Prognostic value, clinical effectiveness and cost-effectiveness of high sensitivity C-reactive protein as a marker in primary prevention of major cardiac events


Background

Ischemic heart diseases remain one of the most frequent causes of morbidity and mortality in Germany and throughout the developed world. In a substantial portion of patients (≥ 25 %) with coronary heart disease (CHD), a myocardial infarction or sudden cardiac death without prior symptoms is the first manifestation of the disease. The risk of CHD can be lowered by changing behaviour alone or in conjunction with medical therapy. The choice of preventive action depends on an estimation of the long-term risk of suffering a serious cardiovascular event (e.g.; death, myocardial infarction). For the prediction of these events, well-known risk factors for CHD such as age, sex, smoking, hypertension, increased blood lipid level and co-morbidities such as diabetes mellitus are used. The question arises as to whether additional risk factors should be used in order to better predict the occurrence of CHD and stratify risk groups. In the pathogenesis of arteriosclerosis a central role is assigned to inflammatory processes. The high-sensitivity C-reactive Protein (hs-CRP) is a biomarker that indicates systemic inflammation processes. Hs-CRP-assays have been proven to be appropriate in practice because of sufficient stability, precision and availability of standards for calibration. Therefore, hs-CRP can be considered a potential candidate. Does the additional information gained through the measurement of hs-CRP lead to a clinically relevant improvement in risk prediction as compared to risk prediction based on traditional risk factors that are more easily measured and economically attractive? It would be clinically relevant if the prevention strategies changed for a portion of people and hence ultimately the cardiovascular mortality or burden of disease in general could be decreased or quality of life increased.

Apart from its medical use, the economic implications of a test procedure are also important. It is of interest to better characterize the relationship between the additional overall gain associated with use of hs-CRP and the additional costs as compared to risk assessment using traditional factors.
Research questions

The aim of the HTA report was to evaluate the available evidence in order to address the following questions:

- Does use of hs-CRP-tests contribute to better risk prediction of cardiovascular events in asymptomatic patients as compared to previously established prediction models (risk scores)?
- How does accuracy criteria of the hs-CRP-test compare to accuracy criteria of the previously established risk scores?
- If hs-CRP improves prediction, is this improvement clinically relevant? i.e.; would prevention strategies change for a portion of people and as a result could cardiovascular mortality or burden of disease generally be decreased or quality of life increased?
- Is the use of hs-CRP as a screening test in addition to the common risk scores cost-effective, i.e.; what is the relationship between the additional costs and the additional overall gain as compared to risk assessment based only on traditional risk factors?

Methods

Inclusion criteria

Prognostic studies were included in the review in cases for which the study population was asymptomatic and the study itself involved a prospective population-based observation of cardiovascular events. The C-reactive Protein in the serum had to be measured using a high-sensitive assay and the prediction model with hs-CRP had to be compared to a prediction model using traditional risk factors such as age, sex, smoking, cholesterol, glucose metabolism, and blood pressure.

In addition, for the comparison of prediction models with and without hs-CRP an effect measure had to be reported for the test accuracy (e.g. sensitivity, specificity, ROC, area under curve (AUC) and C-statistics, respectively) and clinical endpoints used in the prediction models had to contain cardiac death, non-fatal myocardial infarction separately or in combination. Intervention studies with hs-CRP-Screening were limited to randomized clinical trials, non-randomized controlled studies with parallel group comparisons and decision-analytic modelling studies.

All systematic reviews, meta-analyses and HTA reports that referenced primary prediction studies examining the risk for incident CHD or CVD on the basis of hs-CRP measurements, involving study populations, technologies and outcomes as specified above, were included in the literature screening.

In addition all health-economic study types (cost studies, cost-minimization analyses, cost-consequence analyses, cost-effectiveness analyses, cost-ef ficacy analyses and cost-benefit analyses) which fulfilled the above specified criteria regarding study population, comparative technologies, outcomes and epidemiological study type were enclosed for intervention studies of hs-CRP-Screening. No restrictions were made regarding the perspective and time horizon of the studies.

Literature search

The literature search was completed by searching 26 electronic databases of the German Institute for Documentation and Information (DIMDI). The search period used was from 1995 to January, 2007.
HTA reports, systematic reviews, and health-economic evaluations were searched without temporal restriction in the databases of the Cochrane LIBRARY CDSR, NHS CRD DARE, the International Agency for Health Technology Assessment NHS CRD HTA, the National Health Service of the United Kingdom NHS-EED, the HTA database of the German Agency for Health Technology Assessment of the DIMDI, and the INAHTA database.

**Selection, validity assessment and data abstraction**
The aforementioned inclusion and exclusion criteria were used to pre-select articles thematically on the basis of their titles and abstracts in order to retrieve potentially relevant articles in full-text version. At least two authors judged independently the full-text literature with respect to whether it would fulfill the inclusion criteria. All selection steps were recorded in the reference lists and retained within DIMDI. Reasons for exclusion of literature obtained in full text were indicated. The evaluation of the enclosed articles took place on the basis of standardized check lists, the extraction on the basis of extraction tables and forms that were developed prior to the evaluation.

**Data synthesis**
The qualitative characteristics and quantitative parameters of all included studies were arranged and described systematically in evidence tables. For cost data utilized in the studies, currency conversions were performed by using purchasing power parities of the OECD and adjustment for inflation was performed to the year 2006.

**Results**

**Results of the literature search**
The literature search of the DIMDI databases, the manual search of the CRD HTA databases, and the inspection of bibliographies from secondary publications resulted in the identification of 1,577 references after the exclusion of duplicates. After consideration of title, author and abstract, 315 articles among these were obtained in full text. After application of inclusion and exclusion criteria, nine publications were included in the medical evaluation and three in the economic evaluation. Seven studies (eight publications) investigated the incremental prediction of hs-CRP for myocardial infarction and cardiac-related death, one study assessed the effectiveness of hs-CRP as a screening test for prevention of cardiovascular events, and three studies examined health-economic aspects of the hs-CRP-test.

**Results of the clinical evaluation**
Within the seven identified studies (eight publications), there were four cohort studies and three nested case-control studies that included data from a total of 46,458 people. The study quality was partially ambiguous with respect to the representativeness of the study population and the definition of risk factors for cardiovascular events. Outcomes measurement primarily took place in a non-blinded fashion but the proportion of the observed subjects was typically below 80% due to the long observation period or was unclear. The applied model-building methods and presentation of results were adequate. Only one of the models had been validated in another study population.

**Does the use of hs-CRP add to existing prediction for risk prediction of cardiac events in asymptomatic persons?**
This question can be answered affirmatively.
In six of the seven studies, crude and adjusted association measures such as odds ratio (OR), relative risk (RR) or hazard ratio (HR) of the hs-CRP-value and the later occurrence of cardiovascular events were reported. Adjustment for traditional risk factors was performed.
The unadjusted values for the OR, RR or HR, which typically compared the stratum with the highest hs-CRP-value to that with the lowest, fell between 1.2 and 4.5, the adjusted values between 0.7 and 2.47. Only in two of the eight publications were the adjusted association measures slightly above 2, while other values fell between 0.7 and 1.4. In three of the studies, the association measures were no longer statistically significant for hs-CRP.

The comparability of the absolute values of the association measures between the studies was limited due to the variation in the categorization of the hs-CRP-value, the slightly different clinical events that were considered as outcomes, and the various risk factors that were included in the adjustment. The tendency for adjustment of the association to result in a weakened predictive value was uniform across all studies.

**How does accuracy of the hs-CRP-test compare with accuracy of the commonly used risk scores?**

The accuracy data, at least on the basis of the AUC, generally improved marginally, though this improvement was not statistically significant in some cases. All seven studies estimated the incremental predictive value of the hs-CRP-value for cardiovascular events using regression models which contained only the traditional risk factors of age, sex, smoking, cholesterol, glucose metabolism, blood pressure as predictors as compared to regression models which additionally contained the hs-CRP level as predictor. The gain in prognostic value of the risk models was examined by means of the discrimination of the models on the basis of the area under the Receiver Operator Characteristics curve (AUC). The values of AUC for the models that contained the traditional risk factors without the CRP value as a predictor fell between 0.64 and 0.813, while the AUC values of the models that also used the CRP value as a predictor fell between 0.65 and 0.815; the differences between both models were between 0.00 and 0.027. Only in four of the seven studies was the difference in the AUC statistically significant. Since only one of the prediction models was validated in another study population, it is possible that the predictive value and discrimination of the models were over-estimated.

**Can high or low hs-CRP test results modify the overall risk for cardiovascular events as predicted using previous risk factors in a manner that would result in altered actions, including either additional or omission of a preventive measure?**

This question cannot ultimately be clarified since the clinical relevance of the above-mentioned increase in the AUC was examined only rudimentarily in one of the studies by means of a reclassification analysis. In this study, the study population was dispensed into four risk categories on the basis of the prediction model without CRP according to cardiovascular prevention guidelines: 10-year risk for experiencing a cardiovascular event of greater than 20 %, 10 to 20 %, 5 to 10 %, less than 5 %. The proportions of the study population in these categories were 0.8 %, 3.0 %, 8.4 % and 87.9 % respectively. The study population was reclassified after reassessing the risk using the model with CRP. Among the high risk study population (14.4 %) and the two middle risk categories (18.7 % and 21.3 %, respectively), 15 % were reclassified into a higher risk category whereas for the majority of women with low risk, only 2.1 % were reclassified. The actions implied by this reclassification were not investigated.

**Does a decrease in hs-CRP-level or a change in strategy as introduced by the hs-CRP-test, lead to a reduction in myocardial infarctions and cardiac deaths?**

This question cannot be answered since neither randomized nor non-randomized trials comparing the effectiveness of preventive actions introduced on the basis of a risk assessment using only traditional risk factors to
the effectiveness of preventive actions introduced on the basis of a risk assessment using traditional risk factors and hs-CRP-level could be identified. One decision-analytic modelling study used a Markov model to compare the increase in life expectancy by statin therapy in three groups of persons: persons without hyperlipidemia but elevated hs-CRP-levels (group 1), persons with elevated cholesterol levels requiring treatment (group 2) and persons with normal cholesterol and hs-CRP levels (group 3). The gain in life expectancy was comparable for 58 year old persons with elevated hs-CRP but normal LDL values and for persons with cholesterol levels requiring treatment (6.6 months vs. 6.7 for men, 6.4 vs. 6.6 for women), whereas persons without elevated cholesterol and hs-CRP-levels did not benefit considerably (0.6 months for men and women). In sensitivity analyses, the assumptions regarding the rate of myocardial infarctions and the efficacy of statin therapy with regard to the prevention of myocardial infarctions influenced the results most. They varied between 2.5 and 18 months of gained lifetime.

**Results for the economic evaluation of hs-CRP**

The question as to whether CRP screening is a cost-effective action cannot be answered, both because the effectiveness of an additional CRP screening has not yet been sufficiently proven and because there are no reliable cost data for the German context. Regarding the question of cost effectiveness of hs-CRP-screenings, three publications including two decision-analytic modelling studies were found for primary prevention with statins after stratifying the populations based on the results of a CRP test. In the first model, the assumption regarding the intervention strategy was such that all asymptomatic persons 35 years and older were tested with hs-CRP and statin therapy was started for elevated hs-CRP- and borderline lipid levels. This situation was compared to no hs-CRP-screening and statin therapy according to guideline recommendations. In the model, the cost-effectiveness was estimated for various age groups in five different European countries including Germany using a 5-year time horizon and adopting a societal perspective. For Germany, the additional cost of the hs-CRP-screening strategy in comparison to standard therapy according to guidelines for the different age groups fell between Euro 49,800 (35 to 44 years) and Euro 8,700 (55 to 64 years) per life-year gained. The calculated cost-effectiveness ratio for the higher age groups fell in a range that is usually regarded as cost-effective. The second model examined the outcomes of two groups of patients in a US health care context: those with hyperlipidemia who underwent hs-CRP-screening and were given statin therapy in the case of high hs-CRP levels and those who did not undergo CRP testing and were not given statin therapy. Cost-effectiveness- and cost-utility-analyses were conducted using a lifetime horizon and adopting a societal perspective and resulted in estimated additional costs for 58 year old men of Euro 52,000 per life-year gained and per quality-adjusted life year (QALY), respectively, and for 58 year old women, Euro 96,800 per life year and Euro 102,000 per QALY, respectively. The sensitivity analyses demonstrated screening is increasingly cost-effective for men and women if the 10-year risk of coronary artery disease (CAD) increases, the costs of the statin therapy decrease or the efficacy of statin therapy increases.
Discussion

The additional contribution of CRP screening to the risk prediction of cardiovascular events, adequate parameters for its assessment, and the clinical relevance of the results

In a majority of the studies included in this report, statistically significant associations between hs-CRP and cardiovascular events were best-proved with a risk estimate of less than 2.0 after controlling for well-known risk factors. A statistically significant increase in the AUC was reported in only three studies and in these cases the increase appeared to be small. A majority of the authors concluded that hs-CRP is not a clinically relevant predictor. However, no reference values exist regarding at what point the clinical increase can be considered relevant. Other authors argue that the AUC is not a suitable measure for selecting variables for a risk prediction model because other established risk factors such as low density lipoprotein (LDL) also did not cause a stronger increase in the AUC when added to the risk model and more generally because the assessment of the model fit is too narrow if only made on the basis of its discrimination. In one study, several different goodness-of-fit criteria were used for further assessment of the model fit, however, it remains unclear how the quantitative changes after adding hs-CRP as a predictor to the model are to be interpreted. The clinical importance of these changes is also unclear. If a new model can more accurately stratify individuals into higher and lower risk categories than a prior model, the risk prediction is considered improved. Therefore, the approach which is most likely to offer an indication of the clinical importance of the use of hs-CRP as an additional predictor is the reclassification into different risk categories as was accomplished in one of the previous studies. However, this study did not examine how the resulting decisions with regard to treatment would differ. Because clinical intervention studies describing the effect of hs-CRP-screening, the potential reclassification of individuals based on this screening and associated measures to prevent cardiovascular events are lacking, it is not possible to make statements regarding the clinical relevance of hs-CRP-screening.

The effectiveness of CRP as a screening test for the avoidance of cardiovascular events

A decision-analytic model examined the effect of statin therapy on the life expectancy of asymptomatic individuals with elevated CRP- and normal LDL cholesterol levels in comparison to other subgroups who received statin therapy. The gain in life expectancy attributable to statin therapy in this group was comparable to the gain in persons with elevated LDL cholesterol levels. This decision-analytic model relied on a single post-hoc analysis of a randomized clinical trial with regard to the increase in risk for persons with increased CRP values and the risk reduction resulting from statin therapy. Consequently, the results were highly uncertain and the modeling can only offer a first hint that the introduction of additional primary preventive actions such as statin therapy could be reasonable; the question has to be addressed as to whether additional CRP-screening of all asymptomatic persons or only of certain risk groups would be beneficial using modeling and most importantly randomized clinical studies.

The in November 2008 published JUPITER trial provided evidence that statin therapy can reduce the occurrence of cardiovascular events for symptomatic individuals with normal lipid and elevated hs-CRP levels. However, a direct assessment of the clinical value of universal hs-CRP-testing is still lacking and it should be noted that this trial does not yield a predictive value of hs-CRP, and therefore, was not included in our systematic assessment.
Economic evaluation

No economic evaluation studies could be identified that directly collected data on health outcomes and costs of hs-CRP-screening. The three studies included are decision-analytic models that utilized data from various sources about the costs and effects of screening, the primary efficacy and costs of statin therapy initiation and the rate of subsequent cardiovascular events. The quality of the results of the model estimations thus essentially depends on the validity of the sources used and the adequacy of the assumptions. A central question related to the effectiveness and cost-effectiveness of CRP screening is whether therapy exists for patients identified by the screening process that can reduce patient illness or death. The post-hoc analysis of hs-CRP of the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS Study) was used in only one of the decision-analytic models, while in the other models there were no adequate data at that time point. The cost data used for the cost-effectiveness analysis either did not refer to the German health care context or were intransparent, incomplete or outdated. New data regarding the efficacy of statin therapy administered in the case of increased CRP values are published since November 2008 by the JUPITER trial. Therefore the assumed treatment efficacy by statins in this population seems to be confirmed. Cost data for the resulting events and diagnostic or therapeutic actions resulting from screening in Germany would have to be collected.

Conclusion

No sufficient evidence is available to support the notion that hs-CRP-values should be measured during the global risk assessment for CAD or cardiovascular disease in addition to the traditional risk factors of age, sex, smoking, cholesterol, glucose metabolism, and blood pressure. The additional measurement of the hs-CRP-level increases the incremental predictive value of the risk prediction. It has not yet been clarified whether this increase is clinically relevant and results in a reduction of cardiovascular morbidity and mortality. An altered assessment of the cardiovascular risk by hs-CRP-testing would result in a different decision as to whether additional statin therapy should be initiated for primary prevention, most likely affecting those who fall in an intermediate cardiovascular risk group. Statin therapy can reduce the occurrence of cardiovascular events for asymptomatic individuals with normal lipid and elevated hs-CRP levels. However, this is not enough to provide evidence for a clinical benefit of hs-CRP-screening.

The cost-effectiveness of general hs-CRP-screening as well as screening among only those with normal lipid levels remains unknown at present due to the fact that the question of efficacy of screening-tests has not yet been definitely clarified and sufficiently up-to-date cost data for Germany are lacking.

In order to determine cost-effectiveness, it is essential to assess how many people would be affected by such a screening; that is, data regarding distribution of CRP- and lipid level in the German population would have to be collected or published in the event that this has already been done in previous population-based German observation studies of CAD risk factors.