This is a summary of a clinical study in type 2 diabetes. It is written for the general reader and uses language that is easy to understand. It includes information about how researchers did the study and what the results were. The simplified title for the study is: 'A study of heart safety in patients with type 2 diabetes and cardiovascular disease who are treated with empagliflozin'.

We thank all patients who took part in this study. Through your participation, you helped researchers answer important questions about empagliflozin and the treatment of type 2 diabetes and cardiovascular disease.

What was this study about?

This was a study in patients with type 2 diabetes who also had cardiovascular disease. Patients with type 2 diabetes have too much sugar in their blood. This can increase the risk of serious health problems such as cardiovascular disease. Cardiovascular disease is any disease that affects the heart or the blood vessels. Common examples are heart attack, heart failure, and stroke.

Researchers wanted to see if patients who also took empagliflozin were more likely or less likely to have serious cardiovascular problems. Researchers also collected information about any side effects the patients had during the study.

This study started in August 2010 and finished in April 2015. The sponsor of this study was Boehringer Ingelheim.

Why was the study needed?

Patients with type 2 diabetes are more likely to have cardiovascular disease and to die from cardiovascular disease than from any other cause. It is important to find out whether medicines that are given to treat type 2 diabetes make cardiovascular disease more likely, or if they may lower the risk of cardiovascular disease.

Which medicines were studied?

The researchers studied a medicine called empagliflozin (also known as BI 10773). Empagliflozin is a medicine that is used to treat type 2 diabetes. Empagliflozin helps the kidneys to remove sugar from the blood. The sugar is removed in the urine. Empagliflozin belongs to a class of medicines called SGLT-2 inhibitors.

Some patients were given empagliflozin tablets and some patients were given placebo tablets. The placebo tablets looked like the empagliflozin tablets, but did not contain active medicine.

Who participated in the study?

Patients who had type 2 diabetes and cardiovascular disease participated in this study. They had followed a diet and exercise plan or had been treated with other diabetes medicines. However, they still had high blood sugar.

The patient's average age was 63 years. The youngest patient was 30 years old and the oldest was 90 years old.

Overall, 7020 patients were treated in the study. There were 5016 men (72%) and 2004 women (29%). The table below lists the regions and countries where patients took part in the study.

Geographical region	Countries	Patients
Europe and Israel	Austria, Belgium, Croatia, Czech Republic, Denmark, Estonia, France, Georgia, Greece, Hungary, Israel, Italy, Netherlands, Norway, Poland, Portugal, Romania, Russia, Spain, Ukraine, United Kingdom	2885
North America and Western Pacific	Australia, Canada, New Zealand, United States	1394
Asia	Hong Kong, India, Indonesia, Japan, Korea, Malaysia, Philippines, Singapore, Sri Lanka, Taiwan, Thailand	1347
Latin America	Argentina, Brazil, Colombia, Mexico, Peru	1081
Africa	South Africa	313

How was this study done?

Patients were divided into 3 groups of similar size. It was decided by chance who got into which group. Neither the patients in the groups nor the study doctors knew which treatment the patients received.

The patients in each group took 1 of the following medicines each day:

Empagliflozin 10 mg group: 1 tablet containing 10 milligrams (mg) of empagliflozin

Empagliflozin 25 mg group: 1 tablet containing 25 mg of empagliflozin

Placebo group: 1 placebo tablet

Patients in this study took empagliflozin or placebo tablets for about 2 years and 7 months on average. During the study, patients continued to receive their usual medicines for the treatment of type 2 diabetes and/or cardiovascular disease if they had been taking them before the study started.

Except for taking the different medicines, all patients followed the same procedures:

- Patients went to the study doctor every 4 to 14 weeks.
- Doctors took blood samples at certain visits.
- Doctors collected information on side effects at every visit.
- Patients had measurements of their heart rhythm taken at certain visits (electrocardiograms, or ECGs).

The doctors reviewed all medical test results at every visit. They discussed any health problems with the patients and performed further tests when needed.

The researchers wanted to know how many patients had a heart attack or a stroke, or died due to cardiovascular disease. Researchers call these events '3-MACE' which means 3 Major Adverse Cardiovascular Events. They combined the information from the 2 doses of empagliflozin to compare with placebo.

What were the results of this study?

In the placebo group, 282 out of 2333 patients (12.1%) had a heart attack, a stroke, or died due to cardiovascular disease. In the empagliflozin groups, 490 out of 4687 patients (10.5%) had a heart attack, a stroke, or died due to cardiovascular disease. These results show that empagliflozin lowered the chance of having a heart attack, a stroke, or dying due to cardiovascular disease by 14%.

Researchers looked into more detail at each type of event that is included in 3-MACE: heart attacks, strokes, and death due to cardiovascular disease. The results showed that the main effect of empagliflozin was to lower the risk of dying from cardiovascular disease.

How does empagliflozin affect the chances of dying from cardiovascular disease?

In the placebo group, 137 out of 2333 patients (5.9%) died due to cardiovascular disease. In the empagliflozin groups, 172 out of 4687 patients (3.7%) died due to cardiovascular disease. These results show that empagliflozin lowered the chance of dying from cardiovascular disease by 38%.

Researchers also looked at how many patients died in the study from any cause. In the placebo group, 194 out of 2333 patients (8.3%) died from any cause. In the empagliflozin groups, 269 out of 4687 patients (5.7%) died from any cause. These results show that patients who took empagliflozin had a 32% lower chance of dying from any cause than patients who took placebo.

Does empagliflozin affect the chances of having a heart attack?

In the placebo group, 126 out of 2333 patients (5.4%) had a heart attack. In the empagliflozin groups, 223 out of 4687 patients (4.8%) had a heart attack. These results do not clearly show that there was any difference in the chance of having a heart attack between patients taking empagliflozin and patients taking placebo.

Does empagliflozin affect the chances of having a stroke?

In the placebo group, 69 out of 2333 patients (3.0%) had a stroke. In the empagliflozin groups, 164 out of 4687 patients (3.5%) had a stroke. These results do not clearly show that there was any difference in the chance of having a stroke between patients taking empagliflozin and patients taking placebo.

What side effects did patients have?

A greater percentage of patients who took empagliflozin had side effects than patients who took placebo.

About the same percentage of patients in the empagliflozin groups and the placebo group had low blood sugar (hypoglycaemia).

The table below shows side effects that occurred in at least 1% of patients in the combined empagliflozin group or in the placebo group.

	Empagliflozin 10 or 25 mg (4687 patients)	**Placebo (2333 patients)**
Patients with any side effects	1309 patients (28%)	549 patients (24%)
Low blood sugar (Hypoglycaemia)	600 patients (13%)	284 patients (12 %)
Bladder infection (Urinary tract infection)	226 patients (5%)	120 patients (5%)
Frequent urination (Pollakiuria)	65 patients (1%)	15 patients (less than 1%)
Urinated large amounts of urine (Polyuria)	50 patients (1%)	9 patients (less than 1%)

Doctors keep track of all health problems patients have during a study. Some of these health problems might be caused by the study medicines, and some by other medicines taken by the patient. Others might be caused by the disease, and some have yet a different cause. Here we describe health problems that the doctors thought were caused by the study medicines. These health problems are called side effects.

Some patients in the study had serious side effects. A side effect was serious if it caused the patient to go to the hospital or stay longer in the hospital. Or if it needed a doctor's immediate attention, was life-threatening, or caused death.

In the placebo group, 28 of 2333 patients (1%) had at least 1 serious side effect. In the combined empagliflozin group, 93 of 4687 patients (2%) had at least 1 serious side effect.

Are there follow-up studies?

No follow-up studies are planned.

Where can I find more information?

You can find the scientific summaries of the study results at these websites:

www.trials.boehringer-ingelheim.com	search for the study number: BI 1245.25
www.clinicaltrialsregister.eu	search for the EudraCT number: 2009-016178-33
www.clinicaltrials.gov	search for the NCT number: NCT01131676

The full title of the study is:

'A Phase III, multicentre, international, randomised, parallel group, double blind cardiovascular safety study of BI 10773 (10 mg and 25 mg administered orally once daily) compared to usual care in type 2 diabetes mellitus patients with increased cardiovascular risk (The EMPA-REG OUTCOME® Trial)'.

Important notice

This summary shows only the results from one study and may not represent all of the knowledge about the medicine studied. Usually, more than one study is carried out in order to find out how well a medicine works and the side effects of the medicine. Other studies may have different results.

You should not change your therapy based on the results of this study without first talking to your treating physician. Always consult your treating physician about your specific therapy.

Boehringer Ingelheim has provided this lay summary in accordance with European Union transparency obligations.