



HAL
open science

Effects of Dapagliflozin on Echocardiographic Measures of Cardiac Structure and Function in Patients with Chronic Kidney Disease: The DECODE-CKD Trial

Katja Vu Bartholdy, Niklas Dyrby Johansen, Nino Landler, Kristoffer Grundtvig Skaarup, Jesper Jensen, Iain Bressendorff, Morten Schou, Jacob Christensen, Bo Feldt-Rasmussen, Muthiah Vaduganathan, et al.

► To cite this version:

Katja Vu Bartholdy, Niklas Dyrby Johansen, Nino Landler, Kristoffer Grundtvig Skaarup, Jesper Jensen, et al.. Effects of Dapagliflozin on Echocardiographic Measures of Cardiac Structure and Function in Patients with Chronic Kidney Disease: The DECODE-CKD Trial. *Kidney360*, 2023, 4 (2), pp.143-149. 10.34067/KID.0006982022 . hal-04025795

HAL Id: hal-04025795

<https://hal.univ-lorraine.fr/hal-04025795>

Submitted on 13 Mar 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution 4.0 International License

Effects of Dapagliflozin on Echocardiographic Measures of Cardiac Structure and Function in Patients with Chronic Kidney Disease: The DECODE-CKD Trial

Katja Vu Bartholdy,¹ Niklas Dyrby Johansen,¹ Nino Landler,¹ Kristoffer Grundtvig Skaarup,¹ Jesper Jensen,¹ Iain Bressendorff,² Morten Schou,^{1,3} Jacob Christensen,¹ Bo Feldt-Rasmussen,^{3,4} Muthiah Vaduganathan,⁵ Scott Solomon,⁵ Richard Haynes,⁶ Frederik Persson,⁷ Peter Rossing,^{3,7} Lars Køber,^{3,8} Faiez Zannad,⁹ Ditte Hansen,^{2,3} and Tor Biering-Sørensen¹

Key Points

- SGLT2 inhibitors (SGLT2i) exert cardioprotective effects in patients with CKD through unknown mechanisms.
- DECODE-CKD is the first randomized controlled trial (RCT) to evaluate the effects of SGLT2i on cardiac structure and function in patients with CKD.

Abstract

Background SGLT2 inhibitors, originally developed as glucose-lowering agents for treatment of type 2 diabetes, have been shown to have cardio- and kidney-protective effects among CKD patients with and without diabetes. However, the mechanisms remain largely unknown.

Methods Dapagliflozin on Echocardiographic Measures of Cardiac Structure and Function in Patients with Chronic Kidney Disease (DECODE-CKD) is an investigator-initiated, prospective, single-center, randomized, placebo-controlled trial evaluating the effects of 6 months of treatment with 10 mg of dapagliflozin compared with placebo on cardiac structure and function in 222 adults with CKD.

Results The primary objective was to assess whether dapagliflozin improves left ventricular mass index. Secondary and exploratory end points include changes in cardiac and kidney markers, quality of life, depressive symptoms, and cognitive function.

Conclusions This is the first study to address the effects of SGLT2 inhibitors on cardiac structure and function in patients with CKD. The results will provide valuable insights into the mechanisms underlying the cardioprotective benefits of SGLT2 inhibitors in patients with CKD.

Clinical Trial registry name and registration number NCT05359263

KIDNEY360 4: 143–149, 2023. doi: <https://doi.org/10.34067/KID.0006982022>

Introduction

CKD is a global health concern, affecting nearly 700 million persons worldwide.¹ According to the World Health Organization, CKD accounts for 12.2 deaths per 100,000 people, and the death rate from CKD is estimated to continue to increase.² Furthermore, CKD is associated with substantial morbidity and has been recognized as an important risk factor for cardiovascular disease (CVD).³ Individuals with CKD are likely to die due to cardiac disease before they reach

ESKD.³ Strategies to prevent kidney disease onset and progression are of importance to reduce the clinical and financial burden of CKD. The current standard of care of CKD is inhibition of the renin angiotensin system (RAS) to reduce albuminuria and slow progression to ESKD and treatments that lower blood pressure and low-density lipoprotein cholesterol to reduce cardiovascular risk. However, a considerable risk of ESKD and CVD remains. Originally developed as glucose-lowering agents, large clinical outcome trials on the SGLT2 inhibitors have

¹Department of Cardiology, Copenhagen University Hospital—Herlev and Gentofte, Copenhagen, Denmark

²Department of Nephrology, Copenhagen University Hospital—Herlev and Gentofte, Copenhagen, Denmark

³Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

⁴Department of Nephrology, Copenhagen University Hospital—Rigshospitalet, Copenhagen, Denmark

⁵Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts

⁶MRC Population Health Research Unit, Nuffield Department of Population Health, University of Oxford, Oxford, United Kingdom

⁷Steno Diabetes Center Copenhagen—Copenhagen University Hospital, Herlev, Denmark

⁸Department of Cardiology, Copenhagen University Hospital—Rigshospitalet, Copenhagen, Denmark

⁹Université de Lorraine, Inserm, Center d'Investigations Cliniques—Plurithématique 14-33, and Inserm U1116, CHRU, F-CRIN INI-CRCT (Cardiovascular and Renal Clinical Trialists), Nancy, France

Correspondence: Dr. Tor Biering-Sørensen, Center for Translational Cardiology and Pragmatic Randomized Trials, Cardiovascular Non-Invasive Imaging Research Laboratory, Department of Cardiology, Gentofte Hospital, Gentofte Hospitalsvej 8, 3th, 2900 Hellerup, Denmark. Email: tor.biering@gmail.com

demonstrated favorable effects on cardiovascular outcomes in people with type 2 diabetes (T2DM), regardless of CVD history at baseline⁴⁻⁶. Similar effects on important cardiovascular outcomes were later extended to people with heart failure (HF), regardless of the presence or absence of diabetes.⁷

Recently, the Dapagliflozin on Echocardiographic Measures of Cardiac Structure and Function in Patients with Chronic Kidney Disease (DAPA-CKD) trial showed that persons with CKD and albuminuria who received dapagliflozin had a significantly lower risk of a composite outcome of a sustained decline in the eGFR of at least 50%, ESKD, or death from kidney disease or cardiovascular causes than those who received placebo, independent of the presence or absence of T2DM and history of HF.⁸ The EMPA-KIDNEY trial (which is assessing empagliflozin in a broader population with CKD using a similar primary outcome) has also been stopped at its prespecified formal interim analysis for efficacy.

SGLT2 inhibitors act to reduce glucose reabsorption in the proximal tubules of the kidney, thereby enhancing urinary glucose excretion and conferring antihyperglycemic effects that are predominantly independent of insulin.⁹ In CKD, SGLT2 inhibitors have limited effect on hemoglobin A1c (HbA1c) when eGFR is reduced,¹⁰ suggesting that the effect of SGLT2 inhibitors is potentially mediated by glucose-independent pathways. The mechanism by which SGLT2 inhibitors reduce cardiovascular outcomes may involve natriuresis, reduction in interstitial edema, reduced preload and afterload, stabilized kidney function and cardiorenal physiology, inhibition of cardiac sodium-hydrogen exchange, and improved cardiac bioenergetics.¹¹ One potential mechanism for the cardiovascular effects of treatment of dapagliflozin in patients with CKD may be the mechanisms leading to regression of left ventricular (LV) hypertrophy, a strong predictor for cardiovascular mortality, through a combined effect of glycemia/insulin resistance, reduced preload and afterload, and weight loss.

Treatment with SGLT2 inhibitors has been found to reduce LV volumes¹²⁻¹⁴ and LV mass¹⁴⁻¹⁹, and improve diastolic function¹⁹⁻²¹ in people with T2DM as well as in patients with HF with reduced ejection fraction (HFrEF). The effect of SGLT2 inhibitors on cardiac remodeling in patients with CKD has not yet been studied in depth. Among CKD patients with or without T2DM, we hypothesize that SGLT2 inhibitors induce reverse cardiac remodeling by improvements in LV mass index. The results will provide further insight into the mechanism of this promising drug in patients with CKD and potentially guide treatment in the future.

Methods

Study Design

The study is an investigator-initiated, single-center, double-blind, parallel-group, randomized controlled trial conducted at the Cardiovascular Non-Invasive Imaging Research Laboratory, Gentofte Hospital, Denmark designed to evaluate the effect of 6-month treatment with dapagliflozin on cardiac structure and function compared with placebo. The study follow-up duration is 180 days (Figure 1).

Study Population

The trial participants are adults with CKD with an eGFR between ≥ 20 and < 60 mL/minute per 1.73 m^2 or between ≥ 60 and < 90 mL/minute per 1.73 m^2 with urinary albumin:

creatinine ratio ≥ 200 mg/g or protein:creatinine ratio ≥ 300 mg/g. Additional inclusion and exclusion criteria are listed in Table 1. We will mainly recruit from an existing outpatient research cohort. Patients will also be recruited through general practitioners, International Classification of Diseases (ICD) codes, and laboratory values from the Danish Registries if deemed necessary.

Screening and Randomization

Participants will be invited to a screening visit where informed consent will be obtained and eligibility assessed according to inclusion and exclusion criteria. Eligible participants will be randomly assigned 1:1 to dapagliflozin 10 mg/day or matched placebo at the following randomization visit. Randomization will be performed through a computer-generated randomization schedule, concealed to investigators and participants. A stratified randomization scheme in blocks of two, four, and six was designed to ensure a balanced ratio of dapagliflozin and matching placebo. The stratification factors are baseline eGFR ($<$ or ≥ 40 mL/minute per 1.73 m^2) and the presence of T2DM (on the basis of either diagnosis or HbA_{1c} of $\geq 6.5\%$ (48 mmol/mol [6.5%]) at screening). Enrollment is closely monitored to ensure that a minimum of 30% of the patients are recruited to either the subpopulation with or without T2DM.

Participants will be randomized using REDCap's integrated randomization tool be necessary.

During the randomization visit, echocardiography, pulse wave velocity and analysis, blood and urine samples, and questionnaires will be obtained for each participant.

Schedule of Enrollment, Interventions, and Assessments

After the randomization visit (day 0), patients will be asked to return to the trial site on day 14–21 and at the end of study visit (6 months+6 weeks).

After randomization, an in-person visit is scheduled after 14–21 days to draw blood and urine samples and to encourage compliance. A telephone contact will be performed after 3 months to assess and follow-up on adverse events (AEs), concomitant medication, and study drug compliance. The study end visit takes place after 6 months, where participants will return to repeat baseline assessments and AE ascertainment.

Unscheduled visits may be performed if deemed appropriate by the investigator.

The full assessment schedule is outlined in Table 2.

Concomitant Medications

Patients should receive standard drug therapy, in accordance with Danish Society of Nephrology's guidelines, except SGLT2 inhibitors. For all other comorbidities, patients are treated according to the Danish standard of care.

Results

Primary Objective

The primary objective of DECODE-CKD is to determine whether treatment with dapagliflozin compared with placebo reduces LV mass index measured by echocardiography.

Secondary and Exploratory End Points

Secondary and exploratory end points will be analyzed as between-group differences in the change of the given end

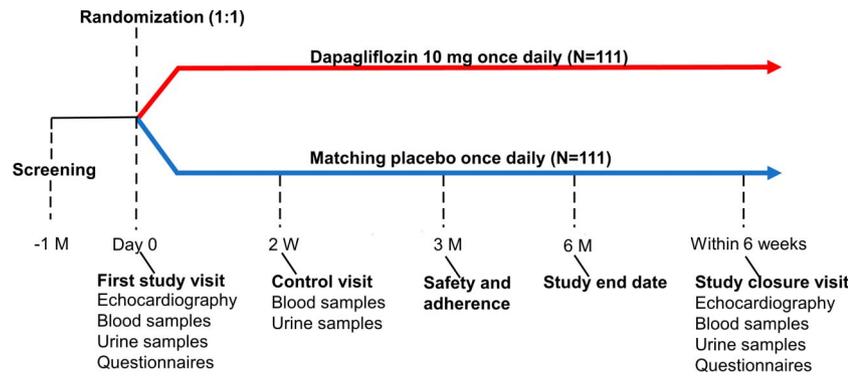


Figure 1. DECODE-CKD study diagram.

point from baseline to 6 months. Secondary end points include kidney function assessed by measuring eGFR using creatinine- and cystatin C-based CKD epidemiology collaboration equations, serum neutrophil gelatinase-associated lipocalin, cystatin C, erythrocyte and reticulocyte count, serum iron, transferrin, ferritin, erythropoietin concentration, insulin growth factor binding protein 7, uric acid, and urine albumin-to-creatinine ratio; cardiac biomarkers assessed by measuring N-terminal pro brain natriuretic peptide, high

sensitivity cardiac troponin I, growth differentiation factor 15, soluble suppression of tumorigenesis-2; cardiac systolic and diastolic function including LV global longitudinal strain and LV ejection fraction assessed by transthoracic echocardiography (TTE); diastolic function measured by electrocardiogram technology; arterial stiffness assessed by pulse wave velocity and pulse wave analysis; inflammatory biomarkers assessed by measuring high sensitivity c-reactive protein, TNF- α ; and glucose metabolism assessed by measuring HbA_{1c}.

Table 1. Inclusion and exclusion criteria

Inclusion criteria

Signed informed consent

≥18 yr of age

Chronic kidney disease (CKD), defined as evidence of decreased eGFR (eGFR ≥ 20 and < 60 mL/minute per 1.73 m^2) or between eGFR ≥ 60 and < 90 mL/minute per 1.73 m^2 with urinary albumin:creatinine ratio ≥ 200 mg/g or protein:creatinine ratio ≥ 300 mg/g At least 3 mo before and at the time of screening optimal and stable medical therapy as defined by the clinician

For patients with T2DM

Stable antihyperglycemic treatment >30 d before screening

Female patients should either not be of childbearing potential, defined as postmenopausal for at least 1 yr or surgically sterile, or is of childbearing potential and practicing one of the following methods of contraception throughout the study and for 30 days after study completion: hormonal contraception (oral contraceptives, contraceptive implant, injectable birth control, contraceptive patch, or vaginal ring) or intrauterine device

Ability to understand and read Danish

Exclusion criteria

Type 1 diabetes

For patients with T2DM

History of diabetic ketoacidosis

Patients undergoing dialysis

History of organ transplant

Treatment with SGLT2 inhibitor within 8 wk before enrollment

Known allergy or hypersensitivity to SGLT2 inhibitors or placebo ingredients

Myocardial infarction, unstable angina, stroke, or transient ischemic attack within 12 wk of enrollment

Coronary revascularization (percutaneous coronary intervention or coronary artery bypass grafting) or valvular repair/replacement within 12 wks before enrollment

Any condition outside the renal and cardiovascular study area with a life expectancy of < 2 yr on the basis of investigator's clinical judgment

Hepatic impairment (aspartate transaminase or alanine transaminase > 3 times the ULN or total bilirubin > 2 times the ULN at the time of enrollment)

Known blood-borne diseases, such as Hepatitis A, B, C, D, and E and hHIV types 1 and 2, ebola, and lassa fever virus

Female patients who are pregnant, lactating, or are considering becoming pregnant during the study or for 6 mo after study completion

Participation in another clinical study with an IP within the last month before enrollment

Inability to understand or comply with the IP, procedures, and/or follow-up or any conditions that may prevent the participant to complete the study

T2DM, type 2 diabetes; ULN, upper limit of normal; IP, investigational product.

Table 2. Assessment schedule

	Screening	Visit 1 Randomization and Baseline Examinations	Visit 2 Blood Sample Control	Phone Control	Visit 3 End of Study and Follow-Up Examinations
Time (d)	-30/-7	0	14+10	90±10	180±10
General					
Informed consent	✓	(✓)			
Inclusion and exclusion criteria	✓	✓			
Demographics	✓	✓			
Medical and surgical history	✓	✓			
General physical examination		✓			✓
Height and weight		✓			✓
Vital signs		✓			✓
12-ECG		✓			✓
Screening blood samples	✓	✓	✓		✓
End points					
TTE		✓			✓
Blood samples		✓	✓		✓
Spot urine sample	✓	✓	✓		✓
24 h urine sample		✓			✓
Pulse wave velocity		✓			✓
QoL		✓			✓
MoCA		✓			✓
HADS		✓			✓
Safety					
AEs and SAEs		✓	✓	✓	✓
Blood samples (safety)			✓		
Medication					
Concomitant (adherence)		✓		✓	✓
IP (Adherence)			✓	✓	✓

12-ECG, 12-lead electrocardiogram; TTE, transthoracic echocardiography; QoL, quality of life; MoCA, montreal cognitive assessment; HADS, hospital anxiety and depression scale; AEs, adverse events; SAEs, severe AEs; IP, investigational product.

Exploratory outcomes include health-related quality of life (QoL) measured by Kidney Disease QoL,²² cognitive impairment measured by the Montreal Cognitive Assessment,²³ and depressive symptoms measured by Hospital Anxiety and Depression Scale.²⁴

Statistical Considerations

The power calculation of the primary end point, LV mass index, is based on a previous study¹⁷ that found a significant ($P < 0.001$) reduction of 8 g/m² in LV mass index measured by TTE 6 months after administration of dapagliflozin (75.0 g/m² [IQR 61.7–92.0] to 67.0 g/m² [IQR 55.0–81.9]) in a population with T2DM and HF). Assuming a standard deviation of the change in LV mass index of 20 g/m² in both the treatment and control group,²⁵ the trial will have 80% power to detect a treatment effect of 8 g/m² with the recruitment of 222 patients (111 patients in each group), when accounting for a dropout rate of 10%.

Analyses of the primary and secondary end points will be performed on the full analysis set according to the intention-to-treat principle. In case of missing data, imputation will be performed.

The change in LV mass index will be analyzed using analysis of covariance (ANCOVA), with treatment group

as fixed effect and the baseline value as covariate. All comparisons will be two-sided with $P < 0.05$ considered statistically significant.

Prespecified subgroup analyses will be performed on the primary outcome using ANCOVA (covariates: baseline age (<65 or ≥65 years), baseline HbA_{1c} (<8 or ≥8%), baseline kidney function (eGFR <40 or ≥40 mL/minute per 1.73 m²), and baseline body weight (<60, ≥60 kg) and presence and absence of HF at baseline. Furthermore, exploratory analyses will be performed on the primary outcome in subgroups on the basis of blood pressure, albuminuria, heart rate, metabolic syndrome, and cardiovascular risk factors.

The final statistical analysis plan will be developed by the sponsor, the principal investigator, and a biostatistician before the completion of patient recruitment and database locking.

All statistical analysis will be performed using STATA version 14.0.

Safety

No safety end points are defined for this trial. AEs will be collected from the time of obtained informed consent until a period of 4 days after the last dose of trial medication. The severity and relationship to the drug will be assessed. All suspected unexpected serious adverse reactions will be

Table 3. Previous studies on SGLT2-inhibitors and left ventricular function

Author	SGLT2 Inhibitor	Cohort	Imaging Modality	Imaging Findings
Verma <i>et al.</i> ¹⁸ (2016)	Empagliflozin	Ten adults with T2DM and CVD	TTE at baseline and 3 mo after	Improved LV diastolic function according to early lateral annular tissue Doppler velocity Reduced LV mass index No difference in LV volumes and LVEF
Cohen <i>et al.</i> ¹³ (2019)	Empagliflozin	25 adults with T2DM (17 drug and 8 placebo)	Cardiac MRI at baseline and 6 mo after	Reduced LV end-diastolic volume No difference in LV mass, LVEF, atrial volumes, and markers of cardiac fibrosis
Matsutani <i>et al.</i> ¹⁹ (2018)	Canagliflozin	37 adults with T2DM and \geq CVD risk factors or CVD	TTE at baseline and 3 mo after	Improved diastolic function according to E/e' ratio Reduced LV mass index No difference in LV diameters, LVEF, and left atrial diameter
Soga <i>et al.</i> ¹⁷ (2018)	Dapagliflozin	53 adults with T2DM and stable HFrEF or HFpEF	TTE at baseline and 6 mo after	Improved diastolic function according to the E/e' ratio Reduced LV mass index and left atrial volume index No difference in LV volumes Improved LVEF
Verma <i>et al.</i> ¹⁶ (2019)	Empagliflozin versus placebo	97 adults with T2DM and CAD (49 drug and 48 placebo) without severe HF	Cardiac MRI at baseline and 6 mo after	Improved LV mass index No difference in LVEF and LV end-systolic volume No effect on RV mass index and RV volumes
Brown <i>et al.</i> ¹⁵ (2020)	Dapagliflozin	66 normotensive adults without HF with T2DM and evidence of echocardiographic LVH (32 drug and 34 placebo)	Cardiac MRI at baseline and 12 mo after	Reduced LV mass Reduced LV mass indexed to height
Eickhoff MK <i>et al.</i> ²¹ (2020)	Dapagliflozin	36 adults with T2DM and albuminuria	TTE at baseline and 12 wk after	Increased diastolic function of 19.8% using computed averages of e', E/e', atrial volume, and pulmonary artery pressure
Singh <i>et al.</i> ²⁶ (2020)	Dapagliflozin	56 adults with T2DM and HFrEF (NYHA I-III) with LVEF <45%	Cardiac MRI at baseline and 12 mo after	No difference in LV volumes, LVEF, or LV mass
Lee <i>et al.</i> ¹² (2021)	Empagliflozin	105 adults with HFrEF (NYHA II-IV) with LVEF \leq 40 and T2DM or prediabetes (52 drug and 53 placebo)	Cardiac MRI at baseline and 36 wk after	Reduced LV volumes No changes in LVEF, LV GLS, and LV mass index
Santos-Gallego <i>et al.</i> ¹⁴ (2021)	Empagliflozin	84 adults with HFrEF (NYHA II-III) with LVEF <50 (42 drug and 42 placebo)	Cardiac MRI at baseline and 6 mo after	Reduced LV mass Reduced LV volumes Improvement in LVEF

T2DM, type 2 diabetes; CVD, cardiovascular disease; TTE, transthoracic echocardiography; LV, left ventricular; LVEF, LV ejection fraction; CAD, coronary artery disease; GLS, global longitudinal strain; MRI, magnetic resonance imaging; E/e' ratio, ratio of the peak early mitral inflow velocity over the early diastolic mitral annular velocity; LVH, LV hypertrophy; HF, heart failure; HFpEF, HF with preserved ejection fraction; HFrEF, HF with reduced ejection fraction; NYHA, New York Heart Association Classification of Heart Failure.

reported to the Danish Medicines Agency and the National Committee on Health Research Ethics. Patients with AE or other safety reasons that contraindicate further treatment with the investigational product will be discontinued.

Ethical Statement

The study will be carried out in compliance with the principles of the Declaration of Helsinki and monitored according to the International Conference on Harmonization

guidelines for Good Clinical Practice. The study has been approved by the regional research committee (H-21014848), The Danish Medicines Agency (2021-121907), and the data authority in the Capital Region of Denmark (P-2022-19). The study is registered in the European Union Clinical Trials Register (EudraCT no. 2021-000995-13) and on ClinicalTrials.gov (NCT05359263).

Discussion

The global burden of CKD continues to increase with the rising prevalence of hypertension and T2DM, two of the leading causes of CKD. Until recently, pharmacological management of CKD has mainly focused on RAS blockade and lowering of blood pressure to reduce the risk of CVD.

SGLT2 inhibitors are a very effective group of drugs for treating CKD, as they are antihypertensive, cardioprotective, and kidney protective. Many hypotheses regarding the cardioprotective effects of SGLT2 inhibitors in people with CKD have been proposed; however, the underlying mechanisms of these benefits remain unclear.

In diabetic populations, studies using TTE have demonstrated reduction in LV mass index^{17–19} and improvements in diastolic function^{17–20} after only 3–6 months of therapy. However, these studies are limited by a relatively small sample size and the absence of a randomized, controlled protocol. Studies using a randomized, control design have used cardiac magnetic resonance imaging with somewhat inconsistent results regarding the effect on LV structure and function. Although most studies found a reduction in LV mass or improvement of LV mass index,^{13–15} other studies failed to show a significant reduction in LV mass.^{12,13} The heterogeneity of the population, different treatment durations, and small sample sizes may explain inconsistencies in the existing evidence. The previous studies are summarized in Table 3.

Although the previously mentioned mechanistic studies were conducted in populations with HFrEF and T2DM, no studies have examined the effect of SGLT2 inhibitors on cardiac structure and function among patients with CKD with and without diabetes. The regression in LV mass in other HFrEF and T2DM populations suggests that reverse modeling initiated by treatment with SGLT2 inhibitors may partly contribute to the cardioprotective effects. Understanding the mechanistic benefit of novel drugs in general is crucial to guide treatment among clinicians in the future.

In conclusion, DECODE-CKD is the first randomized, clinical trial to evaluate the effect of an SGLT2 inhibitor on cardiac structure and function among patients with CKD with and without diabetes. The results will be particularly important as an increasing number of patients with CKD are expected to be prescribed an SGLT2 inhibitor in the near future.

Disclosures

K.V. Bartholdy reports the following: Research Funding: Danish Cardiovascular Academy and Novo Nordisk Foundation. T. Biering-Sørensen reports the following: Research Funding: AstraZeneca, GE Healthcare, Novo Nordisk, and Sanofi Pasteur; Honoraria: Bayer, GSK, Novartis, and Sanofi Pasteur; and Advisory or Leadership Role: Amgen, GSK, and Sanofi Pasteur. I. Bressendorff reports the following: Research Funding: Novo Nordisk Foundation;

and Speakers Bureau: Bayer AG. J. Christensen reports the following: Research Funding: Novo Nordisk Fonden. D. Hansen reports the following: Research Funding: AstraZeneca A/S, Bayer A/S, Boehringer Ingelheim, Gedeon Richter, Kappa Bioscience AS, and Vifor Pharma; Advisory or Leadership Role: Pharmacosmos; and Speakers Bureau: AstraZeneca A/S and UCB Nordic. R. Haynes reports the following: Research Funding: Boehringer-Ingelheim and Novartis. J. Jensen reports the following: Honoraria: Boehringer Ingelheim; Advisory or Leadership Role: AstraZeneca, Boehringer Ingelheim; and Other Interests or Relationships: The CARDIOHGH Foundation and The Danish Heart Foundation. L. Køber reports the following: Honoraria: Speakers honorarium from AstraZeneca, Bayer, Boehringer, and Novartis. F. Persson reports the following: Consultancy: Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Novo Nordisk, and Sanofi; Research Funding: Amgen, AstraZeneca, Boehringer Ingelheim, and Novo Nordisk; and Honoraria: Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Novo Nordisk, and Sanofi. P. Rossing reports the following: Research Funding: AstraZeneca, Bayer, and Novo Nordisk; Honoraria: all honoraria to institution, AstraZeneca, Boehringer Ingelheim, and Novo Nordisk; and Advisory or Leadership Role: Astellas, AstraZeneca, Bayer, MSD Gilead all honoraria to institution, and Novo nordisk. M. Schou reports the following: Speakers Bureau: lecture fees from AstraZeneca, Boehringer, Novartis, and Novo. K.G. Skaarup reports the following: Advisory or Leadership Role: Sanofi Pasteur. S. Solomon reports the following: Consultancy: Abbott, Action, Akros, Alnylam, American Regent, Amgen, Anacardio, Arena, AstraZeneca, Bayer, Boehringer-Ingelheim, BMS, Cardiac Dimensions, Cardior, Cardurion, CellProThera, Corvia, Cytokinetics, Daiichi-Sankyo, Dinaqor, GSK, Janssen, Lexicon, Lilly, Merck, Moderna, Myokardia, Novartis, Puretech Health, Quantum Genomics, Roche, Sanofi-Pasteur, Sarepta, Tenaya, Theracos, and Tremear; Research Funding: Actelion, Alnylam, Amgen, AstraZeneca, Bayer, Bellerophon, BMS, Celladon, Cytokinetics, Eidos, Gilead, GSK, Ionis, Lilly, Mesoblast, Myokardia, Neurotronik, NIH/NHLBI, Novartis, NovoNordisk, Respicardia, Sanofi Pasteur, Theracos, and US2.AI; and Advisory or Leadership Role: *Braunwald's Heart Disease* (Editor), Cardurion (scientific advisory board), Dinaqor (scientific advisory board), and *European Journal of Heart Failure* (Editor). M. Vaduganathan reports the following: Consultancy: American Regent, Amgen, AstraZeneca, Baxter Healthcare, Bayer AG, Boehringer Ingelheim, Chiesi, Cytokinetics, Lexicon Pharmaceuticals, Novartis, Novo Nordisk, Pharmacosmos, Relypsa, Roche Diagnostics, Sanofi, and Tricog Health; Research Funding: American Regent, Amgen, AstraZeneca, Bayer AG, Boehringer Ingelheim, Galmed, Impulse Dynamics, Novartis, Occlutech, Roche Diagnostics; and Speakers Bureau: AstraZeneca, Novartis, Roche Diagnostics. F. Zannad reports the following: Ownership Interest: Cardiorenal and CVCT; Honoraria: Actelion, Amgen, applied therapeutics, AstraZeneca, Bayer, Boehringer, cardior, cellprothera, cereneo, Corvidia, CVRx, Janssen Boston-Scientific Novartis, Novo Nordisk, owkin, and Vifor-Fresenius; and Speakers Bureau: Boehringer Ingelheim.

Funding

This work was supported by a research grant from the Danish Cardiovascular Academy, which is funded by the Novo Nordisk Foundation and The Danish Heart Foundation (NNF20SA0067242), and a grant from Novo Nordisk Foundation (NNF21OC006824).

Author Contributions

K.V. Bartholdy, T. Biering-Sørensen, N.D. Johansen, and D. Hansen conceptualized the study; K.V. Bartholdy and T. Biering-

Sørensen were responsible for formal analysis; K.V. Bartholdy, T. Biering-Sørensen, and B. Feldt-Rasmussen were responsible for funding acquisition; K.V. Bartholdy, T. Biering-Sørensen, D. Hansen, N.D. Johansen, N. Landler, F. Persson, and K.G. Skaarup were responsible for investigation; K.V. Bartholdy, T. Biering-Sørensen, D. Hansen, R. Haynes, N.D. Johansen, N. Landler, and F. Persson were responsible for methodology; K.V. Bartholdy, T. Biering-Sørensen, D. Hansen, N.D. Johansen, N. Landler, and K.G. Skaarup were responsible for project administration; K.V. Bartholdy, T. Biering-Sørensen, D. Hansen, N.D. Johansen, N. Landler, and K.G. Skaarup were responsible for resources; K.V. Bartholdy, T. Biering-Sørensen, B. Feldt-Rasmussen, D. Hansen, R. Haynes, and F. Persson provided supervision; T. Biering-Sørensen was responsible for data curation; T. Biering-Sørensen was responsible for software; T. Biering-Sørensen was responsible for validation; T. Biering-Sørensen was responsible for visualization; K.V. Bartholdy wrote the original draft; and K.V. Bartholdy, T. Biering-Sørensen, I. Bressendorff, J. Christensen, B. Feldt-Rasmussen, D. Hansen, R. Haynes, J. Jensen, N.D. Johansen, L. Køber, N. Landler, F. Persson, P. Rossing, M. Schou, K.G. Skaarup, S. Solomon, M. Vaduganathan, and F. Zannad reviewed and edited the manuscript.

Data Sharing Statement

All data are included in the manuscript and/or supporting information.

References

- GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2018; 392(10159):1789-1858. doi:10.1016/S0140-6736(18)32279-7
- Webster AC, Nagler EV, Morton RL, Masson P. Chronic kidney disease. *Lancet*. 2017;389(10075):1238-1252. doi:10.1016/S0140-6736(16)32064-5
- Sarnak MJ, Levey AS, Schoolwerth AC, et al. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American heart association councils on kidney in cardiovascular disease, high blood pressure research, clinical cardiology, and epidemiology and prevention. *Circulation*. 2003; 108(17):2154-2169. doi:10.1161/01.cir.0000095676.90936.80
- Wanner C, Inzucchi SE, Lachin JM, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. *N Engl J Med*. 2016;375(4):323-334. doi:10.1056/nejmoa1515920
- Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med*. 2017;377(7):644-657. doi:10.1056/nejmoa1611925
- Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2019; 380(4):347-357. doi:10.1056/nejmoa1812389
- McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2019;381(21):1995-2008. doi:10.1056/nejmoa1911303
- Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med*. 2020;383(15):1436-1446. doi:10.1056/nejmoa2024816
- Gallo LA, Wright EM, Vallon V. Probing SGLT2 as a therapeutic target for diabetes: basic physiology and consequences. *Diab Vasc Dis Res*. 2015;12(2):78-89. doi:10.1177/1479164114561992
- Petrykiv S, Sjöström CD, Greasley PJ, Xu J, Persson F, Heerspink HJ. Differential effects of dapagliflozin on cardiovascular risk factors at varying degrees of renal function. *Clin J Am Soc Nephrol*. 2017;12(5):751-759. doi:10.2215/CJN.10180916
- Verma S, McMurray JJV. SGLT2 inhibitors and mechanisms of cardiovascular benefit: a state-of-the-art review. *Diabetologia*. 2018;61(10):2108-2117. doi:10.1007/s00125-018-4670-7
- Lee MMY, Brooksbank KJM, Wetherall K, et al. Effect of empagliflozin on left ventricular volumes in patients with type 2 diabetes, or prediabetes, and heart failure with reduced ejection fraction (SUGAR-DM-HF). *Circulation*. 2021;143(6):516-525. doi:10.1161/CIRCULATIONAHA.120.052186
- Cohen ND, Gutman SJ, Briganti EM, Taylor AJ. Effects of empagliflozin treatment on cardiac function and structure in patients with type 2 diabetes: a cardiac magnetic resonance study. *Intern Med J*. 2019;49(8):1006-1010. doi:10.1111/imj.14260
- Santos-Gallego CG, Vargas-Delgado AP, Requena-Ibanez JA, et al. Randomized trial of empagliflozin in non-diabetic patients with heart failure and reduced ejection fraction. *J Am Coll Cardiol*. 2021;77(3):243-255. doi:10.1016/j.jacc.2020.11.008
- Brown AJM, Gandy S, McCrimmon R, Houston JG, Struthers AD, Lang CC. A randomized controlled trial of dapagliflozin on left ventricular hypertrophy in people with type two diabetes: the DAPA-LVH trial. *Eur Heart J*. 2020;41(36):3421-3432. doi:10.1093/eurheartj/ehaa419
- Verma S, Mazer CD, Yan AT, et al. Effect of empagliflozin on left ventricular mass in patients with type 2 diabetes mellitus and coronary artery disease: the EMPA-HEART CardioLink-6 randomized clinical trial. *Circulation*. 2019;140(21):1693-1702. doi:10.1161/CIRCULATIONAHA.119.042375
- Soga F, Tanaka H, Tatsumi K, et al. Impact of dapagliflozin on left ventricular diastolic function of patients with type 2 diabetic mellitus with chronic heart failure. *Cardiovasc Diabetol*. 2018; 17(1):132. doi:10.1186/s12933-018-0775-z
- Verma S, Garg A, Yan AT, et al. Effect of empagliflozin on left ventricular mass and diastolic function in individuals with diabetes: an important clue to the EMPA-REG OUTCOME trial? *Diabetes Care*. 2016;39(12):e212-e213. doi:10.2337/dc16-1312
- Matsutani D, Sakamoto M, Kayama Y, Takeda N, Horiuchi R, Utsunomiya K. Effect of canagliflozin on left ventricular diastolic function in patients with type 2 diabetes. *Cardiovasc Diabetol*. 2018;17(1):73. doi:10.1186/s12933-018-0717-9
- Sakai T, Miura S. Effects of sodium-glucose cotransporter 2 inhibitor on vascular endothelial and diastolic function in heart failure with preserved ejection fraction - novel prospective cohort study. *Circ Rep*. 2019;1(7):286-295. doi:10.1253/circrep.CR-19-0018
- Eickhoff MK, Olsen FJ, Frimodt-Møller M, et al. Effect of dapagliflozin on cardiac function in people with type 2 diabetes and albuminuria - a double blind randomized placebo-controlled crossover trial. *J Diabetes Complications*. 2020;34(7):107590. doi:10.1016/j.jdiacomp.2020.107590
- Hays RD, Kallich JD, Mapes DL, Coons SJ, Carter WB. Development of the kidney disease quality of life (KDQOL) instrument. *Qual Life Res*. 1994;3(5):329-338. doi:10.1007/bf00451725
- Nasreddine ZS, Phillips NA, Bédirian V, et al. The montreal cognitive assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc*. 2005;53(4):695-699. doi:10.1111/j.1532-5415.2005.53221.x
- Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand*. 1983;67(6):361-370. doi:10.1111/j.1600-0447.1983.tb09716.x
- Devereux RB, Dahlöf B, Gerdts E, et al. Regression of hypertensive left ventricular hypertrophy by losartan compared with atenolol: the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) trial. *Circulation*. 2004;110(11):1456-1462. doi:10.1161/01.cir.0000141573.44737.5a
- Singh JSS, Mordi IR, Vickneson K, et al. Dapagliflozin Versus Placebo on Left Ventricular Remodeling in Patients With Diabetes and Heart Failure: The REFORM Trial. *Diabetes Care*. 2020;43(6):1356-1359. doi:10.2337/dc19-2187

Received: November 9, 2022 Accepted: November 30, 2022