Drugs in diabetes in 2016, changes in endocrinology in 2015

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

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In a previous interview,[1] you told us about empagliflozin. How about the other classes of drugs used in the treatment of type 2 diabetes? Which one would you say we use—I do not know whether it could be said—routinely, regularly? I know already that there is no such thing as an average patient.

Right now we have 12 different classes of drugs available to treat people with type 2 diabetes and that is wonderful. When I started and when you started training, Roman, there were essentially 3: insulin, sulfonylureas, and metformin.

Life was simpler.

That was all there was. Now we have 12 classes in the United States—in other countries it is about 10 or 11. That to me is wonderful; it means that we have choice and it means that we can tailor more the therapy to the individual patients that we have. Several of the drugs we have cause weight loss as a side effect: actually 2 of them, sodium-glucose cotransporter 2 (SGLT2) inhibitors and the glucagon-like peptide (GLP)-1 receptor agonists do have a weight loss effect. Many of the drugs do not cause hypoglycemia and very few cause weight gain now. The only drugs that cause a little bit of weight gain are sulfonylureas and insulin, and thiazolidinediones, which are not used that often today. I think most people would not argue that unless there was a contraindication or people could not tolerate the drug, people today should probably be taking metformin as an agent for diabetes for lots of reasons, including its long safety record, the fact that it may be associated with a lower risk of cardiovascular events and other outcomes, and that it has really proven itself over the years.

After that, I think it depends on how hyperglycemic the patient is and what their comorbidities are. If they have renal failure, you cannot use many drugs; if they have a very low glomerular filtration rate (GFR), insulin is probably the only safe drug to use for people with a low GFR. If they are very hyperglycemic, you are probably wise to start with insulin right away or in addition to metformin because you have to lower their blood glucose levels and get them down quickly; if they are at high cardiovascular risk, I think empagliflozin is a reasonable drug. If weight loss is an important criterion, then one can consider GLP-1 receptor agonist plus empagliflozin. If they had previous pancreatitis, then you would not want to use the drugs that have concerns about pancreatitis, like the incretins-ipeptidyl peptidase-4 (DPP-4) inhibitors. So I guess I do not have an easy answer for the question. There are also issues of

whether they have reimbursement, who is paying for the drug, of whether they have coverage.

In the end, you want your patients to have the best glucose levels to reduce their risk of eye, kidney, and nerve disease, and that means the best that can be safely achieved in that patient. You want them to have good blood pressure levels, ideally less than 135 mmHg systolic blood pressure (SBP) in order to reduce the risk of stroke and cardiovascular diseases in general. You want them to be on a statin. If the risk of cardiovascular events is anything significant, more than 1.5% to 2.0% per year, add an angiotensin-converting--enzyme inhibitor or angiotensin receptor blocker. After that, the drugs that you are going to choose from a glucose perspective are the ones that have additional effects: they are lowering blood pressure in addition to glucose levels, they are having cardiovascular benefits. Those are the types of things one must think about.

Thank you. It is sure helpful to me when I see my patients with diabetes. Last question: We are around the new year time, 2015–2016. If you were to reflect on roughly the last year of development in endocrinology or in diabetes, what would be the milestones, if any?

I think the EMPA-REG trial[2] that I told you about in the previous interview,[1] the empagliflozin study, is certainly a milestone and I think it will stand out as being one of the research findings that really has very direct and immediate relevance to our patients with diabetes. It also has brought this whole new class of drugs into the fore, the SGLT2 inhibitors, and now we have a drug that acts on the kidney and is reducing cardiovascular outcomes, and that is causing paradigm shifts as we speak. People are rethinking cardiovascular disease, dysglycemia, and renal disease, and the interactions amongst all three. Very important.

There have been other trials that have been presented this year in the diabetes space. The first trial of a GLP-1 receptor agonist that I helped lead, called the ELIXA trial,[3] showed that in post--acute coronary syndrome patients the drug had a neutral effect on cardiovascular outcomes and it obviously does lower glucose levels in a different way. There was another DPP-4 inhibitor trial, the sitagliptin trial, that showed also a neutral effect when the drug was given to people who had previous cardiovascular events, similar to those in the EMPA-REG study.[2] We are learning that many of our type 2 diabetes drugs are safe. In fact, with respect to long-term bad outcomes they are actually not causing the bad outcomes, and with empagliflozin they are actually protective; that is really important.

The other broad area just linked to diabetes is that some are beginning to focus on what is causing all the problems that occur in people with diabetes and in fact how is diabetes linked to aging, because diabetes is in fact a disease of accelerated aging. There has been a lot of interest starting to emerge as to can we start to develop and test drugs that may slow the aging process. Maybe in a way we are doing it now by some of the antihypertensive drugs that we are studying and we know, and the glucose drugs and the lipid drugs. There was the lipid trial —the ezetimibe trial— which showed that another lipid-lowering drug does reduce some events. So maybe we are starting to push back the age. Interestingly, there have been epidemiological studies published in the last year or 2 showing that even the incidence of cardiovascular outcomes in people with diabetes has been falling a little bit in the last 10 years. I think we are making a dent and that is really good news.

In the nondiabetes field, I do not think there have been any major breakthroughs. There continues to be work in a variety of areas. But the encouraging thing is that outcomes-based research—where we are assessing the effect of our interventions on health outcomes that are relevant to not just doctors but to *The New York Times* and the general public—are really becoming the norm, and that we are actually, certainly in the diabetes world, and in other places, testing our therapies against things that mean something to the average person in the street. That is really important. It means that we are doing relevant things.

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