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Assessments tools for risk prediction of cardiovascular diseases

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Scientific background

Cardiovascular diseases caused 358,684 deaths in Germany 2007 and have an enormous epidemiological importance. Cardiovascular diseases are also of extreme relevance from the health-economic view. The costs of cardiovascular diseases 2006 were nearly 35 billion euros.
It is assumed that cardiovascular morbidity and mortality are modifiable through different prevention interventions. Besides of the population-targeted prevention interventions the individual-targeted (e. g. drug-based) prevention interventions are usually indicated in persons with an increased total risk. For the selection of persons with an increased total cardiovascular risk, so-called risk prognosis instruments are constructed and used.
Risk prognosis instruments in form of equations, point scores and table charts (risk charts) are constructed through a statistical analysis of the data derived from populations. These instruments enable to estimate a risk for a cardiovascular event and/or a survival probability without this event in dependence of the values of the risk factors. Risk prognosis instruments may be also represented graphically, for example as nomograms.
There are a number of different risk prognosis instruments. Unfortunately, these instruments are based on different primary studies or databases which usually do not include the German population. The transferability of these prognostic instruments on the populations not examined in these data sources as well as the comparability of the validity of these prognostic instruments is questioned.

Research questions

The evaluation addresses the following questions:

- Which instruments for the risk prediction of cardiovascular diseases are available?
- What is the evidence for a transferability of the available risk prognosis instruments for cardiovascular diseases on populations not involved in the prognostic study?
- To what extent are the available methods for risk prediction of cardiovascular diseases comparable?

Methods

Information sources and search strategy

A literature search was performed in the most important medical electronic databases (MEDLINE, EMBASE etc.) in April 2008. The search strategy was restricted to the years beginning from 2004 as well as to the languages German and English. Moreover, an expanded hand search was performed to identify publications on prognostic instruments for cardiovascular diseases as well as publications on the external validity of different prognostic instruments.

Within the scope of the

Bundesministerium
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Inclusion and exclusion criteria

Publications on prognostic instruments for cardiovascular diseases in persons without previous cardiovascular disease as well as publications addressing external validation and/or the comparison of different prognostic instruments were included in the evaluation. The instruments focusing on specific patient risk groups were not considered. Discrimination and calibration were used as accuracy criteria.

Data analysis and information synthesis

Systematic surveys and primary publications on prognostic instruments as well as publications on the evaluation of the validity and the comparability of different prognostic instruments were considered as an information sources. The information synthesis was performed qualitatively.

Results

Results of the literature search

The systematic literature search yielded 734 hits. 116 publications were selected for the review in full text and were examined for the inclusion in the evaluation. Three systematic reviews, eight publications with descriptions of prognostic instruments and 13 publications addressing the validity of the prognostic instruments were identified through the literature search. The hand search in the reference lists of the relevant articles revealed 30 further publications with descriptions of prognostic instruments and 16 further publications addressing the validity of the prognostic instruments.

Risk prognostic instruments

Most risk prognosis instruments are based on the Framingham cohort of the USA, almost all other on European cohorts, mostly on British or Italian. Only the PROCAM study is completely based on the German reference population. Two other instruments, the SCORE Charts for Germany and the WHO/ISH-charts for the European risk region EUR-A, are partially based on this population. Population-based, patient-based and occupational cohorts, in some studies only men or women, were used as a reference population for the derivation of the prognostic instruments.

Almost all prognostic instruments use the variables sex, age, smoking and one or several parameters on lipid status and blood pressure. Many prognostic instruments use the variables diabetes mellitus and/or blood glucose for the risk calculation, several instruments the variables left ventricular hypertrophy on electrocardiogram (ECG), body-mass-index, antihypertensive therapy and some prognostic instruments other variables. The multinational studies stratify their prognostic instruments also regionally. Mostly, only five to six prognostic variables are used in the prognostic instruments.

The most important endpoints are death from coronary heart disease, death from cardiovascular disease, coronary heart disease and coronary event (death, myocardial infarction, in some studies also angina pectoris and/or coronary revascularization) as well as cerebrovascular event (stroke, in some studies also transient ischemic attack), cardiovascular disease and cardiovascular event (coronary event, cerebrovascular event some studies also intermittent claudication and/or heart insufficiency). The time span for predicted events comprises mostly ten years.

Constructing the scores, three different statistical regression models, namely logistic, Weibull or Cox regression models, are used for the data analysis of the reference population. A stepwise regression model is selected in all procedures.

External validity of the risk prediction instruments of cardiovascular diseases

Data on calibration of the prognostic instruments (a quotient of the predicted by the observed risk) are presented in nearly half of the studies. Only a single study shows a level of calibration between 0.9 and 1.1. In all three studies from Germany data on the calibration of the prognostic instruments are missing.
Many studies on the transferability of the prognostic instruments show an AUC value for the discrimination (value for the correct differentiation of persons with different risk levels; AUC = area under the curve; best value 1.0) between 0.7 and 0.8 for different prognostic instruments (sufficient discrimination), few studies an AUC value between 0.8 and 0.9 (good discrimination) and no study an AUC value of more than 0.9 (excellent discrimination).
From studies addressing the discrimination of the prognostic instruments (different Framingham equations) on the German population all but one find AUC values between 0.73 and 0.78 (sufficient discrimination). Studies evaluating the external validity of the new prognostic instruments such as PROCAM (2007) and SCORE-Germany, derived from the German population, are lacking.

Comparison of the validity of different risk prediction instruments of cardiovascular disease

The comparison of the validity of different risk prognostic instruments on the derivation cohort of one of these prognostic instruments (accuracy) showed a trend for a better calibration and a better discrimination for the prognostic instruments calculated on the bases of the derivation cohort.
The comparison of the validity of different risk prognostic instruments on the validation cohort of one of these prognostic instruments (reproducibility) found a trend for a better calibration and a better discrimination for the prognostic instruments calculated from the data of the corresponding derivation cohort.
Comparing the prognostic instruments on other populations (transferability), the newly derived Framingham prognostic instruments showed a slightly better discrimination in comparison with previously calculated instruments. The value of the German prognostic instrument PROCAM 2002 in comparison with Framingham instruments for the European population is not clear. No studies comparing different prognostic instruments on the German population exist.

Discussion

Literature search

In spite of an extended search strategy in the most important medical databases, missing of relevant articles addressing the theme of the report due to the problem of the complexity of the literature search for prognostic studies is possible.

Risk prognostic instruments

The representativity of the study participants for the corresponding total population is questionable in many derivation studies of the risk prognostic instrument. The reference populations in the studies are not homogenous concerning the disease stages.
The high number of rarely used variables in the risk prognostic instruments suggests that the relevance of these variables for the risk prognosis is not clearly estimated.
The use of endpoints comprising clinical events is more subjective than the exclusive use of the mortality; however, it has clearly higher clinical and social importance for the individual.

The Cox regression should be preferred for the derivation procedure, because this regression analysis can calculate the risk at different follow-ups and enables a relatively simple adaptation of the model for other populations.
In spite of the reduction of the precision, transforming a risk equation to a point score and to a risk chart, a risk chart permits a better illustration of the actual and the targeted risk of a person compared with a value directly determined from the risk equation.

External validity of the risk prediction instruments of cardiovascular disease

Different components of the transferability, mostly geographic, historic as well as methodological and disease spectrum, were evaluated in the presented studies on the external validation. The geographic transferability appears to be the most important of these components because of the substantial differences in the cardiovascular morbidity and mortality between different countries and regions.
The populations underlying the prognostic instruments in most studies were recruited many years ago; therefore, the prognostic instruments derived from these populations may be not transferable on the currently living populations.
It is not to be expected that the slightly different measurement methods and disease spectrums in different studies relevantly limit the transferability of the prognostic instruments.
An exact threshold value for a good or poor calibration is not clearly determined in the literature yet. In order to restrict the problem of poor calibration, the average values of the risk factors and the average event rates of the reference population used in the prognostic instrument should be replaced in the equations by the corresponding parameters of the predicted population (recalibration).
An exact and plausible threshold value for a good or poor discrimination of the prognostic instruments is also not stated in the literature. The differentiation in excellent, good, sufficient, weak and very weak discrimination is subjective. Moreover, it is recommended to perform the evaluation of the discrimination only after the recalibration of the instruments for the corresponding population.

Comparison of the validity of different risk prediction instruments of cardiovascular disease

The higher validity of the risk prognostic instruments examined on the derivation cohort than on the validation cohort of these prognostic instruments and especially on other populations may be explained due to the considerable geographic variance of the cardiovascular morbidity and mortality.
The lack of studies on the comparison of different prognostic instruments on the German population enables no statements on their comparability.

Conclusions

The identified instruments for the risk prediction of cardiovascular disease are not sufficiently validated on the German population; their use can lead to false risk estimation for a single person. Therefore, the existing prognostic instruments should be used for the informed decision-making and for the therapy selection in Germany only with critical caution. Studies on external validation of the prognostic instruments and on the comparison of different prognostic instruments on the German population (if possible after previous recalibration) as well as randomized studies on therapeutic consequences and on clinical benefit of the prognostic instruments are needed.