odds ratio of 28 (95% CI 19-41).[140] Across meta-analyses, GLP-1 RA appear to reduce risk of stroke by 15% to 17% in persons with T2D and prior ASCVD or at high risk for ASCVD.[9,130,141,142] The 3 GLP-1 RA agents approved by the FDA to reduce the risk of MACEs (including stroke) are dulaglutide (with or without established ASCVD), liraglutide, and subcutaneous semaglutide (in persons with established CVD).[143] In persons with T2D and ASCVD or those at high risk for ASCVD, use of GLP-1 RA with proven benefit is recommended to reduce stroke risk.[9] Pioglitazone, a TZD, appears to reduce the risk of recurrent stroke and should also be considered to reduce the risk of recurrent stroke in persons with insulin resistance, prediabetes, or T2D and a prior transient ischemic attack (TIA) or stroke.[9,144,145] With regard to stroke and SGLT2i, 2 meta-analyses have shown that there was a reduced HR of 0.5 for hemorrhagic stroke when pooling data from completed SGLT2i trials, while there was no significant impact on ischemic stroke.[146,147]

Nearly 50% of U.S. adults with kidney failure have DM.[148] The evidence for benefit of SGLT2is to reduce adverse renal outcomes is robust, with an approximately 38% reduction in composite outcomes, which varied across trials but included worsening of eGFR or creatinine, end-stage kidney disease with or without need for kidney replacement therapy or transplant, kidney death, or CV death.[133] Use of an SGLT2i with proven benefit is recommended as foundational therapy to reduce progression of DKD and CVD risk for persons with T2D and DKD with eGFR 25 mL/min/1.73 m^2 or 20 mL/min/1.73 m^2 if HF is also present.[9,149,150] Two prospective placebo-controlled trials have examined the impact of dapagliflozin (included participants with eGFR 25 to 70 mL/min/1.73^2 and 200-5000 mg urine albumin/g creatinine) and empagliflozin (included participants with eGFR 20 to <45 mL/min/1.73 m^2 or >45 mL/min/1.73 m^2 with >200 mg urine albumin/g creatinine) decline in eGFR and progression of CKD, with a majority of participants enrolled with known T2D.[151,152] Dapagliflozin slowed the rate of decline more in patients with T2D than in patients without T2D, while the impact on eGFR decline was similar for both groups with empagliflozin. GLP-1 RAs also are an option to reduce progression of albuminuria, eGFR decline, and ASCVD risk in persons with T2D and DKD with eGFR 15 mL/min/1.73 m^2.[9,153,154]

The A1C target should be individualized in persons with T2D and ASCVD or at high risk for ASCVD, with a target A1C of ≤6.5% in most nonpregnant adults if it can be achieved safely. Consideration of life expectancy, disease duration, presence or absence of micro- and macrovascular complications, CV disease risk factors, comorbid conditions, and risk of hypoglycemia as well as cognitive and psychological status must be considered.[9,16] Newer antihyperglycemic agents such as GLP-1 RA and SGLT2i are associated with a lower risk of hypoglycemia unless used with SUs, glinides, and/or insulin. Less stringent A1C goals (7%-8%) should be adopted in persons with a history of severe hypoglycemia, hypoglycemia unawareness, limited life expectancy, advanced renal disease, extensive comorbid conditions, or longstanding DM in whom the A1C goal has been difficult to attain despite intensive efforts as long as the person remains free of hyperglycemia-associated symptoms.[9,13,14,17]

If further lowering of the A1C is needed to achieve the individualized glycemic target(s) and renal function is GFR >30 mL/min/1.73 m^2, metformin should be considered if the patient is not already taking this agent. Each medication should be up-titrated to the maximally tolerated approved dose and additional antihyperglycemic agents should be added on to achieve glycemic targets. If the initial A1C is >7.5%, early combination therapy with 2 agents may be needed, and for those with an initial A1C of >9% or 1.5% above goal, then 2 or 3 antihyperglycemic agents should be initiated concomitantly. If there is symptomatic hyperglycemia, an A1C >10% and/or BG >300 mg/dL, suggestive of marked insulin deficiency, basal insulin should be initiated to reduce glucose as safely and promptly as possible. In this scenario, use of a combination basal insulin with a GLP-1 RA can also be considered, but with the understanding that GLP-1 RA will require a titration phase that could potentially delay glycemic control. Clinicians should refer to the Algorithm for Adding/Intensifying Insulin section (Algorithm Fig. 8) and the Profiles of Antihyperglycemic Medications table (Algorithm Fig. 9) for additional guidance.

If a person with T2D does not have established or high risk for ASCVD, HF, stroke/TIA, or CKD, then the clinician should refer to the Glucose-Centric Algorithm for Glycemic Control section (Algorithm Fig. 7) and the Profiles of Antihyperglycemic Medications table (Algorithm Fig. 9).

Glucose-Centric Algorithm for Glycemic Control

The Glucose-Centric Algorithm for Glycemic Control (Algorithm Fig. 7) is for determining initial and add-on therapies for persons with DM but without established or high risk for ASCVD, HF, stroke/TIA, or CKD. Metformin should be initiated if there is no contraindication (eg, GFR <30 mL/min/1.73 m^2). In order to maximize tolerability, metformin should be started at a low dose and titrated over the course of a few weeks to the maximally tolerated dose.[16] The newer antihyperglycemic agents such as GLP-1 RA and SGLT2i are associated with low risk of hypoglycemia unless combined with SUs, glinides, and/or insulin.

Given that T2D is a progressive disease, many individuals will require >1 antihyperglycemic medication to achieve their individualized A1C target over the course of the disease. Clinicians should consider multiple factors when selecting the second agent, including presence of overweight or obesity, hypoglycemia risk, access/cost, and presence of severe hyperglycemia. Patients often present with >1 of these factors, so using a patient-centered, shared decision-making approach is important. The order that medications are listed in the algorithm denotes the suggested preference hierarchy for selection. In those patients with overweight or obesity and the additional goal of weight loss, dual GIP/GLP-1 RA, GLP-1 RA, or SGLT2i class are preferred options. Persons with a history of hypoglycemia, at high risk of hypoglycemia. and/or at risk for severe complications from hypoglycemia should preferentially be initiated with an agent associated with low risk for hypoglycemia, including GLP-1 RA, SGLT2i, dual GIP/GLP-1 RA, TZD, or DPP-4i.

For many persons with T2D, access and cost are barriers to receiving newer antihyperglycemic agents. In this situation, a TZD, SU, or glinide would be the more economical choices. While TZDs are associated with low risk for hypoglycemia and have shown benefit for NAFLD, they also can increase weight, so patients must be counseled accordingly. Lastly, patients with symptomatic hyperglycemia and/or an A1C >10% suggestive of marked insulin deficiency should start basal insulin to improve glycemia as quickly as possible. Basal insulin can be initiated with or without initiation and titration of a GLP-1 RA if the patient is not already on this class of agents. Some patients with severe hyperglycemia may need simultaneous initiation of bolus insulin. Clinicians should refer to the Algorithm for Adding/Intensifying Insulin section (Algorithm Fig. 8) for more guidance about initiating or advancing insulin therapy.

In persons with newly diagnosed T2D who are drug naive, prospective studies support the initiation of combination therapy to achieve glycemic targets more quickly as compared with a stepwise approach.[155,156] For recently diagnosed individuals with