Clinical outcomes in diabetes: It's not just the glucose (and it's not so simple)

The pharmacologic management of patients who have a chronic disease such as heart failure or diabetes is not straightforward. As the understanding of the pathophysiology of these disorders has become more comprehensive, new therapies have been developed that target specific disease pathways. And as the drugs are developed and tested in preclinical models and then in large-scale clinical trials, we learn more about the pathophysiology and the complex relationship between the disease, the patient, and associated comorbidities. The management of heart failure is no longer only about managing the patient's volume status and attempting to improve myocardial contractility. And as Makin and Lansang discuss in this issue of the *Journal* (page 595), management of the patient with diabetes is no longer just about lowering their glucose.

There has been increasing emphasis from drug regulatory agencies on collecting robust data on multiple outcomes from clinical trials in addition to the efficacy outcomes and usual safety data. For about a decade, the US Food and Drug Administration has required the collection of cardiovascular outcome data during the testing of new antidiabetic therapies. There are several potential consequences of this mandate, in addition to our now having a better understanding of cardiovascular risk. Studies are likely to be larger, longer, and more expensive. Patient cohorts are selected with this in mind, meaning that studies may be harder to compare, and labeled indications may be more specific. And we now have several drugs carrying a specific indication to reduce cardiovascular death in patients with diabetes!

But as we dig deeper into the reduction in cardiovascular deaths seen in clinical trials with some of the sodium-glucose cotransporter 2 (SGLT2) inhibitors, several questions arise. Why is their effect on mortality and cardiovascular events (and preservation of renal function) not a consistent drug class effect? All of these inhibitors decrease glucose reabsorption and thus cause glucosuria, resulting in lower blood glucose levels with modest caloric wasting and weight loss, as well as natriuresis with mild volume depletion. But the individual drugs behaved slightly differently in clinical trials. Perhaps this was due to slightly different trial populations, or chance (despite large trial numbers), or maybe molecular differences in the drugs despite their shared effect on glucosuria, resulting in distinct "off-target" effects. Perhaps the drugs differentially affect other transporters, on cells other than renal tubular cells, altering their function. An additional known effect of the drug class is uricosuria and mild relative hypouricemia. The differential effects of these drugs on urate transport into and out of different cells that may influence components of the metabolic syndrome and cardiovascular and renal outcomes has yet to be fully explored.

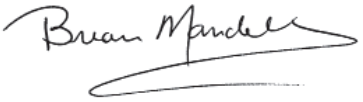
But one thing that seems to be true is that the effect of empagliflozin and canagliflozin on cardiac mortality is not due to simply lowering the blood glucose. Trials like the UK Prospective Diabetes Study[1] demonstrated that better glucose control

doi:10.3949/ccjm.86b.09019

reduced microvascular complications, but they did not initially show a reduction in myocardial infarction. It took long-term follow-up studies to indicate that more intensive initial glucose control could reduce cardiovascular events. But a beneficial effect of empagliflozin (compared with placebo) on cardiovascular mortality (but interestingly not on stroke or nonfatal myocardial infarction) was seen within 3 months.[2] This observation suggests unique properties of this drug and some others in the class, in addition to their glucose-lowering effect. Puzzling to me, looking at several of the SGLT2 inhibitor drug studies, is why they seemed to behave differently in terms of different cardiovascular outcomes (eg, heart failure, stroke, nonfatal myocardial infarction, need for limb amputation). While some of these seemingly paradoxical outcomes have also been seen in studies of other drugs, these differences are hard for me to understand on a biological basis: they do not seem consistent with simply differential drug effects on either acute thrombosis or chronic hypoperfusion. We have much more to learn.

For the moment, I suppose we should let our practice be guided by the results of specific clinical trials, hoping that at some point head-to-head comparator drug trials will be undertaken to provide us with even better guidance in drug selection.

We can also hope that our patients with diabetes will somehow be able to afford our increasingly complex and evidence-supported pharmacotherapy, as now not only can we lower the levels of blood glucose and biomarkers of comorbidity, we can also reduce adverse cardiovascular outcomes.



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1. **Holman RR, Paul SK, Bethel MA, Matthews DR, Neil AW**. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008; 359(15):1577–1589. doi:10.1056/NEJMoa0806470
2. **Zinman B, Wanner C, Lachin JM, et al; EMPA-REG OuTCOME Investigators**. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015; 373(22):2117–2128. doi:10.1056/NEJMoa1504720