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Angina pectoris and heart attacks: What are the advantages and disadvantages of using ASA and clopidogrel together?



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Over time, fats and other substances in our blood attach to the inner walls of our blood vessels (arteries) and build up. As a result, the arteries gradually become narrower and harder. The medical term for this is “arteriosclerosis”: hardening of the arteries. The arteriosclerosis itself does not cause any symptoms at first. It only becomes a problem if it stops enough blood from getting through the vessels. The symptoms that people then have depend on which blood vessels are affected.

If it is the coronary arteries (around the heart) that are affected by arteriosclerosis, the heart gradually gets less and less oxygen over time. This is called coronary heart disease (CHD) or coronary artery disease (CAD). It is not known exactly how many people in Germany have CHD, but it is a common disease.

The main symptoms of coronary heart disease are sudden chest pains which can last anything between a few seconds and several minutes. The medical name for this symptom is angina pectoris, which means “tight chest” in Latin. Most people who are affected have stable angina pectoris. This means that symptoms only arise when they do physical exercise, like climbing stairs, and then disappear again when they are at rest. Unstable angina pectoris, which is much less common, is already noticeable following very light physical activity or even when the person is resting. Unlike the stable form, unstable angina pectoris poses an immediate threat: the person is in danger of having a heart attack (myocardial infarction). Unstable angina pectoris and heart attacks are also called “acute coronary syndrome”.

Heart attacks happen when a coronary artery suddenly becomes so blocked that part of the heart muscle is no longer supplied with oxygen. Without quick treatment, part of the muscle tissue dies. This can be life-threatening. The likelihood of surviving a heart attack has greatly increased over the years, thanks to better treatment options: in Germany, about 3 out of 4 people survive a heart attack nowadays.

The signs of a heart attack include chest pain, breathing difficulties and nausea. The signs may be less typical though, like sudden pain in the upper abdomen. You can

find more information about how to recognise the signs of a heart attack in our feature (URL: <http://www.gesundheitsinformation.de/heart-attack.314.56.en.htm>) .

If someone is suspected of having a heart attack, a blood test and an electrocardiogram (ECG) are done to confirm the diagnosis. The blood test detects particular proteins that are released by the heart muscle during a heart attack. The ECG test measures the electrical impulses that control heart beat, and these are shown in a graph. The graph looks different in people who have had a heart attack because a part of the heart muscle dies. Doctors differentiate between heart attacks where a particular section of the ECG – called the ST segment – is elevated, and heart attacks where the ST segment is not elevated. This is an important difference in terms of how it is treated.

Treatment of unstable angina pectoris and heart attacks

Unstable angina pectoris and heart attacks are first treated with medication or a procedure to open the blocked blood vessel as quickly as possible, so that the heart gets enough oxygen again. To prevent further heart attacks, people usually take medication to slow down the blood-clotting process. These anti-clotting drugs are often called “blood thinners” but this term is, strictly speaking, misleading: they do not actually thin the blood. The medical term for this medication is thrombocyte function inhibitors. It prevents the blood platelets (thrombocytes) in the blood from sticking together and attaching to the walls of blood vessels. This medication is used over long periods of time. You can read more about the long-term use of medication here (URL: <http://www.informedhealthonline.org/index.405.en.html>) .

The most well-known of these anti-clotting medications is acetylsalicylic acid (ASA, called ASS in Germany; the drug in medications like Aspirin). This is the best studied anti-clotting medication, and it is used in almost everyone who has unstable angina pectoris or has had a heart attack, as long as there are no important reasons not to. A fairly new anti-clotting medication called clopidogrel can be taken together with ASA to increase the anti-clotting effect. But this also increases the risk of adverse effects. The most common adverse effect of anti-clotting medication is bleeding. Light bleeding, as with nose bleeds or traces of blood in the urine, are usually not a problem. But heavy bleeding is also possible, and urgent

medical treatment is needed if that happens.

Together with researchers from Bielefeld and Bremen in Germany, researchers at the German Institute for Quality and Efficiency in Health Care (IQWiG) looked into whether taking clopidogrel as well as ASA had any advantages for people with acute coronary syndrome. Patients were not included in the analysis if they had an elective coronary stent (in other words, a stent that was not a part of treatment for acute coronary syndrome, for example). This is because combined therapy using ASA and clopidogrel has not been approved for use in this group of people in Germany.

Research on combined treatment with ASA and clopidogrel

IQWiG looked for trials that compared treatment using ASA alone with treatment in which both ASA and clopidogrel were used. The trials had to meet certain criteria to be included in the analysis. One of these criteria was that they had to be randomised controlled trials, where participants were randomly assigned to a treatment group. You can read about why this approach is important here (URL: <http://www.gesundheitsinformation.de/evidence-based-medicine.61a91.com/>). Another criterion was that they had to look at aspects that are important for people who have heart problems, such as whether the treatment prevented heart attacks or strokes. Five trials met these criteria.

Research on treatment after acute coronary syndrome without ST segment elevation

One trial – called the CURE trial – looked at treatment used by people who had acute coronary syndrome without ST segment elevation. Most of them were using it because of unstable angina pectoris. A total of 12,500 people took part in this trial, and about 40% of them were women. Their average age was 64 years.

The patients were randomly assigned to one of two groups. One of the groups took both ASA and clopidogrel, and the other group took ASA and a dummy medication (placebo). The participants did not know which group they were in. The doses of ASA used in the research were between 75 and 325 mg per day, and the doses of clopidogrel used were 300 mg on the first day, followed by 75 mg per day after that. The participants were monitored for up to 12 months.

The CURE trial showed that more heart attacks can be prevented in people who have acute coronary syndrome

without ST segment elevation if they take clopidogrel in addition to ASA: only 52 out of 1,000 people who took both ASA and clopidogrel had a heart attack within 12 months (5.2%), compared to 66 out of 1,000 people who took ASA alone (6.6%). In other words: for every thousand people who take clopidogrel in addition to ASA, 14 heart attacks can be prevented (1.4%).

However, using both ASA and clopidogrel also increases the risk of adverse effects: in the group of people who only took ASA, 24 out of 1,000 had mild bleeding (2.4%). In the group of people who took both ASA and clopidogrel, 51 out of 1,000 had this adverse effect (5.1%). The rate of heavy bleeding events – where, for example, surgery or a blood transfusion are needed – was 2.7% in the “ASA only” group (27 out of 1,000 people) and 3.7% in the “ASA plus clopidogrel” group (37 out of 1,000 people). In both groups, the risk of bleeding was lower in people who took lower doses of ASA (up to 100 mg per day) than it was in people who took higher doses.

Because the people in the CURE trial were only monitored for up to 12 months, it is not possible to draw conclusions about the long-term benefits and harms of this combined treatment.

Research on treatment after a heart attack with ST segment elevation

Four of the trials looked at the additional use of clopidogrel in people who had previously had a heart attack in which the ST segment of the ECG was elevated. A total of about 36,000 men and 14,000 women took part in these trials. They had an average age of 60 years. After initial treatment, half of the patients took ASA and a placebo drug, and the other half took ASA and clopidogrel. The drug dose used in the biggest trial, involving nearly 46,000 people, was 162 mg of ASA and 75 mg of clopidogrel per day. The participants only had this treatment during their hospital stay and were followed up for four weeks at the most.

The risk of having a new heart attack was lower if people took both ASA and clopidogrel rather than ASA alone. In the group of patients who only took ASA, 27 out of 1,000 people had another heart attack (2.7%). In the group of patients who took both ASA and clopidogrel, 22 out of 1,000 people had another heart attack within four weeks (2.2%). In other words, taking clopidogrel as well as ASA protected 5 out of 1,000 people (0.5%) from having a new heart attack. Strokes were also somewhat less

common in the group of people who took both ASA and clopidogrel. Because the people in the trial were only monitored for up to four weeks, it is not possible to say whether this positive effect increases or decreases in the long term.

The trials also found that taking both drugs was associated with a slightly higher risk of bleeding. More specifically: 35 out of 1,000 people in the “ASA plus clopidogrel” group had light bleeding (3.5%), compared to 30 out of 1,000 people in the “ASA only” group (3%). So there was a difference of 0.5%. Heavy bleeding was rare in both groups.

Weighing up the pros and cons

It is important for people who have had a heart attack to take an anti-clotting medication like ASA if there are no serious reasons not to. Taking ASA lowers the risk of further cardiovascular disease. When deciding whether to take clopidogrel as well, however, the possible benefits and harms have to be weighed up: do I want to lower my risk of a heart attack or stroke and, at the same time, accept a higher risk of bleeding? Another reason why this decision is so important is because, for instance, the CURE trial (of acute coronary syndrome without ST segment elevation) only lasted 12 months, but indicated that the risk of bleeding increases over time, whereas the benefits of combining ASA with clopidogrel decrease. That is why it is important to discuss all of the factors with your doctor, and then decide whether taking clopidogrel in addition to ASA would be the right choice for you.

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Note

This health information is a summary of a scientific report published by IQWiG. It is not an assessment of the right to have health care services reimbursed by statutory health insurance funds in Germany. By law, decisions about the reimbursement of diagnostic and therapeutic procedures can only be made by the German Federal Joint Committee (G-BA). The Federal Joint Committee takes IQWiG reports into consideration in its decision-making process. You can find information about the decisions of the German Federal Joint Committee on its English-language website, www.english.g-ba.de (URL: <http://www.english.g-ba.de/>).

Glossary

thrombocyte

Thrombocytes or platelets are cells that play an important role in stopping bleeding. The word thrombocyte comes from the Greek "thrombos" meaning a "thick drop" or clot, and "cyte" means cell. If a blood vessel is damaged, thrombocytes line the wall of the vessel. The thrombocytes clump together into a ball. This process is called aggregation. Eventually a clot forms and that stops the bleeding.

stroke

A stroke (also sometimes called brain attack, or apoplexy, which is Greek for "struck down") is an acute condition where the brain does not get enough oxygen. It is most commonly caused by a blood clot that has travelled through the bloodstream and is blocking blood vessels in the brain. In rarer cases bleeding in the brain may also result in a stroke. Depending on which part of the brain is affected, there may be paralysis of either all or certain parts of one half of the body, facial nerve impairment, vision problems, trouble balancing and severe problems speaking. A stroke is a medical emergency: the parts of the brain that are affected need to be supplied with oxygen as quickly as possible, to avoid the death of more brain tissue. The risk of having a stroke is greater for older people and people who have hypertension or chronic arteriosclerosis.

diagnosis

The term diagnosis (from the Greek word *diagnosi*: "distinguishing") is used to mean the identification and naming of an illness or a disease. A diagnosis is usually made by evaluating the medical history, symptoms and test results. The tests include both comprehensive physical examination and blood tests or examinations using medical instruments such as ultrasound or x-ray.

Sources

German Institute for Quality and Efficiency in Health Care (IQWiG). *Clpidogrel plus acetylsalicylic acid in acute coronary syndrome. Final report A04-01B. Version 1.0*. Cologne: IQWiG. January 2009. [Executive summary (URL: http://www.iqwig.de/download/A04-01B_Executive_summary_Clopidogrel_plus_acetylsalicylic_acid_in_acute_coronary_syndrome.f)] [Full text (URL: http://www.iqwig.de/download/A04-01B_AB_Clopidogrel_plus_ASS_bei_akutem_Koronarsyndrom.html) - in German]

The German Institute for Quality and Efficiency in Health Care (IQWiG)

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Evidence basis of our health information

Our information is based primarily on systematic reviews of the effects of health care. Systematic reviews are necessary to gain an objective picture of health care. In order to do this, a clear question is formulated. Researchers then find all the relevant studies that could answer this question. They then evaluate those studies.

You can find a list of the evidence and other scientific literature on which this information is based at **www.informedhealthonline.org**

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