



## Some complexities of diabetes and the heart

Patients with diabetes are at greater risk of coronary artery disease, including severe and diffuse coronary disease, than their peers without diabetes. That's straight and simple. But there the simplicity ends. Patients with diabetes have comorbidities that contribute to the development of coronary artery disease, including chronic kidney disease, obesity (often with obstructive sleep apnea), hypertension, and dyslipidemias. An individual may have none or all of these shared cardiac risk factors. Successful treatment of some of these comorbidities can reduce the risk of coronary and cardiovascular events, and current guidelines call for aggressive management of blood pressure and lipid levels as well as treatment of proteinuria in an effort to reduce progression of kidney disease.

Diabetes is defined by the presence of hyperglycemia or an elevated level of glycosylated proteins, its biochemical footprint. And for 100 years (insulin was first administered in 1922), the control of blood glucose levels has been the target of diabetic therapies. Control of blood glucose levels results in reduced microvascular complications, but reduction of the hemoglobin A1c level has not been uniformly shown to reduce coronary risk. Some controlled studies have instead indicated that aggressive diabetes control may paradoxically increase cardiac events. While it can be argued that some events may have been related to hypoglycemic stress, specific drugs may also play a contributory role.

There are many drugs now available that lower the blood glucose. Many share the ability to increase insulin levels and have efficacy in treating type 2 diabetes. Other drugs have unique biologic mechanisms of action that lower blood glucose without relying entirely on insulin for their effect. They are uniquely different in biochemical structure and thus, not surprisingly, differ in their off-target pharmacologic effects. Subanalyses of clinical trials and observational studies led to the hypothesis that different diabetes drugs have different effects on cardiovascular outcomes, with some contributing to cardiovascular morbidity. Although this was contentious for a while, and total clarity is still not apparent for every drug, it led the US Food and Drug Administration to mandate that clinical trials of new diabetes medications need to include cardiovascular outcome data. And we now have a lot of information on the cardioprotective effects of the sodium-glucose cotransporter 2 inhibitors, even in patients without diabetes.

But our patients with diabetes often have comorbidities that can independently contribute to cardiovascular morbidity, and those comorbidities need to be treated—with more drugs. What about off-target effects of those medications that are demonstrably effective at reducing cardiac disease? Might they do the reverse of what I discussed above and, while decreasing cardiac disease, increase the development or worsen the progression of diabetes? It is well known that the thiazides can increase blood glucose levels, and we have generally worked around their usually mild hyperglycemic effect. A thornier issue for some patients (and physicians) has been the back-alley concern that statins can cause or hasten the development of diabetes. I think this has been a particularly challenging issue, because at least in my experience the question is most often raised by the well-read, Internet-savvy patient who already has concerns with the safety profile of statins—perceived muscle problems and dementia risk. That statins may cause an increased risk of diabetes may, for some patients, be the final nail in the medicine cabinet.

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In this issue of the *Journal*, Dr. Byron Hoogwerf presents a comprehensive discussion of statin use and diabetes risk,<sup>1</sup> contributing clinical and data-enriched context to the relationship between statins and diabetes. He provides us with concrete guidance from his perspective as an experienced clinical diabetologist and trialist as to what we can say to patients and how we can sort out this therapeutic conundrum. It is well worth the read.

As we await the snow in Cleveland, on behalf of the entire *CCJM* editorial team, I wish us all a healthy, much kinder, and peaceful 2023.



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1. Hoogwerf BJ. Statins may increase diabetes, but benefit still outweighs risk. *Cleve Clin J Med* 2023; 90(1):53–62. doi:10.3949/ccjm.90a.22069