Summary HTA

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HTA-Report | Summary

DAHTA@DIMDI
Waisenhausgasse 36-38a
D-50676 Köln

Tel.: +49 221 4724-525
Fax +49 221 4724-444
dahta@dimdi.de
www.dimdi.de

The role of Homocysteine as a predictor for coronary heart disease.

Lühmann D, Schramm S, Raspe H

Health political background

Evidence from case-controls studies and cross-sectional studies points out, that there is a strong association of elevated homocysteine plasma levels with manifestations of coronary heart disease, which is partially independent of classical risk factors. Furthermore, evidence from randomized controlled trials demonstrates that elevated homocysteine plasma levels may effectively be lowered by the intake of folate and B-vitamins. Taken together, these results lead to the suggestion of a new preventive strategy against coronary heart disease: screening of asymptomatic individuals for elevated homocysteine plasma levels and subsequent treatment of those identified with high levels with folate and B-vitamins. This suggestion, which is mainly expressed by professional advocacy groups contrasts with current reimbursement regulation: in Germany the determination of homocysteine plasma levels is reimbursed for by statutory health insurance in patients with manifest coronary heart disease and in patients at high risk for coronary heart disease but not for screening purposes in asymptomatic low risk populations.

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Scientific background

Assessment of homocysteine plasma levels is being discussed as a technology possibly contributing to the prevention of coronary heart disease. Coronary heart disease is the cardiac manifestation of arteriosclerosis, characterised by narrowing of coronary arteries. Symptoms and consequences result from an imbalance between oxygen demand and oxygen supply in the myocardial muscle. In western industrialised countries coronary heart disease is very widespread. Mortality statistics point out that myocardial ischemia accounts for 10.9 % and myocardial infarction in particular for 7.5 % of all deaths. Therefore every fifth death may be attributed to coronary heart disease.
Arteriosclerosis, a systemic disease of the arteries, is characterised by apposition of lipid deposits and plaque formation in the affected vessels, finally leading to stenosis and occlusion. Up to date formal and causal pathogenesis of arteriosclerosis is not fully understood. It is evident though that a number of influencing factors and their interactions determine the risk of developing arteriosclerosis or coronary heart disease respectively. Classical risk factors, which demonstrate a strong, independent and biologically plausible association with coronary heart disease and which may be therapeutically controlled are: smoking, physical inactivity, malnutrition (overweight, adverse lipid profiles) and high blood pressure. At least 75 % of incident cases of coronary heart disease may be explained by these risk factors. Typically, the risk mediated by one single risk factor is quite weak. Not until there are a number of factors found in one individual they cumulatively mediate clinically relevant elevation of absolute risk for coronary heart disease. This individual's absolute risk may be determined by valdidated algorithms (e. g. PROCAM-Score).
The long asymptomatic stage and the knowledge about modifiable risk factors make coronary heart disease an attractive target for prevention – for

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the individual as well as for society. Modifying risk factors is the key element of prevention. Information concerning the role of risk factors in the pathogenesis of arteriosclerosis, instructions and motivation to modify risk factors are pivotal parts of every cardiac prevention program. On the other hand, risk factors are utilized to determine an individual's absolute cardiac risk and to target intervention.
Aside from the classical risk factors, the status of a number of parameters is controversially debated. It is not clear, whether they are risk factors (= associated with the target disease and causally involved in its development), risk indicators (= associated with the target disease but not causally involved with its development) or none of the two. It is particularly unclear what role they may play in risk estimations for individuals.
One of these factors is homocysteine. Homocysteine is a sulphur containing amino acid with cytotoxic properties. It is formed by demethylation of the essential amino acid methionine. Remethylisation or degradation of homocysteine requires folic acid, vitamin B 6 and vitamin B 12. Especially the cytotoxic potential of homocysteine led to a number of biologically plausible explanatory theories that suggest a causative role of homocysteine in the pathogenesis of arteriosclerosis.
The association of elevated homocysteine plasma levels and coronary artery disease was first described in 1976 and afterwards confirmed by the results of many epidemiological studies. Especially case-control studies demonstrate an association of elevated homocysteine plasma levels and manifest coronary artery disease. At the same time randomised controlled trials find that elevated homocysteine plasma levels may be lowered by the intake of folate and B-vitamins. Against this background there is an ongoing controversy whether elevated plasma homocysteine levels are a risk factor for coronary heart disease and whether lowering these levels therapeutically also reduces cardiac risk.
In order to solve this controversy two different types of evidence are needed. A strong and independent (from other risk factors) association of elevated homocysteine plasma levels and cardiac risk must be demonstrated in prospective studies. In these studies exposition (homocysteine plasma levels) is measured before the onset of coronary heart disease. Positive results would support causality. Another support of causality would be contributed by results of studies which demonstrate that alleviation of exposition (lowering homocysteine plasma levels) results in risk reduction for cardiac events. This type of evidence requires the results of randomized controlled trials.

Research questions

Scientific question

In order to clarify whether elevated homocysteine plasma levels are actually a risk factor for coronary heart disease the following questions have to be answered:

1. In asymptomatic people without existing coronary artery disease, is there a strong, consistent and independent (from other risk factors) association of elevated homocysteine plasma levels and cardiac risk (cardiac events)? (Risk question)
2. Can lowering of plasma homocysteine levels reduce cardiac risk, and if so, by how much? (Interventional question)

Furthermore, before deciding upon implementing a screening strategy the following points have to be clarified:

3. How cost-effective is a preventive strategy for coronary heart disease consisting of measurement of homocysteine plasma levels and subsequent treatment with folate and B-vitamins? (Economic question)
4. Are there morally, socially or legally relevant aspects that should be considered when implementing a preventive strategy as outlined above?

Policy question

Currently measurement of homocysteine plasma levels for the purpose of risk assessment in asymptomatic individuals is not reimbursed by statutory health insurance but has to be paid out of pocket by the patients. Against this background the technology assessment shall clarify what the significance of homocysteine assessment is in the context of risk assessment for coronary heart disease by clarifying medical benefit and cost-effectiveness. Upon these grounds it may be decided whether homocysteine assessment in asymptomatic individuals, maybe above a certain age threshold, should be included into the catalogue of the periodic health examination reimbursed by statutory health insurance.

Methods

Medical assessment

Systematic literature searches are conducted by the German Institute of Medical Documentation and Information (DIMDI) in electronic literature databases relevant for HTA. In order to answer the risk question prospective studies (cohort studies, nested case-control-studies) are included that examine the association of homocysteine plasma levels and manifestations of coronary heart disease (coronary deaths, myocardial infarctions, other manifestations) in probands without pre-existing coronary heart disease or in population-based samples. Furthermore, systematic reviews summarizing the results of studies with the characteristics outlined above are also sought and analysed.
In order to answer the interventional question, randomised controlled trials are included that examine the efficacy of therapeutic interventions aimed at lowering plasma homocysteine levels (e. g. folate plus, if applicable, B-vitamins) on the risk reduction for coronary events. Systematic reviews of this type of studies are also included.
Methodological quality of studies and reviews is assessed by the use of checklists established by the German Scientific Working Group for Technology Assessment in Health Care (GSWG-TAHC). Study selection and quality assessment is conducted by two independent assessors. Information synthesis is performed in a qualitative manner (tables, narrative description).

Economical assessment

The search strategy for economic evaluations and systematic economic reviews is integrated into the overall search strategy. The following study types are classified as potentially relevant: cost of illness studies on the basis of attributable risks for elevated homocysteine plasma levels, primary economic studies and modelling studies that relate the costs of a strategy “assessment of homocysteine plasma levels + targeted intervention (= screen and treat strategy)” to achievable medical benefits measured in natural or monetary units and, economic studies and models that compare

the cost-effectiveness of different management strategies (“screen + treat”, “treat only”, “usual care”). Assessment of relevant studies is performed by the criteria catalogues for relevance and methodological quality established by the economic working group of the GSWG-TAHC. Information is synthesised in a descriptive manner.

Ethical, social and legal implications

The search module for publications with morally, socially of legally relevant contents is embedded into the overall search strategy. Abstracts of publications retrieved with the respective search module are screened, whether they contain discussions of ethical, social or legal implications of homocysteine plasma level determination in the context of prevention of coronary heart disease.

Results

After a first selection of abstracts, 300 out of 2747 publications potentially fulfil the inclusion criteria. The second selection on the grounds of full text publications further reduces the number of relevant papers to 70.

Medical assessment

Concerning the risk question, eleven systematic reviews, 21 primary studies included in these reviews and twelve studies published after deadline for the reviews are analysed. Details of included studies and reviews are compiled in tables in the annex.
Analysis of the eleven systematic reviews yields ambiguous results concerning the association of elevated homocysteine plasma levels and future cardiac events. Only one systematic review with metaanalysis concludes on the basis of the available evidence that elevated homocysteine plasma levels may be judged as a risk factor for coronary heart disease, another review concludes that elevated homocysteine plasma levels may be a predictor for coronary heart disease.
A methodologically sound systematic review performs metaanalysis on the basis of individual patient data from twelve prospective studies. Hereby it is possible to consistently account for confounders in the analyses. Results of the metaanalyses are presented as Odds Ratios for cardiac events per reduction of homocysteine plasma levels by 3 µmol / l. The Odds Ratio for any manifestation of coronary artery disease for a difference in homocysteine plasma levels of 3 µmol / l is found to be 0.83 (95 % CI: 0.77-0.89). The authors conclude from their results that the predictive abilities of homocysteine plasma levels for future cardiac events are, if present at all, much weaker than assumed so far.
The conclusions of the remaining eight systematic reviews are indifferent. Especially the contrasting results from cohort studies and case-contols studies as well as heterogeneities between studies (concerning study populations, measurement of exposition, duration of studies, outcomes measured and adjustment for confounding) hamper the interpretation of results. Against this background four systematic reviews do not perform metaanalyses.
21 prospective studies – six prospective cohort studies and fifteen nested case-control studies- are included in the systematic reviews. Analysing the studies individually it becomes clear that whenever patients with pre-existing coronary artery disease are actively excluded from the study population results were consistently negative, in the sense that no association between

elevated homocysteine plasma levels and future cardiac events could be established. Studies with heterogeneous study populations (population-based samples) yield unequivocal results.
These results are confirmed by the results of the new studies published after deadline for the reviews. With one exception all studies in populations without pre-existing coronary heart disease show negative results, while the ones with unselected populations again have unequivocal results.
Concerning the interventional question, one systematic review, which summarizes the results of twelve primary studies and one further trial reported as a conference abstract and methods paper is analysed.
Eight of the twelve trials included in the systematic review report results from patient populations which according to their cardiovascular history have to be classified as cardiac high risk populations. In all trials the average homocysteine plasma concentration measured at baseline is markedly elevated above the recommended „normal“-threshold of 10 µmol / l. In all trials folate treatment (+ B-vitamins) reduces the average homocysteine plasma concentration by 13 % to almost 30 %, while it remains unchanged in the control arms (placebo or ultra-low dose treatment) of the trials. Results concerning cardiac events are metaanalytically pooled and reported as summary Odds Ratios. The pooled Odds Ratio for any cardiac event under active treatment as compared to placebo or ultra-low dose treatment is found to be 1.04 (95 % CI: 0.90-1.19), the pooled Odds Ratio for a cardiovascular death is 0.96 (95 % CI: 0.88-1.05).
The second group of trials included in the systematic review includes patients with end stage renal disease with extremely high average homocysteine plasma concentrations at baseline (between 27 µmol / l and 50 µmol / l). In this group of trials as well homocysteine plasma concentrations are readily lowered by folate and B-vitamin treatment while the incidence of cardiac events remains unchanged: the pooled Odds Ratio for cardiac events is 1.06 (95 % CI: 0.75-1.51), the pooled Odds Ratio for cardiovascular deaths is found to be 0.89 (95 % CI: 0.4-1.08) in the actively treated groups compared to the control groups.
Five trials perform predefined subgroup analyses for patients with markedly elevated homocysteine plasma concentrations at baseline. Even these analyses cannot find any efficacy of folate and B-vitamin treatment on cardiac outcomes. Still, this type of analysis has, due to the small number of patients included only reduced statistical power so that minor effects may have been overseen.

Economical assessment

After the second selection, three out of 99 papers remain which fulfil the inclusion criteria. All three are modelling studies based on data and assumptions which are falsified by the newer literature. In particular, the much lower than expected strength of the “risk factor” homocysteine and the fact, that lowering homocysteine plasma levels does not lead to a reduction of cardiovascular risk are not compatible with the input used in the models. Therefore the results of the economic models must be considered invalid.

Ethical, social and legal implications

None of the ten potentially relevant publications retrieved from the literature searches yields useful information to answer the fourth research question.

Discussion

Medical assessment

Analyses of the available materials retrieved to answer the risk question point out, that the results of single studies are hardly comparable using qualitative methods. There are massive heterogeneities concerning:

- the study populations included (age, sex, comorbidities),
- measurement of exposition (measurement of total homocysteine (bound and unbound) in plasma or serum, different assay systems, single or multiple measurements),
- units and cut-offs for elevated homocysteine levels that are related to the cardiac risk (different percentiles, continuous measures (e. g. per one, three, four or five µmol / l difference of homocysteine plasma level)),
- the outcomes measured (cardiac events, deaths, need for cardiac intervention, hospital admissions),
- reporting and provision for confounders – namely the „classical“ risk factors for coronary heart disease but also diet and dietary supplements.

Taking these heterogeneities into consideration, metaanalyses on the basis of single patient data, with adjustments for relevant confounders, seems the only valid method for combining data from the various studies because it allows for adequate adjusting for confounders. Their results point out that the ability of homocysteine plasma levels to predict future coronary heart disease in asymptomatic individuals is very limited – especially in comparison to the predictive abilities of the classical risk factors. Therefore, the causality criterion evidence for a strong, consistent and independent association of homocysteine plasma levels and future cardiac risk in individuals without pre-existing coronary heart disease is not fulfilled.
All trials analysed to answer the interventional guestion again show marked heterogeneity, concerning

- the study populations (comorbidities, age) included,
- the average plasma homocysteine concentration measured at baseline (which are at least partially in the same order of magnitude as those encountered in the risk studies),
- the outcomes measured (e. g. combined outcomes with or without inclusion of cerebrovascular events, with or without outcomes that require a special indication (e. g. PTCA, CABG)),
- duration of the trials.

All trials confirm the efficacy of folate treatment to lower plasma homocysteine levels. Concerning clinical endpoints, none of the metaanalyses contained in the systematic review finds any advantage of active folate treatment over that of placebo or ultra-low dose treatment. These overall results are confirmed by multiple sensitivity analyses. Analysing the primary studies, one trial yields potentially biased results (favouring folate therapy). The results of all other trials support the findings of the metaanalyses. Of particular importance is the fact, that even in subgroups with extraordinarily high plasma homocysteine levels at baseline no benefit of folate therapy concerning cardiac outcomes was encountered. These findings lead to the conclusion that currently there is no evidence from interventional studies that supports a causal role of homocysteine in the development of coronary heart disease since the causality criterion “reversibility” is not fulfilled.
Further evidence is expected to arise from the results of currently ongoing large randomised controlled trials.

Economical assessment

Since the literature overview yielded no valid economic evaluation, no results can be discussed.

Ethical, social and legal implications

The fact, that no publications discussing the moral, social or legal problems concerning the role of homocysteine assessment in the prevention of coronary heart disease have been found, leads to the conclusions that these aspects are currently not widely discussed in the scientific literature. In order to further discuss ethical, social and legal implications of homocysteine assessment it would have been necessary to conduct information searches beyond the peer reviewed scientific literature, especially clarifying patients' and experts' expectations and perspectives. Due to limited time and monetary resources this was not possible in the context of this HTA-project.

Conclusions / Recommendations

The conclusions refer to the policy question:

1. Current scientific evidence rather refutes than supports the role of plasma homocysteine as a causal risk factor for coronary heart disease. Against the background of the Bradford-Hill criteria for causality at least the demands for proof of a clear timely sequence of exposition before outcome, proof of a strong, consistent and independent association and proof of reversibility are not fulfilled. This means that elevated homocysteine plasma levels have, if at all, the status of a risk indicator for coronary heart disease. As concerns prevention of coronary heart disease in asymptomatic individuals current evidence does not support the view that knowledge of plasma homocysteine levels yields any useful information concerning cardiac risk, that exceeds the information obtained from classical risk factors. Therefore, currently there is no evidence that homocysteine measurement yields any discernable benefit in context of prevention of coronary heart disease. Against this background, there is no basis for cost-effectiveness or cost-benefit analyses.
Although not systematically reviewed in the context of this HTA-report, current evidence suggests that homocysteine plasma levels may play a different role as a risk or prognosis indicator in patients with existing coronary heart disease. It remains to be clarified how large the additional information concerning risk and prognosis is and whether it would add any precision to the estimates obtained by the currently used score models (e. g. PROCAM-Score).
2. Current scientific evidence does not support a decision to include the assessment for homocysteine plasma levels into the catalogue of the periodic health examination (of asymptomatic individuals).

There is a need for more research in two directions:
Basic research must clarify the observation from case-control and cross-sectional studies that homocysteine levels are elevated in patients with cardiovascular disease. Is there a confounding factor associated with both parameters?
Epidemiological research must clarify whether and how knowledge of elevated plasma homocysteine levels can be integrated into existing risk and prognosis models for patients with manifest coronary heart disease.

Contact at DAHTA@DIMDI:
Head: Dr. Alric Rüther
E-Mail: dahta@dimdi.de