Risk of myocardial infarction and re-operation is greater than for drug-coated stents

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If narrowed or blocked coronary vessels have to be widened or opened, a vascular support (stent) is usually inserted. Drug-coated stents are preferred for patients at high risk of renewed narrowing of vessels (restenosis). However, the use of antibody-coated stents has been increasing in recent years. Current studies provide indications that these new antibody-coated stents more frequently lead to myocardial infarction and make re-operation necessary. This is the conclusion reached in the rapid report of the German Institute for Quality and Efficiency in Health Care (IQWiG), as published on 12 October 2012.

The Federal Joint Committee (G-BA) had commissioned IQWiG to investigate the advantages and disadvantages of antibody-coated stents in comparison to alternative measures, focussing on patients with coronary heart disease (CHD) at high risk of restenosis. This depends on factors including the duration and degree of the narrowing as well as its precise localization. The curvature of the affected vessels can also play a role.

Narrowed coronary vessels are generally expanded by surgery and stabilized with stents (tubes of wire mesh). But even vessels supported by stents can become blocked again, if there is excessive tissue growth. Re-operation is then necessary (revascularization). Moreover, stents are foreign bodies. If they are not fully covered with a smooth cell layer (epithelium), platelets are more likely to stick to them and blood clots (thromboses) are more likely to form on them. It is attempted to

counteract these two main risks (thrombosis formation and tissue proliferation) by specifically coating the stent and by treating the patient with anticoagulants.

The first generation of stents consisted of pure metal (bare-metal stents, BMS) and are now rarely used for patients at high risk of restenosis. The second generation of stents were coated and released small quantities of drugs (drug-eluting stents, DES). These drugs are meant to inhibit cell growth and thus avoid restenosis and the need for revascularization.

On the other hand, this coating delays incorporation of the stent, thus increasing the risk of thrombosis. Therefore patients with a DES must generally take antithrombotic drugs for at least 12 months after the operation. The active substances acetylsalicylic acid (ASS) and clopidogrel - so called platelet inhibitors - are most frequently used.

The third generation of stents act by using specific antibodies to stimulate cells growing into the vascular wall to form epithelium. This is supposed to accelerate the incorporation of the wire network and reduce the risk of thrombosis. The manufacturer claims that this greatly shortens the period for which antithrombotic drugs must be taken, thus helping to avoid the side effect of an increased tendency to bleed and also helping to reduce costs.

Three randomized controlled trials (RCTs) were available to IQWiG. Two studies compared antibody-stents with DES; one study compared antibody-stents with BMS. One DES study and one BMS study had only a few participants and were prematurely discontinued. These discontinuations were not planned, i.e. the criteria for stopping the studies had not been specified before the start of the studies. Moreover, it was unclear in one of the studies whether the randomized allocation to the two treatment groups was adequately concealed. These studies were thus highly susceptible to bias and the results can only be used to a

limited extent.

In accordance with the mechanism of action of antibody-stents, the patients in all three studies were only given clopidogrel for one month. In contrast, the patients in the control groups were given clopidogrel for either 3 months (DES) or for six months (BMS).

The comparative benefit assessment of DES- and antibody-stents is mainly based on a single study (TRIAS-HR). This was comparatively large - with 600 patients - and the risk of bias was low. Of the 304 patients who had been given an antibody-stent, 13 (4.3%) suffered a myocardial infarction, in comparison with 5 of 318 patients (1.6%) in the control group with DES.

The results for antibody-stents were also less favourable with respect to revascularization: re-operation was necessary for 71 of 297 (23.9%) patients in the antibody-stent group, in comparison with 51 of 315 patients (16.2%) in the DES group. As this conclusion was only based on a single study, IQWiG considers that there is no proof, but only an indication, of lesser benefit. This applies both to the outcome of myocardial infarction and to the outcome of revascularization.

An additional outcome criterion was a composite outcome including myocardial infarction and deaths due to other types of heart failure (cardiac mortality). Here too the results suggest that the antibody-stents are at a disadvantage. However, this is not an indication, but only a hint.

The manufacturer of the antibody-stent claims that clopidogrel can be administered for a shorter period with their product. This may be of particular importance for patients undergoing surgery, as platelet inhibitors increase the risk of bleeding. Moreover, antibody-stents are supposed to be particularly effective in preventing restenoses in the vessels that are primarily affected.

Jürgen Windeler, the IQWiG Director, commented that, if this was the case, the rate of revascularization in these vessels would be lower. However, the TRIAS-HR study suggested that the opposite was the case. This called the mechanism of action of antibody-stents into doubt. It could also not be excluded that the disadvantage of antibody-stents found in the studies was due to the early discontinuation of clopidogrel. He added that antibody-stents were just another example of how not only the medical device, but also its manner of application, were decisive, and that if we wanted reliable information on benefit, we had to consider both the product and its application.

Contrary to what the manufacturers of medical devices often assert, these benefit studies are feasible. According to Jürgen Windeler: "If you take the patient's safety seriously, you have to insist on these studies. Antibody-stents have been used for many years, but we don't know how many patients have received this intervention. It is only now that we learn that its harm outweighs its benefit."

The G-BA commissioned IQWiG to prepare the report in an accelerated process, known as a "rapid report". Unlike the normal procedure, no preliminary reports are published in this case. Although a draft version of the report is reviewed by external experts, no hearing at which all interested parties can comment takes place.

The first report (Version 1.0) was prepared in the middle of August 2012 and sent to the G-BA. Shortly afterwards, the Institute was sent additional and previously unpublished data on the decisive study TRIAS-HR, which had been requested by the Institute from the responsible research group in Amsterdam (data on the overall rate of myocardial infarctions and revascularization). The report was then revised and Version 1.1 sent to the G-BA at the start of September 2012.