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► **To cite this version:**

Faiez Zannad, Steven Macari. Drug treatment with empagliflozin lowered risk for hospitalization in people with heart failure with reduced ejection fraction. *Future Cardiology*, 2023, 19 (13), pp.625-670. 10.2217/fca-2023-0090 . hal-04317336

HAL Id: hal-04317336

<https://hal.univ-lorraine.fr/hal-04317336v1>

Submitted on 1 Dec 2023

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Plain Language Summary of Publication

Drug treatment with empagliflozin lowered risk for hospitalization in people with heart failure with reduced ejection fraction: plain language summary of the EMPEROR-Reduced study

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First draft submitted: 1 July 2023; Accepted for publication: 29 September 2023; Published online: 9 November 2023

Summary

What is this summary about?

This is a summary of the article describing the EMPEROR-Reduced study of empagliflozin, which was published in the *New England Journal of Medicine*. Empagliflozin (brand name Jardiance®) is a new drug therapy for the treatment of chronic heart failure. Chronic heart failure is a long-term condition where the heart cannot pump enough blood around the body, leading to symptoms such as shortness of breath, fatigue and build-up of too much water in the body (fluid retention). It also increases the risk for premature death.

How to say (double click sound icon to play sound)...

- **Empagliflozin:** em-pa-gli-FLOE-zin
- **Jardiance:** jar-DEE-ans

What was the EMPEROR-Reduced study?

The EMPEROR-Reduced study looked at the effects of empagliflozin, a medication taken once daily, in people with reduced ejection fraction. This is a type of heart failure where insufficient blood is pushed out of the heart muscle as it contracts. The study was conducted because more evidence is needed on the effects of empagliflozin and similar drugs in people with heart failure, including those with reduced ejection fraction. The main aim of the EMPEROR-Reduced study was to see if empagliflozin reduces the risk of being taken to hospital for complications of heart failure or dying from heart disease.

What happened during the study?

Over 3700 people with heart failure and reduced ejection fraction were randomly given either empagliflozin or placebo (an identical pill lacking medication) daily for about 16 months. This was a double-blind study, which means that neither the participants nor the researchers knew which treatment participants were receiving.

What were the results?

After an average of 16 months of continuous treatment, fewer patients taking empagliflozin (13.2%) needed to be hospitalized for complications of heart failure than those taking placebo (18.3%). Also, fewer patients taking empagliflozin (1.6%) developed serious kidney problems than those taking placebo (3.1%). Side effects were generally similar in participants who received empagliflozin and those who received placebo, except for genital tract infections, which affected more participants who received empagliflozin (1.7%) than placebo (0.6%).

What do the results mean?

This study suggests that people with chronic heart failure with reduced ejection fraction may benefit from treatment with empagliflozin, mainly by needing to go to hospital less often because of complications of heart failure.

Where can I find the original article on which this summary is based?

This summary is based on the article titled 'Cardiovascular and renal outcomes with empagliflozin in heart failure', which can be read for free at <https://www.nejm.org/doi/full/10.1056/NEJMoa2022190>

Who is this article for?

This plain language summary may be helpful for healthcare professionals who want to learn more about chronic heart failure, as well as people living with heart failure and their family and friends.

Who sponsored this study?

The EMPEROR-Reduced study was sponsored by Boehringer Ingelheim and Eli Lilly and Company Diabetes Alliance.

What is chronic heart failure with reduced ejection fraction?

Chronic heart failure is when the heart is unable to pump enough blood around the body. As a result, the brain, muscles and other organs do not receive enough oxygen and nutrients, while waste products such as carbon dioxide are not fully removed from the body. This leads to the typical symptoms of heart failure such as shortness of breath, fatigue and swelling of the stomach and lower legs because of fluid retention (build-up of too much water in the body).

Side effects of heart-failure medications such as diuretics (water pills) and blood-pressure-lowering drugs might also cause the symptoms listed above.

- So, it is important that people with heart failure receive medication and dosages that are suitable for the individual, rather than just the maximum dosages of all medications

Classification of heart failure

The New York Heart Association (NYHA) Functional Classification is one example of how chronic heart failure can be classified according to how severely it affects a person.

NYHA classification of heart failure



Class I

No symptoms and no limitation in ordinary physical activity, e.g., shortness of breath when climbing stairs, etc.



Class II

Mild symptoms (mild shortness of breath and/or chest pain/angina) and slight limitation during ordinary activity.



Class III

Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g., walking short distances (20–100 meters). Comfortable only at rest.

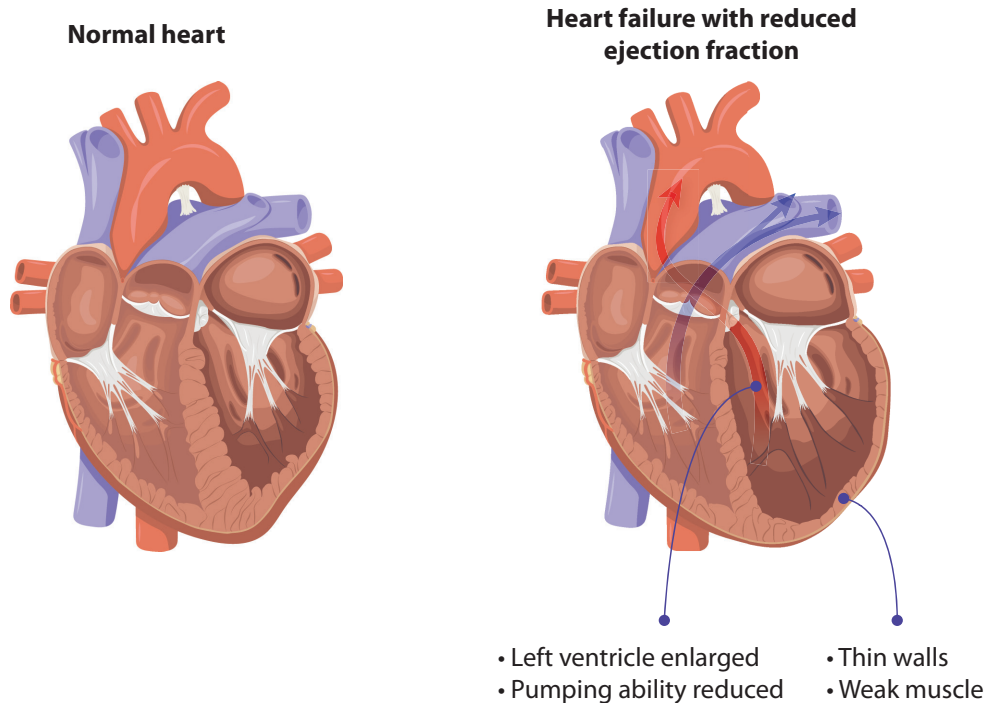


Class IV

Severe limitations. Experience symptoms even while at rest. Mostly bedbound patients.

Heart failure can also be classified by the percentage of blood pushed out of the left main chamber of the heart (the left ventricle) with every beat. This is called the ejection fraction.

- Reduced ejection fraction means that the heart cannot push out enough blood from the left ventricle with each beat
- Generally, reduced ejection fraction is considered to be when less than 40% of the blood is pushed out of the left ventricle
- The EMPEROR-Reduced study only included people with heart failure who had reduced ejection fraction



What is empagliflozin?

A protein in the kidney called SGLT2 normally reabsorbs sugar (glucose) that the kidney has removed from blood back into the blood. Empagliflozin is a medication that stops SGLT2 from reabsorbing glucose into the blood. Treatment with empagliflozin therefore causes glucose to be passed out of the body in urine, which lowers blood glucose levels in people with type 2 diabetes.

In addition, empagliflozin improved heart and kidney function in previous studies and has since been approved by health authorities in the US, Canada, Japan and many European countries to date for:

- Treatment of type 2 diabetes
- Treatment of symptomatic heart failure, including heart failure with reduced ejection fraction

What did the EMPEROR-Reduced study look at?

The EMPEROR-Reduced study was designed to see if empagliflozin would improve the health and well-being of people with heart failure and reduced ejection fraction.

The study mainly measured the following issues in participants:

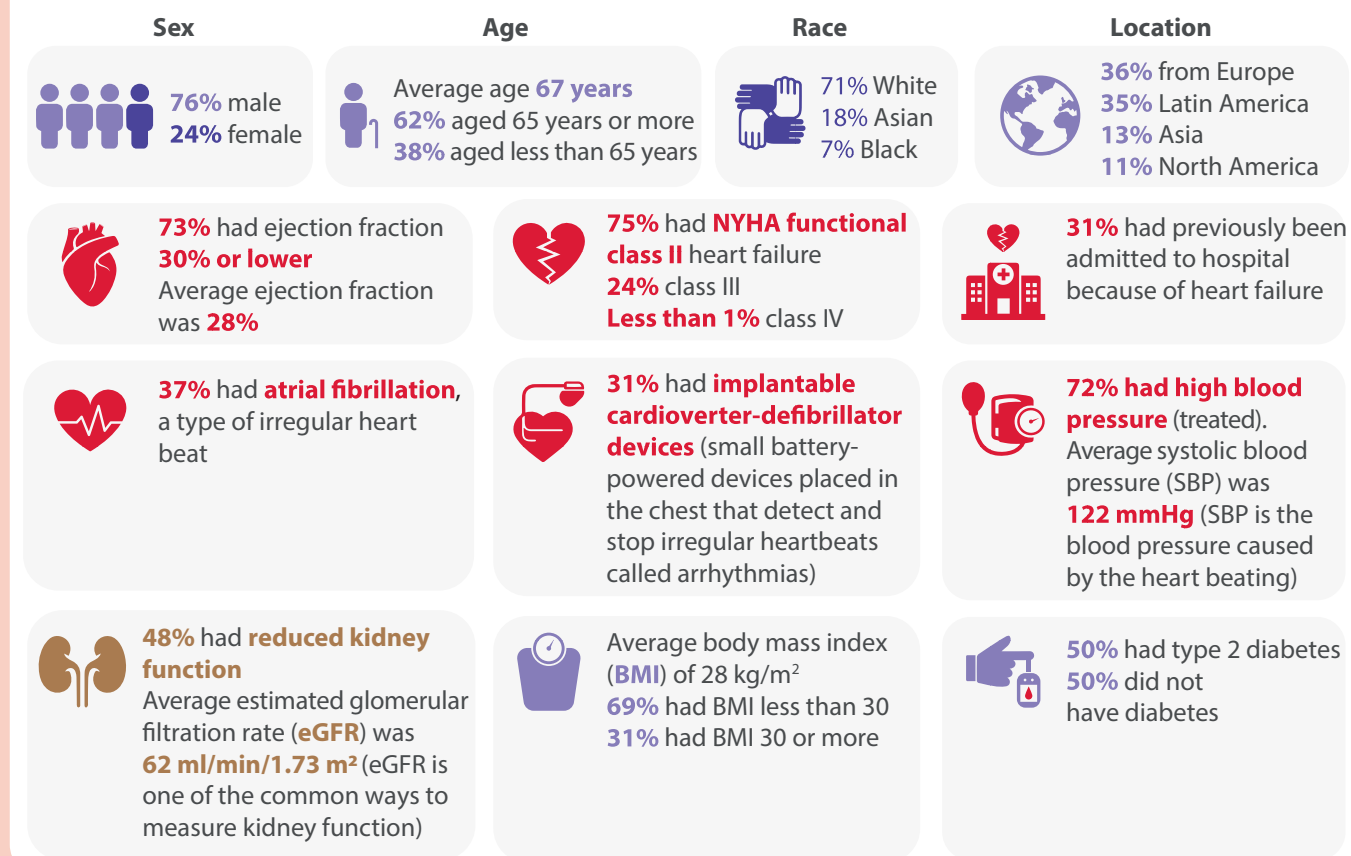
- Hospitalization and/or re-hospitalization for heart failure
- Death from heart disease
- How well the kidneys were working (kidney function)
- Quality of life. This was evaluated through a questionnaire called the Kansas City Cardiomyopathy Questionnaire (KCCQ)
- Side effects (unintended problems caused by a medication)

Who took part in this study?

The EMPEROR-Reduced study involved 3730 people who had been diagnosed with chronic heart failure with reduced ejection fraction.

Participants had to be in NYHA classes II to IV and have an ejection fraction of 40% or less.

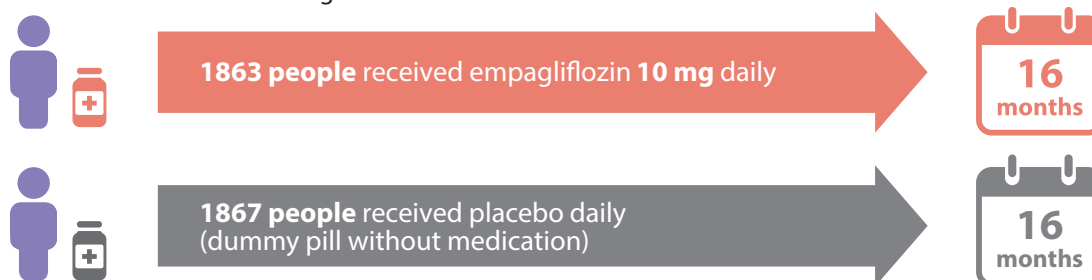
Study participant characteristics



What happened during the study?

Participants were randomly assigned to one of two groups. One group received empagliflozin in a daily 10 mg dose and the other group received a placebo pill, which looked identical to empagliflozin but did not contain any medication.

- This was a double-blind study, meaning that neither the participants nor their doctors knew who received which pill
- Participants with and without type 2 diabetes were evenly distributed in both groups
- Participants were observed for an average time of 16 months

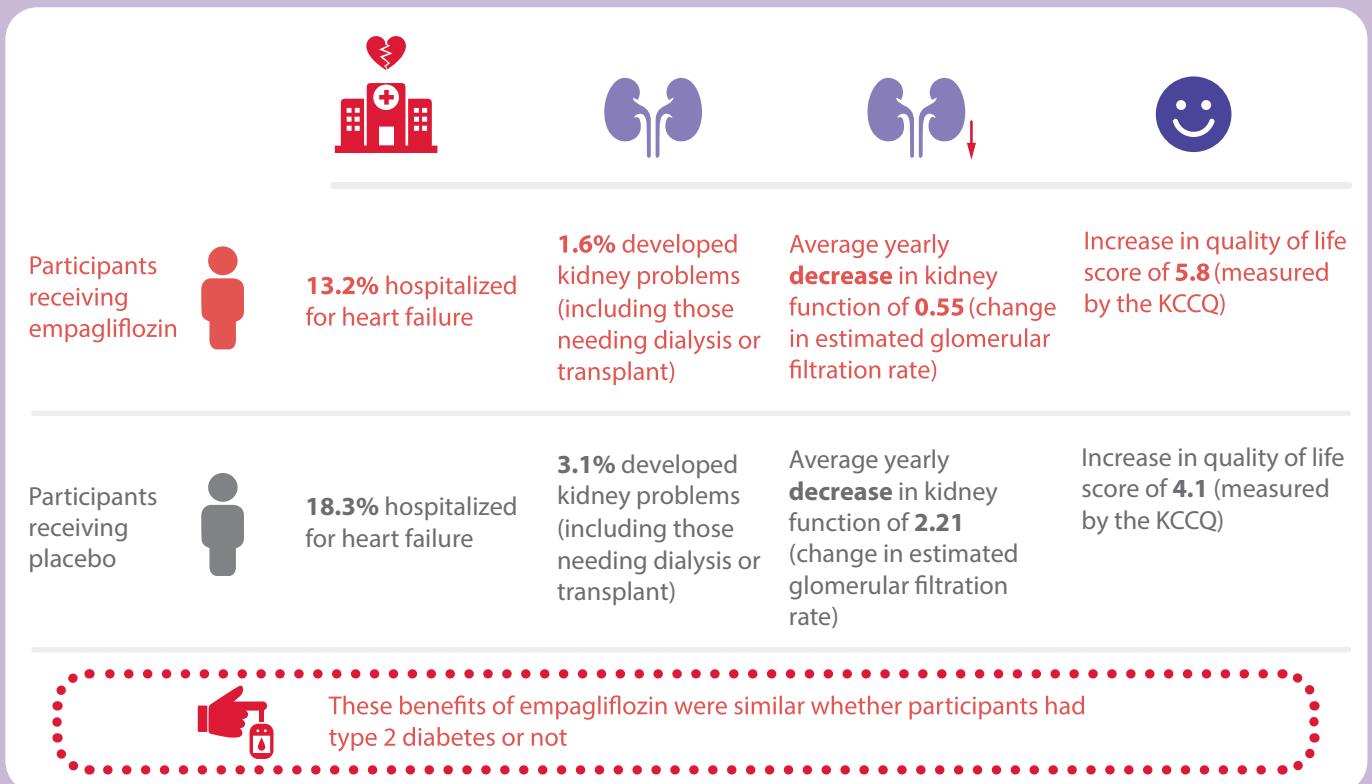


What were the results of the study?

Empagliflozin treatment was found to have the following effects, on average:

- Reduced the need for hospitalization for heart failure
- Improved quality of life (as measured with the KCCQ questionnaire)
- Did not damage the kidneys
- Slowed further loss of kidney function
- Had similar effects in people with or without type 2 diabetes

These results were similar regardless of participant age, sex, ethnicity or other characteristics.



Overall, the side effects of empagliflozin treatment in the EMPEROR-Reduced study were very similar to previous studies and no new unexpected ones occurred.

The rates of side effects caused by empagliflozin in the EMPEROR-Reduced study were comparatively low when the rates in the placebo group were also considered.

The most frequent type of side effect was a reduction in bodily fluid that can cause symptoms such as dizziness, fatigue, low blood pressure and slow heartbeat, which is called volume depletion.

- Volume depletion occurred in 10.6% of participants receiving empagliflozin and 9.9% of those receiving the placebo

Low blood sugar (hypoglycemia) also occurred in a similar number of participants receiving empagliflozin (1.4%) compared with those receiving the placebo (1.5%).

Genital infections were the only side effect reported in more participants receiving empagliflozin (1.7%) than placebo (0.6%). Even so, more than 98% of participants treated with empagliflozin did not experience genital infections.

What do the results of this study mean?

These results show that empagliflozin in people with heart failure and reduced ejection fraction:

- Has a positive effect on the heart
- Reduces the risk of having to be taken to hospital
- Protects the kidneys
- Reduces fluid retention (build-up of too much water in the body)
- Can improve quality of life
- Lowers blood glucose in people who also have type 2 diabetes
- Is generally safe

Where can I find more information about this study?

This summary is based on the article titled 'Cardiovascular and renal outcomes with empagliflozin in heart failure'

- Packer *et al.* *N. Engl. J. Med.* 383, 1413–1424 (2020).
- You can read the full article for free at <https://www.nejm.org/doi/full/10.1056/NEJMoa2022190>

The reason for the EMPEROR-Reduced study and how it was designed has been discussed in detail in a previous article.

- Packer M *et al.* Evaluation of the effect of sodium-glucose co-transporter 2 inhibition with empagliflozin on morbidity and mortality of patients with chronic heart failure and a reduced ejection fraction: rationale for and design of the EMPEROR-Reduced trial. *Eur. J. Heart Fail.* 21, 1270–1278 (2019).
- You can access the full article for free at <https://onlinelibrary.wiley.com/doi/10.1002/ejhf.1536>

You can also read more about the EMPEROR-Reduced study at ClinicalTrials.gov (www.clinicaltrials.gov). Type the NCT number, NCT03057977, into the search bar to find this study.

You can find further information about heart failure at <https://www.heart.org/en/health-topics/heart-failure/what-is-heart-failure>

Acknowledgments

The authors and study sponsors thank all the people who participated in the study.

Financial disclosure

Faiez Zannad received personal consulting fees or fees for participating in running clinical trials from Boehringer Ingelheim during the conduct of the EMPEROR-Preserved study, from Applied Therapeutics, AstraZeneca, Bayer, Cardior, Cellprothera, Cereno Pharmaceutical, CVRx, Janssen, Merck, Novartis and Vifor Fresenius outside the submitted work, and other support from Cardiorenal and CVCT outside the submitted work. Steven Macari has worked on projects with AstraZeneca, Bayer, Boehringer Ingelheim, CLS Vifor, CVCT, Global Heart Hub, INSERM CIC-P CHRU de Nancy – INI CRCT, Kidney Disease Clinical Trialists, Optim'IC, Pfizer, Novartis, Servier and The Heart Failure Policy Network. Steven Macari did not receive any financial remuneration for this Plain Language Summary of Publication. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Competing interests disclosure

Faiez Zannad was one of the authors of the original article in the *New England Journal of Medicine* (*N. Engl. J. Med.* 383, 1413–1424 [2020]). The authors have no other competing interests or relevant affiliations with any organization or entity with the subject matter or materials discussed in the manuscript apart from those disclosed.

Writing disclosure

Writing assistance for this plain language summary was provided by Giles Brooke, PhD, of Elevate Scientific Solutions, and was supported financially by Boehringer Ingelheim.