exposure when CV risk in the population generally was higher than nowadays
Framingham 2008 USA D'Agostino Sr et al., <i>Circulation</i> 2008;117:743–53.	Population cohort (original +offspring) 8491	30–74	Global CVD/ Non-fatal and fatal CVD events	10-year risk of CVD events Risk age	Sex, age, T-Chol, HDL- Chol, SBP, smoking, diabetes, hypertensive treatment	<ul style="list-style-type: none"> • Most closely phenotyped cohort, therefore most complete data with high validity for risk factors • Takes into account the multifactorial nature of CVD • Most widely published, utilized and validated of all CVD risk scores • Multi-generational • Can be adjusted for individual countries 	<ul style="list-style-type: none"> • Based on a small US largely white community • Does not take into account ethnicity, family history, or socio-economic factors • Associations with events include many years of exposure when CV risk in the population generally was higher than nowadays
SCORE 2003 Europe Conroy RM et al. <i>Eur Heart J</i> 2003;24: 987–1003.	Pooled data set of cohort studies/ 205.178	45–64	CVD Death	10-year risk of CVD mortality	Sex, age, T-Chol, HDL- Chol or T-Chol/HDL-Chol ratio, SBP, smoking	<ul style="list-style-type: none"> • Based on contemporary large population based studies in 12 European countries • Intuitive, easy to use • Takes into account the multifactorial nature of CVD • Modifiable for individual country CVD data • Versions in high and low-risk countries 	<ul style="list-style-type: none"> • Only predicts risk of CV death—does not take into account nonfatal CVD events • May underestimate risk in patients with diabetes, central obesity, family history of premature CVD, low HDL or elevated triglyceride, fibrinogen, Lp(a) and B, hs-CRP, or homocysteine levels

PROCAM 2007 Germany Assmann <i>et al. Circulation</i> 2002;105:310–5.	Occupational cohort 35.105	20–75	Hard CHD	10-year risks of major CVD events	Age, sex, LDL-Chol, HDL-Chol, diabetes, smoking, SBP	<ul style="list-style-type: none"> • Takes into account family history of premature myocardial infarction, diabetes, and triglycerides • Separate scores calculate 10-year risk of major coronary events and stroke 	<ul style="list-style-type: none"> • Only based on German males • Only estimates risk for fatal or non-fatal myocardial infarction and acute coronary death.
Progetto Cuore 2004 Italy The Italian Atlas of Cardiovascular Diseases. <i>It Heart J</i> 2004;5: 1S–101S.	Pooled data set of cohort studies 20.647	35–69	Global CVD, Non-fatal and fatal CVD events	10-year risks of major CVD vents	Age, SBP, T-Chol, HDL-Chol, smoking, diabetes, hypertensive therapy	<ul style="list-style-type: none"> • Representative of general Italian population (17 cohorts, 15 enrolled from the general population, two from working sites) • Includes both a categorical and a punctual estimation 	<ul style="list-style-type: none"> • No external validation carried out
ASSIGN UK Woodward <i>et al. Heart</i> 2007;93: 172–6.	Population cohort 13.297	30–74	Global CVD	10-year risk of CVD events	Sex, age, T-Chol, HDL-Chol, SBP, smoking status, diabetes, family, history of CHD	<ul style="list-style-type: none"> • Takes into account social deprivation and family history of CVD • Uses a quantitative measure of smoking number of cigarettes • Include an area-based index of deprivation 	<ul style="list-style-type: none"> • Only based on Scottish population • Not well validated yet • Does not take into account obesity or BMI
Reynolds (men) USA Ridker <i>et al. Circulation</i> 2008;118:2243–51.	Physician Health Study trial 10.724	50–80	Global CVD	10-year risk of incident MI, stroke, coronary revascularization, CV death	Sex, age, SBP, smoking, hs-CRP, T-Chol, HDL-Chol, family history of premature MI, HbA1C if diabetic	<ul style="list-style-type: none"> • Incorporates hs-CRP and family history of premature CVD • Improved global CVD risk prediction 	<ul style="list-style-type: none"> • Does not exhibit improved calibration compared with models based on standard ATP III • Controversial about incremental prognostic prediction with the addition of CRP and related inflammatory biomarkers to the Framingham Heart Study risk score model (ARIC)
Reynolds (women) USA Ridker <i>et al. JAMA</i> 2007;297:611–9.	Women's Health Study trial 16.400	45+	Global CVD	10-year risk of incident MI, stroke, coronary revascularization, CV death	Sex, age, SBP, smoking, Hs-CRP, T-Chol, HDL-Chol, family history of premature MI, HbA1C if diabetic		
QRISK UK Hippisley-Cox <i>et al. BMJ</i> 2007;335:136. QRISK-2 UK Hippisley-Cox <i>J et al. BMJ</i> 2008;336:1475–82.	Electronic medical database/ 1283174 Electronic medical database/ 1535583	35–74	CVD	10-yr risk of CVD events	Sex, age, T-Chol/HDL-Chol ratio, SBP, smoking status, diabetes, area-based index of deprivation, family history, BMI, antihypertensive treatment	<ul style="list-style-type: none"> • Huge contemporary population derived data set • Takes into account social deprivation, family history of premature CVD, BMI, and the effect of existing antihypertensive treatment 	<ul style="list-style-type: none"> • Only from England and Wales • Data set incomplete for several risk factors; thus, imputation and statistical modelling is needed to reduce biased estimates • Not well validated yet • Underestimates risk in European populations

Discrimination

A good prediction model should discriminate between patients with the outcome from those without the outcome (up to a certain point in time) (discrimination).¹² Discrimination is commonly expressed by a measure of concordance, the C-statistics, representing how the score discriminates between cases (people who will have the event) from controls (people who will not have it). The C-statistics ranges from 0.5 (random chance, no better than flipping a coin) to 1.0 (absolute discrimination between cases and controls). For binary outcomes, C is identical to the area under the receiver operating characteristic curve (AUROC).¹² When the C-statistics is <0.70, discrimination is considered inadequate, between 0.70 and 0.80 acceptable, and >0.90 excellent. For most of the risk estimate systems, the combination of multiple RF provides an increase in the magnitude of the C-statistics (generally from 0.75 to 0.80) that cannot be reached by single RF even when strongly associated with the disease.^{2,3,12,13}

Calibration

Risk calibration is the ability of a model to predict the absolute level of risk subsequently observed (of 10% over 10 years).^{2,3,12} In other words, when a risk prediction model is well calibrated, the risk estimate provided for a certain subgroup of individuals (for example 10%) will be close to the observed event rate in that subgroup.³ Calibration is usually assessed by using the calibration plots. The 'calibration-in-the-large' which indicates whether predictions are systematically too low or too high,¹² and a calibration slope, the regression slope of linear predictor, are also used as measures of calibration.¹²

Risk models calibration may vary with time and place.² A well-calibrated model for a region could overestimate or underestimate CVD risk in another one. Similarly, differences in the rates of CVD over time can make the score systems outdated. Ideally, risk functions should be continuously updated but the feasibility of risk recalibration depends upon the availability of local mortality data and upon risk factors distribution in a given population at a given time.

The performance of a risk function can be assessed in the same data set (internal validation) or in an external database (external validation). For example, the FRS showed a good discrimination (C-statistics: 0.66–0.88) when compared with both internal and external databases.^{2,14} Good results have also been reported for the SCORE,¹⁵ the QRISK¹⁶ and the PROCAM algorithms (Table 1).

Finally, it is noteworthy that any prediction model will always show a certain discrepancy between calibration and discrimination. In other words, a system with both perfect calibration and discrimination does not exist.²

Re-classification

Re-classification assesses the value of adding new risk factors or risk markers into existing risk charts in order to improve risk prediction.^{2,3,12} Current clinical thresholds for CV risk prediction define risk level as low, intermediate, high or very high risk.⁸ Hence, re-classification can be appropriate (when moving individuals who will develop future CV events into higher estimated-risk levels) or can be not appropriate.^{3,12}

Various methods have been proposed to assess re-classification. Among these, a meaningful 'net reclassification improvement (NRI)' proposed by Pencina et al.¹⁷ assumes that the performance of the re-classification model is acceptable if at least 10% of people are more appropriately reclassified with the new method compared with the old one.¹⁷

Limits of current CVD risk scores

Although risk charts are 'aimed' to individualize risk, they have some of well-acknowledged limitations. Actually most subjects with ≥ 1 RF will never develop coronary heart disease (CHD). Thus, it cannot be excluded that risk charts might overestimate risk resulting in the overtreatment of people that will never develop CV events.^{2,3} On the other hand, most CV events will develop in people at low risk, simply because they are more than those at high risk (as learned from the Rose paradox). As a consequence, people with low risk estimate but underlying subclinical atherosclerosis could be undertreated. Second, risk charts performance is affected by the reference population, by changes of CVD incidence over time and in different geographic areas.^{14–17} Third, risk charts do not take into account the time of risk exposure that is associated with the development of atherosclerosis, with the single exception of the scoring system of the European Society of Hypertension (ESH).¹⁸

Moreover, risk estimate is less accurate in particular subgroups like diabetics, women, young people, and the elderly.⁸ Ethnicity or socio-economic strata issues might also affect their performance.^{2,3}

Risk charts do not take into account neither the metabolic changes that precede diabetes conferring adjunctive risk (fasting hyperglycaemia, glucose intolerance, the metabolic syndrome) nor the time of the exposure to the disease. Hence, observed risk in diabetes might be higher than charts based risk.^{8,11}

Furthermore, women show a lower CVD risk than men at any given age because in the SCORE system, women risk is deferred of 10 years compared with men risk.⁸ This might be misleading since CV mortality in women has increased in the last years.

Young people risk is often underestimated by risk charts. The ESC guidelines recommend using the relative risk charts (i.e. to calculate what the subject risk would be if he/she were 60 years old with the same RF) in males <45 years and in women <65 years. It has also been suggested to lower treatment thresholds for younger adults (e.g. treat those <50 years of age with a calculated SCORE <5%).^{3,8} The long-term risk (projected to 95 years of age) assessment¹⁹ might be useful in young persons to encourage lifestyle modifications. Alternatively, it has been suggested to perform imaging tests in all middle-aged adults in order to identify those with premature atherosclerosis.^{3,20}

Since most risk functions have been derived from cohorts of middle-aged people that excluded old individuals, risk charts may underestimate risk in the elderly² (Table 1). In the SCORE chart all men >65 years of age will have a 10-year CVD risk >5% that could result in an overmedication. For this reason, the latest ESC guidelines recommend to increase the threshold from 5 to 10% for considering old people at high risk.⁸ However, the utility of stratifying risk in this range of age is not demonstrated.

Adding markers to improve risk prediction models

Markers of subclinical organ damage

Risk prediction may be improved by adding markers of SOD to risk charts. Some of them as glomerular filtration rate (GFR) and microalbuminuria (MAU) or urinary albumin-to-creatinine ratio (UACR) can be easily identified by biochemical analyses. It has been reported that asymptomatic subjects with a reduced e-GFR showed higher prevalence of RF and had an increased mortality risk compared with those with normal renal function.²¹ Adding the evaluation of MAU to the calculated SCORE in the subgroup of patients with a SCORE $\leq 5\%$, reclassified subjects from moderate-to-high risk. Thus most guidelines recommend^{8,11} or encourage¹⁸ the use of MAU in clinical practice at least in adults with hypertension or T2DM¹¹ (Table 2).

Novel risk markers of CV risk as prognostic tools

Non-traditional risk markers of CV risk are often inflammatory or thrombotic biomarkers measurable in plasma or in serum (Table 3). The clinical value of a novel marker should be assessed taking into account its effects on patient management, especially its capacity to reclassify patients at intermediate risk.^{22,23}

High sensitivity (hs)-C-reactive protein has long been considered the best candidate for screening. An elevated hs-C-reactive protein level is a strong and independent predictor of future vascular events²⁴ carrying additive prediction value over TRF. However, criticism has been raised^{25–28}: data from the analysis of 20 536 patients of the Heart Protection Study (HPS) did not support the role of hs-C-reactive protein.²⁶ Furthermore, the ARIC study did not show incremental prognostic prediction with the addition of hs-C-reactive protein to the FRS.²⁷ On the other hand, in the meta-analysis from the Emerging Risk Factors Collaboration²⁹ (160,309 people without history of CVD from 54 prospective studies) hs-C-reactive protein was associated with increased risk of CHD, stroke, CV, and death. However, its role depends considerably on conventional RFs and other markers of inflammation (e.g. interleukin 6, fibrinogen) or markers of rupture-prone plaque (e.g. Lp PLA2). As a result of those still inconclusive evidences, its use into routine practice is not recommended⁸ except by the ACCF/ACC guidelines¹¹ in selected people (Table 2). Lipoprotein (a) [Lp(a)] is a plasma lipoprotein constituted of an LDL particle with one molecule of apolipoprotein B100 and one of apolipoprotein(a) whose levels are associated with an increased risk of CVD.³⁰ Both pro-thrombotic effects (structural homology with plasminogen without fibrinolytic activity) and an accelerated atherogenesis due to increased deposition of Lp(a) cholesterol in the vessels intima, have been proposed as causal mechanisms. Recently, the European Atherosclerosis Society Consensus Panel³¹ stated that Lp(a) should be measured once in subjects who present with premature CVD, familial hypercholesterolaemia, family history of premature CVD, recurrent

CVD despite statin treatment, or a 10-year risk of fatal CVD $\geq 3\%$ using SCORE chart, or a 10-year risk $\geq 10\%$ according to the FRS.

Lipoprotein-associated phospholipase A2 (Lp-PLA2) is a pro-atherogenic enzyme that hydrolyses oxidized phospholipids in LDL generating oxidized fatty free acids and other inflammatory mediators. In a meta-analysis of 14 studies, Lp-PLA2 resulted in an increased CV risk (OR = 1.60; 95% CI: 1.36–1.89)³² that was additive to TRF and independent from CRP levels. In an analysis of 32 prospective studies³³ (79,036 participants), Lp-PLA2 was positively correlated with non-HDL cholesterol and Apolipoprotein B and inversely correlated with HDL cholesterol. Lp-PLA2 showed a strong association with both major CV outcomes but this effect is at least in part mediated by lipids and apolipoproteins. However, it has been suggested that it may be assessed in patients with recurrent CV events,⁸ though the strength of the recommendation is not high (Table 2).

The apoB/apo A-1 ratio showed to carry predictive value in the assessment of CVD risk.³⁴ However, it is considered a second line marker for CVD risk estimation both for the high cost and for the lack of definitive evidence on the effect of its detection in the general population.⁸

Since the predictive power of single RF is low, lacking of sufficient sensitivity and specificity,^{12,13} multimarker scores obtained by adding novel risk markers to TRF, have been proposed^{8,11,22,23,28,35,36} (Table 4) and their NRI above TRF models often assessed (Table 5). In a recent population-based study³⁷ conducted on an elderly cohort (mean age 69.1 years) among 12 CHD risk old and new markers, including NT-pro BNP, von Willebrand factor antigen levels, fibrinogen levels, chronic kidney disease, leukocyte count, CRP levels, homocysteine levels, uric acid levels, carotid intima–media thickness (CIMT), peripheral vascular disease, pulse wave velocity (PWV), and coronary artery calcium score (CACS), improvements in FRS predictions were significantly higher with CACS yielding to an increase in C-statistics and in NRI (39.3; 95% CI: 26.8–51.7) compared with FRS in intermediate risk subjects and in the general population. However, increasing the number of variables might also have some disadvantages: the systems become more complex, more time consuming, and more expensive.² Therefore, interest is growing on how to reduce the number of measurements for risk estimation to improve cost/effectiveness. The WHO/ISH risk charts are available in formats without lipid measurement¹ that can be used in deprived areas where access to medical facilities is limited.²

In summary, (i) risk charts must be used in asymptomatic event-free middle-aged people to identify subjects at moderate or high CV risk; (ii) subjects at very high risk or high risk for the presence of diabetes, renal failure, or markedly elevated single risk factors should not have risk estimate by charts; (iii) novel risk markers do not add predictive power to risk charts neither when used alone nor in multi-marker models; (iv) simple, low-cost renal markers of SOD (MAU and GFR) can reclassify subjects with moderate SCORE risk. However, large-scale studies on well-selected population are needed.

Table 2 Summary of recommendations of scientific societies for stratifying CVD risk above risk charts

	FH	Gen.	LP	NP	C-reactive Protein	HbA1C	LpPLA2	MAU	ECG	Echo	CIMT	FMD	ABI	CTA	CACS	MRI	AS
ESC Prevention (2012)	Class I; LOE:B	Class III; LOE:B	R	NC	Class IIb; LOE:B	R	Class IIb; LOE:B	R	R	R	Class IIa; LOE:B	NC	Class IIa; LOE:B	NC	Class IIa; LOE:B	NR	NC
ACPM (2011)	NC	NC	NR	NC	U	NC	NC	NC	NR	NR	NR	NC	NR	NC	NR	NC	NC
ACCF/AHA (2010)	Class I; LOE:B	Class III; LOE:B	Class III; LOE:C	Class III; LOE:B	Class IIa, LOE:B ^a Class IIb; LOE:B ^b	Class IIb, LOE:B ^c	Class IIb, LOE:B ^d	Class IIa; LOE:B ^e Class IIb; LOE:B ^f	Class IIa, LOE:C ^g	Class IIb, LOE:B ^g	Class IIa, LOE:B ^d	Class III, LOE:B	Class IIa; LOE:B ^d	Class III, LOE:C	Class IIa; LOE:B ^d	Class III, LOE:C	Class III; LOE:C
ESH (2009)	NC	NC	NC	NC	NC	NC	NC	R	R	E	E	E	NC	NC	NC	NC	E
ESC Prevention (2007)	NC	NC	E	NC	U	NC	NC	E	NC	NC	E	NC	E	NC	NR	NR	NC
ASE (2006)	NC	NC	NC	NC	NC	NC	NC	NC	NC	E	U	U	NC	NC	NC	NC	U
SHAPE (2006)	NC	NC	NC	NC	E	NC	NC	NC	NC	NC	E	NC	E	NC	E	U	U
NCEP (2004)	NC	NC	U	NC	NR	NC	NR	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC
USPSTF (2004)	NC	NC	NR	NC	U	NC	NC	NC	NR	NR	NR	NC	NR	NC	NR	NC	NC

FH, family history; Gen., genomics; LP, lipid profile; NP, natriuretic peptides; HbA1C, haemoglobin A1C; LpPLA2, Lipoprotein-associated phospholipase A2; MAU, urinary microalbuminuria; ECG, electrocardiogram; Echo, echocardiogram; CIMT, carotid intima-media thickness; FMD, flow-mediated dilatation; ABI, ankle-brachial index; CTA, computer tomography angiography; CAC, computed tomography for coronary calcium; MRI, magnetic resonance imaging; AS, arterial stiffness. ACCF/AHA, American College of Chest Physician/American Heart Association; ACPM, American College of Medical Physics; NCEP, National Cholesterol Education Program; ASE, American Society of Echocardiography; ESH, European Society of Hypertension; ESC, European Society of Cardiology; SHAPE, Society for Heart Attack Prevention and Eradication; Class, class of recommendation; LOE, level of evidence; R, recommended; E, encouraged; NR, not recommended; U, unclear; NC, not considered.

^aIn men, 50 years of age or older or women 60 years of age or older with LDL cholesterol <130 mg/dL; not on lipid-lowering, hormone replacement, or immunosuppressant therapy; without clinical CHD, diabetes, chronic kidney disease, severe inflammatory conditions, or contraindications to statins.

^bIn intermediate-risk, men 50 years of age or younger or women 60 years of age or younger.

^cIn adults without a diagnosis of diabetes.

^dIn intermediate-risk adults.

^eIn adults with hypertension or diabetes.

^fIn adults at intermediate risk without hypertension or diabetes.

^gTo detect left-ventricular hypertrophy in hypertensive adults.

^hMay be reasonable in persons at low to intermediate risk (6–10% 10-year risk).

Table 3 Criteria to evaluate the clinical value of a new risk factor

To be useful for reclassifying patients currently considered to be at intermediate risk for major CHD events, a new risk factor must meet the following criteria:

1. It should be easily and reliably measured. Laboratory, radiographic, or clinical measurement should have accepted population reference values. A relatively high prevalence of abnormal values and a substantial proportion of normal values should be found among intermediate-risk persons.
2. It should be an independent predictor of major CHD events in intermediate-risk persons who have no history of coronary artery disease and no coronary equivalents, such as cerebrovascular or peripheral vascular disease.
3. When assessed in intermediate-risk persons, it should reclassify a substantial proportion of them as high-risk.
4. Reclassified individuals should be managed differently than they would have otherwise been, and new or additional treatment they receive should reduce their risk for CHD events.
5. If two or more risk factors provide similar prognostic information, then convenience, availability, cost, and safety may be important in choosing among them.

Source: Helfand M, Buckley DI, Freeman M, Fu R, Rogers K, Fleming C *et al*. Emerging Risk Factors for Coronary Heart Disease: a summary of systematic reviews conducted for the U.S. preventive services task force. *Ann Intern Med* 2009;151:496–507. Reprinted with permission.

The role of imaging in detecting subclinical atherosclerosis

Imaging is considered superior to risk estimation of risk charts since: (i) direct detection of atherosclerosis is better than identifying only RFs exposure; (ii) reclassification of low-risk subjects into higher strata may guide therapy; (iii) the identification of high-risk subjects might improve adherence to risk-modifying therapy.³⁸

From a pathophysiological point of view, atherosclerosis *per se* is not comparable with an RF (that may or may not induce the atherosclerotic process): the finding of atherosclerosis means simply that atherosclerosis is present. Since most of CV deaths in a community come from those at lower risk (50% of Framingham individuals experiencing acute MI had normal cholesterol levels according to guidelines), preclinical examinations might definitely improve risk assessment at least in middle aged individuals. Cardiovascular risk algorithms leave open important 'black boxes' in respect of causative aspects of pathogenesis (the individual genotype) that are indirectly covered by the morphologic substrate (the phenotype) of the atherosclerotic finding.³⁸ In the majority of patients with acute MI, the event is due to the rupture of clinically silent flat plaques (which do not induce ischaemic symptoms). Thus to identify the atherosclerotic progression at a pre-clinical stage anywhere in the vascular tree has gained relevance (Table 6).

Ultrasonography

B-mode ultrasonography of carotid arteries

Carotid intima-media thickness is a non-invasive, unexpensive, radiation-free technique with well-established evidence as an

indicator of CV risk. Both atherosclerosis (reflected more by the CIMT value at the bifurcations) and vascular hypertrophy (reflected more by the common carotid CIMT) confer an additional prognostic value to that of high BP levels in hypertensive subjects.¹⁸ Risk reclassification through CIMT or carotid plaque into the FRS was investigated in the ARIC study³⁹: adding both CIMT and plaque to TRF in a sample of 13 145 subjects (45–64 years) improved the AUROC significantly both in men and women, resulting in a reclassification of about 23% of the subjects. Particularly, among subjects at intermediate-high risk (10–20% estimated 10-year CHD risk), 340 (13.5%) were reclassified to the high-risk category. Overall, CIMT plus plaque model when compared with the TRF-only model was associated with an NRI of 9.9% suggesting effective reclassification. These results are similar to those of a recent analysis conducted on 2965 patients enrolled in the Framingham Offspring Study cohort followed for 7.2 years reporting a significant increase in the net reclassification index after addition of CIMT (7.6%, $P < 0.001$).⁴⁰

The Carotid Atherosclerosis Progression Study (CAPS),⁴¹ however, did not confirm the previous findings. Although CIMT was significantly and independently predictive of CVD, adding CIMT to the FRS reclassified only 357 subjects (8.1%) with an NRI of 21.41% ($P = \text{NS}$). Carotid intima-media thickness determined more subjects moving from the intermediate risk category towards lower risk than towards higher risk categories. Meta-analyses have also shown contrasting results. In one analysis comprising eight studies (37 197 subjects), the age- and sex-adjusted estimates of the relative risk of MI and stroke per 0.10 mm common CIMT difference were, respectively, 1.15 (95% CI, 1.12–1.17) and 1.18 (95% CI, 1.16–1.21).⁴² On the contrary, another meta-analysis of 41 randomized trials (18 307 participants) demonstrated that despite significant reduction in CVD and all-cause death induced by active treatments, there was no significant relationship between CIMT regression, CV events, and all-cause mortality.⁴³ Accordingly with the CAPS,⁴¹ a recent meta-analysis by Den Ruijter *et al.*⁴⁴ shows that measurement of the CIMT has no clinical value for the total asymptomatic population, and only a limited value in those at intermediate risk.

However, the recent meta-analysis by Peters *et al.*⁴⁵ evaluated the incremental predictive value of different imaging techniques as flow-mediated vasodilation (FMD), CIMT, carotid plaques and/or CACS in 25 studies. Both CIMT and carotid plaque, as well as CACS, showed additional value for screening in asymptomatic subjects at intermediate risk, improving the C-statistic (from 0.00 to 0.03 for CIMT and from 0.01 to 0.05 for carotid plaque) and the NRI (from –1.4 to 12% for CIMT, and from 8 to 11% for carotid plaques).

The reliability of CIMT in single-patient risk assessment is still controversial mostly for the high variability and relatively low intra-individual reproducibility^{8,11,18,46} (Tables 6 and 2). These limitations can be overcome nowadays by using the newer radio-frequency systems (Figure 1). Vascular age (i.e. the age at which a given CIMT value would be normal or the age at which the patient's CIMT value would be at the 50th percentile for his/her sex and race)⁴⁷ has been proposed as a surrogate index of the progression of atherosclerosis. In the FRS model, 50% of intermediate-risk subjects could be reclassified into a higher (36%) or a lower (14%) risk stratum when chronological age was substituted with CIMT-derived

Table 4 Additive predictive value of adding multiple novel risk factors (multimarker scores) to TRF algorithms

Study/year	Author/s	Type of Population	CVD risk factor/risk markers used	Incremental value test over traditional risk scores (in (discrimination* or reclassification))
Reynolds Risk Score	Ridker et al. <i>Circulation</i> 2008;118:2243–51. Ridker et al. <i>JAMA</i> 2007;297:611–9.	General population	C-reactive protein + family history of CHD added to traditional RFs	No incremental prediction with the addition of hs-CRP to the FRS score in the ARIC study.
Framingham Heart Study (FHS)	Wang et al. <i>N Engl J Med</i> 2006;355:2631–2639.	3209 participants of the FHS. 10 new biomarkers	C-reactive protein, BNP, NT-pro-atrial natriuretic peptide, aldosterone, renin, fibrinogen, D-dimer, plasminogen-activator inhibitor type 1, homocysteine, albumin-to-creatinine ratio (UACR)	BNP (adjusted HR = 1.25); UACR (adjusted HR = 1.20). Individuals in the highest quintile of the score showed a four-fold increased risk of death (adjusted HR = 4.08; $P < 0.001$), and two-fold increase in major CV events (adjusted HR = 1.84; $P = 0.02$) respect to those in the lowest two quintiles. *The C-statistics analysis showed only small increases in the ability to classify risk with the addition of multimarker score to TRF
Cardiovascular Health Study	Shlipak et al. <i>JAMA</i> 2005;293:1737.	1249 patients ≥ 65 years. with chronic kidney disease (CKD)	C-reactive protein, fibrinogen, IL-6, and haemoglobin), (Lp[a], factor VIII coagulant activity	*Addition of novel risk markers resulted in only a minimal increase of the AUROC (from 0.73 to 0.74, $P = 0.15$)
Uppsala Longitudinal Study of Adult Men (ULSAM)	Zethelius et al. <i>N Engl J Med</i> 2008;358:2107–16.	1135 men > 50 years. (mean age, 71 years at baseline).	Troponin I, N-terminal pro-brain natriuretic peptide, cystatin C, and C-reactive protein.	*Significant improvement of the C-statistics respect to the model of TRF both in the whole cohort of 1135 subjects (AUROC = 0.766 vs. 0.664; $P < 0.001$) than in the group of 661 participants without CVD at baseline (AUROC: 0.748 vs. 0.688, $P = 0.03$).
Nine systematic reviews on novel RFs for the US Preventive Services Task Force	Helfand et al. <i>Ann Intern Med.</i> 2009;151:496–507.	No baseline CVD. Data adjusted for at least six Framingham risk factors.	C-reactive protein, (EBCT-CACS), Lp(a), homocysteine (HM), leukocyte count, fasting blood glucose, periodontal disease, ABI, CIMT.	No improvement in risk stratification in intermediate-risk subjects compared with TRF. The current evidence does not support the routine use of any of the nine risk factors for further risk stratification of intermediate-risk persons.
Malmö Diet and Cancer study	Melander et al. <i>JAMA</i> 2009;302:49–57.	5067 participants (mean age, 58 years; 60% women)	C-reactive protein, cystatin C, Lp-PLA2, midregional proadrenomedullin, midregional proatrial natriuretic peptide, and NT-proBNP	Improvements in reclassification were observed only in intermediate-risk mainly towards the lower rather than towards the higher risk categories (CV events: 7.4%; 95%CI: 0.7–14.1%; $P = 0.03$; coronary events: 14.6%; 95% CI: 5.0–24.2%; $P = 0.003$).
Women's Health Initiative Hormone Trials	Chang Kim et al. <i>J Am Coll Cardiol</i> 2010;55:2080.	27.47 post-menopausal women (50–79 years)	(1) TRF + statin treatment, hormone treatment, and CVD history, (2) additional biomarkers model: interleukin-6, D-dimer, coagulation factor VIII, von Willebrand factor, HM.	*The TRF model showed to be better than the FRS model (AUROC = 0.729 vs. 0.699, $P < 0.001$). The additional biomarker model showed further improvement in the C-statistics (AUROC = 0.751 vs. 0.729, $P < 0.001$), and NRI (6.45%) compared with the TRF model resulting in a moderate improvement in CHD risk prediction in post-menopausal women.

Table 5 Net reclassification improvement using different multimarker scores

Risk Marker/Factor	NRI (%)	Intermediate 10-year risk definition (%)	P-value	First author
Multiple biomarker score (troponin I, NT-proBNP, cystatin C, C-reactive protein)	26.0	6–20	0.005	Zethelius <i>et al. N Engl J Med</i> 2008;358:2107–16
Multiple biomarker score (MR-proADM, NT-proBNP)	4.7	6–20	NS	Melander <i>et al. JAMA</i> 2009;302:49–57.
HDL cholesterol (Framingham)	12.1	6–20	0.001	Pencina <i>et al. Stat Med.</i> 2008;27:157–172
HDL cholesterol (SCORE data)	2.2	2–5 and 5–10	0.006	Cooney <i>et al. Eur J Cardiovasc Prev Rehabil</i> 2009;16:304–14.
hs-CRP (women)	5.7	5–20	0.0001	Cook <i>et al. Ann Intern Med</i> 2006;145:21–9.
hs-CRP (men)	8.4	5–20	0.001	Wilson <i>et al. Circ Cardiovasc Qual Outcomes</i> 2008;1:92–7.
hs-CRP (men and women)	11.8	6–20	0.009	Ridker <i>et al. Circulation</i> 2008;118:2243–51. Ridker <i>et al. JAMA</i> 2007;297:611–9.
HbA1c (men)	3.4	5–10 and 10–20	0.06	Simmons <i>et al. Arch Intern Med</i> 2008;168:1209–16.
HbA1c (women)	–2.2		0.27	
CACS (men and women, including revascularization)	25.0	6–20	0.001	Polonsky <i>et al. JAMA.</i> 2010;303:1610–6.
CACS (model based on FRS-variables with and without CAC, all subjects)	19.6	6–20	0.004	Erbel <i>et al. J Am Coll Cardiol</i> 2010;56:1397–406.
CACS (model based on FRS-variables with and without CAC, all subjects)	19.6	6–20	0.004	
	22.4	10–20	0.0009	
CACS (reclassification based on the FRS only of intermediate-risk subjects)	30.6	6–20	0.0001	
	21.7	10–20	0.0002	
FRS + CACS (men and women, including revascularization, mean age 69.1)	39.3	10–20	NR	Kavousi <i>et al. Ann Intern Med.</i> 2012;156:438–444.

HbA1c, haemoglobin A1c; hsCRP, high-sensitive C-reactive protein; MR-proADM, mid-regional pro-adrenomedullin; NT-proBNP, N-terminal pro-B-type natriuretic peptide; CACS, coronary artery calcium score; NS, not significant; NR, not reported.

Source: Erbel R *et al.* Coronary risk stratification, discrimination, and reclassification improvement based on quantification of subclinical coronary atherosclerosis. The Heinz Nixdorf Recall Study. *J Am Coll Cardiol* 2010;56:1397–406. Reprinted with permission, modified.

'vascular age'. Thus CIMT should be evaluated within sex- and age-referenced normograms (Figure 2).

However, carotid ultrasound can give information besides CIMT: the presence of carotid plaques conferred a two-fold increase of risk of future CV adverse events (HR = 2.3) in a population sample free of overt CV disease.¹⁸ The characteristics of carotid plaques are associated to future cerebrovascular ischaemic events as well. Echolucent structures are suggestive for the presence of haemorrhage, thrombi, and lipids within the plaque as well as intra-plaque neovascularization⁴⁸ is associated with a higher risk of stroke.

Echo-Doppler of peripheral vessels and the aorta

Asymptomatic peripheral vascular disease (PVD) detected by a positive ankle-brachial index (ABI) has been found to be associated with an incidence of CVD in men of about 20% at 10 years.^{49,50} Ankle-brachial index measurement is simple, unexpensive, and accurate, (sensitivity: 97%, specificity: 100%) compared with angiography.⁴⁸ Since ABI is strongly related to the development of angina, MI, congestive heart failure, coronary artery bypass surgery, stroke, and carotid surgery, the ACC/AHA and ESC prevention guidelines recommend measurement of ABI for

CV risk assessment in asymptomatic adults with intermediate risk (Table 2).

Echo-Doppler examination of the abdominal aorta can help to detect abdominal aortic aneurysm (AAA) that implies preventing its often fatal potential rupture. A Cochrane review reported that AAA screening can lead to a significant decrease in AAA-related mortality.⁵¹ Thus, one-time AAA screening has been recommended in men aged 65–75 years who ever smoked by the American College of Preventive Medicine,⁵² in men aged 60 years whose sibling or offspring had an AAA by the American College of Cardiology/American Heart Association,¹¹ in all men aged 60–85 years and women aged 60–95 years with CV RF, or in all individuals aged 50 years with a family history of AAA by the Surgeon Vascular Society and the Society for Vascular Medicine and Biology.⁵² Both the ESC and the ESH did not give specific indications about this issue (Tables 6 and 2). Although ruptured AAA is usually not considered as an endpoint in most risk assessment tools and it is generally not used for decision-making on primary prevention by pharmacological and lifestyle therapies, the detection of AAA by USA has been demonstrated to be cost-effective in selected populations.⁵³

Table 6 Structural direct or surrogate indexes of progression of atherosclerosis (subclinical organ damage) obtained by different imaging techniques

Method	Index	Prognostic value (main studies)	Incremental value test over risk scores (reclassification)	Mostly used cut-offs	Limitations
B-mode ultrasonography of carotid arteries	Carotid intima-media thickness (CIMT)	O'Leary DH et al. <i>N Engl J Med</i> 1999; 340:14–22. Zanchetti et al. (ELSA study), <i>Circulation</i> 2009; 120:1084–1090. Nambi V. et al. (ARIC study). <i>JACC</i> 2010; 55:1600–7. Lorenz MW et al. (CAPS study) <i>Eur Heart J</i> 2010;31(16): 2041–48	Cuspidi C et al. (APROS), <i>J Hypertens</i> 2002;20:1307–14. Bots ML et al (Rotterdam study) <i>Circulation</i> 1997;96:1432–7. O'Leary DH et al (CHS) <i>N Engl J Med</i> 1999;340:14–22. Nambi V et al. (ARIC), <i>J Am Coll Cardiol</i> 2010; 55:1600–7. Erbel R et al. The Heinz Nixdorf Recall Study. <i>J Am Coll Cardiol</i> 2010;56: 1397–406.	CIMT >0.9 mm or plaque. Sex- and age-referenced nomograms	Intraobserver and interobserver variability. Repeated measures.
Magnetic resonance imaging (MRI) of carotid arteries	Plaque detection and composition:	Wasserman BA et al. The Multi-Ethnic Study of Atherosclerosis (MESA). <i>Stroke</i> . 2008;39: 329–35. Yuan C et al. <i>Circulation</i> 2002;105:181–5.	Takaya N et al. <i>Stroke</i> . 2006;37:818–23. Takaya N et al. <i>Circulation</i> 2005;111: 2768–75.	Not known	Time consuming. Use of contrast agents. Lack of prospective data on 10-year CV risk.
2D/M-Mode echocardiography	LV mass index (g/m ²)	Levy D. et al. <i>N Engl J Med</i> 1990;322:1561–1566. Koren MH et al. <i>Ann Intern Med</i> 1991;114: 345–352.	Cuspidi (APROS), <i>J Hypertens</i> 2002;20:1307–1314. Sehested T et al. <i>J Hypertens</i> 2009, 27:2351–2357.	LVMi > 125 g/m ² (men); > 110 g/m ² (women) Concentric geometry: (RWT ≥ 0.42)	Intraobserver and interobserver variability. Repeated measures. True LV mass variation probability > 90% if the LVM change is > 20% of the initial value in skilled laboratories.
	Cardiac calcifications	Otto CM, et al. <i>N Engl J Med</i> 1999; 341: 142–7. Fox CS. et al. <i>Circulation</i> 2003; 107: 1492–1496. Kanjanathai S. et al. The Multi-Ethnic Study of atherosclerosis (MESA). <i>Atherosclerosis</i> 2010; 213: 558.	?	0 (normal) to 3 (severe)	Intraobserver and interobserver variability. Repeated measures.
Doppler untrasonography of peripheral vessels	Ankle-brachial index (ABI)	Fowkes GF, <i>JAMA</i> 2008; 300:197–200. De Buyzere M, et al. <i>Progr Cardiovasc Dis</i> 2008;50:238–263.	?	ABI < 0.9	Lack of studies addressing harm/benefits of screening
B-mode ultrasonography of abdominal aorta	Abdominal aortic aneurism (AAA)	Fleming C. et al. <i>Ann Intern Med</i> 2005;142:203–11. Kim LG et al. <i>Ann Intern Med</i> 2007;146:699–706. Cosford PA, et al. <i>Cochrane Database Syst Rev</i> 2007;CD002945	US Preventive Services Task Force. <i>Ann Intern Med</i> 2005;142: 198–202 (43% relative risk reduction for deaths from AAA with screening)	> 5.5 cm increased risk of rupture	Technical feasibility may be difficult in obese subjects. Potential harms: psychological distress and possible complications from AAA management.
Computed tomography	CACS	Budoff MJ et al. <i>J Am Coll Cardiol</i> 2007;49:1860–70. Sarwar A, et al. <i>J Am Coll Cardiol Img</i> 2009;2:675–88; Peters SAE et al. <i>Heart</i> 2012;98:177–84	Low CACS score can reclassify subjects at intermediate risk in very low CV risk. High CACS score provide independent incremental information over TRF to predict CV risk.	CACS = 0 vs CACS > 0	Costs; Radiation exposure.

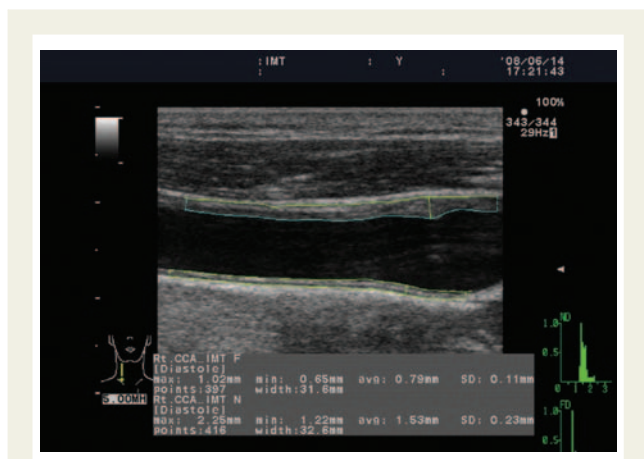


Figure 1 Doppler ultrasound imaging of the right common carotid artery (CCA). Measured about 2 cm below the CA bifurcation. Carotid IMT is obtained by using the radio-frequency (RF) signal to obtain a precision six- to 10-fold higher than with video-image systems, which are limited by the spatial resolution of pixel analysis. Instantaneous standard deviation (<0.25 mm) ensure the good reproducibility of the measurements.

Conventional (2D/M-Mode) echocardiography

The presence of calcium deposits at the aortic valve and/or the mitral apparatus (annulus, leaflets, papillary muscles) or a relevant thickening of ascending aorta walls, as detected by conventional transthoracic echocardiography (TTE) (Figure 3), is associated with higher CV morbidity and mortality rates in several prospective studies.^{54,55}

Other surrogate indexes of atherosclerotic burden, even if not specific are markers of SOD like LV hypertrophy (LVH) or LV concentric remodelling (CR) detected by 2D/M-Mode TTE^{18,21} (Table 2). Detection of cardiac (or vascular) damage allows reclassifying a large quote of intermediate-risk individuals within the high-risk group (Table 2). Technical limitations in detecting regression of LVH have been pointed out⁵⁶: the probability that a true LV mass variation occurs is $>90\%$ if the change of the initial value (obtained in skilled laboratories) is at least $>20\%$. Hence the ACCF/AHA guidelines recommendation is weak¹¹ (Table 6).

Computed tomography

Coronary artery calcium score

Coronary artery calcium (Figure 4) has been proposed as a marker of incident CHD³⁷ (Table 5). The knowledge of the pre-test probability of CAD in candidates to CAC evaluation is critical.^{57,58} Both in a cohort of 25 253 consecutive asymptomatic individuals,⁵⁹ and in a systematic review of 13 studies for a total of 64 873 asymptomatic patients,⁶⁰ the presence of CAC provided independent incremental information in addition to TRF to predict all-cause mortality, whereas its absence identified a group of asymptomatic subjects at very low CV risk, excluding the need for aggressive therapy or further diagnostic tests.

In a recent meta-analysis⁴⁵ on 25 studies carried out to evaluate the incremental role of subclinical atherosclerosis in CV risk prediction (fatal or non-fatal CV events), CACS showed an

improvement in C-statistic from 0.05 to 0.13 and in the NRI from 14 to 25% with respect to conventional risk models. Therefore, CACS might help to reclassify asymptomatic patients at intermediate risk for CAD as assessed by TRF models (Tables 5 and 6).

In the 6814 participants from the Multi-Ethnic Study of Atherosclerosis (MESA),⁶¹ a population-based cohort without known CVD, CACS was able to improve risk prediction over TRF including age, sex, current smoking, systolic BP, antihypertensive treatment, total and HDL cholesterol, and ethnicity. The NRI was 0.25 (95% CI: 0.16–0.34; $P < 0.001$). Among intermediate-risk individuals, adding CACS to TRFs resulted in a reclassification of 292 subjects (16%) from moderate to high risk, while 712 (39%) were re-classified as low risk (NRI, 0.55; 95% CI, 0.41–0.69; $P < 0.001$). This finding was confirmed in the subset of 1330 subjects at intermediate risk of the MESA.⁶²

In the 4129 subjects (45–75 years) without overt CHD at baseline from the Heinz Nixdorf Recall study,⁶³ TRF and CACS scores were obtained. Cardiovascular disease risk was defined according to both the FRS and the ATP III guidelines. A CACS < 100 yielded an NRI of 21.7% ($P < 0.0002$) in reclassifying intermediate risk subjects to the low-risk category and a CACS > 400 an NRI of 30.6% ($P < 0.0001$) reclassifying subjects to the high-risk category, respectively (Table 5). These results confirmed those reported by the MESA study, ultimately showing that the benefit of imaging of subclinical coronary atherosclerosis was even greater than using a multiple biomarker models including HDL-cholesterol,⁶⁴ hs-C-reactive protein,^{65,66} or HbA1c⁶⁷ (Table 5). Hence, measurement of CAC may be reasonable for CV risk assessment in asymptomatic adults at moderate risk.^{8,57}

Coronary computed tomographic angiography

64-channel coronary computed tomographic angiography (CCTA) and its latest evolution (dual source) is an accurate method for identifying atherosclerosis. It can detect calcified plaques as well as the total coronary calcium burden (EBCT), but even more important it also can identify non-calcified plaques.

The CONFIRM study, a multicentre registry of 23 854 patients without known CAD⁶⁸ studied by CCTA showed that after a mean 2.3-year follow-up, both obstructive and non-obstructive CAD detected with a 64-detector row CCTA conferred an increased risk of mortality compared with patients without evident CAD. The absence of CAD by CCTA was associated with a low rate of incident death. However, in patients without a history of CAD, a CACS of 0 cannot exclude the presence of an obstructive CAD.⁶⁹

The relationship between CCTA and CV outcomes has been clarified by two recent studies. The Early Identification of Subclinical Atherosclerosis by Non-invasive Imaging Research (EISNER) prospective trial showed that in a cohort of 2137 individuals, randomization to CAC scanning was associated with best risk factor's control (i.e. BP, LDL cholesterol, waist circumference, weight loss).⁷⁰ Imaging could also be useful to improve therapies and adherence of patients at risk. In the Study of Myocardial Perfusion and Coronary Anatomy Imaging Roles in Coronary Artery Disease (SPARC), enrolling 1703 patients without known CAD, those who underwent non-invasive imaging tests (cardiac EBCT, positron emission tomography, or CCTA) where more likely to

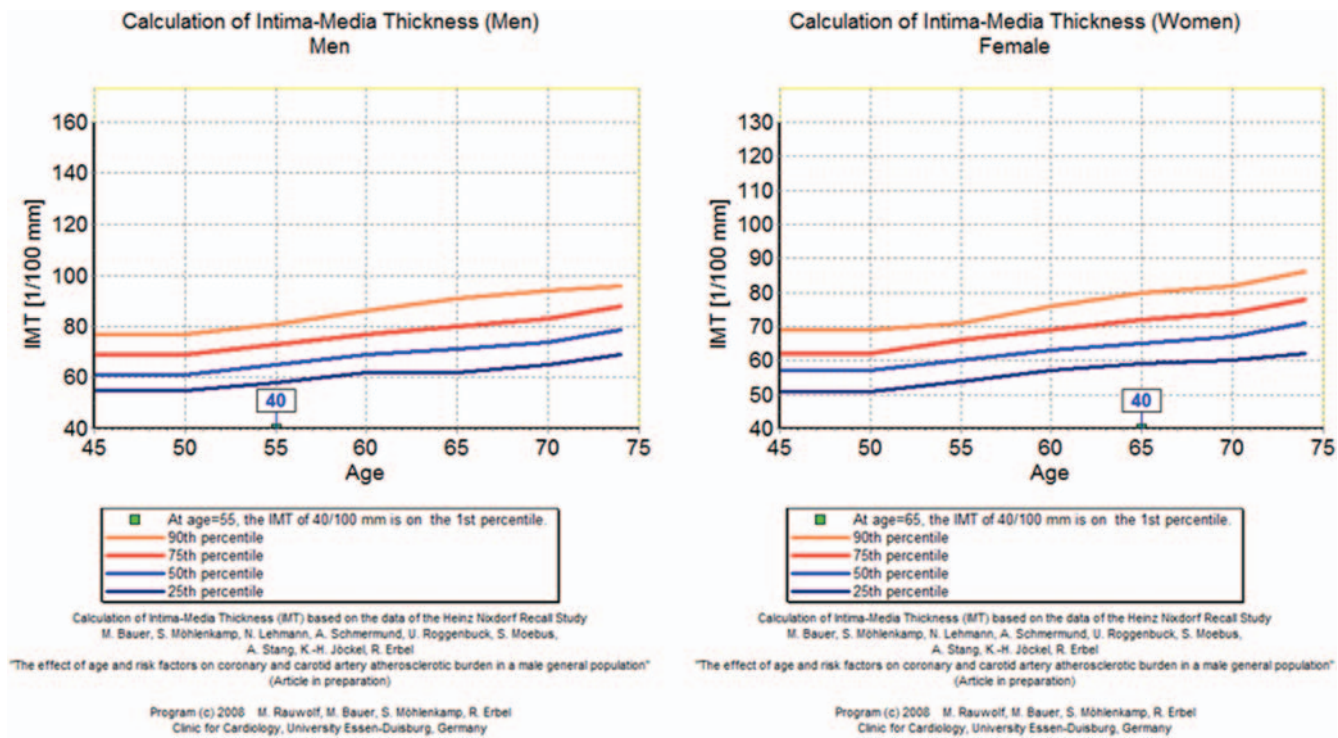


Figure 2 Age- and gender-corrected calculation of the intimal–media thickness (IMT) according to the Heinz Nixdorf Recall study. Men (left panel) and women (right panel). The 25th, 50th, 75th, and to 90th percentiles values are shown as black, blue, red, and orange lines, respectively. The green marker on the abscissa's line shows the IMT 25th percentile for a man aged 55 years (left panel) and the IMT 25th percentile for a woman aged 65 years. (Courtesy of the Nixdorff Recall study).⁶³

undergo cardiac catheterization and receive aspirin and a lipid lowering agent.⁷¹ The ACC/AHA guidelines and a position paper of the ESC, published before the above-mentioned trials did not recommend CCTA to stratify risk in asymptomatic persons (class of recommendation: III; level of evidence: C).^{11,57,72} However, the recently published ESC prevention guidelines



Figure 3 Imaging of coronary artery calcium score (CACS). Calcifications are seen just in the left anterior descending (LAD) coronary artery, before and after the origin of a first diagonal branch in a asymptomatic individual.

provide a Class IIa with Level of Evidence B for asymptomatic patients at moderate risk⁸ (Table 2).

Other techniques

Magnetic resonance imaging (MRI) of carotid arteries seems to be more accurate than ultrasound in identifying high-risk carotid stenoses by plaque composition. In a prospective study of asymptomatic patients who had a 50–70% carotid stenosis, the presence of a thin ruptured fibrous cap, intraplaque haemorrhage, or a large lipid necrotic core as recognized by MRI, were associated with an increased risk of ipsilateral haemorrhage.⁷³ Prognostic value and incremental value test over TRF (reclassification) have been reported (Table 6).

Thus, although both the ESC⁸ and ACC/AHA¹¹ prevention guidelines do not recommend the use of MRI to detect vascular plaques in asymptomatic adults, recent ESC guidelines on peripheral vascular disease⁷⁴ do recommend it (Table 2). As well as CTA, MRI includes the simultaneous imaging of the aortic arch, the intracranial circulation, as well as the brain parenchyma other than the study of carotid arteries. Moreover, MRI is radiation-free and requires less nephrotoxic contrast agent.

A 12-lead resting ECG may be considered for CV risk assessment in asymptomatic hypertensive or diabetic subjects and to a less extent in those without arterial hypertension or diabetes¹¹ (Table 2). ECG-detected LVH is associated to an increased CV risk for fatal and non-fatal CV events^{75,76} and its regression with reduced CV risk.⁷⁷

Atherosclerosis of retinal arteries correlates with the extent of coronary plaques and RF. Newer non-invasive methods for assessing the media–lumen ratio of small retinal arteries have been developed and they are promising for large-scale evaluation.⁷⁸ However, their value in reclassifying subjects at intermediate risk

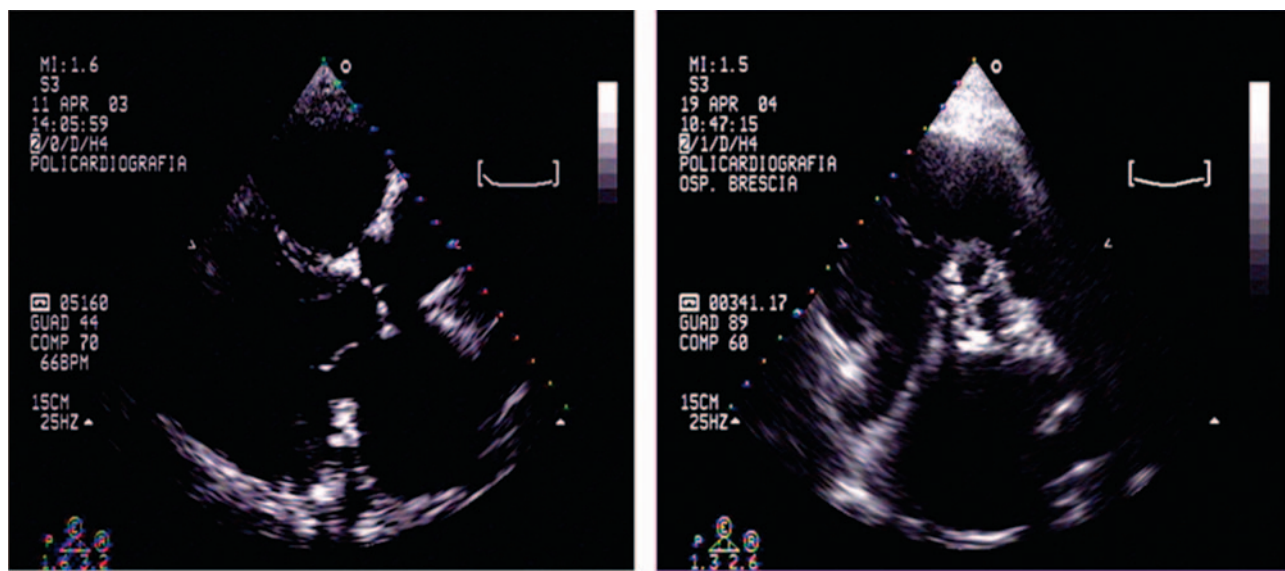


Figure 4 Two-dimensional echocardiographic detection of cardiac calcifications as markers of subclinical atherosclerosis in a 58-year old man. Left panel: parasternal long-axis view: mitral annulus calcification, sclero-calcification of aortic valve, and thickened ascending aortic walls are evident. Right panel: parasternal short axis view: calcific nodules are seen on all the aortic valve leaflets.

needs further investigation; hence, its place in vascular disease risk assessment remains uncertain.⁸

In summary, the recommendations of the scientific societies on the utilization of the current available markers and imaging modalities to stratify CVD risk above risk charts are quite heterogeneous (Table 2). In summary: (i) most imaging techniques can really improve risk stratification over risk chart estimates especially when applied to subjects at intermediate risk; (ii) newly developed imaging modalities reducing intraobserver and intraobserved variability and providing high spatial resolution, can impact on risk stratification identifying early atherosclerosis; (iii) since new diagnostic modalities are often expensive, given the continuous rise of healthcare cost, the need for accurate cost-effectiveness analyses and decision-making trees is high.

Conclusions

Although current CVD prediction systems based on the TRF have shown certain limitations, scientific societies still recommend their use to assess absolute risk in asymptomatic adults. Adding novel biomarkers to conventional risk prediction in the general population has shown only minimal improvement. As pointed out by guidelines, the use of simple, low-cost markers of SOD (such as MAU and GFR) should be encouraged to refine CV risk prediction over TRF, at least in subjects with hypertension and diabetes. The increasing use of imaging allows overcoming the risk charts limits by directly identifying the individual atherosclerotic burden. Among imaging techniques, both CACS and carotid ultrasound (the latter mainly for the detection of plaque) are the most useful in asymptomatic subjects at intermediate risk.

Conflict of interest: none declared.

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