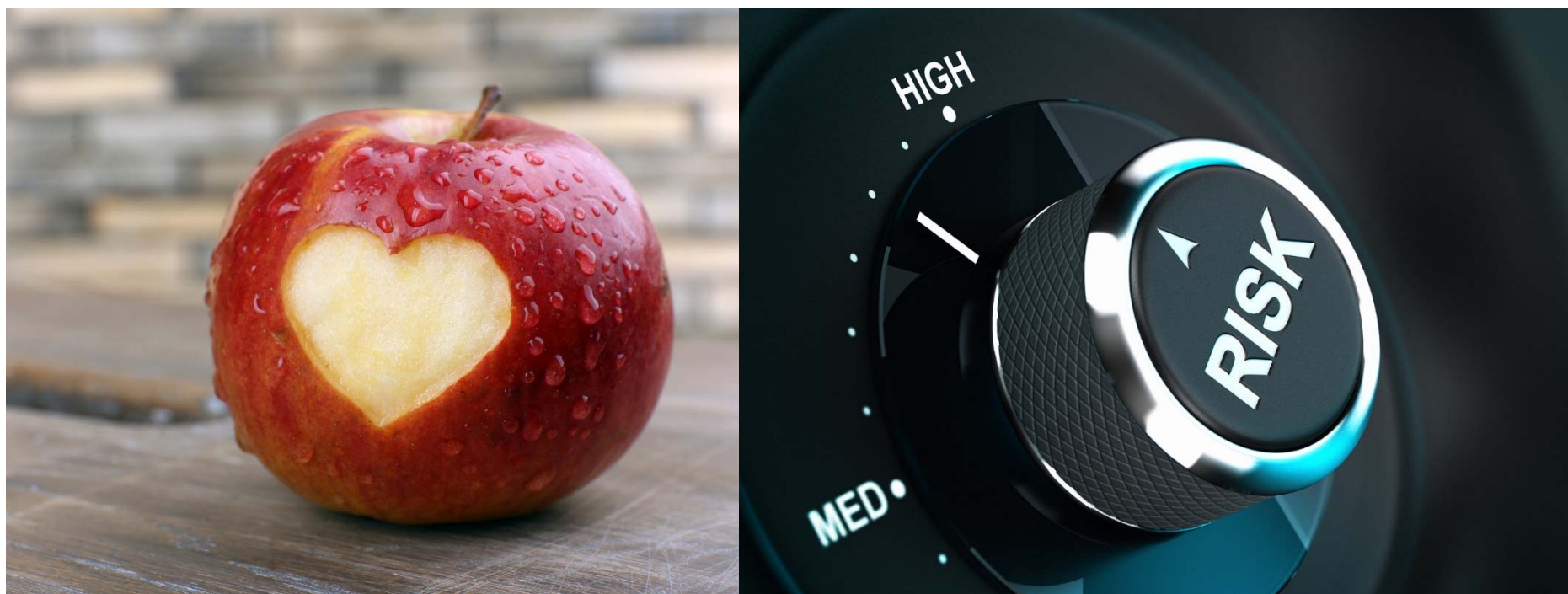


SYNTHESIS

NON-INVASIVE MARKERS OF SUBCLINICAL ATHEROSCLEROSIS FOR PREDICTING A PRIMARY CARDIOVASCULAR EVENT: A RAPID SYSTEMATIC REVIEW



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NON-INVASIVE MARKERS OF SUBCLINICAL ATHEROSCLEROSIS FOR PREDICTING A PRIMARY CARDIOVASCULAR EVENT: A RAPID SYSTEMATIC REVIEW

DOMINIQUE ROBERFROID, LORENA SAN MIGUEL, DOMINIQUE PAULUS



■ FOREWORD

In the March 2015 issue of *Circulation: Cardiovascular Quality and Outcomes*, the journal of the American Heart Association, one can read a very interesting article entitled Quantifying the Utility of Taking Pills for Cardiovascular Prevention^a. The topic is far from trivial. Because once we hit 50 – as in the case of both signatories of this foreword – we all run the risk of having to start, for one reason or another, swallowing every day one or more drugs. This article demonstrates, by means of robust methods, what was long suspected: 'pills' affect our quality of life, in a limited but objective manner. The impact can go from a simple scratch to our self-esteem, to a full range of side effects, imaginary or not. Respondents to the survey conducted by the researchers would pay up to € 1000 in order to avoid this daily burden!

It is therefore essential to limit the use of drugs to individuals likely to derive a significant health gain, in other words, to those most at risk of developing a cardiovascular problem. Unfortunately, predicting the future and identifying such population is not an easy task. Our classical tools for cardiovascular risk assessment remain imprecise. Thus, we continue to look for *the* simple and accurate test that would facilitate the identification of those individuals for whom it would make sense to prescribe preventive treatments. Unfortunately, in April 2013, we already critically appraised some serum biomarkers with very disappointing results. The present study focuses on a series of markers of asymptomatic atherosclerosis and yet once more, there is no reason to rejoice.

Clearly, adopting a healthy lifestyle remains at the core of the agenda, but the decision to add or not any further drug is unfortunately not simplified. This last decision remains a choice for which, more than ever, the preferences of the patient – clearly and objectively informed – must play a decisive role.

Christian LÉONARD
Deputy general director

Raf MERTENS
General director

^a

<http://circoutcomes.ahajournals.org/content/early/2015/02/03/CIRCOUTCOMES.114.001240.full.pdf+html>



■ ABSTRACT

BACKGROUND

Cardio-vascular diseases (CVD) remain the most frequent cause of mortality in our population. Risk prediction models, such as the SCORE (Systematic COronary Risk Evaluation), allow the stratification of individuals in risk categories and to adapt the preventive management accordingly. The accuracy of SCORE could be improved by incorporating markers of subclinical atherosclerosis, particularly in individuals classified at intermediate risk.

METHODS

A rapid literature review was performed on the predictive increments (net reclassification index), clinical effectiveness and cost-effectiveness of non-invasive markers of subclinical atherosclerosis in asymptomatic individuals.

RESULTS

Coronary artery calcium score provided the highest incremental predictive value, with a net reclassification index ranging from 22% to 66% in individuals classified at intermediate risk. The added value of the ankle-brachial index, aortic pulse wave velocity and carotid plaque in risk reclassification was lower than for coronary calcium, at around 15%.

The clinical benefit of integrating these 4 markers to SCORE was not formally assessed in studies. Economic evaluations were only identified for one marker: coronary artery calcium. The studies showed highly unstable results, sensitive to a number of assumptions, and in particularly to those relating to the price and efficacy of preventive treatments.

CONCLUSION

In the absence of high quality studies on the clinical effectiveness of measuring atherosclerosis markers beyond the traditional cardiovascular risk markers, and the consequent uncertainty surrounding their cost effectiveness, the utilization of these markers is not recommended. Improving the predictive value of SCORE by the addition of easy to collect information in first-line consultation (e.g. BMI, sedentarity) is a priority.



■ SYNTHESIS

1. THE NEED FOR MORE ACCURATE CVD RISK PREDICTION

Key message

Current tools for predicting individual cardiovascular risk on the basis of traditional risk factors lack accuracy. Incorporating markers of subclinical atherosclerosis could improve the predictive value, particularly in individuals classified at intermediate cardiovascular risk, and may allow a more appropriate preventive management.

1.1. CVD risk prediction

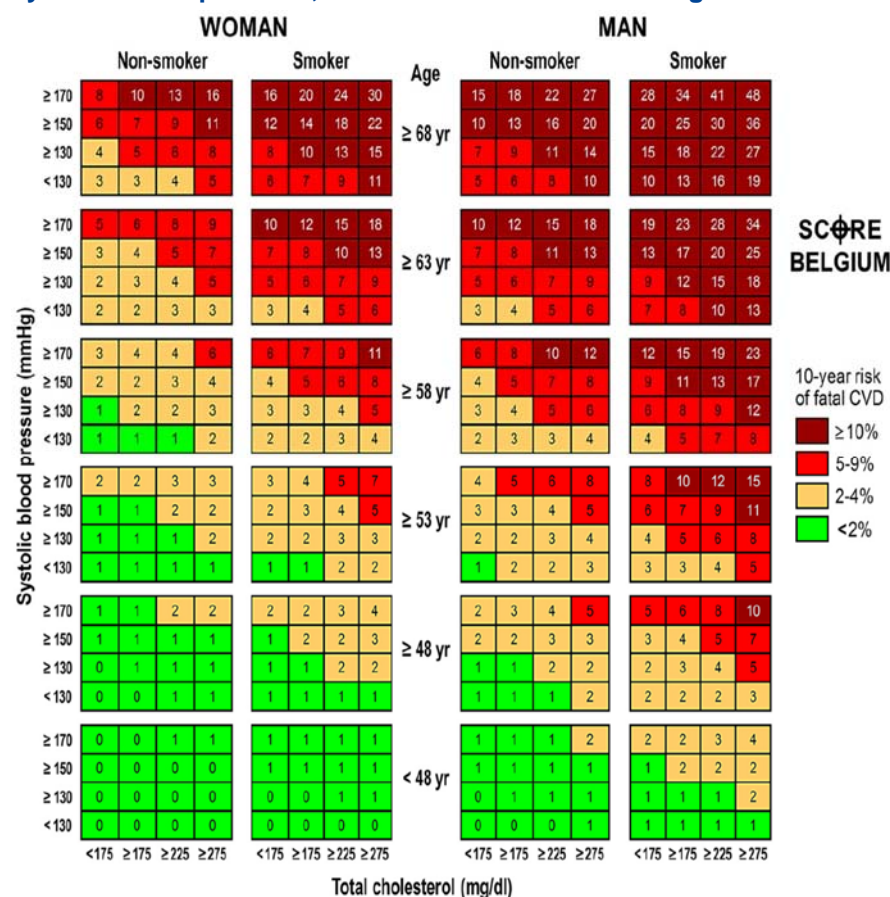
Cardiovascular diseases (CVD) remain the most important cause of mortality in Belgium. Primary prevention is thus crucial. CVDs have a long asymptomatic period, which provides an opportunity for early preventive interventions. Current trends in primary prevention of CVD emphasize the need to manage individuals based on their global cardiovascular risk. Risk prediction models, such as the SCORE model (**S**ystematic **C**oronary **R**isk **E**valuation) used in Belgium and other European countries (see Figure 1), or the Framingham score (FRS), primarily used in the USA, allow the computation of such individual cardiovascular risk^{1, 2}. Individuals are then classified at low risk (<1% of CVD death at 10 years with the SCORE, or <10% of CVD event at 10 years for the Framingham score), intermediate risk (≥1-<5% in SCORE, 10-20% in FRS), or high-risk (≥5% in SCORE, >20% in FRS). Such stratification will orientate the appropriate clinical management with a more aggressive therapy in high-risk individuals and lifestyle recommendations alone in low-risk individuals^{3,4}. Correspondingly, in Belgium, statins are currently reimbursed only if SCORE≥5%.

However, there is increasing recognition of the inaccuracy of risk classification generated by these prediction models^{3, 5-7}. With a cut-off of 5% in 10-year mortality risk, the sensitivity of the SCORE model is 52% (13% for women, 60% for men) and its specificity is 85% (98% for women, 76% for men)⁸. With a SCORE calibrated for the Belgian epidemiology, the sensitivity and specificity are 77% (60% in women, 85% in men) and 72% (83% in women, 61% in men)⁹. This is particularly an issue for the



intermediate-risk group, as a more accurate evaluation of their CVD risk could result in a different clinical management, with a substantial impact on the incidence of CVD⁶, as well as on the appropriateness of healthcare resources utilization.

Figure 1 – SCORE chart: 10 year risk of fatal CVD by gender, age, systolic blood pressure, total cholesterol and smoking status



Source: De Bacquer D., Be Backer G.⁹

The performance of traditional prediction models could be improved by integrating novel markers of cardiovascular risk. In a previous KCE report, we reviewed the added predictive value of serum biomarkers, such as the C-Reactive Protein (CRP) or the B-type natriuretic peptide⁵. We assess here the added predictive value of another set of CVD risk markers, i.e. non-invasive markers of subclinical atherosclerosis^{10, 11} (see table 1); for more details on the measurement of these markers, please see the scientific report (section 1.1)).

Table 1 – Markers of subclinical atherosclerosis evaluated in this report

Flow-mediated dilation (FMD) measurement evaluates the function of the endothelium in the brachial artery. Endothelial dysfunction are considered to be the first stage of atherosclerosis. It can be measured using high-resolution ultrasound.

Aortic pulse wave velocity (aPWV) evaluates arterial stiffness. It is generally measured using applanation tonometry but can also be measured by Doppler ultrasound.

Ankle-brachial index (ABI) measures the presence of extremity peripheral artery disease. It is measured as the ratio of Doppler-recorded systolic pressures in the lower and upper extremities.

Carotid intima-media thickness (cIMT) is a structural anatomical measure of the thickness of the arterial wall which is used to detect early to late stages of subclinical atherosclerosis. It is measured by ultrasound.

Carotid plaques (CP) represent an advanced stage of atherosclerosis and are focal structures in the arterial wall that intrude into the lumen or areas of a homogeneously severely thickened arterial wall. They are detected and measured by ultrasound.

Coronary artery calcium score (CAC) can be measured by CT-scan¹². Calcium in the vessel wall reflects late stages of the atherosclerotic process. The quantity of calcium within the coronary arteries is typically scored as the area affected on the scan, multiplied by a weighting factor¹¹.



1.2. How to assess the added predictive value of CVD risk markers?

There are various metrics to assess the incremental predictive value of CVD markers⁵. The most useful for clinical purposes is the Net Reclassification Index (NRI). The NRI summarizes the net proportion of individuals with “correct” reclassification (e.g., those who develop CVD events who were up-classified, and those who do not develop events who were down-classified) and “incorrect” reclassification (those who develop events who were down-classified, and those who do not develop events who were up-classified)¹³.

$$\text{NRI} = (P_{\text{up}|D=1} - P_{\text{down}|D=1}) - (P_{\text{up}|D=0} - P_{\text{down}|D=0})^b$$

Patients who have a risk that is either just above or just below a treatment threshold might be moved across the threshold and have their management changed by the ascertainment of additional risk information. The NRI is of particular interest when applied exclusively to individuals classified in the intermediate-risk category by the reference prediction model, as it is mostly in that group that the refinement of the individual CVD risk could lead to a change in treatment decisions¹⁴. It is then referred to as clinical NRI (CNRI), and it is usually higher than the NRI as treatment uncertainty is greater in this specific subgroup. Using the CNRI would assume a 2-step screening strategy where individuals would be first classified based on the reference prediction model of CVD risk, and the CVD marker be measured only in intermediate-risk individuals⁵.

^b Where “D” denotes the event indicator, “up” an up-reclassification and “down” a down-reclassification. The null hypothesis of NRI=0 can be formally tested with a simple asymptotic test. Macros/program files for calculating NRI using Stata, SAS, and R can be found at <http://www.ucr.uu.se/downloads>

2. THE AVAILABLE EVIDENCE

Key messages

1. Coronary artery calcium score provided the highest incremental predictive value, with a CNRI ranging from 22% to 55%. The added value of the ankle-brachial index, aortic pulse wave velocity and carotid plaque in risk reclassification was lower than for coronary calcium (CNRI around 15%).
2. The clinical benefit of integrating these 4 markers into the Framingham risk score or to SCORE was not formally assessed in studies.
3. Economic evaluations were only identified for one marker: coronary artery calcium. The studies showed highly unstable results, sensitive to a number of assumptions, and in particularly to those relating to the price and efficacy of preventive treatments.

We carried out a rapid systematic review of the literature to assess the incremental predictive value, as measured by the net reclassification index, of markers of subclinical atherosclerosis when measured in addition to traditional risk prediction models in asymptomatic individuals with no history of CVD, i.e. in primary prevention.

We followed the international standards for performing systematic reviews, and details of our work can be found in the scientific full report (sections 2.1., 3.1, 4.1). The findings from our reviews were discussed with a panel of external experts. This report as well as the scientific full report was peer-reviewed by 3 additional external experts^c.

^c Please see the colophon for names of experts.



We retrieved 17 studies reporting the NRI and/or CNRI of the selected markers. High heterogeneity in study methods hampered the pooling of results. The vast majority of studies used the Framingham model as the base model. The incremental prediction performance of FMD could not be assessed given the paucity of data (and events) and contradictory findings (Table 2).

Table 2 – NRI and CNRI from atherosclerosis markers added to traditional risk factors (FRS)

Marker	Studies	Cohorts	N	Quality of evidence	NRI% (95%CI)	CNRI% (95%CI)	Subgroup
1. Flow-mediated dilation (FMD)	2 ^{3, 15}	1	3 026	Very low	NA ^d	NA	-
2. Ankle-Brachial Index (ABI) ^e	5 ^{3, 16-19}	19	46 082	Moderate	4.3 (0.0; 7.6)	15.9 (6.1; 20.6)	Men
					9.6 (6.1; 16.4)	23.3 (13.3; 62.5)	Women
3. Aortic Pulse Wave Velocity (aPWV) ^f	3 ^{17, 20, 21}	18	20 275	Moderate	4.9 (4.0; 5.9)	14.8 (12.4; 17.1)	-
4. Coronary Artery Calcium (CAC)	7 ^{3, 17, 22-26}	3	13 685	High	14.0 (NR)	21.7 (NR)	Lowest value
					25.0 (16; 34)	54.8 (41; 69)	Highest value
5. Carotid Intima-Media Thickness (cIMT) ^g	2 ^{27, 28}	16	48 793	High	0.8 (0.1; 1.6)	3.6 (2.7; 4.6)	-
6. Carotid Plaques (CP) ^h	3 ²⁸⁻³⁰	3	22 924	High	7.7 (2.3; 11.4)	17.7 (10.9; 24.7)	-

NA: Not applicable; NR: not reported

^d NA: Not applicable. The 2 studies were performed on the same study population but reported contradictory findings.

^e Results presented are from the study by Fowkes 2014¹⁶ which had a predominant weight (including 18 cohorts with 44 752 individuals)

^f Results presented are from the study by Ben-Shlomo et al.²⁰ which had a predominant weight (16 cohorts, 14888)

^g Results presented are from the study by Den Ruijter 2012²⁷ which had a predominant weight (14 cohorts with 45 828 individuals)

^h Results presented are from the study by Nambi 2010²⁹ which had a predominant weight (13 145 individuals)



The reclassification performance of the carotid intima-media thickness (cIMT) was low, and thus, this marker could unlikely serve as a useful CVD marker beyond traditional risk factors. The coronary artery calcium score (CAC) provided the best improvement in CVD risk reclassification. Improvements in CVD risk reclassification with the ankle-brachial index (ABI) and carotid plaques (CP) were lower than for CAC, but could still reclassify correctly around 15% of the intermediate risk group. The aortic pulse wave velocity (aPWV) may be in the same range as ABI and CP, but the evidence was less strong.

For markers with a substantial CNRI (CNRI>15%), we carried out a systematic review to assess the effectiveness and cost-effectiveness of using such markers in the clinical setting.

We found no studies designed to assess the clinical benefit of refining the individual CVD risk by the measurement of one of the 4 above-mentioned atherosclerosis markers (ABI, CP, CAC, and aPWV).

Economic evaluations were only available for CAC (n=5)³¹⁻³⁵. Only the two most recent ones based their clinical input on NRI data. Nevertheless, their overall results were extremely unstable because of the many assumptions not well backed-up by appropriate evidence which underlied the models. The resulting uncertainty hampered the formulation of any operational recommendations and was a direct consequence of the lack of long-term clinical data on patient outcomes after reclassification and consequent treatment.

3. DISCUSSION

Key message

In the absence of high quality studies on the clinical effectiveness of measuring atherosclerosis markers beyond the traditional cardiovascular risk markers, and the consequent uncertainty surrounding their cost effectiveness, the utilization of these markers is not recommended. Improving the predictive value of SCORE by the addition of easy to collect information in first-line consultation (e.g. BMI) is a priority.

We reported in a previous KCE report that measuring novel serum biomarkers to improved CVD risk classification beyond the SCORE model was not indicated⁵.

In this report, we found that four markers of subclinical atherosclerosis (ABI, CP, CAC, and aPWV) could help refining the individual CVD risk, particularly in individuals classified at intermediate risk by traditional models. CAC had the highest clinical reclassification index. Although the reclassification improvement was mainly assessed in comparison with the Framingham model, the results can be extrapolated to the SCORE. However, no study has formally assessed whether the measurement of CAC, or any other CVD marker, on top of the FRS or SCORE would result in better clinical management, including a better use of downstream testing and treatment, and in better health outcomes.

Despite the dearth of good quality evaluations, there is a common belief that refining individual CVD risk will lead to a better clinical management, and, hence, to better outcomes, through two main mechanisms.

First, it is assumed that current preventive therapies with statins, aspirin or other drugs, effectively reduce the additional CVD risk associated with the presence of a marker of atherosclerosis³⁶. Whether this assumption is correct is still a question mark. For example, the majority of existing drugs do not seem to lower aPWV in a blood pressure-independent manner. The benefits of long-term blockade of the renin-angiotensin system and of novel agents targeting elastic fiber cross-linking or calcification remain speculative³⁷.



Provision of aspirin to people with an unfavourable ABI was not proven successful³⁸. Even for CAC, which yields the highest CNRI and is the most studied atherosclerosis marker, good quality prospective studies on the clinical benefit are extremely rare. The only RCT to date assessing the effect of statin treatment on clinical outcomes in asymptomatic patients with significantly elevated CAC scores reported no significant effect³⁹. This negative result might be due to the limited sample size (i.e. N=1005), and it underlines the need of large-scale outcome trials to better ascertain the role of medical treatment in individuals reclassified at high CVD risk. Such trials should also evaluate the potential harms associated with CVD risk assessment, e.g. the risk attributable to radiation exposure associated with CAC scoring^{26,40}. Similarly, the outcomes of conservative approaches in individuals reclassified at low-risk should be properly assessed.

Second, measuring atherosclerosis markers could be a motivational tool for positive behavioural change, risk perception, and medication adherence. A recent systematic review suggested that CAC enhances medication utilization and adherence, with mixed results in other domains⁴¹. This review included 15 studies, only 3 of which were RCTs, and the overall quality of the evidence was low (notably, the main outcome was self-reported in most studies). At any rate, whether using a prognostic test such as CAC to improve medication adherence is ethically justified is a debatable question.

Our review highlights another major shortcoming related to the design of the studies on NRI. It is well acknowledged that the predictive value of traditional risk scoring models is modified by other parameters such as central obesity, parental history of premature CVD, sedentarity, or social deprivation. For example, a parental history of premature CVD doubles the CVD risk obtained by SCORE^{42, 43}. The European Guidelines on CVD prevention recommend to take these elements into account when using SCORE for assessing the CVD risk of an individual⁴⁴. Unfortunately, SCORE does not integrate formally these elements, nor did the base model of the studies included in our review. What would be the NRI of atherosclerosis risk markers if this would have been the case is thus unknown. Studies assessing the predictive value of models integrating all the CVD risk factors which can be easily measured, either by the anamnesis or a simple clinical examination, and a revision of SCORE are urgently needed. Such studies should be based on new cohorts for two reasons. The first one is obvious: the information required to upgrade SCORE was not collected in past

cohorts. The second reason is that historical cohorts are not adapted for such an upgrade: unmeasured risk factors may have changed over time, such as salt and trans-fat intakes, and modern therapy (e.g. statins) may change the quantitative relationship between risk factors and CVD outcomes⁴⁵.

Without such evidence, i.e. the NRI of novel CVD markers when the base model integrate additional clinical information and the risk-benefit balance of adding novel CVD markers for measuring individual CVD risk, we cannot recommend the utilization of CVD markers in clinical practice. Meanwhile, first-line recommendation in asymptomatic subjects remains a healthy lifestyle including smoking cessation, regular physical activity, weight control, and a healthy diet, with medical treatment for controlling hypertension, high blood cholesterol and diabetes when appropriate. Clinical skills remain central to adapt risk evaluation and management according to each individual situation.



■ RECOMMENDATIONSⁱ

To the clinicians, to the Scientific Associations of Doctors

- Given the current lack of evidence on the clinical benefit of measuring markers of subclinical atherosclerosis beyond traditional CVD risk factors, we do not recommend their utilization in routine practice.

Recommendations for further research

- It is advised to initiate, in collaboration with the other European cardiology societies, the evaluation of an upgraded SCORE model. This new SCORE would integrate additional risk factors easily assessed during first-line medical consultation, such as central obesity, sedentarity, or social deprivation.

The clinical effectiveness of markers of subclinical atherosclerosis beyond traditional CVD risk factors should be assessed in high-quality studies against this new SCORE.

ⁱ The KCE has sole responsibility for the recommendations.



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COLOPHON

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Authors:	Dominique Roberfroid (KCE), San Miguel Lorena (KCE), Dominique Paulus (KCE)
Reviewers:	Mattias Neyt (KCE), Roos Leroy (KCE)
External experts:	Johan De Sutter (Universiteit Gent), Bernhard Gerber (UCL), Geert Goderis (KU Leuven), Alexandre Persu (UCL), Ernst Rietzschel (Universiteit Gent), Muriel Sprynger (CHU-ULG), Jean-Claude Wautrecht (ULB)
External validators:	Christian Brohet (UCL), Olivier Descamps (Polyclinique du Centre Hospitalier de Jolimont), Guy De Backer (Universiteit Gent)
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Layout:	Ine Verhulst

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