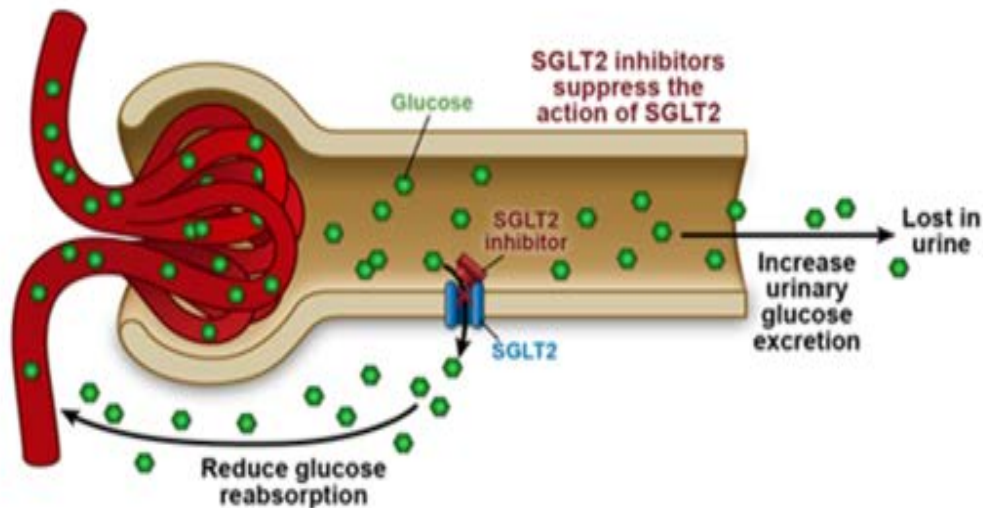


SGLT2 Inhibitors Improve CardioRenal Outcomes in DM2-Get Rid of the Sugar

SGLT2 Inhibitors for Type 2 Diabetes

- SGLT2 inhibitors lower fasting, postprandial, and HbA_{1c}
 - Extra-glycemic effects include reduction of body weight and blood pressure



Zaccardi F, et al. *Diabetes Obes Metab*. 2016;18:783-794.

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Internal Medicine Grand Rounds

10/6/17

This is to acknowledge that David Balis, M.D. has disclosed that he does not have any financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. David Balis will not be discussing off-label uses in his presentation.

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Professor of Internal Medicine

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Interests: Smoking Cessation, Hyperlipidemia, DM2, HTN, Prevention, Vaccines, Fitness

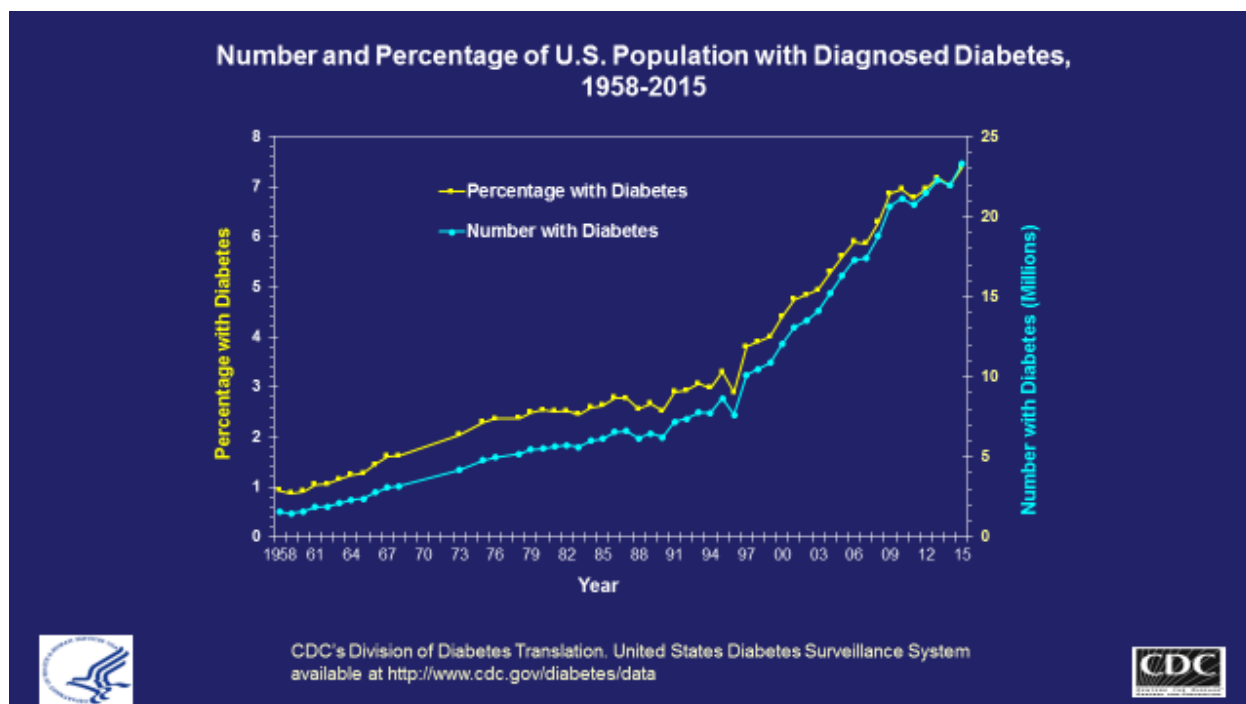
Purpose and Overview: Review treatment options for DM2, emphasizing improved CV and Renal outcomes with SGLT2 Inhibitors

Educational Objective: Review data showing improved CV and Renal Outcomes with SGLT2 Inhibitors

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Educational Objectives: Review data showing improved CV and Renal Outcomes with SGLT2 Inhibitors

1. At the conclusion of this lecture, the listener should be able to appreciate the rising incidence of DM2 and increased CV risks with DM2.
2. At the conclusion of this lecture, the listener should be able to recall the lack of CV outcome benefits with SU's, TZD's, DPP4 inhibitors.
3. At the conclusion of this lecture, the listener should be able to appreciate the improved CV and Renal outcomes with SGLT2 Inhibitors, as well as GLP1 agonists.



Introduction

Imagine a patient with type 2 Diabetes on Metformin whose Diabetes is not controlled. Should one add a Sulfonylurea, TZD, DPP-4 Inhibitor, GLP-1 agonist, basal insulin, or a SGLT2 Inhibitor? In a survey in NEJM, the majority chose a DPP-4 Inhibitor, but I'll hopefully convince you otherwise.

Interestingly, Aretaeus in the 2nd century recognized the symptoms of thirst and excess urination, and named the disorder Diabetes, meaning "a flowing through". For centuries the kidneys were thought to be a major cause of Diabetes due to the frequency of urination, but was subsequently established as a pancreatic disorder with the isolation of insulin in 1921.

Type 2 Diabetes is a major risk factor for cardiovascular disease

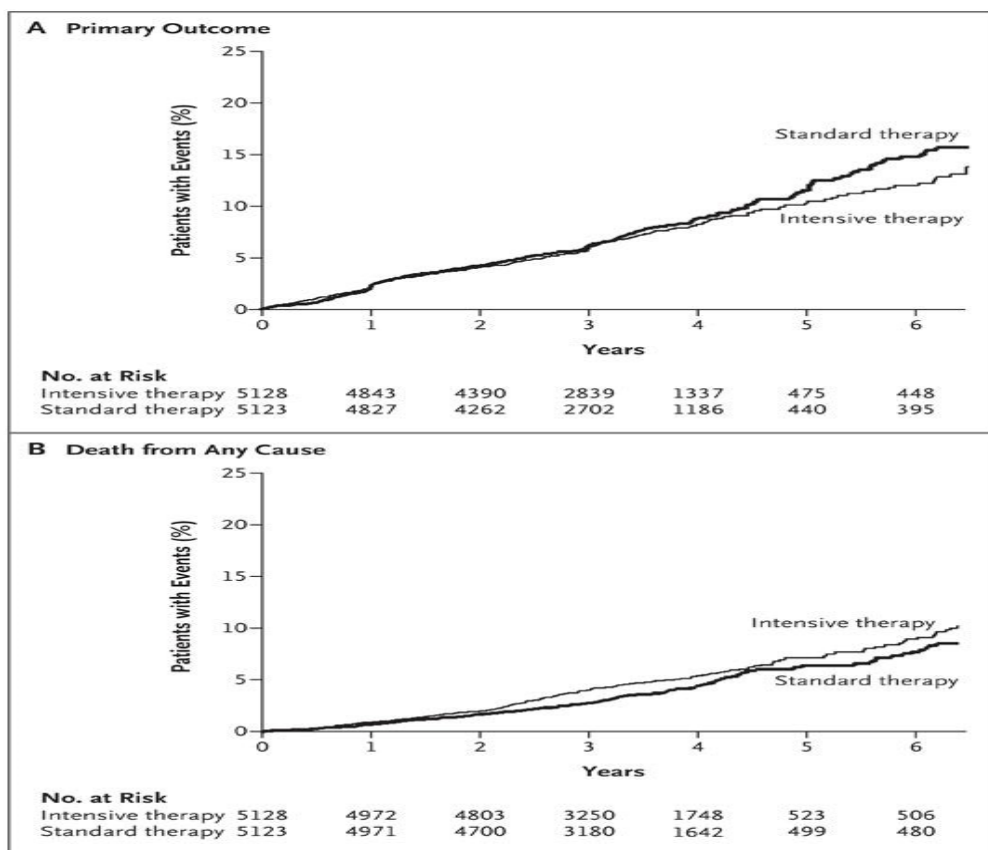
Type 2 Diabetes (DM2) is a major health problem with increasing rates of obesity driving up the number of patients affected and reducing the age at diagnosis. The progressive nature of the hyperglycemia and the failure of drugs to alter this progression means that with time, increasing numbers of agents are required to maintain glycemic control. A plethora of glucose lowering medications have become available. These drugs have different mechanisms and for each there has been a balance between their desired effect and undesired side effects. Previously, a medication was picked based on its side effects, costs, and the patient's co-morbidities. Whereas previous glucose lowering medications caused hypoglycemia, weight gain without improving outcomes, 2 new classes of medications, GLP-1 agonists and SGLT 2 Inhibitors, have been shown to improve outcomes while promoting weight loss.

The world-wide prevalence of Diabetes is 8.5% and increasing, with most being type 2 Diabetes (DM2). It is associated with many complications, including premature microvascular and macrovascular disease affecting the eyes, heart, kidney, and circulation. Diabetes is associated with major morbidity and

mortality with 1.5 million deaths in 2012. Various treatments exist, but premature CV disease, kidney failure, retinal disease, and PVD still wreak havoc.

CV disease is the leading cause of death and complications in DM2. However, evidence that glucose lowering reduces cardiovascular events and deaths in DM2 has surprisingly not been convincingly shown. In fact, aggressive glucose lowering or use of specific glucose lowering medications may be associated with increased cardiovascular outcomes. It is therefore necessary to establish the safety and benefits of all glucose lowering agents.

New glucose-lowering agents for type 2 diabetes are expensive compared with older drugs, so it is important for patients, those treating them, and payers that information used to guide treatment decisions is based on a clear analysis of the benefits and risks of each drug. Although the benefit of glucose lowering to reduce microvascular complications was established in the UKPDS trial, uncertainty remains in relation to the risk of cardiovascular disease, as highlighted by the controversy about rosiglitazone and the adverse effects on cardiovascular death seen in the ACCORD trial of intensive glucose lowering in patients with longstanding diabetes.



ACCORD (Effects of Intensive Glucose Lowering in DM2, NEJM 2008)

As seen in the graph, the ACCORD trial found that intensive glucose lowering with insulin, SU's, Pioglitazone, or Metformin increased all-cause mortality and did not reduce CV events. The ADVANCE trial found that reducing Hgba1c to 6.5 vs 7.3% with SU's, insulin, or Metformin reduced nephropathy, but not mortality or CV events. Similarly, CV events were not reduced with intensive therapy in VADT

(Follow up of Glycemic Control and Cardiovascular Outcomes in DM2, NEJM) or UKPDS. We need to focus on therapies that have been shown to reduce CV complications.

New treatments in DM2

Whereas historically the only options for DM2 were Metformin, Glyburide, and insulin, there are now many new treatments for DM2 currently available, including 11 different classes of medications. A brief review of their mechanisms, side effects, and CV outcome effects will help compare them to the new SGLT2 Inhibitors.

Insulin sensitizers

Metformin

Metformin is first line therapy for DM2 and is inexpensive. It decreases hepatic gluconeogenesis and improves insulin sensitivity. Metformin does not cause hypoglycemia and can lead to weight loss. Side effects include nausea, diarrhea, and rarely lactic acidosis. It is contra-indicated with GFR<30. It improved CV outcomes in UKPDS.

Thiazolidinediones (TZD's)

TZD's such as Pioglitazone (Actos) improve insulin sensitivity. They do not cause hypoglycemia. However, they can cause weight gain, fluid retention, and possibly increase fractures in women. They are contraindicated with class 3 or 4 CHF or bladder cancer. There's no adjustment for renal or liver disease. The possible increase in CV risk with Rosiglitazone resulted in the FDA mandating CV safety trials for all new DM therapies. Actos was neutral in the Pro-Active trial for its primary outcome, but there is a black box warning for CHF with TZD's.

Insulin secretagogues

Insulin secretagogues such as sulfonylureas and glinides stimulate insulin secretion regardless of the glucose.

Sulfonylureas (SU)

Sulfonylureas stimulate pancreatic islet beta cell insulin release. They unfortunately cause hypoglycemia and weight gain, but are inexpensive and may increase CV events.

In a meta-analysis, sulfonylureas were shown to increase all-cause mortality and CV mortality vs other DM agents. In fact, the hazard ratio (HR) was 45 for SU vs GLP-1 agonists and 42 for SU vs SGLT2 Inhibitors.

Glinides

Repaglinide and Nateglenide have a shorter onset of action and duration, so have a lower risk of hypoglycemia than sulfonylureas.

Amylin mimetic

Pramlintide (Symlin) suppresses glucagon, slows gastric emptying, and promotes satiety, as well as decreases postprandial glucoses. It is given as an injection with meals, can cause hypoglycemia, and nausea. There's no evidence of improved CV/Renal outcomes in DM2.

Alpha-glucosidase inhibitors (AGI)

AGI such as Acarbose block carbohydrate absorption in the small intestine, but are limited in their clinical use due to the resulting diarrhea, flatulence, and bloating from the malabsorption. They do not cause hypoglycemia, but are to be avoided with creatinine >2 or cirrhosis. There's no evidence of improved CV/Renal outcomes in DM2.

Bile acid Sequestrants (BAS, resins)

Colesevelam (Welchol) binds bile acids and lowers cholesterol, but is also FDA approved to lower glucose in DM2. It's rarely used, blocks absorption of medications, and causes constipation. Could be used as 2nd line for lowering LDL as well glucose as in DM2. It may improve CV outcomes as a lipid lowering agent in the pre-statin era, but no data with DM2.

Dopamine receptor agonist

Bromocriptine is a Dopamine receptor agonist used for Prolactinomas, Acromegaly, Parkinson's, and NMS, but can also lower glucose. There's no evidence of improved CV/Renal outcomes in DM2.

Incretin based therapy

Dipeptidyl peptidase-4 (DPP-4) inhibitors

DPP-4 degrades Glucagon-like peptide-1 (GLP-1). DPP-4 inhibitors, like Linagliptin, Sitagliptin, Saxagliptin, and Alogliptin, increase insulin and decrease glucagon in a glucose dependent manner. They do not cause hypoglycemia or weight gain. They are well tolerated, convenient, and can be given with multiple common co-morbidities, but may cause pancreatitis. Saxagliptin and Alogliptin may increase the risk of CHF.

Unfortunately, Alogliptin in EXAMINE (Examination of CV Outcomes with Alogliptin vs Standard of Care), Saxagliptin in SAVOR-TIMI 53 (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with DM), and Sitagliptin in TECOS (Trial Evaluating CV Outcomes with Sitagliptin) all failed to show improvement in CV outcomes.

SAVOR-TIMI 53, Saxagliptin and Cardiovascular Outcomes in DM2, NEJM, 2013

Type 2 Diabetes doubles the risk of cardiovascular disease and the majority of patients with DM2 die of cardiovascular disease. Although improved glycemic control reduces microvascular disease, it was uncertain whether any DM agents or strategies lowered cardiovascular risk. In the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes (SAVOR-TIMI 53), 16,492 patients with DM2 and at risk for cardiovascular events were randomized to Saxagliptin vs placebo for 2.1 years. There was no difference in the primary outcome of cardiovascular death, MI, or stroke. It improved glycemic control and reduced microalbuminuria, but increased the rate of hospitalization for heart failure. Thus, there remains an enormous need for DM agents that improve glycemic control and reduce cardiovascular complications.

Glucagon-like peptide-1 (GLP-1) Agonists

GLP-1 agonists, like Exenatide, Liraglutide, Dulaglutide, and Lixisenatide, stimulate insulin secretion and inhibit glucagon in a glucose-dependent manner. They also delay gastric emptying and suppress appetite, thereby causing weight loss, but not hypoglycemia. They commonly cause n/v and diarrhea and are injected daily or weekly. They may cause pancreatitis. Recently, Liraglutide (LEADER) and Semaglutide (SUSTAIN-6) showed improved CV outcomes, but Lixisenatide did not (ELIXA-Evaluation of Lixisenatide in ACS).

LEADER-Liraglutide Effect and Action in DM: Evaluation of CV Outcome Results, NEJM, 2016

Liraglutide is a GLP1 agonist and is approved to treat diabetes as well as promote weight loss. The LEADER trial, Liraglutide Effect and Action on Diabetes: Evaluation of Cardiovascular Outcome Results was published in NEJM in 2016. Liraglutide or placebo was added to standard therapy in 9340 patients with Diabetes and high cardiovascular risk for 3.8 years. The first occurrence of death from cardiovascular causes, nonfatal MI, or nonfatal stroke was reduced by Liraglutide by 13%. There was a lower risk of death from cardiovascular causes and death from any cause. In addition, there was a lower risk of Nephropathy. The NNT to prevent one event in 3 years was 66.

There has been concern of a possible association between GLP-1 agonists with pancreatitis and pancreatic cancer. In LEADER, there was no difference in pancreatitis. There were more pancreatic cancer cases with Liraglutide (13 vs 6) with a $p=.06$.

SUSTAIN-6, Semaglutide and Cardiovascular Outcomes in DM2, NEJM, 2016

For patients with incomplete control of DM2 after lifestyle and Metformin, the 2016 ADA guidelines suggest adding 1 of 5 classes of medications-Sulfonylureas, DPP-4 Inhibitors, SGLT2 Inhibitors, GLP 1 agonists, or basal insulin. However, few studies have compared these second line agents. The Trial to Evaluate Cardiovascular and Other Long Term Outcomes with Semaglutide in Subjects with DM2 (SUSTAIN-6) was published in NEJM in 2016. 3297 patients with DM2 and high cardiovascular risk were randomized to Semaglutide or placebo for 2 years. Semaglutide reduced the risk of cardiovascular death, nonfatal MI, or nonfatal stroke by 26%. The risk of new or worsening nephropathy was also lower.

However, in the Evaluation of Lixisenatide in ACS (ELIXA) trial, the GLP1 agonist, Lixisenatide, did not show any cardiovascular benefit.

Sodium-glucose cotransporter-2 Inhibitors (SGLT-2 Inhibitors)

Glucose is a polar compound and its solubility and transport occurs through 2 specialized glucose transporters in the renal tubule, small intestine, brain, and peripheral tissues: sodium-glucose cotransporters (SGLT's) and facilitated glucose transporters (GLUT's). Whereas GLUT's facilitate passive transport, SGLT's are involved in active transport.

Normally, 180 gm of glucose/day is filtered and then SGLT-2 reabsorbs glucose in the proximal convoluted tubules of the kidney. 90% of glucose reabsorption is mediated by SGLT-2 in the S1 and S2 segments of the proximal convoluted tubules and the remaining 10% by SGLT-1 in the S3 segment. At glucoses above 180, the resorptive capacity is overwhelmed, resulting in glycosuria. Inhibition of SGLT-2 reduces hyperglycemia by reducing glucose reabsorption and increasing urinary excretion. They lower Hgba1c by .66% and decrease weight by 1.8 kg.

SGLT2 inhibition is kidney specific, whereas SGLT1 is more widely expressed, so its inhibition would be expected to have wider physiological effects. SGLT2 Inhibitors have insulin-independent effects. Untreated Diabetics have increased sodium resorption with less sodium delivered distally to the nephron and juxtaglomerular apparatus. Accordingly, there is increased intraglomerular pressure, hyper filtration, and increase in blood pressure. SGLT2 Inhibitors reverse these changes by blocking proximal sodium resorption resulting in a negative sodium balance and reduced blood pressure. Thus, SGLT2 Inhibitors alter intrarenal hemodynamics.

Some may be concerned over possible excess dehydration with loss of renal function from glycosuria with inhibiting SLGT-2. However, individuals with Familial Renal Glycosuria from mutations on the gene

encoding SGLT-2 have asymptomatic urinary glucose excretion, but no polyuria, polydipsia, kidney disease, or urogenital infections.

SGLT2 Inhibitors including Canagliflozin, Dapagliflozin, and Empagliflozin are the newest DM medications. They inhibit glucose reabsorption in the proximal tubule in the kidney leading to glycosuria. They lower glucose independent of insulin, without hypoglycemia, and have the advantage of also lowering blood pressure and weight, without increases in heart rate. SGLT2 inhibitors also have favorable effects on arterial stiffness and vascular resistance, adiposity, albuminuria, and urate. They have been associated with increase in LDL and HDL cholesterol. They are conveniently given orally once daily in the morning and could be given early in DM2 or in advanced disease. They may cause polyuria and genital yeast infections and are limited in CKD with GFR <30. Most importantly, SGLT2 Inhibitors have been shown to improve outcomes in EMPA-REG OUTCOME, CANVAS, CANVAS-R, CVD-REAL, and CVD-REAL Nordic.

EMPA-REG OUTCOME, Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes, NEJM 2015

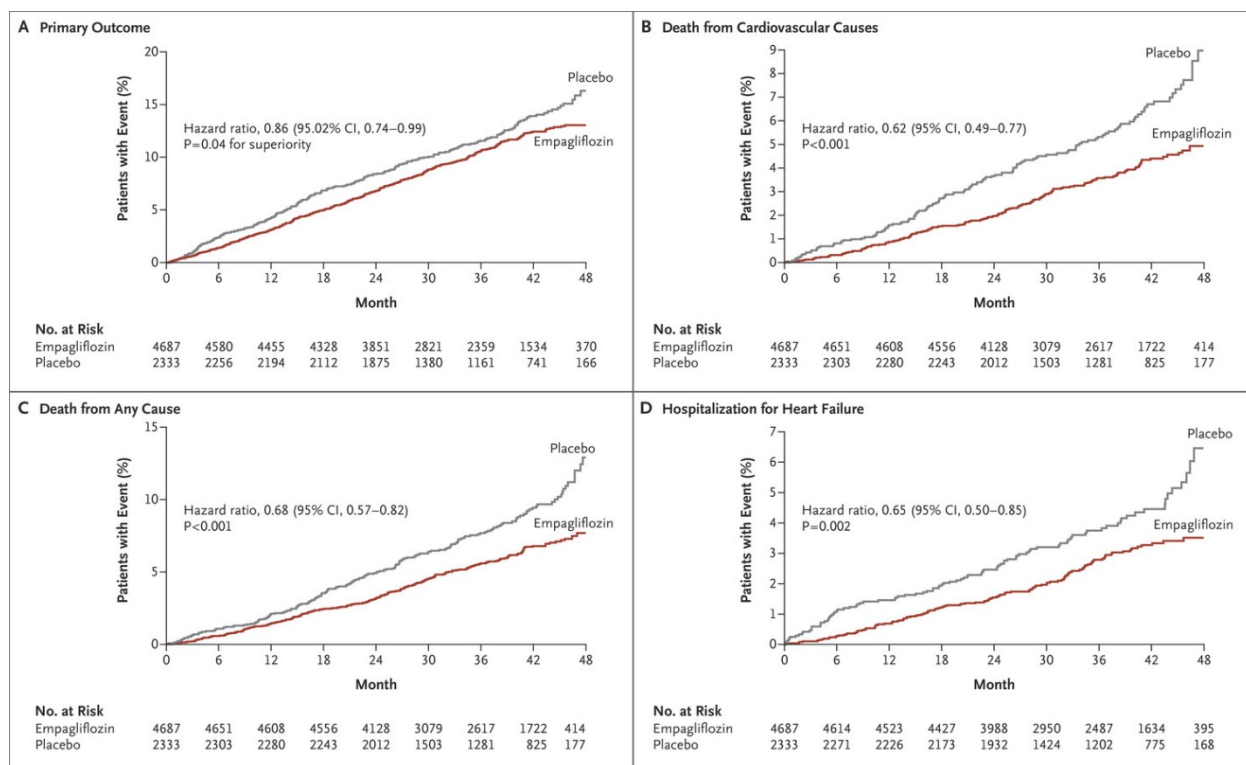
The EMPA-REG OUTCOME trial, published in NEJM in 2015, examined the effects of Empagliflozin (Jardiance) vs placebo, in addition to standard care, on cardiovascular morbidity and mortality in type 2 Diabetes at high risk for cardiovascular events. This was a randomized, double blind, placebo controlled trial of Empagliflozin 10 or 25 mg daily versus placebo. Eligible patients from 590 sites in 42 countries with type 2 diabetes were adults >18 yo with BMI of <45 and a GFR >30. All patients had established cardiovascular disease. They had been off glucose lowering medications x 12 weeks with a Hgba1c of 7-9 or stable glucose lowering medications x 12 weeks with Hgba1c 7-10.

Exclusion criteria included fasting glucose >240, LFT's > 3x ULN, planned cardiac surgery/angioplasty in 3 months, GFR <30, Bariatric surgery < 2 yrs, blood dyscrasias, cancer (except BCC) or cancer treatment < 5ys, weight loss drugs < 3 months, systemic steroids, change thyroid dose <6 weeks, pre-menopausal women nursing, pregnant or not on birth control, alcohol/drug use < 3 months, or ACS/CVA/TIA < 2 months.

Patients were randomized 1:1:1 to Empagliflozin 10 or 25 mg or placebo. "Investigators were encouraged to adjust glucose lowering therapy at their discretion to achieve glycemic control according to local guidelines." They "were encouraged to treat other cardiovascular risk factors to achieve the best available standard of care according to local guidelines."

The primary outcome was a composite of death from cardiovascular causes, nonfatal MI, or nonfatal stroke. The key secondary outcome was a composite of the primary outcome plus hospitalization for unstable angina. The primary hypothesis was noninferiority for the primary outcome with Empagliflozin vs placebo. 7020 patients were treated for a mean of 3.1 yrs with 97% completion and a final status available for 99.2%.

The primary outcome occurred in a lower percentage in the Empagliflozin group (490 of 4687, 10.5%) than in the placebo group (282 of 2333, 12.1%) (Hazard ratio .86, CI .78 to .99, P<0.001 for noninferiority, P=.04 for superiority). Absolute risk reduction of 1.6%. The key secondary outcome occurred in 12.8% in the Empagliflozin group vs 14.3% in the placebo group (hazard ratio .89, CI .78 to 1.01, P<0.001 for noninferiority, P=.08 for superiority).



Empagliflozin resulted in a lower risk of death from cardiovascular causes (HR .62, CI .49 to .77, $P<.001$), death from any cause (HR .68, CI .57 to .82, $P<.001$), and hospitalization for heart failure (HR .65, CI .50 to .85, $P=.002$). There was no difference in MI or stroke. There was no difference between the 10 and 25 mg dose.

In terms of glycemic control, at 12 weeks (during which glucose lowering therapy was unchanged), Hgba1c fell .54 with 10 mg and .60 with 25 mg.

In terms of cardiovascular risk factors, Empagliflozin was associated with small reductions in weight, waist circumference, uric acid, and blood pressure. There was no increase in heart rate and small increase in LDL and HDL cholesterol. More placebo patients received additional glucose lowering medications (sulfonylureas, insulin), antihypertensives, and anticoagulants, with no difference in lipid drugs.

Adverse events, serious adverse events, and adverse events leading to discontinuation were actually lower with Empagliflozin than placebo. Genital infections were higher with Empagliflozin (6.4 vs 1.8%), especially in female patients (10 vs 2.6%). There was no difference in UTI's, but urosepsis was reported in .4% with Empagliflozin vs .1% with placebo. However, there were less cases of acute renal failure and AKI with Empagliflozin. There was no difference in DKA, thromboembolism, fractures, or volume depletion. There were no changes in electrolytes, but hematocrit values were higher with Empagliflozin.

Among patients with type 2 Diabetes and cardiovascular disease, those on Empagliflozin has a lower rate of the primary outcome of death from cardiovascular causes, MI or stroke. The difference was driven by a reduction in death from cardiovascular disease, with no difference in MI, stroke. Patients in the Empagliflozin group had a lower risk of death from any cause and hospitalization for CHF. Although

there's a small dose response curve for 10 vs 25 mg for metabolic parameters, the 2 doses had similar HR for cardiovascular outcomes.

These benefits were observed in patients with cardiovascular disease whose risk factors were well controlled with ACEI/ARB's, statins, and ASA. Notably, reductions in death from cardiovascular disease and death from any cause occurred early in the trial and continued. The 32% RRR and 2.6% ARR in death from any cause gives a low NNT of 39 patients over 3 years.

Although investigators were encouraged to adjust glucose lowering medications, Hgba1c at week 206 was 7.8% with Empagliflozin vs 8.1% with placebo.

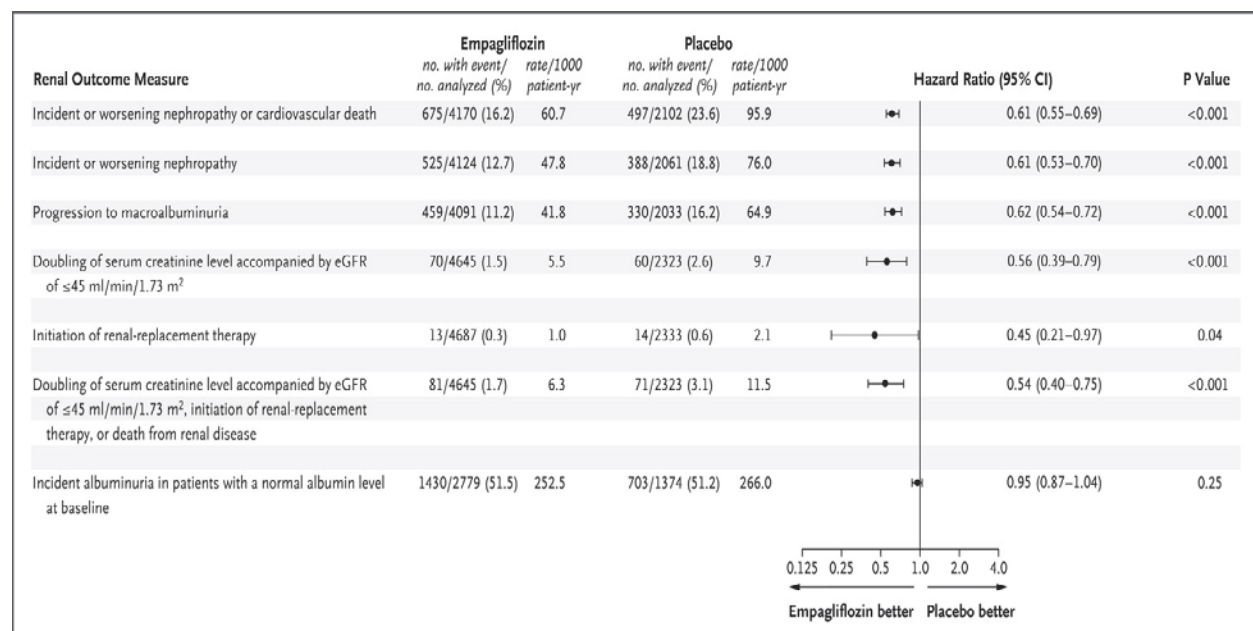
The trial was designed to assess clinical outcomes. The mechanisms behind the benefits could be multidimensional including improved arterial stiffness, cardiac function, reduction in albuminuria, uric acid, glucose, weight, adiposity and blood pressure.

In summary, in patients with type 2 Diabetes and cardiovascular disease, Empagliflozin reduced cardiovascular outcomes and mortality when added to standard therapy.

Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes, NEJM 2016

Kidney disease develops in 35% of patients with type 2 Diabetes and is associated with increased mortality. Glucose lowering reduces surrogate markers of renal complications, but improved advanced renal complications is limited. Despite glucose control and RAAS blockade, patients remain at increased risk for cardio renal disease. Empagliflozin reduces intraglomerular pressure and improves hyperfiltration. A prespecified secondary objective of EMPA-REG OUTCOME was to examine the progression of kidney disease in patients with type 2 Diabetes and cardiovascular disease. Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes was published in NEJM in 2016.

Primary renal microvascular outcome was incident or worsening nephropathy which was defined as progression to macroalbuminuria (albumin/creat >300mg/g), doubling of serum creatinine with GFR <45, initiation of renal replacement therapy, or death from renal disease.



Incident or worsening nephropathy occurred in 12.7% in Empagliflozin vs 18.8% in placebo (HR.61) for a 39% RRR and 6.1% ARR. Progression to macroalbuminuria occurred in 11.2% in Empagliflozin vs 16.2% in placebo ((HR .62) for a 38% RRR. Doubling of creatinine occurred in 1.5% of Empagliflozin vs 2.6% of placebo (HR .56) for a 44% RRR. Initiation of renal replacement therapy occurred in .3% with Empagliflozin vs .6% in placebo (HR .45) for a RRR of 55%. There was no difference in incident albuminuria with normal albuminuria at baseline.

Results for the composite renal outcomes were validated in a post hoc sensitivity analysis and subgroup analysis. The effect of Empagliflozin was consistent when progression to macroalbuminuria was excluded from the composite renal outcome.

In looking at renal function over time, the initial decrease in GFR with Empagliflozin was reversed after cessation of the drug (similar to ACEI). GFR was 4.7 ml higher in the Empagliflozin group at the follow up visit.

Patients with type 2 Diabetes with cardiovascular disease who received Empagliflozin had a lower risk of progression of kidney disease. There was also a lower risk of progression to macroalbuminuria and important clinical outcomes of doubling creatinine and initiation of RRT. The benefit occurred despite controlled blood pressure with extensive RAAS blockade.

Empagliflozin lowered hyperglycemia, weight, and blood pressure. A prior trial of intensive multifactorial intervention with type 2 Diabetes and microalbuminuria did not show benefit on renal function. Therefore, the effect on these risk factors over 3 years, was felt unlikely to fully account for the benefits in renal function. The mechanism of the renal benefits is probably multifactorial, but renovascular effects may play a role, including reducing intraglomerular hypertension. The renal benefits were still apparent even with the wide spread use of RAAS blockade. This supports their use in combination in type 2 Diabetes and CKD.

In summary, in patients with type 2 Diabetes and cardiovascular disease, Empagliflozin slowed the progression of kidney disease when added to standard care and lowered the risk of clinically relevant renal events.

What is the possible mechanism of this renal protective effect of SGLT2 Inhibitors? Kidney disease is a critical determinant of death from CV disease in DM. Previously only RAAS inhibition had shown renoprotective effects. Normally the macula densa transduces increase in sodium in the tubule into release of adenosine and increase renin in the juxtaglomerular apparatus. Stimulation of the tubuloglomerular feedback leads to vasoconstriction of the afferent arteriole and a decrease in GFR. A decrease in tubular sodium at the macula densa has the opposite effect.

The renoprotection from RAAS inhibition is related to vasodilation of the efferent arteriole with decrease in intraglomerular pressure, especially if glomerular hyperfiltration and hypertension are present.

In Diabetic kidney disease, the hyperglycemia persistently inhibits the direct vasoactive tubuloglomerular feedback. SGLT2 in the proximal tubule facilitates reuptake of glucose and sodium in a 1:1 ratio. This process is stimulated by hyperglycemia. As a result, hyperglycemia lowers the sodium the macula densa is exposed to and inhibits tubuloglomerular feedback, dilates the afferent arteriole, and induces glomerular hyperfiltration. The inhibition of the tubuloglomerular feedback in Diabetes exposes the delicate filtration barrier to increased filtration pressure which promotes barotrauma and nephron loss.

However, SGLT2 Inhibitors terminate the massive resorption of glucose and sodium in the proximal tubule, increase sodium delivery to the macula densa. This stimulates the tubuloglomerular feedback

which normalizes the filtration pressure, attenuates the loss of nephrons, and decreases GFR. There is a stabilization of the GFR which is a nephron protective effect. Like failing hearts, kidneys last longer when protected from overload. In addition, SGLT 2 Inhibitors also block renal gluconeogenesis and induce an osmotic diuresis which favorably effect weight, blood pressure, heart failure, and CV outcomes.

Because of their glycosuric mechanism, SGLT2 Inhibitors also reduce weight. The osmotic diuretic and natriuretic effects contribute to plasma volume contraction, with decreases in systolic and diastolic blood pressures by 5/2, which may underlie part of their CV and renal benefits. SGLT2 Inhibition is also associated with an acute reduction in GFR by 5 ml and a 40% reduction in albuminuria. Proximal tubular natriuresis activates renal tubuloglomerular feedback through increased sodium delivery, leading to afferent vasoconstriction.

CANVAS, CANVAS-R, Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes, NEJM 2017

SGLT2 inhibitors improve glucose, blood pressure, weight, intrarenal hemodynamics, albuminuria, and may also reduce the risk of cardiovascular complications, kidney disease, and death. The Canagliflozin Cardiovascular Assessment Study (CANVAS) and CANVAS-Renal (CANVAS-R) were combined and reported in NEJM in 2017. Patients had type 2 Diabetes with Hgba1c 7-10.5% and GFR >30. They were either >30 yo with “symptomatic atherosclerotic cardiovascular disease” or >50 yo with 2 or more risk factors (DM > 10 yrs, SBP >140 on meds, current smoking, microalbuminuria, macroalbuminuria, or HDL < 38). Patients were from 667 centers in 30 countries.

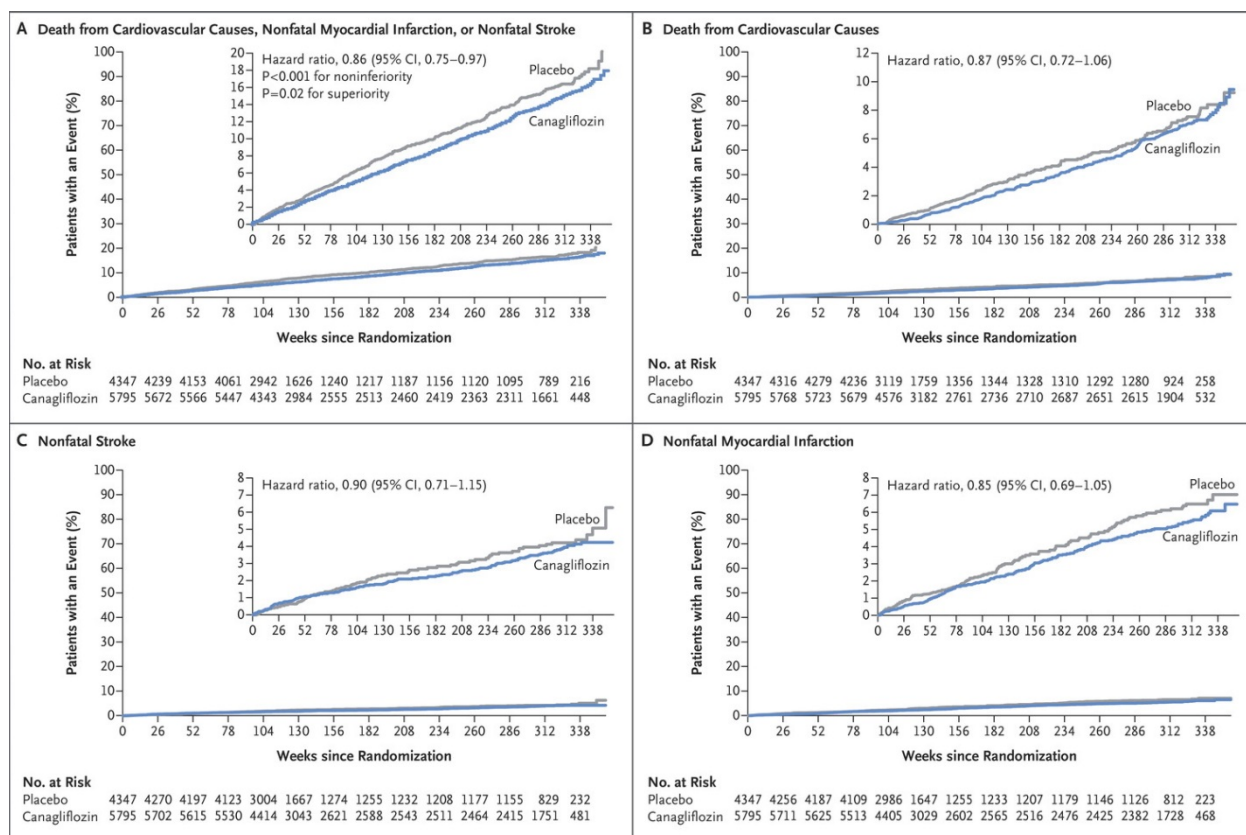
Patients in CANVAS were randomized 1:1:1 to Canagliflozin 100 mg or 300 mg or placebo. Patients in CANVAS-R were randomized 1:1 Canagliflozin 100 mg with an option to increase to 300 mg at week 13 vs placebo. Background meds for glycemic and risk factor control was “guided by best practice in line with local guidelines”.

10,142 patients were randomized and followed for 3.6 years. The primary outcome was a composite of death from cardiovascular cause, nonfatal MI, or nonfatal stroke. The primary test was of noninferiority with a margin of 1.3. On average, patients were 63 yo, 35% women, 78% white, had DM for 13.5 years, GFR of 76, with urinary albumin to creatinine ratio of 12. 71% of patients had the Canagliflozin increased from 100 to 300 mg. Annualized incidence rates were calculated per 1000 patient years of follow up.

Canagliflozin lowered Hgba1c by .58%, weight by 1.6 kg, SBP by 3.9 mm, and DBP by 1.4 mm. In addition, HDL was 2 mg/dl higher and LDL was 4.7 mg/dl higher, but there was 9% less use of antihyperglycemic agents in the Canagliflozin group.

Canagliflozin reduced the primary outcome-26.9 vs 31.5 patients with an event per 1000 patient years (HR .86, CI .75-.97, P<.001 for noninferiority, P<.02 for superiority). There was a trend, but no statistical difference in death from cardiovascular disease, death from any cause, MI or stroke. There was a significant reduction in hospitalization for heart failure (HR .67).

In terms of renal outcomes, progression of albuminuria occurred less frequently with Cangliflozin-89 vs 129 patients with an event per 1000 patient years (HR .73, CI .67-.79). Regression of albuminuria occurred more frequently with Canagliflozin-293 vs 188 patients per 100 patient years (HR 1.7). The composite of 40% reduction in GFR, need for renal replacement therapy, or death from renal causes occurred less frequently with Canagliflozin-5.5 vs 9 patients with outcome per 1000 patient years (HR .60).

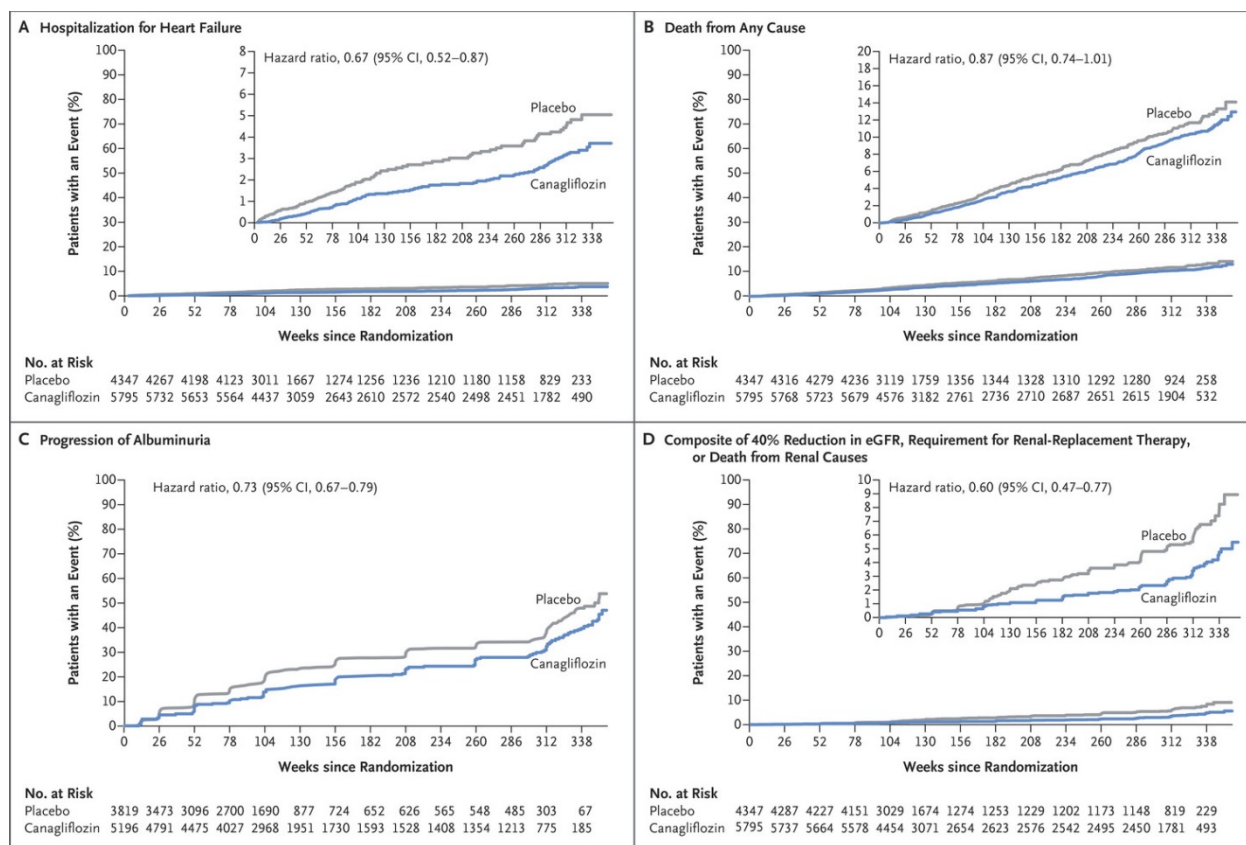


Serious adverse events were less common with Canagliflozin. Adverse events leading to discontinuation did not differ. There was a higher risk of amputation-6.3 vs 3.4 patients per 1000 patient years (HR 1.97). There was an increase in infection of male or female genitalia, volume depletion, and osmotic diuresis. There was no difference in hypoglycemia, hyperglycemia, DKA, hyperkalemia, AKI, pancreatitis, CA, or VTE. However, the rate of fractures was increased with Canagliflozin (HR 1.26).

Patients with type 2 Diabetes and established cardiovascular disease or at high risk for cardiovascular disease had lower rates of the primary cardiovascular outcome with Canagliflozin. All 3 individual components of the primary outcome showed a trend toward benefit, but did not reach statistical significance. Patients treated with Canagliflozin also had a lower risk of hospitalization for heart failure, progression of albuminuria, and loss of kidney function.

The improvement in glycemic control, blood pressure, weight, decrease in intraglomerular pressure, reduction in albuminuria, and improved volume overload may all contribute to the Cardiovascular and Renal protection.

The impressive renal benefits are supported by the magnitude of the effects, the consistency across renal outcomes, and the consistency with other trials. Further evidence will be provided by the ongoing Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Trial (CREDENCE), to be completed in 2019. CREDENCE will study the effects of canagliflozin on renal and cardiovascular outcomes in participants with type 2 diabetes mellitus and diabetic nephropathy, who are receiving standard of care including a maximum tolerated daily dose of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB).



Adverse events were generally consistent with other trials, with the increase in bone fractures having been previously reported. However, the increase risk of amputation was a new finding.

Strengths include the large size and duration of the trial and extending the inclusion to those with and without established cardiovascular disease. Limitations include the small proportion with CKD and the resulting few ESRD events.

In summary, CANVAS, CANVAS-R showed that in patients with Diabetes and an increased risk for cardiovascular disease, Canagliflozin reduced the risk of death from cardiovascular disease, nonfatal MI, or nonfatal stroke, as well as hospitalization from heart failure and nephropathy progression.

CVD-REAL, Comparative Effectiveness of CV Outcomes in New Users of SGLT2 Inhibitors, Circulation, 2017

Heart failure is an especially common complication in DM2 with poor outcomes and 5-year survival <25%. This highlights the need for treatments that not only improve glycemic control, but also reduce the risk of CVD including heart failure. Although higher Hgba1c is associated with greater risk of CVD, intense glucose control has failed to reduce the development of heart failure, CVD death, or all-cause mortality. EMPA-REG OUTCOME trial and CANVAS demonstrated reduction in CV death and hospitalization for heart failure with Empagliflozin and Canagliflozin. Several questions remained including applicability to real world clinical practice with other glucose lowering drugs (oGLD), whether this is a class effect, and whether benefits included DM2 patients without CV disease. Using data from multiple countries in the CVD-REAL study (Comparative Effectiveness of CV Outcomes in New Users of SGLT2 Inhibitors), they

compared the risk for HHF, death, and combined end point with DM2 who were new users of SGLT2 Inhibitors vs oGLD's in real practice.

After propensity matching, there were 309,056 DM2 patients >18 yo, with or without CV disease, from routine clinical practice in 6 countries (US, Germany, Sweden, Norway, Denmark, UK) who were newly initiated on either SGLT2 Inhibitor or oGLD's. Exposure time was 53% Canagliflozin, 42% Dapagliflozin, and 5% Empagliflozin.

Use of SGLT2 Inhibitors vs oGLD's, was associated with lower rates for HHF (HR .61, CI .51-.73, $p<.001$), death (HR .49, CI .41-.57, $p<.001$), and composite HHF or death (HR .54, CI .48-.60, $p<.001$).

87% did not have CV disease, suggesting CV benefits for a broad population of DM2. CVD-REAL showed similar outcomes in the real world to EMPAG-REG in regards to HHF and mortality.

CVD-REAL is an example of a large, observational, multicountry epidemiological study with almost 200,000 patient-years of observation to show the real-world effectiveness (vs efficacy) of new a class of treatment and is complimentary to clinical trials.

Although intense glucose lowering has failed to reduce important outcomes, SGLT2 Inhibitors have demonstrated improved CV and Renal outcomes. Given that CV disease is the leading cause of morbidity/mortality, these trials suggest the time has come to shift from the narrow focus on Hbga1c to a more comprehensive focus on treatments that have been proven to improve important outcomes.

In this large multinational study, treatment with SGLT2 Inhibitors vs oGLD's was associated with a 46% reduction in HHF or death, suggesting a class effect applicable to a broad population of DM2 in real-world practice.

CVD-REAL Nordic, CV mortality and morbidity in DM2 following initiation of SGLT2 Inhibitors vs oGLD's, Lancet Diabetes & Endocrinology, 2017

Similarly, CVD-REAL Nordic used real-world data from clinical practice to compare CV morbidity and mortality in new users of SGLT2 Inhibitors vs oGLD's in DM2 with a broad CV risk profile. 22,830 SGLT2 Inhibitor patients were matched with 68,490 oGLD patients with a mean age of 61 yo, 40% female, and 25% CV disease. Exposure was 94% for Dapagliflozin, 5% Empagliflozin, and 1% Canagliflozin. SGLT2 Inhibitors decreased CV mortality (HR .53, CI .40-.71, major CV events (HR .78, CI.69-.87) and hospital events for heart failure (HR .70, CI .61-.81) with $p<.001$ for all. There was no difference in MI, CVA, or AFib. In addition, there was a decreased risk for hypoglycemia (HR .76, CI .65-.90, $p=.001$).

CVD-REAL Nordic is another example of DM2 patients with a broad CV risk profile in real world practice. SGLT2 Inhibitors reduced CV disease and CV mortality vs oGLD's similarly to clinical trials.

Adverse Events

The FDA added a warning to Canagliflozin (only) for increased risk of lower limb amputation seen in CANVAS and CANVAS-R. The most common amputations were of the toe and middle of the foot. The warning advises physicians to consider a patient's history of prior amputation, PVD, neuropathy, and DM foot ulcers before prescribing Canagliflozin and to monitor for pain, tenderness, ulcers, or infections of the feet and legs.

A correspondence in Lancet Diabetes reported the number of amputations reported to the FDA Adverse Event Reporting System (FAERS). There were more reported amputations and toe amputations with Canagliflozin vs other SGLT2 inhibitors and vs oGLD's. There were fewer DM foot infections with SGLT2

inhibitors. The data is early and not causal, but deciphering the predisposing factors and mechanism of this rare event will be important in maximizing the benefits of SGLT 2 inhibitors.

Canagliflozin also has a FDA warning for increased bone fracture risk and decrease in bone density.

Case reports have suggested SGLT2 Inhibitors may be associated with an increased risk of DKA which led to a FDA warning in May, 2015. A report in NEJM in 2017 showed that SGLT2 Inhibitors were associated with twice the risk of DKA vs DPP-4 inhibitors, although cases of DKA were infrequent.

Implications

Given that SGLT 2 Inhibitors improve CV and Renal outcomes and that it has been duplicated in 3 large trials, we need to change our paradigm and emphasize treatments that lower risk. SGLT2 Inhibitors were the first class to receive an FDA indication to improve outcomes. Many guidelines are recommending SGLT2 Inhibitors to reflect the new outcome data (ADA, ESC HF, ESC CVD). Conversely, we need to avoid meds that cause hypoglycemia and weight gain, but don't improve outcomes.

1. Consider SGLT2 Inhibitor as 2nd line to Metformin in DM2 with elevated Hgb1c
2. Consider upgrading others meds (SU, DPP-4, TZD) to SGLT2 Inhibitor regardless of Hgb1c to improve outcomes
3. Consider adding SGLT2 Inhibitor for DM2 regardless of Hgb1c to improve outcomes, especially if high risk (like statins for DM)

Future

There are at least 3 on going, large, outcome trials of SGLT 2 Inhibitors. It will be important to follow those results to confirm their safety and efficacy of this class of medications: CREDENCE-Canagliflozin and Renal Endpoints in DM with Established Nephropathy Trial-to be completed in 2019, DECLARE-TIMI 58-Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of CV Events-expected release 2019, and VERTIS-Cardiovascular Outcomes Following Ertugliflozin Treatment in DM2 with Vascular Disease.

The use of SGLT 2 Inhibitors is also being investigated in type 1 DM. In addition, SGLT 1 Inhibitors are being studied as well as combination SGLT 1 and 2 Inhibitors.

This new data has already changed guidelines and could change more guidelines, including Diabetes, CV, and Renal recommendations to encourage the use of these new agents. Given the multitude of new options and new studies, comparative effective trials are needed to demonstrate the best treatments and combinations for the millions with DM2.

Summary

There's a worldwide epidemic of DM2 with its resulting CV and Renal disease. Intensive therapy and other new oral DM meds have not shown improved CV, Renal outcomes. SGLT2 Inhibitors lower glucose, BP, and weight by inhibiting glucose reabsorption. SGLT2 Inhibitors are the 1st class to improve CV and Renal outcomes in EMPA-REG OUTCOME, CANVAS, and CVD-REAL. This provides yet another example of the need to focus on hard outcomes, not surrogate markers.

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