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Drug-eluting stents vs. coronary artery by-pass-grafting in coronary heart disease

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Scientific background

The coronary heart disease (CHD) is a disease with enormous epidemiological and economic importance. The stationary morbidity for CHD 2004 was 952 per 100,000 residents, mortality 185 per 100,000 residents. About 8500 days of absence due to illness per 10,000 members of the “Allgemeine Ortskrankenkasse“ insurance company were caused in Germany 2005 due to CHD. 2004 the costs for CHD were 6.2 billion euro, in average ca. 80 euro per resident. 2006 30,379 rehabilitation services of the social pension funds in Germany were performed due to CHD.
The most important methods of the CHD treatment in cause of stenosed coronary arteries are coronary artery bypass graft operations (CABG) and percutaneous artery revascularisations (vessel lumen dilatations), so-called percutaneous coronary interventions (PCI) or percutaneous transluminal coronary angioplasties (PTCA), among them balloon dilatation and PTCA with implantation of a small vessel prostheses, called stents.
The CABG operation is a clinically established procedure, which is increasingly carried out as an off-pump intervention and sometimes also with a minimally invasive approach (without splitting of the breast bone). The balloon dilatation was developed as a less invasive alternative to the CABG, however, it is frequently associated with repeated constrictions of the vessels (restenosis) and thereby with repeat revascularisations. Firstly, the development of bare metal stents (BMS) and, later, of drug-eluting stents (DES) has raised expectations on diminishing stenosis, on reduction of restenosis rate as well as on better clinical results in comparison to CABG.
Moreover, the average costs of CABG are higher than those of PTCA, also in case of simultaneous implantations of multiple DES during PTCA. Therefore, a scientific evaluation of the efficacy and economic efficiency of DES vs. CABG seems to be indicated.

Research questions

Medical evaluation

- The medical evaluation addresses questions on the medical effectiveness and the complications of the use of DES in comparison to CABG in CHD.

Health economic evaluation

- The health economic evaluation addresses questions on health economic parameters of the use of DES in comparison to CABG in CHD.

Ethic, social and legal aspects

- This part of the evaluation addresses questions on specific ethic, social and legal implications of the use of DES in comparison to CABG in CHD.

Within the scope of the

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Medical evaluation

Methods

The literature search was conducted in the medical electronic databases MEDLINE, EMBASE, SciSearch, AMED, BIOSIS, GLOBALLY Health, MED-IKAT, INAHTA, NHS-CRD-DARE, NHS EED, SOMED, Cochrane database etc. The search strategy was restricted to the years beginning from 2004 as well as to the languages German and English.

The evaluation of the literature search was performed in three steps (titles, abstracts and full texts). Two independent reviewers were involved into the selection of the relevant publications.

Publications about registry data for DES and about controlled clinical studies (randomised and/or not-randomised) for the comparison of DES vs. CABG were included into the evaluation. Reference lists of the identified publications and MEDLINE (repeatedly during the review process) were searched for further relevant studies.

Data from the included studies were summarized with respect to methods, patients, interventions and endpoints using a prepared extraction form. The single studies were checked on their methodical quality and validity. The information synthesis was performed descriptively. Finely, the results of the information synthesis were ordered according to evidence levels of the classification of the Oxford Centre for Evidence Based Medicine.

Results

The literature search was performed in December 2006 and yielded 2,312 hits. 2,312 titles and 379 abstracts were reviewed. 98 publications were selected to the review in full text. Five publications about two registers and eleven articles about five controlled cohort studies were included into the analysis. Hand search revealed three further publications about one cohort study.

Results of the hospital stay

Detailed results about events after DES implantation during the hospital stay were derived from two registers with more than 400,000 observed patients as well as from some cohort studies. The mortality based on the register data was low (0.2 % and 0.7 %), however, for patients with ST-elevation myocardial infarction and patients with chronic total occlusions somewhat higher (2.9 % and 2.5 %, respectively). The rates of myocardial infarction as well as the rates of CABG in the hospital stay were also low and ranged according to indication from 0.5 % to 1.4 %, and from 0.2 % to 0.4 %, respectively. Stent thromboses were registered in 0.3 % of the patients and urgent PTCA was performed in 2.1 % of the patients. In cohort studies, the event rates after DES use were also low. For patients with unprotected left main coronary artery (LMCA) stenosis, one study showed a significantly higher rate of myocardial infarction and another of stroke after CABG, respectively. Also in multivessel disease significantly more patients after a CABG suffered a myocardial infarction, almost all of them a Q-wave myocardial infarction.

Results in the medium-term follow up

Two studies reported results for interventions in patients with stenosis in proximal left anterior descending coronary artery. The only one up-to date published randomised controlled trial (RCT) was not able to demonstrate any significant difference in the event rates between both interventions. In several analyses of the data from the study at Israeli Medical Centers for different patient's subgroups and off-pump CABG, the reinterventions rate in the DES group was consistently significantly higher in the follow-up until 22.5 months (9.5 % vs. 2.1 %, $p < 0.05$, 9 % vs. 0 %, $p < 0.001$, 10.3 % vs. 2.6 %, $p < 0.05$ and 16.8 % vs. 3.6 %, $p < 0.01$). Angina pectoris (31 %

vs. 11 %, p < 0.001, 32 % vs. 1 %, p < 0.001, 31 % vs. 11 %, p < 0.001, 35 % vs. 8 %, p < 0.001) appeared also consistently significant more frequently in the DES group. Correspondingly, the rate of angina-free survival was significantly lower in DES patients in three studies in different follow-ups up to two years (68 % vs. 87 %, p < 0.01, 41 % vs. 86 %, p < 0.001 and 57 % vs. 87 %, p < 0.01), the intervention-free survival in one study at 18 months (84 % vs. 93 %, p < 0.01). The rate of MACE (cardial deaths, myocardial infarctions or reinterventions) in DES patients was significantly higher in one study at 22.5 months (20.5 % vs. 7.2 %, p < 0.05) and the MACE-free survival at 24 months, respectively, significantly lower (79 % vs. 95 %, p < 0.01).

For interventions in unprotected left main coronary artery (LMCA) lesions publications about three cohort studies with a follow-up up to two years are available. In one study a survival without myocardial infarction or stroke at six months and at one year was significantly higher in the DES group (96 % vs. 83 % and 96 % vs. 79 %, both p < 0.05). In the second study, the target lesion and the target vessel revascularisations at one year were significantly more frequently in the DES as in the CABG group (15.8 % vs. 3.6 %, p < 0.001 and 19.6 % vs. 3.6 %, p < 0.0001). Both, unadjusted and by means of the propensity score analysis adjusted odds ratios (OR) showed a significant chance reduction for the combined endpoints "deaths or myocardial infarction" and "death or myocardial infarction or stroke" for DES vs. CABG, however, a significant chance increase for target vessel revascularisations (unadjusted 95 %-CI for OR correspondingly 0.048 to 0,580, 0,102 to 0,617 and 1,321 to 8,960; adjusted 95 %-CI for OR correspondingly 0.078 Until 0,819 and 1,486 to 14,549). In the third study, DES patients showed a significantly higher rate of revascularisations (ca. 25 % vs. 5 %, p < 0.0001) and a significantly lower MACE-free survival (no death, myocardial infarction or revascularisation, ca. 55 % vs. 85 %, p < 0.0001) in the average follow-up of 417 days.

Results for interventions in patients with multivessel disease were reported in two studies. The ARTS-II-study showed significantly higher rates of percutaneous revascularisations (6.4 % vs. 3.5 %, p < 0.05) and of all revascularisations (8.5 % vs. 4.2 %, p < 0.05) for the DES group for follow-up at one year. However, the mortality in the DES group was significantly lower (1.0 % vs. 2.7, p < 0.05) as well as the rate of myocardial infarction (1.3 % vs. 4.2 %, p < 0.06; through difference in Q-wave myocardial infarctions: 0.8 % vs. 4.0 %, p < 0.05). The rate of the combined endpoint "death or stroke or myocardial infarction" was also significantly lower in the DES group (3 % vs. 8 %, p < 0.05). In two patients of the DES group a late thrombosis (0.3 %) was found. In the direct comparison of the results of both interventions in patient subgroups with diabetes mellitus, the rate of stroke (0.0 % vs. 5.2 %, p < 0.05) as well as the rate of the combined endpoint “death or stroke or myocardial infarction" (3.1 % vs. 10.4 %, p < 0.05) were significantly lower in the DES group, however, the rate of percutaneous revascularisations (10.1 % vs. 3.1 %, p < 0.05) and the rate of all revascularisations (12.6 % vs. 4.2 %, p < 0.05) were significantly higher. In almost all analyses of the data from the study at Israeli Medical Centers the reinterventions rate (14.2 % vs. 5.3 %, p < 0.05, 12.5 % vs. 5.7 %, NS and 29.1 % vs. 5.8 %, p < 0.001) and the rate of repeated angina pectoris (28 % vs. 12 %, p < 0.01, 30 % vs. 13 %, p < 0.01 and 40 % vs. 15 %, p < 0.01) were significantly higher in the DES group in the follow-up after 18 months. Correspondingly, in almost all analyses up to the follow up at two years the rate of angina-free survival (72 % vs. 88 %, p < 0.001, 65 % vs. 86 %, p < 0.001 and 55 % vs. 87 %, p < 0.001) and the rate of reintervention-free survival (87 % vs. 96 %, p < 0.01, 88 % vs. 96 %, p < 0.05 and 76 % vs. 94 %, p < 0.05) were significantly lower for DES patients. The study analysis for patients with diabetes mellitus showed additionally a significantly

higher rate of MACE (cardial deaths, myocardial infarctions or reinterventions) in the DES group at follow-up up to 18 months (23 % vs. 3 %, p < 0.01).

Discussion

All significant results found were derived from not randomised controlled cohort studies and therefore can be influenced systematically through different factors in favour of one of the intervention. These results serve only as limited evidence for possible effects which should be proven in randomised studies.

Health economic evaluation

Methods

The literature search was conducted in the same databases as for the medical evaluation. Health economic studies for the comparison of DES vs. CABG were searched.

Additionally, health economic modelling for the treatment of multivessel disease from a restricted social perspective for time horizons of one and three years was conducted.

Clinical assumptions (rates for deaths, myocardial infarctions and revascularisations) were taken from the corresponding clinical studies.

Cost assumptions for the resources used were derived from the German Diagnosis-related Groups (G DRG, version 2007). The basis case value was assumed to be 2,800 euro. The price of one DES was assumed corresponding to the additional remuniration to be 1,200 euro, the average DES use per patient to be 3.7. The average daily costs of the treatment with clopidogrel were estimated to be 2.57 euro per patient, the implied duration of the Clopidogrel therapy was twelve months. Because of the short time horizon discounting was not applied.

Within the scope of the sensitivity analysis, different model parameters were varied and the evaluation was tested for its robustness.

Results

The literature search was performed in December 2006 and yielded 728 hits. 728 titles and 54 abstracts were reviewed. 24 publications were selected for the evaluation in full text, one of these publications was included into the analysis, however the medical and economic assumptions used in this study were not up-to date.

The estimated total costs per patient after CABG operation at one year were 13,373 euro and after DES implantation 10,443 euro, the difference was 2,930 euro per patient in favour of PTCA with DES use. The estimated total costs per patient three years after CABG operation were 13,675 euro and after DES implantation 10,989 euro. The calculated difference in costs three years after interventions was 2,686 euro per patient in favour of PTCA with DES use and was similar as after one year.

Changes in cost-weights for CABG and angioplasties, DES price, DES use per patient as well as the duration of the clopidogrel use in the sensitivity analysis influenced the cost differences considerably, however, they did not reach a break even point. The total costs per patient for angioplasties with DES use remained still lower. Changes in the clinical follow-up assumptions showed a lower effect on the difference in total costs.

Discussion

The performed health economic modelling was conducted from a restricted societal perspective. In this modelling, costs of possible rehabilitations, costs of productivity loss due to illness and intangible costs were not considered because these data were missing in the studies.

The assumptions for medical efficacy DES vs. CABG in the performed modelling were derived from non-randomised cohort studies and therefore the analysis has several methodical limitations.

Ethic, social and legal aspects

Methods

In the performed literature search it was also screened for publications focused on ethic, social and legal aspects in the use of DES vs. CABG for the German context.

Results

No publications with explicit view of ethic, social and legal aspects in the use of DES vs. CABG for the German context could be identified.

Discussion

The access of different social and ethnic groups to DES as well as the independence and the privacy of the patients seem to be not restricted in Germany.

Summary discussion of all results

According to the classification of the Oxford Centre for Evidence Based Medicine an evidence level 2a should be attributed to the performed systematic review on the basis of cohort studies. Evidence level of 2b should be attributed to the results of the health economic modelling with assumptions derived from not randomised cohort studies.

Conclusions

Some limited evidence exist for the advantage of the CABG operation vs. DES implantations with sirolimus-eluting stents in patients with stenosis of the proximal left anterior descending coronary artery with respect to angina pectoris and repeated revascularisations rates in follow-up up to two years after the primary intervention.

In patients with LMCA lesions there is limited evidence of an advantage of the sirolimus and of the paclitaxel coated DES vs. CABG with respect to higher survival rate without myocardial infarction or stroke at one year, however, a disadvantage with respect to higher revascularisation-rates in follow-up up to two years after performed interventions.

Limited evidence exists also for an advantage of the DES implantations with sirolimus coated Cypher-Stent vs. CABG operation in patients with multivessel disease with respect to lower mortality and rate of myocardial infarctions at one year, however, for a disadvantage with respect to a higher revascularisation rate and the rate of repeated angina pectoris in follow-up up to two years after the primary intervention.

The identified evidence for the differences in efficacy of DES vs. CABG was derived from non-randomised cohort studies with middle-term follow-up and should be proven in long-term follow-up and in RCT.

The evidence for a possible economic advantage of DES implantation vs. CABG in multivessel disease at one and three years after the primary intervention is also limited and should be proven on the basis of RCT. As far as this hypothesis is not confirmed in appropriate RCT, none of the interventions should be preferred from a health economic view.

There is no evidence for specific ethic, social or legal consequences of DES use. The independence and the privacy of the patients should only be restricted as low as possible. An informed consent of the patients is important and should be documented.