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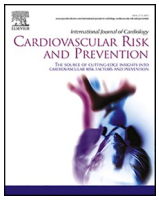

Objectively measured medication adherence using assays for carvedilol and enalaprilat in patients with heart failure in Mozambique and Nigeria

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ABSTRACT

Background: Poor medication adherence leads to poor health outcomes and increased healthcare costs among patients with heart failure (HF). This study aimed to objectively assess medication adherence by measuring carvedilol and enalaprilat plasma concentrations among patients with HF.

Methods: The present sub-study of the Safety, Tolerability, and Efficacy of Rapid Optimization, helped by NT-proBNP testing, of Heart Failure therapies (STRONG-HF) study involved adult patients with acute HF admitted in two Mozambican and two Nigerian hospitals who were not optimally treated with oral enalapril and carvedilol. Patients in the high-intensity arm of the STRONG-HF study, and those not meeting the biomarker criteria for persistent congestion, were included in the "frequent visit" (FV) arm. In the FV arm, blood for bio-analysis of plasma enalaprilat or/and carvedilol was drawn at the 2,6,12th week post-discharge. Patients in the usual care arm of STRONG-HF were included in the "standard visit" (SV) arm, which followed the usual local practice with blood sampling in week 12.

Results: The study involved 113 (79 FV and 34 SV) participants with a mean age of 48.6 years and a mean left ventricular (LV) ejection fraction of 33.1%. Theenalaprilat below the lower level of quantification (LLOQ) was documented in 7.7%, 11.9%, and 15.6% of participants in FV during the 2,6 and 12th weeks. Carvedilol concentration below LLOQ was documented in 37%, 30%, and 44.4% of participants in the FV arm during the 2,6 and 12th weeks, respectively. For the SV arm, enalaprilat and carvedilol concentrations below LLOQ in the twelfth week were documented in 37.3% and 42.9% of patients, respectively.

Conclusion: Up to a third of patients using enalapril and carvedilol did not take any medication during the 12 weeks of follow-up. Non adherence was more common in patients who had less follow up, emphasizing the

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importance of close follow up to adherence. No adherence was also more common in medications know to have more side effects such as carvedilol.

1. Introduction

Heart failure (HF) affects about 64 million people globally, at a 1–2% prevalence in the general adult population [1]. This number has been increasing because of a growing and ageing global population and improved HF survival due to enhanced therapeutic options [2]. However, HF syndrome still has high case fatality rates in most parts of Africa [3–5]. Angiotensin-converting enzyme inhibitors (ACEi), angiotensin-II receptor blockers (ARB), beta-blockers (BB), mineralocorticoid antagonists (MRA), and angiotensin receptor neprilysin inhibitors (ARNi) have apparent mortality and morbidity benefits in patients with lower ejection fractions [3,6]. These proven benefits will only translate into the real world if patients in the general population can replicate levels of adherence achieved in clinical trials [7]. As HF medications are often prescribed for life-long use, measuring and monitoring adherence is vital for reducing HF exacerbations, symptom burden, admissions, mortality, and healthcare costs [8]. Despite these clear benefits, poor adherence remains a prevalent cause of morbidity and mortality in the HF population [9,10]. Given the negative impact of poor adherence on HF treatment outcomes, there have been efforts to quantify it in different populations. With much heterogeneity in definitions of medication adherence and the method used to analyse adherence across studies, the rate of poor medication adherence varies in patients with HF, from 29% to 64% [11]. Adherence measures are either subjective, using the provider's or patient's evaluation of their medication-taking behaviour with questionnaires, patients' self-reports, pill counts, prescription refills, or objective measures, including pill counts, electronic monitoring, and biochemical measures of the drug (or a metabolite) concentration in body fluids or direct observation by healthcare practitioners [12–14].

While objective methods are more robust than subjective methods, they are often expensive, burdensome to the healthcare provider, and may be impractical for routine clinical use [12,13,15]. Given these drawbacks, most available clinical and research data on medication adherence in patients with HF is based on subjective methods, primarily from the Western world [16]. Measurement of patient medication adherence is rare in Africa, where HF mortality remains high. More accurate, objective measures are necessary to validate the subjective ones and reliably develop interventions to improve HF management in these settings [17]. As carvedilol and enalapril are common drugs used to treat HF, plasma concentrations of carvedilol and the active enalapril metabolites (enalaprilat) provide an objective approach to measuring medication adherence among HF patients [18]. Carvedilol is an α1-adrenoreceptor blocker and nonselective β-adrenoreceptor blocker, while enalapril is a prodrug of enalaprilat, an angiotensin-converting enzyme inhibitor (ACE-I) [19,20]. The current study was planned to objectively assess medication adherence by measuring drug or metabolite concentrations of carvedilol and enalaprilat in plasma.

2. Methods

2.1. Study design and participants

The STRONG-HF study's rationale, design and inclusion criteria have been described in detail elsewhere [21]. The STRONG-HF study was a multicentre, randomised, open-label, parallel-group study assessing the safety and efficacy of rapid up-titration of evidence-based, guideline-recommended therapies initiated just before discharge from an acute HF admission, coupled with frequent follow-up after discharge. Participants were eligible if they were admitted for acute HF, had N-terminal pro-B-type natriuretic peptide (NT-proBNP) >2500 pg/mL at screening that had decreased at randomisation by more than 10% but was still >1500 pg/mL, and were not optimally treated with oral HF medications, defined as taking either (a) no BBs, and ≤50% the recommended dose of ACEIs/ARBs/ARNis and MRAs, or (b) no ACEis/ARBs/ARNis and ≤50% the recommended dose of BBs and MRAs. Enrolled patients were randomised in a 1:1 ratio to either 'usual care' or 'high-intensity care'. While patients enrolled in the usual care arm were discharged and managed according to usual clinical practice at the site, for those in the high-intensity care arm, doses of oral HF medications were up-titrated to 50% of recommended doses before discharge and to 100% of recommended doses within two weeks of hospital discharge, guided by clinical assessments and laboratory values. Patients randomised to high-intensity care were seen at weeks 1, 2, 3, 6 and 12 after hospital discharge.

The adherence sub-study was a prospective cohort study that included patients enrolled in the STRONG-HF study and those screened for STRONG-HF but who did not meet the biomarker criteria for persistent congestion (NT-proBNP >2500 pg/mL at screening and NT-proBNP >1500 pg/mL at randomisation). Patients from the high-intensity care arm of the STRONG-HF study and those with HF but ineligible for STRONG-HF were included in the FV arm of the adherence sub-study. Patients in the usual care arm were included in the SV arm. Two centres in Mozambique (Maputo Central and Mavalane General Hospitals) and two in Nigeria (Amino Kano Teaching Hospital and Murtala Muhammad Specialist Hospital) agreed to participate in the sub-study (Fig. 1). The study was approved in each country by the relevant local ethics committees.

2.2. Baseline measurements and follow-up

Demographic, clinical, laboratory and echocardiographic data collected at baseline as part of the STRONG-HF study included age, gender, country, symptoms and signs of HF, plasma creatinine, urea, potassium, sodium NT-proBNP, and the echocardiographic left ventricular (LV) ejection fraction. While patients in the FV arm were followed up after 2, 6 and 12 weeks after hospital discharge, patients in the SV arm were only followed up after 12 weeks. Blood for bioanalysis of plasma enalaprilat and or/carvedilol was drawn at the second, sixth- and twelfth weeks post-discharge in the FV arm and during the twelfth week in the SV arm. On sampling day, patients were asked to omit the morning dose until the blood had been drawn. We recorded the times of the last dose and the blood draw. Venous blood was collected via phlebotomy into ethylenediaminetetraacetic acid (EDTA) tubes, centrifuged to separate plasma from red blood cells, transferred into cryovials and stored at −80° Celsius until shipment to the pharmacology laboratory at the University of Cape Town, in South Africa.

2.3. Laboratory analysis and pharmacokinetic simulation

Plasma concentrations of carvedilol and enalaprilat were quantified using a validated liquid chromatography with tandem mass spectrometry (LC-MS-MS) method developed at the University of Cape Town's Division of Clinical Pharmacology [18]. Dose and weight-specific enalaprilat trough concentrations were simulated using a population-validated pharmacokinetic model developed in treatment adherent patients and used as reference concentrations to evaluate adherence (Supplementary material). Observed enalaprilat plasma concentrations were compared to predicted concentrations from the simulation and classified as concentrations below the LLOQ (0.2 ng/mL) or those greater than LLOQ but below the 5th percentile of predicted enalaprilat plasma concentrations. While patients with plasma concentrations below the LLOQ were classified as having poor adherence, there

is less than a 5% probability that those with a concentration greater than LLOQ but below the fifth percentile of predicted enalaprilat plasma concentrations 12 h after the last enalapril dose took their previous dose. Given the short half-life of carvedilol, estimation of the dose- and weight-specific concentrations 12 h after the last carvedilol dose was impossible. Therefore, we identified participants with plasma carvedilol concentrations below LLOQ and considered them poor adherents.

2.4. Statistical analysis

Clean data were exported from the Research Electronic Data Capture (RedCap) and analysed using Stata Version 16 (Stata Corp, College Station, TX). We evaluated the distribution of continuous variables using the Shapiro–Wilk test and considered it normally distributed when the p-value was >0.05. While we reported normally distributed variables as mean and standard deviation (SD), non-normally spread continuous variables are presented as medians with the interquartile range (IQR). Categorical variables are presented as frequencies and percentages.

2.5. Ethical considerations

Informed consent in compliance with the current national and local regulations was obtained from each patient before participation in the study. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the University of Cape Town (480/2018), Mozambique (221/CNBS/19) and Nigeria (MOH/Off/797/T.1/934) human research committees.

3. Results

3.1. General characteristics of enrolled patients

The sub-study involved 113 participants from Mozambique (n = 61) and Nigeria (n = 52) (Fig. 1). Participants had a mean age of 48.3 years and were predominantly women (63.1%). Of the 79 (69.4%) participants who were in the FV arm and required regular follow-up, 19 (24.1%) patients were ineligible for the STRONG-HF as they did not meet the biomarker criteria for persistent congestion (NT-proBNP >2500 pg/mL at screening, and NT-proBNP >1500 pg/mL at randomisation). Thirty-four (30.6%) participants were in the SV arm and were followed up only once, in the twelfth week (Fig. 2). Echocardiographic results were available for 99 participants, showing a mean LVEF of 33.1%, and most participants were categorised as having HF with reduced ejection fraction. The aetiology of HF was largely non-ischemic (81%). Ninety-two participants had laboratory results that revealed a median NT-proBNP of 2760 pg/mL, mean haemoglobin of 12.8 g/dl and plasma sodium of 137.6 mmol/L (Table 1).

3.2. Reported use of enalapril and beta-blocker among enrolled patients

While enalapril was the most common ACE inhibitor, carvedilol was the beta-blocker (Table 2). Enalapril was prescribed in both the Nigerian and Mozambican cohorts. While none of the patients in Mozambique received carvedilol, the drug was the only beta-blocker prescribed for patients at the Nigerian sites. Among the 79 patients in the SV arm, the

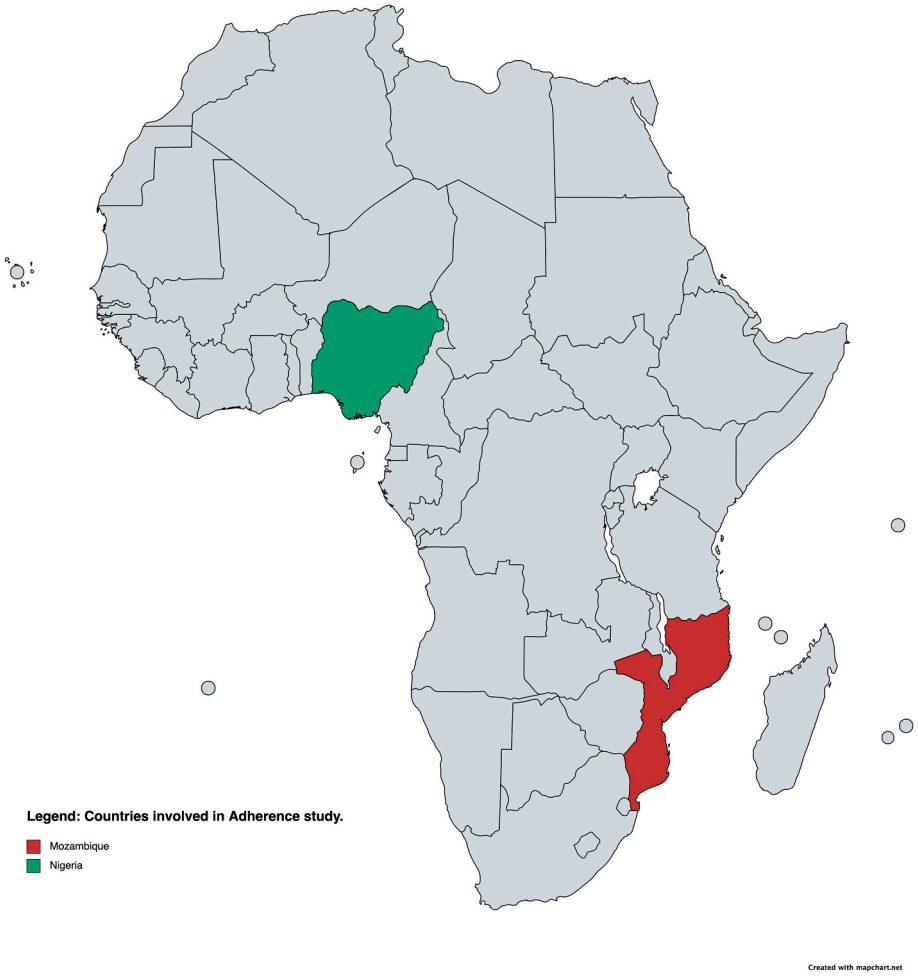

Fig. 1. Countries involved in the Adherence study – Nigeria and Mozambique.
The figure was created with MapChart [22]

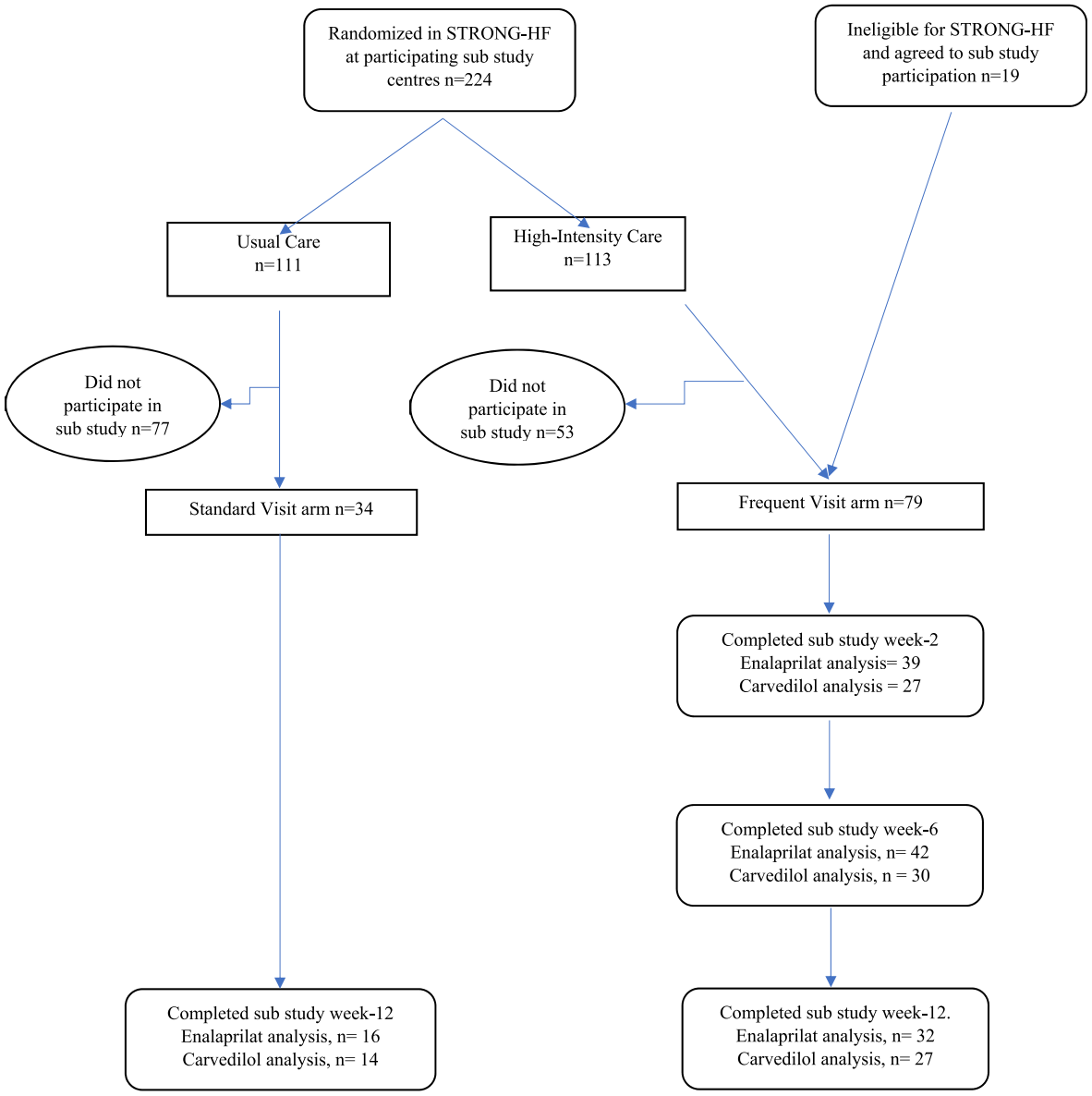

Fig. 2. HF patients enrolled in the adherence study.

reported use of ACE inhibitors declined from 52 (65.8%) at week 2 to43 (54.4%) after twelve weeks. The use of enalapril was reported in 44 (55.7%), 42 (53.2%), and 38 (48.1%) participants in the second, sixth- and twelfth weeks, respectively. Beta-blocker use was above 75%, and most patients were reportedly on carvedilol during all the visits. For patients in the SV arm, ACE inhibitors were reported in 17 (50%) participants, while beta-blockers were noted in 16(47.1%) participants at 12 weeks.

3.3. Plasma concentration of enalaprilat and beta-blocker in enrolled patients

Participants with a concentration of enalaprilat below LLOQ were 3/39 (7.7%), 5/42(11.9%), and 5/32(15.6%) of participants in the FV arm during the second, sixth- and twelfth-weeks post-discharge (Table 2). The concentration of carvedilol below the LLOQ was documented in 10/27(37%), 9/30(30%) and 12/27 (44.4%) of participants in the FV arm during the second, sixth- and twelfth weeks, respectively, after hospital discharge. Participants with enalaprilat concentrations above the LLOQ but below the fifth percentile of predicted concentrations were 9 (23.1%),7 (16.7%) and 10 (31.3%) during the second-, sixth- and twelfth week, respectively, after hospital discharge. For the standard visit group, concentrations of enalaprilat and carvedilol below the LLOQ were documented in 6/16 (37.3%) and 6/14 (42.9%) patients, respectively.

4. Discussion

This study found that a substantial proportion of participants with regular and frequent follow-up visits had concentrations of enalaprilat and carvedilol below the LLOQ 12 weeks after discharge. In those in the SV arm, the proportion of participants with concentrations below the LLOQ was higher for carvedilol (42.9%) than those with enalaprilat (37%). The lower adherence to Carvedilol as compered to Enalapril is probably related to the known more frequent adverse events associated with Carvedilol initiation. Furthermore, many patients had enalaprilat concentrations above the LLOQ but below the 5th percentile of expected plasma concentrations of enalaprilat, indicating that there was less than a 5% probability of adherence to a previous dose. This study also demonstrated that quantifying and comparing the concentration of

Table 1
Baseline characteristics of patients with HF enrolled in the adherence study.

Variables	All	FV(n = 79)	SV(n = 34)
Country			
Nigeria – n (%)	61(54.0)	43(54.4)	18(52.9)
Mozambique – n (%)	52(46.0)	36(45.6)	16(47.1)
Gender – n (%)			
Female	72(63.70)	55(69.6)	17(50)
Age, mean (SD), years	48.6(14.6)	49.0(14.7)	47.8(14.7)
BMI, mean (SD), years	25.9(6.2)	25.9(6.8)	26.1(4.8)
LVEF, mean (SD), %	33.1 (10.5)	34.4(11.1)	30.5(8.5)
LVEF category			
LVEF≤40%	86(76.1)	57(72.2)	29(85.3
LVEF >40%	14(12.4)	10(12.7)	3(8.8)
Missing	13(11.5)	12(15.2)	2(5.9)
Stroke/TIA – n (%)	4(3.6)	3(3.8)	1(2.9)
Diabetes – n (%)	5(4.4)	5(6.3)	32(94.1)
Atrial fibrillation	3(2.7)	3(3.8)	0
NT-ProBNP, median (IQR),pg/mL	2760.0 (1977.5, 6776.5)	2654 (1834.5,6696.5)	2749.5(2059.8, 7130.5)
Pulse, mean (SD), bpm	89.7(11.0)	89.9(11.7)	89.5(9.6)
SysBP, mean (SD), mmHg	127.2(17.4)	129.3(17.5)	123.6(16.8)
DiaBP, mean (SD), mmHg	84.89(11.1)	86.0(11.8)	89.5(9.6)
Sodium, mean (SD), mmol/L	137.6(3.4)	137.4(3.1)	138.0(3.9)
Potassium, mean (SD), mmol/L	4.0(0.5)	4(0.5)	4.1(0.5)

Legend: ALT-alanine aminotransferase; AST-aspartate aminotransferase; BMI – body mass index; DiaBP – diastolic blood pressure; HF – heart failure; LVEF – left ventricular ejection fraction; IQR – interquartile range; SD−standard deviation, SysBP – systolic blood pressure; TIA-transient ischemic stroke.

Table 2
Plasma concentrations of Enalapril and Carvedilol among patients with reported use in the adherence study.

Adherence	Frequent-visit arm			Standard-arm visit
	Week-2	Week-6	Week-12	Week-12
ACE inhibitors use reported – n	52	42	43	17
Enalapril use reported – n	44	42	38	17
Enalaprilat measured, – n	39	42	32	16
Concentration < LLOQ – n (%); 95%CI	3(7.7) [0–17.3]	5(11.9) [0.9–22.9]	5(15.6) [1.5–29.8]	6(37.3) [13.8–61.2]
LLOQ < concentration <5th Percentile– n (%); 95%CI	9(23.1) [6.7–37.6]	7(16.7) [4.2–29.1]	10(31.3) [13.6–48.9]	4(25.0) [0.7–49.3]
Beta blocker use reported, – n	61	63	61	15
Carvedilol use reported, – n	43	39	43	14
Carvedilol measured, – n	27	30	27	14
Concentration < LLOQ– n (%); 95%CI	10(37.0) [17.0–57.1]	9(30) [11.9–48.1]	12(44.4) [23.8–65.0]	6(42.9) [16.9–68.8]

Legend: LLOQ -lowest limit of quantification (0.2 ng/mL for both carvedilol and enalaprilat.

enalaprilat with dose- and weight-specific simulated concentrations can assess medication adherence in HF patients.

Although the poor adherence rate in our cohort is within the 29% to 64% reported in patients with HF in a different setting, most of the available evidence is from methods marred by subjectivity [10,23]. Nevertheless, the poor adherence to enalapril and carvedilol is concerning, given that most of our participants were from a clinical trial where adherence to prescribed medications is expected, and the study environment is usually controlled [21]. The positive effects of a rapid up-titration of guideline-directed medication and close follow-up after an acute HF admission on morbidity, quality of life and mortality in the STRONG-HF study are likely an underestimation [21]. Translating these findings into routine clinical practice, where clinicians take for granted that patients follow instructions and understand why they were prescribed medications, it is apparent that poor medication adherence is a growing concern in clinical practice. As a result, many patients with HF have problems following their prescribed regimen and may not obtain optimum clinical benefits. Failure to identify poor medication adherence can promote needless intensification of therapy, which may adversely affect compliance due to the increased pill burden or regimen complexities. However, the available methods of assessing medication adherence in patients with HF are based on self-reported adherence measures subject to subjectivity [16]. As a result, the estimation of adherence in clinical practice correlates poorly with actual adherence due to recall bias and social desirability responses from interviewees, leading to an overestimation of actual adherence [13,16]. In this study, we estimated plasma drug and metabolite concentrations as objective adherence measures. With an average plasma half-life of 7–10 h, carvedilol requires twice-daily dosing [19]. Therefore, a plasma concentration of carvedilol below LLOQ may imply missing at least a single dose of carvedilol.

On the contrary, enalapril has detectable inhibition of plasma ACE for more than 24 h after a single clinical dose [20]. Hence, plasma concentrations of enalaprilat below the lowest limit of quantification may signify missed doses of enalapril for a few days, making enalaprilat concentration a better marker of adherence than carvedilol in our model. Though considered an adequate and objective method, routine quantification of enalapril may be expensive and burdensome to the healthcare provider. Efforts to make them more practical for everyday clinical use are paramount because of mounting evidence that objectively assessed poor medication adherence is related to increased morbidity and mortality in HF [10,16].

Although the current study may be limited by potentially enrolling individuals likely to be adherent, participants' mean age and gender distribution are like HF cohorts in sub-Saharan Africa. Like our participants, HF cohorts in sub-Saharan Africa are young and predominantly women, thus confirming the significance of our findings in the region [4,24,25]. While the assessment of plasma concentration of carvedilol and enalaprilat offers objective evidence of adherence, variations in drug pharmacokinetics and drug-drug interactions may interfere with the accuracy of the evaluation.

In conclusion, the concentrations of carvedilol and enalaprilat below the LLOQ that may indicate poor medication adherence are prevalent in HF patients. Over time, there appears to be a progressive decline in adherence to carvedilol and enalapril. Poor adherence was also prevalent in patients with fewer follow-up visits. Poor adherence was more common with carvedilol which is known to have more side effects. These findings highlight the potential role of regular objective measurement of medication adherence in HF management.

Credit author statement

Julius Chacha Mwita contributed to the data cleaning, formal analysis, Visualization, writing of the original draft and editing of the manuscript. Andre Joubert contributed to the manuscript review and editing of the manuscript. Hadiza Saidu contributed to the conception, data collation, review and editing of the manuscript. Mahmoud Umar Sani contributed to the conception, data collation, review and editing of the manuscript. Albertino Damasceno contributed to the conception, data collation, review and editing of the manuscript. Ana Olga Mocumbi contributed to the conception, review and editing of the manuscript.

Phumla Sinxadi contributed to the review and editing of the manuscript. Charle Andre Viljoen contributed to the review and editing of the manuscript. Julian Hoevelmann contributed to the review and editing of the manuscript. Manna Semere Gebreyesus contributed to the review and editing of the manuscript. Paolo Denti contributed to the review and editing of the manuscript. Roeland Wasmann contributed to the review and editing of the manuscript. Gary Maartens contributed to the review and editing of the manuscript. Lubbe Wiesner contributed to the review and editing of the manuscript. Simon Stewart contributed to the review and editing of the manuscript. Beth Davison contributed to the review, visualization and editing of the manuscript. Gad Cotter contributed to the conception, review and editing of the manuscript. Karen Sliwa contributed to the conception, supervision, project administration, data collation, review and editing of the manuscript Funding acquisition.

Declaration of competing interest

The authors have no conflict of interest to declare.

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Appendix A. Supplementary data

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