

Rationale and protocol of the Dapagliflozin And Prevention of Adverse outcomes in Chronic Kidney Disease (DAPA-CKD) randomized controlled trial

Hiddo J.L. Heerspink, PhD^{1,2}, Bergur V. Stefansson, MD³, Glenn M. Chertow, MD⁴, Ricardo Correa-Rotter, MD⁵, Tom Greene, PhD⁶, Fan-Fan Hou, MD⁷, Magnus Lindberg, MSc², John McMurray, MD⁸, Peter Rossing, MD^{9,10}, Roberto Toto, MD¹¹, Anna Maria Langkilde, MD², David C Wheeler, MD^{12,2} for the DAPA-CKD investigators.

1. Department of Clinical Pharmacy and Pharmacology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands
2. The George Institute for Global Health, Sydney, Australia
3. Astra Zeneca, Gothenburg, Sweden
4. Division of Nephrology, Department of Medicine, Stanford University School of Medicine, Stanford, CA, USA
5. National Medical Science and Nutrition Institute Salvador Zubirán, Vasco de Quiroga # 15, Belisario Dominguez Sección 16, Tlalpan, Mexico City, Mexico 14080
6. Department of Internal Medicine University of Utah, Salt Lake City, Utah, USA
7. Division of Nephrology, Nanfang Hospital, Southern Medical University; National clinical research center for kidney disease; Guangzhou, China
8. BHF Cardiovascular Research Centre, University of Glasgow, Glasgow, UK
9. Steno Diabetes Center Copenhagen, Gentofte, DK
10. University of Copenhagen, Copenhagen, DK
11. University of Texas Southwestern Medical Center, Dallas Texas, USA
12. Department of Renal Medicine, University College London, UK.

Correspondence:

Hiddo Lambers Heerspink, PhD

Department of Clinical Pharmacy and Pharmacology

De Brug 50C-1-002; EB70

University Medical Center Groningen

Postbox 30001

9700 RB Groningen,

The Netherlands

Tel: +31-50-3617859

Fax: +31-50-3617889

E-mail: h.j.lambers.heerspink@umcg.nl

Running head: Rationale and study design of the DAPA-CKD trial

Keywords: Sodium Glucose Co-transporter inhibitor, dapagliflozin, chronic kidney disease, randomized controlled clinical trial

Word count abstract: 250

Word count: 3340 (excluding list of contributors and investigators)

Note to editors: A desire has been expressed to have the publication come up in a search of a study investigator's name. This functionality will need to be assessed with the journal and/or PubMed following acceptance.

Abstract

Background: Recent cardiovascular outcome trials have shown that sodium glucose co-transporter 2 (SGLT2) inhibitors slow progression of chronic kidney disease (CKD) in patients with type 2 diabetes at high cardiovascular risk. Whether these benefits extend to patients without type 2 diabetes or cardiovascular disease is unknown. The Dapagliflozin And Prevention of Adverse outcomes in Chronic Kidney Disease (DAPA-CKD) trial (NCT03036150) will assess the effect of the SGLT2 inhibitor dapagliflozin on renal and cardiovascular events in a broad range of patients with CKD with and without diabetes.

Methods: DAPA-CKD is a randomized, double-blind, placebo-controlled, trial in which approximately 4300 patients with CKD stage 2–4 and elevated urinary albumin excretion will be enrolled. The vast majority will be receiving a maximum tolerated dose of a renin-angiotensin system inhibitor at enrolment.

Results: After a screening assessment, eligible patients with UACR ≥ 200 mg/g and eGFR between 25 and 75 ml/min/1.73m² are randomly assigned to placebo or dapagliflozin 10 mg/day. Enrolment is monitored to ensure that at least 30% of patients do not have diabetes and that no more than 10% have an eGFR above 60 ml/min/1.73m². The primary endpoint is a composite of a sustained decline in eGFR of $\geq 50\%$, end-stage renal disease, renal death or cardiovascular death. The trial will conclude when 681 primary renal events have occurred, providing 90% power to detect a 22% relative risk reduction (alpha level of 0.05).

Conclusion: DAPA-CKD will determine whether the SGLT2 inhibitor dapagliflozin, added to guideline-recommended therapies, safely reduces the rate of renal and cardiovascular events in patients across multiple CKD stages with and without diabetes.

Introduction

Sodium glucose co-transporter 2 SGLT2 inhibitors reduce plasma glucose and haemoglobin A1c (HbA1c) in patients with type 2 diabetes mellitus by increasing urinary glucose excretion in a non-insulin dependent fashion.[1] To date, three large cardiovascular outcome trials have demonstrated that the beneficial effects of these agents extend beyond glycemic control.[2-4] These trials recruited patients with type 2 diabetes and either established cardiovascular disease or cardiovascular risk factors. In all three of these trials, preservation of renal function has been reported.[2-4] However the proportion of participants with chronic kidney disease (CKD) was low and the numbers of patients reaching end-stage renal disease small, highlighting the need for dedicated outcome trials to define the efficacy and safety of SGLT2 inhibitors in patients with established CKD. The first trial of SGLT2 inhibition to include patients with type 2 diabetes and CKD reported that canagliflozin 100 mg/day reduced the risk of a composite renal endpoint (comprised of doubling of serum creatinine, end-stage renal disease (ESRD), or death due to renal or cardiovascular disease) by 30% compared to placebo.[5]

In the cardiovascular and renal outcome trials described above, the reno-protective benefits of the SGLT2 inhibitors did not appear to be completely explained by the modest reductions in HbA1c, which are attenuated in patients with a low eGFR. Other mechanisms of benefit including activation of tubuloglomerular feedback and reduction in intra-renal hypoxia have been proposed to explain the salutary effects of SGLT2 inhibitors on renal function; these may be relevant to patients with CKD who do not have diabetes.[6] [7]

The **Dapagliflozin And Prevention of Adverse outcomes in CKD (DAPA-CKD)** trial is testing the hypothesis that treatment with dapagliflozin is superior to placebo in reducing the risk of renal and cardiovascular events in patients with CKD (with or without concomitant type 2 diabetes) already receiving an optimized dose of either an angiotensin converting enzyme

inhibitor (ACEi) or an angiotensin receptor blocker (ARB) as background reno-protective therapy.

Methods

Study objective

The primary objective of DAPA-CKD is to assess whether dapagliflozin compared with placebo reduces the composite endpoint of worsening of renal function (defined as a composite endpoint of 50% eGFR decline, ESRD, or renal death) or cardiovascular death in patients with CKD. In addition, the trial will examine the effects of dapagliflozin, compared with placebo, on a) the composite endpoint of worsening of renal function, b) the composite endpoint of hospitalization for heart failure or cardiovascular death, and c) all-cause mortality. Additional exploratory endpoints include changes in estimated glomerular filtration rate (eGFR), urinary albumin:creatinine ratio (UACR), as well as health-related quality-of-life. The trial is registered with www.clinicaltrials.gov (NCT03036150).

Overall study design

DAPA-CKD is a multinational, multicentre, event-driven, randomized, double-blind, parallel-group, placebo-controlled trial that will recruit approximately 4,300 patients at nearly 400 sites in 21 countries (Figure 1). Figure 2 shows the overall study design.

Trial participants

The trial participants are adults with CKD with an eGFR of ≥ 25 to ≤ 75 ml/min/1.73 m² and a UACR of ≥ 200 mg/g but $\leq 5,000$ mg/g. Additional inclusion and exclusion criteria are listed in **Table 1**.

Study periods

Enrolment

Potentially eligible patients are invited for screening. Those with a central laboratory eGFR ≥ 25 and ≤ 75 ml/min/1.73m² and a UACR between ≥ 200 mg/g and ≤ 5000 mg/g, and who meet all other inclusion and no exclusion criteria, can be randomized within 14 (+/- 7) days after the screening visit. Patients with autosomal dominant or autosomal recessive polycystic kidney disease, lupus nephritis, or ANCA vasculitis are not enrolled. Additionally, patients receiving immunotherapy for primary or secondary renal disease within six months prior to enrolment are also excluded.

Due to the high day-to-day variation in serum creatinine (eGFR) and UACR, a disqualifying laboratory test for these variables during the screening period can be repeated once at the discretion of the local investigator. Patients who do not qualify based on inclusion or exclusion criteria can be re-enrolled once after appropriate changes to clinical management.

Randomization and stratification

Approximately 4,300 patients will be randomly assigned 1:1 to dapagliflozin 10 mg/day or matched placebo. These patients comprise the primary intention to treat (ITT) population for assessing the safety and efficacy of dapagliflozin. Randomization is performed centrally through an interactive web response system on the basis of a computer-generated randomization schedule prepared by the trial sponsor. The stratified randomization scheme is designed to ensure balance in baseline UACR (\leq or >1000 mg/g), and the proportion of patients with and without type 2 diabetes, between treatment groups.

Patients and all study personnel (except the Independent Data Monitoring Committee) are kept blinded to treatment allocation. Study drug (dapagliflozin and placebo) are packaged

in an identical manner, with uniform tablet appearance, labelling and administration schedule, Dapagliflozin 10 mg/day was selected for this study based on broad clinical experience demonstrating favourable efficacy and tolerability. Patients are instructed to take their study medication in the morning at approximately the same time of the day throughout the study.

Recruitment is monitored to ensure a) a minimum of 30% of patients were recruited to either the diabetic or non-diabetic sub-population; b) adequate geographical representation of different regions of the world; and c) that patients are taking an optimized dose of an ACEi or ARB at randomization -i.e. the guideline-recommended, evidence-based, dose or highest tolerated dose. The number of patients with an eGFR between 60 and 75 ml/min/1.73m² at the time of randomization was capped on November 27, 2017 to ensure that no more than 10% of trial participants would start the trial within the eGFR range classified as stage 2 CKD.

Double-blind treatment and management of patients

After randomization, in-person visits are scheduled after 2 weeks; 2, 4, and 8 months, and at 4 monthly intervals thereafter. Each follow-up visit includes collection of information about potential endpoints, adverse events, concomitant therapies, and study drug adherence. In addition, vital signs are recorded, and blood and urine are collected for laboratory measurements. Finally, further study medication is dispensed. A final study close out visit will be conducted within six weeks of the end of the study, which will occur once 681 patients have experienced a primary outcome event (see below and Figure 2).

Patients who experience a renal or a cardiovascular event are advised to continue study medication. A (temporary) dose reduction to dapagliflozin 5 mg/day (or equivalent reduction in matching placebo), or temporary study drug discontinuation is permitted in

patients with clinically relevant volume depletion, hypotension, or unexpected worsening of renal function.

Discontinuation of study drug is required for patients who develop diabetic ketoacidosis or become pregnant. Patients can also decide to discontinue study drug at any time. Patients who prematurely discontinue study drug (but do not withdraw consent) are encouraged to continue follow-up visits as scheduled, or if that is not possible, are given the option of follow-up by telephone, contact with a family member, or through healthcare professionals known to the patient.

Outcome definitions and event adjudication

Efficacy outcomes

The primary outcome for the evaluation of the effect of dapagliflozin on delaying the progression of renal disease is the time to the first occurrence of any of the following components of the composite renal endpoint: $\geq 50\%$ eGFR decline (confirmed by a second serum creatinine measurement at least 28 days later), the onset of ESRD, or renal or cardiovascular death (**Table 2**). Secondary and exploratory endpoints are listed in Table 2. A blinded and independent event adjudication committee (EAC) consisting of nephrologists, cardiologists, and neurologists will adjudicate the primary and secondary endpoints, except for the sustained $\geq 50\%$ eGFR decline and sustained $\text{eGFR} < 15 \text{ ml/min/1.73m}^2$ (which will be ascertained from central laboratory measurements).

ESRD is defined as the need for maintenance dialysis (peritoneal or hemodialysis) for at least 28 days, renal transplantation, or sustained $\text{eGFR} < 15 \text{ mL/min/1.73m}^2$ for at least 28 days. Renal death is defined as death due to ESRD when dialysis treatment was deliberately withheld (dialysis was not started or discontinued) for any reason. The 28-day timeframe is included in the definition of the ESRD endpoint definition to avoid misclassification of acute

kidney injury as ESRD. If the dialysis treatment was stopped before day 28 due to death, futility or patient electing to stop dialysis, the EAC will decide whether or not the need for dialysis was likely to be permanent and meets the ESRD criteria.

The EAC will also be responsible for adjudicating possible myocardial infarction, unstable angina, stroke, and transient ischemic attack.

Safety outcomes

Selected adverse event data are being collected, given the extensive prior experience with dapagliflozin. Only serious adverse events and adverse events of interest or leading to premature study drug discontinuation, study drug interruption or dose reduction are recorded. Adverse events of interest include volume depletion, renal events, major hypoglycemia, fractures, potential diabetic ketoacidosis, adverse events leading to amputations or adverse events leading to an increased risk of lower limb amputations.

Background medication

Efforts are being made to maintain patients on their stable optimized dose of ACEi or ARB for the duration of the trial. Management of blood pressure, lipids and glucose, and use of other essential therapies, is left to the discretion of the investigator, in keeping with local clinical practice and guidelines.

Statistical considerations

Sample size calculation

DAPA-CKD is an event driven trial. The sample size is based on the expected rate of the primary efficacy endpoint and the anticipated size of the effect of dapagliflozin treatment. With recruitment of at least 4000 patients, the trial will have 90% power to detect a relative

risk reduction of 22% in the primary endpoint based on primary events being observed in 681 patients, and a two-side p-value of 0.05. Assumptions underlying the sample size calculation included a placebo event rate of 7.5% events per year (based on event rates observed in relevant patients in prior trials), an annual drug discontinuation rate of 6%, 1% loss to follow-up, a recruitment period of 24 months, and a total study duration of approximately 45 months.

An interim analysis will be conducted when approximately 75% of the primary events are confirmed, using a Haybittle-Peto rule. At the time of the interim analysis, early termination of the trial can be recommended if superiority of dapagliflozin over placebo is demonstrated for the primary composite at a one-sided alpha level of 0.001. The significance level for the final analysis will be determined by the Haybittle-Peto function based on the actual number of events and timing of the interim analysis.

Efficacy assessment – primary analysis

The primary efficacy analysis will be based on the intention-to-treat population, defined as all validly randomized patients. In the analysis of the primary composite endpoint, the treatments (dapagliflozin and placebo) will be compared using a Cox proportional hazard regression model with a factor for treatment group, stratified by the factors used at randomization (type 2 diabetes, UACR) and adjusted for baseline eGFR. In general, the analysis will use each patient's last contact as the censoring date for patients without any primary outcome event. The p-value, hazard ratio and 95% confidence interval will be reported. Kaplan Meier estimates of the cumulative incidence to the first occurrence of any event in the primary endpoint will be calculated and plotted.

Secondary and exploratory efficacy assessment

The secondary efficacy outcomes will be tested in a similar manner as the primary efficacy outcomes. If superiority is achieved for the primary efficacy outcomes, the secondary outcomes will be tested hierarchical order as follows: 1) composite renal endpoint consisting of 50% eGFR decline, ESRD, or renal death; 2) composite endpoint of CV death or hospitalization for heart failure; 3) time to death from any cause. Statistical significance is required before proceeding to test the next hypothesis in the hierarchical procedure.

Longitudinal repeated eGFR measurements from the two treatment groups will be compared using the mixed-effects maximum likelihood repeated measures (MMRM) analysis. The change in eGFR using on-treatment values will be the dependent variable. The treatment time interaction term is the parameter of interest and indicates the eGFR slope difference between dapagliflozin and placebo.

Patient-reported outcomes

Health-related quality-of-life outcomes will be recorded using the EuroQol 5 Dimensions 5 Levels (EQ-5D-5L) index score and Kidney Disease Quality of Life questionnaires assessed at baseline and every 4 months during the trial.

Study oversight

The trial is overseen by an executive committee, consisting of nine academic members and two non-voting members from the study sponsor. The executive committee designed the trial, oversees its conduct, and will supervise the analysis of the data. The sponsor is responsible for collection and analysis of the data in conjunction with the executive committee. All authors will have access to the study results. An independent data and safety monitoring committee (DMC) reviews safety data and overall study conduct throughout the trial.

Discussion

SGLT-2 inhibitors have emerged as powerful agents to reduce the incidence of renal events, as well as cardiovascular events, in patients with type 2 diabetes. Their apparent ability to slow the progressive decline in renal function over time is not completely explained by improved glycemic control, implicating other, non-glycemic pathways. These include natriuretic/osmotic diuresis, restoration of tubulo-glomerular feedback leading to glomerular afferent vasoconstriction with reduction in single nephron hyperfiltration, amelioration of renal tissue hypoxia, and attenuation of inflammation and fibrosis. [1, 7] If one or more of these mechanisms are operative, SGLT-2 inhibitors may also be beneficial in patients with CKD without diabetes. DAPA-CKD will test this hypothesis by assessing whether dapagliflozin safely reduces the risk of a composite renal and cardiovascular death endpoint in a broad spectrum of patients with CKD, with and without diabetes, who are already on optimized standard-of-care reno-protective therapy.

An important consideration in the design of DAPA-CKD was the likely efficacy and safety of dapagliflozin in patients with CKD without diabetes. Some patients without diabetes have been exposed to SGLT2 inhibitors in prior studies. Collectively, these earlier studies showed that SGLT2 inhibition induced glycosuria and led to reductions in blood pressure, body weight, and serum urate.[8, 9] With most glucose-lowering drugs, hypoglycaemia is a particular safety concern. However, the glycosuria induced by SGLT-2 inhibitors diminishes with diminishing blood glucose concentrations and filtered glucose load, which is why hypoglycaemia is not, inherently, a risk with these agents. In addition, a compensatory increase in basal hepatic glucose production following urinary glucose loss helps maintain fasting plasma glucose at euglycemic levels in individuals without diabetes.[10] Additionally, in patients with CKD, the filtered glucose load is reduced due to decreased glomerular glucose filtration. It is perhaps not surprising therefore that in a pooled analysis of

randomized controlled trials enrolling patients with type 2 diabetes and eGFR between 15 and 45 ml/min/1.73m², the occurrence of hypoglycemia was similar in the placebo and dapagliflozin treatment groups.[11]

We are collecting other specific safety data relevant to glucose-lowering therapy in general and SGLT-2 inhibitors in particular, including information on fractures, diabetic keto-acidosis, amputations, and acute kidney injury (AKI). AKI is of particular interest in DAPA-CKD because the haemodynamic actions of SGLT2 inhibitors may lead to an initial reduction in eGFR, similar to that seen with an ACEi or ARB, albeit due to a different purported haemodynamic mechanism (i.e. afferent arteriolar constriction with SGLT2 inhibitors compared to efferent arteriolar dilatation with renin-angiotensin system blockers).[12] Despite these similarities, fewer episodes of AKI were reported with SGLT-2 inhibition in the DECLARE TIMI-58, EMPAREG-OUTCOME, CANVAS, and CREDENCE programs, although these findings are based on investigator reported adverse events which did not have a specific definition and which were not adjudicated.[2-5] To properly determine the effects of dapagliflozin on AKI in patients with CKD, all potentially severe AKIs, defined as a doubling of serum creatinine compared to the last central laboratory measurement, are being adjudicated by the independent EAC. An unexpected increase in the rate of lower limb amputation was reported with canagliflozin in the CANVAS Program but not in the CREDENCE trial.[3, 5] This has not been observed with dapagliflozin in any prior study, including DECLARE TIMI-58 and DAPA-Heart Failure (DAPA-HF), and it was also not seen with empagliflozin in EMPAREG-OUTCOME.[2, 4, 13] However, it is a regulatory requirement that all amputations, and events predisposing to increased risk of an amputation, are collected in all ongoing SGLT-2 inhibitor trials, including DAPA-CKD.

From an efficacy perspective, DAPA-CKD will determine the effect of dapagliflozin on a composite renal endpoint, which has been used in previous CKD outcome trials. The most clinically meaningful component of this endpoint is ESRD, defined as initiation of dialysis for more than 28 days or renal transplantation. A sustained eGFR below 15 ml/min/1.73m² is also included in the definition of ESRD. It is considered clinically relevant given the increased risk of mortality and decreased quality of life in individuals in whom the eGFR falls below this level. A 50% eGFR decline, equivalent to an approximate 80% increase in serum creatinine, is an additional component, contrasting with some other trials which instead have variously used a doubling of serum creatinine or 40% eGFR decline as a component of a composite renal endpoint.[14] We decided not to use a 40% eGFR decline, given that dapagliflozin may cause an acute, haemodynamically-mediated, reduction in eGFR. This can potentially cause declines in eGFR of up to 40% which do not reflect true progression of CKD, diminishing the ability to differentiate between placebo and dapagliflozin and increasing the risk of a type 1 error.[15] A doubling of serum creatinine was not chosen because a 50% eGFR decline has been shown to be an equally robust measure of significant decline in renal function and may decrease the sample size and operational complexity of the trial. The primary endpoint also includes death due to renal or cardiovascular causes. All-cause mortality was not included since dapagliflozin is not expected to influence deaths unrelated to renal or cardiovascular causes.

How do DAPA-CKD participants compare to participants enrolled in other SGLT2 inhibitor trials? A minority of patients recruited into cardiovascular outcome trials of SGLT2 inhibitors had CKD defined by eGFR or UACR. CREDENCE is the only trial to date that has recruited only patients with both type 2 diabetes and CKD. In DAPA-CKD, approximately 90% of patients will have an eGFR below 60 ml/min/1.73m² and at least 80% of participants a UACR above 300 mg/g (Figure 3). Considering that both a low eGFR and high UACR are

strong risk markers for renal as well as cardiovascular events, it is expected that cardiovascular event rates in DAPA-CKD will be at least comparable to the prior SGLT2 cardiovascular outcome trials. In comparing DAPA-CKD with the two other SGLT2 renal outcome trials (CREDESCENCE and EMPA-KIDNEY), DAPA-CKD enrolled a broader population than CREDESCENCE, the latter included only patients with type 2 diabetes (Figure 4). The EMPA-KIDNEY trial, assessing the effect of empagliflozin compared to placebo, extends the inclusion criteria further and also enrolls patients with type 1 diabetes and patients with UACR <200 mg/g if their eGFR is between 20 and 45 ml/min/1.73m² (Figure 4). Overall, these three trials will help to define the optimum use of SGLT2 inhibitors in the management of CKD.

During the conduct of the DAPA-CKD trial, the results of two other large cardiovascular outcome trials with dapagliflozin, DECLARE TIMI-58 and DAPA-HF, became available. The DECLARE TIMI-58 trial reported that in patients with type 2 diabetes with predominantly preserved renal function who had, or were at risk of cardiovascular disease, dapagliflozin significantly lowered the rate of the composite endpoint heart failure or cardiovascular death by 17% and the risk of a composite endpoint of 40% eGFR decline, ESRD, and renal death by 47%. [4] The DAPA-HF trial demonstrated that in patients with heart failure and reduced ejection fraction with or without type 2 diabetes, dapagliflozin significantly reduced the risks of the composite primary outcome of heart failure or cardiovascular death. [13] These effects were remarkably consistent both in patients with and without type 2 diabetes as well as in patients with or without CKD. Moreover, the trial reported that the rate of serious renal related adverse events was significantly lower in the dapagliflozin (1.6%) compared to the placebo group (2.7%; p=0.009). These results set expectations for patients with CKD but they have to be confirmed in the DAPA-CKD study.

In summary, DAPA-CKD study is the first dedicated clinical trial to explore the potential benefits and risks of SGLT2 inhibitors in patients across multiple CKD stages both with and without diabetes who are already receiving evidence-based reno-protective therapy.

Contributors

Members of the DAPA-CKD Executive Committee:

H.J.L. Heerspink (co-chair), D.C. Wheeler (co-chair), G. Chertow, R. Correa-Rotter, T. Greene, F-F Hou, J.McMurray, P. Rossing, R. Toto, B. Stefansson, AM Langkilde.

Members of the DAPA-CKD Independent Data Monitoring Committee:

Marc A. Pfeffer (Chair; Brigham and Women's Hospital, Boston, USA). Stuart Pocock, (London School of Hygiene and Tropical Medicine, London, UK); Karl Swedberg, (University of Gothenburg , Göteborg, Sweden); Jean L. Rouleau (Montréal Heart Institute, Montreal, Québec, Canada); Nishi Chaturvedi (University College London, London, UK); Peter Ivanovich (Northwestern University, Chicago, USA); Andrew S. Levey (Tufts Medical School, Boston, USA); Heidi Christ-Schmidt (Statistics Collaborative, Washington DC, USA).

Members of the DAPA-CKD Event Adjudication Committee:

Johannes Mann (Co-chair; Friedrich Alexander University Erlangen, Erlangen, Germany); Claes Held, Professor (Co-Chair; Uppsala Clinical Research Center, Sweden); Christoph Varenhorst (Uppsala Clinical Research Center, Sweden); Pernilla Holmgren (Uppsala Clinical Research Center, Sweden); Theresa Hallberg (Uppsala Clinical Research Center, Sweden)

National Coordinators:

Argentina, Walter Douthat, Hospital Privado, Córdoba

Brazil, Roberto Pecoits Filho, Irmandade Santa Casa de Misericórdia de Curitiba (PUC-PR), Curitiba

Canada, David Cherney, The Toronto Hospital, Toronto,

China, Fan Fan Hou, Southern Medical University; National clinical research center for kidney disease; Guangzhou, China

Denmark, Frederik Persson, Steno Diabetes Center Copenhagen, Gentofte

Germany, Hermann Haller, Medizinische Hochschule Hannover, Hannover;

Hungary, István Wittmann, Pécsi Tudományegyetem, Pécs

India, Dinesh Khullar, Max Super Speciality Hospital, New Delhi

Japan, Kashihara Naoki, Kawasaki Medical School Hospital, Kurashiki

Mexico, Richardo Correa-Rotter, Inst Nac de Ciencias Médicas y Nutrición Salvador Zubiran, Tlalpan, Mexico City

Peru, Elizabeth Escudero, Hospital Nacional Arzobispo Loayza, Lima;

Philippines, Rey Isidto, Healthlink Iloilo, Inc., Iloilo City

Poland, Michal Nowicki, SPZOZ Uniwersytecki Szpital Kliniczny, Łódź

Russia, Mikhail Batiushin, Rostov State Medical University, Rostov-on-Don

South Korea, Shin-Wook Kang, Yonsei University Severance Hospital, Seoul

Spain, José Luis Górriz Teruel, Hospital Clínico Universitario de Valencia, Valencia

Sweden, Hans Furuland, Akademiska sjukhuset, Medicincentrum/Njurmedicinska, Uppsala;

Ukraine, Oleksandr Bilchenko, Kharkiv City Clinic of Urgent and Emergency Care, Kharkiv

United Kingdom, Patrick Mark, Queen Elizabeth University Hospital, Glasgow

United States, Jamie Dwyer, Vanderbilt University Medical Center
Nashville, TN, USA and Kausik Umanath, Henry Ford Hospital, Detroit;

Vietnam, Pham Van Bui, Nguyen Tri Phuong Hospital, Ho Chi Minh City.

Disclosures

HJLH is consultant for AbbVie, AstraZeneca, Boehringer Ingelheim, CSL Pharma, Gilead, Janssen, Merck, Mundi Pharma, Mitsubishi Tanabe and Retrophin. He received research support from Abbvie, AstraZeneca, Boehringer Ingelheim and Janssen.

GMC serves on the Board of Director for Satellite Healthcare. He has served as a consultant for Akebia, Amgen, Ardelyx, AstraZeneca, Baxter, Cricket, DiaMedica, Gilead, Miromatrix, Outset, Reata, Sanifit, and Vertex. He has received research support from Amgen and Janssen. He has served on DSMBs for Angion, Bayer, and Recor.

PR is consultant for AstraZeneca, Boehringer Ingelheim, Eli Lilly, Gilead, Mundi Pharma, Novo Nordisk, Bayer, Sanofi Aventis Merck Sharp and Dome (all honoraria to his institution) and research support from AstraZeneca and Novo Nordisk.

JMcM's employer, Glasgow University, has been paid by Alnylam, Amgen, AstraZeneca, Bayer, BMS, Cardurion, GSK, Novartis, and Theracos for one or more of participation in clinical trials, advisory boards or symposia (presentations).

RCR is member of DAPACKD executive committee and has consulted in clinical trials for Abbvie, and Amgen. Has served on advisory boards and received honoraria from Boehringer, Astra Zeneca and has been speaker for Astra Zeneca, Boehringer, Abbvie, Takeda, Amgen, and Janssen.

RDT is a consultant for Amgen, Astra-Zeneca, Boehringer-Ingelheim, Bayer, Quintiles, Quest Diagnostics, Relypsa, Reata, MedScape.

FFH is consultant for AbbVie and AstraZeneca. She received research support from Abbvie and AstraZeneca.

DCW has received honoraria from AstraZeneca, Amgen, Bayer, Boehringer Ingelheim, Janssen, Napp, Mundipharma, Mitsubishi Tanabe, Ono Pharma, GlaxoSmithKline and Vifor

Fresenius. PR is consultant for AstraZeneca, Boehringer Ingelheim, Eli Lilly, Gilead, Mundi Pharma, Novo Nordisk, Bayer, Sanofi Aventis Merck Sharp and Dome (all honoraria to his institution) and research support from AstraZeneca and Novo Nordisk.

BVS, ML and AML are AstraZeneca employees.

Table 1: Main inclusion and exclusion criteria of the DAPA-CKD trial

Inclusion criteria
<ul style="list-style-type: none">• ≥ 18 years of age• eGFR ≥ 25 and ≤ 75 ml/min/1.73m² at screening• UACR ≥ 200 and ≤ 5000 mg/g at screening• Stable and for the patient maximum tolerated labelled dose of an ACEi or ARB for at least 4 weeks before screening, if not medically contraindicated

Exclusion criteria
<ul style="list-style-type: none">• Type 1 diabetes mellitus• Autosomal dominant or autosomal recessive polycystic kidney disease, lupus nephritis or ANCA-associated vasculitis• Receiving cytotoxic therapy, immunosuppressive therapy or other immunotherapy for primary or secondary renal disease within 6 months prior to enrolment• New York Heart Association (NYHA) class IV Congestive Heart Failure• MI, unstable angina, stroke or TIA within 8 weeks prior to enrolment• Coronary revascularization (percutaneous coronary intervention or coronary artery bypass grafting) or valvular repair/replacement within 8 weeks prior to enrolment• Any condition outside the renal and CV study area with a life expectancy of less than 2 years based on investigator's clinical judgement• Hepatic impairment (aspartate transaminase (AST) or alanine transaminase (ALT) $>3x$ the upper limit of normal (ULN); or total bilirubin $>2x$ ULN at time of enrolment)

Table 2: Primary, Secondary, Exploratory, and Safety Endpoints of DAPA-CKD

Primary composite endpoint:

1. Time to $\geq 50\%$ eGFR decline from baseline (confirmed by ≥ 28 -day serum creatinine)
 2. Time to end-stage renal disease (ESRD) defined as eGFR < 15 mL/min/1.73 m², need for chronic dialysis (both confirmed after ≥ 28 days), renal transplantation
 3. Time to renal or cardiovascular Death
-

Secondary endpoints:

1. Time to a composite renal endpoint:
 1. $\geq 50\%$ eGFR decline from baseline (confirmed by ≥ 28 -day serum creatinine)
 2. ESRD defined as eGFR < 15 ml/min/1.73m², need for chronic dialysis or renal transplantation
 3. Renal death
 2. Time to the first occurrence of either CV death or hospitalization for heart failure
 3. Time to death from any cause
-

Exploratory endpoints include (but not limited to):

1. Time to individual components of the primary renal endpoint
 2. Time to a composite endpoint of chronic dialysis, renal transplantation, or renal death
 3. Time to the first sustained $\geq 40\%$ decline in eGFR from baseline
 4. Time to the first sustained $\geq 30\%$ decline in eGFR from baseline
 5. eGFR change over time calculated
-

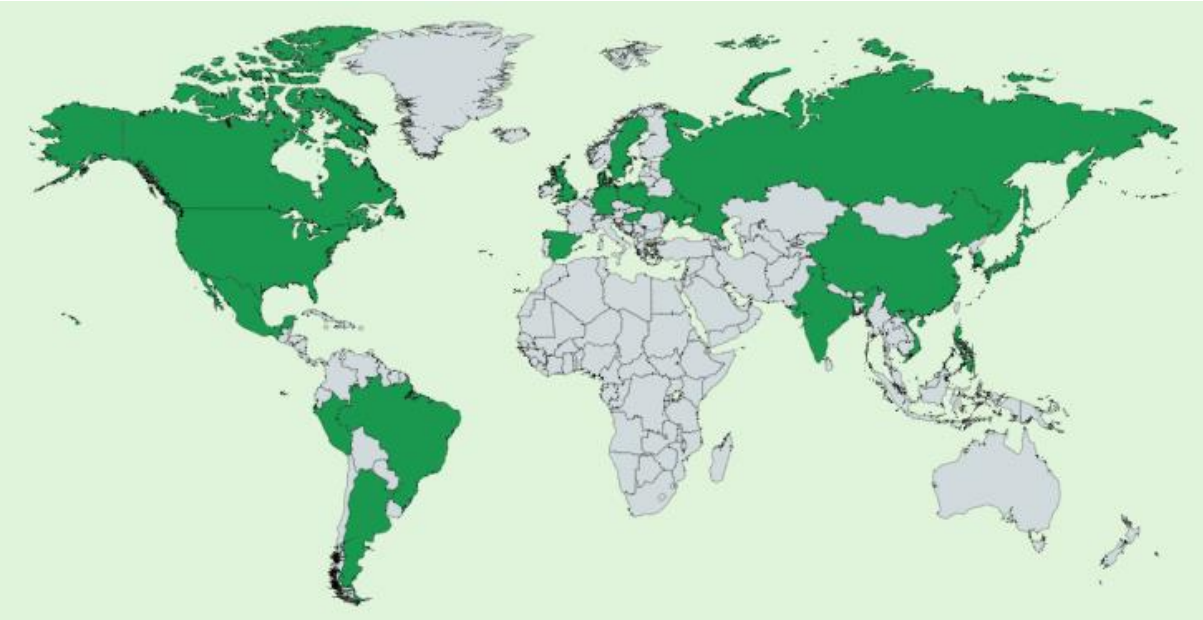
-
- a. From baseline to end of treatment
 - b. From first on treatment measurement to end of treatment
 6. Proportion of patients with eGFR > 40 ml/min/.173m² at baseline who enter CKD stage 4 during the study
 7. Change in UACR from baseline
 8. Time to the first occurrence of each of any of the following central laboratory values levels of serum potassium
 - a. > 6.0 mmol/L
 - b. > 5.5 mmol/L
 - c. < 3.5 mmol/L
 - d. < 3.0 mmol/L
 9. Time to first occurrence of doubling of serum creatinine (compared to the most recent central laboratory measurement)
 10. Proportion of patients without diabetes at baseline with a new diagnosis of type 2 diabetes during the study
 11. Changes in HbA1c from baseline
 12. Time to a composite major cardiovascular endpoint of non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death
 13. Time to the first hospitalisation for heart failure
 14. Time to the first fatal or non-fatal myocardial infarction
 15. Time to the first fatal or non-fatal stroke of any cause
 16. Change from baseline in the overall summary score of the KDQOLTM-36 and EQ-5D-5L

Safety endpoints

1. Serious adverse events
-

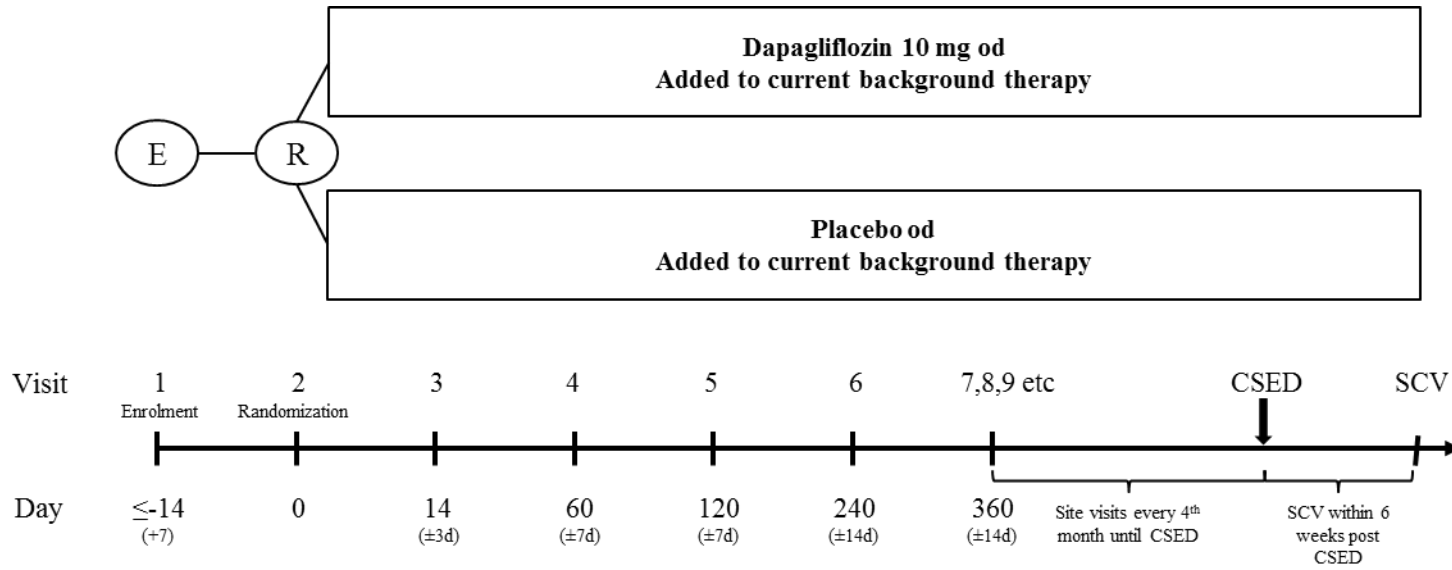
-
2. Discontinuation of investigational product due to adverse events
 3. Changes in clinical chemistry / haematology parameters
 4. Adverse events of interest (volume depletion, renal events, major hypoglycemic events, fractures, diabetic ketoacidosis, AEs leading to amputation and AEs leading to a risk for lower limb amputations)
-

Figure 1. Countries participating in DAPA-CKD.



Argentina	China	Hungary	Mexico	Poland	Spain	United Kingdom
Brazil	Denmark	India	Peru	Russia	Sweden	United States
Canada	Germany	Japan	Philippines	South Korea	Ukraine	Vietnam

Figure 2. DAPA-CKD study diagram.



CSED = Common study end date (ie, date when the predetermined number of adjudicated primary events are anticipated)

E = enrolment

SCV = Study closure visit

od = once daily

R = Randomization

Figure 3: Proportion of patients with eGFR <60 ml/min/1.73m² and UACR ≥300 mg/g in completed SGLT2 inhibitor trials compared to DAPA-CKD. Interim baseline data from DAPA-CKD (data cut September 2019) are used to create the figure.

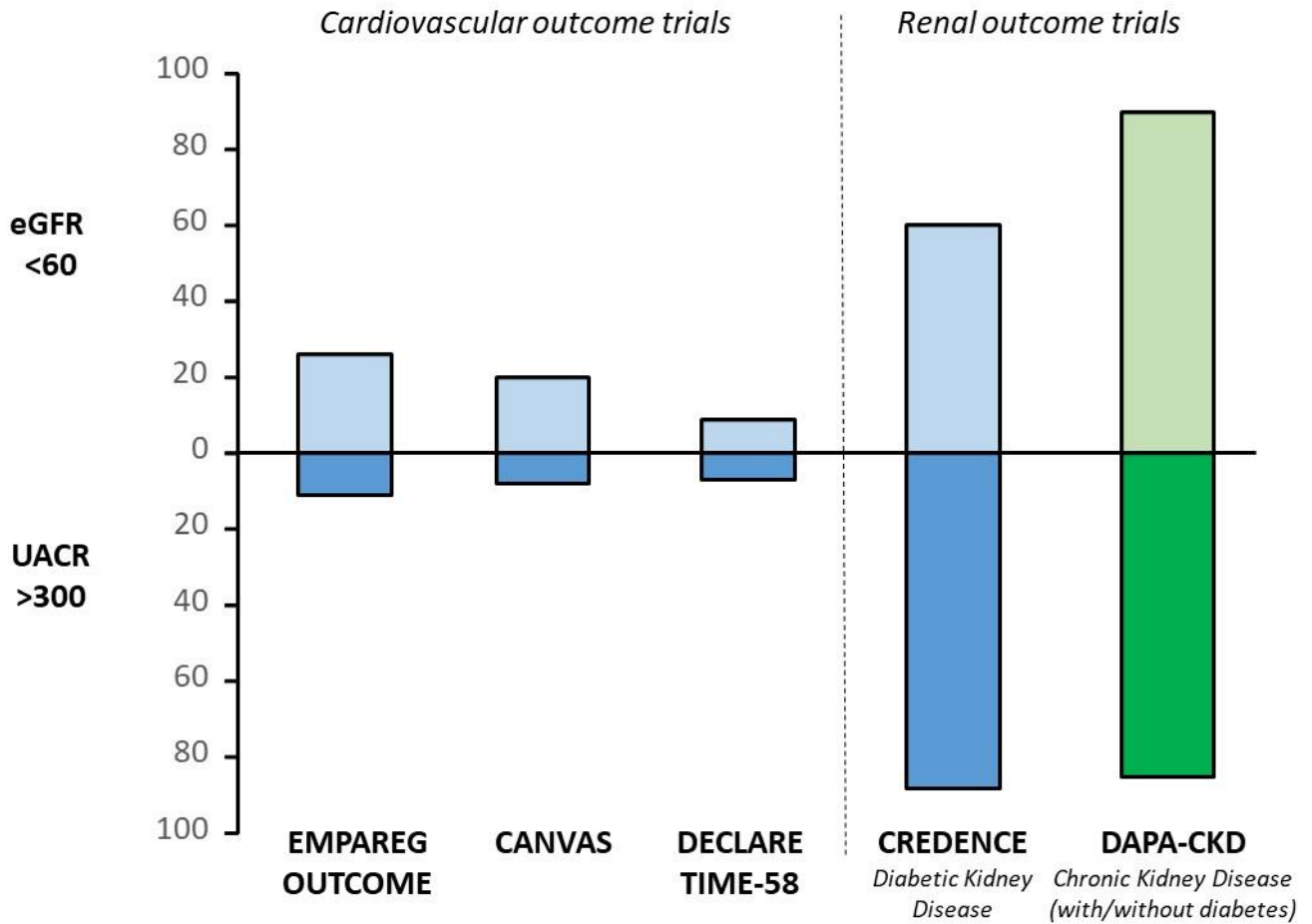
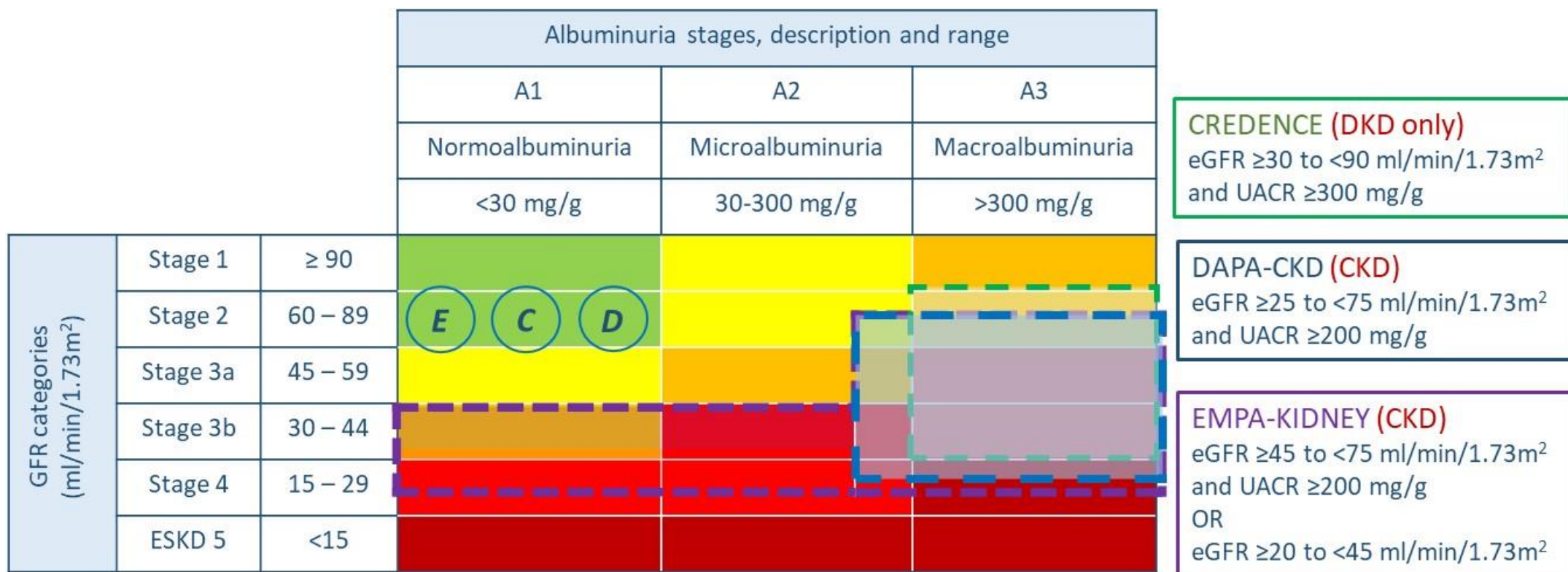


Figure 4: National Kidney Foundation Classification of Chronic Kidney Disease. The UACR and eGFR range for enrollment in the CREDENCE (green), DAPA-CKD (blue), and EMPA-KIDNEY (purple) trials are shown. Blue shaded area indicates the eGFR and UACR inclusion criteria in the DAPA-CKD trial. Cardiovascular outcome trials are indicated in the circles and positioned based on their mean eGFR and median UACR level.



E=EMPAREG-Outcome; C=CANVAS; D=DECLARE TIMI-58

References

1. Heerspink, H.J., B.A. Perkins, D. Fitchett, et al., Sodium Glucose Cotransporter 2 Inhibitors in the Treatment of Diabetes: Cardiovascular and Kidney Effects, Potential Mechanisms and Clinical Applications. *Circulation*, 2016.
2. Zinman, B., C. Wanner, J.M. Lachin, et al., Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med*, 2015. 373(22): p. 2117-28.
3. Neal, B., V. Perkovic, K.W. Mahaffey, et al., Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *N Engl J Med*, 2017. 377(7): p. 644-657.
4. Wiviott, S.D., I. Raz, M.P. Bonaca, et al., Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med*, 2019. 380(4): p. 347-357.
5. Perkovic, V., M.J. Jardine, B. Neal, et al., Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. *N Engl J Med*, 2019. 380(24): p. 2295-2306.
6. Dekkers, C.C.J., R.T. Gansevoort, and H.J.L. Heerspink, New Diabetes Therapies and Diabetic Kidney Disease Progression: the Role of SGLT-2 Inhibitors. *Curr Diab Rep*, 2018. 18(5): p. 27.
7. Rajasekeran, H., D.Z. Cherney, and J.A. Lovshin, Do effects of sodium-glucose cotransporter-2 inhibitors in patients with diabetes give insight into potential use in non-diabetic kidney disease? *Curr Opin Nephrol Hypertens*, 2017. 26(5): p. 358-367.
8. Komoroski, B., N. Vachharajani, D. Boulton, et al., Dapagliflozin, a novel SGLT2 inhibitor, induces dose-dependent glucosuria in healthy subjects. *Clin Pharmacol Ther*, 2009. 85(5): p. 520-6.
9. Lundkvist, P., C.D. Sjostrom, S. Amini, et al., Dapagliflozin once-daily and exenatide once-weekly dual therapy: A 24-week randomized, placebo-controlled, phase II study examining effects on body weight and prediabetes in obese adults without diabetes. *Diabetes Obes Metab*, 2017. 19(1): p. 49-60.
10. Al Jobori, H., G. Daniele, J. Adams, et al., Determinants of the increase in ketone concentration during SGLT2 inhibition in NGT, IFG and T2DM patients. *Diabetes Obes Metab*, 2017. 19(6): p. 809-813.
11. Dekkers, C.C.J., D.C. Wheeler, C.D. Sjostrom, et al., Effects of the sodium-glucose co-transporter 2 inhibitor dapagliflozin in patients with type 2 diabetes and Stages 3b-4 chronic kidney disease. *Nephrol Dial Transplant*, 2018.
12. Pleros, C., E. Stamataki, A. Papadaki, et al., Dapagliflozin as a cause of acute tubular necrosis with heavy consequences: a case report. *CEN Case Rep*, 2018. 7(1): p. 17-20.
13. McMurray, J., Dapagliflozin in patients with heart failure and reduced ejection fraction (DAPA-HF). *Presented at: ESC 2019. September 1, 2019. Paris, France*, 2019.
14. Perkovic, V., D. de Zeeuw, K.W. Mahaffey, et al., Canagliflozin and renal outcomes in type 2 diabetes: results from the CANVAS Program randomised clinical trials. *Lancet Diabetes Endocrinol*, 2018. 6(9): p. 691-704.
15. Greene, T., GFR decline as an alternative endpoint for kidney failure - A Simulation Study of the Validity and Utility of eGFR-Based Surrogate Time-to-Event Endpoints in Chronic Kidney Disease. *Am J Kidney Dis.*, 2014. Submitted.