Intracranial stents: More strokes than with drug treatment alone

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The risk of having another stroke is higher if patients, after dilation of their blood vessels in the brain, not only receive clot-inhibiting drugs, but also have small tubes called stents inserted. However, studies have provided no hint of a benefit from stenting, which is also referred to with the abbreviation "PTAS". This is the conclusion reached in the rapid report of the German Institute for Quality and Efficiency in Health Care (IQWiG), as published on 9 October 2014.

Stents are supposed to prevent restenosis

Blood vessels in the brain that are narrowed or blocked can cause stroke. If patients have already had a stroke or temporary ischaemia (transient ischaemic attack, TIA), there is a high risk that this occurs again. These patients therefore receive drugs that prevent blood clotting. Another option is to additionally widen the narrowed vessels.

Nowadays this is often done using a small balloon in a procedure known as percutaneous transluminal angioplasty (PTA). But even after PTA and simultaneous blood-thinning medication, vessels often remain narrow (stenosis) or new narrowing occurs (restenosis). The treatment has therefore been expanded to include stenting (percutaneous transluminal angioplasty and stenting, PTAS): Small wire mesh tubes are inserted to support the widened blood vessels and prevent restenosis. This stenting has been available for approximately 10 years.

Compare PTAS with treatment alternatives

The Federal Joint Committee (G-BA) had commissioned IQWiG to assess the benefit of PTAS for patients with symptoms of narrowed blood vessels in the brain (symptomatic intracranial stenosis). PTAS was to be compared with drug treatment with blood-thinning medications alone and with balloon dilatation without stenting (PTA). Like PTAS, PTA always involves administration of blood-thinning drugs.

Four studies identified

IQWiG identified a total of four randomized controlled trials (RCTs) that included patients with symptomatic intracranial stenosis. In three studies, PTAS was compared with drug treatment alone. One study tested PTAS versus PTA.

One relevant study on PTAS versus medication alone

The SAMMPRIS study was relevant for the assessment of PTAS in comparison with drug treatment alone. SAMMPRIS included a total of 451 participants and is the largest study currently available. It is also the only study to provide data both on mortality and side effects and on stroke in all areas of the brain.

The two other studies (Miao 2012 and Gao 2013) only reported strokes that occurred in the territory of the treated vessels. However, it is relevant for the patients whether strokes occur at all – irrespective of their localization. Hence only data from the SAMMPRIS study were available for the outcome "stroke" as well.

Lack of data for important outcomes

Besides mortality (all-cause mortality and from stroke), the burden of disease in the form of stroke, TIA, and other physical or psychological impairments from ischaemia, the patient-relevant outcomes of this assessment also include side effects (e.g. bleeding events or myocardial infarction) and dependence on others or requiring care. However, these were not fully reported in any of the studies. None of the four studies provided results on further criteria that are important for patients such as health-related quality of life, hospitalization or physical endurance.

Considerably more strokes in temporal proximity to the intervention

As the SAMMPRIS data showed, a new stroke is considerably more common in patients who have received an intracranial stent than in patients who only received medication: This was the case in 59 participants (26.3%) in the PTAS group, and in only 42 participants (18.5%) in the comparator group.

Differentiated by type of stroke, these differences can be determined in haemorrhagic stroke, i.e. stroke caused by bleeding, but not in ischaemic stroke, which is caused by narrowing. The haemorrhagic strokes were often periprocedural events occurring within 30 days of the intervention. In many cases, these strokes were apparently caused by mechanical manipulation during the placement of the stent.

No differences in morbidity and revascularization

These disadvantages are not accompanied by advantages in other outcomes: There was no relevant difference between the treatment groups in mortality (all-cause mortality and cerebrovascular mortality). The IQWiG report came to the same conclusion with regard to repeated revascularization, i.e. the necessity to widen narrowed vessels again.

Results potentially biased

All the studies included by IQWiG were subject to uncertainty and their results might be biased. The main reasons were unclear issues regarding randomization and the premature unplanned termination of the studies.

This is also true for SAMMPRIS, which started in November 2008, but was ended prematurely in April 2011 because considerably more events (counting deaths and strokes) had occurred in the PTAS group. Even though this decision is comprehensible, the results can be biased because of the premature termination of the study.

Despite the uncertainty described, IQWiG overall considers there to be a hint of harm from PTAS in comparison with drug treatment alone.

Drugs were not used in compliance with their approval

The interpretation of the SAMMPRIS results was made more difficult because the drugs were not used according to the specifications in the Summary of Product Characteristics valid in Germany: The patients in both groups received a combination of two clot-inhibiting drugs, acetylsalicylic acid (ASA) and clopidogrel (dual antiplatelet therapy). This combination is used in Germany, but is not approved for stroke because it is known to increase the risk of bleeding. It can also not be excluded that there is an interaction between the drugs and stent placement (PTAS), which particularly might influence the occurrence of bleeding.

RCTs indispensable in medical devices as well

PTAS is another example that high-quality studies are needed for risk

class III medical devices, which also include stents: In the United States, intracranial stents had at first been approved for treatment of a specific, relatively small group of fewer than 4000 patients affected. This approval was based on case series and on the Humanitarian Device Exemption. However, Medicare, an American health insurance for elderly and disabled people, then demanded an RCT as prerequisite for its reimbursement of stents.

So the SAMMPRIS study, funded by the National Institutes of Health, was initiated. Only this RCT, i.e. a study with a higher level of evidence, revealed that more strokes occurred under the new, allegedly innovative Treatment.

Product safety is not the same as patient safety

This confirmed the conclusion already drawn in the case of antibody-coated stents inserted in coronary vessels: Not only the medical device is decisive, but also its manner of application. "The entire application including its accompanying factors has to be investigated, and not only the stents themselves, to obtain reliable knowledge about the benefit stents have for patients", concludes Stefan Sauerland, Head of the IQWiG Department of Non-Drug Interventions.

Process of report production

The Federal Joint Committee (G-BA) commissioned IQWiG on 28 February 2014 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 report (version 1.0) was sent to the commissioning agency on 11 September.

More information: www.iqwig.de/download/N14-01_E … racranial-stents.pdf

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