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Commentary

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The evolution of type 2 diabetes management: glycemic control and beyond with SGLT-2 inhibitors and GLP-1 receptor agonists

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Abstract: Diabetes mellitus (DM) is one of the most prevalent diseases encountered by the primary care physician on a daily basis. Complications associated with DM can include nephropathy, neuropathy, and retinopathy ("microvascular complications"), along with cardiovascular disease (CVD), which can include myocardial infarction (MI) and strokes ("macrovascular complications"). In the 1990s, landmark clinical trials demonstrated that intensive glycemic control can reduce the risk of developing microvascular complications, but reduction in macrovascular complications with intensive glycemic control was not clearly demonstrated. At this point, intensive glycemic control became the standard of care (SOC). In the 2000s, additional trials evaluating the effect of intensive glycemic control in patients with type 2 diabetes mellitus (T2D) and established CVD, or risk factors for CVD, subsequently failed to identify a macrovascular benefit from intensive glycemic control, and one of the trials was terminated early because of an increase in the risk of mortality observed among patients assigned to receive intensive glycemic control. These results led to less strict glycemic targets being recommended in older patients, particularly those with established CVD. In 2007, everything changed after a report surfaced suggesting that rosiglitazone was associated with a significant increase in the risk of MI, as well as an increase in the risk of cardiovascular death that was of borderline significance. As a result, in 2008, the FDA mandated that all new diabetes medications must exclude an unacceptable level of risk for atherosclerotic cardiovascular disease (ASCVD) prior to drug approval, and thus undergo additional cardiovascular safety trials. Accordingly, through these trials, some of the newer agents, particularly sodium-glucose cotransporter-2 inhibitors (SGLT-2i) and glucagon-like peptide-1 receptor agonists (GLP-1RA), were demonstrated to reduce the risk of major adverse cardiovascular events (MACEs), independent of their effect on glycemic control. These findings subsequently led to further trials to evaluate the effects of some of these therapies on the risk of chronic kidney disease (CKD) progression, as well as adverse heart failure-related outcomes. SGLT-2 inhibitors have been demonstrated to reduce the risk of CKD progression, as well as a reduction in the risk of cardiovascular death or hospitalization secondary to heart failure in patients with both reduced ejection and preserved ejection fractions. A trial evaluating the effects of GLP-1RA on CKD outcomes is ongoing. The aim of this narrative review article, compiled by identifying relevant studies via the utilization of PubMed, is to provide a broad overview over the various clinical trials and analyses that have led to current diabetes management guidelines, and ultimately, help guide primary care physicians in selecting therapies that will not only improve glycemic control and reduce the risk of microvascular complications, but also reduce the risk of macrovascular disease in their patients with T2D.

Keywords: albuminuria; chronic kidney disease; electronic health records; healthcare resource utilization; type 2 diabetes

With over 37.3 million people living with a diagnosis of diabetes mellitus (DM) in the United States [1], diabetes is one of the most common and widespread conditions that primary care physicians manage in their day-to-day practice. DM is a chronic disease in which the body is unable to regulate serum blood glucose levels. There are two main types: type 1 diabetes mellitus (T1D) and type 2 diabetes mellitus (T2D). T1D is due to the autoimmune destruction of insulin-producing-cells in the pancreas. For T2D, there are two main problems: the pancreas does not produce enough insulin, and there is insulin resistance in peripheral tissues. This lack of blood glucose regulation can subsequently put affected patients at higher risk for both microvascular (nephropathy, retinopathy, and neuropathy) and

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macrovascular (CVD, i.e., MI, stroke) complications [2, 3, 4]. In fact, DM is the leading cause of renal failure, blindness, and nontraumatic lower-limb amputations in the United States [1]. Thus, adequately managing blood glucose levels has been of paramount importance in trying to prevent these complications.

Although the early landmark clinical trials, including the Diabetes Control and Complications Trial (DCCT) [2] and United Kingdom Prospective Diabetes Study (UKPDS) [5], managed to demonstrate statistically significant reductions in microvascular disease with intensive glycemic control, they did not identify any significant reduction in the occurrence of macrovascular disease. However, more recently, clinical trials, including the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) [4], the Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6) [6], and the Researching Cardiovascular Events With a Weekly Incretin in Diabetes (REWIND) [7] trials, have established that glycemic control alone can no longer be the main focus of the management of patients with T2D. Newer classes of therapies to manage glycemia in patients with T2D have been demonstrated to have reduced the risk of major adverse cardiovascular events (MACEs) independent of their effect on glycemic control. Accordingly, T2D management is in the midst of evolving from a glycemic control-centric approach to one that also prioritizes taking an outcome-centric approach, that focus on cardiovascular risk reduction (atherosclerotic cardiovascular disease [ASCVD] and/or heart failure) and renal risk reduction, as well as on weight management and the avoidance of hypoglycemia. The aim of this article is to provide a broad overview of the various clinical trials and analyses that have led to current diabetes management guidelines, and ultimately, help guide primary care physicians in selecting therapies that will not only improve glycemic control and reduce the risk of microvascular complications, but also reduce the risk of macrovascular complications in their patients with T2D.

Intensive glycemic control reduces the risk of developing diabetes-related complications

DCCT, EDIC, and UKPDS

The first major trial to evaluate the relationship between glycemic control and the progression of microvascular and macrovascular complications was the Diabetes Control and Complications Trial (DCCT), which was conducted from 1982 to 1993 [2]. In the DCCT, a total 1,441 patients with insulin-dependent T1D were divided into two cohorts: one with patients who had no history of diabetic retinopathy ("primary prevention group," n=726) and one with patients with mild retinopathy ("secondary intervention group," n=715). These two cohorts were randomized into a control group that received standard insulin therapy (2 doses of insulin/day) and an experimental group that received intensive insulin therapy (3 or more doses of insulin/day or insulin pump therapy guided by self-glucose monitoring). After being followed for a mean duration of 6.5 years, those who received intensive therapy demonstrated a 35–76 % reduction in the early stages of microvascular disease with a median hemoglobin A_{1c} (HbA_{1c}) of 7 % (compared to a median HbA_{1c} of 9 % for those on standard therapy). Moreover, those who received intensive therapy in the primary prevention cohort had a mean reduced risk of retinopathy of 76 %, a reduced risk of microalbuminuria of 34 %, and a reduced incidence of neuropathy of 69 %. In the secondary intervention cohort, intensive glycemic control demonstrated delayed progression of retinopathy by 54 % and reduced the occurrence of proliferative or severe nonproliferative retinopathy by 47 %. There was also a 41 % risk reduction of combined cardiovascular and peripheral vascular disease, but this was not found to be statistically significant.

After the conclusion of the DCCT, study participants were offered to be followed longitudinally in an observational study known as Epidemiology of Diabetes Interventions and Complications (EDIC) [3]. At this time, participants in the DCCT were given the option to continue to follow up with their personal primary care physicians where their diabetes was now being managed with a goal A_{1c} of <7 % with intensive insulin therapy, which became the new standard of care (SOC) after the DCCT was published. As such, those participants who opted to be followed longitudinally and received conventional therapy in the DCCT were now receiving intensive insulin therapy, and their A_{1c} improved during the EDIC observational trial. In contrast, glycemic control deteriorated among those who were assigned to intensive insulin therapy in the DCCT and had subsequently returned to their personal primary care physicians to resume management of their diabetes. After the DCCT concluded, the control and treatment groups' HbA_{1c} levels converged to approximately 8 %. However, despite eventually having similar A_{1cs} during the course of the EDIC trial, the risk of adverse microvascular outcomes remained lower during the course of follow-up among those originally assigned to the intensive therapy group. That is, the benefit of the earlier period of intensive glycemic control persisted, even though the A_{1c} subsequently deteriorated during the EDIC trial. This phenomenon was termed "metabolic

memory." Overall, the long-term follow-up with EDIC further demonstrated beneficial effects on advanced complications including retinopathy, nephropathy, and neuropathy, and also observed an emerging reduction of any CVD event occurring by 42 % and risk of nonfatal myocardial infarction (MI), stroke, or death by 57 %. Although these results regarding macrovascular disease risk were promising, they were observed after the randomized control trial period ended and thus are only hypothesis-generating and do not establish causality. It was postulated that the impact of early intensive glycemic control on cardiovascular risk may simply just take longer to be observed.

From 1977 to 1997, the UKPDS was conducted in which researchers sought to gather similar information as the DCCT but as it applied to T2D in contrast to T1D [5]. This study sought to further assess not only the effects of glycemic control on microvascular and macrovascular risk, but also the specific benefits of sulfonylurea therapy vs. insulin therapy vs. standard therapy. In this study, 5,102 patients were again randomized into standard and intensive glycemic therapies with the use of sulfonylureas, insulin, and metformin, and these patients were followed over the course of 10 years. The results of the UKPDS showed that patients who received intensive therapy had an average A_{1c} of 7.0 %, a 12 % relative risk reduction (95 % CI, 1–21; p=0.029) of any diabetes-related endpoint, a 10 % relative risk reduction (95 % CI, –11 to 27; p=0.34) for any diabetes-related death, and a 6 % relative risk reduction (95 % CI, –10 to 20; p=0.44) of all-cause mortality compared to the standard therapy cohort. The average A_{1c} for the standard therapy cohort was 7.9 %. Additionally, there was a 25 % relative risk reduction (CI, 7–40; p=0.0099) in microvascular disease endpoints (i.e., retinopathy requiring photocoagulation). Overall, these results were similar to those from the DCCT, in which there were significant reductions in the risk of developing microvascular complications, but no significant risk reduction in the development of macrovascular complications.

After the completion of the UKPDS, a 10-year follow-up study was completed in which the original participants from the study continued to follow-up with their personal physicians and made no attempt to maintain their previously assigned therapies [8]. As such, the degree of glycemic control was not necessarily maintained for many participants because the between-group differences in A_{1c} were lost after the first year of follow-up. However, the beneficial relative risk reductions that were observed in the intensive therapy cohort in the original UKPDS persisted at the 10-year mark. Similar findings were also observed in the EDIC trial after the DCCT, where it was noted that patients continued to have long-lasting relative risk reduction in adverse microvascular disease outcomes despite worsening glycemic control [3]. This phenomenon was ultimately termed the "legacy effect" and served to show that obtaining intensive glycemic control, even if relatively briefly over the course of longitudinal treatment, can have a lasting effect on diabetic microvascular disease outcomes. As a result of the DCCT/EDIC, and the UKPDS and its observational follow-up study, the achievement of early and intensive glycemic control became the SOC for most patients with diabetes.

ACCORD, ADVANCE, and VADT

While the results from previous trials were promising for microvascular complications of DM, the effect of glycemic control on macrovascular complications remained murky. As such, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) [9], Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) [10], and Veterans Affairs Diabetes Trial (VADT) [11] trials further evaluated the effect of more intensive glycemic control on the occurrence of microvascular and macrovascular complications in patients with T2D. All three of these trials showed that while intensive glycemic control reduced the incidence of microvascular complications, the incidence of macrovascular events—defined as the occurrence of a nonfatal MI, nonfatal stroke, or fatal cardiovascular event—was not reduced in a statistically significant fashion. In fact, there was an increase in overall mortality in the ACCORD trial that resulted in early termination of the study after only 3.5 years. Although this observation has been investigated thoroughly through subsequent subanalyses of the ACCORD data, and multiple potential theories for this observation have been published, a few interesting observations have been reported: (1) the rate of 1-year change in A_{1c} showed that a greater decline in A_{1c} was associated with a lower risk of death; (2) excess mortality risk among those in the intensively treated group occurred for A_{1c}>7 %; and (3) a higher mortality risk was associated with little change in A_{1c} from baseline during the first 4 months in the intensive group [12]. As a result of these studies, a change in treatment guidelines was made from a blanket goal A_{1c}<7 % for all individuals to less strict targets of <8 % in older patients, particularly in those with established CVD or at high risk of CVD and those who were using therapies associated with a higher risk of hypoglycemia (i.e., sulfonylureas and/or insulin).

Like the DCCT and UKPDS, there were also longitudinal observational follow-up analyses for the ADVANCE and VADT trials. When evaluating outcomes in the VADT, there was a reduction in the risk of a primary cardiovascular event (i.e., MI, ischemic stroke, new/worsening heart failure) in the

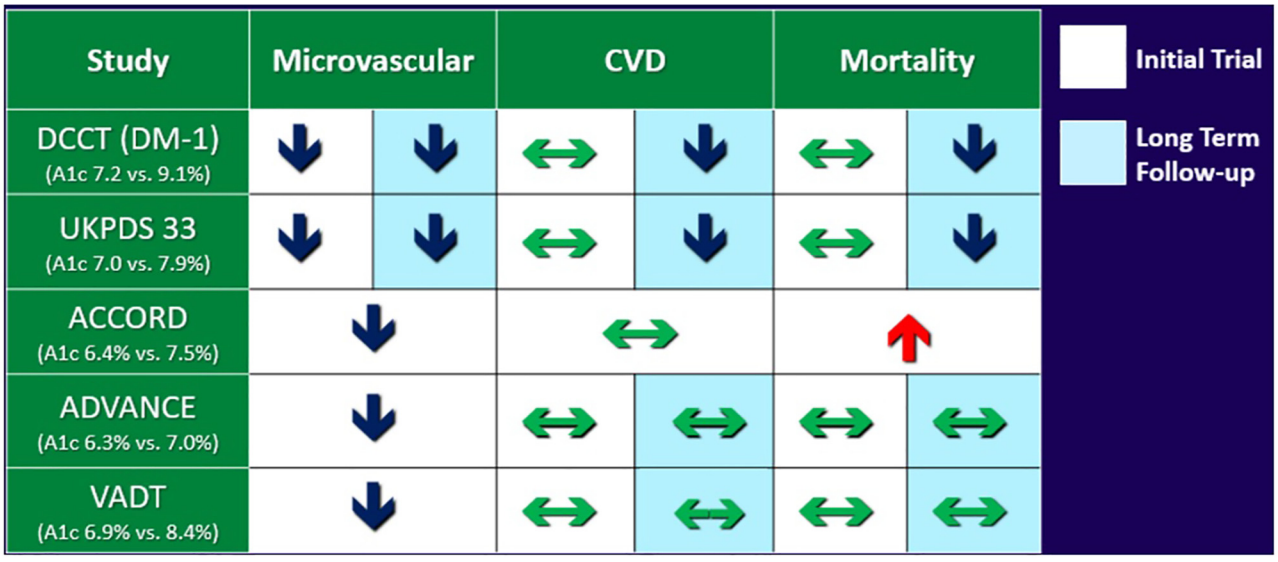

Figure 1: Adapted and modified, with permission, from David Kendall's 2009 American Diabetes Association Symposium.

intensive therapy cohort (HR 0.83; 95 % CI, 0.70–0.99; p=0.04) after a median of 9.8 years of follow-up [13], but there was no reduction in risk of the same events with 15 years of follow-up (HR 0.91; 95 % CI, 0.78–1.06; p=0.23) [14]. Moreover, there was no reduction in total mortality evident at 10-years post–follow-up or 15-years post–follow-up. Similarly, after a median follow-up of 5.4 years after the conclusion of the initial ADVANCE study, no differences were observed in the risk of a major cardiovascular event or death from any cause in the intensive-glucose therapy cohort relative to the standard therapy cohort (HR 1.00; 95 % CI, 0.92–1.08) [15]. Unlike the UKPDS, no "legacy effect" was observed in those who had received intensive glucose-reducing therapy and there was further evidence that intensive glycemic therapy did not provide any benefit toward the reduction of macrovascular complications.

Although it became very clear that intensive glycemic control was effective in terms of reducing the risk of microvascular complications in DM, it failed to identify a benefit in terms of reducing the risk of developing macrovascular disease. Please refer to Figure 1 for a summary of the findings regarding the effect of glycemic control in the previously mentioned trials.

Rosiglitazone controversy prompts safety concerns

Around the same time as the ACCORD, ADVANCE, and VADT studies, a class of diabetic medications came under scrutiny. In 2007, a meta-analysis was published in the *New England Journal of Medicine* that analyzed thiazolidinediones, which are peroxisome-proliferator-activated receptor (PPAR-) agonists that increase insulin sensitivity in peripheral tissues, which had previously been shown to have glucose-reducing effects similar to that of other drugs such as metformin and sulfonylureas [16]. This meta-analysis assessed the effects of rosiglitazone in particular and analyzed its effect on CVD morbidity and mortality in comparison to other glucose-lowering agents in other drug classes or placebo, yielding a surprising result. Rosiglitazone was reported to be associated with a significant increase in the risk of MI and with an increase in the risk of death from cardiovascular causes that had borderline significance. It was found by Nissen et al. that across 42 individual trials in which the mean age of subjects was 56 years old and the mean A_{1c} was 8.2 %, the odds ratio for MI was 1.43 (95 % CI, 1.03–1.98; p=0.03) and the odds ratio for death from any cardiovascular cause was 1.64 (95 % CI, 0.98–2.74; p=0.06) when compared to placebo or other antidiabetic regimens [17]. Following this revelation, in 2008, the United States Food and Drug Administration (FDA) mandated that all new diabetes medications must exclude an unacceptable level of risk for ASCVD prior to drug approval and thus undergo additional cardiovascular safety trials [18]. Furthermore, the FDA went as far as placing restrictions on the prescription and dispensation on rosiglitazone in 2010 [19].

However, the results of this meta-analysis and subsequent actions taken by the FDA were very controversial. These results led the FDA to impose restrictions on the prescribing of rosiglitazone, and the manufacturer

subsequently ceased marketing of the medication. However, in November 2013, the FDA removed the restrictions for rosiglitazone that were in initially put in place in 2010 because a re-evaluation of the data did not support the initial findings reported by Mahaffey et al. [20]. Nonetheless, the increased scrutiny surrounding the cardiovascular safety of diabetic medications would lead to serendipitous findings in the coming years.

Reduction of CVD risk independent of glycemic control

As newer diabetes drugs began to be developed and introduced into the market, cardiovascular outcome trials (CVOTs) were being performed in order to establish cardiovascular safety following the FDA's 2008 mandate. One class of drugs, the dipeptidyl peptidase-4 inhibitors (DPP-4i), despite proving to be safe, failed to identify a cardiovascular benefit in their respective CVOTs [21–24]. However, two additional new classes of diabetes agents stood out in particular due to their observed beneficial effects on CVD outcomes: the sodium-glucose cotransporter-2 inhibitors (SGLT-2i) and the glucagon-like peptide-1 receptor agonist (GLP-1RA) therapies.

SGLT-2i therapies, which inhibit the renal absorption of sodium and glucose in the proximal convoluted tubule via inhibition of SGLT-2 protein, cause a reduction of serum glucose levels via increased glucosuria [25]. SGLT-2i therapies were the first notable class of drugs after the FDA's mandate that demonstrated positive clinical effects on macrovascular risk that were independent of glycemic control. Several outcome trials, including the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG), Canagliflozin Cardiovascular Assessment Study (CANVAS/CANVAS-R), Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction (DECLARE-TIMI), and eValuation of ERTugliflozin effIcacy and Safety Cardiovascular Outcomes Trial (VERTIS CV), examined the use of SGLT-2i and their effects on primary outcomes related to CVD, as well as heart failure and renal outcomes. However, these trials had some variation in the definitions of their primary outcomes and had differences in the numbers of patients enrolled that had established CVD (secondary prevention) vs. risk factors for CVD (primary prevention); i.e., 100 % of patients in the EMPA-REG and VERTIS CV outcome trials had established CVD, but only about two-thirds of the patients had established CVD in the CANVAS/CANVAS-R trial, and only one-third in the DECLARE-TIMI trial [26–29]. See Table 1 for a summary of the primary outcome data for these CVOTs. These differences in study populations made comparisons of the results between the trials challenging, but overall, it was clearly demonstrated that the use of SGLT-2i had a positive impact on cardiovascular risk. Importantly, these beneficial effects were independent of the effect of SGLT-2i on glycemic control and A_{1c} levels.

Table 1: SGLT-2i CVOTs.

	SGLT-2i CVOTs			
	Primary outcome definition	**Primary outcome hazard ratio**	**95 % CI**	**p-Value**
EMPA-REG (empagliflozin)	Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke	0.86	0.74–0.99	0.04 for superiority
CANVAS/ CANVAS-R (canagliflozin)		0.86	0.75–0.97	0.02 for superiority
[a]DECLARE TIMI (dapagliflozin)		0.93	0.84–1.03	0.17 for superiority
VERTIS (ertugliflozin)		0.97	0.85–1.11	>0.001 for noninferiority

[a]In DECLARE TIMI, the primary safety outcome was a composite of MACEs, defined as cardiovascular death, myocardial infarction, or ischemic stroke. The primary efficacy outcomes were MACEs and a composite of cardiovascular death or hospitalization for heart failure. CI, confidence interval; CVOTs, cardiovascular outcome trials; MACE, major adverse cardiovascular events; SGLT-2i, sodium-glucose cotransporter-2 inhibitors.

Following the success and reassuring results from the SGLT-2i CVOTs, subsequent trials were carried out that specifically assessed the effects of SGLT-2i on outcomes related to congestive heart failure (CHF). These trials included the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) [30] and Empagliflozin Outcome Trial in Patients With Chronic Heart Failure and a Reduced Ejection Fraction (EMPEROR Reduced) [31] trials, which assessed dapagliflozin and empagliflozin, respectively, in heart failure with reduced ejection fraction (HFrEF), and the Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction (EMPEREROR Preserved) [32] and Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure (DELIVER) [33] trials, which assessed empagliflozin and dapagliflozin, respectively, in heart failure with preserved ejection fraction (HFpEF). See Table 2 for detailed data regarding these trials. Overall, both empagliflozin and dapagliflozin were shown to have beneficial effects on both death and hospitalizations secondary to CHF. In fact, the use of SGLT-2i is now standard therapy in the treatment of CHF irrespective of a history for T2D [34]. Thus,

Table 2: SGLT-2i CHF trials.

SGLT-2i CHF trials[a]				
	Primary outcome	**Primary outcome hazard ratio**	**95 % CI**	**p-Value**
EMPEROR reduced (empagliflozin)	Composite of cardiovascular death or hospitalization for worsening heart failure	0.75	0.65–0.86	<0.001
EMPEROR preserved (empagliflozin)		0.79	0.69–0.90	<0.001
Dapa-HF (dapagliflozin)		0.74	0.65–0.85	<0.001
DELIVER (dapagliflozin)		0.82	0.73–0.92	<0.001

[a]Note: trials included patients both with and without T2D. These agents are approved to reduce cardiovascular death and hospitalization for heart failure in patients with CHF irrespective of whether or not they have T2D. CHF, congestive heart failure; CI, confidence interval; CVOTs, cardiovascular outcome trials; SGLT-2i, sodium-glucose cotransporter-2 inhibitors; TD2, type 2 diabetes mellitus.

these trials further solidified the use of SGLT-2i as a beneficial treatment that is again not secondary to these agents' effects on blood glucose levels.

In addition to the various SGLT-2i CVOTs and CHF trials, there were also dedicated trials that focused on chronic kidney disease (CKD) outcomes. These trials include the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) [35], Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) [36], and the Study of Heart and Kidney Protection With Empagliflozin (EMPA-Kidney) [37], whose primary endpoints of interest included variations of end-stage kidney disease (ESKD), a sustained decrease in estimated glomerular filtration rate (eGFR) 40 % from baseline, and death secondary to renal causes. See Table 3 for detailed data for these trials. Results from these studies demonstrated significant reduction in the progression to ESKD and mortality related to CKD or CVD. Although these studies did have varying definitions of their primary outcomes, these trials succeeded as a whole to demonstrate the efficacy of SGLT-2i therapy against worsening renal outcomes in patients with T2D.

GLP-1RA, which achieve glycemic control via stimulating glucose-dependent insulin release while simultaneously inhibiting glucagon secretion as well as reduce appetite and increase postprandial satiety [38], were another class of agents that also demonstrated beneficial risk reduction of CVD. The major trials for this class of drugs included the Evaluation of LIXisenatide in Acute coronary syndrome (ELIXA) [39], LEADER [4], Exenatide Study of Cardiovascular

Table 3: SGLT-2i CKD trials.

SGLT-2i CKD trials				
	Primary outcome	**Primary outcome hazard ratio**	**95 % CI**	**p-Value**
CREDENCE (canagliflozin)[a]	End-stage kidney disease (dialysis, transplantation, or a sustained eGFR of <15 mL/min/1.73 m^2), a doubling of serum creatinine, or death from renal or cardiovascular causes	0.7	0.59–0.82	0.00001
Dapa-CKD (dapagliflozin)	Sustained decline in eGFR of at least 50 %, end-stage kidney disease, or death from renal or cardiovascular causes	0.61	0.51–0.72	<0.001
EMPA-KIDNEY (empagliflozin)	Progression of kidney disease (end-stage kidney disease, a sustained eGFR of <10 mL/min/1.73 m^2), a sustained decrease in eGFR of ≥40 % from baseline, or death from renal or cardiovascular causes	0.72	0.64–0.82	<0.001

[a]Note: CREDENCE only included patients with T2D, whereas Dapa-CKD and EMPA-KIDNEY included patients both with and without T2D. CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; SGLT-2i, sodium-glucose cotransporter-2 inhibitors; T2D, type 2 diabetes mellitus.

Event Lowering (EXSCEL) [40], REWIND [7], HARMONY [41], Peptide Innovation for Early Diabetes Treatment 6 (PIONEER-6) [42], and SUSTAIN-6 [6] trials. See Table 4 for the primary outcome results from these trials. However, there are some differences among these trials, most notably in terms of the patient populations they enrolled (i.e., the percentage of patients with established CVD). Some agents within the GLP-1RA class, such as lixisenatide and long-acting exenatide, were not found to be associated with a statistically significant reduction in CVD outcomes vs. placebo. However, a reduction in the risk of MACEs was specifically demonstrated with liraglutide, dulaglutide, albiglutide, and subcutaneous semaglutide. A study evaluating oral semaglutide demonstrated cardiovascular safety but did not identify a cardiovascular benefit (it was not

Table 4: GLP-1RA CVOTs.

GLP-1RA CVOTs				
	Primary outcome	**Primary outcome hazard ratio**	**95 % CI**	**p-Value**
SUSTAIN (subcutaneous semaglutide)	Death from cardiovascular causes, myocardial infarction, or nonfatal stroke	0.74	0.58–0.95	<0.001 for superiority
LEADER (liraglutide)		0.87	0.78–0.97	0.007 for superiority
EXSCEL (exenatide)		0.91	0.83–1.00	0.06 for superiority; <0.001 for noninferiority
HARMONY (albiglutide)		0.78	0.68–0.90	0.0006 for superiority
REWIND (dulaglutide)		0.88	0.79–0.99	0.026 for superiority
PIONEER-6 (oral semaglutide)		0.79	0.57–1.11	<0.001 for noninferiority
ELIXA (lixisenatide)	Identical as above, but with the addition of the hospitalization for unstable angina	1.02	0.89–1.17	0.81 for superiority; <0.001 for noninferiority

CI, confidence interval; CVOTs, cardiovascular outcome trials; GLP-IRA, glucagon-like peptide-1 receptor agonists.

powered to do so). The Semaglutide cardiovascular outcomes trial in patients with type 2 diabetes mellitus (SOUL) study, specifically designed to identify if cardiovascular risk reduction is also associated with the oral formulation of semaglutide, is currently ongoing [43]. A meta-analysis of these trials conducted in 2019 sought to consolidate these findings and provide a clearer picture of the effect of GLP-1RA on the occurrence of CVD. Overall, this meta-analysis found that the hazard ratios of death secondary to CVD, nonfatal stroke, and fatal/nonfatal MI were 0.88 (95 % CI, 0.86–0.96; p=0.003), 0.84 (95 % CI, 0.76–0.93; p<0.0001), and 0.91 (95 % CI, 0.83–0.95; p=0.0001) respectively [44]. Moreover, GLP-1RA reduced all-cause mortality by 12 %, hospital admission for heart failure by 9 %, and the occurrence of kidney disease (new-onset macroalbuminuria, decline in eGFR, progression to end-stage renal disease [ESRD], or death secondary to kidney disease) by 17 % [44]. Notably, as with SGLT-2i therapies, these findings are also a result of the direct action of the drug, not a secondary benefit from greater glycemic control. Also, of note, another trial known as the FLOW study (effect of semaglutide vs. placebo on the progression of renal impairment in subjects with type 2 diabetes and chronic kidney disease) is currently ongoing and is assessing the effects of GLP-1RA therapy (specifically subcutaneous semaglutide) and the progression of CKD.

Management of patients with GLP-1RA and SGLT2I

Given the potentially groundbreaking findings of their respective trials, the use of SGLT-2i and GLP-1RA therapy has revolutionized the treatment approach for T2D. While previous guidelines emphasized glycemic control and A_{1c} targets to prevent adverse outcomes, SGLT-2i and GLP-1RA therapies are now considered as options for treatment, independent of A_{1c} levels, and are instead indicated based on the presence of established ASCVD or notable risk factors for arteriosclerotic vascular disease (ASVD), as well as heart failure and/or CKD [45]. The use of metformin and comprehensive lifestyle modification remains first-line treatment upon diagnosis of T2D for the majority of patients, but the previously mentioned factors must be accounted for when assessing patients and choosing which medications to initiate first-line or at any point in the management of T2D. Careful considerations of comorbidities must be undertaken, and agents that confer benefits on cardiovascular, heart failure, and CKD risk reduction must be initiated in patients at risk. Moreover, side-effect profiles and potential barriers of use, such as the cost or availability of agents, should be considered and accounted for when deciding to initiate these agents for individual patients. The risks vs. benefits must be reviewed and discussed with the patient, and a shared decision-making process should be leveraged to help the individual patient reach an evidence-based and value-congruent medical decision. A_{1c} targets still have their role in medical management because optimal glycemic control has been shown to reduce the risk of microvascular complications of diabetes, as demonstrated by the DCCT and UKPDS landmark studies, but the use of an SGLT-2i or GLP-1RA should be determined based on the patient's individualized risks and needs in order to mitigate the risk of macrovascular complications.

Conclusions

T2D is a highly prevalent disease associated with the development of both microvascular and macrovascular complications. Accordingly, reducing the risk of both microvascular and macrovascular complications is critical in the management of patients with T2D. GLP-1RA and SGLT-2i therapies

have sparked a major evolution in the management of T2D. T2D is no longer a glucose-centric disease with A_{1c} goal attainment as the primary target. We must also identify patients at risk of CVD, heart failure, and CKD, and initiate therapies with proven benefits, irrespective of whether a patient's A_{1c} is <7 % or at their individualized target. As such, primary care physicians must focus on not only attaining recommended guideline A_{1c} targets in order to reduce the risk of microvascular complications in their T2D patients, but also identifying patients that would benefit from SGLT-2i and GLP-1RA therapy, independent of their effects on glycemic control.

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