Personalizing Glucose-Lowering Therapy in Patients with Type 2 Diabetes and Cardiovascular Disease

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KEYWORDS

• Glucose-lowering therapy • Type 2 diabetes • Cardiovascular disease

KEY POINTS

- Type 2 diabetes is a complex disease with a pathogenesis that is multidimensional.
- Personalized therapy in the patient with established cardiovascular disease (CVD) involves the control of hyperglycemia and the management of other frequently coexisting atherosclerosis risk factors.
- The treating clinician should first determine the optimal hemoglobin A1c target for the individual, based on a variety of patient and disease characteristics.
- The intensiveness of glycemic control may need to be tempered in the setting of overt CVD, particularly when there is a need to use agents associated with hypoglycemia.
- Recently, several specific glucose-lowering agents have been demonstrated to improve cardiovascular outcomes and may be favored in type 2 diabetes patients with coexisting CVD.

BACKGROUND

Over the past 2 decades, the variety of glucose-lowering agents available for treating type 2 diabetes mellitus (T2DM) has increased substantially. As a result, the management of patients with this condition is becoming increasingly complex, with many more choices now available (alone and in combination) to improve glycemic control. Owing to its low cost, absence of significant long-term adverse consequences, and possible inherent cardiovascular (CV) benefit, metformin is endorsed as the best initial therapy by most prevailing treatment guidelines, including the joint position statement from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD).[1,2] Beyond metformin monotherapy, however, there remains

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substantial debate regarding the optimal drug (or even drug class) to use for individuals needing additional reduction in hemoglobin A1c (HbA1c). When the most recent version of the ADA-EASD position statement was published in early 2015, there were few clear distinguishing features related to long-term outcomes to favor one category over another.[2] Specifically from the vantage point of CV disease (CVD), such as myocardial infarction (MI), stroke, CV death, and heart failure, there was considerable clinical equipoise regarding the best next step after metformin. Consequently, prevailing recommendations were not highly prescriptive; clinicians were simply advised to choose subsequent agents based mainly the avoidance of adverse effects while taking into account the financial constraints of patients and/or health systems. Since 2015, however, the results from several major CV outcome trials involving diabetes medications have been released.[3] These data are now allowing for a more refined approach to the management of T2DM, incorporating evidence-based strategies in antihyperglycemic therapy, particularly in patients with heart disease.

This article reviews the individualization of T2DM therapy in the patient with preexisting CVD. First, the calibration of glycemic targets in this population will be described, followed by a discussion of the approach to choosing actual glucose-lowering drugs. Neither is necessarily a straightforward undertaking and should continue to be based on multiple interrelated patient and disease factors. The emerging CV benefits of certain glucose-lowering medications and the need to harness these effects to optimize patient outcomes will be emphasized.

CALIBRATING GLYCEMIC TARGETS IN THE PATIENT WITH CARDIOVASCULAR DISEASE: HOW LOW TO GO

With a change in the diagnostic criteria in 2010, the HbA1c test is now accepted as a screening tool for diabetes.[4] If confirmed on a second occasion, or if paired with an elevated fasting plasma glucose (>126 mg/dL or 7 mmol/L), an HbA1c of greater than or equal to 6.5% is now considered diagnostic of diabetes. Unless very early on in the disease course, it is difficult to uniformly lower the HbA1c to this level once the diagnosis is established. Accordingly, most treatment guidelines suggest that the general HbA1c target be less than or equal to 7.0%, although some latitude is allowed to individualize this based on a variety of patient and disease characteristics. For example, younger and healthier patients may be targeted at less than 6.5%, as explicitly advised by the American Association of Clinical Endocrinologists[5] and inferred by the ADA-EASD position statement.[1,2] The goal here is to mitigate the long-term risk for diabetic microvascular complications, such as retinopathy and kidney disease. In contrast, in older patients, especially in those with preexisting heart disease, the target can be modulated to 7.0% to 7.5%, or even slightly higher, toward the 8.0% range. Moreover, in patients of advanced age who are infirm with multiple comorbidities or in those with a propensity for severe hypoglycemic reactions and who require insulin therapy, even higher targets are reasonable (8.0%–8.5%).

In the original trials to demonstrate a benefit from glucose-lowering (the Diabetes Control and Complications Trial[6] involving patients with type 1 diabetes [T1DM] and the United Kingdom Prospective Diabetes Study [UKPDS][7] involving recently diagnosed individuals with T2DM), participants randomized to the more intensive therapy arms actually achieved an HbA1c of 7.0% to 7.5%. In these studies, most of the benefit from intensive therapy seemed to be on microvascular complications but without substantive effects on macrovascular complications, such as those related to atherosclerosis. Importantly, the latter is the major cause of morbidity, mortality, and excess health care expenditures in this disease. Subsequent large trials