noted. The benefits were consistent in the subgroup with diabetes, suggesting that low-dose anticoagulation added to antiplatelet therapy may be another option for risk modification in high-risk patients with diabetes and provides another option for these patients with enhanced cardiovascular risk.

Antithrombotic Therapy in T2D Summary

Antiplatelet-based secondary prevention is well established in T2D. For primary prevention of CVD in T2D, the relative benefits of antithrombotic approaches need to be weighed carefully against risks using a patient-centered approach.

SCREENING FOR CARDIOVASCULAR AND RENAL COMPLICATIONS

Kidney Disease and Cardiovascular Risk in Diabetes

Diabetic nephropathy is the leading cause of CKD and end-stage renal disease in the United States.[245,246] Defined by the Kidney Disease Improving Global Outcomes Work Group as functional or structural abnormalities of the kidneys persisting for ≥3 months as manifested by decreased estimated glomerular filtration rate (eGFR) ≤60 mL·min^{-1}·1.73 m^{-2} or by evidence of kidney damage (eg, albuminuria or proteinuria),[251] prevalence among patients with diabetes is ≈20%–40%.[248–250] Concomitant CKD and diabetes impacts risk for an array of CVDs, including arrhythmias, HF, acute coronary syndrome, and stroke.[251] Cardiovascular morbidity and mortality is markedly high, and patients with diabetic kidney disease (DKD) are far more likely to die of cardiovascular complications than progress to end-stage renal disease. Although albuminuria is a risk marker of both kidney disease and CVD, it may not be present in patients with reduced eGFR.

Traditional management to reduce risk or delay advancement of kidney disease includes glycemic control, BP control, and renin-angiotensin-aldosterone system inhibition. In the ACCORD trial, a higher risk of hypoglycemia and mortality was seen in patients with baseline CKD. However, a recent meta-analysis of 27 049 participants from 4 landmark RCTs (ACCORD, ADVANCE [The Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation], UKPDS [UK Prospective Diabetes Study], and VADT [Veterans Affairs Diabetes Trial]) noted a 20% relative risk reduction for kidney events (composite of end-stage kidney disease, renal death, development of an eGFR <30 mL·min^{-1}·1.73 m^{-2} or development of overt diabetic nephropathy) with more intensive glucose control over 5 years compared with less intensive.[252] Similar findings were observed in posttrial follow-up of participants in ADVANCE; intensive glucose control was associated with long-term reduction of end-stage kidney disease (defined as need for dialysis or kidney transplantation or death because of kidney disease) without evidence of any increased risk of cardiovascular events or death after 9.9 years of overall follow-up (29 versus 53 events, HR 0.54, $P<0.01$).[253] Stringent glucose control to prevent kidney failure may not be as clear. A meta-analysis by Ruospo et al[254] found that patients with intensive glycemic control had similar risks of kidney failure, defined as doubling of serum creatinine (RR=0.84 [95% CI, 0.64–1.11]; I^2=73%), and development of end-stage renal disease (RR=0.62 [95% CI, 0.34–1.12]; I^2=52%) compared with patients with less stringent treatment goals. Small clinical benefits were observed in the onset and progression of microalbuminuria.

In the CVOTs of SGLT-2Is and GLP-1RAs, secondary end points or subanalyses included renal outcomes (Table 7). When comparing drug classes, a recent meta-analysis of these trials found that GLP-1RAs primarily reduced macroalbuminuria risk, whereas SGLT-2Is reduced the risk of worsening eGFR.[138] Data from clinical trials focused on primary renal outcomes are emerging. In CREDENCE, patients with T2D and albuminuric CKD concurrently receiving renin-angiotensin-aldosterone system blockade were randomly assigned to canagliflozin 100 mg daily or placebo.[141] A 30% relative risk reduction of the primary outcome (composite of end-stage renal disease defined as dialysis, transplantation, or sustained eGFR of <15 mL·min^{-1}·1.73 m^{-2}, doubling of serum creatinine or death from renal or cardiovascular cause) was observed over 2.6 years in the canagliflozin group. Reduced risk of cardiovascular death, MI, or stroke was also noted in the canagliflozin group (HR, 0.80 [95% CI, 0.67–0.95]; P=0.01) and HHF (HR, 0.61 [95% CI, 0.47–0.80]; $P<0.001$). In the DAPA-CKD trial (A Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients With Chronic Kidney Disease), a composite of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes was evaluated over 2.4 years in CKD participants with or without T2D. Dapagliflozin versus placebo reduced the risk of the composite outcome by 39% overall and 36% (HR, 0.64 [95% CI, 0.52–0.79]) among participants with T2D.[255]

The most recent advances have been trials of selective nonsteroidal mineralocorticoid receptor antagonists in patients with T2D and DKD. The FIDELIO-DKD trial (Finerenone in Reducing Kidney Failure and Disease Progression in DKD Trial) evaluated kidney and cardiovascular outcomes over 2.6 years in 5734 participants with T2D and DKD on maximal renin-angiotensin-aldosterone system blockade at baseline.[256] Finerenone reduced the primary renal composite outcome (kidney failure, a sustained decrease of at least 40% in the eGFR from baseline, or death from renal causes) by 18%