Canagliflozin To Slow Renal Insufficiency Progression in Non-Diabetic Chronic Kidney Disease

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CANAGLIFLOZIN TO SLOW RENAL INSUFFICIENCY PROGRESSION
IN NON-DIABETIC CHRONIC KIDNEY DISEASE

A Thesis Presented to
The Faculty of the School of Medicine
Yale University

In Candidacy for the Degree of
Master of Medical Science

April 2020

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Abstract

Chronic kidney disease is a serious illness that reduces the life span and quality of life in diagnosed patients. Despite advancements in medical management, progression to end-stage renal disease persists. While the renoprotective effects of sodium-glucose cotransporter-2 inhibitors in diabetes mellitus patients are well-documented, no studies have examined the efficacy of these drugs in treating renal disease in the absence of diabetes mellitus. The objective of this trial is to determine whether canagliflozin, a sodium-glucose cotransporter-2 inhibitor, can improve renal outcomes in patients with non-diabetic chronic kidney disease. Utilizing a double-blind, randomized control trial design, we will examine the effects of canagliflozin on patients’ glomerular filtration rate and progression to end-stage renal disease. We hypothesize that adding canagliflozin to the standard of care, including a maximum tolerated labeled dose of an angiotensin-converting enzyme inhibitor or an angiotensin II receptor blocker, will decrease the mean glomerular filtration rate decline per year.
Chapter 1 – Introduction

1.1 Background

Epidemiological Data

Kidney disease is among the top fifteen leading causes of death in the United States.\(^1\) Chronic kidney disease (CKD) signifies detrimental changes to the kidneys that leads to irreversible dysfunction.\(^2\) 37 million Americans suffer from this disease and it is estimated that every day approximately 240 patients on dialysis die as a result.\(^3\) Furthermore, patients with CKD are five to ten times more likely to die prematurely, before ever reaching end-stage renal disease and requiring dialysis, due to comorbid conditions that often accompany their kidney disease.\(^4\) To make matters worse, the prevalence of CKD is likely to be higher than what is reported due to the asymptomatic nature of the disease in the early stages, preventing early diagnosis for many patients.\(^4\)

Etiology

Beginning at the age of 40, the glomerular filtration rate (GFR) begins to decline 0.75 mL/min/1.73 m\(^2\) per year in healthy individuals,\(^5\) but many medical conditions can precipitate and progress kidney function decline. Diabetes and hypertension are two common etiologies of CKD and are responsible for approximately two-thirds of CKD cases in the United States.\(^6\) As with many other comorbid disease processes, the danger in having concomitant diabetes and/or hypertension in addition to CKD is a vicious cycle that allows each disease process to perpetuate the other.

Current Treatments

Regardless of etiology, the common final pathway in all CKD is end-stage renal disease in which the patient requires renal replacement therapy in the form of
hemodialysis or kidney transplantation. The goal of all management strategies in kidney disease is to prevent or slow the progression of kidney dysfunction. Therapy comes in many forms including nutritional recommendations, lifestyle modifications, and medical management. The guidelines of medical nutritional therapy in the context of CKD suggest limiting daily sodium, an appropriate allowance of protein intake, and the restriction of phosphorus and potassium. Additionally, in all patients regardless of the extent of kidney damage, smoking cessation and routine physical activity are always recommended.

Although nutritional and lifestyle modifications are beneficial, medical therapy remains the cornerstone of management in CKD. One of the strongest independent risk factors for developing end-stage renal disease is high blood pressure. An early study by Klag et al. demonstrated that patients with blood pressure greater than 200 mmHg systolic and 130 mmHg diastolic carried a relative risk of 22.1 for developing end stage renal disease. For this reason, antihypertensive therapy is one of the main strategies in the management of CKD. It is important to not only control existing hypertension, but to also prevent hypertension in those who are normotensive.

Many studies have been designed to investigate which antihypertensive drug class is most efficacious in slowing renal function decline. Multiple randomized control trials have demonstrated nephroprotection of angiotensin-converting enzyme (ACE) inhibitors in the non-diabetic CKD population. A meta-analysis of several randomized control trials proved the superiority of ACE inhibitors over other antihypertensives by showing a risk reduction of 0.7 in the progression of non-diabetic CKD to end-stage renal disease in those on ACE inhibitor therapy. Angiotensin II receptor blockers (ARB) have also been
shown to be nephroprotective in non-diabetic CKD and have not been shown to be inferior to ACE inhibitor therapy.\textsuperscript{15} Tobe et al. indicate that there was no evidence to suggest that dual therapy with both an ACE inhibitor and an ARB provides superior nephroprotection over monotherapy.\textsuperscript{16} Furthermore, in the ONTARGET trial, investigators sought to determine the safety of dual therapy of both an ACE inhibitor and ARB and found the combination to actually be harmful, with no therapeutic benefit.\textsuperscript{17}

Other classes of antihypertensive drugs have been extensively studied in the context of CKD. Although none have been shown to provide as much nephroprotection as renin-angiotensin-aldosterone system (RAAS) inhibitors, some renoprotective effects have been appreciated. In the literature category of add-on therapy, research has been conducted on the addition of calcium channel blockers and mineralocorticoid receptor antagonists to an ACE inhibitor or an ARB. While there have been studies that show greater nephroprotection when adding a calcium channel blocker to a RAAS inhibitor, a recent meta-analysis by Huang et al. showed that the addition of a calcium channel blocker to an ACE inhibitor or an ARB does not improve the incidence of progression to end-stage renal disease.\textsuperscript{18} The addition of a mineralocorticoid receptor antagonist to a RAAS inhibitor has shown a reduction in surrogate endpoints in both diabetic and non-diabetic CKD.\textsuperscript{19} Unfortunately, the use of this drug class is accompanied by a significant increase in risk of hyperkalemia, which is ubiquitously seen in the literature.\textsuperscript{20,21}

While many studies have focused on add-on therapy in the investigation of effective management of CKD, other studies have focused on comparing different classes of antihypertensive drugs to the current gold standard, RAAS inhibitors. The authors of the African American kidney disease and hypertension clinical trial\textsuperscript{22} studied the effects
of the ACE inhibitor ramipril, the beta blocker metoprolol, and the dihydropyridine calcium channel blocker amlodipine as independent drug regimens in the management of hypertensive kidney disease. The results of the trial demonstrated that ramipril was superior in delaying the progression of renal disease. Compared to metoprolol, ramipril offered a 22% risk reduction. When compared to amlodipine, ramipril offered a 38% risk reduction. However, it is important to take into consideration that proteinuria was an effect modifier for this benefit. In this study, the benefit of ramipril was driven by the slowing of CKD in those with proteinuria and did not offer much added benefit in patients without proteinuria.

Diuretics have also been studied in renal insufficiency and the effect that it has on the progression to end-stage renal disease. In a 2005 post hoc analysis by Rahman et al., chlorthalidone (a diuretic) was compared to amlodipine (a calcium channel blocker) and lisinopril (an ACE inhibitor) to investigate the differences seen in patients’ progression to end-stage renal disease. Interestingly, the authors found that there was no significant difference in the development of renal failure between treatment groups. Yet another drug that has been studied in kidney disease progression is aliskiren, a direct renin inhibitor. In the aliskiren and losartan trial in non-diabetic chronic kidney disease, the authors compared three treatment groups: aliskiren, losartan, and aliskiren plus losartan. While all three groups displayed a reduction in proteinuria, there was no statistically significant difference in change in GFR from baseline.

While the majority of investigational effort has been focused on antihypertensive therapeutic modalities, research has also been conducted on different avenues of kidney disease management. One such avenue is that of alkali therapy. Oftentimes, patients with
CKD succumb to a state of metabolic acidosis due to the decreased ability of the kidneys to reabsorb bicarbonate and bind hydrogen molecules to allow for hydrogen excretion. In order to combat this chronic acidotic state, the administration of sodium bicarbonate has been used in the management of renal disease. In one study looking at sodium bicarbonate levels and the progression of CKD, the authors found that patients with bicarbonate levels less than 22 mEq/L have a 54% greater chance of progression of kidney dysfunction when compared to patients with serum bicarbonate measurements within normal limits. In another study, the authors used a perspective interventional approach to examine patients on ACE inhibitor therapy, with a serum bicarbonate level less than 22 mEq/L, and an eGFR between 20-59 mL/min/1.73m². Patients were split into two groups: one to receive sodium citrate and the other to remain on current therapy. After 24 months, it was shown that the patients adhering to alkali therapy had slower decline in GFR when compared to the control group.

Autosomal dominant polycystic kidney disease (ADPKD) is the most common genetic kidney disease and causes kidney volume growth and cystic abnormalities within the kidney. ADPKD accounts for 5-10% of patients in renal failure and thus considerable time and effort has been dedicated to researching effective therapies for this subgroup of CKD. Unfortunately, this subgroup of CKD does not respond to antihypertensive therapy. The most effective treatment that has been studied is tolvaptan, a selective vasopressin V2 antagonist. In the TEMPO 3:4 phase III clinical trial, authors compared tolvaptan versus placebo in the management of ADPKD. After 3 years of follow-up, it was found that the treatment group benefited from a 49% reduction in the rate of progression of their renal decline compared to the control group.
To summarize what has been discussed in this section, the literature supports the fact that blood pressure control is the mainstay in treatment of CKD, regardless of whether high blood pressure is the underlying cause of an individual’s renal insufficiency or if hypertension is a sequela of the disease. Currently, we know that drugs that block the RAAS are the most effective antihypertensive medication in the CKD population. ACE inhibitors are more widely used in current medical practice, but ARBs are a reasonable choice. Other antihypertensive drug classes have been compared to RAAS inhibitors as well as studied as add-on therapy. The main drug classes that have been studied include calcium channel blockers, mineralocorticoid receptor antagonists, beta blockers, diuretics, and direct renin inhibitors. Additionally, therapeutic modalities outside the antihypertensive realm were discussed, such as alkali therapy and selective vasopressin V2 antagonists in the context of ADPKD. While some of the aforementioned drugs have demonstrated nephroprotection, there has yet to be an add-on drug or alternative medication that has revolutionized CKD management, an advancement that is desperately needed.

**The Promise of Sodium-Glucose Cotransporter-2 Inhibitors**

Sodium-glucose cotransporter-2 (SGLT2) inhibitors are a new class of drug that recently gained FDA approval for the management of type 2 diabetes mellitus. SGLT2 inhibitors block the reabsorption of glucose in the proximal tubule of the kidney, which causes glucose to remain in the filtrate and leads to increased glucosuria. Of course, in diabetes, this drug class logistically works as a management option to aid in the excretion of glucose in the setting of insulin resistance. In trials on SGLT2 inhibitors, there were secondary outcomes of renoprotective effects seen across all trials that measured renal
outcomes. When glucose reabsorption is blocked in the proximal tubule, there is an increased delivery of solute to the distal tubule which, through glomerulotubular feedback, causes the afferent arteriole to constrict and produce a decrease in intraglomerular pressure. Given that diabetic nephropathy is the leading cause of end-stage renal disease and SGLT2 inhibitors decrease blood glucose\textsuperscript{29}, it is reasonable that the majority of research conducted on SGLT2 inhibitors has been focused on diabetes with and without CKD. However, there is an important gap in the literature regarding the relationship between non-diabetic CKD and SGLT2 inhibitors. Regardless of etiology, after initial kidney injury, the kidney undergoes a state of hyperfiltration which leads to glomerulosclerosis. Glomerulosclerosis then leads to further kidney structure deterioration and dysfunction causing nephron loss and eventual end-stage renal disease.\textsuperscript{30} To date, the most effective method of slowing renal function decline is by decreasing glomerular pressure, which decelerates the rate of sclerosis and fibrosis production within the kidney. As discussed in prior sections, the most effective method we have to decrease intraglomerular pressure is via the inhibition of the RAAS. Given that SGLT2 inhibitors decrease intraglomerular pressure, it is reasonable to postulate that the addition of these drugs to a RAAS inhibitor may aid in the battle against CKD.

\textbf{Figure 1. Natural Course and Cycle of Renal Insufficiency}

![Diagram of the natural course and cycle of renal insufficiency](image)
1.2 Statement of the Problem

Medical scientists continue to investigate the use of alternate or adjunctive therapy with hopes of uncovering a drug regimen that is more effective than what is currently available for renal insufficiency. Aside from the use of an ACE inhibitor or ARB, there is little evidence in the literature supporting an effective add-on therapy. To put the need for advancement of treatment in perspective, according to the Global Burden of Disease data, since 1990, CKD has experienced an 89% increase in global incidence, an 87% increase in prevalence, and resulted in a 98% increase in cause specific mortality.31

1.3 Goals and Objectives

The proposed study aims to investigate what effect the addition of canagliflozin to current pharmacologic management of non-diabetic CKD has on the progression of kidney disease in adult patients with moderate to severe renal insufficiency. To study the effect of SGLT2 inhibitors, patients will be divided into two groups: the first receiving a medication regimen that adheres to the current standard of care and the second group receiving the standard of care with the addition of canagliflozin, an SGLT2 inhibitor. This study will utilize change in GFR from baseline as a primary endpoint to compare the difference in disease course between the control and treatment groups.

1.4 Hypothesis

We hypothesize that among patients 18 years and older with moderate to severe non-diabetic CKD, the addition of canagliflozin, an SGLT2 inhibitor, to current
pharmacologic management of CKD will result in significant delay in progression of renal function decline at 18-month follow-up in comparison to the standard of care alone.
References


Chapter 2 – Review of the Literature

2.1 Brief History of Sodium Glucose Cotransporters

In the 19th century, French chemists isolated a chemical compound from the bark of apple trees that was soon after discovered to have glycosuria effects in those who ingested the substance.\(^1\) This compound is known as phlorizin and can be attributed as the origin of the now well known drug class called sodium glucose cotransporter (SGLT) inhibitors. Phlorizin acts as an inhibitor of the SGLT1 protein that is found in both the kidneys and small intestines. The SGLT proteins are responsible for glucose reabsorption and thus inhibition of the protein by phlorizin in the kidney leads to glucosuria.

Sodium glucose cotransporter proteins are present in many organs within the human body. These ubiquitous proteins have been found in the brain, heart, kidneys, intestines, and many other tissue types within the body. While there are six known varietals of the sodium glucose cotransporter protein, the homolog of interest in recent research has been the SGLT2 protein due to its key role in glucose reabsorption within the kidney where it is responsible for 90-95% of glucose reuptake.\(^2\) In an early investigation by Chen et al., researchers extensively studied the SGLT2 protein using quantitative RT-PCR methods and found that SGLT2 expression is extremely specific to the cells located within the kidney.\(^3\) This protein’s extensive role in the reabsorption of glucose coupled with its exclusive expression within the kidney has lead it to be an attractive and logical focus in the evolving research around diabetes management.

2.2 The Need for Therapeutic Advancement in Type 2 Diabetes Mellitus

The worldwide prevalence of diabetes mellitus is currently 463 million with a projected prevalence of 578 million by 2030 and 700 million by 2045.\(^4\) Prior to the
development of SGLT2 inhibitors, the cornerstone of medical management for type 2 diabetes mellitus included metformin, insulin, sulfonylureas, and glitazones.\textsuperscript{5} However, the need for therapeutic advancement is clear due to the difficulty of disease management as evident by inevitable worsening of macrovascular and microvascular damage. In a study by Turner et al. that included 4,075 study participants, the authors showed that after three years of a monotherapeutic approach, 50\% of patients failed to achieve appropriate blood glucose control and had to begin a multidrug regimen.\textsuperscript{6} Many antidiabetic agents, especially when used in combination, often come with a myriad of side effects including a variety of gastrointestinal disturbances, hypoglycemia, weight gain, and hyperinsulinemia.\textsuperscript{7} The most serious of the side effects caused by glucose-lowering agents is hypoglycemia. Extremely low plasma glucose concentrations pose a significant health risk to patients evidenced by a greater than fivefold risk of mortality compared to patients who do not experience hypoglycemic episodes.\textsuperscript{8}

With the combination of inadequate glycemic control despite therapeutic management and the harsh side effect profiles of the available drugs, it is clear why the medical community continues to search for improvements in treatments for type 2 diabetes mellitus.

\section*{2.3 Studies on SGLT2 Inhibitors in the Type 2 Diabetes Mellitus Population}

The current recommendations for newly diagnosed type 2 diabetes mellitus suggests metformin as the initial drug choice in disease management. However as discussed in the previous section, management by a single drug is often not a sufficient deterrent to disease progression. At present there are four drugs within the SGLT2 inhibitor class that are FDA approved for the treatment of type 2 diabetes mellitus either
as monotherapy or combination therapy. The current approved drugs include canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin. In a meta-analysis performed in 2013, the use of SGLT2 inhibitors was found to have a positive effect on patients’ serum glucose concentrations. On average, the use of an SGLT2 inhibitor as monotherapy decreased glucose levels by nearly 80% and, when used in combination with other glucose-lowering agents, decreased glucose levels by approximately 60%. Additionally, SGLT2 inhibitors work under a mechanism that does not interfere with insulin secretion thus protecting against the risk of hypoglycemia and shielding patients from increased risk of cardiovascular and other devastating health events.

In addition to its forefront property of glucose lowering effects, SGLT2 inhibitors have been shown to have positive outcomes that aid in the management of type 2 diabetes mellitus. These advantageous sequels of SGLT2 inhibitors include: weight loss due to osmotic diuresis, decreases in systolic and diastolic blood pressures, lowering of triglyceride levels and rises in high-density lipoprotein, mitigation of several risk factors associated with liver disease, and diminishment of intraglomerular pressure and albuminuria.

2.4 Secondary Outcomes in Early SGLT2 Inhibitor Clinical Trials

Many earlier trials conducted on SGLT2 inhibitors examined cardiovascular endpoints as primary outcomes in the type 2 diabetes mellitus population. Through many of these investigations, renal endpoints were analyzed as secondary outcomes that eventually led to hypotheses about SGLT2 inhibitors and the relationship they have to kidney function.
One of the first clinical trials that utilized renal outcomes as secondary measures was the canagliflozin cardiovascular assessment study (CANVAS). This investigation studied the type 2 diabetes mellitus population and compared cardiac events in a control group versus a treatment group receiving canagliflozin. This trial enrolled 10,142 participants and had a mean follow-up of approximately 3.6 years. Prespecified secondary renal outcomes of this trial included progression of albuminuria, change in GFR, initiation of renal replacement therapy, and renal related death. The results suggest that canagliflozin has a protective effect on renal outcomes as indicated by slower progression of albuminuria in the treatment group with a hazard ratio of 0.73 as well as less frequent occurrences of the other aforementioned renal outcomes calculated as a composite hazard ratio of 0.60.18

The empagliflozin cardiovascular outcome event trial in type 2 diabetes mellitus patients (EMPA-REG) was a clinical trial that was interested in investigating the benefit of adding empagliflozin to type 2 diabetes mellitus patients who were at increased risk for cardiovascular events.19 The trial accrued 7,020 participants and had a 4.6-year follow-up. While the primary outcome of this trial was time to various pre-determined cardiovascular events, theories on renal outcomes were able to be formulated from the data that was collected from the trial results. The statistical results of this trial demonstrated that both the lower dose (10 mg) regimen and higher dose (25 mg) regimen of empagliflozin allowed for a statistically significant reduction of renal outcomes including progression to microalbuminuria, doubling of serum creatinine, initiation of renal replacement therapy, and worsening of nephropathy.20
Another interventional clinical trial on an SGLT2 inhibitor was the multicenter trial to evaluate the effect of dapagliflozin on the incidence of cardiovascular events (DECLARE-TIMI), which sought to investigate the effects dapagliflozin has on cardiovascular outcomes in the type 2 diabetes mellitus patient population. This study recruited an impressive 17,190 study participants and used a renal composite endpoint as a secondary outcome that included a decrease greater than or equal to 40% in eGFR to less than 60 ml/min/1.73² and/or end-stage renal disease and/or renal or cardiovascular death. After the trial’s 5.2-year follow-up, the analysis displayed a 46% reduction in GFR decline by at least 40% to less than 60 ml/min/1.73² in the patient group taking dapagliflozin when compared to the placebo group.²¹

### 2.5 Clinical Trials on SGLT2 Inhibitors with Renal Variables as Primary Outcomes

As suggested in the previous section, many earlier clinical trials on SGLT2 inhibitors served as hypothesis-driving platforms that allowed further investigation into the effect that SGLT2 inhibitors have on renal function.

Perhaps the most well-known and well regarded trial conducted on an SGLT2 inhibitor with renal primary outcomes is the canagliflozin and renal events in diabetes with established nephropathy clinical evaluation (CREDENCE) trial.²² In this double-blind randomized control trial, 4,401 patients were recruited and divided into a canagliflozin treatment group and placebo group and were followed for approximately 2.6 years. In the analysis, Perkovic et al. found that the renal outcomes including end-stage renal disease, doubling of serum creatinine, and renal related death were significantly lower in the treatment group when compared to the placebo group with a hazard ratio of 0.70.
Another clinical trial focused on renal outcome effects of an SGLT2 inhibitor is the empagliflozin and progression of kidney disease in type 2 diabetes trial. The primary outcome used in this study was worsening nephropathy as defined as progression or development of microalbuminuria, doubling of serum creatinine, necessity of renal replacement therapy, and renal related death. The results displayed a hazard ratio of 0.61, again suggesting that the inhibition of the SGLT2 protein provides renoprotective effects in the type 2 diabetes mellitus population.

2.6 The Future of SGLT2 Inhibitor Research

After reviewing the literature on SGLT2 inhibitors it is evident that there is a benevolent relationship between this drug class and not only type 2 diabetes mellitus disease progression, but also renal health. While it has only been since 2013 that SGLT2 inhibitors have been FDA-approved for the treatment of type 2 diabetes mellitus, there is currently a large missed opportunity in the use of SGLT2 inhibitors and the possible benefit they could have on CKD. With the ubiquitous renoprotective effects seen in past clinical trials and the desperate need for therapeutic options for CKD, the investigation on SGLT2 inhibitors in non-diabetic renal disease seems like a pertinent and pragmatic next step in the area of SGLT2 inhibitor research.

2.7 Adverse Effects of SGLT2 Inhibitors

As previously discussed, SGLT2 inhibitors work via an insulin-independent mechanism that offers protection against hypoglycemia. While this is certainly an advantage in this drug class, these drugs come with their own adverse effect profile.

The most common adverse event seen in those taking an SGLT2 inhibitor is genital mycotic infections, which have been reported to occur in both men and women.
The occurrence of mycotic infections is around 13% in women and 3% in men compared to approximately 3% and 0.50%, respectively, in control groups. While these infections are inconvenient and uncomfortable for patients, cases are easily resolved with topical or oral antifungal agents and do not pose harmful long term effects.

Other commonly noted side effects of SGLT2 inhibitors are the effects of osmotic diuresis and volume depletion. In the CANVAS trial, results indicated a statistically significant difference in the event rate of both osmotic diuresis and volume depletion when comparing the canagliflozin and placebo treatment groups. In a pooled analysis of 4 randomized, placebo-controlled, phase 3 clinical trials, the authors investigated the incidence of osmotic diuresis among the 2,313 study participants and found that most events due to osmotic diuresis were mild or moderate in severity and led to only three events of study discontinuation, all in patients older than 65 years. Similarly, the adverse events reported due to volume depletion were classified as mild to moderate in severity and led to a single participant study discontinuation. The patients affected by volume depletion were those under the age of 65 years. While it is important to be aware of the effects of SGLT2 inhibition, providers should not be dissuaded from these medications. Instead, physicians and other providers should be aware and monitor patients for symptoms and be cautious when engaging in polypharmacy with drugs such as loop diuretics.

Less common but equally as important adverse events seen with SGLT2 inhibitor use includes acute renal failure, increased incidence of bone fractures, and amputations. It has been reported that SGLT2 inhibitors present a risk for acute renal failure with an odds ratio of 2.88. While this increase in renal injury may be due to the diuretic effect
of the drug class that causes volume depletion and thus a reduction in intraglomerular perfusion, the disease process of type 2 diabetes and its existing relation with kidney injury makes it difficult to decipher the culprit of renal insufficiency in clinical trials. While acute renal injury needs to be monitored, the benefit of SGLT2 inhibitors outweigh the risks and there are currently no recommendations to discontinue the drug due to a potential increased risk of kidney injury.\(^\text{27}\)

While the proposed theory that SGLT2 inhibitors increase patient susceptibility to bone fractures, the evidence is conflicting and points to conclusions of both increased risk and no additional risk for fractures. The proposed mechanism is that serum phosphate levels are increased by inhibiting the SGLT2 protein, thereby causing increased fibroblast growth factor 23 and parathyroid hormone levels, both of which lead to a decline in the structural integrity of bone.\(^\text{28}\) In a meta-analysis of 20 studies and 8,286 patients looking at the pooled risk for canagliflozin, dapagliflozin, and empagliflozin on bone fractures, the risk ratio was 0.66, 0.84, and 0.57 respectively.\(^\text{29}\)

Lastly, amputations have been noted as a side effect in SGLT2 inhibitor use. While the mechanism of amputation is unknown, the CANVAS trial exhibited a statistically significant difference in the incidence of amputations between the treatment and control groups. In the treatment group, the event rate per 1,000 patient-years was 6.3 while the event rate in the placebo group was 3.4 per 1,000 patient-years (\(p < 0.001\)).\(^\text{18}\) Risk of amputations was not seen in other randomized controlled trials.

Given that SGLT2 inhibitors are still a relatively new class of drugs, all adverse events must be considered and monitored in patients. That being said, the full realm of understanding of the mechanism of this drug class is far from complete. Continued
research, analysis, and observation is needed to lead to definitive statements regarding the adverse events that this drug group may cause in patients.
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Chapter 3 – Study Methods

3.1 Study Design

We will conduct a randomized, double-blind, placebo-controlled, multicenter clinical trial among adult patients with CKD but without a concomitant diagnosis of type 2 diabetes mellitus. We will investigate the effectiveness of canagliflozin plus guideline directed medical therapy compared to placebo plus guideline directed medical therapy for slowing CKD progression by randomizing patients into one of two groups: treatment or placebo. We will compare the control group to a placebo group in the context of renal outcomes over a period of 18 months.

3.2 Study Population and Sampling

The study population will include adults ages 18 years of age and older with CKD stage three or four. Stage three includes GFRs ranging from 30 to 59 mL/min/1.73m². Stage four includes GFRs ranging from 15 to 29 mL/min/1.73m². Pediatric patients will be excluded due to the nature of disease management differences that often exist between pediatric patients and their adult counterparts. Additionally, SGLT2 inhibitors are a new class of drug for which adverse events in the pediatric patient population have yet to be examined. Only patients with CKD stages three and four will be included due to the limited time frame that is available for this research study. By only inviting those with more advanced kidney disease to participate, we hope to enrich the event rate in our population and more efficiently capture the effect that canagliflozin has on renal outcomes. Patients will be recruited from all hospitals within the Yale Affiliated Hospitals Program which include: New Haven, Bridgeport, Danbury, Greenwich, Griffin, Norwalk, St. Mary’s, and Waterbury hospitals. Our study will be limited to these
hospitals once again due to time restraints. Having patient recruitment take place within the state of Connecticut will allow study personnel to easily obtain in-person interviews, when necessary. Furthermore, the Institutional Review Board process will be more manageable with all eligible hospitals sharing a common health care network.

3.3 Inclusion Criteria

Study participants will be adult patients between the ages of 18 and 75 years with stage three or four CKD as defined by current KDIGO guidelines.\(^1\) This includes GFR between 59 and 15 ml/min/1.73m\(^2\). Additionally, patients must have a urine albumin to creatinine ratio greater than 300 milligrams per gram but less than 5,000 milligrams per gram. In order to be eligible for enrollment, patients must be currently adhering to a daily regimen of a maximum tolerated labeled dose of an ACE inhibitor or ARB for at least one month prior to accrual.

3.4 Exclusion Criteria

Patients will be deemed unfit for this study if they have a history or current diagnosis of type 1 or type 2 diabetes mellitus. Patients may not be in a renal state in which immunosuppressive management is required. Individuals diagnosed with mild renal insufficiency or those with end-stage renal disease will not be eligible for enrollment. Mild renal insufficiency is defined as a GFR 60 ml/min/1.73m\(^2\) and greater. End-stage renal disease includes patients with a GFR less than 15 ml/min/1.73m\(^2\) and/or requiring renal replacement therapy by way of kidney transplantation or hemodialysis. Patients may not be allowed to enroll if they have liver disease. Patients may also be excluded if they have stage three or stage four heart failure as defined by the New York
Heart Association. Finally, refusal to sign the study consent will exclude a patient from study participation.

3.5 Subject Protection and Confidentiality

This clinical trial will operate within the confines of the Yale New Haven Health System; thus, appropriate documents will be submitted to Yale University’s Institutional Review Board and Human Investigation Committee. Yale University is registered under FDA regulation and operates in compliance with the laws, regulations, and policies set forward by the administration. Should the committee feel the need to change any detail within our proposal, we will modify as necessary and re-submit our project.

Our research team believes the advancement of medical knowledge should never come at the cost of patient confidentiality. Prior to beginning our clinical trial, all study personnel will be trained in our patient confidentiality protocol and must undergo and successfully complete training that abides by the standards set forth by the Health Insurance Portability and Accountability Act (HIPPA).

Pseudonymization will be used to ensure patient identity is kept protected and separated from study data. Each patient will be assigned an arbitrary number code upon acquisition of signed consent. Identifying information will be entrusted to the Principal Investigator and will be held in a locked cabinet file. Duplication and distribution of documents containing de-identifying information will be prohibited.

Prior to accrual, prospective patients will meet with a trained researcher from our team. We will ensure each patient is thoroughly educated on canagliflozin including: possible adverse events while taking an SGLT2 inhibitor, expected time commitment from the patient, and what we hope to learn from conducting this study. Patients will be
made aware that they hold the right to discontinue their participation during any phase of the trial.

3.6 Recruitment

As previously mentioned, patients will be recruited from hospitals that are within the Yale New Haven Health System and affiliated hospitals. During the recruitment period, study personnel will be placed at each of the eight hospitals and will be available to aid in the accrual of study participants and act as a resource to the providers that have a hand in the recruiting process. Patients that are admitted to internal medicine services as well as those who visit hospital clinics will be screened for eligibility. Prior to the enrollment period, hospital team managers will be contacted and informed of the study so that they may notify the providers with whom they work. Providers will be encouraged to refer patients to the on-site study coordinators as patients are admitted or seen. Additionally, study coordinators will be trained and have access to the electronic medical record system, Epic, used by all participating hospitals. While on-site, patients’ medical records will be actively reviewed by the coordinators to be screened for eligibility based on study inclusion and exclusion criteria. Once a patient is deemed eligible, the coordinator will approach the patient about the possibility of their participation in the project. If a patient is interested in moving forward with the enrollment process, the coordinator will consult the patient’s provider to ensure the patient’s safety and ability to become a study participant. Finally, the coordinator will complete the enrollment process by thoroughly explaining all aspects of the study to the patient. Once the patient provides his or her signature of consent, a de-identified patient number will be assigned.
3.7 Study Variables and Measures

The intervention of interest will be canagliflozin 100 mg oral once daily. The control will be a placebo pill that will be formulated to be aesthetically identical to the canagliflozin pill to ensure patients and medicine distributors will be unable to differentiate between the treatment and placebo. Prior to distribution, the placebo and canagliflozin pills will be carefully sorted and packaged in personalized blister packaging to ensure each patient receives the appropriate capsule.

The primary dependent variable will be mean decline in GFR per year. Secondary outcomes will include end-stage renal disease (defined as dialysis for at least 30 days and/or GFR less than 15 ml/min/1.73m²), renal related death, hospitalizations due to renal etiology, and safety endpoints including mycotic infections, bone fractures, and amputations.

3.8 Methodological Considerations

Experimental Protocol

Subjects who have been deemed qualified to participate in the study will first undergo a two-week trial that will assess medical compliance. During this time, patients will be instructed to take a placebo oral capsule once daily and will be closely monitored by study coordinators via calls and texts, depending on patient preference. Upon successful completion of this two-week compliance run-in period, patients will then be randomly assigned in a 1:1 ratio pattern to either the treatment group of canagliflozin or the placebo control group.

After randomization, patients will return to the outpatient hospital clinics for follow-up at pre-set intervals. At week 2, patients will be scheduled a call with a
coordinator to assess tolerance and side effects of the new medication. After initial check-in, patients will visit their respective hospital clinics at weeks 20, 24, 44, 48, 68, and 72. Visit appointments may be made +/- seven days of the specific recommended date. Should a patient be unable to have an in-person visit, follow-up appointments may be conducted via telephone under the discretion of research personnel. During these appointments, patients will meet with study coordinators who will assess adverse events, concomitant medication use, and endpoints of interest. Additionally, patients will undergo phlebotomy laboratory assessments to allow for estimated GFR calculation. Patients who either choose to discontinue independently or discontinue the study drug under medical guidance will be encouraged to continue follow-up with coordinators via planned telephone encounters to allow for continued adverse event monitoring.

Patients will be provided specific instructions regarding time and method of capsule ingestion. All patients, regardless of treatment group, will be given the same set of instructions. Study participants will be instructed to take a single capsule once per day before the first meal of the day, every day, throughout the 18-month follow-up period. The capsule must be swallowed whole and may not be manipulated in any way (cut, crushed, chewed, etcetera). Should a patient forget or for some reason cannot take their dose in the morning, the patient should skip that day’s dose, record the date and reason for missing the dose, and discuss each skipped dose with study personnel at the subsequent follow-up visit. Patients are not to discard capsules that are not taken. Study personnel will maintain a drug log that will account for number of pills dispensed and pills returned at each visit.
**Figure 2. Study Design**

**Blinding of Intervention**

The treatment and control allocation will be assigned via central randomization that will utilize computer-generated randomization to place patients in either the canagliflozin group or placebo group. Prior to randomization, patients will be stratified based on their estimated GFR in order to match the groups. As previously mentioned, both the treatment and control capsules will be formulated to look identical and will be packaged in identical blister packaging. The capsules will be distributed by study personnel to study participants by de-personalized identification numbers.
Blinding of Outcome

The blinding of this study is not to be lifted until all study participants have completed the 18-month treatment course and study data has been secured in the database. Should there be a medical emergency related to the study drug, blinding may be broken to ensure safety of the patient as well as other study participants. The Principle Investigator and Sponsor of this study must be notified immediately if such a situation occurs. In-depth documentation of the event will be required, as well as continued follow-up for adverse reactions in study participants.

Adherence

Compliance capabilities will be initially assessed during the two-week compliance run-in period. The inability to adhere to the medication schedule for at least five out of seven days per week will disqualify the patient from study participation. After the compliance phase, adherence to study medication will be assessed at follow-up visits. The number of pills returned will be compared to number of pills dispatched in order to assess patient adherence.

Monitoring of Adverse Events

Literature regarding adverse events associated with SGLT2-inhibitors can be found in chapter two of this proposal. We will monitor and record the occurrence of known adverse events including mycotic infections, bone fractures, and amputations. Research personnel will inquire about these events at each follow-up appointment. Patients will also be encouraged to immediately contact their coordinator should any of these events occur between appointments. Since SGLT2-inhibitors have yet to be studied in the non-diabetic population, we will collect data on any adverse event that should
occur during the 18-month period and will investigate the possible association to the study drug during analysis.

**3.9 Data Collection**

Research personnel will be responsible for collecting data at each patient visit during the 18-month follow-up period. Scheduled follow-up appointments will occur at weeks 20, 24, 44, 48, 68, and 72. During each visit patients will be asked questions regarding medication side effects and hospital admissions. Medical record review will take place at this time if deemed necessary due to a recent hospitalization. Patients will also undergo a blood draw at each appointment in order to ascertain estimated GFR. The chronic kidney disease epidemiology collaboration equation (CKD-EPI) will be used to calculate estimated GFR. Patient data will be collected and stored in the password protected database software, Microsoft Access.

**3.10 Sample Size Calculation**

To calculate the sample size for this clinical trial we primarily used data points provided by the canagliflozin and renal events in diabetics with established nephropathy clinical evaluation (CREDENCE) trial. This trial was used as the basis for our calculation due to its robust sample size, well regarded methods, and widely known results. It is important to note that while the CREDENCE trial and our trial utilize the same treatment drug and dose, the CREDENCE trial investigated the impact on CKD within patients with diabetes mellitus while our study is specifically focused on the non-diabetic population. This difference will be considered when interpreting data and running statistical analysis, however we believe this is the most reliable study from which our sample size can be calculated.
Specific numbers and calculations based off the CREDENCE trial can be found in appendix D. Assuming a power of 80% and an alpha of 0.05, we calculate a required sample size of 382 patients per arm, totaling 764 total study participants. In an effort to decrease the number of participants needed without decreasing the power, we have also considered assuming a one-sided hypothesis with 80% power and alpha of 0.05. Under this statistical method and with these assumptions, we calculate a required sample size of 299 patients per arm, totaling 598 study participants.

The first statistical method mentioned would require an average of 16 patients enrolled per hospital per month. The latter method would require an average of 12 patients enrolled per hospital per month. In the 2018 fiscal year, the Yale New Haven Heath affiliated hospitals had 124,688 inpatient discharges and 2.4 million outpatient encounters. We believe the patient load between these eight hospitals will be sufficient to fulfill our targeted sample size.

We recognize that we are utilizing strong assumptions for our statistical calculations. We are assuming that our study population has a normal distribution and that the variance is the same between groups. Additionally, if we feel 598 patients is more plausible and accessible than 764 patients, we will be assuming a one-sided hypothesis, which can be interpreted as the assumption that canagliflozin will have a positive effect on the decline in GFR in our treatment group when compared to the control group. Should we feel the utilization of a one-sided hypothesis yields a more attainable patient recruitment goal, we will contemplate ethical considerations that will be present given the assumptions inherent to a one-sided hypothesis statistical method.
3.11 Analysis

The primary outcome, change in GFR, is a continuous variable. We are interested in the difference of means between the treatment group and the control group. To analyze the difference in means, we will utilize an analysis of covariance in our statistical methods. The secondary outcomes of this study include end-stage renal disease, renal related death, hospitalizations due to a renal etiology, and safety endpoints such as mycotic infections, bone fractures, and amputations. We will utilize Kaplan-Meier curves to analyze time-to-event occurrences of these outcomes.

3.12 Timeline and Resources

The patient screening for this trial will begin May 1, 2020 and will continue for 6 months, ending on November 1, 2020. However, it may be necessary to postpone these dates due to the COVID-19 pandemic. After the screening process is complete and patients have signed the consent paperwork, the medication compliance period will take place during the month of November. Upon successful completion of the run-in trial, all patients will be scheduled to begin either canagliflozin or placebo on December 1, 2020. Follow-up will extend for 18-month, which will conclude on June 1, 2022.

The responsibilities of the Principal Investigator will be divided between Dr. Jeffrey Turner and Mia Wigley. They will share duties in ensuring compliance with federal, state, and local laws, institutional policies, and ethical principles. Dr. Jeffrey Turner will also fill the role of faculty advisor to graduate student Mia Wigley. Ancillary study personnel will be recruited and trained in accordance with study policy. A total of eight individuals will be recruited to allow for one study representative at each hospital location. These research members will be responsible for meeting with patients during
the consenting process as well as scheduled appointments during the follow-up period.

Recruitment of two Yale undergraduate student research assistants (RA) will take place during the 6-month screening period. Student RAs will aid in the tasks of data collection, data entry, and analysis.
References

1. NKF KDOQI Guidelines National Kidney Foundation


Chapter 4 – Conclusion

4.1 Study Advantages

Many advantages of this proposal lie within the chosen methodology. Using a multicenter design strengthens the external validity of our trial. By using multiple sites, we hope to enhance the diversity of our trial population so that our findings are applicable to the U.S. population. By harnessing greater external validity, we are able to increase the generalizability of our results. Internal validity of this study is buttressed by the use of a primary endpoint that is obtained via a standardized equation (CKD-EPI formula) which will buffer data collection variability between study personnel.

Randomization, stratification, and blinding of study participants will prevent selection bias and reduce the probability of confounding variables. By putting forth effort in the randomization process, analysis will be less likely to yield overestimation of effect.

4.2 Study Limitations

The allure of studying an intervention in an original population gives potential for groundbreaking results. However, the risk of this study lies within the unknown interaction between a novel patient population and the treatment of interest. For this reason, the cardinal disadvantage of this study is the possibility of causing harm to patients. Fortunately, many prior investigations have been focused on canagliflozin and a very similar patient population, leading to the reasonable assumption that this study population should have a similar response to the study drug. To protect against patient harm, adverse events will be closely monitored, research personnel will always be available to study participants for questions and/or concerns, and frequent study follow-up appointments will be scheduled.
The length of this study stands as another disadvantage to this trial. Prior studies investigating SGLT2 inhibitors have included median follow-up periods longer than the 18-month follow-up allotted for this trial. Median follow-up times for major studies include: CANVAS trial 3.6 years, EMPA-REG trial 4.6 years, DECLARE-TIMI trial 5.2 years, CREDENCE trial 2.6 years, and empagliflozin trial 3.1 years. We plan to diminish the effect of this potential time deficit by enrolling only patients that have advanced kidney disease as defined by the KDOQI staging, which will enrich the event rate in our population. We understand that by restricting the enrollment to only patients with advanced CKD, we may be lessening the generalizability of this study. However, pending the results, if canagliflozin is demonstrated to slow the progression of non-diabetic CKD, longer studies with a wider range of CKD patients may be warranted.

The utilization of a multicenter design allows for greater generalizability, however there are drawbacks that must be considered in this design decision. Components of each site that may offer variation include different research coordinators, physicians, hospital laboratory protocol, etcetera. Research coordinators will be provided standardized questionnaires and strict instructions regarding the proper conduction of follow-up appointments and phone calls in an attempt to best standardize the process across all research sites.

The primary dependent variable (mean decline in GFR per year) will be ascertained via an estimated GFR predication equation rather than utilizing inulin clearance, the current gold standard. While it is understood that using indirect measures to calculate the GFR may harm the validity of the study, the timeframe and funds allocated to this trial do not support the resources needed for utilization of exogenous
filtration markers. In order to minimize the negative effect that an estimated GFR calculation may have on the validity of the study results, we have created a follow-up schedule that allows for pairs of blood collections to take place approximately 30 days apart. Each pair of estimated GFR values will be averaged and used to monitor a change in the patient’s GFR. By using the average of two estimated GFR values collected 30 days apart, we are able to minimize the effect of transient events such as hypovolemic or pre-renal states that may occur on a single day.

4.3 Clinical Implications

CKD is a health concern that not only hinders the quality of life in those who are diagnosed but is also a major source of medical expenditure in the United States with an estimated Medicare cost of roughly $49 billion per year. Despite considerable effort and years of clinical trials investigating combination and novel management options for CKD, there remains a need to bend the curve of disease progression. This trial will be among the first generation of studies exploring SGLT2 inhibitors in the non-diabetic CKD population. Future studies will most certainly be warranted but SGLT2 inhibitors have the potential to have a major impact on patients’ quality of life, length of life, and healthcare cost at both the individual and national level.
References


Appendices

Appendix A. Patient Consent Form

PERMISSION FOR PARTICIPATION IN A RESEARCH PROJECT
310 FR. 2 (2016-1)³

YALE UNIVERSITY SCHOOL OF MEDICINE – YALE-NEW HAVEN HOSPITAL
YALE UNIVERSITY SCHOOL OF MEDICINE – BRIDGEPORT HOSPITAL
YALE UNIVERSITY SCHOOL OF MEDICINE – DANBURY HOSPITAL
YALE UNIVERSITY SCHOOL OF MEDICINE – GREENWICH HOSPITAL
YALE UNIVERSITY SCHOOL OF MEDICINE – GRIFFIN HOSPITAL
YALE UNIVERSITY SCHOOL OF MEDICINE – NORWALK HOSPITAL
YALE UNIVERSITY SCHOOL OF MEDICINE – ST MARY’S HOSPITAL
YALE UNIVERSITY SCHOOL OF MEDICINE – WATERBURY HOSPITAL

Study Title: Canagliflozin to Slow Renal Insufficiency Progression in Non-Diabetic Chronic Kidney Disease
Principal Investigator: Jeffrey Turner, MD
Co-Principal Investigator: Mia Wigley, PA-SII
Funding Source: Yale Physician Associate Program

Invitation to Participate and Description of Project

We are inviting you to participate in a research study designed to investigate the effect of canagliflozin on the progression of chronic kidney disease. You have been asked to participate because you are an adult with stage three or stage four chronic kidney disease, you do not have a diagnosis of type 2 diabetes mellitus, and you are currently taking a drug that is classified as either an angiotensin-converting enzyme inhibitor or an angiotensin II receptor blocker.

In order to decide whether or not you wish to be a part of this research study you should know enough about its risks and benefits to make an informed decision. This permission form gives you detailed information about the research study, which a member of the research team will discuss with you. This discussion should go over all aspects of this research: its purpose, the procedures that will be performed, any risks of the procedures, possible benefits, and possible alternative treatments. Once you understand the study, you will be asked if you wish to participate; if so, you will be asked to sign this form.

Description of Procedures

Prior to official enrollment, your eligibility will be assessed by your physician and/or a study coordinator. You will be deemed qualified to participant if you are an adult between the ages of 18 and 75 years with moderate to severe chronic kidney disease.
Additionally, you must have a urine albumin to creatinine ratio greater than 300 milligrams per gram but less than 5,000 milligrams per gram. In order to be eligible for enrollment, you must be currently adhering to a daily regimen of a maximum tolerated labeled dose of an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker for at least one month prior to accrual.

Before the study begins, you will first be assessed for your ability to adhere to a medication routine on a daily schedule. You will be given a two-week supply of a sugar pill to assess compliance. You will be instructed to take this pill daily as you do your other prescribed medications. You will be asked to keep all pills that are not ingested. Pills should never be thrown away.

At the end of the two-week period, you will be scheduled for an appointment with a study coordinator and will be asked to bring in all pills that were not taken. At this time, your eligibility to participate in the study will be determined.

If enrolled in the study, you will be randomly placed into a group that will determine if you will be given the study medication (canagliflozin) or a placebo pill. A placebo medication is a capsule designed to look identical to the study medication but does not have any physiological effect on the body. No one involved in this study, including you, will know if you have been assigned to the study medication or the placebo pill.

Group placement will be determined by a computer system that will randomly assign you to a group. The computer program will sort participants equally between the two groups with considerations in age, gender, race, and kidney function.

Study pills will be administered to you at the end of the two-week trial period. Pills will be packaged in blister packaging. One compartment equals one day of medication. The pill is to be taken with your other prescribed medications. Ideally, these are to be taken before the first meal of each day and are never to be chewed, cut, or crushed. If a daily dose is skipped, we ask that you do not double up your dose the next day. Maintain missed doses within their packaging and return packaging and remaining pills at your subsequent appointment.

Study appointments will be made at weeks 20, 24, 44, 48, 68, and 72. These appointments can be made within seven days of the suggested date. Should you be unable to physically attend your appointment, study coordinators will be able to conduct a telephone appointment to monitor adverse event reactions. If absolutely necessary an exception within reasonable limits will be made for scheduling an in-person appointment outside the seven-day range in order to ascertain necessary labs.

During appointments, study coordinators will ask you a series of questions regarding side effects that you may be experiencing. You are encouraged to contact your study coordinator at any time should you experience worrisome symptoms between your appointments.
In order to monitor your kidney function, you will undergo a blood draw at each of your appointments. You will also have blood drawn when you are initially screened and the day you are given your first pack of medication (4 weeks later) in order to obtain your baseline estimated glomerular filtration rate. Approximately 3 mL of blood will be taken during each phlebotomy appointment.

At the conclusion of the 18-month follow-up period, you will be notified of your group assignment. After analysis of study data, you will gain access to all results and literature that is associated with the study.

You will be informed of any significant new findings that are developed during the course of your participation in this study that may affect your willingness to continue to participate.

**Risks and Inconveniences**

Possible side effects of canagliflozin include genital mycotic infections, volume depletion, osmotic diuresis, acute renal failure, increased probability of bone fractures, and amputation.

In previous studies, the risk of mycotic infections was seen in approximately 13% of women and 3% of men. Should a mycotic infection occur, we will be in contact with your primary care physician and will ensure you receive appropriate medication to resolve the infection.

In previous studies, effects of osmotic diuresis and volume depletion was evaluated as mild to moderate in severity. Management for these side effects is suggested as close follow-up and symptomatic management. You will be followed closely by both the study coordinator and your physician who will monitor you for signs and symptoms of these side effects.

Acute renal failure, bone fractures, and amputations are the least common side effects of canagliflozin. Close follow-up will aid in the decision of study discontinuation should the possibility of these risk present at any time.

Canagliflozin is a relatively new drug and has never been studied in the non-diabetic chronic kidney disease population. For this reason, participation in this study may involve risks that are currently not known.

**Benefits**

Participation in the research will help the medical community understand the role that canagliflozin may have in the management of non-diabetic chronic kidney disease.

We expect this study to have a great impact on and be a contributor to the medical community. We hope that our collective effort will one day benefit the non-diabetic
chronic kidney disease community by allowing meaningful decline in the rate of progression of kidney failure which will allow for deferment in the need for hemodialysis and/or kidney transplantation.

This study may not benefit you directly.

**Economic Considerations**

Participation in this research is voluntary.

Monetary compensation will not be given for enrollment and participation.

Parking validation will be given for hospital garage parking for each appointment throughout enrollment.

Please consider the possible impact that study appointments may have on your work schedule as we will be unable to compensate for loss of hourly wage/salary.

**Treatment Alternatives**

There are no alternative treatments to be considered. All participants will continue their prescribed medical management for their kidney disease as decided by their physician.

The use of canagliflozin will be used as an additive therapy rather than an alternative therapy.

**Confidentiality**

Any identifiable information that is obtained in connection with this study will remain confidential and will be disclosed only with your permission or as required by U.S. or State law. Examples of information that we are legally required to disclose include abuse of a child or elderly person, or certain reportable diseases.

This trial will operate within the confines of the Yale New Haven Health System; thus, appropriate documents will be submitted to Yale University’s Institutional Review Board and Human Investigation Committee. Yale University is registered under FDA regulation and operates in compliance with the laws, regulations, and policies set forward by the administration.

Our research team believes the advancement of medical knowledge should never be at the cost of patient confidentiality. Prior to beginning our clinical trial, all study personnel will be trained in our patient confidentiality protocol and must undergo and successfully complete training that abides by the standards set forth by the Health Insurance Portability and Accountability Act (HIPPA).
Pseudonymization will be used to ensure patient identity is kept protected and separated from study data. Each patient will be assigned an arbitrary number code upon acquisition of signed consent. Identifying information will be entrusted to the Principal Investigator and will be held in a locked cabinet file. Duplication and distribution of documents containing de-identifying information will be prohibited.

When the results of the research are published or discussed in conferences, no information will be included that would reveal your identity unless your specific permission for this activity is obtained.

Representatives from Yale University, the Yale Human Research Protection Program, and the Yale Human Investigation Committee (the committee that reviews, approves, and monitors research on human subjects) may inspect study records during internal auditing procedures. However, these individuals are required to keep all information confidential.

Authorized representatives of the Food and Drug Administration (FDA) and the manufacturer of canagliflozin may need to review records of individual subjects. As a result, they may see your name, but they are bound by rules of confidentiality not to reveal your identity to others.

**In Case of Injury**

If you are injured while on study, seek treatment and contact the study doctor as soon as you are able.

Yale School of Medicine and Yale-New Haven Hospital do not provide funds for the treatment of research-related injury. If you are injured as a result of your participation in this study, treatment will be provided. You or your insurance carrier will be expected to pay the costs of this treatment. No additional financial compensation for injury or lost wages is available.

You do not give up any of your legal rights by signing this form.

**Voluntary Participation and Withdrawal**

You are free to choose not to participate and if you do decide to become a subject you are free to withdraw from this study at any time during its course. Refusing to participate or withdrawing from the study will involve no penalty or loss of benefits to which you are otherwise entitled (such as health care outside the study, the payment for your health care, and your health care benefits).

If you decide not to participate or if you withdraw, it will not harm your relationship with your doctors and providers. You would still be treated with standard therapy or, at your request, referred to a clinic or doctor who can offer appropriate treatment.
The researchers may withdraw you from participating in the research, if necessary. Reasons would include progression of kidney disease/poor response to treatment, development of serious side effects, or subject non-compliance.

**Questions**

We have used some technical terms in this form. Please feel free to ask about anything you don't understand and consider this research and the permission form carefully – as long as you feel is necessary – before you decide to participate or to not participate in this research study.
Authorization and Permission

I have read (or someone has read to me) this form and have decided to participate in the project described above. Its general purposes, the particulars of my involvement, and possible hazards and inconveniences have been explained to my satisfaction. My signature also indicates that I have received a copy of this permission form.

By signing this form, I give permission to the researchers to use (and give out) my information for the purposes described in this form. By refusing to give permission, I understand that I will not be able to take part in this research.

Name of Subject: ______________________________

Signature: ____________________________________

Date: ________________________________________

_________________________________________                ___________________
Signature of Principal Investigator                                       Date

or

_________________________________________                ___________________
Signature of Person Obtaining Consent                                       Date

If you have further questions about this project or if you have a research-related problem, you may contact the Principal Investigator, Dr. Jeffrey Turner, at (***) ***-**** or the Co-Principal Investigator, Mia Wigley, at (***) ***-****.

If after you have signed this form you have any questions about your privacy rights, please contact the Yale Privacy Officer at (***) ***-****.

If you would like to talk with someone other than the researchers to discuss problems, concerns, and questions you may have concerning this research, or to discuss your rights as a research subject, you may contact the Yale Human Investigation Committee at (***) ***-****.

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### Appendix B. Estimated GFR Formula

Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation for estimating GFR on the Natural Scale*²

<table>
<thead>
<tr>
<th>Race and Sex</th>
<th>Serum Creatinine Level, μmol/L (mg/dL)</th>
<th>Equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black Female</td>
<td>≤62 (≤0.7)</td>
<td>$\text{GFR} = 166 \times (\text{Scr}/0.7)^{-0.329} \times (0.993)^{\alpha \text{ee}}$</td>
</tr>
<tr>
<td></td>
<td>&gt;62 (&gt;0.7)</td>
<td>$\text{GFR} = 166 \times (\text{Scr}/0.7)^{-1.209} \times (0.993)^{\alpha \text{ee}}$</td>
</tr>
<tr>
<td>Male</td>
<td>≤80 (≤0.9)</td>
<td>$\text{GFR} = 163 \times (\text{Scr}/0.9)^{-0.411} \times (0.993)^{\alpha \text{ee}}$</td>
</tr>
<tr>
<td></td>
<td>&gt;80 (&gt;0.9)</td>
<td>$\text{GFR} = 163 \times (\text{Scr}/0.9)^{-1.209} \times (0.993)^{\alpha \text{ee}}$</td>
</tr>
<tr>
<td>White or other Female</td>
<td>≤62 (≤0.7)</td>
<td>$\text{GFR} = 144 \times (\text{Scr}/0.7)^{-0.329} \times (0.993)^{\alpha \text{ee}}$</td>
</tr>
<tr>
<td></td>
<td>&gt;62 (&gt;0.7)</td>
<td>$\text{GFR} = 144 \times (\text{Scr}/0.7)^{-1.209} \times (0.993)^{\alpha \text{ee}}$</td>
</tr>
<tr>
<td>Male</td>
<td>≤80 (≤0.9)</td>
<td>$\text{GFR} = 141 \times (\text{Scr}/0.9)^{-0.411} \times (0.993)^{\alpha \text{ee}}$</td>
</tr>
<tr>
<td></td>
<td>&gt;80 (&gt;0.9)</td>
<td>$\text{GFR} = 141 \times (\text{Scr}/0.9)^{-1.209} \times (0.993)^{\alpha \text{ee}}$</td>
</tr>
</tbody>
</table>

CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; GFR = glomerular filtration rate.

* Expressed for specified race, sex, and serum creatinine level. To convert GFR from mL/min per 1.73 m² to mL/s per 1.73 m², multiply by 0.0167. We derived equation coefficients from pooled development and internal validation data sets. The CKD-EPI equation, expressed as a single equation, is $\text{GFR} = 141 \times \min(\text{Scr}/\kappa, 1)\alpha \times \max(\text{Scr}/\kappa, 1)^{-1.209} \times 0.993^{\alpha \text{ee}} \times 1.018 [\text{if female}] \times 1.159 [\text{if black}]$, where Scr is serum creatinine, $\kappa$ is 0.7 for females and 0.9 for males, $\alpha$ is $-0.329$ for females and $-0.411$ for males, min indicates the minimum of Scr/$\kappa$ or 1, and max indicates the maximum of Scr/$\kappa$ or 1. In this table, the multiplication factors for race and sex are incorporated into the intercept, which results in different intercepts for age and sex combinations.
Appendix C. KDOQI Chronic Kidney Disease Definition and Staging

**Definition of Chronic Kidney Disease**

Criteria

1. Kidney damage for \( \geq 3 \) months, as defined by structural or functional abnormalities of the kidney, with or without decreased GFR, manifest by either:
   - Pathological abnormalities; or
   - Markers of kidney damage, including abnormalities in the composition of the blood or urine, or abnormalities in imaging tests
2. GFR <60 mL/min/1.73 m\(^2\) for \( \geq 3 \) months, with or without kidney damage

---

**Definition and Stages of Chronic Kidney Disease**

<table>
<thead>
<tr>
<th>GFR (mL/min/1.73 m(^2))</th>
<th>With Kidney Damage*</th>
<th>Without Kidney Damage*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With HBP***</td>
<td>Without HBP***</td>
</tr>
<tr>
<td>( \geq 90 )</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>60-89</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>30-59</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>15-29</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>&lt;15 (or dialysis)</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

*Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies.

**High blood pressure is defined as \( \geq 140/90 \) in adults and \( >90^\text{th} \) percentile for height and gender in children.

May be normal in infants and in the elderly.

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## Appendix D. Sample Size Calculation

### Sample size calculation utilizing CREDECE trial for base reference

<table>
<thead>
<tr>
<th></th>
<th>Treatment</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean decline in GFR/year</td>
<td>3.19</td>
<td>4.71</td>
</tr>
<tr>
<td>Adjusted mean/month</td>
<td>3.19/12 = 0.27</td>
<td>4.71/12 = 0.39</td>
</tr>
<tr>
<td>Standard error</td>
<td>0.15</td>
<td>0.15</td>
</tr>
<tr>
<td>Number of patients</td>
<td>2202</td>
<td>2199</td>
</tr>
<tr>
<td>Variance</td>
<td>(0.15) * (0.15) * 2202 = 49.55</td>
<td>(0.15) * (0.15) * 2199 = 49.48</td>
</tr>
<tr>
<td>Adjusted variance</td>
<td>49.55 → 50/12^2 (round up to be conservative) = 0.35</td>
<td></td>
</tr>
<tr>
<td>Effect size</td>
<td>3.19 – 4.71 = -1.52</td>
<td></td>
</tr>
<tr>
<td>Adjusted effect size</td>
<td>1.52/12 = 0.12</td>
<td></td>
</tr>
<tr>
<td>Sigma</td>
<td>√(0.35) = 0.59</td>
<td></td>
</tr>
</tbody>
</table>

### Statistical analysis for two-sided hypothesis sample size calculation

- Confidence level: 95%
- Power: 80%
- Hypothesised difference: 0.12
- Population variance: 0.35
- Recommended sample size: 382

### Statistical analysis for one-sided hypothesis sample size calculation

- Calculate Sample Size (for specified Power)
- Calculate Power (for specified Sample Size)
- Enter a value for mu1: 0.27
- Enter a value for mu2: 0.39
- Enter a value for sigma: 0.59
- Enter a value for α (default is 0.05): 0.05
- Enter a value for desired power (default is 0.80): 0.80
- The sample size (for each sample separately) is: 299

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Appendix E. Detailed Illustration of the Structure and Physiology of a Nephron

Illustrated by Mia Wigley
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