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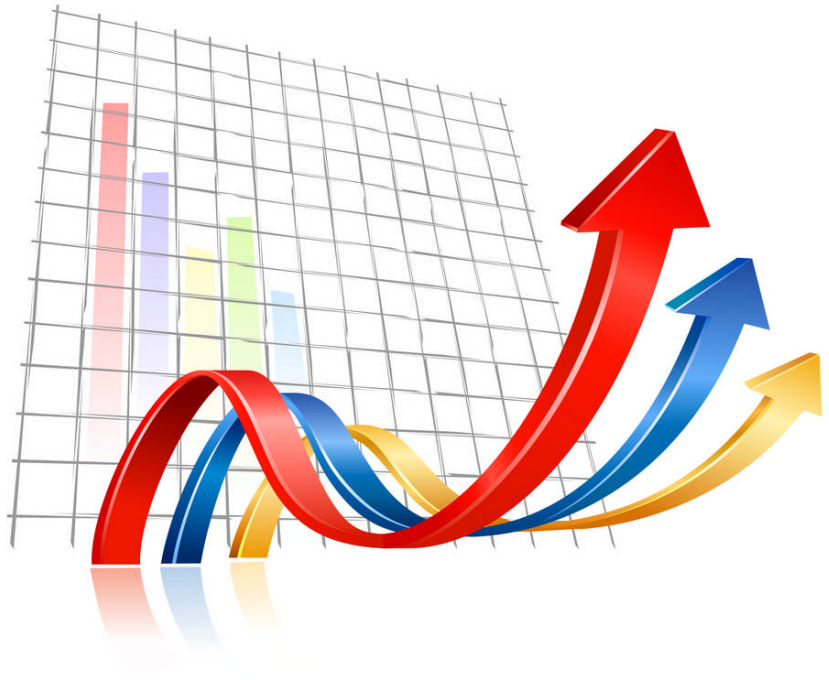
Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

NOVEL SERUM BIOMARKERS FOR THE PREDICTION OF CARDIOVASCULAR RISK

SYNTHESIS



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KCE REPORT 201CS
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SYNTHESIS

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FOREWORD

For years, and even decades, health promotion has hammered the same message into us: to prevent a myocardial infarction or stroke, it is necessary to stop smoking, eat less and especially less fatty or salty foods, moderate the consumption of alcohol, engage in physical exercise, ... One might expect that these messages have gradually become common knowledge. Yet! Our body mass index is not diminishing and cigarettes are far from becoming extinct. Let's face it, prevention, cardiovascular prevention in this case, does not match our idea of "enjoying life". Moreover, in today's society our compulsion for 'more' is not compatible with 'austerity', and this, together with all the marketing surrounding the pleasures of life, does not facilitate the tasks of health promoters. If only we could identify the people most vulnerable to heart disease, and thereby forgive the others for their penchant for gastronomy, oenology or anything else!

If this hope is now already partially fulfilled, it is thanks to the residents of Framingham, a small town of Middlesex, Massachusetts, United States. Since 1948, a cohort of people in this town was carefully monitored - for decades – in order to identify the main risk factors for cardiovascular disease. The Framingham Heart Study, and other studies which have emerged since, have generated easy-to-implement risk assessment systems which are now widely used in everyday clinical practice.

The risk score most commonly used in our country is known - unsurprisingly – as SCORE (Systemic Coronary Risk Evaluation), and facilitates the risk prediction of suffering a fatal cardiovascular event in the next 10 years. Unfortunately, this instrument is far from perfect: some people fall through the cracks and are still victims of a fatal cardiovascular event despite being categorised as low risk individuals. Many more, are categorised as having a higher risk than their actual true risk, and are not only unnecessarily alarmed, but also often wrongly medicalised. Is there not a more accurate test that could allow us to "get it right"? This is indeed the main focus of this report.

However, – a preliminary question would be- what exactly does "getting it right" mean? This question led us to also explore the latest developments in the field of statistics, which is in itself a useful contribution of this report. With regard to the merits of the new tests coming onto the market, the harvest remains sparse. It appears that it would be better to first optimize the already existing tools. This is a door that clinicians themselves, via their scientific societies, will need to open. The stakes are high, and we hope that this work will modestly put a shoulder to the wheel.

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ABSTRACT

Background

Cardio-vascular diseases (CVD) remain the most frequent cause of mortality in our population, and one quarter of CVD deaths occur before the age of 75. Risk prediction models, such as the SCORE (Systematic COronary Risk Evaluation), are key components of prevention strategies by allowing the identification and appropriate management of individuals most at risk. Whereas these models are based on conventional risk factors, such as age and hypertension, novel serum biomarkers of CVD are increasingly available. Whether these biomarkers can improve the predictive performance of conventional risk models is unknown.

Methods

A systematic literature review was performed on the predictive increments and cost-effectiveness of novel CVD biomarkers for the general screening of CVD in asymptomatic individuals.

Results

Seventeen studies provided information on the predictive increment of CVD biomarkers. Evidence mostly concerned markers of inflammation (e.g. C-reactive protein (CRP) and fibrinogen) and lipid-related markers (e.g. apolipoprotein A1 and phospholipase A2). The body of evidence on biomarkers pertaining to other patho-physiological pathways (e.g. homocysteine and N-terminal pro B-type Natriuretic Peptide (NT-proBNP)) was more disparate. The most investigated CVD biomarker was CRP (in 12/17 studies). The predictive increment of biomarkers was mainly evaluated against the Framingham score model (in 13/17 studies).

The Net Reclassification Improvement (NRI) summarizes the net proportion of individuals with correct reclassification (i.e. those who develop CVD who were reclassified in an upper risk category with the new model, and those who do not develop CVD who were down-classified) minus the ones with incorrect reclassification. Adding CRP to the Framingham score model quite consistently resulted in a significant, albeit modest increase of NRI (range: 1.5% to 11.8%). However, the NRI was higher when only individuals classified in the intermediate-risk category by the conventional prediction model were considered (range: 6.5% to

31.4%), as can be done in a 2-step screening strategy. The predictive increment of lipid-based markers was assessed in 6 studies. None of the lipid-based biomarkers significantly improved the risk reclassification in comparison to conventional models which already included total cholesterol and HDL-cholesterol. Among other biomarkers, there is emerging evidence that NT-proBNP, a marker of vascular function, could substantially improve the prediction performance of the conventional model (NRI ranged from 0.4% to 13.3%; 5 studies).

We retrieved no studies assessing the benefit of integrating novel biomarkers in conventional risk prediction models for motivating lifestyle changes or for guiding therapy. Neither did we retrieve robust cost-effectiveness evaluations.

Conclusion

Whether the modest prediction increment provided by CRP or NT-proBNP is clinically significant is unknown as evidence is lacking on the impact of using such biomarkers on risk management (risk communication, lifestyle intervention, or drug therapy) and patient outcomes. It is also unknown how the prediction increment differs from the one that could be obtained by adding conventional risk factors currently not integrated in prediction algorithms (e.g. food intake, physical activity or precise tobacco consumption levels). Given these elements, the systematic measurement of a specific biomarker to complement conventional risk prediction models cannot be recommended at this stage.

SYNTHESIS

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1. BACKGROUND

Cardio-vascular diseases (CVD) remain the most important cause of mortality in our population, as about a third of overall deaths are associated to CVD. In Belgium, approximately 10% of cardiovascular deaths occur before the age of 50, 23% before the age of 75. Primary prevention is thus crucial to reduce those premature CVD deaths. Risk prediction models are key components of prevention strategies by allowing the identification and appropriate management of vulnerable individuals. In Belgium, such clinical management is tailored to individuals on the basis of their absolute risk of a fatal CVD event over the next 10 years. This 10-year risk can be computed with the help of the SCORE model (Systematic COronary Risk Evaluation) based on strong conventional predictors of CVD which are age, sex, smoking, systolic blood pressure, and plasma cholesterol concentrations[1,2], and calibrated to account for the mortality risk in our country.

Box 1

SCORE

Algorithm calibrated to estimate the 10-year risk of first fatal CVD event in apparently healthy Belgian adults with no signs of clinical or pre-clinical disease. The CVD risk is predicted on the basis of age, sex, smoking, systolic blood pressure and plasma cholesterol concentrations. A SCORE chart can be downloaded from:

http://www.escardio.org/communities/EACPR/Documents/score-charts-2012.pdf

Sensitivity

Proportion of individuals with a first fatal CVD event who had been correctly identified by SCORE as being at increased risk of such event (true positives).

Specificity

Proportion of individuals with no fatal CVD event who had been correctly identified by SCORE as being at low risk of such event (true negatives).

ROC curve *(Receiver Operating Characteristics)*

A graphic in which the proportion of true positives (sensitivity) is plotted against the proportion of false positives (1-specificity) for different cut-off points of the diagnosis test. The area under the ROC curve increases with the discriminating power of the test, i.e. with its ability to distinguish individuals who will develop CVD from those who will not.

However, developing screening strategies that safely, accurately, and cost-effectively identify individuals at risk for CVD well before symptoms appear remains a challenge, partly because these conventional cardiovascular risk factors do not fully explain inter-individual variation in cardiovascular risk. For example, 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)[3]. The measurement of “novel” biomarkers could thus be an important component in the fight against CVD by improving the performance of risk prediction models. Potential biomarkers are increasingly numerous, fuelled by technological advances in genomics, proteomics, and noninvasive imaging[4,5,6,7].

This report focuses on the predictive increment of serum biomarkers and has 3 objectives:

1. Synthesizing the statistical methods for assessing the added value of a novel risk marker.
2. Identifying CVD biomarkers that improve the risk prediction of models based on conventional risk factors in apparently healthy individuals.
3. Reviewing the evidence on the health benefit and cost-effectiveness of using CVD biomarkers identified in stage 2, if any.

2. METHODS

The analysis is based on a systematic literature review of the predictive increments and cost-effectiveness of novel CVD biomarkers being added to any conventional risk prediction models. We included any novel CVD biomarker for which information on risk reclassification was available. Although high density lipoprotein cholesterol (HDL-C) is not considered a novel biomarker anymore, we have included it in our review because it has only recently been proposed for inclusion in the SCORE algorithm[3]. We followed the recommendations of the PRISMA statement for high-quality systematic reviews[8].

3. RESULTS

3.1. Metrics for assessing the predictive increment of novel biomarkers

Although it is obvious that a statistically significant association between a biomarker and a disease is a necessary condition for a biomarker to be clinically relevant and useful in risk prediction, such an association is not sufficient[7]. The predictive model including the biomarker should be well calibrated, yield increased discrimination of individuals and allow subject reclassification in risk categories meaningful for risk communication and/or clinical management.

Calibration refers to the alignment between the risk predicted by the model and the actual CVD risk encountered by the subject[4].

Discrimination is the ability of a predictor to distinguish those who will develop a disease from those who will not. Until recently discrimination has been the main metric used to compare predictive models. This is done by testing the difference in the area under the Receiver Operating Characteristics (ROC) curve of 2 models (see Box 1). The value of a new biomarker can be gauged by determining how much higher the area under the ROC curve (AUC) becomes by combining the novel biomarker with conventional risk factors. One difficulty encountered with the AUC statistics is its relative insensitivity to improvement, particularly when the conventional prediction model already has a high value. Another more sensitive metric to measure how average sensitivity improves without sacrificing average specificity has recently been proposed: the integrated discrimination improvement (IDI)[9] (see Box 2).

Box 2

Integrated Discrimination Improvement

$IDI=(P_{new,events} - P_{old,events}) - (P_{new,nonevents} - P_{old,nonevents})$

where:

- $P_{new,events}$ is the mean of the new model-based predicted probabilities of an event for those who develop events,

- $P_{old,events}$ is the corresponding quantity based on the old model,

- $P_{new,nonevents}$ is the mean of the new model-based predicted probabilities of an event for those who do not develop events and

- $P_{old,nonevents}$ is the corresponding quantity based on the old model.

Net Reclassification Improvement

$NRI= (P_{up|D=1} - P_{down|D=1}) - (P_{up|D=0} - P_{down|D=0})$

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.

Reclassification refers to the ability of a test to change an individual's risk classification. It is a very relevant concept in clinical practice because treatment guidelines typically refer to predetermined risk categories. Subjects with a calculated SCORE ≥5% for 10-year risk of fatal CVD are considered at high risk and qualify for intensive advice and possibly for drug therapy, whereas those with a SCORE between ≥1% and <5% and a SCORE<1% are considered respectively at intermediate (or moderate) and low risk. Reclassification can be described by estimating the proportion of individuals in a population who are appropriately reclassified based on the additional measurement of the new biomarker under scrutiny. A new metric, the net reclassification improvement (NRI) (see Box 2), summarizes the net proportion of individuals with "correct" reclassification (e.g., those who develop CVD who were up-classified, and those who do not develop CVD who were down-classified) and "incorrect" reclassification (those who develop CVD who were down-classified, and those who do not develop CVD who were up-classified)[9].

The ascertainment of additional risk information might be even more relevant in individuals classified at moderate CVD risk by means of the conventional model, because the clinical management of such individuals is often less well-defined than for patients well above the treatment threshold or at very low risk[10]. This is why some authors have also introduced the concept of clinical NRI (CNRI), i.e. the amount of reclassification observed only in individuals classified in the intermediate-risk category by the conventional prediction model[11]. The advantage is that it calculates the amount of improvement offered by a strategy where only the individuals for whom the treatment decision could be changed by measuring a biomarker are considered (2-step screening strategy).

Calibration, discrimination and reclassification are complementary metrics for assessing the added value of a biomarker[10]. However, among these statistics appropriate reclassification of patients in categories which might impact on the individual risk management appears to be crucial for both patients and clinicians[9], and thus, we will focus specifically on this metric here.

3.2. Predictive increments of serum biomarkers

Seventeen studies provided information on the predictive increment of CVD biomarkers. Evidence mostly concerned two main groups of biomarkers: markers of inflammation (C-reactive protein (CRP), fibrinogen, leukocyte count), and lipid-related markers (HDL-cholesterol, apolipoprotein A1, apolipoprotein B1, phospholipase A2, lipoprotein(a)). Biomarkers pertaining to other patho-physiological paths were also investigated but with much less consistency: homocysteine (marker of oxidative stress), N-terminal pro B-type Natriuretic Peptide (NT-pro BNP) (marker of vascular function and neurohumoral activity), acid uric, van Willebrand antigen, etc… The most investigated biomarker across studies was CRP (data on CRP reported in 12/17 studies). The predictive increment of biomarkers was mainly evaluated against the Framingham score model (FRS), which includes diabetes and treatment of hypertension in addition to the items included in the SCORE model and estimates the 10-year risk of a first CVD event (whether fatal or not).

CRP

Adding CRP to the FRS model quite consistently resulted in a significant albeit modest overall reclassification of study participants (NRI ranged from 1.52% to 11.8%) for the predicted 10-year categories of low (<10%), intermediate (10% to <20%), and high (≥20%) risk of first CVD event. CNRI was consistently greater than the NRI (range: 6.5% to 31.4%). For example, in Kaptoge et al., by far the biggest study identified in this review, with 166 596 individuals from 52 prospective cohorts, the CNRI among those who developed a cardiovascular event was 23.8%, whereas the CNRI in non-cases was 6.7%[12]. NRI was also consistently higher when the event under scrutiny was coronary heart disease versus all cardiovascular events, the lowest NRI being observed for stroke. Changes in the AUC provided results consistent with those based on NRI, whereas IDI was rarely reported.

Lipid-based markers

The predictive increment of lipid-based markers was assessed in 6 studies totaling 447 499 individuals. Studies assessing the predictive increment of HDL-cholesterol consistently reported an NRI significantly different from 0, although there were large variations in the size of this increment from 1.7%[12] to 12.1%[9] (4 studies). Such variations may be explained by different outcomes (CVD deaths vs. coronary heart disease) and various 10-year risk categories. The predictive increment of HDL-C in intermediate-risk individuals could be recomputed in only one study[9], yielding a CNRI much higher than the NRI (CNRI in cases=9.5%; CNRI in non-cases=13.3%).

None of the other lipid-based biomarkers (apolipoproteins A1 & B1, lipoprotein(a)) significantly improved the risk reclassification in comparison to existing models which already included total cholesterol and HDL-cholesterol.

Other CVD biomarkers

Four additional original studies assessed the predictive increment of other CVD biomarkers, among which NT-pro-BNP, homocysteine, uric acid, and troponin I. Among those biomarkers, NT-proBNP, a marker of vascular function, was the only one substantially improving discrimination and reclassification when added to FRS, in 4 out of 5 studies (NRI ranged from 0.4% to 13.3%).

Overall, the quality of the evidence was moderate. Validation in a population different from the one used to establish the prediction model was seldom used[5], although several studies corrected their estimates for over-optimism. A selection bias in the population under scrutiny was often difficult to assess: characteristics of individuals with missing measurements were rarely compared to those of the eligible study population, and existence of lost-to-follow up was poorly described.

We retrieved no study assessing the benefit of integrating novel biomarkers in conventional risk prediction models for motivating lifestyle changes or for guiding therapy.

3.3. Cost-effectiveness of CVD biomarkers

In spite of the lack of robust clinical evidence in favour of a strong predictive increment by use of the biomarkers reviewed, cost-effectiveness studies are increasingly published in this field. It is therefore important to review and critically appraise such studies, to assess how methodologically robust they are and what specific data inputs remain a challenge. We included 7 full primary economic evaluations with CRP being the main focus in as many as five studies[13-17]. Despite the fact that, overall, the economic evaluation studies tended to show that biomarkers, and more specifically CRP, could be cost-effective for the primary prevention of cardiovascular disease at thresholds for the incremental cost-effectiveness ratio lower than US$50 000 per QALY, only the long-term economic evaluation by Lee et al.[17] taking into consideration both the screening methods and the long-term treatment that could derive from them, compared the result of a strategy using CRP testing to a conventional predictive model (i.e. FRS). Their results showed to be highly sensitive to the rate and severity of adverse events experienced when following statin treatment as well as to the effects on risk reduction from statin therapy in patients with normal CRP levels. Despite the important uncertainties surrounding this evaluation and its results which make the internal validation of the study poor, the possibility of adapting the model once new data become available is an important strength.

4. DISCUSSION AND CONCLUSIONS

This review focused on the predictive increment of novel biomarkers for the general screening of CVD in asymptomatic individuals. Although the use of some biomarkers has been proposed to identify high risk individuals in specific sub-populations (e.g. measurement of lipoprotein(a) in individuals with a family history of premature CVD or hypercholesterolaemia[18]), reviewing the evidence for such sub-population screening was out of the scope of this report.

CRP has been the most studied CVD biomarker so far. Overall, the predictive increment of CRP was relatively modest (from 1.52% to 11.8%) in comparison with the risk prediction based on the conventional factors included in the FRS. A number of hypotheses can be put forward to explain such modest added value in spite of the strong evidence that CRP is associated with CVD. First, CRP may not be a direct risk factor of CVD[19,20] but rather associated with the development of other CVD risk factors such as high BMI[21], hypertension[22], diabetes[23], or smoking. These factors are already captured in the FRS. Whether CRP is on the causal pathway or a mere covariate of these other risk factors, its contribution to prediction models is subsequently reduced. Second, the prediction models integrate CRP as a continuous variable while CRP is log-normally distributed in the general population[24]. A substantial proportion of all CVD events occur among the large number of individuals with near average levels of CRP. It might be more appropriate to use a cut-off point for CRP above which the risk of CVD would greatly increase. Third, accuracy and precision of measurements might be suboptimal. Different laboratory techniques may yield results with various levels of accuracy[25]. The day to day variability of CRP measurements must also be accounted for particularly in view of the fact that 10-year CVD probability is usually based on a single measurement[26].

In individuals identified at moderate 10-year risk of CVD by the conventional model, the measurement of CRP resulted in a much greater clinical net reclassification improvement (CNRI) than previously reported. One of the reasons for this higher CNRI might be that a proportion of intermediate-risk individuals classified by the conventional model have indeed an absolute CVD risk close to the upper bound. Unfortunately, none of the studies included in our review assessed how the actual individual CVD risk within usual risk categories (e.g. 10%-20% risk of CVD in the next 10 years) influenced the reclassification. Another explanation for a CNRI greater than the NRI would be that in intermediate-risk individuals, other risk factors such as smoking or age are less prevalent, letting more room for a larger contribution of CRP to predictive models.

Besides CRP, we found consistent evidence that HDL-cholesterol, which is already integrated in most CVD risk prediction models, improves CVD risk prediction independently of total cholesterol, although the NRI was modest across studies. Other lipid-based biomarkers presented no added value. There is also emerging evidence that NT-proBNP could be a biomarker allowing a better discrimination and classification of individuals. The above considerations on the information and shortcomings of CRP studies, however, also apply to these biomarkers.

Whether the modest prediction increment provided by CRP or NT-proBNP is clinically significant is unknown as evidence is lacking on the impact of using such biomarkers on risk management (risk communication, lifestyle intervention, or drug therapy) and patient outcomes. Consistently, we retrieved no robust cost-effectiveness evaluation. Given these elements, we strongly recommend not to measure novel biomarkers for screening for CVD in asymptomatic individuals. This is in line with the recent recommendations of the European guidelines on cardiovascular disease prevention[27]. It is also important to emphasize here that any genuine patient-based appraisal of CVD risk should account for individual characteristics (such as diet quality or psychosocial factors) which are not included in prediction algorithms, and are unlikely to ever be because their standardization is difficult. Clinical skills remain central to adapt risk evaluation and management according to each individual situation.

We also found consistent evidence that CNRI could be substantial. This opens avenues for a 2-step screening, biomarkers being measured only in patients at intermediate CVD risk according to conventional risk models. This would allow to detect more high-risk patients than with conventional risk models, and to potentially impact their clinical management and health outcomes, for example by adopting more stringent therapeutic targets for conventional risk factors such as hypertension. However, there is not sufficient evidence to this date to recommend one specific biomarker or combination of biomarkers over the others, and not enough evidence on the benefit of such 2-step screening. It is also unknown how the prediction

increment differs from the one that could be obtained by conventional risk factors currently not integrated in prediction algorithms (e.g. food intake, physical activity or precise tobacco consumption levels). Until such evidence becomes available, the systematic measurement of biomarkers in individuals at intermediate 10-year risk of fatal CVD, cannot be recommended, although medical doctors may consider useful to refine the risk assessment of their individual patients[27,28].

It is interesting to note that conventional risk factors have not yet been used to their full potential. Conventional risk factors have been chosen because they were available in the majority of the cohort studies which served to establish the prediction models and because their definition was quite standardized. This also facilitates the utilization of these models in the form of clinical scores. Such approach generates two difficulties though; First, the dose-response gradient of risk factors is not accounted for. For example, the CVD risk of smoking 5 cigarettes a day for 5 years might be very different from smoking 25 cigarettes per day for 25 years. Second, some risk factors on which information is easy to collect during clinical consultation are not included. This is for example the case of physical inactivity, or family history of CVD, which is included in some prediction models, but not in FRS or SCORE. So-called conventional risk factors still need to be further assessed and integrated.

Lastly, we have detected a number of inconsistencies between the current European guidelines for assessing CVD risk and the SCORE tool. First, although it is well acknowledged that LDL-cholesterol is the main lipid-related risk factor of CVD and that HDL-cholesterol is cardio-protective, the paper chart of SCORE still stratifies the CVD risk by total cholesterol concentration[a], and in the electronic equivalent, HeartScore, entering data on HDL-cholesterol is still optional. Second, a corrective factor has been proposed to account for a family history of premature CVD in the SCORE[28]. This corrective factor is however not retrieved in the SCORE charts or in HeartScore. Harmonization of SCORE (paper and electronic versions) with European guidelines would certainly enhance clarity for the clinicians on the field.

[a] SCORE charts by level of HDL-cholesterol can be found in the addenda of one European guidelines[28].

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RECOMMENDATIONS[b]

To medical practioners

- **It is recommended to use the SCORE model during medical consultations to evaluate the total risk of first fatal cardiovascular event in apparently healthy individuals. Measuring biomarkers other than HDL-cholesterol is not indicated.**

To the Belgian Cardiology Society, Domus Medica and the SSMG

- **It is advised to harmonize the various versions of the SCORE model currently available (either in paper or electronic format), to make them consistent with European recommendations for CVD risk assessment, and to circulate an updated version among medical practitioners.**
- **It is advised to initiate, in collaboration with the other European cardiology societies, an upgrade of the SCORE model so as to integrate conventional risk factors which can be easily assessed during medical consultation, such as a family history of CVD or sedentarism.**

Recommendations for future research

- **The added value in terms of risk management and outcomes of a two-step screening model, in which CRP or NT-proBNP are tested in individuals with an intermediate risk on the initial SCORE evaluation should be further investigated.**

[b] The KCE has sole responsibility for the recommendations.