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Comparative Efficacy of Angiotensin Converting Enzymes Inhibitors and Angiotensin Receptor Blockers in Patients with Heart Failure in Tanzania: A Prospective Cohort Study

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Abstract:-

- ***Background***

Heart failure has been a rising concern in Tanzania. New drugs have been introduced, including the group of drugs called Angiotensin receptor Neprilysin inhibitors (ARNI), but due to their high cost, angiotensin-converting enzymes inhibitors (ACEIs) and Angiotensin receptor blockers (ARBs) have been mostly used in Tanzania. However, according to our knowledge, the efficacy comparison of the two groups is yet to be studied in Tanzania. The aim of this study was to compare the efficacy of ACEIs and ARBs among patients with heart failure.

- ***Methodology***

This was a hospital-based prospective cohort study done at Jakaya Kikwete Cardiac Institution (JKCI), Tanzania, from June to December 2020. Consecutive enrollment was done until fulfilling the inclusion criteria. Clinical details were measured at baseline. We assessed the relationship between ARBs and ACEI users with N-terminal pro-Brain natriuretic peptide (NT pro-BNP) levels at admission and at 1-month follow-up using a chi-square test. A Kaplan-Meier curve was used to estimate the survival time of the two groups.

- ***Results***

155 HF patients were enrolled, with a mean age of 48 years, whereby 52.3% were male, and their mean left ventricular ejection fraction (LVEF) was 37.3%. 52 (33.5%) heart failure patients were on ACEIs, 57 (36.8%) on ARBs, and 46 (29.7%) were neither using ACEIs nor ARBs. At least half of the patients did not receive a Guideline directed medical therapy (GDMT), with only 82 (52.9%) receiving a GDMT. A drop in NT pro-BNP levels was observed during admission and at 1-month follow-up on both groups, from 6389.2pg/ml to 4000.1pg/ml for ARB users and 5877.7pg/ml to 1328.2pg/ml for the ACEIs users. There was no statistical difference between the two groups when estimated by the Kaplan-Meier curve, though, more deaths were observed in those who were neither on ACEIs nor ARBs, with a calculated P value of 0.01.

- ***Conclusion***

This study demonstrates that ACEIs have more efficacy and overall better clinical outcome than ARBs, but this should be taken under the patient-based case, considering the side effects of ACEIs and patients' adherence.

Keywords:- *Angiotensin Converting Enzymes Inhibitors, Angiotensin Receptor Blockers, Guideline Direct Medical Therapy, N-Terminal Pro-Brain Natriuretic Peptide.*

I. INTRODUCTION

Heart failure (HF) is a global public health problem, affecting approximately 26 million people worldwide [ ]. The increase of none communicable diseases e.g. Hypertension (HTN), Diabetes Mellitus (DM), dyslipidemia and life style changes in low- and middle-income countries (LMICs) has led to an increment of heart failure cases, as documented in a meta-analysis done in Africa [ ]. Natriuretic peptides have been used as diagnostic and prognostic biomarkers for heart failure [ ]. Due to the burden of heart failure, every year different heart failure societies sit and discuss new regimens to improve the quality of life and heart remodeling. New drugs have been introduced including the group of drugs called Angiotensin receptor Neprilysin Inhibitor (ARNI); Sacubril-Valsartan as published in the PARADGM TRIAL comparing it with angiotensin converting enzyme inhibitors (ACEIs). These drugs have shown more effectiveness in HF with reduced ejection fraction compared to ACEIs [ ]. Long before this drug was introduced, already HF was responsible for more death in LMICs compared to western countries, mostly due to failure in being prescribed guideline directed medical therapy (GDMT) [ ]. In Tanzania, HF has been more prevalent not only on middle class population but also in low class population, whereby not only they cannot afford

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drugs like in ARNI group, but also availability of it, especially in remote areas is difficult [ ]. Drugs in group of Angiotensin receptor blockers (ARBs), have been widely used to these patients than ACEIs, mostly due to adherence, mostly taken as a once daily dose, compared to ACEIs that are mostly taken twice or thrice a day, also considering the side effects of ACEIs, that is mostly cough. A meta-analysis study has shown that ACEIs have been more effective compared to ARBs [ ], bringing the question, could more patients with HF in Tanzania benefit from the use of ACEIs rather than ARBs, should our practice change? However, no studies have compared the efficacy of the two groups by assessing them with the levels of natriuretic peptides. In response to this problem, we therefore used the natriuretic peptide plasma NT pro-BNP and assessed it with the two groups during admission and at 1-month follow-up, and estimated the survival rate between the two groups within the 6-month study period in a Tanzanian population.

- *Objectives*

This study aimed to compare the efficacy of ACEIs and ARBs in patients with heart failure and specifically to associate between plasma NT pro-BNP levels with ARB and ACEIs, and to determine the clinical progression between the two groups.

II. METHODOLOGY

- *Study Design*

This was a hospital-based prospective cohort study.

- *Study Settings*

The study was done at Jakaya Kikwete Cardiac Institution (JKCI), Ilala district, Dar-es Salaam, Tanzania. JKCI is one of a national tertiary level referral hospital basing mainly on cardiac diseases, both medical and surgical. It has a capacity of 103 beds serving about 800 patients per week. It receives patients from the 5 municipalities in Dar es Salaam (Ilala, Kinondoni, Kigamboni, Ubungo and Temeke) but also receives referral cases from the other 26 regions of the country. It also serves as a teaching hospital for Muhimbili University of Health and Allied Sciences (MUHAS). The study was conducted for a period of six months (June 2020- December 2020.) The investigator on a daily basis visited the cardiac wards to look for any patient with a diagnosis of HF as per attending physicians' diagnosis and confirmed the diagnosis using the Framingham criteria**.** Consecutively patients with HF diagnosis were then recruited in the study. One research assistant was engaged to help with data collection to recruit all patients with HF. Patients were given an appointment date to visit the clinic after 1 month from their discharge date. During the visit, a detailed history of any cardiovascular events or change in medication was taken, and a thorough physical examination was done to determine the patient's clinical status and a follow up NT pro- BNP was taken. To maintain contact, patients were called through their mobile phone during the 1-month period post discharge. Patients whose mobile phones were not reached were traced through their next of kin's mobile phones. For patients whose mobile phones were not reached, the investigator determined if the patient was alive or passed away at that time. All alive patients were reminded of their 1-month clinic visit for physical assessment. All information was recorded in the patients' data collection forms.

- *Participants*

All in-patients who were diagnosed to have HF by the attending physician and admitted, aged 18 years and above, and excluded HF patients with CKD.

- *Variables*

Socio-demographics such as age, gender, level of education, occupation, and residence. The primary outcome was the overall clinical progression at 1-month follow-up and mortality within the 6-month study period. Age, sex and smoking were considered as possible confounders.

- *Data Sources/Measurements*

After a consecutive sampling, patients were then categorized into two groups, those who were on ARBs and on ACEIs. Some patients were using neither of the two groups, and were separately grouped. Two different strategies for assessing NT pro-BNP were examined: Admission levels and the percent change in NT pro-BNP levels from admission to follow up. For all patients, a blood sample was taken within 12 hours of admission and this was considered as admission NT pro-BNP. Follow up NT pro-BNP was done at 1 month after the baseline test was taken. Other baseline laboratory results like haemoglobin level, creatinine level as well as Blood Urea Nitrogen (BUN) were obtained from patients' files and recorded in data collection forms. Echocardiogram results were obtained from detailed echocardiogram examination done within the index admission, where the ejection fraction was the main parameter taken though other parameters were also assessed like diastology but was not used in this study.

- *Bias*

To minimize this, all patient was followed equally, when patients returned to their clinics at 1-month follow-up, all physicians were blinded from the study, where patients were asked whether they used their medications daily. Patients who were from outside the city, were advised to remain in the city for 1 month after being discharged, and for those who didn't, an arrangement with their general doctor was done, and at 1-month period, we communicated with their doctors for feedback.

- *Sample Size*

The sample size was calculated by using the following formula, Nr =Z2p (1-p)/e2 and adjusted for finite population, sample size n, n= nr/(1+(nr-1)/N), hence, the required sample was approximated to 155 patients. The prevalence used from this study was 45%, from the Kelsey study [ ].

- *Statistical Methods*

Data was entered on IBM SPSS version 26. Descriptive statistics were analysed using frequency for categorical variables and median (IQR) and mean ± SD for numerical variables. A p-value of less than 0.05 was

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considered statistically significant. A Chi-square test was used to assess the relationship between ARB and ACEIs users with NT pro-BNP levels at admission and at 1-month follow-up, illustrated by a Box and Whiskey plot. A Kaplan-Meier curve was used to estimate the survival time.

- *Ethics Aspect*

Ethical clearance to conduct the study was obtained from Muhimbili University of Health and Allied Sciences' Ethical Review Board. Permission to do the study was obtained from JKCI management. Informed consent was obtained from all study participants before they were enrolled in the study. Cases eligible to participate in the study were included only after being provided with informed consent.

III. RESULTS

Patient baseline demographic and clinical characteristics are reported in Table 1. The mean age of the study patients was 48 ± 16 (range 18-81) years, and 81 (52.3%) of the patients were males. Most study patients were living in Dar es Salaam 108 (69.7%), were married 112 (72.3%) and were college graduates 71 (45.8%). Cigarette smoking and alcohol consumption was present in 19 (10.3%) and 29 (18.7%) of study patients, respectively. Hypertension was present in half of the study patients 78 (50.3%), while history of diabetes mellitus was present in 31 (20%) study patients. The mean systolic and diastolic blood pressure was 124 mmHg ± 20 mmHg and 76 mmHg ± 13 mmHg respectively. The mean BMI among study patients was 22.6 kg/m ± 6.3 kg/m2. Majority of the patient studied had reduced LVEF with a mean of 37.3% ± 10.7%. (Table 1).

- Table 2 shows an almost equal distribution of ACEIs and ARB users. not up to half of the patients did not receive a GDMT", with only 82 (52.9%) receiving a GDMT.

- In Table 3. Shows there was minimal confounding between the two groups in terms of sex. By the direct acyclic graph, smoking and age had direct impact on ARB users compared to ACEI users.

- Figure 1: Flow chart showing enrolment of study patients.

- Figures 2a&2b shows patients who were on ARBs during admission had a median NT pro-BNP levels of 6389.2pg/ml, this was reassessed at 1-month follow-up, as shown in figure 2, where the levels of NT pro-BNP dropped to 4000.1pg/ml. The same was done for ACEIs as shown in Figures 3a&3b, where during admission those on ACEIs had a median level of NT pro-BNP of 5877.7pg/ml and at 1-month follow-up dropped to 1328.2pg/ml.

- Figure 4a&4b shows the mortality estimates during the 6 months study period. There was no statistical difference between ARB and ACEIs groups but more deaths were observed on those who were neither on ACEIs nor ARBs, with a calculated P value of 0.01, while those under GDMT and who were not on GDMT, had a calculated P value of 0.08, which was statistically not significant.

- Figure 5: The spearman correlation ranking test, as plotted in a scatter plot (Figure 5), showed a strong negative correlation between NT-proBNP levels and LVEF (r = -0.7), as the LVEF reduced, the levels of NT-proBNP increased, with a P value of < 0.001, which was statistically significant.

IV. DISCUSSION

Heart failure is known to be a progressive disease, and patients are at higher risks of suffering cardiovascular events at any point of their disease course, despite of the advances of newer drugs and procedures [ ]. Increased prevalence of HF in Tanzania, has made a need to search for regimens to improve the quality of life of these patients and in order to do so, ACEIs and ARBs have been among the groups of drugs recommended to improve the process of cardiac remodeling and improve quality of life [ ]. Different studies have shown the effectiveness of ACEIs over ARBs, although in Tanzania no such studies have been conducted, furthermore, no studies have been conducted using natriuretic peptides (NT pro-BNP) to compare the two group of drugs.

Majority of the patients in Tanzania who are having heart failure are middle aged, as seen in this study, the median age is 48years, with risks like hypertension (50.3%), rheumatic heart disease (31.6%) and Diabetes Mellitus (20%) [ ]. Among the risk factors for the latter diseases includes poverty which mainly lead to life style changes. These factors make it difficult for majority of the patients to be prescribed a GDMT compared to western countries [ ]. To be on a GDMT, at least a patient should be on either ACEIs/ARB or ARNI with a betablocker, mineralocorticoid antagonist receptor (MRA) and a Sodium Glucose Cotransporter 2(SGLT2) Inhibitor [ ]. This has proved to be a challenge in Tanzania, with only 52.9% receiving a GDMT accounting to almost half of the patients not being on GDMT for heart failure. Patient under GDMT in this study were on a loop diuretic, ACEI or ARB, MRA and beta blocker once out of pulmonary edema. Our study has also shown that 33.5 % and 36.8 % of patients had been on ACEIs and ARBs respectively. Enalapril 5mg, twice daily and lisinopril, 10mg, once daily dose was the two ACEIs used within the patients studied, while Candesartan, 8mg, once daily and Telmisartan, 80mg, once daily doses were the ARBs used.

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There is evidence that Natriuretic Peptides are independent predictors of total mortality, cardiovascular mortality, and HF hospitalizations in both acute and chronic HF patients [ ]. In-hospital BNP changes with HF patients appear to be a strong independent predictor of re-hospitalization and mortality [ ]. In this study, patient on ACEIs, not only had, lower levels of NT pro-BNPs on admission, but also at 1 month follow, there was a significant drop of the levels comparing with those who were using ARBs. These biomarkers can predict mortality as published in the previous study done with the same cohort. The survival curves in this study did not show any statistical difference between the two groups (ACEIs and ARBs groups), though using the biomarkers, it still suggests that ACEIs patients will benefit more in terms of the primary outcome. ARNIs have been a newer group introduced, which has showed to be effective than ACEIs, but due to its less availability especially in remote areas and its high cost, it has not yet been widely used in Tanzania. The limitations of this study are, small sample size and study period, which makes a need and way for a larger study to be conducted.The limitation of this study is the sample size is small and the follow-up time period was short. This makes a room for a larger study to be conducted. There was minimal bias in the study and the confounding factors were taken into consideration.

V. CONCLUSION

Heart failure is rising concern in Tanzania. GDMT has not well been practiced, as shown in this study, with cost of medications being a major contributing factor. ACEIs and ARBs have slightly been cost effective compared to ARNI, and this study shows that ACEIs, as shown from other studies, has more efficacy and overall better clinical outcome than ARBs, but this should be taken under patient-based case, considering the side effects of ACEIs and patients adherence.

- *What is Already Know on this Topic*

What this study adds to what was known, is that, it is the first study to compare between the two groups by using biomarker NT pro-BNP in our country.

- *What this Study Adds*

This study will contribute in reminding more Tanzanian doctors on the use of GDMT for heart failure patients.

- *Competing Interests*

The authors declare no financial or non-financial competing interests.

- *Authors' Contributions*

All the authors have contributed to this manuscript in ways that comply with ICMJE authorship criteria. All the authors have read and approved the final version of the manuscript.

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ANNEX

➢ Tables and Figures

- Table 1. Socio-demographic and clinical characteristics of the study patients
- Table 2. Baseline Pharmacological Characteristics
- Table 3. Distribution of Confounder's

- Figure 1: Flow chart showing enrolment of study patients
- Figure 2a. NT pro-BNP (pg/ml) levels and ARBs during admission
- Figure 2b. NT pro-BNP (pg/ml) levels and ARBs at 1-month follow up
- Figure 3a. NT pro-BNP (pg/ml) levels and ACEIs during admission
- Figure 3b. NT pro-BNP (pg/ml) levels and ACEIs at 1-month follow-up
- Figure 4a&4b. Kaplan-Meier curve estimates of survival
- Figure 5. Scatter plot showing correlation between NT-pro BNP levels and LVEF

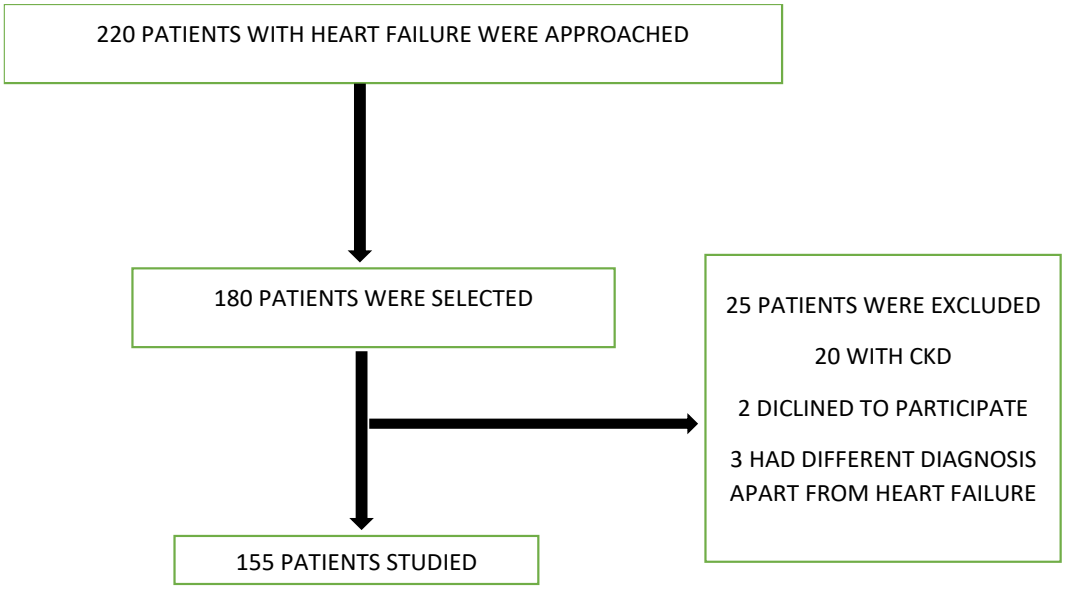

Fig 1 Flow Chart Showing Enrolment of Study Patients

Table 1 Socio-Demographic and Clinical Characteristics of the Study Patients, N=155

Variable	n (%) / mean (SD)
Age group (years), n (%) ≤ 25	8 (5.2)
26 - 35	40 (25.8)
36 - 45	26 (16.8)
46 - 60	45 (29.0)
>60	36 (23.2)
Mean (SD) age (years)	48 (16)
Males, n (%)	81 (52.3)
Residing in Dar es salaam, n (%)	108 (69.7)
Marital status, n (%)	
Single	30 (19.4)
Married	112 (72.3)
Divorced	9 (5.8)
Widowed	4 (2.6)
Education, n (%)	
No formal education	14 (9.0)
Primary	28 (18.1)
Secondary	3 (1.9)
High school	39 (25.2)
College	71 (45.8)
Taking alcohol, n (%)	29 (18.7)
Ever smoked cigarettes, n (%)	19 (10.3)

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Cardiovascular risk factors, n (%)	
Hypertension	78 (50.3)
Diabetes	31 (20)
Rheumatic heart disease	47 (31.6)
Arrhythmias	23 (15.5)
Mean (SD) SBP (mmHg)	124.8 (20.5)
Mean (SD) DBP (mmHg)	76.1 (13.1)
Mean (SD) BMI (kg/m^2)	22.6 (6.3)
BMI category, n (%)	
Normal	152 (98.1)
Underweight	23 (14.8)
Overweight	97 (62.6)
Obese	35 (22.6)
Mean LVEF (%)	37.3 (10.7)

N: Number of patients, SD: Standard deviation, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, BMI: body mass index was calculated using height and weight (BMI= weight in kg /height in meters2

Table 2 Baseline Pharmacological Characteristics, N=155

VARIABLE	N (%)
ACEIs	52 (33.5)
ARBs	57 (36.8)
NO ARBs/ACEIs	46 (29.7)
GDMT	82 (52.9)

Aceis; Angiotensin Converting Enzyme Inhibitors, Arbs; Angiotensin Receptor Blockers; GDMT; Guideline Directed Medical Therapy

Table 3 Distribution of Confounder's

	ARBs	ACEIs
AGE, years (mean)	51	46
Male (mean)	24	20
SMOKING (n)	47	39

ACEIs; Angiotensin Converting Enzyme Inhibitors, Arbs; Angiotensin Receptor Blockers

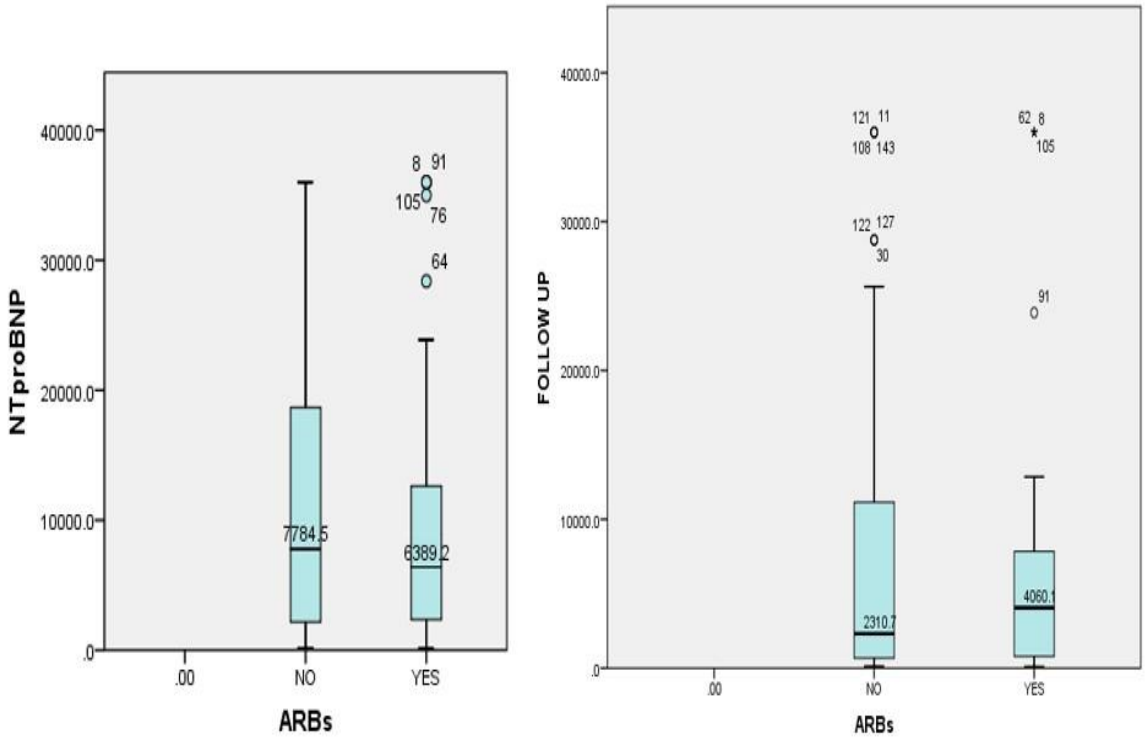

Figure 2a.NT pro-BNP (pg/ml) levels and ARBs during admission Figure 2b.NT pro-BNP (pg/ml) levels and ARBs at 1-month follow up

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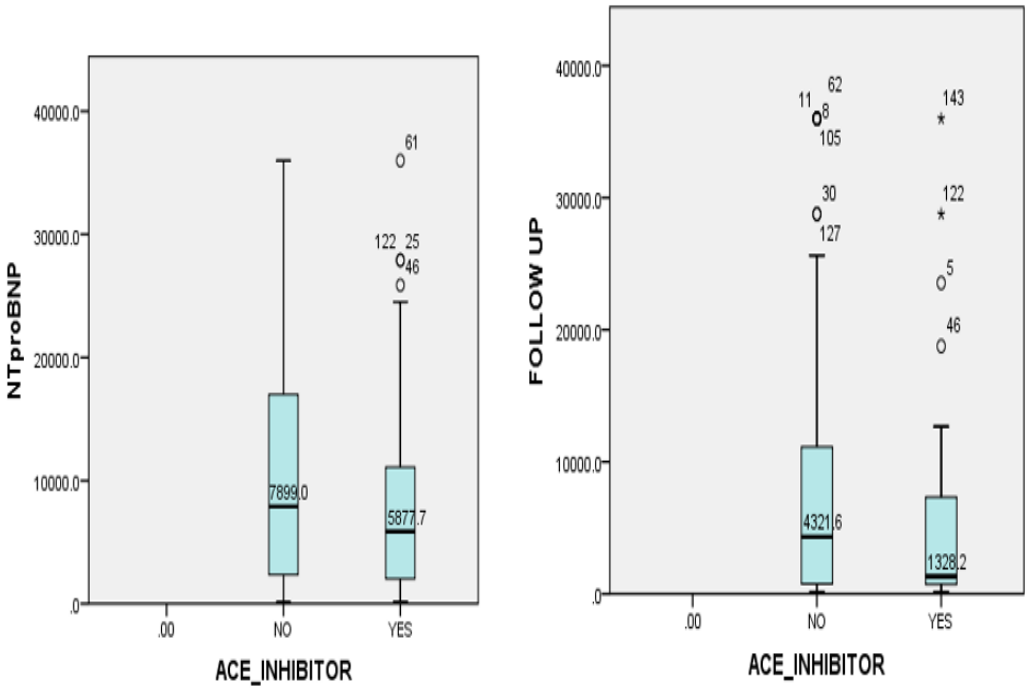

Figure 3a. NT pro-BNP(pg/ml) levels and ACEIs during admission Figure 3b.NT pro-BNP(pg/ml) levels and ACEIs at 1-month follow-up

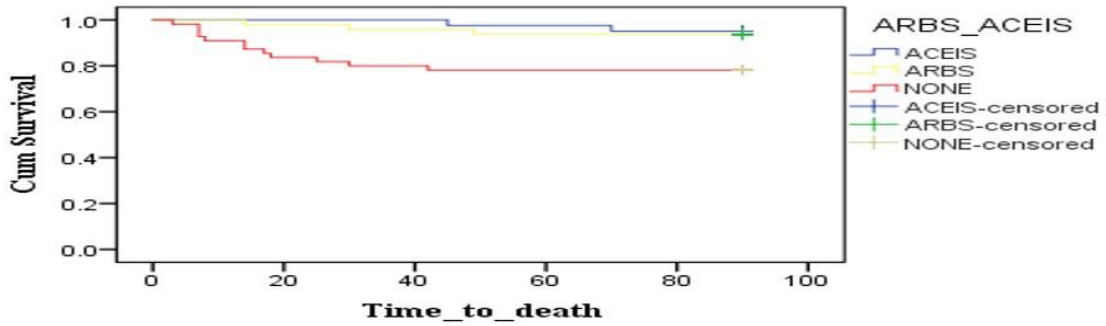

Figure 4a.

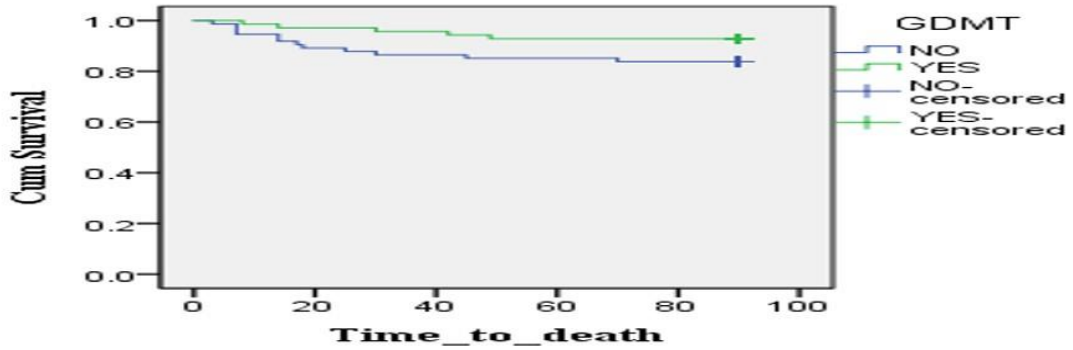

Figure 4b

Figure 4a&4b. Kaplan-Meier curve estimates of survival

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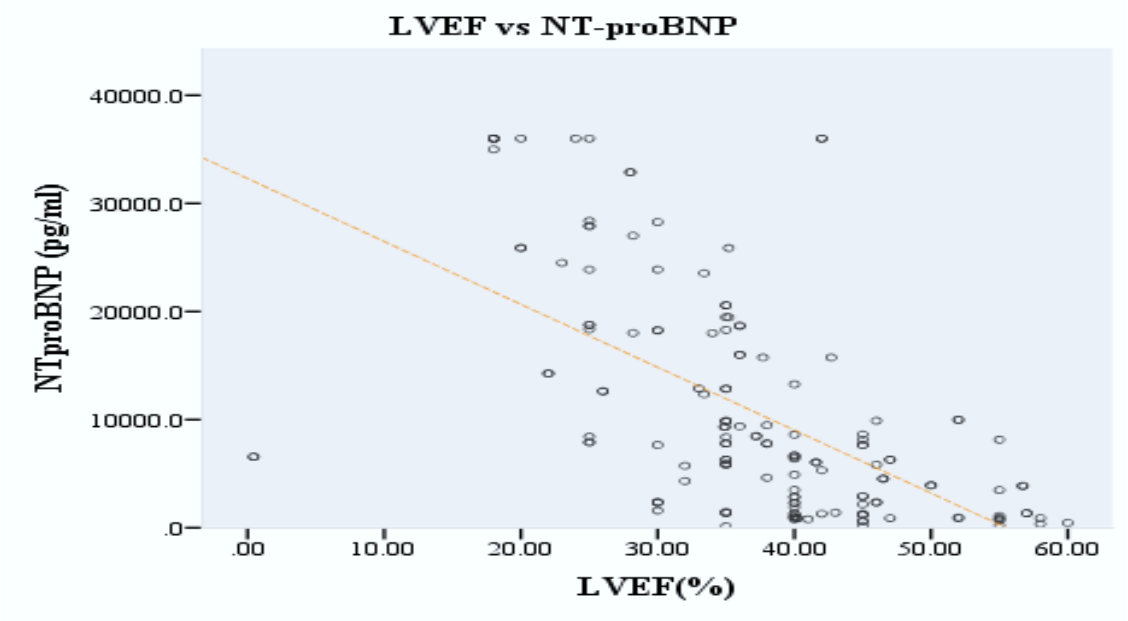

Fig 5 Scatter Plot Showing Correlation Between NT-Probnp Levels and LVEF

STROBE Statement—Checklist of items that should be included in reports of cohort studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	2
Objectives	3	State specific objectives, including any prespecified hypotheses	2
Methods			
Study design	4	Present key elements of study design early in the paper	3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	3
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	3
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	3
Bias	9	Describe any efforts to address potential sources of bias	4
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	4
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	4
		(b) Give reasons for non-participation at each stage	

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		(c) Consider use of a flow diagram	9
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	5,10
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	Report numbers of outcome events or summary measures over time	4,5
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	4,5
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	4,5
Discussion			
Key results	18	Summarise key results with reference to study objectives	5
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	5
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	5
Generalisability	21	Discuss the generalisability (external validity) of the study results	5
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	

*Give information separately for exposed and unexposed groups.

- Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.