Within the scope of the HTA-Report | Summary

Percutaneous coronary intervention with optimal medical therapy vs. optimal medical therapy alone for patients with stable angina pectoris
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Health political and scientific background
The stable angina pectoris (AP) is a main syndrome of the chronic coronary artery disease (CAD). In case of frequent occasion of AP symptoms (mostly chest pain and/or a strangling feeling in the chest), the quality of life of the concerned persons is substantially diminished.

CAD as an underlying cause of stable AP was in 2008 top in the list of the ten most frequent causes of death in Germany. CAD is a disease with enormous epidemiological and health economic relevance; however, no exact data for stable AP in Germany has been presented.

The most important aims of treatment of chronic CAD are:
- Increase of the disease-related quality of life through avoiding of AP symptoms,
- Improvement of exercise capability,
- Reduction of CAD associated mental diseases,
- Prevention of clinical manifestation of severe CAD, especially of acute myocardial infarction and heart failure as well as
- Reduction of mortality.

The most important methods in the treatment of chronic CAD are non-medicamentous and drug therapies as well as invasive procedures such as percutaneous coronary interventions (PCI) and bypass surgery. PCI may be performed as balloon dilatation or stenting with or without release of substances preventing restenosis (drug eluting stents).

The use of a PCI in addition to medical therapy of stable AP was investigated in several randomized controlled trials (RCT); a systematic up-to-date evaluation on this theme for Germany is missing. The ratio of additional costs to potential additional benefit when comparing these technologies for the German situation is also unclear. Potential ethical, social and legal implications of PCI in addition to optimal medical therapy for Germany also need to be investigated.

Research questions
Medical analysis
What is the medical effectiveness of PCI in addition to optimal medical therapy in stable AP?

Health economic analysis
What is the cost-effectiveness of PCI in addition to optimal medical therapy in stable AP?
Ethical, social and legal analysis

Which ethical, social and legal aspects are to be considered in the use of the PCI in addition to optimal medical therapy in stable AP?

Methods

Medical analysis

Search strategy
The literature search was conducted in the medical electronic databases (MEDLINE, EMBASE etc.) in June 2010. The search strategy was restricted to the languages German and English in the abstracts and to publications beginning from the year 2004. The literature search was completed with a hand search in the reference lists of the relevant articles.

Inclusion and exclusion criteria
The evaluation of the literature search hits was performed in three steps. In the first viewing only the titles of the literature hits were analysed, in the second the summaries and in the third the complete publications. Two independent reviewers were involved in the selection of the relevant publications. Primarily, identified systematic reviews of RCT investigating the use of PCI in addition to medical therapy in stable AP were included into the analysis. After estimation of the current criteria for an optimal medical therapy was intended to conduct an original analysis exclusively on the basis of RCT with current optimal medical therapy; corresponding studies were selected. The analysis considered the endpoints death, myocardial infarction, stroke, heart failure, AP, revascularisation, quality of life as well as corresponding combined endpoints.

Data analysis and information synthesis
The identified systematic reviews were evaluated concerning their risk of bias in accordance to the instrument of Oxman and Guyatt. Subsequently, the strength and the applicability of the evidence from the systematic reviews were appraised in accordance to the GRADE and AHRQ instruments. The studies included in the analysis were reviewed concerning their risk of bias in accordance to the corresponding instrument of the Cochrane Collaboration. Study results were investigated on their statistical heterogeneity and were quantitatively summarized using a meta-analysis. Relative risks in a random-effect-model were calculated with the program RevMan 5.0. Subsequently, the strength and the applicability of the determined evidence were appraised in accordance to the GRADE and AHRQ instruments.

Health economic analysis

Search strategy
The literature search was conducted analogous to the medical analysis in the medical electronic databases, including also health economic relevant databases in June 2010 and was completed by a hand search.

Inclusion and exclusion criteria
The evaluation of the literature search hits was performed in the same way as in the medical part of the presenting report by two independent reviewers in three steps.
Health economic studies on the basis of RCT and systematic reviews of
health economic studies on the basis of RCT investigating the use of PCI in
addition to optimal medical therapy in stable AP (criteria defined in the
medical analysis of the presenting report) were included into the analysis.
The analysis considered data on the incremental cost-effectiveness ratio
with respect to AP attacks, quality adjusted life-years, survival and myo-
cardial infarctions.

**Data analysis and information synthesis**

Primarily, health economic studies were evaluated with the same instru-
ments as corresponding publications in the medical analysis. In addition,
health economic parameters such as study perspective, resource use, cost-
units, time horizon and discounting were appraised.

It was appraised whether the medical results of the included studies agree
with the result of the information synthesis of the presenting HTA report as
well as whether the cost-units used in a health economic evaluation are
transferable to the current situation in Germany. The results of the studies
were described.

**Health economic modelling**

A health economic modelling was performed as a simplified linear simula-
tion model with clinical assumptions derived only from the significant results
of the meta-analysis. Cost-units assumptions were derived from the German
Diagnosis Related Groups (G-DRG, version 2011). The modelling was per-
formed from a restricted societal perspective and with a time horizon of five
years.

It were assumed that the costs difference between two technologies was
caused exclusively due to a difference in the rate of revascularisations (pri-
mary and repeat revascularisations in the follow-up), moreover, exclusively
due to a difference in the PCI rate.

Subsequently, the incremental cost-effectiveness ratio per patient with avoid-
ed AP attacks was calculated. Within the scope of the sensitivity analysis,
the results were evaluated with respect to their robustness to the variation in
different model parameters.

**Ethical, social and legal analysis**

**Search strategy**

The used information sources and search strategy are consistent with the
medical analysis.

**Inclusion and exclusion criteria**

The identified literature search hits were searched for publications with ex-

cplicit emphasis of ethical, social and legal aspects.

**Data analysis and information synthesis**

Because no study was identified, corresponding aspects were addressed
only in the discussion.
Results

Medical analysis

Results of the literature search
The systematic literature search yields 949 hits. 136 hits were selected for the evaluation in full text. Primarily, seven systematic reviews and, subsequently, three RCT were included into the analysis.

Information synthesis of the systematic reviews
The applicability of the evidence determined from seven identified systematic reviews was low, because they combined data from studies of different recruitment periods. Only three RCT fulfilled the defined criteria for current optimal medical therapy and were used as a base for the medical analysis.

Information synthesis from the studies
The routine use of PCI additional to optimal medical therapy in patients with stable AP reduces the proportion of patients with AP attacks after one year and after three years in comparison to the optimal medical therapy alone. However, in the follow-up after five years, this effect was not demonstrated. The strength of evidence for results after one year and after three years is moderate, in follow-up after five years it is low. The applicability of the determined evidence for these endpoints is moderate. However, using a strategy of planned optimal medical therapy alone, PCI is expected to be performed in approximately 27% to 30% patients in five years, patients who have refractory or progressing AP.

The effect of additional use of PCI in optimal medical therapy in patients with stable AP was not demonstrated for any further evaluated clinical endpoints in the presenting analysis. The strength of evidence for the endpoints: death, cardiac death, myocardial infarction and stroke is high. The strength of evidence for the combined endpoints death or myocardial infarction as well as for the combined endpoint death or myocardial infarction or stroke is moderate. The strength of evidence for the endpoint severe heart failure is moderate and for the combined endpoint death or myocardial infarction or severe heart failure is low. The applicability of the determined evidence for all these endpoints is high.

Health economic analysis

Results of the literature search
After evaluation of 949 titles and summaries, 136 hits were selected for the evaluation in full text. Four publications to three studies with health economic analysis were identified. As, according to the results of presenting medical analysis, medical therapy based on current standards was optimal only in two studies, exclusively publications to both studies were included in the health economic evaluation.

Summary of the study results
The cost estimates from the studies are inconsistent and also not directly transferable to the corresponding costs in Germany. The analyses used several assumptions which were not derived from clinical studies. Moreover, a quality-adjusted life-year was calculated over indirect parameters and, additionally, using data only for incomplete patient number in follow-up.
**Health economic modelling**

The mean difference in the total costs per patient between PCI and optimal medical therapy alone was 4,217 Euro. On average, approximately 0.17 years per patient in the PCI-group in five years were additionally free from AP attacks. The incremental cost-effectiveness ratio per life-year of a patient with avoided AP attacks was estimated to be 24,805 Euro. The strength of evidence for these results is moderate.

In the sensitivity analysis, the variations in cost-units assumptions revealed the highest effect on the average costs difference per patient between the treatment alternatives. In the sensitivity analysis for the incremental cost-effectiveness ratio, the highest effect on this parameter was found by varying in the rate of patients with avoided AP attacks.

**Ethical, social and legal analysis**

After the evaluation of 949 titles and summaries as well as of the hand search, no publication was identified with respect to ethical, social or legal aspects in the use of PCI in addition to optimal medical therapy in stable AP.

**Discussion**

**Medical analysis**

The determined results can be principally affected through methodical aspects of literature search, systematic reviews, primary studies and information synthesis.

A publication bias can not be completely excluded. The problem of the quality of the systematic reviews has low importance due to the restricted applicability of the results of these reviews on the current situation in Germany.

A very important methodical problem of the studies is a lack of blinding of the patients. Due their preferences, patients may influence at least partially the performed intervention. This may cause, for example, that patients with lower risk for further cardiovascular events in the PCI group will not receive the revascularisation at the planned time; on the other hand, patients with higher risk for these events in the control group will nevertheless be revascularised.

Moreover, the knowledge about performed intervention may lead either to a higher sense of safety or uncertainty, consequently influencing the pain perception and probably the threshold for a renewed intervention, what is especially relevant for the subjective endpoint AP.

The incomplete data for several endpoints (especially for AP) in follow-up may also bias the results of the studies. Both, selectively healthier or more diseased persons, may be so-called “loss to follow-up” leading to under or overestimation of the effect of the performed intervention.

The included studies are not identical with regard to the investigated patients and the performed interventions. Therefore, the comparability of the effects determined from these studies is restricted. Missing data from one study for PCI group for the endpoint revascularisation make the interpretation of the results additionally complicated.
Health economic analysis

Based on the medical analysis, both RCT with health economic evaluations show some methodical limitations. The transferability of the studies and the relevance of the results from these studies are also highly restricted. The conducted modelling partially avoids the intrinsic problems of health economic studies and enables to adopt the high evidence level of the determined results in the medical analysis. Based on indirect data the determined incremental cost-effectiveness ratio per life-year of a patient with avoided AP attacks is appraised not to be cost-effective. The prevention of repeated revascularisation, often the reflection of AP syndrome, was estimated to be cost-effective only by the additional costs of less than 8,000 USD; a value which is markedly under the value determined in the presented analysis with respect to avoided AP attacks. However, the determined evidence for the calculated incremental cost-effectiveness ratio is decreased due to the diminished strength of evidence of the endpoint AP. Consideration of the determined costs from the societal health economic perspective is restricted due to missing data for costs of possible rehabilitation procedures, productivity loss and intangible costs.

Ethical, social and legal analysis

The access to PCI in Germany seems to be unproblematic in recent years, although an east-west-difference according to the provision data may be assumed. It is important to restrict the independence and the privacy of the patients as little as it is possible. From this point of view, the participative decision-making is of special importance in the patient-physician-relation. An informed consent of patients and corresponding documentation are also very important aspects in the use of different PCI modifications. Legal implications by the use or non-use of PCI in addition to optimal medical therapy in Germany are not to be expected.

Conclusions

From a medical point of view, the routine use of PCI in addition to optimal medical therapy in patients with stable AP can be recommended for the reduction in the proportion of patients with AP attacks after one and after three years. The recommendation degree is weak based on moderate strength of evidence and applicability of the results. Reduction in the rates of death, myocardial infarction, stroke and severe heart failure is not to be expected. Otherwise, PCI is to be performed in patients with refractory or progressing AP despite of optimal medical therapy use; in this case PCI use is to be expected in five years in approximately 27 % to 30 % of patients. From a health economic perspective due to failed cost-effectiveness the routine use of PCI in addition to optimal medical therapy in patients with stable AP cannot be recommended. No special considerations can be made concerning special ethical, social or legal aspects in the routine use of PCI in addition to optimal medical therapy in patients with stable AP.