Emerging Cardiovascular Benefits of SGLT2 Inhibitors in Patients Living with T2DM

EXECUTIVE SUMMARY

An estimated 451 million people worldwide have type 2 diabetes mellitus(T2DM), a number expected to rise to 693 million people by 2035 (Cho et al.,2016). Patients living with the disease have twice the risk of developing cardiovascular disease (CVD) compared with the general population, and two-thirds of patients with T2DM will die of CVD (Ali et al., 2016). Patients living with T2DM often die from ischemic heart disease (40%), CVD including congestive heart failure (15%), and stroke (10%) [Wang et al., 2016]. Aggressive cardiovascular (CV) risk management has been the standard in T2DM care since 1999, jointly recommended by both the American Heart Association (AHA) and the American Diabetes Association (ADA) [Ali et al., 2013].

In the late 20th and early 21st centuries, the focus of diabetic management was on glycemic control as a surrogate marker for developing the complications of DM. A strong correlation between hemoglobin A1c(HbA1c) and CV mortality exists: For every 1% increase in HbA1c, CV mortality increases 1.15-fold (Hu, Ying; 2019). Thus, extensive studies anticipated significantly improved outcomes for patients with T2DM with improved glycemic control. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study and the Action in Diabetes and Vascular Disease (ADVANCE) trial garnered startling results: Microvascular complications like peripheral neuropathy were improved, but macrovascular complications (ASCVD) developed unchecked. Shockingly, *more* cardiovascular deaths were observed in the intensive glycemic control group, resulting in early cessation of this study arm (Hu, Ying., 2019). More work from the United Kingdom Prospective Diabetes Study (UKPDS) tempered these findings, observing that a 15% relative risk reduction for non-fatal myocardial infarction and coronary heart disease events was achieved with adequate glycemic control. However, intensive glycemic control did *not* positively influence all-cause mortality (Skyler et al., 2009).

Contemporaneously, common-sense clinical studies were undertaken. Extensive clinical support to achieve weight loss in patients with T2DM portended successful reduction of mortality. Again, disappointment ensued. A 2013 study, The Action for Health in Diabetes Study (Look AHEAD trial) demonstrated that while intensive management of patients *did* result in weight loss, there was *no difference* in CV events between treatment arms (HR, 0.95%: 95% CI, 0.83-1.9, p = 0.51) [Wing et al., 2013] These results prompted researchers and clinicians to focus on the more accessible goals of intensive management of *secondary* cardiovascular risk factors: Hypertension and elevated cholesterol.

Detailed meta-analyses of studies controlling these two risk factors revealed that lowering systolic blood pressure in patients with T2DM reduced all-cause mortality by 13%, cardiovascular events by 11%, and garnered a 27% reduction in stroke events (ADA, 2020). Regarding cholesterol management, large trials adding moderate- to high-intensity statins resulted in primary and secondary prevention of ASCVD events and coronary heart disease (CHD) deaths in patients with DM. Patients with concomitant known ASCVD and T2DM are higher risk: They derived *even more* benefit from secondary prevention of CV risk factors (ADA, 2020). In summary, managing hypertension and hyperlipidemia did improve CV outcomes. But, in a large US cohort study, fewer than half the patients received an appropriate statin for LDL > than

70 mg/dL, fewer than 20% were prescribed glucose-lowering therapies with a defined cardiovascular benefit, and even fewer patients received all therapies recommended in the ADA guidelines (Arnold et al., 2019). However, even with improved management of these risk factors in patients with T2DM, CVD persists as a primary cause of death in these individuals (Wang et al., 2013).

Despite clear support for improving secondary risk factors for ASCVD in patients with T2DM, a large 2019 multicenter US cohort study of this group revealed that few patients received comprehensive guideline-recommended therapy. Surprisingly, physicians were preferentially prescribing sulfonylureas and dipeptidyl peptidase-4 inhibitors (DPP4is), which, at best, neutral cardiovascular impact. Known beneficial therapies for patients who have T2DM with ASCVD, including sodium-glucose transport receptor 2 inhibitors (SGLT2is), glucagon-like peptide-1 receptor agonists (GLP-1 RAs), thiazolidinediones, renin-angiotensin-aldosterone system inhibitors (RAASis), antiplatelet or anticoagulant therapy, statins, high-intensity statins, ezetimibe, fish oil, fibrates, and proprotein convertase subtilisin/kexin type 9 (PCSK9) enzyme inhibitors were all used suboptimally. Fewer than half of the patients were treated with a high-intensity statin despite *not meeting* ADA recommended LDL goal levels, and less than 20% of patients received beneficial glucose-lowering therapies of proven CV benefit (Arnold et al., 2019).

Clinicians and researchers recognized that oral T2DM medications had severe side effects. Hypoglycemia, myocardial infarction, stroke, and CV death were observed with sulfonylureas, an early and dominant oral medication for T2DM (Douros et al., 2018). Work to find better non-insulin alternatives for patients with T2DM led to the development of thiazolidinediones. While highly effective in controlling glycemic levels and delaying progression of patients with T2DM to insulin therapy, multiple studies revealed that this class of drug caused edema, heart failure hospitalization (HHF), and CV death (Douros et al., 2018). Recent work concluded that CV event rates were similar with sulfonylureas and pioglitazone (Powell et al., 2018).

These worrisome developments led the US Food and Drug Administration (FDA) to drastically modify their T2DM drug-trial guidance. Cardiovascular Outcome Trials (CVOTs) were mandated for novel antihyperglycemic medications from 2008 onward. Drug developers are required to demonstrate that new T2DM drugs do not increase risk of myocardial infarction (MI), stroke, or CV death (Zannad et al., 2016). Results were dramatic. Newer classes of drugs, glucagon-like peptide 1 A receptor agonists (GLP-1As) and all sodium-glucose cotransporter-2 receptor inhibitors (SGLT2is) *reduced* CV risk.[19] The SGLT2is demonstrated the strongest benefit: Reducing major adverse coronary events (MACE) (CV death, non-fatal MI, and non-fatal stroke), CV death, and HHF (Kluger et al., 2019).

Broad-spectrum SGLT2is were studied: Canagliflozin, dapagliflozin, and empagliflozin. The Canagliflozin Cardiovascular Assessment Study (CANVAS) revealed a 14% relative risk reduction of MACE. In the Dapagliflozin Effect on Cardiovascular Events (DECLARE – TIMI 58) trial observed MACE events demonstrated 7% in relative risk reduction. Remarkably, the Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG-OUTCOME) trial demonstrated a 14% improvement in MACE outcomes compared with placebo (hazard ratio [HR] 0.86; 95% confidence interval (CI0, 0.74 to 0.099; $P = 0.04$) [Zinman et al., 2015]

Unexpectedly, the EMPA-REG OUTCOME trial showed a substantial decrease in hospitalizations for heart failure (HR, 0.65; 95% CI, 0.50 to 0.85; $P = 0.002$) [Zinman et al., 2015]. Review of the three trials with SGLT2is (EMP-REG OUTCOME, CANVAS, and DECLARE-TIMI 58) all revealed a robust and significant

reduction in the hazard ratios for hospitalization for HF, from 27% to 35%, respectively. (Giugliano et al., 2020). This benefit persisted regardless of prior cardiac history. Multiple further therapeutic benefits were observed: Weight loss, reduced serum uric acid, lower blood pressure, decreased macroalbuminuria and ameliorating new-onset or worsening nephropathy of diabetic kidney disease (DKD) [HR 0.61(95% CI, 0.53 to 0.70); P < 0.001). A review of these major trials and the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) study confirms that these benefits can be considered a class effect of all SGLT2is (Kluger et al., 2019).

SGLT2is can have adverse effects, but most are preventable or treatable with careful observation. As a class, SGLT2is are safe and offer extraordinary benefits for patients living with diabetes in terms of reducing cardiovascular morbidity and mortality (Kosiborod et al., 2018). The observed HHF reduction with SGLT2is in patients with T2DM opens a new avenue for clinical use of this drug class.

Recommended management of T2DM has been revolutionized by the myriad benefits of SGLT2is (Arnold et al., 2019). Despite the recognized reduction in ASCVD events since 2013 in patients using these drugs, suboptimal use of this class by clinicians persists into 2019. This proposed continuing medical education program will provide healthcare providers with the knowledge of how and when to use a safe, effective therapy to reduce the high risk of CV mortality in patients with T2DM. Patients will benefit from their physicians' enhanced understanding of SLGT2i efficacy in reducing ASCVD, HHF, and overall CV mortality.

GAP ANALYSIS

GAP 1. Clinicians are not optimally reducing adverse cardiovascular outcomes in patients living with T2DM	
Current Practice	Patients living with T2DM have twice the risk of developing cardiovascular disease compared with non-T2DM patients. Among these patients 2/3 will die of ischemic heart disease.[3] Diabetic management focused on glycemic control as a marker for reducing the complications of diabetes. However, the ACCORD and ADVANCE trials revealed that intensive glycemic control increased cardiovascular mortality ((Skyler et al., 2008). The UKPDS study confirmed that while non-fatal CHD was moderately reduced, adequate glycemic control did not reduce all-cause mortality (Ray et al., 2009). In addition, nonpharmacologic interventions of weight loss and exercise did not reduce ASCVD (Wing et al., 2013). Despite knowledge that achieving secondary goals of lowering blood pressure and LDL cholesterol lower ASCVD, few patients received these comprehensive guideline-recommended medical therapies for risk reduction. (Arnold, et al 2019). Additionally, physicians are using less than 20% of glucose-lowering therapies with known cardiovascular benefit, preferentially choosing sulfonylureas and DPP4i's (Zannad et al., 2016).

Best Practice	Clinicians have been trained to use euglycemia as a surrogate marker for reduction of ASCVD risk in T2DM patients. When clinicians understand that tight glycemic control and non-pharmacologic interventions of weight loss and exercise do not reduce cardiovascular risk of patients living with T2DM, healthcare delivery systems and clinicians can implement stronger intervention programs to manage secondary risk factors to reduce life-threatening cardiovascular risk to T2DM patients (Skyler et al., 2008). When Clinicians comprehend that widely used sulfonylureas and DPP4is' detract from cardiovascular benefit, clinicians and healthcare delivery systems will be more proactive in ensuring pharmacotherapeutics are individualized to maximize ASCVD risk reduction in their patients.

GAP ANALYSIS (cont.)

Gap 2. Clinicians are not familiar with the benefits of SGLT2 inhibitors in reducing cardiovascular mortality.	
Current Practice	T2DM patients are inherently at risk for developing and dying from ASCVD (Ali et al., 2016). Clinicians currently demonstrate a preponderance of use of sulfonylureas and DPP4i's in the treatment of hyperglycemia in T2DM patients. Yet, both these highly prescribed therapies have no ASCVD risk reduction and known increased cardiovascular risk mortality for T2DM patients (Douros et al., 2017; Vaccaro et al., 2017). Clinicians demonstrate slow adoption of SGLT2 inhibitors in T2DM patients with ASCVD, despite clear benefit (Arnold et al., 2019). Primary care physicians may not be familiar with the benefits of reducing ASCVD risk by the SGLT2 inhibitor class.
Best Practice	For optimal disease management of patients living with T2DM, clinicians require familiarity with new T2DM drug classes that reduce morbidity and mortality from ASCVD. Patients will clinically benefit when physicians comprehend the significant reduction in cardiovascular events gained from treating their patients with SGLT2 inhibitors. (Kluger et al., 2018; Hu, Ying; 2019). Clinicians will recognize that use of SGLT2i's versus other glucose-lowering drugs are associated with a lower risk of

	death, MI, Hospitalized Heart Failure (HHF), and stroke. (Kosiborod et al., 2018).

Gap 3. Clinicians are not up to date on the safety and efficacy of SGLT2 inhibitors.	
Current Practice	Clinicians demonstrate slow adoption of SLGT2 inhibitors in T2DM patients. (Arnold, 2019). Primary care physicians may not be familiar with the safety and efficacy of using SGLT2 inhibitors in their patients and the contrasting risks of prior standard-of-care therapies (Douros et al., 2017; Vaccaro, et al., 2017).
Best Practice	When clinicians recognize that SGLT2 inhibitors are safe and efficacious, they will increase their comfort level prescribing within new ADA guidelines for 2020 to utilize SGLT2 inhibitors. (ADA Diabetes Care 2020; 43(suppl. 1): S111-S134) Clinicians will identify potential risks of SGLT2 inhibitors including UTI, mycotic infections, and euglycemic DKA. Additionally, clinicians will individually stratify potential risks of bone fractures and bladder and breast cancer in the context of surveillance bias. (Kluger et al., 2019).

Gap 4. Clinicians are not familiar with the significant benefits of SGLT2 inhibitors in preventing Hospitalized Heart Failure (HHF) in T2DM patients.	
Current Practice	Heart failure remains an under-recognized complication of diabetes and the second-most common heart disease presentation in T2DM patients (Sattar et al., 2016). T2DM is an independent risk factor for heart failure, resulting in a four-fold increase in T2DM hospitalization for HHF compared with non-diabetic patients (Kluger et al., 2019). Clinicians are not currently using SGLT2 inhibitors with regularity in T2DM patients at risk for HHF (Arnold et al., 2019).
Best Practice	For optimal disease management, clinicians need to remain up to date on recent studies demonstrating that a 30-40% reduction in HHF were consistent among all clinical trials for SGLT2 inhibitors (Sattar et al., 2016; Kluger et al. 2019)

Literature Review

Worldwide, 451 million people live with diabetes mellitus. This number is expected to rise to 693 million by the year 2045 (Cho et al., 2018). In 2015, the prevalence of diabetes was 8.8% and anticipated to rise to 10.4 % by 2040 (Ogurtsova et al., 2017). In addition to the significant human cost of this disease, an estimated $37.3 billion in medical costs are incurred annually: In 2015, direct and indirect costs of diabetes reflected 1.8% of the US Gross Domestic Product (Bommer et al., 2017). On average, patients spend approximately $9000 to $10,000 per year for medical expenditures (Ogurtsova et al., 2017). These daunting figures do not reflect the tragic personal costs T2DM patients endure in pain, loss of physical well-being, and the long-term morbidity and mortality from the complications of living with T2DM.

Patients living with T2DM have twice the risk of developing cardiovascular disease compared with the general population, and two-thirds of diabetic patients will die of cardiovascular disease (Ali et al., 2016) Patients living with T2DM often die from ischemic heart disease (40%), cardiovascular disease including congestive heart failure (15%), and stroke (10%) [Wang et al., 2016]. Aggressive cardiovascular risk management has been the standard in T2DM care since 1999, jointly recommended by both the AHA and the ADA [Ali et al., 2013].

In the late 20th and early 21st centuries, T2DM management focused on hyperglycemia as a surrogate marker for developing the complications of diabetes, both micro- and macrovascular. Therapy revolved around lowering glycemic index, and expectations were that improvement in patients' health would follow. Surprisingly, better glycemic control did not significantly ameliorate macrovascular disease (ASCVD), and clinical focus shifted to managing T2DM patients' secondary risk factors to reduce cardiovascular mortality (Skyler et al. 2008). In addition to these disappointing results, it became apparent that standard-of-care drugs were implicated in worsening cardiovascular outcomes (Douros et al., 2018). Focus of T2DM care moved to managing secondary cardiovascular risk factors including hypertension and elevated Low Density Lipoprotein cholesterol (LDL) with proven benefit to morbidity and mortality (ADA, 2020). Despite known benefit, patients were found to infrequently meet ADA T2DM management guidelines (Arnold et al., 2019).

Gap 1. Clinicians are not optimally reducing adverse cardiovascular outcomes in patients living with T2DM.

Despite clear support for improving secondary risk factors for ASCVD in T2DM patients, a large 2019 multicenter US cohort study of this group revealed few patients received comprehensive guideline-recommended therapy. Surprisingly, this cohort study revealed physicians preferentially prescribing sulfonylureas and dipeptidyl peptidase-4 inhibitors (DPP4i's), which have, at their best, neutral cardiovascular impact. Known beneficial therapies for T2DM patients with ASCVD, including Sodium-Glucose Transport Receptor 2 inhibitors (SGLT2i's), Glucagon-like peptide-1 receptor agonist (GLP-1 RAs), thiazolidinediones, RAAS inhibitors, antiplatelet or anticoagulant therapy, statins, high-intensity statins, ezetimibe, fish oil, fibrates and Proprotein convertase subtilisin/kexin type 9 enzyme inhibition (PCSK9 inhibitors) were all used sub-optimally. Less than half of the patients were treated with a high-

intensity statin despite *not meeting* ADA recommended LDL goal levels, and below 20% of patients received beneficial glucose-lowering therapies of proven cardiovascular benefit (Arnold et al., 2019).

Regarding cholesterol management, large trials adding moderate- to high-intensity statins resulted in primary and secondary prevention of ASCVD events and CHD deaths in diabetic patients. Patients with concomitant known ASCVD and T2DM are higher risk: They derived *even more* benefit from secondary prevention of cardiovascular risk factors (ADA, 2020). In summary, managing hypertension and hyperlipidemia did improve cardiovascular outcomes. In 2015, using NHANES data, meta-analysis revealed that 1 in 6 patients individualized, multifactorial risks were not met (Laiteerapong et al., 2015). Recently, in a large US cohort, less than half of patients were observed to receive an appropriate statin for LDL's > than 70 mg/dl, less than 20 percent were prescribed glucose-lowering therapies with a defined cardiovascular benefit, and even less patients received all recommended ADA guideline therapies (Arnold, et al., 2019).

Detailed meta-analyses of studies controlling for these two risk factors revealed that lowering systolic blood pressure in patients with T2DM reduced all-cause mortality by 13%, cardiovascular events by 11%, and garnered a 27% reduction in stroke events (ADA, 2020). However, even with improved management of these risk factors in T2DM patients, cardiovascular disease persists as a primary cause of death in diabetics (Wang et al., 2013).

Clinicians and researchers recognized that oral T2DM medications had severe side effects. Hypoglycemia, MI, stroke, and cardiovascular death were observed with sulfonylureas, an early and dominant oral medication for T2DM (Douros et al., 2018). Work to find better non-insulin alternatives for T2DM patients led to the development of thiazolidinediones. While highly effective in controlling glycemic levels and delaying T2DM patients' progression to insulin therapy, multiple studies revealed this class of drug caused edema, heart failure hospitalization (HHF), and cardiovascular (CV) death (Douros et al., 2018). Recent work concluded that sulfonylureas had similar rates of CV events to pioglitazone (Powell et al., 2018).

These worrisome developments led the FDA to drastically modify their T2DM drug-trial guidance. Cardiovascular Outcome Trials (CVOTs) were mandated for novel antihyperglycemic medications from 2008 onward (Zannad et al., 2016).

Patients will benefit from clinicians understanding the safety and limitations of hypoglycemic T2DM medications. Clinicians can distinctly improve patient outcomes by adhering to ADA 2020 guidelines managing secondary risk factors and adding standard-of-care medications to enhance ASCVD outcomes.

Gap 2. Clinicians are not familiar with the benefits of SGLT2 inhibitors in reducing cardiovascular mortality.

Previously, modern diabetes management focused on lifestyle, glycemic control, proactive management of decrement in renal function with renin-angiotensin-aldosterone system (RAAS) inhibition, and reduction of the secondary cardiovascular risk factors of hypertension and hyperlipidemia (Low et al., 2016). Worrisome well-known cardiovascular outcomes with older glycemic-lowering medications such as sulfonylureas and newer versions like Thiazolidinediones prompted an FDA 2008 mandate requiring CVOT's to accompany new anti-glycemic medications developed for diabetic patients. Drug developers

are required to demonstrate new T2DM drugs do not increase patients' risk for MI, stroke, or CV death (Zannad et al., 2016).

CVOT's for two new classes of medications for diabetic patients garnered surprising results. Results were dramatic. Newer classes of drugs, glucagon-like peptide-1 agonists (GLP-1as) and all sodium glucose cotransporter-2 inhibitors surprisingly reduced cardiovascular risk (Arnold et al., 2019). The SGLT2 inhibitors demonstrated the strongest benefit: Reducing MACE, CV death, and Hospitalized Heart Failure (HHF) [Kluger et al., 2019].

Rather than simply identifying drugs that were cardiac-neutral or without harm, many individual versions of two modern classes of anti-glycemic medications, SGLT2 inhibitors, and GLP-1 a's (liraglutide, semaglutide, and albiglutide) showed a moderate 10% reduction in three-pronged major adverse cardiovascular events (3p-MACE: death from cardiovascular cause, MI, and non-fatal stroke), 12% reduction in CV mortality and a 13% risk reduction in all-cause mortality. However, two of five GLP-1a's were exceptions to this benefit. When meta-analysis was performed, GLP-1a's, as a class, showed modest cardiovascular benefit. The reasons for these exceptions (exenatide and lixisenatide) are not clear but may be attributable to individual drug characteristics. In addition, G1P-1a's did not demonstrate benefit in reducing hospitalization for heart failure (Hu,Ying; 2019).

Conversely, SGLT2-inhibitors demonstrated significant cardiovascular benefit to T2DM patients with ASCVD or risk factors, as a class of drugs, with no exceptions. SGLT2-inhibitors were developed to assist T2DM patients in maintaining euglycemia and preventing long-term complications of diabetes. Prior to their development, several large studies revealed intensive glycemic control garnered modest results in reduction of cardiovascular mortality. SGLT2-inhibitors demonstrate adequate lowering of HgbA1c (Hu, Ying; 2019). However, most dramatic was a considerable reduction of 3p-MACE outcomes (14% relative risk reduction) and a 38% relative risk reduction in CV death (Zinman et al., 2015). Later meta-analysis confirmed SGLT2 inhibitors, as a class, reduced death from all cause (15%), cardiovascular (CV) death (16%), reduced 3-p MACE outcomes (11%), and risk of non-fatal MI by 11% (Zelniker et al., 2019).

Broad spectrums of the SGLT2 inhibitor drug class were studied: Canagliflozin, dapagliflozin, and empagliflozin. The Canagliflozin Cardiovascular Assessment Study (CANVAS) revealed a 14 percent relative risk reduction of MACE. The Dapagliflozin Effect on Cardiovascular Events (DECLARE – TIMI 58) trial observed MACE events declined 7 percent in relative risk reduction. Remarkably, the Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG-OUTCOME) trial demonstrated a 14% improvement in MACE outcomes compared with placebo (HR 0.86; 95% CI, 0.74 to 0.099; $P = 0.04$) [Zinman et al., 2015]. Most surprising, was a significant 31% reduction in the risk of HHF in patients across the SGLT2 inhibitor class of medications (Hu, Ying, 2019; Zelniker et al., 2019).

Gap 3. Clinicians are not up to date on the safety and efficacy of SGLT2 inhibitors.

The safety of SGLT2 inhibitors has been established and adverse side effects are predictable and well-understood. Most adverse effects are preventable or treatable with careful observation. Given that one of the major class effects of SGLT2 inhibitors is stimulating glycosuria, clinicians must be vigilant in identifying and treating possible urinary tract infections or genital mycotic infections. These infections were observed in 9 to 18% of female study patients and half as often in male study subjects (Heerspink et al.; Vasilakou et al., 2013). Relative risk for genital infections were 4.75(95% CI, 4.48 to 3.34), RR for UTI's were 1.15(95% CI, 10.6 to 1.26) and 1.02(95% CI, 0.95 to 1.10). Empagliflozin did not increase the

RR's for UTI's in the EMPA-REG Outcome trial (Van Bommel et al., 2019). Additional valid concerns include hypovolemia, dizziness, and hypotension, because of the diuretic and natriuretic effects of SGLT2 inhibitors (Heerspink et al., 2016).

A serious adverse event was observed when SGLT2 inhibitors were used, off-label, in patients with type 1 diabetes mellitus (T1DM). Euglycemic diabetic ketoacidosis (DKA) was observed in T1DM patients, presumably due to increased ketogenesis seen with SGLT2 inhibitors. DKA is thus considered a theoretical risk in patients with T2DM. Expected disruptions in electrolyte metabolism were initially observed in smaller trials, but the large EMPA-REG outcome trial did not observe significant electrolyte disturbances (Heerspink et al., 2016).

Early trials revealed minor elevations in serum phosphate, raising concerns for precipitating bone loss. Modest increase in non-osteoporotic bone fractures were observed but were attributed more likely a secondary outcome of hypovolemia and falls, rather than a direct effect on bone structure (Heerspink et al., 2016).

Finally, there was a small amount of increased incidence of bladder and breast cancer in study patients: These incidents were attributed to surveillance bias, as patients were brought to evaluation more frequently based on repeat urinalysis and increased care of patients in general (Heerspink et al., 2016).

While the benefits of SGLT2 inhibitors in reducing cardiovascular outcomes, cardiovascular death, and HHF has been understood since 2015, clinicians have been slow to adopt SLGT2 inhibitors in T2DM in patients with ASCVD or multiple risk factors. A 2019 cohort study demonstrated less than 20% of patients are treated with SGLT2 inhibitors. IN fact, clinicians are still instituting cardiac negative or cardiac-neutral glucose-lowering drugs such as DPP4i's or sulfonylureas (Arnold et al., 2019).

Current ADA 2020 guidelines recommend adding SGLT2 inhibitors to T2DM patients with ASCVD and those with risk factors. Educational initiatives will bring clinicians up to date on the significant benefits of SGLT2 inhibitors in preventing negative cardiovascular outcomes and preventing HHF in T2DM patients. The safety of this class of drugs and proven benefit demonstrated in this program will help physicians modify their practice strategies. As a result of this focused educational activity, clinicians will elevate patients' management to 2020 ADA guidelines.

Gap 4. Clinicians are not familiar with the significant benefits of SGLT2 inhibitors in preventing hospitalized heart failure (HHF) in T2DM patients.

Heart failure affects 6 million adults per year and leads to 1 million hospitalizations per year: It is the leading cause for hospitalization in patients over the age of 65 (Weems et al., 2018). Heart failure remains an underrecognized complication of diabetes, and one which carries a poor prognosis (Shah et al., 2014).

In patients living with diabetes, heart failure is the second-most common presentation of CVD. The pathogenesis of heart failure in diabetic patients is likely to be multifactorial. Diabetic patients have multiple risk factors including hypertension, coronary artery disease, obesity, and chronic kidney disease (Sattar et al., 2106). T2DM is an independent risk factor for heart failure with both preserved and reduced ejection fraction. HHF is approximately four times higher for diabetic patients than non-T2DM

patients (Kluger et al., 2018). For these reasons, searching for appropriate therapies to reduce heart failure in diabetic patients is of crucial importance (Sattar et al., 2018).

SGLT2 inhibitors are proven to reduce HHF events in T2DM patients. SGLT2 inhibitors beneficial effects appear to be a result of their core actions. SGLT2 receptors are present at the proximal renal tubule. SGLT2 inhibitors block glucose reabsorption and allow increased glucose and lower plasma volume due to osmotic diuresis from the elevated glucose in the urine, and natriuresis due to the higher sodium concentration in the urine (Kluger et al., 2019).

Patients living with diabetes demonstrate maladaptive *upregulation* of SGLT2 receptors, allowing paradoxical reabsorption of glucose in an already hyperglycemic patient. Because of this, T2DM patients have increased renal gluconeogenesis and elevated glucose reabsorption into the serum, from the kidney. SGLT2 inhibitor drugs block glucose reabsorption and allow increased glucose and sodium excretion into the urine. As a result, SGLT2 inhibitor-treated patients have lower serum glucose and lower plasma volume due to osmotic diuresis from the elevated glucose in the urine and natriuresis due to the higher sodium concentration in the urine (Kluger et al., 2019).

While these effects are advantageous, by lowering blood pressure and blood glucose, they do not fully explain why SLGT2 inhibitors benefit patients so greatly. SGLT2 inhibitors also incidentally block Sodium-proton antiporter/exchangers, present in both the heart and kidney. This may be a mechanism in reducing heart failure (by reducing cardiovascular tone and hypertrophy) and concomitantly protecting the nephron (Kluger et al., 2019; Sattar et al., 2016). Resultant reduction in blood volume may benefit T2DM patients, who are, by definition, susceptible to or already possess cardiac dysfunction (Sattar et al., 2016).

In the EMPA-REG Outcome Trials, modest reduction in the primary composite outcome of MI, stroke or cardiovascular death in the EMPA-REG outcomes were observed. Even more remarkable, was a 30-40% reduction in heart failure hospitalization (HHF), cardiovascular, and all-cause deaths in patients (Sattar et al., 2016). In the CANVAS studies, reduction in HHF was significant (HR = 0.67, 95% CI 0.45 – 0.87, p = 0.02) [Kluger et al., 2018]. The CREDENCE study established these benefits can be considered a class effect of all SGLT2 inhibitors (Kluger et al., 2019).

SUMMARY: Primary care healthcare providers demonstrate low engagement with the use of SGLT2 inhibitors in their T2DM patients, despite evidence supporting reduction in cardiovascular morbidity and mortality. Clinicians can gain confidence in SGLT2 inhibitors' well-supported indication as a first-line therapy in T2DM patients with continuing medical education that revisits ADA 2020 guidelines (ADA, 2020).

This proposed educational program will reduce barriers to care and benefit patients with T2DM by decreasing their CV morbidity and mortality and risk for HHF.

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