Coated stents to prevent restenosis in coronary heart disease

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Background
Coronary heart disease (CHD) is a disease of enormous epidemiological and economic importance. CHD is one of the most common causes of death in Germany and leads to a substantial reduction of life expectancy.

The most important methods of CHD treatment in stenotic vessels are bypass operations and percutaneous transluminal coronary angioplasties (PTCA), which also include the implantation of vessel prostheses, known as stenting. Stent implantation prevents the narrowing of the expanded vessels due to elastic recoil as well as vessel closure due to fragments of the injured vessel wall.

The In-Stent-Restenosis (ISR) as a repeated narrowing of the vessel segment after stent implantation is considered to be an essential limiting factor of stenting in CHD. A primary factor in the pathomechanism of the ISR is suspected to be the neointima hyperplasia due to vessel injuries through stent implantation.

The development of covered stents has raised expectations on substantially lowering restenosis after stenting resulting in a decrease in the rate of restenosis and a reduction in the rate of clinical events. Firstly stents with chemical inert passive coatings were developed. The latest achievements are covered stents, which slowly release anti-restenotic agents from their active coatings into the local tissue (Drug Eluting Stents, DES). These agents are immunosuppressive, antibiotic or cytostatic substances, which are thought to prevent the development of neointima hyperplasia and so the formation of restenosis. The usage of drug eluting stents is more expensive compared to uncovered stents of the same type.

Objectives
The present analysis addresses the questions of medical effectiveness and cost-effectiveness of the application of various coated stent types in CHD.

Medical Evaluation

Methods
The analysis of medical effectiveness was performed on the basis of randomised controlled trials (RCT). The literature search was conducted in December 2004 in the most relevant medical databases. The medical evaluation was conducted exclusively on the basis of published RCT. The data from studies were extracted independently by two reviewers; differences were solved by consensus.

The data from the included RCT regarding various angiographic, sonographic and clinical endpoints were checked for methodical quality, heterogeneity and then summarised in meta-analyses. To combine the results from different studies weighted mean differences for metric variables and relative risks for dichotomous variables were employed on 95 % level of significance. From the data combined in the meta-analyses estimated values of avoided or additional events were calculated per 1000 to the therapy allocated patients on basis of a 95 % confidence interval.

Results
1. In the course of literature search the evidence of medical efficacy regarding the application of covered stents was generated on the basis of a total of 26 identified randomised studies for ten different covered stent types.

2. The combined results for heparin, silicon-carbide, carbon and PTFE coated stent types could neither reveal any significant differences regarding angiographic parameters of vessel stretching nor clinical endpoints between covered and uncovered stent types.

The application of gold covered and actinomycin-D eluting stents compared with uncovered stents is related to higher restenosis (restenosis-rates: 42.7 % vs. 30.3 %; RR = 1.40 [95 % CI: 1.12; 1.76] and 27.8 % vs. 13.8 %; RR = 2.01 [95%CI: 1.02; 3.94]) as well as to an increase in the rate of restenosis.
The results for sirolimus eluting and for paclitaxel eluting stents showed considerably lower restenosis at six to nine months after intervention as compared to uncovered stents of the same type, including a considerable relative reduction in the rate of restenosis using stents with polymer-based coatings (2.6 % vs. 36.2 %; RR = 0.08 [95 % CI: 0.05; 0.13] and 4.3 % vs. 21.1 %; RR = 0.21 [95 % CI: 0.14; 0.32]). In the covered groups the restenosis in the lesion segment was higher compared to restenosis in the stented zone. Stent thromboses, incomplete stent-appositions or aneurism formations were very rare in the studies and seemed to have no relevant clinical importance.

The application of sirolimus covered (140 µg / cm²) and paclitaxel covered (1 µg / mm²) polymer-based eluting Stents caused a considerable relative reduction in the PCI-rates (3.5 % vs. 19.7 %; RR = 0.19 [95 % CI: 0.11; 0.33] and 3.5 % vs. 12.2 %; RR = 0.30 [95 % CI: 0.20; 0.43]), TLR-rates (4.1 % vs. 20.6 %; RR = 0.20 [95 % CI: 0.12; 0.33] and 4.3 % vs. 14.8 %; RR = 0.29 [95 % CI: 0.21; 0.41]) as well as a considerable relative reduction in the rate of combined endpoints (7.6 % vs. 23.0 %; RR = 0.34 [95 % CI: 0.26; 0.44] and 10.4 % vs. 20.2 %; RR = 0.52 [95 % CI: 0.41; 0.65]) at follow-up six to twelve months as compared to uncovered stents. However, there were no significant results for death, myocardial infarction and CABG rates. These were probably achieved due to in-time conducted repeated percutaneous revascularisations.

The medical effects by application of polymer-based sirolimus and paclitaxel covered stents were similar in patients with or without diabetes mellitus, in patients with different vessels sizes and those with different lesion lengths. The absolute effects of stent application were considerably higher in patient groups with a high risk than in patient groups with a lower risk of restenosis.

Although, the 7-hexanoyltaxol covered stents achieved a significantly lower restenosis at six months as compared to uncovered stents (restenosis-rates: 7.4 % vs. 32.7 %; RR = 0.23 [95 % CI: 0.11; 0.49]), this stent type caused a significant increase in the rates of stent thrombosis and myocardial infarction (19.0 % vs. 2.1 %; RR = 8.9 [95 % CI: 2.7; 28.8]).

In a small study the everolimus-eluting stents showed a significantly lower restenosis at six months without stent thromboses and incomplete stent-appositions.

Discussion
Despite a number of possible biases, the influence of these factors on the results of the studies was not evident, therefore all results of the studies were considered to be valid for the correspondent populations and therapy modifications. The transferability of the results from the present analysis to other (sub-)populations and technology modifications is limited. The direct comparability of the effect estimates from the meta-analyses for sirolimus and paclitaxel eluting stents is also restricted seen from a methodical point of view.

Economic Evaluation
Methods
The literature search was conducted in the most relevant economic databases. For every publication it was checked, whether the used assumptions corresponded to the current standard of knowledge in Germany (taking into account all published RCT to the corresponding stent type as well as current stent prices and treatment costs in Germany).

Within the scope of economic evaluation specific simulation models were developed on the basis of differences in resource use between the interventions. In these models only significantly different and for the cost difference relevant resource use of the interventions was considered. Modelling was performed, applying clinical estimates from the meta-analyses of the medical evaluation and current estimates of German costs. The incremental costs, the incremental cost-effectiveness-ratios, the „break-even”-prices (prices to achieve cost neutrality) for DES and the patients „break-even”-risks (risks to achieve cost neutrality) for in-stent-restenosis to suggest the application of the corresponding drug-eluting-stents were calculated. The uncertainties of the calculations were evaluated in sensitivity analyses.

Results
1. The systematic literature search revealed eight studies on the cost-efficacy of DES, precisely...
concerning sirolimus and paclitaxel covered stents. However no evidence could be generated from these studies, because they did not either take into account the clinical results of all up-to-date published RCT on covered stents, or did not use current (corresponding to German context) stent prices and revascularisation costs in their economic assumptions.

2. The application of heparin, silicon-carbide, carbon, PTFE as well as paclitaxel (non-polymer-based) and everolimus stents causes higher costs with lacking effectiveness than uncovered stents of the same stent type. Gold covered as well as 7-hexanoyltaxol and actinomycin-D eluting stents being more expensive showed moreover worse clinical results, so that the application of these stent types is not considered to be cost-effective. The evidence for everolimus eluting stents is still uncertain.

The application of polymer-based sirolimus eluting (140 µg / cm²) and of polymer-based paclitaxel eluting (1 µg / mm²) stents is clinically efficient and leads to additional incremental costs of approximately 1,421 € and 1,234 € per patient as compared to uncovered stents one year after intervention, and 1,181 € and 1,099 € per patient taking into account all further expected additional revascularisations (long-time perspective) in the model of the main scenario (balloon dilatation by all Re-PTCA). The mean incremental cost-effectiveness-ratio per avoided revascularisation was 8,881 € for sirolimus covered and 13,711 € for placitaxel covered stents in the model for the first year and 7,379 € or 12,209 €, respectively, when taking into account all further expected additional revascularisations.

The mean „break-even“-price for sirolimus eluting stent in the model was 707 € regarding events in the first year after intervention and 892 € when taking into account all further expected additional revascularisations. The „break-even“-price for polymer-based paclitaxel eluting stent was 551 € and 655 €, respectively, and therefore was considerably (two to three times) lower than current prices of these stent types.

The „break-even“-risk for ISR for a patient after stenting with uncovered bare-metal stent, which achieves cost neutrality by the application of DES, was 76 % in main scenario regarding events in the first year after intervention and 50 % taking into account all further expected additional revascularisations for sirolimus stent and 65 % and 43 %, respectively, for paclitaxel stent.

In the scenario with routine use of DES in all primary Re-PTCA (instead of balloon dilatation without stenting as in the main scenario), the routine application of DES in primary interventions was more favourable as in the main scenario.

Discussion
As cost development of the interventions is affected by numerous factors, such as (among others) product acceptance, market dynamics and the predominate reimbursement principles of the health system, the results of economic modelling have to be considered only as a regional and temporal snap-shot. The advantage of the resource-based simulation models used in this report is the possibility to adapt the calculations rapidly with current data.

The application of polymer-based sirolimus and polymer-based paclitaxel eluting stents in patients with a higher risk for restenosis (for example in patients with diabetes mellitus) seems to be more cost-efficient than in patients with a lower risk of restenosis. In the course of a price decline for these stent types the cost-effectiveness of the application of DES ought to increase and the borderline for the „break-even“-risk ought to move toward a lower risk for ISR.

Summarising Discussion of all Results
The transferability of the results from the present analysis to other (sub)-populations and technology modifications is limited. The direct comparability of the results for sirolimus and paclitaxel eluting stents is also restricted.

Conclusions
According to the evidence of the present evaluation the analyzed heparin, silicon-carbide, carbon and PTFE stent covered stent types as well as the non-polymer-based paclitaxel eluting stents can be applied. However, their application yield neither advantages in regard to the decline of restenosis after stenting (here, however, with the exception of non-polymer-based paclitaxel stents), nor in regard to the reduction in the rate of restenosis, revascularisations and in the rate of
combined endpoints. The use of these covered stent types also causes higher costs as compared to uncovered stents of the same stent type and therefore is not cost-efficient.

The use of gold-covered and of actinomycin-D eluting stents is not recommendable due to an increase in restenosis after stenting. Likewise, on the basis of present results, the application of 7-hexanoyltaxol covered stents should be avoided because of the increase in stent thrombosis and therefore an increased rate of myocardial infarction. The use of these stents furthermore causes higher costs as compared to uncovered stents of the same stent type.

From a medical point of view the application of polymer-based sirolimus eluting stents (140 µg / cm²) as well as of polymer-based paclitaxel eluting (1 µg / mm²) stents can be recommended to decrease restenosis and to reduce the rate of restenosis and the rate of repeated percutaneous revascularisations at six to twelve months after stenting and therefore (even if only temporary) improve quality of life. The decision above corresponding borderline of cost-effectiveness (as a requirement for the application of these covered stent types in the target population) on the basis of determined incremental cost-effectiveness-ratios is located by the appropriate decision-makers themselves. Especially by application of these interventions in patients with a high individual risk for ISR higher rates of avoided restenosis and revascularisations than in the whole target population can be expected and for this reason the use in these patient groups can be more cost-efficient. The broad application of these stent types in the whole target population can also be intended by a sufficient price reduction.

From a medical as well as from an economic point of view the evidence for an appropriate evaluation of the everolimus covered stent types is not sufficient. The use of these stents has to be evaluated in future clinical trials.

The long-term results from the previous RCT and the results from clinical studies to other coatings remain to be awaited. In addition to this the application of diverse new agents in stent coatings should be evaluated in further clinical studies. The number of studies on the efficacy of DES is rapidly increasing and new results are being published permanently, so that an update of the HTA report is recommended for 2007.

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