

## Heart disease and diabetes: Which statins have been well-investigated?



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The statins are medicines that might be able to lower the risk of another heart attack among people who have already had one. These five types of statins are licensed for use in Germany: atorvastatin, fluvastatin, lovastatin, pravastatin and simvastatin. Statins are known as cholesterol-lowering or fat-lowering medicines. This is because they can reduce the levels of cholesterol in the blood.

Many doctors are convinced that this cholesterol-lowering effect is also responsible for lowering the risk of a heart attack. However, it is not known exactly how this might work. Statins have an impact on the blood vessels, and there could also be other, yet unknown effects. Which of these might be responsible for the effectiveness of statins is still unclear.

The answer to this question is important for patients. If statins had a benefit simply because they lowered cholesterol, it would mean that the statin that lowered cholesterol the most would also be the best at preventing heart attacks. A reliable answer to this question can only come from trials which compare two or more statins directly with each other. These are sometimes called head-to-head trials. However, IQWiG's research shows that there are few such trials for statins.

In most of the statin trials, the statins are compared with a placebo or dummy medication. These placebo trials show that statins are more effective than placebos. But they cannot show which statin is the best, because the statins were not often enough compared with each other.

IQWiG evaluated all the statin trials that had been published up to August 2005 to try to find out which of the statins might benefit people with the following illnesses:

- Stable coronary artery disease (inadequate blood flow to the heart): This includes everyone in particular who has had a heart attack.

- Acute coronary syndrome: This includes people who are in hospital because of a heart attack or a severe heart problem.
- Type 1 and Type 2 diabetes.

The detailed evaluation of the trials showed:

- Simvastatin and pravastatin can increase length of life among people with stable coronary artery disease. This effect has not been shown for the other three statins studied here.
- There are not enough conclusive trials for acute coronary syndrome. This means it is unclear how statins work for this group of people, especially for longterm use.
- Simvastatin has been shown to increase length of life for people with diabetes, but there is no evidence that this also goes for the other four statins studied.
- In the highest dose licensed for use in Germany, there are more adverse effects with atorvastatin than there are with the highest available doses of pravastatin and simvastatin.
- An analysis of these trial results showed no link between how much the level of LDL-cholesterol was reduced, and the risk of a heart attack or dying.

## How did IQWiG evaluate the effectiveness of the statins?

The effectiveness of statins was evaluated by systematic review of randomised controlled trials. The principle: Volunteers are assigned by chance (randomised) into two or more groups. One group took a statin every day for years. There was usually another group where the people took a placebo (dummy tablet). During this time, researchers gathered information on whether people had a heart attack or a stroke or if they died. They could then compare the two groups at the end of the trial.

For this evaluation, IQWiG looked for all trials that had been published in German or English, and which studied statins that are licensed for use in Germany. It was also essential for the evaluation that the trials included people with heart disease or diabetes.

The trials had to be able to help answering the following questions:

- Do statins reduce the rate of heart attack and/or death among people with stable coronary artery disease?
- Do statins reduce the rate of heart attack and/or death among people with acute coronary syndrome?
- Do statins reduce the rate of heart attack and/or death among people with diabetes?

IQWiG paid particular attention to the trials where any statins could be compared with each other. This was particularly relevant for the drug atorvastatin. The manufacturer of this statin had been publicly claiming in Germany that high doses of their product were an advantage that justified charging a higher price than for other statins. IQWiG also compared the adverse effects between the statins. In addition, IQWiG evaluated the suggestion that a greater reduction in cholesterol levels also leads to a greater reduction in the risk of dying.

### **Are there high quality studies?**

IQWiG found the largest amount of trials of good enough quality that addressed the above questions for atorvastatin, pravastatin and simvastatin. For stable coronary artery disease, seven randomised controlled trials including about 42,000 people met the evaluation criteria. None of the trials compared the different statins with each other. They compared a statin to a placebo, or two different doses of the same statin. Only six of these trials studied the influence of statins on the risk of dying.

There were four randomised controlled trials with about 15,000 people that filled the evaluation's criteria for acute coronary syndrome. For people with diabetes, there were eight randomised controlled trials that met the criteria, including about 17,000 people.

There was not enough evidence to compare the statins directly with each other. That means no judgment is

possible as to whether one type of statin has an advantage over any other. It did show, however, that simvastatin is the statin that has been best studied for people with stable coronary artery disease or diabetes.

### **What about adverse effects?**

Statins can be prescribed in daily doses of up to 80 mg in Germany. In five trials of mostly adequate quality, adverse effects of atorvastatin were studied.

Adverse effects of atorvastatin compared with the highest available dose of other statins were studied in five trials of mostly adequate quality. These trials showed that people who take the highest available dose of atorvastatin are likely to have more adverse effects than people who take the highest available dose of simvastatin.

In comparison with the highest doses of pravastatin and simvastatin, taking the highest dose of atorvastatin was more likely to have an effect on the liver. An uncommon adverse effect that all the statins have in common is muscle symptoms. The trials were not large enough, though, to be able to reach conclusions about whether these adverse effects happen more often with any statin in particular.

### **This additional information has been provided by the U.S. National Library of Medicine:**

In the U.S., rosuvastatin is also licensed for use by the Food and Drug Administration (FDA).

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### **Note**

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## Glossary

### cholesterol levels

Cholesterol levels are a way of measuring the concentration of cholesterol in the blood. It is often called fat levels, although cholesterol is not really a fat. Fat is found in the tiny droplets that transport cholesterol through the blood. Depending on the type of transport molecule, doctors differentiate between HDL, LDL and VLDL cholesterol. The total level of cholesterol, measured in milligrams per decilitre (mg/dl), combines the individual values of all these types of cholesterol.

### statins

Statins are a class of drugs that are described as cholesterol-lowering. Statins affect the metabolism of building blocks of cholesterol in the body, which slows down the production of cholesterol.

### evidence

Evidence is what we call scientific proof from well-conducted, good-quality scientific trials that have been carefully designed to answer specific questions. Depending on the types of questions, different scientific research methods (types of study) are most appropriate to find reliable answers to these questions. Randomized controlled trials (RCTs), for example, are the best way to get reliable evidence on the effectiveness of medical treatments (interventions). This type of study, however, is not the best form of evidence for all possible questions, and does not provide the best answers to all kinds of questions, either. Epidemiological studies, for example, are very suitable for establishing well-founded proof for the spreading of a disease in the population.

### systematic review

Systematic reviews pull together the evidence on a specific question. A systematic review sets out to find all the trials that have put that particular question to the test. The quality of the trials are then evaluated and then results analyzed and explained. Often, the results of trials can then be summarized together through a statistical method called meta-analysis.

### 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.

## **Sources**

German Institute for Quality and Efficiency in Health Care (IQWiG). *Evaluation of the effects of statins (with particular consideration of atorvastatin). Working paper. Version 1.0.* Cologne: IQWiG. August 2005. [Full text (URL: [http://www.iqwig.de/download/06-01-30\\_Evaluation\\_of\\_the\\_effects\\_of\\_statins\\_fina\\_report.html](http://www.iqwig.de/download/06-01-30_Evaluation_of_the_effects_of_statins_fina_report.html)) ]

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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](http://www.informedhealthonline.org)**

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