Region Hovedstaden

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Implementation of Sodium-Glucose Cotransporter (SGLT)-2 Inhibitors in Patients with Heart Failure through a New Digital Strategy (EMAIL HF): A Randomized Clinical Trial

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Objectives

Primary objective

The primary objective of the study is to investigate whether it is possible to implement novel medical therapies, in this case a sodium-glucose co-transporter-2 (SGLT-2) inhibitor to heart failure patients, through a new digital strategy and hereby increase the number of eligible patients initiating therapy and shorten the time to initiation compared to the process today.

Secondary objectives

Secondary objectives include developing a digital message system linked to an outpatient clinic that can be implemented and used across the healthcare system in Denmark and abroad when new scientific discoveries or therapies need to be implemented effectively.

As we are investigating the implementation of a SGLT-2 inhibitor in heart failure patients, we also intend to prevent all-cause death and hospitalizations for heart failure as a secondary objective. Further, we will evaluate whether subgroups like elderly patients and patients with lower socioeconomic status have the same effect of the digital platform intervention. And finally, relevant health economic analyses, including cost-benefit analyses, will be conducted.

Background

In the last few decades, we have witnessed a great proliferation of new medical breakthroughs and discoveries across various medical fields, that have had great impact on the public health. At the same time, the recent and still ongoing COVID-19 pandemic has also revealed how vulnerable the health care system is to sudden and major challenges and its urgent need for structural and digital transformation.

Today, literature states that when new scientific discoveries are published, it takes 10 years in average from the publication process of new guidelines to implementation in the health care system. Furthermore, it is stated that the complete process from research to clinical practice takes an average of 17 years. (1-3) Despite the continuous improvements in science, this loss of potential patient benefit remains one of the biggest challenges in the health care systems across the world.

The explanation for the prolonged process is multifactorial. However, the most important factor seems to be the complexity of cross-institutional patient care involving several links, including out-patient clinics, general practitioners, patient associations etc.

With this randomized clinical trial, we wish to address this issue by developing a digital strategy based on a simple e-mail system, where uniform information regarding new scientific discoveries including new therapy options, are sent directly from the healthcare experts to the patients in real time, bypassing the existing and delaying links as illustrated in Figure 1. Also, in a world where patients continue to take more control of their own health, this becomes even more important.

Today, a large patient group that is experiencing the issues stated above is the patients diagnosed with heart failure - a severe and continuously growing public health issue that is associated with substantial patient morbidity and mortality. As many as 1 in 5 people are expected to develop heart failure during their lifetime and only a quarter of the patients admitted to hospital for the first time will survive longer than 5 years. Researchers around the world have continuously been focusing on improving existing therapies and on finding new ways to treat this complex group of patients. Since 2019, strong and consistent evidence has accrued from clinical trials that a new heart failure therapy can reduce mortality risk and prevent admission for heart failure – the SGLT-2 inhibitors, dapagliflozin and empagliflozin. (4-6) Less than two years after, the therapy was already approved for clinical use in the treatment of heart failure by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA), and clinical guidelines have also been updated accordingly.
Despite the approval for clinical use, studies in the population have shown that the majority of eligible heart failure patients are not started on therapy, mainly due to the issues stated above, where some patients are followed by their general practitioner, some at the department of cardiology and some patients at the department of internal medicine due to coexisting comorbidities (7).

To increase the number of eligible patients with heart failure initiating therapy with a SGLT2 inhibitor, we plan to use the digital strategy to provide evidence-based and uniform information from clinical experts directly to the patients. In this way, we are evaluating in a randomized clinical trial design whether a new scientific discovery can be implemented faster by a digital strategy and direct involvement of the patients than by usual care in patients with chronic heart failure followed in a public healthcare system.

Methods

Study design

The study is a pragmatic two-armed, multicentre, randomised clinical trial, that will be coordinated from the Department of Cardiology, Herlev-Gentofte University Hospital. All patients with a

registered diagnosis of heart failure living in The Capital Region of Denmark and Roskilde, who have not yet been started on therapy with SGLT-2 inhibitors will be identified and recruited from Danish nationwide registries through their personal identification number (CPR-number). In Denmark, the CPR-number is also linked to a personal secure mailbox, *Digital Post*, where all government letters including healthcare related letters are sent to the Danish citizens. These heart failure patients will be randomized 1:1 to receive a government e-mail from heart failure specialists, with information about the novel heart failure therapy, SGLT-2 inhibitors. Beside information, the patients will be offered a consultation (phone or in person at a heart failure clinic) where a heart failure specialist will prescribe and initiate the therapy if the patient is eligible. Depending on the patients' residential address and postal code, he or she will be referred to one of the following heart failure clinics: Herlev-Gentofte Hospital, Amager-Hvidovre Hospital, Bispebjerg-Frederiksberg Hospital, Rigshospitalet Blegdamsvej-Glostrup, Nordsjællands Hospital, or Zealand University Hospital, Roskilde.

Hypothesis

The main hypothesis of this study is that through a new digital strategy where patients with a certain registered diagnosis are contacted via e-mail (*Digital Post*) and informed about novel and approved therapy, in this case SGLT-2 inhibitors for heart failure patients, we can increase the number of eligible patients initiated on therapy significantly and shorten the time to initiation compared to a control group. It is expected that the strategy will be highly cost effective, and that elderly and patients with a lower socioeconomic level, also will benefit from the digital implementation of SGLT-2 inhibitors.

Study population

The study population consists of all registered patients with heart failure living in the Capital Region of Denmark and in Roskilde who have not yet initiated therapy with SGLT-2 inhibitors. Patients with and without type 2 diabetes will be included, and it is expected that approximately 20% of the patients with heart failure will have co-existing type 2 diabetes (10).

Inclusion and exclusion criteria

Eligible participants should fulfil all the following criteria:

(1) Registered diagnosis of heart failure (ICD-10 code: DI50) within the last 10 years

(2) Living in the Capital Region of Denmark or Roskilde

(3) Age >=20 years (adults)

Patients matching any of the following criteria will be excluded:

(1) Redeemed prescription of a SGLT-2 inhibitor after 2015
(2) Type 1 diabetes mellitus
(3) History of ketoacidosis
(4) Chronic kidney disease in long-term dialysis
(5) Living in a nursing home
(6) Dementia
(7) Cancer diagnosis within the last year (except prostate cancer and non-melonoma skin cancer).
(8) Exemption from the public digital mailbox system

Endpoints

Primary endpoint

1. Proportion of patients initiating therapy with a SGLT-2 inhibitor between the control and intervention group (from randomisation up to six months).

Secondary endpoint

2. Time to first occurrence of a composite heart failure endpoint consisting of all-cause death or heart failure hospitalisation, with examination of the components of this composite (from randomisation to study end)

Other outcome measures

3. Number of all-cause deaths and heart failure hospitalisations, with examination of the components of this composite (from randomisation to study end)

4. Time to first occurrence of a 3-point expanded composite heart failure endpoint consisting of all-cause death, heart failure hospitalisation, or renal failure (from randomisation to study end)

5. Time to first occurrence of a 4-point expanded composite heart failure endpoint consisting of all-cause death, heart failure hospitalisation, non-fatal myocardial infarction, non-fatal stroke (from randomisation to study end)

6. Time to initiation of therapy with a SGLT-2 inhibitor (from randomisation to study end)

7. Adherence to therapy (from randomisation to study end)

8. Proportion of elderly (>75 years) initiating therapy with SGLT-2 inhibitors (from randomisation to study end)

9. Proportion of patients with lower educational level initiating therapy with SGLT-2 inhibitors (from randomisation to study end)

10. Proportion of patients with lower socioeconomic level initiating therapy with SGLT-2 inhibitors (from randomisation to study end)

11. Proportion of immigrants initiating therapy with SGLT-2 inhibitors (from randomisation to study end)

12. Proportion of patients with type 2 diabetes initiating therapy with SGLT-2 inhibitors (from randomisation to study end)

13. Proportion of male and female patients initiating therapy with SGLT-2 inhibitors (from randomisation to study end)

Randomisation, blinding, the intervention, and schedule of enrolment

The setup of enrolment is illustrated in figure 2 and 3. All patients with heart failure living in the Capital Region of Denmark and Roskilde are identified through nationwide health care registers and randomised 1:1 (simple randomisation) to receive an e-mail via *Digital Post* regarding the novel therapy with SGLT-2 inhibitors (figure 4). The patients receiving an e-mail are encouraged to follow a weblink where they can register to be contacted by their local Heart Failure Clinic if they are interested in the therapy. A reminder is sent to those who have not responded or registered within 14

days. A heart failure specialist will then contact the patients and inform them about the therapy, evaluate their medical history through their medical record and obtain informed consent. When the cardiologist has confirmed eligibility with fulfilment of all inclusion criteria and no exclusion criteria the patients are then started on therapy with follow up at the Heart Failure Clinic or via the patient's general practitioner. Due to the trial design, it is not possible to blind the patients nor the investigators. SGLT-2 inhibitors that are approved by the EMA (empagliflozin and dapagliflozin) and are in accordance with heart failure guidelines will be used equally. It is planned that n≈5,000 patients will receive an e-mail with information on SGLT-2 inhibitor therapy and n≈5,000 will not. The patients will be randomized in blocks of approximately 200-400 patients each month except for July and December, which corresponds to ≈10,000 during the study period.

Statistical analyses

Patients allocated to receive an e-mail will be compared to the control group by conventional statistical methods (chi^2 tests, log rank tests (non-parametric), and Cox proportional hazard regression analyses). Clinical information on the patients based on ICD-10 codes (see appendix) and other covariates including level of education, socioeconomic position, ethnicity etc. will be obtained by the Danish Health Data Authority. Prescriptions of a SGLT-2 inhibitor and other relevant therapies will also be obtained from the Danish Health Data Authority (11).

Sample size considerations

The trial's primary objective is to evaluate the effect of the digital implementation strategy on SGLT2 inhibitor uptake. However, powering the study solely for uptake would require a substantially smaller sample size and would not allow a meaningful assessment of whether increased uptake translates into differences in patient-important clinical outcomes. Therefore, the sample size was determined based on the key secondary clinical endpoint, defined as time to first HF hospitalization or all-cause mortality, while still ensuring sufficient precision for the primary analysis of uptake.

Power calculations assume 80% statistical power with a two-sided significance level of 0.05. The anticipated intervention effect for the clinical endpoint is a hazard ratio of 0.80 (corresponding to a 20% relative risk reduction), informed by evidence from large outcome trials of SGLT2 inhibitors in HF. Using a Cox proportional hazards model (with the assumed event rate, effect size, and variability in the population), the minimum required number of events to detect this difference is 631. The study population is expected to have a median time-to-event of approximately 5 years based on historical

data, and each participant is expected to be followed for at least 1 year. A 15% censoring rate is anticipated, reflecting withdrawal of consent and loss to follow-up (including emigration). Under these assumptions, the total required sample size is 5,788 patients to ensure accrual of the target number of events.

Health economic analyses

Health economic consequences of the study will be estimated by determining the annual healthcare utilization of HF patients receiving an e-mail via *Digital Post* compared with the matched controls. Data will be obtained from the Danish Health Data Authority. The cost estimates will be divided into direct and indirect costs. The direct costs include total cost of inpatient hospital care, total cost of outpatient clinic services provided, total drug prescription use and pharmacy costs, inpatient hospitalization by length of stay, outpatient clinic and general practitioners' visits weighted by frequency. The indirect costs include reduced labour supply and public transfer payments (sick pay, pension, unemployment benefit, etc.) measured on an annual basis.

Study organization

Research team

The EMAIL HF trial will be conducted by a highly specialized research team, based on a long-term collaboration in heart failure research between six hospitals (Herlev-Gentofte University Hospital, Rigshospitalet, Amager-Hvidovre-Glostrup Hospital, Bispebjerg-Frederiksberg Hospital, Nordsjællands Hospital, Roskilde University Hospital) and the Department of Biostatistics, University of Copenhagen in the Capital Region of Denmark. The research team includes epidemiologists, heart failure specialists, professors of cardiology, and a professor in statistics. The trial will be conducted in collaboration with experienced trialists and epidemiologists in cardiovascular medicine from University of Glasgow, Scotland.

Steering committee

The executive steering committee consists of Mariam Elmegaard Malik (MEM), Emil Fosbøl (EM), Emil Wolsk (EW), Jesper Jensen (JJ), Charlotte Andersson (CA), Lars Køber (LK), Nadia Dridi (ND), Morten Petersen (MP), Mads Kristian Ersbøll (MKE), Nis Ottesen Stride (NOS), Anders Barasa (AB), Jens Jakob Thune (JJT), Christian Ditlev Tuxen (CDT), John McMurray (JM), Mark Petrie (MP) and Morten Schou (MS). The primary investigator is MS from Herlev-Gentofte

University Hospital and LK from Rigshospitalet is chairman. The steering committee is responsible for the study design, patient enrollment, reporting, registration at www.clinicaltrials.gov and publication of the trial. Members of the steering committee will have full access to the final trial data.

Data Safety and Monitoring

Adverse events will be recorded continuously via the nationwide health registers by the investigators (discontinuation of the drug, urinary tract infections, genitalia infections, hypoglycaemic events, volume depletion, acute renal failure, diabetic ketoacidosis, thromboembolic events, bone fractures). Before initiation of SGLT-2 inhibitor therapy, all patients will be informed to contact their primary physician in case of side effects. Information on drug discontinuation will be obtained by the nationwide health registries.

Study center and time schedule

All patients with heart failure are identified from nationwide Danish registers. Patient screening, randomization, and all protocol-specified assessments will take place at the Departments of Cardiology in each of the five sites/hospitals. It is expected that the trial process will begin in November 2021 and end in December 2025:

2021 Q1-Q4: Application for funding

2022 Q1-Q3: Approval by Danish authorities, preparation of study start

2023 Q1: First patient first visit

2025 Q1: Last patient last visit

2026 Q2-Q4: Presentation of results and publication

Patient involvement

Two heart failure patients are involved in the process of formulating the e-mail with the information on SGLT-2 inhibitor therapy that will be sent to the heart failure patients during the study. One patient will be offered to be a member of the steering committee. The patients have already been introduced to the research idea and concept and find the study highly relevant from a patient perspective.

Ethics and severe adverse events

During the trial, all adverse events (AEs) and severe adverse events (SAEs) related to the study drug (i.e., volume depletion, renal events, major hypoglycaemic events, bone fractures, diabetic

ketoacidosis, and amputations) will be monitored continuously from the patients' medical record that is linked to the nationwide health registers. Data on other adverse events will not be routinely collected in view of the extensive previous collection of safety data regarding dapagliflozin/empagliflozin (4,12). Relevant authorities including the principal investigator will be informed in accordance with applicable laws and International Conference of Harmonization Good Clinical Practice (ICH-GCP) guidelines (13). Dapagliflozin has been approved for treatment of heart failure patients with reduced ejection fraction since 2019 and empagliflozin in 2021. Guidelines have been updated accordingly. In the recent phase III trials, dapagliflozin and empagliflozin were very well tolerated thus the risk of adverse side effects to both drugs is expected to be low (4). If, however, a patient should suffer any harm from study participation, compensation is set by the public Patient Compensation Association in Denmark.

The EMAIL HF trial has been evaluated and approved by The Ethical Committee of the Capital Region in Denmark which concluded that the study is ethically justifiable and that it can be initiated (F-22035916). The Ethical Committee of Denmark has also previously approved the suggested study design where patients are identified by nationwide registries and then contacted by e-mail via *Digital Post* (14,15).

Dissemination of results

After completion of the trial, the results of the study will be submitted to international peer-reviewed scientific journals, irrespective of the outcome. Based on the recommendations of the International Committee of Medical Journal Editors (ICMJE), the steering committee will assess authorship eligibility for the scientific papers related to the trial. Furthermore, the results will be presented at national and international conferences by members of the steering committee. The study will result in one main publication and at least five publications of the predefined substudies of interest.

Conclusions and clinical implications

Based on a simple digital strategy, where scientific information regarding novel therapy options is sent directly from clinical experts to the patients via *Digital Post*, the EMAIL HF trial is expected to increase the number of eligible patients initiating therapy and to shorten the time to initiation markedly, compared to the process today. The trial will also answer the question whether a digital strategy is effective in vulnerable patient subgroups like elderly patients and patients with lower

education level. If the study hypotheses are confirmed the results have to potential to change the structure and organization of the healthcare system in Denmark and abroad.

Secondary, because the digital strategy will be investigated in patients with heart failure where the patients will receive information regarding the new therapy option with SGLT-2 inhibitors, dapagliflozin and empagliflozin the trial is also expected to reduce the burden of morbidity and increase quality and length of life in this large and vulnerable patient group.

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Figure 1. Study hypothesis

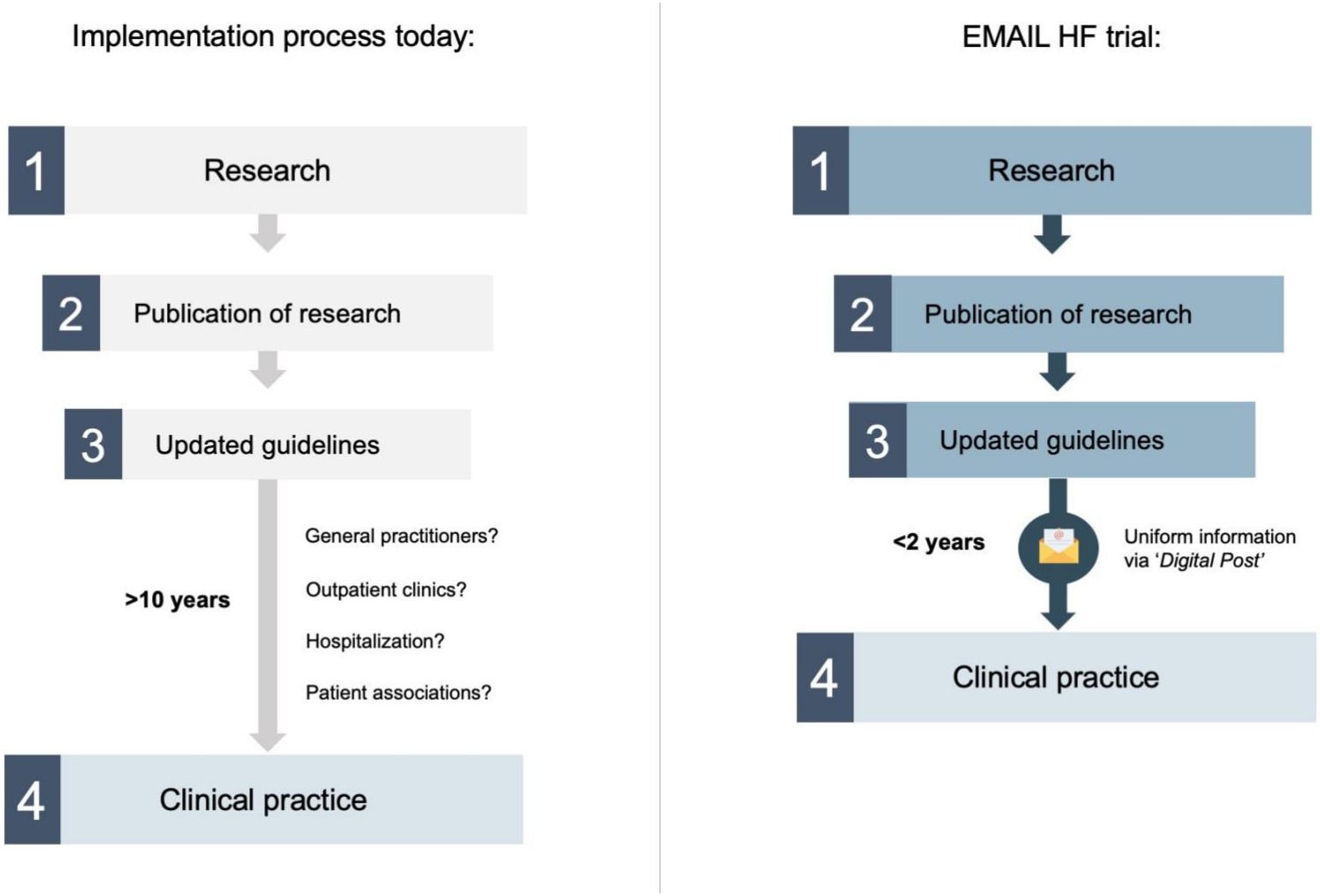


Figure 2. Study design

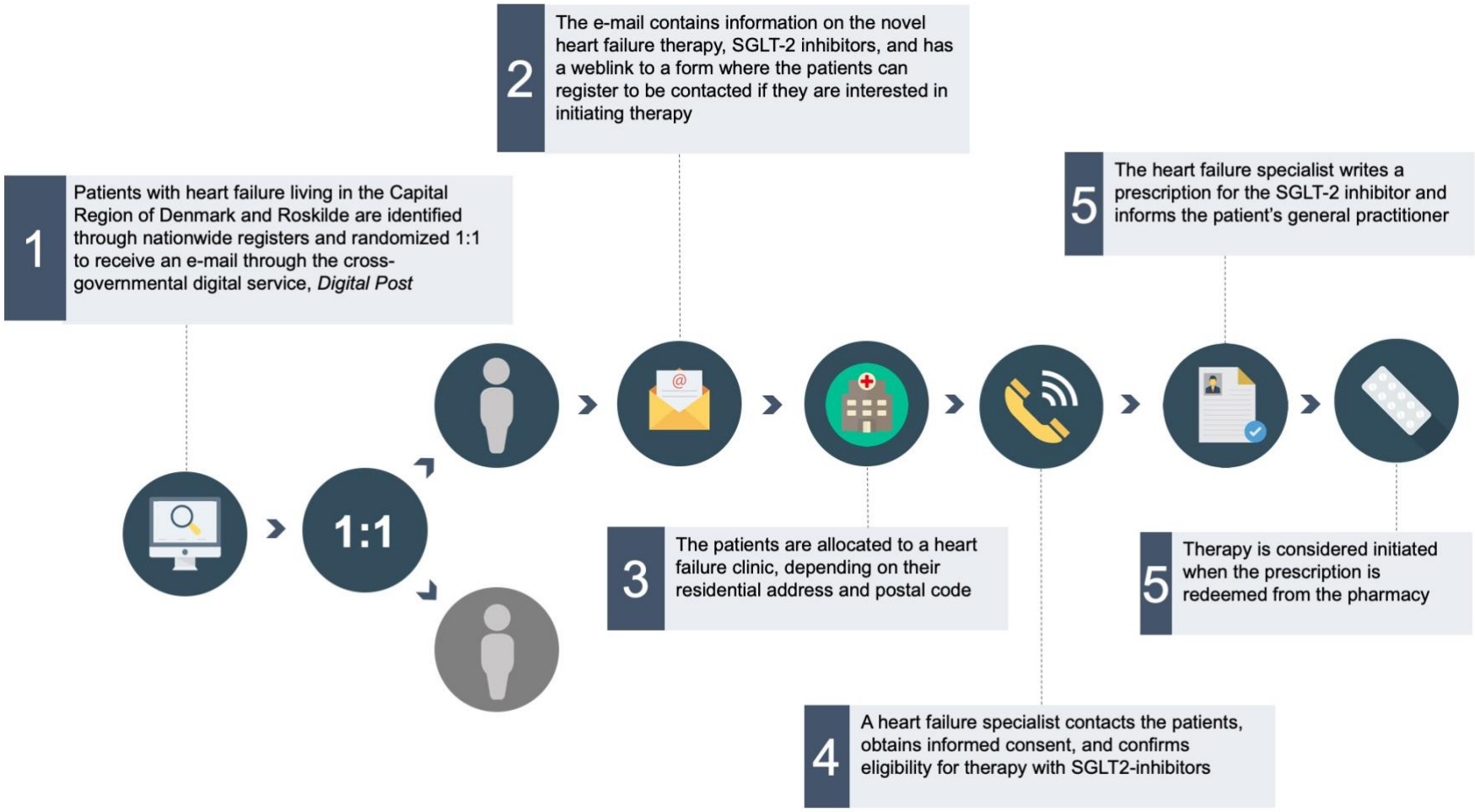
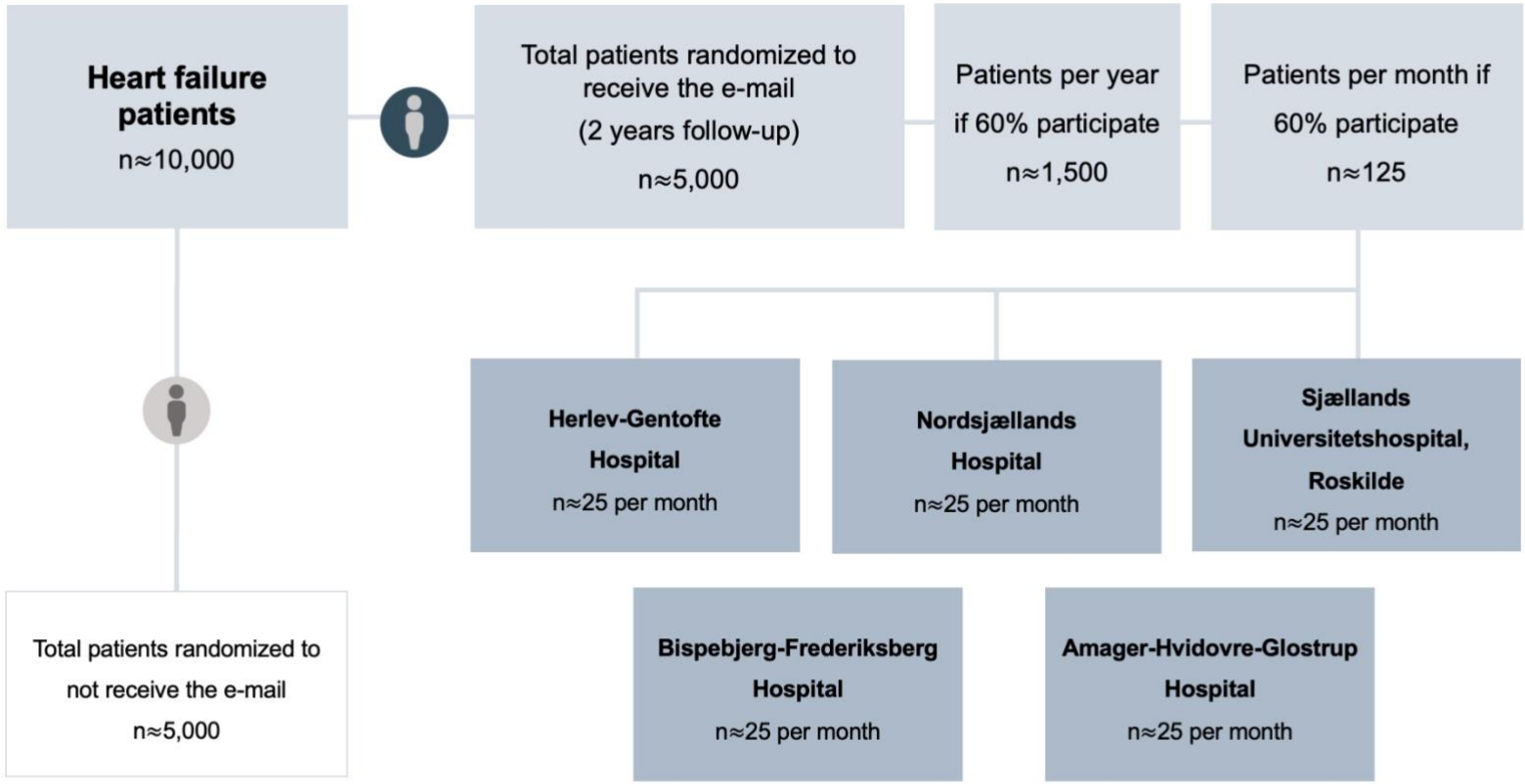


Figure 3. Patient enrolment



**One study year accounts for 44 weeks, with no patient inclusion in July and December.*

Figure 4. Patient randomisation