Adjuvant testosterone therapy in chronic heart failure (ATTIC): a randomised open-label trial

Minakshi Dhar, Kartik Mittal, Ashwin Parchani, Manu Sharma, Yogesh Bahuropui, Sanjay Kalra, Nowneet Kumar Bhat

ABSTRACT

Introduction Heart failure is a major contributor to morbidity and mortality in the geriatric population, with no promising therapy currently available with considerable benefit. Testosterone therapy is an emerging viable treatment option given its beneficial effects, including improving cardiac functional capacity, alleviating symptoms and low cost, among others.

Methods We have planned an open-label, parallel design, 1:1 randomised controlled trial, which aims to recruit 986 adult males above the age of 60 diagnosed with chronic stable heart failure fulfilling the eligibility criteria. The participants will be randomised into 2 groups of 493 each. Both groups will receive standard recommended treatment regimen of chronic stable heart failure and intervention arm participants will receive additional testosterone gel. All participants will be assessed at baseline, 4 weeks, 6 weeks and 12 weeks. The primary endpoints will assess the differences in functional capacity, frailty and quality of life at 3 months compared with baseline. The secondary endpoints will include the mean change from baseline at 3 months in cardiac remodelling using echocardiography, serum brain natriuretic peptide levels, the incidence of adverse drug reaction.

Statistical analysis The data will be analysed with the help of SPSS 23 software. Primary objectives of change in 6-minute walk test, frailty index and quality of life will be analysed using the student’s t-test. The statistical significance will be defined as p value<0.05 and taking confidence level as 95%.

Ethical clearance Institutional Ethics Committee clearance taken via letter no AIIMS/IEC/20/847, dated 21 November 2020. This study involves human participants and was approved by institutional ethical committee, DHR Reg: EC/NEW/Inst/2020/1046CDSCO, Reg No: ECR/736/Inst/UK/2015/RR-18. Participants gave informed consent to participate in the study before taking part.

Trial registration number (CTR)—REF/2020/12/030292.

INTRODUCTION

The population share of the elderly or geriatric population is overgrowing worldwide. As per WHO people with age 60 years and above are considered as geriatric age group. The number of the elderly is estimated to rise from 524 million in 2010 to nearly 1500 million in 2050, and most of this increase in developing countries. The factors responsible for this transition are declining fertility, increased longevity and ageing of ‘baby boom’ generations. Heart failure is a unique metabolic syndrome and is rapidly increasing in India due to the rising number of coronary artery disease, hypertension, diabetes, smoking, alcoholism and the ageing of our society. Due to the unavailability of any promising therapy of heart failure and despite advances in evidence-based pharmacological therapies being evaluated and tested, these patients continue to exhibit significant morbidity and excessive mortality at rates as high as 30% per year, and coupled with ongoing symptoms of fatigue, cardiac cachexia and metabolic shift towards catabolism has led to an intensive search for new therapies. Due to this unmet need, novel and low-cost treatments such as testosterone hormone replacement therapy are being considered for improving the lives of heart failure patients. Evidence has shown that testosterone improves lean body mass and exercise tolerance and is being investigated worldwide in improving cardiac functional capacity. Chronic heart failure is linked to maladaptive and prolonged neurohormonal
and proinflammatory cytokine activation, resulting in a metabolic shift favouring catabolism, skeletal muscle atrophy and vasodilator incapacity. Malkin et al discovered that testosterone replacement treatment improves functional capacity and gives symptomatic relief to men with moderately severe heart failure in a randomised, double-blind, placebo-controlled parallel study of transdermal testosterone therapy.3 4 In 2014, Mirdamadi et al investigated the link between low testosterone levels and decreased exercise ability. They aimed to see if testosterone treatment can help individuals with stable chronic heart failure improve their clinical and cardiovascular symptoms and quality of life. In a double-blind, placebo-controlled trial, they randomised 50 male patients with congestive heart failure to receive an intramuscular (gluteal) long-acting androgen injection (1 mL of testosterone enanthate, 250 mg/mL) once every 4 weeks for 12 weeks or intramuscular injections of saline (1 mL of 0.9% w/v NaCl) with the same protocol. The researchers discovered that the two groups’ changes in body weight, haemodynamic parameters and left ventricular dimensions echocardiographic indices were all comparable. In contrast to the placebo group, those who received testosterone had a substantial increase in 6-walk mean distance during the research (p value=0.019).5

This study is aimed to improve the quality of life in chronic heart failure patients in the Indian subpopulation of older men, so that transdermal supplementation of testosterone can be adopted as an adjunct therapy to the existing treatment protocols.

**Trial design**

An open-label trial with 1:1 allocation.

**Aim**

To assess the beneficial effect of adjuvant testosterone therapy in older men with chronic stable congestive heart failure.

**Primary objectives**

- To determine the effect of testosterone replacement therapy on the functional capacity of older men with chronic congestive heart failure.
- To determine the effect of testosterone replacement therapy on the frailty of older men with chronic congestive heart failure.
- To assess the effect of testosterone on metabolic parameters of older men with chronic congestive heart failure.

**Secondary objectives**

- To assess disease progression by evaluating the status of cardiac remodelling in older men with chronic congestive heart failure by echocardiography.
- To determine the effect of transdermal testosterone therapy on brain natriuretic peptide levels in older men with chronic congestive heart failure.
- To study the safety profile of transdermal testosterone therapy in chronic congestive heart failure.

**MATERIAL AND METHOD**

**Study design**

This study will be a randomised open-label clinical trial, parallel design with a 1:1 allocation ratio as shown in figure 1.

**Study setting for recruitment**

The study will be conducted in outpatient and inpatient of the Geriatric Unit, Department of Internal Medicine in tertiary care level teaching hospital.

**Study duration**

The study will be conducted over 2 years.

**ELIGIBILITY CRITERIA**

**Inclusion criteria**

Male participants, ≥60 and ≤90 years of age, in outpatient and inpatients, who have:

- Chronic stable heart failure (with both preserved and reduced ejection fraction) with The New York Heart Association (NYHA) class 2 or 3 irrespective of aetiology and whose treatment has not been modified in the past 4 weeks. Heart failure will be defined as per American College of Cardiology Foundation/American Heart Association. Heart failure with preserved ejection fraction (HFrEF) will be taken as those with ejection fraction of 50% or greater, while those with EF of 40% or less will be taken as heart failure with reduced ejection fraction (HFrEF). Patients with an EF of more than 40% but less than 50% will represent an intermediate group whose treatment will be similar to HFrEF. In addition to HF type, NYHA will be used to define the four classes of HF.6
- Testosterone treatment-naïve patients.
- Testosterone level low or in the lower half of normal range. (Normal range is 241–827 ng/dL).
Patients are willing to provide written informed consent.

Exclusion criteria
Any contraindication to transdermal testosterone therapy.
► Deranged prostate-specific antigen profile (cut-off 4 ng/mL).
► Deranged liver function.
► Deranged renal function (serum creatinine level ≥ 1.5 mg/dL).
► Malignancy.

Sample size
T-tests: Means: difference between two independent means (two groups).
Analysis: A priori: compute required sample size.
Input: Tail(s)=two.
Effect size d=0.2.
α err prob=0.05.
Power (1-β err prob)=0.80.
Allocation ratio N2/N1=1.
Output: Sample size group 1=394.
Sample size group 2=394.
Total sample size=788.

The sample size was estimated after assuming Cohen’s effect size convention (small effect size) with G*Power software.

We expect a 20% attrition rate; the total sample size would be 986 493 in each group.

METHODOLOGY
Randomisation
Computer-generated random allocation sequence will be generated using WINPEPI (PEPI for windows). Block randomisation with block size four will be done by one of the authors, YB. Sequentially numbered opaque sealed envelopes will be followed for allocation concealment by AP. KM and MD will do enrolment of the participant to the intervention.

As depicted in table 1, participants in arm ‘A’ will be receiving 5 g of testosterone gel on top of optimal medical therapy for 12 weeks. A nurse will disperse the drug. Testosterone is available as a 10 g pouch. Participants will be told to squeeze half of the pouch on a finger and apply it on the deltoid region by gentle massage over an area equal to the size of one-rupee coin. The drug will be withheld if the testosterone level increases to above normal range (>827 ng/dL).

Justification of dose
The low dose of testosterone used in the study is not associated with any significant adverse effects and is postulated to improve haemodynamic characteristics in these patients. Gel preparation is preferred because of its good efficacy, lack of variability and short duration of action (which allows immediate discontinuation in case of adverse events).

Choice of comparators
Control will be similar group of patients with heart failure and will be treated based on current standard of care as established in international guidelines.

Intervention modification
Any participant on the trial intervention, who undergoes hospitalisation or death, will be discontinued from the trial, with detailed analysis of the event in each discontinued case at the end of the study.

Intervention adherence
The participant will be asked by the nurse dispensing the trial therapy to follow-up with empty pouches of testosterone gel on the regular predefined in-person follow-ups.

Endpoints
Primary endpoints
At the end of three months
► Change in functional capacity assessment by 6-minute walk test (6MWT). This will be assessed by improvement in walking distance. Improvement of walking distance by >50 m will be taken as significant.
► Change in frailty assessment score by using FRIED criteria of frailty phenotype.
► Change in quality-of-life assessment score using Kansas City Cardiomyopathy Questionnaire (KCCQ).

Secondary endpoints
► Status of cardiac remodelling by echocardiography in improved ejection fraction (in patients with HFrEF), change in end systolic volume from baseline and change in relative wall thickness as a prognostic marker for disease progression.
► Change in BNP level from baseline as a surrogate marker.
► Adverse drug reactions related to testosterone transdermal patch.

Data collection using performa after written informed consent evaluation for all the patients will be as follows:
1. A performed proforma will be used to collect the patients’ demographic data and examination findings, along with a detailed consent form explaining the study aims, objective, methodology, conflicts and benefits as well as harms of the particular intervention.
2. All patients will undergo an echocardiographic assessment at the beginning and the completion of the study.
3. All patients will undergo baseline laboratory investigations, which will be repeated as shown in the timeline table. Testosterone will be done in a fasting state.

### Table 1

| Treatment arm | Drug |
|---------------|------|
| A             | 5 mg testosterone gel+recommended standard therapy for chronic stable heart failure |
| B             | Recommended standard therapy for chronic stable heart failure |
4. Functional capacity assessment; 6MWT\(^8\) will be performed according to standardised procedures. 6MWT distance of <300 m is a simple and useful prognostic marker of subsequent cardiac death in patients with mild-to-moderate heart failure. 6MWT is a widely available, accessible, low-cost and well-tolerated test for the assessment of the functional capacity of patients with HF. Although the cardiopulmonary exercise test (a maximal exercise test) remains the gold standard for the evaluation of exercise capacity in patients with HF, the 6MWT (submaximal exercise test) may provide reliable information about the patient’s daily activity.

5. Frailty will be assessed using FRIED criteria of frailty phenotype (most widely used and validated frailty assessment tool).\(^9\) It uses five frailty criteria: weight loss, exhaustion, low physical activity, slowness and weakness. The sum score of these five criteria classifies people into one of three frailty stages (or groups): not frail (score 0), pre frail (score 1–2) and frail (score 3–5). Fried frailty phenotype criteria are helpful for geriatric inpatient assessment, despite diagnostic limitations and has been validated for a large number of clinical settings.

6. Assessment of quality of life: this will be done and KCCQ\(^10\) comprised of the following clinically relevant domains: physical limitations, symptoms (frequency, severity and change over time), self-efficacy and knowledge, social interference and health-related quality of life.

7. Insulin resistance: glucose and insulin will be measured after overnight fasting. The blood samples will be collected in 5 mL tubes, immediately placed on ice and transferred to the biochemistry laboratory, where samples will be processed. A commercially available kit will measure plasma insulin levels by immunoradiometric assay (Siemens ADVIA CENTAUR XP immunoassay system). Insulin resistance will be estimated by the homeostasis model assessment.\(^11\)

8. Echocardiographic evaluation: it will be done by two-dimensional, M mode, and Doppler echocardiogram at baseline and at the end of the study by the same physician unaware of the patient’s clinical details.\(^12\) Cardiac remodelling will be assessed by end systolic volume, relative wall thickness of left ventricle before and after therapy in both groups by same cardiologist. Blinding: open-label trial. Table 2 shows the timeline of the study.

### Data management

All the data collected during the trial will be stored in an encrypted computer, whose access will be available to the authors of this study only. Due to the unavailability of a data and security management board in our institute, and as the data are going to be used only for academic purposes and there is or role of external industry conflicts of interest, the authors themselves will ensure the data quality is maintained according to the best available protocols, which includes collection, storage and analysis, and maintaining a registry of all reported adverse events, including individual details of those cases, which have discontinued therapy due to loss of follow-up, hospitalisation or death.

### Patient and public involvement

Patients of chronic heart failure coming to our department will be informed about the study design. They will be informed about study intervention, outcomes both favourable and unfavourable. Written informed consent will be taken from them before recruiting them into the study.

### Statistical analysis

The data will be tabulated in an Excel sheet and analysis will be done with the help of SPSS 23 software. Distribution of variables by Shapiro-Wilk’s test. Based on nature and distribution of variables, appropriate tests of significance will be applied. Primary objectives of change in 6MWT, frailty index and quality of life will be analysed using the student’s t-test or Mann-Whitney test if non-normal distribution observed. Secondary objectives of change in ejection fraction and BNP (Brain natriuretic Peptide) levels will be done by student’s t-test or Mann-Whitney test if non-normal distribution observed, and adverse drug reaction will be represented as percentages. The statistical significance will be defined as p value<0.05 and taking confidence level as 95%. Data will be analysed as per protocol and intention to treat method.

| Table 2 Timelines |
|-------------------|
| Investigations    | Baseline | 4 weeks | 6 weeks | 12 weeks |
| CBC               | ✓        |         |         |         |
| LFT               | ✓        | ✓       | ✓       |         |
| KFT               | ✓        |         |         |         |
| HBAIC and blood (F/PP) | ✓    |         |         |         |
| Serum insulin levels | ✓    |         |         |         |
| Serum testosterone | ✓ ✓ ✓ ✓ |         |         |         |
| PT/INR            | ✓ ✓     |         |         |         |
| NT pro-BNP        | ✓ ✓ ✓     |         |         |         |
| X-ray of the chest | ✓ ✓ ✓     |         |         |         |
| ECG               | ✓ ✓ ✓ ✓ |         |         |         |
| Echocardiography  | ✓        |         |         |         |
| 6MWT Score        | ✓        |         |         |         |
| Frailty test      | ✓        |         |         |         |
| KCCQ Score        | ✓        |         |         |         |
| Adverse drug reaction | ✓ ✓ ✓ ✓ |         |         |         |

CBC, Complete Blood Count; F/PP, Fasting/Post Prandial blood Sugars; HBA1C, Glycosylated Hemoglobin; KCCQ, Kansas City Cardiomyopathy Questionnaire; KFT, Kidney Function Test; LFT, Liver Function Test; 6MWT, 6-minute walk test; NTpro-BNP, N-Terminal Pro-B-Type Natriuretic Peptide; PT/INR, Prothrombin time/International normalised ratio.
Confidentiality of data and data access
The data and documents will be kept in confidentiality by the principal investigator. Patients data will not be shared and will be used only for study purposes. Patient identity will be kept confidential. The institutional ethics committee will have access to the data for study-related inspection, if necessary, but only subject to author approval and mentioning of such inspection in the final draft of publication.

Dissemination policy
All the results and analysis, including a detailed discussion of merits, demerits, shortcomings, adverse events and further research, will be made accessible to both academicians and public using publication of the data in a research journal, and the access of such a publication will be unrestricted as much as possible, for the use of larger benefit and further studies.

Ethical clearance
Clearance from the Institutional Ethics Committee of the Institution has been taken via letter no AIIMS/IEC/DHR/Reg:2020-2021/20/847, dated 21 November 2020. Written informed consent will be obtained from each study participant (Annexure-VI/VII). Information about the study and study procedure will be unrestricted as much as possible, for the use of larger benefit and further studies.

Patient Safety
All adverse events detected during the study will be informed to institute ethics committee. The patient’s adverse drug reactions in the intermediate period will be reported to the PI. In case of an injury occurring to the participant during the study, free medical management shall be given to the patient during the study, free medical management shall be given as long as required, or till such time it is established that the injury is not related to the study intervention, whichever is earlier. In case there is a permanent injury, the quantum of compensation paid shall be as per the clause mentioned in Drugs and Cosmetics Act, 1945.

DISCUSSION
This study will be an interventional study in a tertiary care centre in the northern state of India, focusing on chronic heart failure, using all standard treatment protocols, and adding testosterone, which is approved and easy to use, with better compliance. The project will help in expanding the current knowledge regarding the improvements with current standard treatments and compare them to those where testosterone is added, with data on various parameters where improvement is expected, that include, but are not limited to functional capacity, metabolic parameters and objective cardiac parameters.

Despite the concern about the long-term risk of prostate cancer, currently available data do not support a link between testosterone therapy and prostate cancer. Analysis of 18 prospective studies done by Roddak et al did not show significant changes in the level of prostate-specific antigen in any individual trial; the pooled estimates indicate a slight, although significant, increase in prostate-specific antigen levels.13

Low testosterone levels were linked to overall and cardiovascular mortality in a meta-analysis by Araujo et al, which comprised of 12 trials with over 17,000 individuals.14 Corona et al included 70 papers in their meta-analysis and showed a clear association between low testosterone and high oestradiol levels and increased CV mortality risk.15 Muraleedharan et al studied 581 males with type 2 diabetes who were followed up for 6 years. Testosterone treatment was given to 51 males for at least 2 years. Independent of comorbidities and other therapies, death rates in the low testosterone group were 20.0% against 9.1% in the normal control, and testosterone therapy decreased mortality equivalent to the controls.16 Daka et al demonstrated that low testosterone concentrations predicted acute MI (Myocardial infarction) in men with T2Diabetes Mellitus.17 Yap et al studied 3690 older males over 10 years and showed that both low and high testosterone levels were associated with all-cause mortality.18 Ischaemic heart disease mortality was lowered when dihydrotestosterone levels were higher.

A review by Muraleedharan and Jones showed that testosterone level might not be pathological, but low levels maybe a marker of illness.19

Certain studies pointed out that the use of testosterone can be detrimental to cardiac health, owing to its ability to proliferate myocardial tissue and retain fluids and salt, which can be detrimental in the long run. A study by Basaria et al in 2012, known as the TOM Trial (Testosterone in Elderly Men with Mobility limitation), showed that in men with mobility limitation, the increase in serum level of testosterone can be used to predict the risk of cardiovascular events, wherein those with the highest increase in free serum testosterone level showed the most significant risk of such events; however, logistic regression analysis of this study showed such effect is not significant to owe any harm. Other studies do not support this adverse profiling.20 An extensive review of the literature published between 1940 and 2014 found only 4 studies that reported increased CV risk.21

Owing to its proven safety profile, lower cost and wide availability, the use of testosterone has the potential to become a valuable adjuvant to the current standard of care in heart failure, as even the current regimen is not very effective, and all the approved mechanical strategies to relieve heart failure are expensive, although not shown to be more effective than conventional treatment.
modalities.\textsuperscript{22} Owing to this unmet need for a newer, more effective intervention, our study aims to fill this lacuna by including improvement not just in objective parameters but also symptom-based questionnaires to, in a way, some extent proves benefit in quality of life in such elderly patient, which in recent past has become our prime aim as physicians caring for the increasing population of elderly.

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Contributors MD conceptualised the study, MD and YB designed the study. KM and AP contributed to acquisition of data and statistical analyses. MD, MS, YB, SK and NKB drafted the manuscript. All authors reviewed the manuscript.

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Competing interests The investigators have no conflicts of interest to declare. The study will have no involvement with any organisation or entity with any financial interests. This study is not industry sponsored. This study will not use sponsored professional writers and the data will neither be accessible to the industry nor will the results be scrutinised from any external sources before publication.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Consent obtained directly from patient(s)

Provenance and peer review Not commissioned; externally peer reviewed.

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ORCID iDs
Minakshi Dhar http://orcid.org/0000-0001-6336-5179
Yogesh Bahurupi http://orcid.org/0000-0003-2433-1624

REFERENCES
1. Shah A, Gandhi D, Srivastava S, et al. Heart failure: a class review of pharmacotherapy. P T 2017;42:464–72.
2. Huffman MD, Prabhakaran D. Heart failure: epidemiology and prevention in India. Natl Med J India 2010;23:283–8.
3. Malkin CJ, Pugh PJ, West JN, et al. Testosterone therapy in men with moderate severity heart failure: a double-blind randomized placebo controlled trial. Eur Heart J 2006;27:57–64.
4. Malkin CJ, Pugh PJ, Morris PD, et al. Low serum testosterone and increased mortality in men with coronary heart disease. Heart 2010;96:1821–5.
5. Mirdamadi A, Gararyaraghi M, Pourmoghaddas A, et al. Beneficial effects of testosterone therapy on functional capacity, cardiovascular parameters, and quality of life in patients with congestive heart failure. Biomed Res Int 2014;2014:1–7.
6. WRITING COMMITTEE MEMBERS, Yancy CW, Jessup M, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of cardiology Foundation/American heart association Task force on practice guidelines. Circulation 2013;128:e240–327.
7. Perera S, Mody SH, Woodman RC, et al. Meaningful change and responsiveness in common physical performance measures in older adults. J Am Geriatr Soc 2006;54:743–9.
8. Olsson LG, Swedberg K, Clark AL, et al. Six minute corridor walk test as an outcome measure for the assessment of treatment in randomized, blinded intervention trials of chronic heart failure: a systematic review. Eur Heart J 2005;26:778–93.
9. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001;56:M146–57.
10. Greer CP, Porter CB, Bresnahan DR, et al. Development and evaluation of the Kansas City cardiomypathy questionnaire: a new health status measure for heart failure. J Am Coll Cardiol 2000;35:1245–55.
11. Matthews DR, Hosker JP, Rudenski AS, et al. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412–9.
12. Stevens ALM, Hansen D, Herbots L, et al. Exercise training improves insulin release during glucose tolerance testing in stable chronic heart failure patients. J Cardiopulm Rehabil Prev 2015;35:37–46.
13. Endogenous Hormones and Prostate Cancer Collaborative Group, Roddam AW, Allen NE, et al. Endogenous sex hormones and prostate cancer: a collaborative analysis of 18 prospective studies. J Natl Cancer Inst 2008;100:170–83.
14. Araujo AB, Dixon JM, Suarez EA, et al. Clinical review: endogenous testosterone and mortality in men: a systematic review and meta-analysis. J Clin Endocrinol Metab 2011;96:3007–19.
15. Corona G, Rastrelli G, Monami M, et al. Hypogonadism as a risk factor for cardiovascular mortality in men: a meta-analytic study. Eur J Endocrinol 2011;165:57–701.
16. Muraldeh Bahrain, Marsh H, Kapoor D, et al. Testosterone deficiency is associated with increased risk of mortality and testosterone replacement improves survival in men with type 2 diabetes. Eur J Endocrinol 2013;169:725–33.
17. Daka B, Langer RD, Larsson CA, et al. Low concentrations of serum testosterone predict acute myocardial infarction in men with type 2 diabetes mellitus. BMC Endocr Disord 2015;15:35.
18. Yeap BB, Alfonso H, Chubb SP, et al. In older men an optimal plasma testosterone is associated with reduced all-cause mortality and higher dihydrotestosterone with reduced ischemic heart disease mortality, while estradiol levels do not predict mortality. J Clin Endocrinol Metab 2014;99:E9–18.
19. Muraldeh Bahrain, Jones TH, Testosterone and mortality, Clin Endocrinol 2014;81:477–87.
20. Basaria S, Covello AD, Travison TG, et al. Adverse events associated with testosterone administration. N Engl J Med 2010;363:109–22.
21. Morgentaler A, Miner MM, Caliber M, et al. Testosterone therapy and cardiovascular risk: advances and controversies. Mayo Clin Proc 2015;90:224–51.
22. Tseng AS, Kunze KL, Lee JZ, et al. Efficacy of pharmacologic and cardiac implantable electronic device therapies in patients with heart failure and reduced ejection fraction. Circulation 2019;12:e006951.