IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Antibody-coated stents for the treatment of coronary artery stenosis in patients at high risk of restenosis[1]

Executive Summary

[1] Translation of the executive summary of the rapid report "Antikörperbeschichtete Stents zur Behandlung von Koronargefäßstenosen bei Patienten mit hohem Restenoserisiko" (Version 1.1; Status: 07.09.2012). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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This report was prepared in collaboration with external experts. According to § 139b (3) No. 2 of Social Code Book (SGB) V, Statutory Health Insurance, external experts who are involved in the Institute's research commissions must disclose "all connections to interest groups and contract organizations, particularly in the pharmaceutical and medical devices industries, including details on the type and amount of any remuneration received." The Institute received the completed form "Disclosure of conflicts of interest" from each external expert. The information provided was reviewed by a Committee of the Institute specifically established to assess conflicts of interests. The information on conflicts of interest provided by the external experts is presented in Appendix G of the full report. No conflicts of interest were detected that could endanger professional independence with regard to the work on the present commission.

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Executive summary

On 15.03.2012, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess antibody-coated (AB) stents in the treatment of coronary artery stenosis in patients at high risk of restenosis.

Research question

The aim of the present investigation was the comparative benefit assessment of AB stents and control interventions (no restrictions were defined for the studies to be considered) in patients at high risk of restenosis. The assessment was carried out in respect of patient-relevant outcomes.

Methods

The assessment was undertaken on the basis of available randomized, controlled trials on the above-named research question. For this purpose, a systematic literature search was performed in the following databases: MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials (Clinical Trials). In addition, a search for relevant systematic reviews took place in the databases MEDLINE and EMBASE in parallel with the search for relevant primary studies. Searches were also conducted in the databases Cochrane Database of Systematic Reviews (Cochrane Reviews), Database of Abstracts of Reviews of Effects (Other Reviews), and the Health Technology Assessment Database (Technology Assessments). The search took place on 18.05.2012.

Systematic reviews and publicly accessible trial registries were also screened for other relevant studies. Documents provided by the G-BA, as well as the website of the manufacturer (OrbusNeich) of the antibody-coated stent approved in Germany (Genous™) were inspected for published or unpublished studies. In addition, the authors of publications on 2 relevant studies were contacted to clarify questions relating to methodology and in respect of additional data.

Randomized controlled trials in which the implantation of an AB stent in patients at high risk of restenosis was compared with control interventions were included in the assessment. Following an evaluation of study quality, the results of the individual studies, arranged according to comparisons and outcomes, were described and compared with each other.

Results

A total of 3 randomized controlled trials on 2 comparisons were identified as relevant for the research question of this benefit assessment. The trials investigated patients with coronary stenosis at high risk of restenosis in whom elective stent implantation was indicated.

Comparison of the AB stent versus DES implantation

In 2 of the studies (TRIAS Pilot and TRIAS HR) an AB stent was implanted and a drug-coated stent (drug-eluting stent [DES]) used as comparator. Patients in both study arms

received 300 mg clopidogrel as loading dose plus long-term treatment with 75 to 100 mg acetylsalicylic acid (ASA) daily as co-medication. In patients of the intervention group (AB stent), the daily dose of 75 mg clopidogrel was given for at least one month, in the control group (DES) for at least 6 months. Results after 1 and 2 years were available for the TRIAS pilot study. 1-year data were available for the TRIAS HR study. The planned follow-up of both studies is 5 years. 193 patients were investigated in the TRIAS pilot study and 622 in the TRIAS HR study.

The randomization sequence generation in the TRIAS pilot study was not adequately described. But the main feature of this study is that there was an unplanned premature discontinuation of the study after 193 patients had been recruited. Due to this methodological deficiency, this study was rated as having a high risk of bias. Thus, the TRIAS HR study had a decisive role in the comparison of AB stents versus DES, because only this study had a low risk of bias.

In the comparison of AB stents and DES, there was no statistically significant difference in the outcomes “all-cause mortality” and “cardiac mortality”, which were recorded in both studies.

Both studies recorded myocardial infarctions, but solely those in the area supplied by the target vessel were reported in the publications. In order to determine the overall rate of myocardial infarctions, these data were requested from the group of authors of the “low risk of bias” TRIAS HR study. The unpublished data subsequently provided by the authors of the TRIAS HR study showed a statistically significantly higher overall rate of myocardial infarctions ($p = 0.046$) after AB stent implantation compared with DES implantation: in the intervention group (AB stent) 13 out of 304 patients (4.3%) suffered a myocardial infarction, compared to only 5 out of 318 patients (1.6%) in the control group (DES) (odds ratio = 2.80; 95% confidence interval [0.98; 7.94]). The fact that, despite the significance of the result, the confidence interval includes 1, is explained by the different methods of calculation (p value calculated exactly and the confidence interval asymptotically). The data of the “high risk of bias” TRIAS pilot study, which considered myocardial infarctions in the target vessel, showed no statistically significant effect. Since meta-analysis of the results of both studies revealed a considerable heterogeneity ($p = 0.046$), no overall estimator was calculated. Due to the differing risks of bias of the two TRIAS studies, the conclusion regarding benefit is based principally on the study with the low risk of bias, namely the TRIAS HR. In summary, there was an indication of a lesser benefit of implantation of an AB stent in comparison with a DES with regard to the outcome “myocardial infarction”.

Neither of the two studies reported results concerning the overall rate of repeat revascularization. Since this rate cannot be reliably reconstructed from the components reported (target lesion revascularization (TLR), target vessel revascularization (TVR)/Non-TLR and Non-TVR), the data were requested from the group of authors of the “low risk of bias” TRIAS HR study. The unpublished overall rate of repeat revascularization subsequently

provided by the authors showed a statistically significant result ($p = 0.018$) to the disadvantage of the AB stent versus DES. A repeat revascularization was performed in 71 (23.9%) of 297 patients in the intervention group (AB stent), whilst this event occurred in 51 (16.2 %) of 315 patients in the control group (odds ratio = 1.63, 95% confidence interval [1.09; 2.43]). In summary, an indication of a lesser benefit of the implantation of an AB stent in comparison with a DES could be derived from this result.

Both TRIAS studies recorded combined patient-relevant outcomes. There were no statistically significant differences regarding the outcome "all-cause mortality or myocardial infarction" (TRIAS HR study). There was likewise no difference concerning the outcome "cardiac mortality or myocardial infarction" (in the target vessel) in the TRIAS pilot study, whereas a statistically significantly increased risk of event ($p = 0.044$) was found in the AB stent group in the TRIAS HR study, where the odds ratio was 2.47 (95% confidence interval [1.001; 6.086]). Since meta-analysis of the results showed a considerable heterogeneity ($p < 0.2$), no overall estimator was calculated. Due to the differing risk of bias of the two studies included in the assessment, the conclusion regarding benefit is based principally on the study with the low risk of bias, namely the TRIAS HR. Thus a hint of a lesser benefit of the implantation of an AB stent instead of a DES can be assumed for the combined outcome "cardiac mortality or myocardial infarction".

No data were reported on other patient-relevant outcomes such as "quality of life", "hospitalizations", "adverse events and complications of treatment", "dependence on help from others" or "need for care", or for "exercise capacity", "managing everyday activities" or "ability to work".

Comparison of AB stent versus BMS implantation

An uncoated metal stent (bare-metal stent [BMS]) was implanted as comparator in the third study included in the assessment (Boshra 2011) with a sample size of 38 patients. Dual platelet aggregation inhibition was recommended in both arms of the study, using 150 mg of ASA as long-term treatment and 75 mg of clopidogrel. In the control group (BMS), 75 mg of clopidogrel was recommended for at least 3 months, in the intervention group (AB stent) for 1 month. Patients were followed up for 6 months.

The non-blinded study published by Boshra in 2011 contained no information about random sequence generation and allocation concealment. No entry in a trial registry could be found. In addition, the study was apparently discontinued after the recruitment of 38 enrolled patients. No information was given about the planned sample size. Due to this methodological deficiency, this study was rated as having a high risk of bias.

No hint of an added benefit could be derived from the comparison AB stents versus BMS concerning the outcomes "mortality" and "myocardial infarction".

No results on the overall rate of clinically indicated revascularization were reported in the study.

The outcome “angina pectoris” showed a statistically significant result (p = 0.036). Of the 19 patients in each of the two groups, this event occurred in 2 patients in the AB stent group (11%) and in 9 patients (47%) in the control group (BMS). Due to the study’s high risk of bias, this result was interpreted as a hint of an added benefit of AB stents compared with BMS.

Although the outcome “bleeding events” was considered by Boshra 2011, neither severe nor minor bleeding events occurred and hence no hint regarding a lesser harm can be derived for this outcome.

No data were reported on other patient-relevant outcomes such as “quality of life”, “hospitalizations”, “dependence on help from others”, “need for care”, or for “exercise capacity”, “managing everyday activities” or “ability to work”.

Conclusions

In comparison with DES, there was an indication of a lesser benefit of the implantation of an AB stent with regard to the outcomes of “myocardial infarction” and “clinically indicated repeat revascularization”. For the combined outcome “cardiac mortality or myocardial infarction”, a hint of a lesser benefit of the implantation of an AB stent instead of a DES could be demonstrated. For all other patient-relevant outcomes, this comparison showed no advantages or disadvantages for either intervention, or no data were available.

For the comparison AB stents versus BMS, there was a hint of an added benefit of AB stents for the outcome “angina pectoris”. For all other patient-relevant outcomes, this comparison showed no advantages or disadvantages for either intervention, or no data were available. The importance of this comparison for the German care context is doubtful.

Keywords: stents, coronary artery disease, myocardial infarction, benefit assessment, systematic review

The full report (German version) is published under www.iqwig.de.