Protocol, version 3.2
September 6th, 2024

A Pragmatic Trial Comparing Empagliflozin and Dapagliflozin Through Cluster Randomization Embedded in the Electronic Health Record (APPLE TREE)

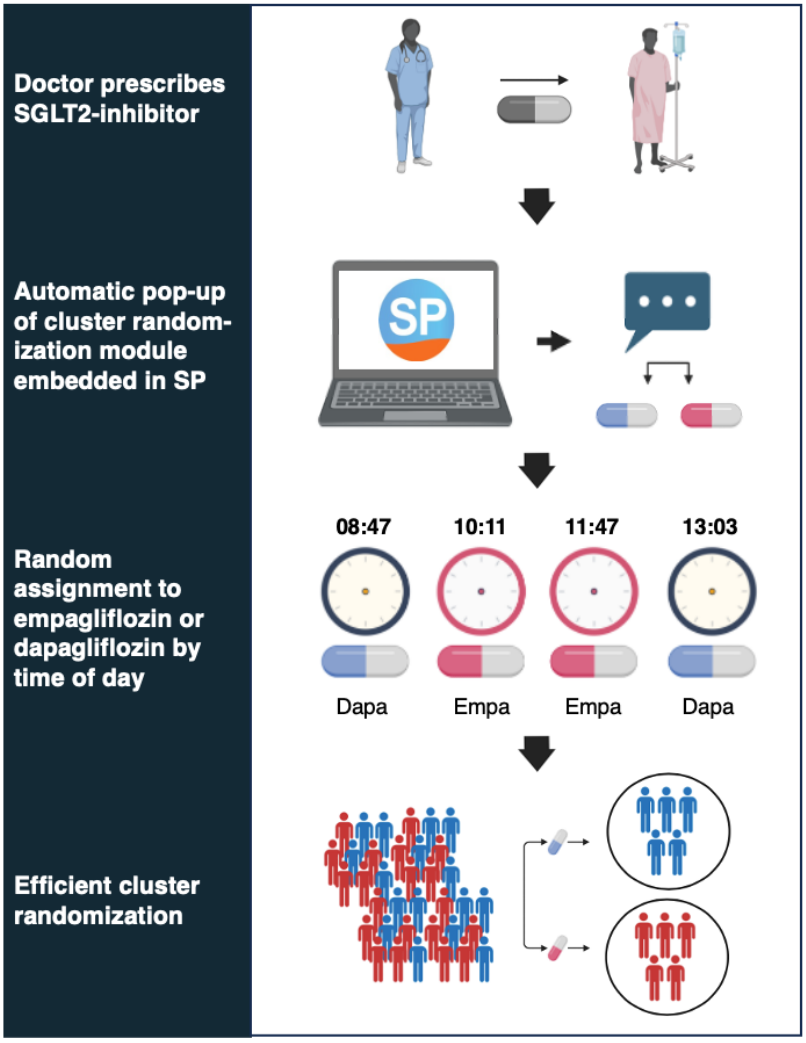

Figure 1: APPLE TREE study setup. SGLT2, sodium-glucose cotransporter 2; SP, Sundhedsplatformen.

Sponsor & Principal Investigator

Professor Morten Schou
Department of Cardiology
Herlev and Gentofte University Hospital
Borgmester Ib Juuls Vej 1, 2730 Herlev
Region Hovedstaden
morten.schou.04@regionh.dk
+4540523920

Coordinating Investigator

Daniel Mølager Christensen, MD, PhD
Department of Cardiology
Herlev and Gentofte University Hospital
Borgmester Ib Juuls Vej 1, 2730 Herlev
Region Hovedstaden
dmc@dadlnet.dk
+4526248546

List of abbreviations

SGLT2 = sodium-glucose cotransporter-2

T2D = type 2 diabetes

CKD = chronic kidney disease

HF = heart failure

EHR = electronic health record

eGFR = estimated glomerular filtration rate

Table of Contents

Trial purpose

SGLT2-inhibitors are expected to become widely used due to their therapeutic effectiveness and wide palette of indications, which may further expand pending results of ongoing trials. Empagliflozin and dapagliflozin are the most widely used SGLT2-inhibitors and large trials have demonstrated their ability to reduce cardiovascular and renal outcomes in both HF, T2D, and CKD.(1-9) They are the only two SGLT2-inhibitors currently approved for treatment of all three conditions, and are considered equal in Danish and international guidelines for HF,(10-12) T2D,(13, 14) and CKD,(15, 16) due to a presumed class effect. This presumption is based on similar effectiveness and safety profiles demonstrated in these trials,(1-9) but direct head-to-head comparisons are lacking. Due to increasing use, possible differential effectiveness and safety profiles of specific SGLT2-inhibitors have a substantial public health impact. While there is evidence for a class effect of SGLT2-inhibitors, their pharmacokinetic and pharmacodynamic properties vary; dapagliflozin potentially exhibits a longer lasting pharmacological effect due to slower renal excretion compared with empagliflozin.(17) Small-scale observational studies also suggest that there may be a more favorable cardioprotective effect of dapagliflozin compared with empagliflozin.(18, 19) Nonetheless, the lack of direct head-to-head randomized clinical trials comparing various SGLT2-inhibitors remains a prominent gap. Such trials are rarely pursued due to anticipated marginal differences between treatment arms necessitating an extensive sample size. Furthermore, regulatory approvals often stem from randomized controlled trials featuring rigid inclusion and exclusion criteria, rendering extrapolation to real-world scenarios complex. As such, in daily clinical practice, deciding between two treatments within the same drug class is often subject to arbitrariness and bias. Resolving these challenges demands a novel approach, including innovative trial designs.

The proposed protocol outlines a pioneering approach (Figure 1) - a pragmatic cluster randomized trial comparing the effectiveness and safety of dapagliflozin and empagliflozin seamlessly integrated within the Epic (Sundhedsplatformen) electronic health record (EHR) platform, currently operational in Eastern Denmark (Region Hovedstaden and Region Sjælland). The cluster randomized nature allows treatments to be assigned within patient clusters, mitigating the logistical challenges associated with individual patient randomization. Notably, this novel setup streamlines trial enrollment, ensuring prompt recruitment, cost-efficiency, and minimal disruptions for both healthcare providers and patients, in contrast to traditional randomized trials (Figure 2). Pragmatic alludes to the inclusion of patients from real-world clinical practice and the endpoint ascertainment from administrative registries. As opposed to traditional trials, this setup improves generalizability of the findings and eliminates the need for in-person follow-up visits. This study represents

an important step forward for medical evidence-generation, not only delivering important clinical insights into head-to-head differences of SGLT2 inhibitors, but also serving as a proof-of-concept model for forthcoming trials within this innovative framework. Ultimately, APPLE TREE (A Pragmatic Trial Comparing Empagliflozin and Dapagliflozin Through Cluster Randomization Embedded in an Electronic Health Record Platform) has the potential to improve care and inform treatment decisions for the millions of patients globally affected by T2D, HF, and CKD.

Hypothesis

We hypothesize that there will be no significant difference in the effectiveness and safety of dapagliflozin and empagliflozin.

Primary objective

To evaluate comparative effectiveness of dapagliflozin versus empagliflozin on the risk of all-cause mortality, HF hospitalization, myocardial infarction, ischemic stroke, and incident or worsening nephropathy.

Secondary objectives

To evaluate the risks of individual effectiveness and safety outcomes for dapagliflozin vs empagliflozin. Furthermore, to determine differences in risks for dapagliflozin vs empagliflozin in relevant subgroups.

Trial design

The study will be conducted as a pragmatic, prospective, open-label, multicenter cluster randomized trial where all hospitals in Region Hovedstaden and Region Sjælland will be included. The study will enroll patients during a 2-year period and will run for an additional year to ensure an average follow-up of trial participants of 2 years.

Trial organization and data collection

The sponsor-investigator site, Herlev-Gentofte University Hospital, will act as the central organizing trial site which holds overall responsibility for trial conduct, data collection, and quality control. The executive committee is responsible for the scientific aspects of the trial, and represents experienced and skilled trialists, statisticians, and clinicians from the three specialties from which trial patients are recruited. Through collaboration with the Danish Health Data Authority, data on baseline characteristics and endpoints will be collected directly from Sundhedsplatformen and the Danish nationwide administrative healthcare registries, which store data on all healthcare encounters in the universal public Danish healthcare system. Pre-defined diagnosis codes, procedural codes, laboratory sample codes, and Anatomical Therapeutical Classification codes will be used to ascertain endpoints and patient characteristics. Data analysis will be performed at the Department of Public Health, Section of Biostatistics, University of Copenhagen, and treatment assignment will be blinded to the statisticians analysing the trial data. All patient data will be processed and stored in accordance with the General Data Protection Regulation (GDPR), the Data Protection Act, and the Health Act and the appropriate authorities will be properly notified in accordance with applicable rules and regulations. The executive steering committee assumes responsibility to monitor the developments in the therapeutic area closely, and halt the trial if necessary if unanticipated emerging data regarding safety or efficacy indicates that the drugs are no longer able to be considered equivalent. The clinical trial will be conducted in compliance with the protocol, with the Regulation (EU) No 536/2014, and with the principles of Good Clinical Practice. Upon completion of the trial, the anonymized trial data will be shared through a public repository.

Primary endpoint

The primary endpoint will be the 2-year risk of a composite of death from any cause, hospitalization for HF, myocardial infarction, ischemic stroke, and incident or worsening nephropathy. Incident or worsening nephropathy will be defined as a sustained decrease in estimated glomerular filtration rate (eGFR) of ≥40% from baseline, a sustained decrease in eGFR of ≤10 per minute per 1.73 m2, initiation of dialysis, or kidney transplantation. A broad composite endpoint was chosen to encompass the entire spectrum of benefit shown in outcome trials across the three therapeutic areas of T2D (major adverse cardiovascular events and incident/worsening nephropathy),(7, 8), HF (cardiovascular death, HF, and incident/worsening nephropathy)(1, 2, 4, 20), and CKD (worsening nephropathy and HF).(6, 9) SGLT2-inhibitors have been shown to reduce all-cause mortality in meta

analyses,(21, 22) and this endpoint was chosen rather than cause-specific mortality due to the lack of accuracy in registry-based ascertainment of cause of death. Potential treatment and endpoint heterogeneity will be examined in secondary endpoint and subgroup analyses.

Secondary endpoints

The 2-year risks of the following secondary endpoints will be assessed:

- Death from any cause
- Hospitalization for HF
- Incident or worsening nephropathy
- Myocardial infarction
- Ischemic stroke
- Coronary revascularization
- Hospitalization for unstable angina

Participants

We will include all patients who receive a new prescription for dapagliflozin or empagliflozin during a hospital contact in Region Hovedstaden or Region Sjælland. This includes:

- Patients with T2D
- Patients with HF
- Patients with CKD

Exclusion criteria

- Patients under the age of 18
- Patients who are incapable of giving consent
- Patients who withdraw consent

Treatment

Only empagliflozin and dapagliflozin in regular doses (10 mg) will be included in the study. Prescriptions for empagliflozin 25 mg, dapagliflozin 5 mg, or in combination tablets with other drugs will not be subject to randomization. Nor will other SGLT2-inhibitors, namely canagliflozin, be subject to randomization, as only dapagliflozin

and empagliflozin are approved for treatment of both T2D, HD, and CKD, and can thus be considered equal. Physicians will still be able to prescribe combination products or canagliflozin for T2D, as per usual practice.

Sample size and power

Based on extrapolations from Danish registry data spanning from 2018 to 2021 (Figure 3), we estimate that 8,600 patients (of whom 30% and 15% will have HF and CKD, respectively), will initiate treatment with dapagliflozin or empagliflozin per year in Region Hovedstaden and Region Sjælland. This will result in randomization of 17,200 patients (8,600 per group) over 2 years. Based on the registry data, we assume a 19% event rate of the primary endpoint during 2 years of follow-up. This will yield 90% power to detect an absolute reduction of 1.9% (corresponding to a 10% relative reduction) in the 2-year rate of the primary endpoint at a statistical significance level of 5%. The expected width of the 95% confidence interval is 2.3%; in other words, the trial can establish that any difference is not larger than 2.3% on the risk difference scale.

Subgroups

We will analyze the primary endpoint in the following subgroups:

- Patients with T2D
- Patients with HF
- Patients with CKD
- Age <65 years/age ≥65 years
- Males/females

Randomization and blinding

The randomization will be done in clusters which in the present study will consist of 1-hour time frames (Figure 1). In random order, every hour, the treatment assignment will be either dapagliflozin or empagliflozin. A generic module will be developed that allows direct cluster randomization through Epic (Sundhedsplatformen), the EHR platform currently used in Region Hovedstaden and Region Sjælland. The module will alert the physician to the treatment assignment of the current time frame (cluster) when she places a prescription (best./ord.) for either dapagliflozin or empagliflozin. As an example: when a physician makes a prescription for empagliflozin between 11.00 and 11.59 am on a given day, the

randomization module will alert the prescribing physician to which treatment is assigned at the present time frame (cluster). The next hour, the assignment may stay the same or change from e.g., empagliflozin to dapagliflozin in a random fashion. As such, treatment allocation is concealed to patients and caretakers until randomization. In this study design, blinding is not possible to patients and caretakers, but treatment assignment will be concealed to the data collectors and the responsible statistician until the final trial database is locked.

Statistical analyses

The primary analyses will be performed according to the intention-to-treat principle. Follow-up will be conducted until occurrence of the primary outcome or the last date of the study period, whichever comes first. Time-to-event outcomes (including the primary endpoint) will be analyzed with Cox proportional-hazards models yielding hazard ratios with 95% confidence intervals. For outcomes with competing risks cumulative event curves will be presented.

Justification of endpoints

We chose a composite endpoint consisting of death from any cause, major adverse cardiovascular events, hospitalizations for HF, and incident or worsening nephropathy. Outcome trials have shown that SGLT2-inhibitors reduce major adverse cardiovascular events in T2D,(8) cardiovascular death or hospitalizations for HF in HF,(1) and renal events in CKD, HF, and T2D.(6, 7, 20) Furthermore, meta-analyses of randomized trials have found a reduction in death from any cause associated with SGLT2-inhibitors versus placebo.(21, 22) Thus, we chose the broadest possible primary endpoint encompassing the entire spectrum of potential clinical benefit from treatment with SGLT2-inhibitors reflecting real-world clinical practice in the diverse study population. Secondary endpoints will be used to assess the individual components of the primary endpoint.

Adverse events and safety

In light of the extensive safety data on dapagliflozin and empagliflozin from previous trials,(1-9) only serious adverse events and side effects of SGLT2-inhibitors will be registered, specifically:

- Hospitalization for ketoacidosis
- Limb amputation
- Hospitalization for genitourinary infection

- Hospitalization for fracture

Ethics and trial justification

The study will seek approval from the Danish Research Ethics Committees. The trial will be registered at ClinicalTrials.gov. The efficacy and safety of dapagliflozin and empagliflozin has been well-documented in phase 3 trials.(1-9) In the present study, patients will receive either dapagliflozin or empagliflozin based on the current guideline recommendations, in which the two drugs are considered equal.(11, 14, 16) Patients included in the study would have received an SGLT2-inhibitor regardless, as the decision to initiate treatment is under discretion of the treating physician. Randomization to either of the study drugs will not results in detriment to study participants with regards to the ability to receive other medical or surgical treatment. As data on the head-to-head effectiveness and safety are sparse, choice of either drug is based on physician preference and thus subjective or arbitrary, i.e., there is clinical equipoise. The present study will remove this subjectivity through randomization and provide data to answer an important clinical question. If guideline changes, or effectiveness or safety concerns emerge during the study period that eliminates clinical equipoise, the executive steering committee will assume responsibility to discontinue the trial and inform study participants in a timely manner.

Recruitment arrangements

Potential participants will be identified when they are admitted to the hospital and have indication for treatment with dapagliflozin or empagliflozin as per usual practice. The participating departments will include patients automatically through the Sundhedsplatformen (Epic) prescription module for cluster randomization. This means that only patients who would have received dapagliflozin or empagliflozin regardless will be subject to randomization. As such, no screening of health records will be performed to identify study participants. Likewise, treating physicians (not limited to the prescribing physician) have discretion to halt or change the assigned treatment, regardless of inclusion in the trial, as per usual practice. Follow-up will be conducted through automatically collected registry data, resulting in no additional study visits or collection of additional non-standard data from patients. Information about the study will be provided through a pamphlet which will be handed to the patient, who can choose to opt out by informing clinical staff at the trial site orally. If a patient chooses to opt out, the treating physician will simply click a button (specifically designed for opt-out) in the randomization module in

Sundhedsplatformen and proceed to prescribe the preferred treatment, as per usual practice. The withdrawal of consent will then be automatically registered. Enrollment only occurs when the randomization is accepted in Sundhedsplatformen. As such, patients who opt out at this point will not be enrolled in the study and none of their data are collected. According to Danish and EU-legislation, informed consent can be obtained by simplified means when a cluster randomized study is conducted.

To ensure that all participants understand the written material, this will be available in multiple languages by authorized translations. The information will be written in lay terms and will comply with what is described in the protocol and will state that the patients can refuse to participate and can withdraw at any time. If the patient is permanently incapable of understanding the written material, this patient will not participate in the study. Examples of such conditions include severe dementia or mental deficiency. The treating physicians at the trial sites will be instructed to not enroll patients in the study if they fulfill this criterion according to their own discretion. In addition, it will be pointed out that opting out will not have any influence on the patient's further treatment. One month after patients have been discharged or their outpatient contact has ended, they will also receive an email through E-boks describing that they have been included in the study and that they can choose not to participate in the study by actively withdrawing their consent. Additionally, if concerns arise regarding safety, guideline-changes, or significant price changes (threefold or more) of the investigational medicinal products, an update will be sent to study participants through E-boks.

The nurses and doctors will have received both oral and written material regarding the study, which will make them capable of answering questions regarding the study. Either the doctor or the nurse will hand out the written material to the patient (Appendix).

Consent

As of January 2022, a new regulation (EU regulation No 536/2014 of the European parliaments and of the council of 16th of April 2014 on clinical trials on pharmaceutical products for human use article 30 (informed consent in cluster trials)) has been implemented, that allows for omission of traditional informed consent in cluster randomized trials. Likewise, corresponding Danish legislation was implemented on January 1st, 2024 (LOV nr 1776 af 28/12/2023). As such, informed consent can be given based on written material, and lack of objection from the trial participants is considered as informed consent. Practically, this means that participants are given written information in accordance with the protocol, and that

the information material stipulates that the participant may refuse to participate in the study or withdraw at any point without any resulting detriment.

Additional conditions must be fulfilled:
a) The simplified means does not contradict national law.
b) The methodology requires groups of participants rather than individual subjects (justified in section; Trial purpose).
c) The clinical trial is low-intervention and that the pharmaceutical products are used in accordance with the terms of the marketing authorization (the study drugs are only investigated in patients with the indications specified in the marketing authorization, and are already used in everyday clinical practice, where the choice as of now is mainly being dictated by physician preference).
d) There are no interventions other than the standard treatment of the subjects concerned.
e) The protocol justifies the reasons for obtaining informed consent with simplified means and describes the information given to the patients.

Withdrawal of consent

Patients can choose to withdraw consent from the study and/or withdraw consent for usage of their data. If a patient withdraws, they will not enter the study and their data will not be used or analysed. Data regarding withdrawal will be collected via Sundhedsplatformen. The patients will be able to withdraw their consent at any time, including after the hospital contact has ended and will also receive an email via E-boks 1 month after discharge describing their participation in the study, potential significant price changes, and the possibility of withdrawing their consent. They will be instructed to notify their withdrawal of consent through secure email to forskning-s-herlev.herlev-og-gentofte-hospital@regionh.dk, which will be monitored by members of the executive committee.

Information material to patients

All patients will be given written information material when are prescribed one of the study drugs (Appendix). The information will be written in lay man terms and in different languages based on authorized translations, and will comply with what is described in the protocol and will state that the patients can refuse to participate and can withdraw at any time. In addition, it will be pointed out that opting out will not have any influence on the patient's further treatment.

Information to healthcare professionals and organization of trial sites

An endocrinologist, cardiologist, and nefrologist from each site, which includes all hospitals in Region Sjælland and Region Hovedstaden, will be appointed by the executive committee to participate in the trial's steering committee. The management at each hospital have been contacted and have signed a site suitability form, stating that they have the facilities and equipment (Sundhedsplatformen) and have suitable agreements in place to ensure that the trial can run. Healthcare professionals at the trial sites will be informed both verbally and with written material about the design and rationale of the study as well as how to navigate the randomization module in Sundhedsplatformen. A contact person (co-investigator) has been appointed at each trial site. They are informed about the informed consent process by simplified means and are instructed on how to handle the process of informed consent by simplified means, and agree to take responsibility for doing so. These contact persons have been instructed in the process by the principal and the coordinating investigator. The contact person at each trial site is responsible for in-person training of current and new staff in the procedures of the trial, including navigation of the randomization module, and obtainment of consent by simplified means. No significant disruption of the daily clinical workflow is expected, as the cluster randomization module will be embedded in the EHR, and individual consent is not required. However, trial sites where SGLT2-inhibitors are initiated in-hospital will be required to have both empagliflozin and dapagliflozin available.

Organization of training at departments

The Principal investigator and the Coordinating investigator (Daniel Mølager Christensen) will be in charge of daily operations, but will have the possibility to delegate certain tasks to the members of steering committee and co-investigators.

These tasks include:
1. The preparation and distribution information material to local health professionals which includes:
    a. Medical doctors who prescribe SGLT2-inhibitors (Video and written material about the project, pocket cards regarding dosages)
    b. Nurses who SGLT2-inhibitors (Video and written material about the project, and pocket cards regarding dosages)

c. Adminitrative staff (Information material on distribution of information material to patients, and Information material describing how to exclude patients from the study in Sundhedsplatformen)
2. The organization of training at local departments which includes physical meetings, presentations and webinars about the study. This focuses mainly on prescription of the study drugs in the randomization module in Sundhedsplatformen, as administration of either drug will not differ from current clinical practice.
3. The organization and monitoring of changes in Sundhedsplatformen and the software module.

Patient insurance

Insurance of patients is secured through Patienterstatningen.

Financing

The patients will have no extra costs in relation to the trial, as SGLT2-inhibitors are administered free of charge at the hospitals or purchased through a regular prescription at the pharmacy. The hospitals and patients will not have substantial additional costs, since dapagliflozin and empagliflozin currently have equal market shares in Denmark. Currently, empagliflozin costs 16 DKK/DDD for the 10 mg dosis, while dapagliflozin costs 17 DKK/DDD for the 10 mg dosis. Prices are not expected to change until expiration of the patents (2028), by when completion of follow up is planned to have occurred. In the event of price changes for two consecutive two week periods leading to a ≥1000 DKK per annum difference compared to the current price difference between empagliflozin and dapagliflozin, the executive steering committee will inform enrolled study participants about the price difference through E-boks. As only patients already being prescribed either empagliflozin or dapagliflozin will be enrolled in the study, and current choice of either drug is arbitrary, enrolment in the study will not incur extra cost to patients. The costs related to operating the trial are relatively modest and consist of consultation fees for software developers within EPIC, production of informational material, and employment of PhD fellows and postdocs. These costs are covered by an independent research grant of DKK 5,053,553 from the Novo Nordisk Foundation, Investigator Initiated Clinical Trials Grant: A Pragmatic Trial Comparing Empagliflozin and Dapagliflozin Through Cluster Randomization Embedded in the Electronic Health Record (APPLE TREE) - NNF23OC0085981.

Timeline

2023 Q3-Q4: Application for funding.
2024 Q1-Q2: Approval by authorities, information meetings at participating departments, preparation of study initiation.
2024 Q3: First patient enrolled.
2026 Q4: Last patient enrolled (December 31).
2027 Q4: End of follow-up (December 31). After the last patient is enrolled, outcome data will be collected from the registries for an additional year before database lock, to ensure an average follow-up time of 2 years for all study participants.
2028 Q1-: Presentation of results and publication.

Figures

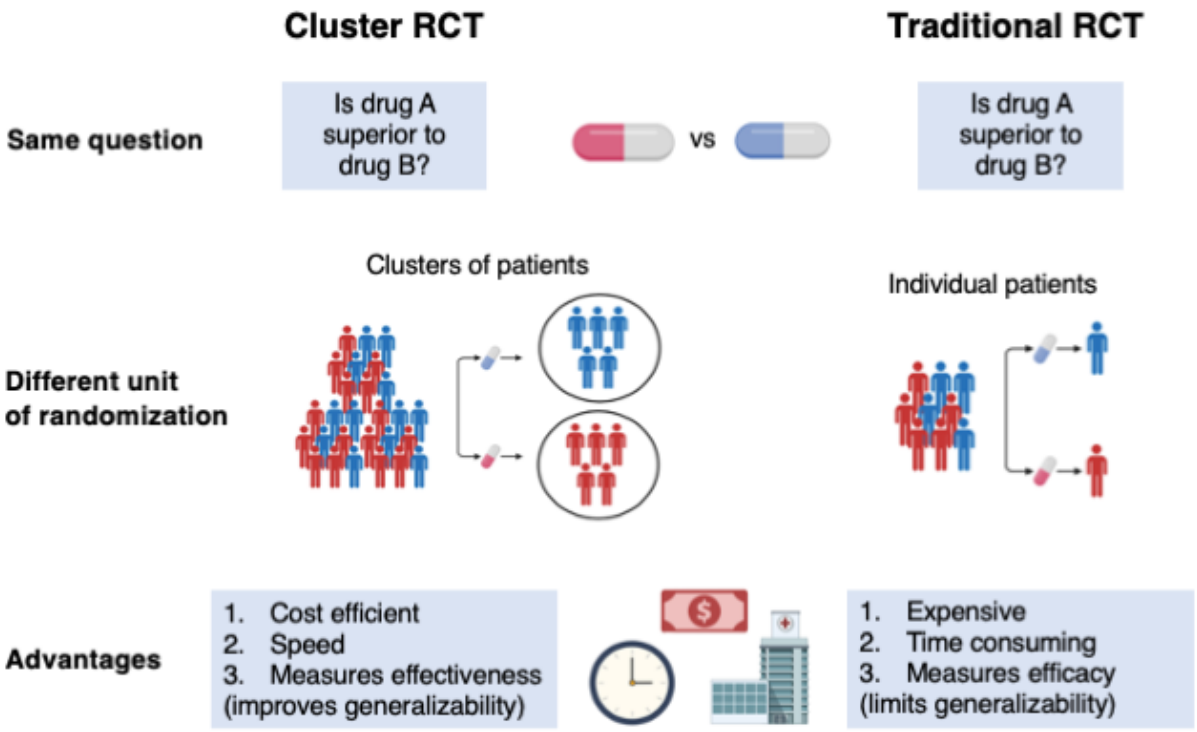

Figure 2: Comparison of cluster RCTs and traditional RCTs. RCT, randomized controlled trial.

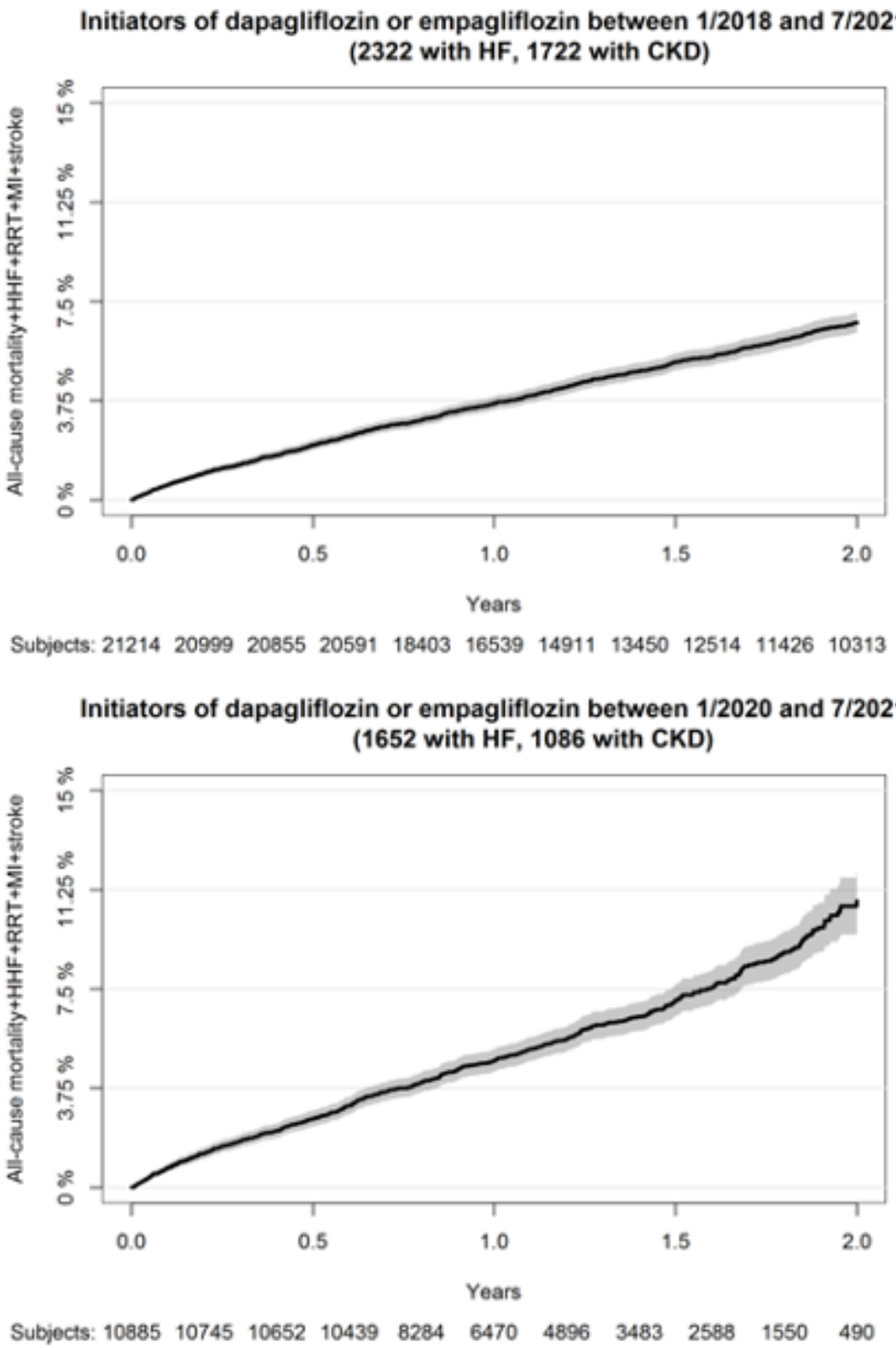

Figure 3: Event rates of the primary endpoint in patients initiating empagliflozin and dapagliflozin in Eastern Denmark between January 1st, 2018 and July 31st, 2021. Data were extracted from the Danish nationwide registries. During this period, most patients initiating empagliflozin or dapagliflozin had type 2 diabetes without heart failure or chronic kidney disease. As guidelines are implemented in clinical practice, it is expected that more patients with heart failure and chronic kidney disease will initiate empagliflozin and dapagliflozin, leading to higher anticipated event rates than those observed between 2018 and 2021.

References

1. McMurray JJV, Solomon SD, Inzucchi SE, Kober L, Kosiborod MN, Martinez FA, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med. 2019;381(21):1995-2008.
2. Solomon SD, McMurray JJV, Claggett B, de Boer RA, DeMets D, Hernandez AF, et al. Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. N Engl J Med. 2022;387(12):1089-98.
3. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2019;380(4):347-57.
4. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Bohm M, et al. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. N Engl J Med. 2021;385(16):1451-61.
5. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. N Engl J Med. 2020;383(15):1413-24.
6. The E-KCG, Herrington WG, Staplin N, Wanner C, Green JB, Hauske SJ, et al. Empagliflozin in Patients with Chronic Kidney Disease. N Engl J Med. 2023;388(2):117-27.
7. Wanner C, Inzucchi SE, Lachin JM, Fitchett D, von Eynatten M, Mattheus M, et al. Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes. N Engl J Med. 2016;375(4):323-34.
8. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med. 2015;373(22):2117-28.
9. Heerspink HJL, Stefansson BV, Correa-Rotter R, Chertow GM, Greene T, Hou FF, et al. Dapagliflozin in Patients with Chronic Kidney Disease. N Engl J Med. 2020;383(15):1436-46.
10. https://www.cardio.dk/chf. [Accessed April 23, 2024]
11. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2021;42(36):3599-726.
12. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2022;145(18):e895-e1032.

13. https://endocrinology.dk/nbv/diabetes-melitus/behandling-og-kontrol-af-type-2-diabetes/. [Accessed April 23, 2024]
14. Davies MJ, Aroda VR, Collins BS, Gabbay RA, Green J, Maruthur NM, et al. Management of hyperglycaemia in type 2 diabetes, 2022. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia. 2022;65(12):1925-66.
15. https://nephrology.dk/vejledninger/ckd-mbd/kronisk-nyresygdom/sglt2i_ckd_uden_dm/. [Accessed April 23, 2024]
16. KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int. 2024;105(4s):S117-s314.
17. Tahara A, Takasu T, Yokono M, Imamura M, Kurosaki E. Characterization and comparison of sodium-glucose cotransporter 2 inhibitors in pharmacokinetics, pharmacodynamics, and pharmacologic effects. J Pharmacol Sci. 2016;130(3):159-69.
18. Lim J, Hwang I-C, Choi H-M, Yoon YE, Cho G-Y. Comparison of cardiovascular and renal outcomes between dapagliflozin and empagliflozin in patients with type 2 diabetes without prior cardiovascular or renal disease. PLoS One. 2022;17(10):e0269414.
19. Shao S-C, Chang K-C, Hung M-J, Yang N-I, Chan Y-Y, Chen H-Y, et al. Comparative risk evaluation for cardiovascular events associated with dapagliflozin vs. empagliflozin in real-world type 2 diabetes patients: a multi-institutional cohort study. Cardiovasc Diabetol. 2019;18(1):120.
20. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. N Engl J Med. 2020;383(15):1413-24.
21. Silverii GA, Monami M, Mannucci E. Sodium-glucose co-transporter-2 inhibitors and all-cause mortality: A meta-analysis of randomized controlled trials. Diabetes, Obesity and Metabolism. 2021;23(4):1052-6.
22. Zannad F, Ferreira JP, Pocock SJ, Anker SD, Butler J, Filippatos G, et al. SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials. Lancet. 2020;396(10254):819-29.

Appendix

INFORMATION OM IGANGVÆRENDE UNDERSØGELSE AF LÆGEMIDLER

A Pragmatic Trial Comparing Empagliflozin and Dapagliflozin Through Cluster Randomization Embedded in the Electronic Health Record (APPLE TREE)

Undersøgelsens baggrund og formål

Region Hovedstaden og Region Sjælland gennemfører i øjeblikket en undersøgelse med lægemiddeltypen SGLT2-inhibitor, der blandt andet bruges mod sukkersyge, hjertesvigt og kronisk nyresygdom. Du får dette informationsmateriale, fordi din læge har vurderet at du skal have denne type lægemiddel.

Formålet med undersøgelsen er at studere effekten og sikkerheden af de to forskellige SGLT2-inhibitorer (empagliflozin og dapagliflozin). Behandlingerne betragtes i dag som lige effektive til at forebygge bl.a. død, hjertesvigt, nyresvigt, og forhøjet blodsukker og lige sikre i forhold til risiko for bivirkninger. Der er imidlertid ikke lavet undersøgelser der sammenligner lægemidlerne direkte over for hinanden, og derfor er formålet at undersøge om lægemidlerne i virkeligheden er lige effektive og sikre.

Hvordan udføres undersøgelsen?

Gennem et modul i Sundhedsplatformen, udvælges tilfældigt hvilket af de to lægemidler (empagliflozin eller dapagliflozin), som du skal have. Rent praktisk betyder det, at når lægen har vurderet, at du skal have denne type medicin, så går lægen ind på Sundhedsplatformen og udskriver det til dig. Her vil Sundhedsplatformen automatisk trække lod om hvilket af de to forskellige lægemidler, der skal gives. Det vil sige, at der er mulighed for, at du vil modtage den behandling, som lægen alligevel ville have udskrevet til dig, hvis der ikke var blevet trukket lod.

Er der en risiko for mig?

Lægemidlerne bliver i dag brugt, som om de er ens, hvilket betyder at valget af lægemiddel ofte udelukkende er baseret på pris, eller på lægens præference. I undersøgelsen vil det være et computersystem, der bestemmer hvilket lægemiddel, som du får, fremfor at du blot får det billigste produkt eller det lægen normalvis udskriver. Der er i øjeblikket ikke nogen betydelig prisforskel mellem lægemidlerne, og priserne forventes ikke at ændre sig væsentligt før producenternes patenter

udløber efter studiets afslutning i 2028. I tilfælde af fremtidige prisændringer på empagliflozin og dapagliflozin, der fører til en prisforskel på ≥1000 DKK om året i forhold til det nuværende niveau, vil du blive informeret om dette via E-boks. De hyppigste bivirkninger for begge lægemidler er blærebetændelse, svampeinfektion i underlivet, lavt blodsukker og forstoppelse, og det tyder foreløbigt ikke på at der er forskel herpå mellem dem. Dvs. hvis uagtet hvilke af de to lægemidler du får, anses det ikke for at være forbundet med nogen øget risiko. Du er endvidere forsikret gennem Patienterstatningen, hvis noget uventet skulle opstå.

Simpelt samtykke

I henhold til ny Dansk og EU lovgivning, behøves der ikke det traditionelle informerede samtykke, men samtykket kan baseres på skriftelig information, som består af dette dokument. Du har dog muligheden for at sige fra, hvis ikke du ønsker at deltage. Et nej vil ikke have nogen indflydelse på din videre behandling. Hvis du ikke ønsker at deltage, så skal du blot informere lægen eller sygeplejersken, hvorved du vil modtage vanlig behandling, altså enten dapagliflozin eller empagliflozin, som du vælger i samråd med lægen.
Hvis du vælger at deltage i studiet, kan du også på et senere tidspunkt trække dit samtykke tilbage, så vi ikke må bruge dine data. Du vil 1 måned efter du er udskrevet modtage et brev i E-boks, hvor du også får muligheden for at trække dit samtykke tilbage til at vi må bruge dine data.

Behandling af personoplysninger

Vi skal gøre dig opmærksom på, at der i forsøget behandles personfølsomme oplysninger; disse inkluderer diagnoser givet under og før indlæggelse, medicin givet under indlæggelse, blodprøvesvar og procedurer udført i forbindelse med indlæggelsen. Dette bliver indsamlet automatisk via de nationale sundhedsregistre indtil d. 31. december 2027, hvor forsøget slutter. Disse data vil blive behandlet i henhold til Databeskyttelsesloven og Databeskyttelsesforordningen.
Personhenførbare data, herunder journaloplysninger, blodprøver osv., opbevares i henhold til Europa-Parlamentets og Rådets forordning nr. 2016/679 af 27. april 2016 om beskyttelse af fysiske personer i forbindelse med behandling af personoplysninger og om fri udveksling af sådanne oplysninger og i henhold til, Databeskyttelsesforordningen, Databeskyttelsesloven og Sundhedsloven. Alle data (noter, helbreds- baggrunds- og kontaktoplysninger mv.) opbevares sikkert og utilgængeligt for uvedkommende. Data opbevares frem til september 2031, hvorefter de slettes. Vi behandler dine personoplysninger med hjemmel i GDPR Art. 6(1)(a) samt Art. 9(2)(a) på baggrund af de simplificerede samtykke.

Kontaktoplysninger

Ved spørgsmål vedrørende undersøgelsen bedes du skrive til denne sikre digitale postkasse: forskning-s-herlev.herlev-og-gentofte-hospital@regionh.dk.

Med venlig hilsen
Morten Schou, MD, PhD, Professor
Daniel Mølager Christensen, MD, PhD