Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes mellitus

Dr. Hertzel Gerstein in an interview with Dr. Roman Jaeschke

Hertzel C. Gerstein, MD, MSC, FRCPC
An endocrinologist and professor at McMaster University and Hamilton Health Sciences, Hamilton, Ontario, Canada; research interests focus on prevention and therapy of diabetes and evidence-based diabetes care

Professor Gerstein, your research changed diabetic management through the last decades. However, I would like to ask you to talk about somebody else's research. There is a study that could potentially change how we practice diabetic care. Could you give us your views on that?

Thanks very much, Roman. The study you are talking about is called the EMPA-REG OUTCOME study,[1] and it was a study done in 7020 people with type 2 diabetes mellitus who had previous cardiovascular disease or clear evidence of cardiovascular disease, such as angiographic evidence of coronary narrowing. These people were randomized to either placebo or a drug called empagliflozin, and they were actually randomized to 2 different doses of empagliflozin, either 10 mg or 25 mg. The primary analysis was to compare the placebo group to the combined both-doses group. The study continued for 3.1 years, patients were seen periodically, and as I said, it was a blinded study, so investigators were told to manage the patients' blood pressure, lipids, and glucose levels to the best of their abilities, obviously unaware of the drug the people were taking.

At the end of a median follow-up of 3.1 years, the study ended and the results were presented at the European diabetes meeting in September. They showed that people randomized to empagliflozin had a 14%—very significant—reduction in the composite outcome of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes. Even more interesting and more striking was that there was a totally independent reduction in death from all causes as well as death from cardiovascular causes, and a 30% to 35% reduction additionally in death from heart failure with no major effect on myocardial infarction or stroke alone. This study is very unique in that it really showed a very clear benefit of this glucose-lowering drug on serious health outcomes.

That is quite amazing in terms of diabetic trials so far in terms of lowering the overall mortality. What kind of populations have they involved?

This was a study done in people who really had established cardiovascular risk factors. Interestingly, about 35% to 40% of them had evidence of albuminuria, either microalbuminuria or macroalbuminuria, about 25% had a glomerular filtration rate that was less than 60 ml/min/1.73 m^2, and everybody in the trial had evidence of cardiovascular disease, either an event in the past or evidence of cardiovascular disease. The rate of death from all causes in these participants was about 3% per year, and if you look at what we see in many large cardiovascular outcome studies in diabetes

patients, we used to recruit a lower-risk group of people than that with event rates more typically in the range of 2.5% to 3% per year for total cardiovascular composite events, and in this group, the death rate was 3% per year, and the total event rate was about 4% per year. This was a higher--risk group than we typically see, and that brings questions as to how this drug may have worked.

It also involves the question of who should be exposed to this drug. Could you give us your feel for where this class of drugs, or that particular drug, fits into the whole armamentarium of diabetic treatment?

Empagliflozin is part of what is called the SGLT2--inhibitor class of drugs—these are sodium--glucose linked transporters—and this is a glucose transporter, which is on the proximal tubule of the kidney. Normally, when blood goes through the glomerulus, 90% of the glucose is reabsorbed in the proximal tubule along with sodium with this transporter, the sodium-glucose linked transporter. What this drug does is it blocks that transporter, so that glucose is delivered more distally to the renal tubule and you actually excrete a lot of glucose in your urine. That is the way the drug lowers glucose typically.

The question is: How would that have an effect on cardiovascular outcomes and specifically on heart failure and death from cardiovascular causes? If one looks at the survival curves on this study, it is pretty clear this not a metabolic effect, and this is not due to a glucose-lowering effect, for instance, especially because the study was not designed as a glucose-lowering trial. Investigators were intervening to keep the glucose levels the same in both groups because they did not know what they were on, so there was only a very small difference in the glucose level. Despite the fact there was lower blood pressure in the treatment group—one of the things this drug does is lower blood pressure—this is clearly not a blood pressure trial, first because the curves diverge almost immediately after randomization, which is not what you see with blood-pressure lowering interventions, and there was also no clear effect on stroke, which we see with almost every blood pressure intervention, so I do not think this is a blood pressure effect.

The question is, why was there a benefit on cardiovascular outcomes, and the short answer is (and I have been to many meetings where we have had many debates about this)—we do not really know. However, there are some suspicions. One of the suspicions may be that what this drug essentially does is that it does cause you to urinate out glucose and it does drop your blood pressure a bit, and in effect it is a bit of an osmotic diuretic. If a lot of these patients with diabetes had undetected left ventricular (LV) dysfunction (and I suspect they did because they had a long history of diabetes and they had previous cardiovascular events, a lot of these people do have stiff ventricles and LV dysfunction and a proportion of them, I think it was 10%, had previous heart failure) and you are giving an osmotic diuretic to half of these people, or actually it was two-thirds of the people because of the randomization, perhaps we are seeing the effect of diuresis in people who are at risk for heart failure. The strong signal for mortality and heart failure hospitalization, the fact that the Kaplan–Meier curves diverge almost immediately (which is what you see with studies with the eplerenone and with other diuretic-type drugs) really makes me suspect that that is the mechanism of action, but a lot of research is being now done to try to understand this surprising result. I could say that it was surprising to everybody who was involved in the diabetes community, both the people who are investigators and the people who were observers of this study.

Surprising and they are probably quite happy to see that. So taking it all into account, how does this drug find its way into your own practice, if you are already using it?

If you have a patient in front of you with diabetes who also happens to have a number of other cardiovascular risk factors similar to the types of patients in this study, you say: Well, what can I do for this patient that is going to help to mitigate their risk? They are on a statin, on an angiotensin--converting enzyme inhibitor, on all the right drugs, and this is a drug that I would personally consider in every patient as long as they are eligible for the drug. If they had no renal function, it is not good—obviously in renal failure patients it is not good. The drug can cause some side effects, like urosepsis or genital infections in a small percentage of people; I would not consider it for those patients.

Otherwise, I think it is a very reasonable drug to consider. When it is used to lower glucose levels, it does not cause hypoglycemia on itself, it seems to be fairly safe, and it has a reasonably good profile. It is not to be used in type 1 diabetes until we understand more, only in type 2 diabetes, and there have been a few reports of ketoacidosis in patients with type 2 diabetes even, so one has to be a little cautious. But I think it is something that could be considered in many of our patients at high risk for cardiovascular disease. On the other hand, if you see a patient with type 2 diabetes who does not have a lot of other cardiovascular risk factors, we do not know whether there would still be a benefit. Maybe the benefit is restricted to people who are at risk for these problems. I think it has actually risen fairly quickly into the list of drugs that people are considering using because we have a drug that not only lowers glucose levels, and that means it has all the benefits of glucose lowering on eye disease and kidney disease, but it also now seems to have a benefit for mortality. There was a recent paper just presented at the American Society of Nephrology showing that you actually improved renal outcomes and

reduced progression of hard renal outcomes. So I think there is a lot of interesting stuff with this drug right now, and this class of drugs is probably related to it.

Maybe a difficult a question, or maybe impossible to answer, but if you see a referral of a patient— I would say, an average diabetic, a little bit of obesity, a little bit of hypertension—how do you find your way? What can you advise people in the community who are faced with a similar decision?

I think the most important message that I tend to say when I speak to other colleagues who are asking about this is that there really is no such thing as an average patient. Every patient is a unique individual and research tells us what the average patient does and responds to with therapy on average, but no one person is an average. Every person is unique, and our jobs as doctors is to look at the patient, asses all of the circumstances that the patient has, the history, the physical examinations, and make a decision based on that patient. If somebody I see has a lot of other cardiovascular risk factors, they have type 2 diabetes, they kind of fit the profile of the patient in this study, then this would really march very quickly to the top of my list. If their sugar levels are perfectly controlled and they are doing very well, their blood pressures are perfect, and I think they have really good cardioprotection, then I am not going to change their therapy around because I am probably asking for trouble. Unfortunately, not all my patients are in that situation. I do have patients that despite our best efforts are still not optimally controlled, with a lot of weight, and I say: "Well, this drug lowers blood pressure, causes some weight reduction, low side effects, it will lower glucose levels, and it has a cardiovascular protective effect. I am considering it a lot sooner than other drugs that do not necessarily do that.

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