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The elephant in the room: Why cardiologists should stop ignoring type 2 diabetes☆

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ABSTRACT

Type 2 Diabetes (T2D) is a growing public health threat that is evolving into a global pandemic with debilitating, expensive and often lethal complications. Even when hemoglobin A1c (HbA1C) levels are well controlled, and concomitant cardiovascular (CV) risk factors are effectively treated, two out of every three patients with T2D are destined to die from CV complications.

Several large randomized controlled trials (RCT) indicate that two classes of glucose-lowering medications, oral sodium-glucose cotransporter type 2 inhibitors (SGLT2-i) and injectable glucagon-like peptide-1 receptor agonists (GLP-1RA), confer significant CV benefits, including reductions in: hospitalizations for heart failure (HF), progression of diabetic kidney disease, atherosclerotic CV events, and (with some agents) CV death. These CV benefits appear to be independent of the glucose-lowering effects of these agents. These compelling findings are triggering a fundamental paradigm shift in T2D management whereby the focus is no longer on HbA1c alone, but instead on implementing a comprehensive CV risk reduction strategy prioritizing the use of these evidence-based therapies (along with other evidence-based treatment strategies) with the objective of reducing the risk of morbid complications, and improving the quantity and quality of life of patients with T2D.

Cardiologists are uniquely positioned to become more involved in the management of T2D and established CV disease, which at this time should include initiation (either by prescribing or by making recommendations) of agents proven to reduce CV risk. Specifically, SGLT2-is and/or GLP-1RA have now been shown to have a favorable risk-benefit balance, and are being increasingly emphasized by the practice guidelines as preferable treatment options in vulnerable patients with T2D. The cardiology community should collaborate with other care providers to ensure that when and where appropriate these new T2D therapies are used along with other evidence-based therapies to improve patient outcomes.

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Abbreviations and acronyms: ASCVD, Atherosclerotic Cardiovascular Disease; CI, Confidence Interval; CKD, Chronic Kidney Disease; CV, Cardiovascular; DPP, Dipeptidyl Peptidase; HbA1c, Hemoglobin A1c; HF, Heart Failure; HR, Hazard Ratio; LDL, Low Density Lipoprotein; MI, Myocardial Infarction; NNT, Number Needed to Treat; PCSK9, Proprotein Convertase Subtilisin-kexin type 9; RCT, Randomized Controlled Trial; SGLT2-i, Sodium-Glucose Cotransporter Type 2 Inhibitors; T2D, Type 2 Diabetes; US, United States.

☆ Statement of conflict of interest: see page 368.

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Introduction

During the past 60 years the number of people in the United States (US) with diabetes mellitus has risen 10-fold, up from 2.5 million in 1959 to 25 million today.[1,2] Even when hemoglobin A1c (HbA1C) levels are well controlled and concomitant cardiovascular (CV) risk factors are effectively treated, two-thirds of patients with type 2 diabetes (T2D) are destined to die from CV complications.[1,3,4] Recent statistics from the Centers for Disease Control and Prevention indicate that after several decades of progress, the rates of CV complications in patients with T2D have plateaued, and in younger patients are on the rise.[4]

The first effective drug for lowering hyperglycemia was discovered by Dr. Frederick Banting in 1921, when he isolated insulin from the pancreas of fetal calves and began using it for treating his patients with diabetes. Now approximately 100 years later, 12 classes of glucose-lowering agents are available, comprising hundreds of different medications that have been approved by the US Food and Drug Administration (FDA) for the treatment of diabetes. Yet, until 2015, when the EMPA-REG Outcome study using a sodium glucose cotransporter 2 inhibitor (SGLT-2i) empagliflozin (an insulin independent glucose lowering therapy) in patients with established atherosclerotic CV disease was published, not one of these T2D medications had been proven to lower the ominously high risk of major adverse cardiovascular events (MACE), defined as CV mortality, myocardial infarction (MI), and stroke, or reduce hospitalizations for heart failure (HF) – another common and morbid CV complication of T2D.[5]

Landmark SGLT2-i CV outcome trials

Drugs in the sodium-glucose cotransporter type 2 inhibitors (SGLT2-i) class act in the proximal tubule to increase urinary excretion of glucose and sodium, resulting in modest but significant reductions in HbA1c, weight, and blood pressure (BP).[5–8] A large and consistent body of data from randomized controlled trials and large observational real-world studies indicates that SGLT2-i are effective in the prevention of atherosclerotic CV disease (ASCVD) events (among patients with established ASCVD or diabetic kidney disease), hospitalizations for HF and progression of chronic kidney disease (CKD) (regardless of prior ASCVD, HF or CKD status) (Figs. 1-3).[5–11]

A recent meta-analysis of SGLT2-i evaluated the three large CV outcomes trials of agents in this class that have been published thus far.[11] This meta-analysis combined the EMPA-REG OUTCOME trial, CANVAS Program, and DECLARE-TIMI 58 trial, which collectively comprised 34,322 T2D patients (mean age 63 years, 35% women), of whom 60% had established ASCVD and 40% had multiple CV risk factors but no known ASCVD.[11] SGLT2-i modestly reduced the relative risk of MACE by 11% in the overall group, and by 14% in the subgroup with known ASCVD, which was significant.[11] Additionally, SGLT2i reduced the relative risk of CV death or hospitalization for HF by 23%, and lowered the relative risk for HF hospitalization as a single endpoint by 31%.[11] This meta-analysis also demonstrated that SGLT2-i significantly reduced the relative risk of composite renal endpoint (renal death, end-stage renal disease, or doubling of serum creatinine) by 45%, with a similar benefit among patients with and without ASCVD.[11] Another meta-analysis showed that SGLT2-i improve CV and renal outcomes in patients with CKD.[12]

The very recent CREDENCE trial was a landmark randomized placebo-controlled outcome trial that enrolled 4401 patients with T2D and CKD.[13] Compared to placebo canagliflozin reduced the relative risk of the renal-specific composite (end-stage kidney disease, a doubling of the creatinine level, or death from renal causes) by 34% ($P < 0.001$), lowered MACE (death, MI, or stroke) by 20% ($P = 0.01$) and reduced the hospitalization for HF by 39% ($P < 0.001$).[13]

Landmark GLP-1 RA CV outcome trials

Recent large CV outcome trials show that glucagon-like peptide-1 receptor agonists (GLP-1RA) also confer cardio-protection for patients with T2D.[14–17] A meta-analysis of four RCTs reported that GLP-1RA compared with placebo showed a hazard ratio (HR) for MACE of 0.90 (95% confidence interval [CI] 0.82 to 0.99; $p = 0.033$).[18] Since that meta-analysis, two additional large CV outcome trials of GLP-1RA have reported results. Harmony Outcomes trial assessing albiglutide,[15] and the REWIND study assessing dulaglutide[14] both showed significant

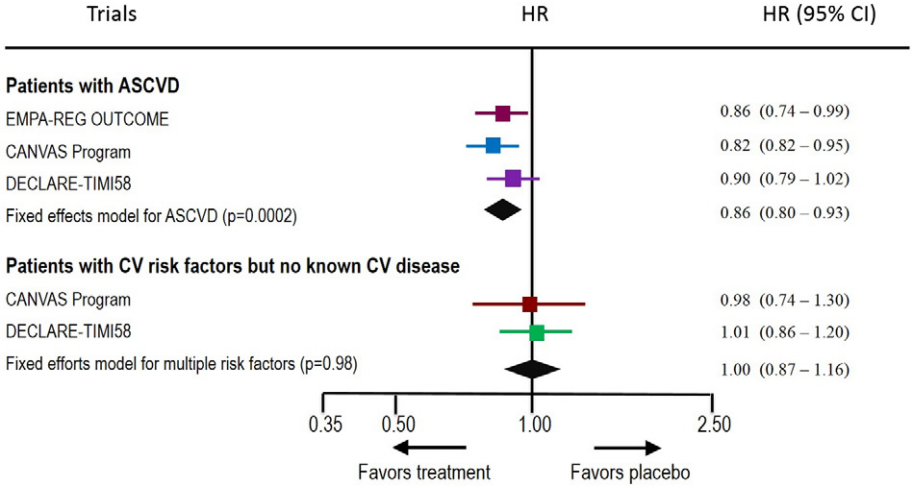

Fig. 1. Meta-analysis of randomized controlled trials show that SGLT2-i agents significantly reduce risk of MACE in patients with known ASCVD, but not in those without documented ASCVD.[11] ASCVD = atherosclerotic cardiovascular disease CI = confidence interval HR = hazard ratio.

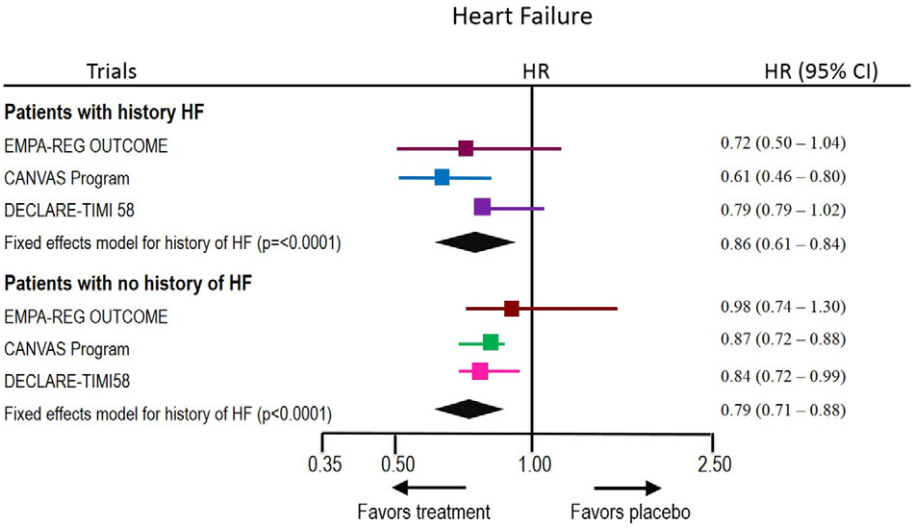

Fig. 2. Meta-analysis of randomized controlled trials show that SGLT2-i agents significantly reduce risk of new or worsening HF in patients with and without a prior history of HF.[11] HF = heart failure CI = confidence interval HR = hazard ratio.

relative risk reductions for MACE of 22% and 12%, respectively. Although four of the GLP-1RA outcome studies—LEADER (liraglutide), SUSTAIN-6 (semaglutide), Harmony Outcomes (albiglutide), and REWIND (dulaglutide)—showed significant reduction in MACE, two other GLP-RA—lixisenatide and exenatide—did not show statistically significant reduction in MACE in their RCT outcome (Fig. 4).[18,19]

Why cardiovascular specialists should take an active role in T2D management

Patients with T2D in the US see a cardiologist as often as they see their primary care provider, and are three times more likely to see a cardiologist than an endocrinologist.[20] Cardiologists are accustomed to having large randomized outcome trials to guide many of our clinical decisions, rather than simply treating surrogate laboratory targets. Accordingly, we tend to deploy therapies that have been proven to lower risk of morbid events such as MACE, and hospitalizations for HF. The SGLT2-i and GLP1-RA provide the greatest absolute benefit among patients with T2D that are at the higher absolute risk – i.e. those that already have established CV disease—the very same patients we, as cardiologists, are seeing daily in our offices and on hospital rounds. Thus, cardiologists are well positioned to take the lead in maximizing comprehensive risk reduction strategies in this vulnerable patient group, which now includes deploying these novel anti-diabetic agents. Even so, only a small minority (<5%) of cardiologists report that they are comfortable prescribing these agents (Fig. 5).[20–22]

Why are more cardiologists not using SGLT2-i and GLP-1RA? Several practical hurdles are typically brought up as justifications. Most cardiologists feel uncomfortable prescribing medications for diabetes due to understandable reservations about the daunting array of anti-diabetic agents and complex treatment algorithms, concerns about hypoglycemia and/or hyperglycemia, and lack of time and resources in their clinical practices to deal with issues related to the management of diabetes. They may also be uncomfortable encroaching on the territory of the referring clinicians including family practitioners, primary care providers and endocrinologists. However, it is of fundamental importance to understand that the CV benefits conferred by the SGLT2-i and GLP-1RA are unrelated to reductions in blood glucose and HbA1c. And compellingly, the SGLT2-i and GLP-1RA now have been incorporated into the ADA

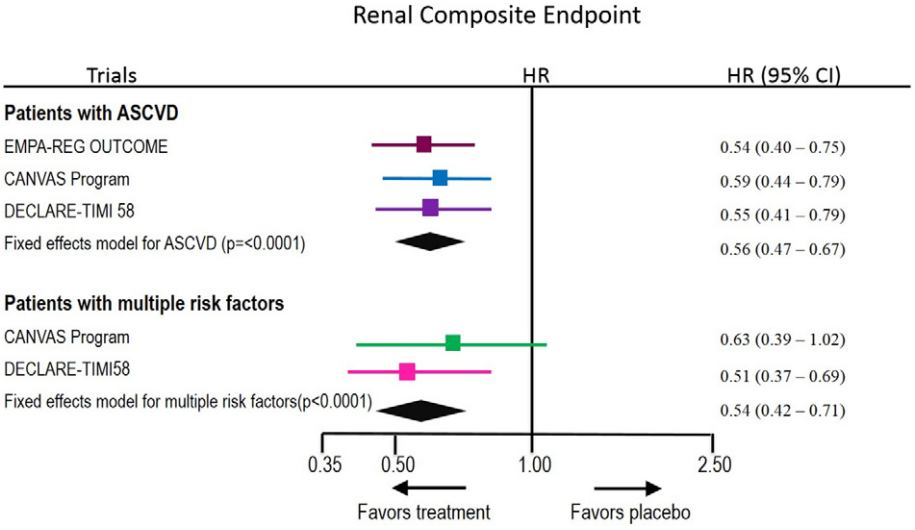

Fig. 3. Meta-analysis of randomized controlled trials show that SGLT2-i agents significantly reduce risk composite renal endpoint (renal death, end-stage renal disease, or doubling of serum creatinine) in patients with and without documented ASCVD.[11] ASCVD = atherosclerotic cardiovascular disease CI = confidence interval HR = hazard ratio.

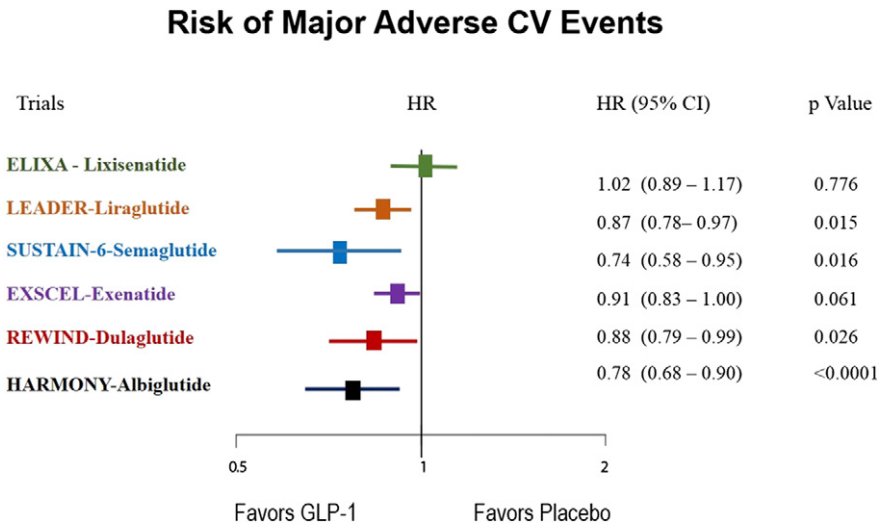

Fig. 4. In large randomized CV outcome studies, four of the GLP1-RA significantly reduced risk of MACE, although lixisenatide and exenatide did not reduce risk. CI = confidence interval HR = hazard ratio.

EASD position document, ADA Standards of Care for Diabetes, and ACC/AHA Primary Prevention Guidelines.[23–25]

Lack of cardioprotection of traditional T2D therapies

Physicians managing T2D have traditionally been incentivized to focus primarily on management of HbA1c, which will improve microvascular outcomes (retinopathy, neuropathy, etc.) but have modest (if any) impact on cardiovascular outcomes.[1,9,25–29] Consequently, the majority of patients with T2D remain on therapies that have not been proven to reduce CV events (such as MACE or hospitalizations for HF). An analysis of 313 institutions showed only 5% of T2D patients who met EMPA-REG inclusion criteria were on a SGLT2i, and 6% of patients meeting the LEADER inclusion criteria were on a GLP-1RA.[21] Instead, these patients were eight times more likely to be on insulin, seven times more likely to be on a sulfonylurea, and three times more likely to be on a dipeptidyl peptidase (DPP) 4 inhibitor—all therapies with no proven CV benefit.[21]

The "primum non nocere" maxim of the Hippocratic Oath urges physicians to "first do no harm". In years past insulin and sulfonylureas have been mainstays in the treatment regimens of T2D, and close scrutiny indicates that these agents may not meet this essential principle for many of these patients. Both of these classes of medications have potential adverse CV effects which likely explains why tight glycemic control has not been shown to reduce MACE or improve CV prognosis in prior large randomized trials.[30]

Excessively high blood insulin predisposes to inflammation, hypertension, dyslipidemia, atherosclerosis, HF, and arrhythmias, and is a fundamental driver of CV disease in T2D.[30] While insulin was a revolutionary treatment for type 1 diabetes, it inherently made less sense as a therapy for patients with T2D. The hallmark of type 1 diabetes is a lack of insulin production, while the great majority of type 2 diabetics have 2 to 3 times more insulin production as healthy controls. In spite of this, the strategy of insulin replacement and stimulating insulin secretion persisted for decades, with little progress made in preventing CV mortality. One likely reason that insulin has a neutral at best effect on CV outcomes in T2D is it predictably causes weight gain and increases risk for hypoglycemic spells.[30] Large observational studies show significant dose-dependent correlations between high insulin and increased risk of MACE and CV mortality among patients with T2D.[30]

Similarly, sulfonylureas lower glucose by stimulating the pancreatic beta cells to secrete more insulin. RCT of sulfonylureas at best show neutral effects on CV outcomes, and these agents do not decrease risk of MACE.[26,27] Sulfonylureas frequently cause hypoglycemia and induce weight gain, and all agents in this class carry an FDA "black-box" warning regarding an increased risk for CV mortality.[27] Therefore, insulin and sulfonylureas should be considered a last-line option for the management of T2D, particularly for patients with established CV disease.[26,27]

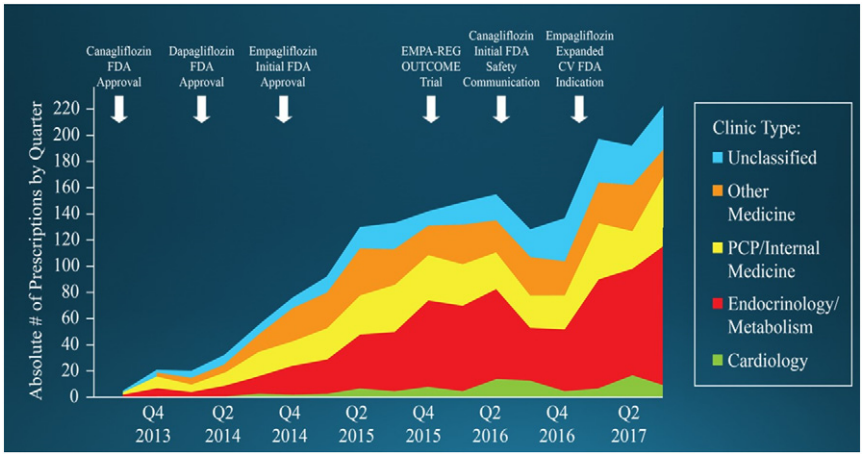

Fig. 5. Cardiologists have not substantially increased use of SGLT2-i agents despite recent randomized trials showing their effectiveness in improving CV prognosis.[20]

Safety of GLP-1RA and SGLT2i

In contrast, the GLP-1RA and SGLT2i agents do not commonly cause hypoglycemia (except when co-administered with insulin and/or SU), are associated with weight loss, and generally have favorable safety profiles with infrequent serious adverse events.[31] A systematic review and meta-analysis of all RCT data published to date on the safety of SGLT2-i showed no increased risk of harm compared to placebo or active comparators with respect to acute kidney injury, diabetic ketoacidosis, urinary tract infection, hypoglycemia, and bone fractures.[32] Increased rates of lower limb amputations and fractures were initially observed with canagliflozin,[6] but not with the other drugs in the SGLT2-i class.[5–8,32] SGLT2i do increase risk of genital mycotic infections which is more commonly seen in women than men.[32] However, these genital fungal infections are typically easily treatable and usually do not require discontinuation of the SGLT2-i.[10,31] As an endorsement to the safety of SGLT-2is in both CANVAS and EMPA-REG is the fact that the serious adverse events were statistically significantly more likely to occur in the placebo arm than with empagliflozin or canagliflozin.[4,5]

Currently available GLP-1RA are all injectable agents, and thus, some training would be required for cardiology practitioners to become comfortable prescribing them. Yet, many of us regularly prescribe enoxaparin and/or the proprotein convertase subtilisin–kexin type 9 (PCSK9) inhibitors in the outpatient setting. Moreover, compared to many of the agents we routinely prescribe such as amiodarone, warfarin, and dofetilide, the risk—benefit ratio for SGLT2i or GLP-1RA is highly favorable.[31]

CV event reduction agents that coincidentally lower glucose

The hypothesis that aggressive glucose management using traditional glucose-lowering agents can reduce MACE and lower CV mortality has been disproven in multiple large RCTs.[27] Moreover, the mechanisms driving the cardio-protective effects of GLP-1RA and SGLT2i appear to be unrelated to reductions in HbA1c and/or blood glucose levels.[9,25–27,29] A large body of evidence emerging from RCTs has forced us to re-think the traditional paradigm of T2D, which should not be viewed simply as a disturbance of glucose metabolism but rather as a complex disease state that markedly increases CV risk.[31] In this model, SGLT2i and GLP-1RA are preferred in patients with T2D (particularly if they have established ASCVD) to improve their otherwise poor CV prognosis.[9,25–27,29,31]

Cardiologists should not avoid initiating these cardio-protective T2D therapies simply because they also lower blood glucose, just as we do not shy away from initiating carvedilol or sacubitril/valsartan in our patients with heart failure with reduced systolic function because these drugs can cause hypotension. Indeed, it may be useful for cardiologists to consider SGLT2i and GLP-1RA as potent therapies to improve CV prognosis that also happen to lower blood glucose and HbA1c. For example, starting empagliflozin in a patient with T2D and optimal CV risk factors bestows robust reduction in risk of CV death, with a number needed to treat of 39 for a treatment duration of just 3.1 years; and this benefit is noted even if this SGLT2-i does not substantially lower HbA1c.[5]

Because SGLT2i and GLP-1RA rarely cause hypoglycemia, and their cardioprotective effects occur independently of reductions in HbA1c, cardiologists should be able to recommend these agents without taking over future responsibility for glucose management, which ideally should be deferred to the care providers who have been directing the patients' diabetes regimen.

SGLT2-i and GLP1-RA endorsed by national guidelines

Recent guidelines from the American College of Cardiology, the American Heart Association, and the American Diabetes Association all strongly endorse the use of SGLT2-i and/or GLP1-RA for patients with T2D and established ASCVD.[25,26,29] Of note, most trials that demonstrated reduced MACE with SGLT2i and GLP-1RA were comprised of patients who were already on metformin as the first-line therapy. So metformin, if it is tolerated and not contraindicated, should be considered as an option in the standard T2D cardio-protective therapeutic regimen. Latest guidelines recommend the use of metformin in patients who have an estimated glomerular filtration rate (eGFR) of over 30 mL/min/1.73 m^2.[27]

Call to action for cardiologists

Dr. William J Mayo taught that "The best interest of the patient is the only interest to be considered."[33] As cardiologists, our raison d'être is to prevent and/or treat CV disease and improve our patients' quantity and quality of life. After decades of futility we finally have glucose-lowering agents that significantly improve the CV prognosis for our diabetic patients.[21] Cardiologists can take ownership of this issue by deploying these new evidence-based therapies in appropriate T2D patients to lower their risk of morbid CV events. The cardiology community will need to work closely with other care providers involved in managing patients with T2D to ensure that when and where appropriate these new therapies are utilized in preference over agents which have not been shown to provide similar CV benefits.

Cardiologists have grappled with the laws of diminishing returns in novel antiplatelet, anti-inflammatory and cholesterol lowering therapies. In our quest to improve CV outcomes for our patients, TD2 is the elephant in the room and it can no longer be ignored. Even with dramatic low-density lipoprotein (LDL) reduction with evolocumab, LDL reduction coupled with HDL augmentation with anaceptrapib, and targeting inflammation in those with elevated HS-CRP with canakinumab number needed to treat (NNT) to prevent one composite CV outcome are 75, 100, and 156, respectively. Instead treating patients with T2D and established ASVCD has an NNT of 39 to prevent all-cause mortality. If we seek to help as many patients as possible, we should consider recommending the SGLT2i and GLP1-RA for our appropriate T2D patients.

The SGLT2i and GLP1-RA are potent therapies in the cardiogists' tool kit for comprehensive, aggressive secondary CV prevention strategies. Cardiologists are ideally positioned to take a greater ownership in the management of T2D – with the main objective of reducing its morbid complications, and improving the quantity and quality of life for our patients. Not taking action will be a missed opportunity both for our profession, and for our patients.

Statement of conflict of interest

Dr. James O'Keefe declares that he is on the speaker's bureau for Amgen, AstraZeneca, Boehringer Ingelheim, Proctor & Gamble, and Sanofi.

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