

Novel versus Conventional sequencing of Beta-blockers, SGLT2i's, ARNI's and MRAs in stable patients with HFrEF (NovCon sequencing study): Protocol for a 5-year pragmatic, real world, single-blinded, randomised controlled trial

Sumanth Karamchand, Tsungai Chipamaunga, Poobalan Naidoo, Kiolan Naidoo, Virendra Rambiritch, Kevin Ho, Robert Chilton, Kyle McMahon, Rory Leisegang, Hellmuth Weich, Karim Hassan

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Sumanth Karamchand¹ MBChB, MMed (InternalMed), BPharm, FCP(SA), MMedSSc; Tsungai Chipamaunga² MBChB, FCP(SA), Cert Cardiology (SA); Poobalan Naidoo³ MBChB, MMedSc, BPharm; Kiolan Naidoo⁴ MPharm, BPharm; Virendra Rambiritch⁵ PhD; Kevin Ho⁶ MBBCh, FCP(SA), Cert Cardiology (SA); Robert Chilton⁷ DO, FACC, FACP, FACOI, FAHA; Kyle McMahon⁸ BSc (Maths); Rory Leisegang⁹ MBChB, BSc Eng, PhD; Hellmuth Weich² MBBCh, FCP(SA), MMed(Int), Cert Cardiology (SA); Karim Hassan¹⁰ MBChB, FCP(SA), Cert Cardiology (SA)

¹Department of Cardiology, Tygerberg Hospital, Western Cape, South Africa and Division of Cardiology, Department of Medicine, Faculty of Medicine and Health Sciences, Stellenbosch University Stellenbosch ZA

²Department of Cardiology, Tygerberg Hospital, Western Cape, South Africa and Division of Cardiology, Department of Medicine, Faculty of Medicine and Health Sciences, Stellenbosch University Stellenbosch ZA

³Department of Internal Medicine, Nelson R Mandela School of Medicine, University of Kwa-Zulu Natal, South Africa and Department of Medicine, King Edward VIII Hospital, Umbilo, South Africa Durban ZA

⁴University of South Africa Pretoria ZA

⁵Department of Pharmaceutical Sciences, Division of Pharmacology, University of Kwa-Zulu Natal Durban ZA

⁶Department of Cardiology, Life Flora Hospital, Roodeport, Gauteng Roodeport ZA

⁷Department of Medicine, Division of Cardiology, University of Texas Health Science Center at San Antonio, San Antonio, Texas San Antonio US

⁸ABX-CRO advanced pharmaceutical services, Dresden, Germany Dresden DE

⁹Department of Pharmacy, University of Uppsala, Uppsala Uppsala SE

¹⁰Department of Cardiology, Life Bay View Private Hospital, Mossel Bay, Western Cape Mossel Bay ZA

Corresponding Author:

Kiolan Naidoo MPharm, BPharm
University of South Africa
Pretoria, South Africa
Pretoria
ZA

Abstract

Background: Chronic heart failure has a high morbidity and mortality, with approximately half of patients demising within 5 years of diagnosis. Recent additions to the armamentarium of anti-heart failure therapies include the angiotensin receptor-neprylisin inhibitors (ARNIs) and sodium/glucose co-transmitter 2 inhibitors (SGLT2i). Both classes have demonstrated mortality and morbidity benefits.

Objective: To determine if early addition of ARNIs, SGLT2i's, beta blockers and mineralocorticoid receptor antagonists (within 4 weeks) will reduce all-cause mortality and hospitalisations for heart failure in patients with stable heart failure with reduced ejection fraction.

Methods: This is a single center, randomised, controlled, double arm, open label, active control, pragmatic clinical trial. Adults with stable heart failure with reduced ejection fraction and idiopathic dilated cardiomyopathy will be randomised to conventional sequencing (the control arm) (over 6 months) of anti-failure therapies and a second arm will receive rapid sequencing (over 4 weeks). Study participants will be followed for 5 years to assess safety, efficacy and tolerability of the two types of sequencing. Post-trial access and care will be provided to all study participants throughout their lifespan.

Results: We are currently in the process of obtaining ethical clearance and funding.

Conclusions: We envisage that the current study will help inform clinical practice guidelines on the optimal sequencing of anti-heart failure therapies.

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Novel versus Conventional sequencing of Beta-blockers, SGLT2i's, ARNI's and MRAs in stable patients with HFrEF (NovCon sequencing study): Protocol for a 5-year pragmatic, real world, single-blinded, randomised controlled trial

Dr Sumanth Karamchand¹, Dr Tsungai Chipamaunga¹, Dr Poobalan Naidoo², Mr Kiolan Naidoo³, Prof Virendra Rambiritch⁴, Dr Kevin Ho⁵, Prof Robert Chilton⁶, Mr Kyle McMahon⁷, Dr Rory F Leisegang⁸, Dr Helmuth Weich¹, Dr Karim Hassan⁹

¹Department of Cardiology, Tygerberg Hospital, Western Cape, South Africa and Division of Cardiology, Department of Medicine, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town South Africa.

²Department of Internal Medicine, Nelson R Mandela School of Medicine, University of Kwa-Zulu Natal, South Africa and Department of Medicine, King Edward VIII Hospital, Umbilo, South Africa

³School of Law, University of South Africa, Pretoria, South Africa

⁴Department of Pharmaceutical Sciences, Division of Pharmacology, University of Kwa-Zulu Natal, South Africa

⁵Department of Cardiology, Life Flora Hospital, Roodeport, Gauteng, South Africa

⁶Department of Medicine, Division of Cardiology, University of Texas Health Science Center at San Antonio, San Antonio, Texas, United States

⁷ABX-CRO advanced pharmaceutical services, Dresden, Germany

⁸Department of Pharmacy, University of Uppsala, Uppsala, Sweden

⁹Department of Cardiology, Life Bay View Private Hospital, Mossel Bay, Western Cape, South Africa

Abstract

Background: Chronic heart failure has a high morbidity and mortality, with approximately half of patients demising within 5 years of diagnosis. Recent additions to the armamentarium of anti-heart failure therapies include the angiotensin receptor-neprilysin inhibitors (ARNIs) and sodium/glucose co-transmitter 2 inhibitors (SGLT2i). Both classes have demonstrated mortality and morbidity benefits. Although these new therapies have morbidity and mortality benefits, it is not known whether rapid initiation is beneficial when compared to the conventional slower stepped approach. Theoretically, the quicker the right combinations are used, the more likely the beneficial effects will be experienced. However, rapid up-titration must be balanced with patient safety and tolerability.

Objective: To determine if early addition of ARNIs, SGLT2i's, beta blockers and mineralocorticoid receptor antagonists (within 4 weeks), when compared to the same therapies initiated slower (within

6 months) will reduce all-cause mortality and hospitalisations for heart failure in patients with stable heart failure with reduced ejection fraction.

Methods: This is a single centre, randomised, controlled, double arm, assessor blinded, active control, pragmatic clinical trial. Adults with stable heart failure with reduced ejection fraction and idiopathic dilated cardiomyopathy will be randomised to conventional sequencing (the control arm) (over 6 months) of anti-failure therapies and a second arm will receive rapid sequencing (over 4 weeks). Study participants will be followed for 5 years to assess safety, efficacy and tolerability of the two types of sequencing. Post-trial access and care will be provided to all study participants throughout their lifespan.

Results: We are currently in the process of obtaining ethical clearance and funding. We do not have results.

Conclusions: We envisage that the current study will help support evidence-based medicine and inform clinical practice guidelines on the optimal rate of sequencing of anti-heart failure therapies. A third placebo arm was considered, but costs would be too much and not providing study subjects with therapies with known morbidity and mortality benefits, may be unethical, in our opinion. Given the post-COVID economic downturn, and post-trial access to interventions, a major challenge will be acquiring funding for this study.

Introduction

Background

The current management of heart failure with reduced ejection fraction (HFrEF) has been revolutionized by the emergence of novel classes of drugs, namely, angiotensin receptor inhibitors/neprilysin inhibitors (ARNI's) and sodium/glucose co-transporter 2 inhibitors (SGLT2is) [1-2]. With landmark clinical trials [3-6] demonstrating efficacy of the latter drugs, there has been a paradigm shift in initiating and sequencing optimal anti-failure therapy and a concomitant re-evaluation of the evidence base that guides conventional heart failure management. The American Heart Association heart failure guideline supports the rapid titration of guideline based therapies every 1-2 weeks, with the goal of achieving target doses [7]. However, the European Society of Cardiology, does not contain a time-line for initiation of guideline based heart failure therapy [8]. Pharmacologically it is rational to use a combination of drugs that target multiple pathological mechanisms, as there is potential synergism, and better therapeutic outcomes. Theoretically, the quicker the right combinations are used, the more likely the beneficial effects will be experienced.

However, rapid up-titration must be balanced with patient safety and tolerability.

Sacubitril/valsartan, β -blockers, mineralocorticoid receptor antagonists (MRAs), and SGLT2is are disease-modifying agents that are used as combination therapy and are now regarded as foundational therapy for HFrEF [1-2]. The conventional approach to initiating and optimizing HFrEF therapy reflects the sequence in which drugs were developed and trialled over the past 40 years [1]. Clinicians initiate therapy with an angiotensin converting enzyme inhibitor or angiotensin receptor blocker, followed by a β -blocker, then an MRA, then a neprilysin inhibitor, and, finally, an SGLT2i. Each drug required up-titration to target dose, or maximally tolerated, before initiating another class of drug, a treatment period usually spanning > 6 months [1].

This approach is limited by several clinical misconceptions and assumptions as follows: 1) the most efficacious anti-failure therapies were developed first. The counter argument is exemplified by the fact that digitalis has been used in clinical practice for 200 years yet is no longer considered a key therapeutic agent, 2) drug efficacy is only achieved at maximum target doses [1]. However, studies have demonstrated morbidity and mortality reduction with the use of low dose anti-failure therapy in HFrEF, with maximum target doses adding only a smaller clinical benefit, 3) the efficacy and safety of individual anti-failure drug class was assessed in clinical trials that required patients to be receiving all background therapy at target doses. However, most trials were conducted with patients receiving sub-target doses of anti-heart failure therapy [2].

Initiating drugs over a 6-month period is undesirable for several reasons. Practically, target doses of anti-heart failure therapy are infrequently achieved due to patient factors (non-adherence, perceived adverse effects, costs), drug factors (adverse effects, frequency of dosing) physician factors (clinical inertia, limited time), inadequate patient follow up and lack of perceived benefit of higher drug doses. Furthermore, there is a strong evidence base suggesting that the use of each of the foundation drugs has demonstrated morbidity and mortality reduction within 30 days of therapy initiation [1].

The objective of this study is to determine if early addition of ARNIs, SGLT2i's, beta blockers and mineralocorticoid receptor antagonists (within 4 weeks), when compared to the same therapies initiated slower (within 6 months) will reduce all-cause mortality and hospitalisations for heart failure in patients with stable heart failure with reduced ejection fraction.

Rationale

The use of ARNIs and SGLT2i's in low-middle income country settings is limited by high cost and accessibility. Despite the strong body of evidence supporting safety and efficacy of ARNIs and SGLT2i's, these agents are not yet included in the South African Essential Drug List. ARNIs and SGLT2i's are available to private funders, yet access is limited as costs are only partially reimbursed by medical insurance schemes. Furthermore, SGLT2i's have not yet been approved for heart failure by the South African Health Products Regulatory Authority (SAHPRA) and use within clinical practice is predominantly off-label. Donations by the pharmaceutical industry have enabled limited access to ARNIs and SGLT2i's in the public sector.

The challenge in this regard, is maximising access and rationalizing use of ARNIs and SGLT2i's, whilst canvassing for widespread cost-effective roll-out in the public sector.

The data on ARNIs and SGLT2i's from high-income country settings suggest that morbidity and mortality reduction is achieved early in the clinical presentation of heart failure [1-2]. There however remains a paucity of data on the safety and efficacy of these drugs in sub-Saharan Africa.

Within sub-Saharan Africa, the main driver of heart failure remains hypertension, with ischemic heart disease emerging as a key aetiology. There however is a growing cohort of young patients with idiopathic dilated cardiomyopathy (iDCMO) with heart failure with reduced ejection fraction (HFrEF), who are often sub-optimally medically treated with minimum prospects of receiving heart transplants. In our opinion, such a group of patients would ideally benefit from ARNI's and SGLT2i's. Data from key clinical trials have demonstrated the use of ARNIs as *de novo* therapy in patients presenting with heart failure [9-11]. The latter trials have argued against the use of ACE inhibitors/angiotensin receptor blockers upfront with a transition phase to ARNI therapy, as there would be merely a delay in utilizing the most effective therapy with a concomitant risk of sudden cardiac death.

The rapid initiation of anti-failure therapy described above seems rational in a high income country setting where drug monitoring and assessment of adverse reactions are facilitated by ease and rapidity of access to healthcare facilities [1-2]. However, in low-middle income country settings, the infrequent and irregular access to healthcare facilities limits instituting the rapid initiation algorithm for heart failure therapy. Furthermore, there is a lack of robust data and randomized controlled trials comparing rapid initiation versus a slower/phased initiation of heart failure therapy [1].

- Study Objectives
 - o Primary

The primary efficacy endpoint is the composite endpoint of all-cause mortality and hospitalisation

for heart failure

- o Secondary

Secondary end points include death from cardiovascular cause (e.g., cardiogenic shock, myocardial infarction, tachy or brady-arrhythmia), improvement in 6-minute walk test (6MWT), improvement in NYHA functional class, improvement in symptoms as per the Kansas City Cardiomyopathy Questionnaire, Trans oesophageal echo determined ejection fraction [chamber dilatation, left ventricular systolic function, global longitudinal strain, speckle tracking] and NT-pro BNP levels.

Adverse drug reactions will also be collected and analysed.

Methods

Definitions

Heart failure is not a single pathological diagnosis, but a clinical syndrome consisting of cardinal symptoms (e.g. breathlessness, ankle swelling, and fatigue) that may be accompanied by signs (e.g. elevated jugular venous pressure, pulmonary crackles, and peripheral oedema). It is due to a structural and/or functional abnormality of the heart that results in elevated intracardiac pressures and/or inadequate cardiac output at rest and/or during exercise.¹² Reduced left ventricular ejection fraction: defined as ejection fraction $\leq 40\%$, i.e. those with a significant reduction in left ventricular systolic function.¹²

Proposed novel and rapid sequencing

The proposed algorithm for initiation of anti-failure therapy comprises of three steps once clinical euvolemia has been achieved with diuresis [2].

Step 1 is the concurrent initiation of treatment with a β -blocker and an SGLT2i. β -Blockers are pertinent in the treatment of HFrEF, especially in the context of reducing sudden cardiac death. Evidence has demonstrated reduced hospitalization for heart failure with use of SGLT2is. The early diuretic effect of SGLT2i's may attenuate the early risk of worsening heart failure when β -blockers are initiated [2].

Step 2 comprises of the addition of an ARNI (sacubitril/valsartan), within 1 to 2 weeks of step 1. The presence of hypotension (systolic blood pressure <100 mmHg) warrants evaluation of blood response with an ARB prior to switching to an ARNI.

Step 3 is the addition of an MRA, within 1 to 2 weeks of step 2, depending on the serum potassium and the presence and degree of renal impairment. ARNI's and SGLT2i may improve renal function and potassium homeostasis thereby permitting the use of aMRAs. In patients with hypotension MRAs may be used as step 2[2].

The above algorithm represents a generic approach and may be individualized to specific scenarios. Patients with decompensated heart failure are a subgroup that require greater caution when initiating anti-failure therapy. β -blocker therapy should only be initiated in the hospital after discontinuation of intravenous therapy for several days and the patient is clinically euvolemic, defined as the absence of rales and ascites and the presence of minimal peripheral oedema [2].

In the appropriate patient, treatment with all 4 foundational treatments may be achieved within 4 weeks, with subsequent dose up-titration. This strategy increases the probability that highly effective therapies will be implemented in a manner that reduces mortality and

hospitalizations and enhances the tolerability of subsequently administered treatments [1]. Figure 1 shows the proposed study flow diagram which contains the novel and conventional sequencing approach. A key difference is the rate at which therapies are added, with the novel sequence arm having patients on all the efficacious therapies initiated within 4 weeks.

Figure 1: Study flow attached under supplementary material

Study design

This is a prospective, double arm, randomised, assessor blinded , pragmatic clinical trial.

Study/clinical setting and recruitment procedures

The study will take place at a single site i.e. Department of Cardiology, Tygerberg Hospital, Western Cape, South Africa. Tygerberg Hospital is a teaching hospital affiliated to the University of Stellenbosch. The department is staffed by cardiologists, medical registrars, cardiac technologists and nurses with a specialisation in cardiology. There is a 25 bed coronary care unit, out-patient clinics, cardiac catheterization laboratory and echocardiography. Study participants will be recruited from the Western Cape area. Hospitals within the Western Cape area will be notified of the study via e-mail and asked to refer potential study subjects to the Department of Cardiology at Tygerberg Hospital. In addition, patients already attending the cardiology clinic at Tygerberg Hospital will be invited to participate in the study.

Recruitment site and

Selection of patients

Study participants will be adults with idiopathic DCMO who consent to participate in the study. Patients will be free to withdraw at any time. The recruitment period will be 1 year.

Study subjects will be randomised to the study arms by using a computer-generated randomisation sequence.

Inclusion, exclusion, and withdrawal criteria are listed in Table 1.

Selection of investigators

This study will be conducted at a Tertiary Level Public Hospital Department of cardiology. Investigators will be authors of this publication and other staff based at Tygerberg Hospital.

Statistical considerations

Sample size

We determined that a target number of 248 primary outcome events would provide a power of 80% to detect a 30% lower relative risk of the primary outcome in the novel sequencing arm than in the conventional sequencing arm at a two-sided alpha level of 0.05. Assuming an incidence of the primary outcome of at least 50% over 5 years in the conventional sequencing arm, and a dropout of 10 percent per arm, we established a planned enrolment of 584 patients (292 per study arm).

Analysis population

The analysis population will include all study participants included in the study. This is an intention to treat analysis and even participants that have withdrawn, or dropped out, from the study after randomisation will have their data analysed.

Statistical methods

The primary outcome, the combined risk of all-cause mortality or hospitalisation for heart failure, will be assessed in a time-to event analysis. Differences between the conventional sequencing and rapid sequencing groups for the primary objective will be assessed for statistical significance at an alpha level of 0.05, with the use of a Cox proportional-hazards model, with adjustment for prespecified baseline covariates. Treatment effects will be expressed as hazard ratios with 95% confidence intervals. Secondary objectives will be evaluated at each timepoint post-baseline using a mixed model repeated measures ANCOVA (MMRM) with baseline score used as a covariate. No imputation will be used for missing data.

All continuous parameters will be summarised using descriptive statistics: number of values, mean, standard deviation, median, minimum and maximum. All discrete(ordinal) parameters will be summarised by means of number of values, median minimum and maximum. All categorical parameters will be summarised using frequency tables (number of values %).

Patient demographic and clinical profile will be described using the statistical software SAS version 9.4. Continuous variables will be expressed as an absolute number, with associated percent, mean, standard deviation, median and range where applicable. Clinical assessment of response to heart failure therapy will be performed using the Kansas City Cardiomyopathy Questionnaire (KCCQ), New York Heart Association (NYHA) functional classification, 6-minute walk distance, and hospital admission for heart failure. Objective measures of therapy response will be ascertained via serial NT-proBNP levels and 2D Echocardiography. Echocardiographic features of response to therapy will be characterized according to left ventricular ejection fraction (LVEF) as determined by Simpson's Biplane, global longitudinal strain and speckle tracking.

Associations between outcomes and indicator variables will be explored via logistic regression. Where appropriate indicator variables and specific outcomes will be investigated individually via a univariate analysis. Where significant, variables will be entered into and controlled for in a cox-proportional hazards regression model. Adjustment for confounding will be performed via a competing risks analysis and propensity score matching.

Table 1: Statistical Methods

Ethical Principles

This study will be conducted in accordance with the principles laid down by the 18th World Medical Assembly [13]. Study participants data will be de-identified of names and surnames and identifying information. An application for ethical approval will be submitted to the Stellenbosch University Research and Ethics committee. The study will be performed in accordance with local regulations including local data protection regulations and requisite hospital and Provincial Department of Health Approval. Post-trial access and care will be provided to all study participants, throughout their lifespan.

Results

We are currently in the process of generating funding. If funding is obtained, we will apply for ethical clearance and requisite permissions

Discussion

This study aims to determine if rapid sequencing of anti-heart failure drugs with proven morbidity and mortality benefit would be superior to slower titration of these therapies.

We chose a composite endpoint to reduce the sample size as higher sample size would result in greater costs and reduce the feasibility of the study. Given the high mortality and frequent hospitalisations for heart failure, we included both events in the combined primary efficacy endpoint. Intuitively, it makes sense to ensure that the most efficacious heart failure therapies are initiated as soon as possible. Given that the therapies have varied mode of actions, we hypothesize that if they are started together as soon as possible, they would have greater benefit than starting them later. Combination therapies are likely to target different pathophysiological aspects of heart failure and thus improve clinical outcomes. Issues with rapid initiation may potentially include hypotension and other adverse effects. We will guard against hypotensive events by starting with lowest possible dose and stopping the drug if patient becomes haemodynamically unstable. Furthermore, study participants are required to be euvoletic before rapid sequencing so that we don't worsen patients heart failure and thus limit haemodynamic instability and decompensated heart failure. It is standard clinical practice to ensure euvoemia before titration of anti-heart failure therapies [9]. Euvoemia is

usually achieved by loop diuretics [9].

We chose a relatively young group of patients so that underlying issues like ischaemic heart disease is less probable and would not serve as confounders. Furthermore, this group of patients may benefit from the increased life expectancy as compared to older group.

The public health sector in South Africa has resource constraints. Often there is not enough clinicians to adequately manage the patients. Thus, doing trials in this setting is challenging. However, given the proven safety and efficacy, widespread use in developed countries, of ARNIs, SGLT2i's and MRA's we envisage limited problems. Furthermore, making these novel therapies available to a vulnerable population, would serve as a motivation for clinicians who work in this setting. The setting is a teaching and training facility and having exposure to these novel therapies will grow the expertise and skills of health care practitioners. Furthermore, we envisage reducing the complexity of the study by using a pragmatic study design so that we can integrate the trial into routine clinical practice in the department of cardiology. This will reduce the administration burden while also resulting in collection of safety, efficacy, and tolerability data. We feel that the trial would not add to the administrative burden of the clinicians as we will not ask them to do any work beyond what they usually do in the clinic. Furthermore, a separate designated individual will collect and analyse the data, so that clinicians will not be burdened with this task and not impinge on their demanding clinical work.

Post-trial access and post-trial care are contentious issues [14]. In the current study we plan to provide both post-trial access and post-trial care because it is in our opinion ethically justified. Given that the newer therapies are efficacious, safe, and tolerable, it would be unkind to stop the therapies after the trial is completed as the study participants would not be able to procure the therapy privately because of their limited financial resources. Provision of post-trial care would also increase the cost of the study, but we will continue to provide post trial care in our cardiology clinic, at no cost to the study participants.

We hope to acquire funding from the manufacturers of ARNI's, SGLT2i's, beta blockers and MRAs, as the data generated from this study as the potential to inform clinical practice guidelines. Given the high costs of doing such trials, we hope companies assist if they are only providing the drug and not covering the other clinical trial costs like investigator fees, protocol development, manuscript writing and statistical analysis, etc. The study has dual objectives of generation of evidence whilst also providing patients with access to highly efficacious and premium therapies for heart failure.

Given that both study groups will receive the same therapies, we don't pitch drugs head-to-head as we feel that the combination of drugs with proved mortality and morbidity data would be most likely

to have synergistic effects and further reduce morbidity and mortality. This approach is also more likely to generate funding as all companies can contribute to financing the study, not with risk of their products being negatively affected by head-to-head trials that show one drug being superior to another drug.

We have tried to create a “win-win” situation by generating data to inform clinical practice guidelines and also providing access to novel therapies in resource limited settings. The research can help with Masters and PhD degrees, given the rich data set generated.

Limitations

The study is proposed to utilise one study site in the Western Cape of South Africa which may not be reflective of the demographics of the South African population. Due to the nature of the study and means of intervention, implementation of a placebo controlled arm will not be possible but is nonetheless cited as a limitation.

Conclusions

Recent additions to the armamentarium of anti-heart failure therapies such as ARNIs and SGLT2is have demonstrated morbidity and mortality benefits. Earlier use of such therapy within patients with stable heart failure with reduced ejection fraction may impact upon patient outcomes. The current study will provide important data to support evidence-based medicine and will help inform clinical practice guidelines on the optimal rate of sequencing of anti-heart failure therapies.

Data availability

The data set will be made available upon written request.

Acknowledgements

We are grateful to Sanofi for paying the article processing fee

Conflicts of interest

PN: sponsored by Novartis for online attendance to ESC 2022; received drug sponsor for phase IV clinical trial from Sandoz, a subsidiary of Novartis. PN was previously employed as Medical Manager by Boehringer and was responsible for pre-registration medical activities related to empagliflozin. KH was previously employed as Medical Director by Boehringer and was responsible for pre-registration medical activities related to empagliflozin. KN is currently employed as a medical advisor at Sanofi.

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References

Multimedia appendix

Table 1: Selection criteria

Inclusion criteria:

- All patients aged 18 to 50 years who fulfils the clinical criteria for idiopathic dilated cardiomyopathy with reduced ejection fraction.
- NYHA Functional class II-IV

Exclusion criteria:

- Age > 18 years, <50years
- Unable or unwilling to provide informed consent to undergo any of the recommended investigations or to participate in the study
- Acute coronary syndrome, bypass graft surgery or other major cardiac surgery, stroke or transient ischaemic attack $\leq$ 90 days from visit 1.
- Acute decompensated heart failure

- Systolic blood pressure ≥ 180 mmHg or < 100 mmHg
- eGFR < 30 ml/min/1.73 m²
- A serum K level > 5.4 mmol/l
- History of angioedema

Withdrawal criteria:

- Patient decision to leave study
 - Adverse drug reactions
-

Supplementary Files

Untitled.

URL: <http://asset.jmir.pub/assets/62769cb1bc2b84ed03dbcbf0109257a2.pdf>

Figures

Flow diagram.

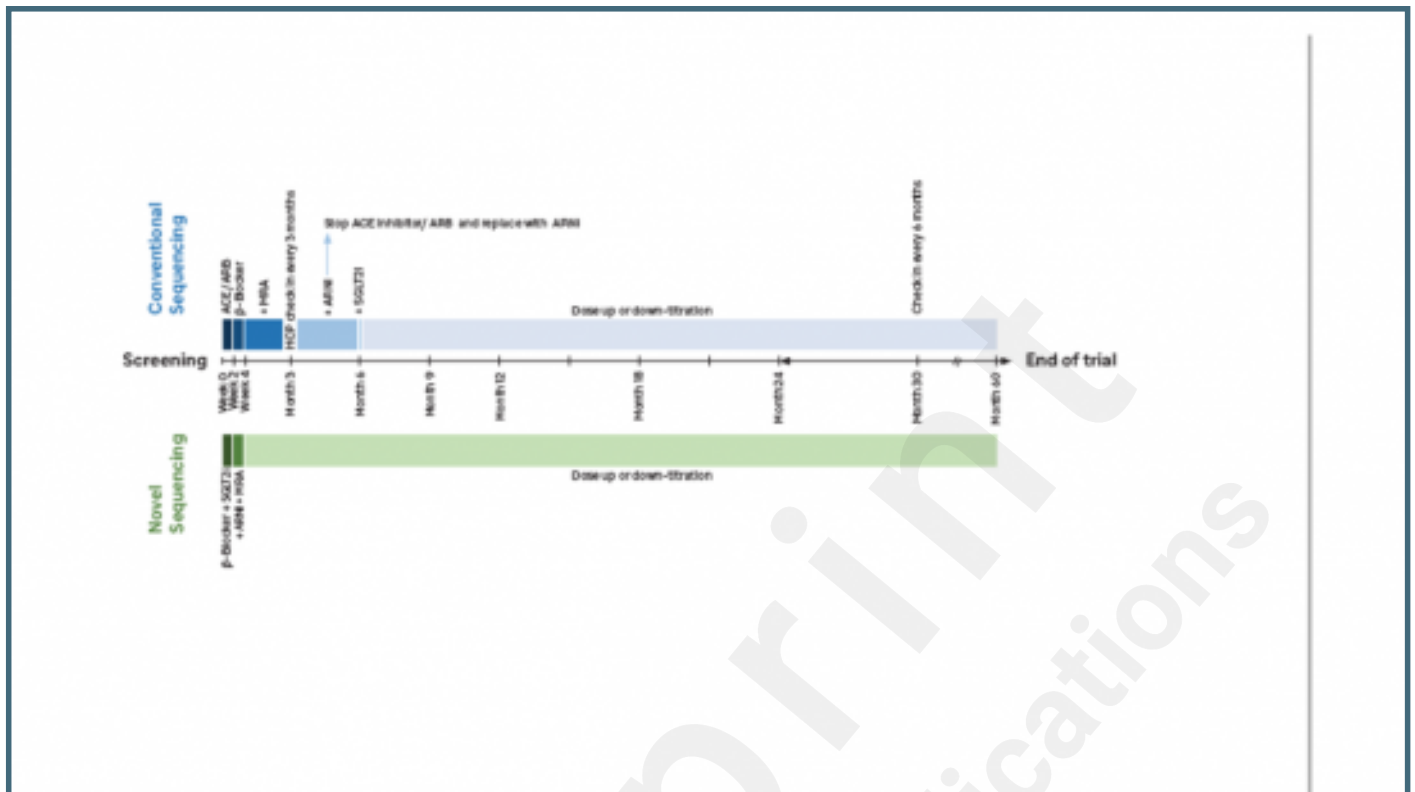


Table 1: Statistical Methods.

TABLE 1:				
Outcome measures	Hypothesis	Measure	Time points	Analysis Method
1) Primary (composite endpoints)	Intervention will reduce outcome from baseline to 5 years			
a) All-cause mortality	Rapid sequencing of anti-heart failure therapy will reduce all cause mortality	All-cause mortality (binary)	End of trial	Cox-proportional hazards regression
b) Hospitalisation	Rapid sequencing of anti-heart failure therapy will reduce all-cause mortality	Hospitalised for heart failure (binary)	End of trial	Cox-proportional hazards regression
2) Secondary endpoints				
Deaths (from cardiovascular cause)	Intervention will reduce cardiovascular related deaths	Cardiovascular mortality (binary)	End of trial	Chi-squared
6-minute walk test	Improvement in distance walked in 6 minutes	Distance in meters (continuous)	Baseline and end of trial	X
NYHA functional class	Improvement in dyspnoea	Functional class 1, 2, 3, 4 (ordinal)	Baseline and end of trial	X
KCCQ	Improvement in symptoms of heart failure	Questionnaire (ordinal)	Baseline and end of trial	X
Trans-esophageal echo	Improvement in ejection fraction	Ejection fraction measured in percentage (%) (continuous)	Baseline and end of trial	X
NT-pro and BNP levels	Reduction in levels	Concentration units (pg/ml)(continuous)	Baseline and end of trial	X