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Adherence to Guideline Directed Medical Therapy in Heart Failure Patients in a Tertiary Hospital in Southern Nigeria: A Real-World Experience

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Abstract: *Background*: There is an increase in the incidence of heart failure among the sub-Saharan population. The use of guideline-directed medical therapy has been shown not only to reduce disease progression but also frequent hospitalization, morbidity, and mortality from heart failure. This study was directed at identifying which of the major drug class for treatment of heart failure was incorporated by the physicians in the area. *Methodology*: The study involved collection of data from patient's records using an observational checklist. A total of 166 heart failure patients with reduced EF were recruited between the age ranges of 33 and 95 years. The medications prescribed, date of drug initiation and progress in optimization of therapy were assessed over a 1-year period and data analyzed using SPSS version 25. A p-value of 0.05 and below was considered statistically significant. *Results*: The result showed that the most prevalent causes of heart failure were hypertensive heart disease (70.5%), followed by dilated cardiomyopathy (15.7%) and valvular heart disease (6.6%). The use of diuretics was prevalent among study cohorts at 87.4%, followed by Mineralocorticoid antagonist (MRAs) (78.3%), ARB/ACEI/ARNI (68.1%), beta blockers (40.4%), and less than a third of patients were on SGLT2 inhibitors (28.9%). The dosing of heart failure medications was noticed to be fixed without up-titration of doses at intervals for most classes of GDMT except the MRAs. Only about 2.4% of the study cohorts had dose optimization over this period and most study patients were not on optimal maximal doses of heart failure therapy. *Conclusion*: The use of guideline directed medical therapy has improved amongst HF patients however up titration of doses remains a major problem amongst patients managed in our clinic. The implementation of a multi-disciplinary HF clinic focused on improvement of outcomes of HF patient is essential in improving not only the use of Guideline- directed medical therapy (GDMT) but up-titration to optimal doses for maximal benefits.

Keywords: GDMT, Medication, Heart Failure, Optimization, Dosing

1. Introduction

Heart failure is regarded as a clinical syndrome characterized by symptoms emanating from structural and/or functional cardiac abnormality resulting in impairment of ejection of blood or ventricular filling. At diagnosis, heart failure (HF) is classified into HFrEF, HFmrEF, HFpEF, HFimEF (signifying heart failure with reduced, mildly reduced, preserved, or improved ejection fraction respectively). [1] This classification is used to grade the functional capacity at the time of diagnosis to determine if there is an improvement later. It can also be used to ascertain patients that are eligible for the various therapy regimens. [2] In the management of heart failure with reduced ejection fraction (HFrEF), it has been postulated that the use of all four major classes of therapy led to about 73% reduction in mortality when compared with patients that did not receive any treatment at all. [3] According to the American Heart Association 2022 HF Guidelines, Treatment recommendations for patients with HFrEF can be started simultaneously at low doses or started consecutively, guided by clinical and other factors such as patients' response, side effects without the need to achieve optimal maximal dose before initiating the next

medication. [4]

In a previous study, patients with HFrEF showed improvements in left ventricular ejection fraction when given beta blockers while ACEI/ARB reduced hospitalizations and lower risk of cardiovascular death. [5] The combination of the various classes of medication should be based on individual patients as not all patients with a particular stage of heart failure will respond to same kind of medication regimen. [6] A recent study stated that there is a clear-cut benefit in administering the four major classes of heart failure medications namely (angiotensin converting enzymes inhibitors, angiotensin receptor blockers, angiotensin receptor neprilysin inhibitors (ACEI/ARB/ARNI), Beta-blockers, Mineralocorticoid antagonist and sodium glucose transporter 2 (SGLT2) inhibitors. Although it was noted that patients with HFrEF and HFmrEF benefitted more from these therapies [7] Recently studies have also shown gross benefits of SGLT2 in patients with ejection fraction > 50%. [8]

More guideline studies have also stated that the simultaneous administration of the four classes of medication reduced cardiovascular mortality and overall hospitalizations if there was strict adherence and appropriate up-titration to medications [9-11]. The present study is therefore aimed at evaluating the adherence to guideline- directed medical therapies (GDMT) in the cardiology clinic and to ascertain the compliance to optimization of therapy.

2. Methodology

The study was a descriptive retrospective study carried out on heart failure patients of the University of Port Harcourt Teaching Hospital. It involved the recruitment of a total of 166 HFrEF patients attending the cardiology clinic which comprised of 75 males and 91 females. The study was conducted with the use of observational checklist that extracted relevant data from patient's records. The observational checklist included data on sociodemographic information, clinical data, and current medication as well as optimization (frequency of dose adjustments and number of patients who achieved maximally tolerated dose (MTD). All data obtained were analyzed using Statistical Package for Social Sciences (SPSS) version 25 and descriptive results were presented in mean ± SD for numerical and frequency/proportion for categorical data. P values of 0.05 and below were considered statistically significant.

3. Results

The mean age of study participants was 59.50 years with a minimum age of 33 years and the maximum age being 95 years. A total of 166 heart failure patients were recruited in the study with 45.2% males and 54.8% females. From the results displayed in the table 1 below. Fifty – four percent attained tertiary level of education (LOE) education followed by 34.3% with secondary LOE and 11.4% with primary LOE. The female study cohorts were significantly younger than their male counterparts (p - 0.027), with a significantly higher mean body mass index (BMI) than males (31 vs 28) (p= 0. 019). The average BMI however was 29.8. Eighty four percent (84.3%) of study participants were either overweight or obese See table 1 below.

Table 1. *Descriptive statistics of the patients in the study.*

Variables	Sex		t test	p-value
	Male Mean ±SD	Female Mean ±SD		
Age (years)	62.29 ± 14.59	57.20 ± 14.67	2.234	0.027*
BMI (kg/m2)	28.17 ± 3.71	31.14 ± 11.16	-2.204	0.019*
Heart rate (bpm)	83.63 ± 13.36	83.99 ± 13.77	-0.171	0.864
SBP (mmHg)	121.60 ± 18.34	128.68 ± 19.10	-2.420	0.016*
DBP (mmHg)	78.60 ± 13.15	80.45 ± 12.33	-0.934	0.355
HF duration (years)	1.913 ± 1.68	2.07 ± 1.63	-0.610	0.543

BMI- Body mass index, SBP -systolic blood pressure, DBP – Diastolic blood pressure

Table 2. *Clinical characteristics of patients.*

Variables	Mean ±SD (n=166)	Range (Min-Max)
NYHA General class		
Class 1	17 (10.2)	
Class 2	82 (49.4)	
Class 3	64 (38.6)	
Class 4	3 (1.8)	
HF Duration (years)	2.00±1.65	0.5-13
Previous HF hospitalization in the last 1yr		
None	69 (41.6)	
One HF hospitalization	91 (54.8)	
Two HF hospitalization	6 (3.6)	
Total HF hospitalization	97 (58.4)	

NYHA -New York Heart Association, HF – Heart failure

Table 2 shows the clinical characteristics of the patients. The mean heart rate was 84bpm with a range between 60bpm - 141bpm. The mean SBP & DBP were 125.48mmHg and 79.61mmHg respectively. Atrial fibrillation was seen in 19.9%

of the study population. The mean duration of heart failure was about 2 years. Ten percent of patients were in NYHA class 1, 49.4% in class 2, 38.6% in class 3 and 1.2% in NYHA class 4. A total of 58.4% of the patients have had past hospitalizations for HF.

The causes of heart failure in the study were hypertensive heart disease (70.5%), followed by dilated cardiomyopathy (15.7%), hypertension (15.1%), valvular heart disease (6.6%). Other comorbidities observed in the study were diabetes ((10.2%), Chronic obstructive pulmonary disease (COPD) (3.6%), chronic kidney disease (4.8%) and osteoarthritis (5.4%). See Table 3.

Table 3. *Causes of heart failure and major co-morbidities.*

Variables	Frequency (%)
Causes of Heart failure (n=166)	
Hypertensive heart disease	117 (70.5)
Dilated cardiomyopathy	26 (15.7)
Valvular heart disease	11 (6.6)
Peripartum cardiomyopathy	9 (5.4)
Ischemic Heart Disease	3 (1.8)
Major co-morbidities	
Diabetes Mellitus	17 (10.2)
COPD	6 (3.6)
CKD	8 (4.8)
Osteoarthritis	9 (5.4)

COPD -chronic obstructive pulmonary disease, CKD – chronic kidney disease

Table 4. *HF Medications and their frequency.*

Baseline medications	Frequency (%)
Anti- Failure medications	
ARB/ACEI/ARNI	113 (68.1)
Beta blocker	67 (40.4)
MRA	130 (78.3)
SGLT2	48 (28.9)
Diuretics	
-Loop	106 (63.9)
-Thiazide like	3 (1.8)
-Both	36 (21.7)
Other adjuvant Medications	
Statins	41 (24.7)
Anticoagulants	47 (28.3)
Digitalis	69 (41.6)
Antiplatelets	24 (14.5)
Amiodarone	7 (4.2)
PDE5	8 (4.8)
Anti ischemic	4 (2.4)
Oral iron	2 (1.2)

ARB- Angiotensin receptor blockers, ACEI – Angiotensin converting enzyme, MRA – Mineralocorticoid receptor antagonist, SGLT2- Sodium Glucose Transporter inhibitors, PDE5 – Phosphodiesterase 5 inhibitors.

Table 4 shows the frequency of the medications used for HF treatment, Diuretics use was in 87.4% of HF patients. The MRA was used by 78.3%, the use of ARB/ACEI/ARNI for HF was 68.1%, Beta blockers use was 40.4% and SGLT2 were the least prescribed medications at 28.9%. Among other classes of medications used, 41.6% of patients were on digoxin, 24.7% on statins, 28.3% were on anticoagulant and 14.5% were on anti-platelets therapy. The frequently used medications were diuretics, MRAs and RAAS blockers. About 47% of study cohorts were on 2 drugs, 25.9% on the three drugs while only 5.4% were on all 4 classes of GDMT.

Among those on GDMT, only 2.4% were on guideline recommended optimal doses while 97.6% were not up-titrated to maximally tolerated doses of GDMT over the 1-year study period. See Figure 2 below. The use of Beta-blockers was significantly associated with a better NYHA class. See Table 6.

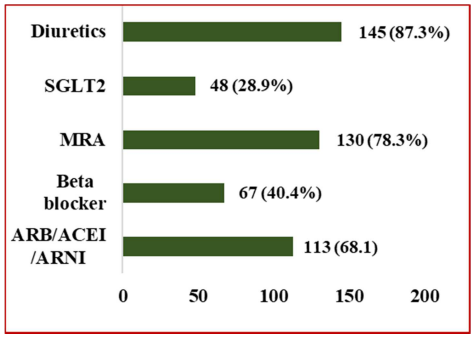

Figure 1. *Chart showing frequency of use of GDMT in HF patients.*

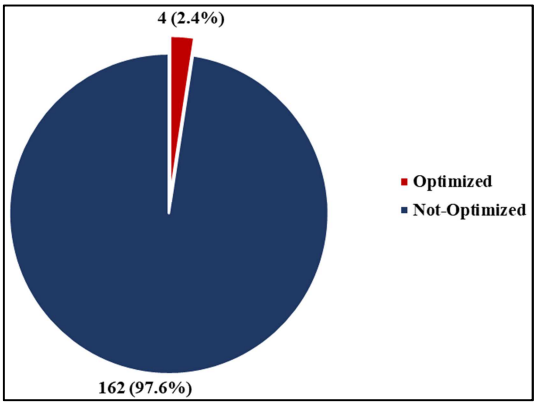

Figure 2. *GDMT Optimization of baseline medications of patients in the study.*

Table 5. *No of GDMT among males and females in the study.*

Variables	Sex		Total (N=166)
No of Drug (GDMT)	Male (n=75)	Female (n=91)	
1 drug	15 (20.0)	21 (23.1)	36 (21.7)
2 drugs	44 (58.7)	34 (37.4)	78 (47.0)
3 drugs	14 (18.7)	29 (31.9)	43 (25.9)
4 drugs	2 (2.7)	7 (7.7)	9 (5.4)

GDMT – Guideline- directed medical therapy.

Table 6. *Comparison of GDMT use based on NHYA classification.*

Variables	NYHA Class		Statistics	p-value
	class I & II (n=99)	class 3 & 4 (n=67)		
ARB/ACEI/ARNI	69 (69.7)	44 (65.7)	0.298	0.585
Beta Blockers	46 (46.5)	21 (31.3)	3.796	0.036*
MRA	74 (74.7)	56 (83.60	1.836	0.175
SGLT2	32 (32.3)	16 (23.9)	1.386	0.239

ARB- Angiotensin receptor blockers, ACEI – Angiotensin converting enzyme, MRA – Mineralocorticoid receptor antagonist, SGLT2- Sodium Glucose Transporter inhibitors.

4. Discussion

Optimization of medical therapy is recommended in guidelines for better HF patients' outcomes, however real-life situations show that only a small percentage of patients are placed on Guideline recommended doses of HF therapy and have their doses up-titrated progressively to OMT doses. The challenges in achieving dose up-titration and optimization ranges from physician inertia, poor adherence of patients to follow up visits, lack of specialized HF clinics and training of nurses specialized in HF care.

This study was aimed at assessing the frequency of use of Guideline- directed Medical Therapy (GDMT) and the proportion of HF patients who were on maximally tolerated doses of these medications. It was a retrospective study and patients' medical records were assessed to obtain relevant data. The mean age of the study cohorts was 59 years, and this was comparable to the mean age of African HF patients in The Sub-Saharan Africa Survey of Heart Failure (THESUS–HF study, a prospective, multicenter, observational survey of 1006 patients with AHF admitted to 12 university hospitals in 9 countries where a younger mean age of 55 years was reported compared to developed countries where HF is majorly a disease of the elderly and occurs about two decades later. [12]

The sex distribution shows a slightly higher female prevalence when compared to males at fifty – four percent. The female patients in this study were also significantly younger than their male counterparts. The THESUS -HF study also found a similar female prevalence in their study at 50.8%. The overall lifetime risk of heart failure (HF) tends to be similar among men and women, however, sex differences may occur based on etiology of HF with peripartum cardiomyopathy and rheumatic heart disease being more common in females than their male counterparts. [13] An Egyptian study comparing GDMT optimization between the general cardiology out-patient department and Heart failure clinic found a male predominance in both clinics at 80% and 73 % respectively [14].

According to ESC guidelines, the use of the ACEI/ARB/ARNI, β blockers, MRA and sodium-glucose co-transporter 2 (SGLT2) inhibitors are the major therapy in heart failure with reduced ejection fraction and reduces the risk of CV death and worsening HF symptoms. [15] In a Swedish HF registry comprising of about 1500 patients with systolic blood pressure ≤ 100mmhg and eGFR ≤ 60ml/min, the use of GDMT was associated with improved survival even in patients with low BP and renal impairment. [16]

This study found that most HF patients were on atleast 2 of the four main classes of HF medications. ACEI/ARB/ARNI and MRAs were the most widely used drugs after diuretics. More than two-thirds of all study participants were on MRA and ACEI/ARB/ARNI, about 40% of patients were on beta-blockers while SGLT2 inhibitors use was seen in about a quarter of recruited patients. The limited use of SGLT2 inhibitor can be attributed to its affordability and lack of comprehensive health insurance coverage with many patients paying out of pockets.

Ninety-five percent of patients in this study did not receive all 4 classes of GDMT with only five percent receiving all 4 classes of GDMT. About 2.4% of studied participants had regular titration of doses and were optimized at maximal doses over the 1- year study period. Mineralocorticoid receptor antagonist was the only class group attaining more than 90% dose optimization. The impact of focused care provided by a heart failure clinic was compared in a retrospective Egyptian study over the general cardiology out-patient clinic with 200 patients in each arm. Eighty-eight percent of patients in the HF clinic compared to 55% in the general cardiology OPD were found to use GDMT with a significant number of patients in the HF clinic achieving target dose when compared to the cardiology OPD. Betablockers use was 58% vs 29%, ACEI/ARB/ARNI (45% vs 9%) (p= 0.000), when both clinics were compared. [14]

In a case-control population-based study of HFrEF patients in a quality improvement program using a remote, algorithm-driven, navigator-administered medication optimization program over a 3-months period using telephone to direct adjustment of medications, and conduct surveillance of symptoms, blood pressure and laboratory investigations under supervision of a cardiologist, pharmacist and nurse practitioner led to an enhancement in implementation of GDMT and closed the gap between guidelines and clinical practice. [17] The use of remote optimization can also be explored in our setting.

The use of diuretics at 87% was still found to be high among our study cohorts probably due to paucity in use of all 4 classes of GDMT at recommended doses. Diuretics play a significant role in the management of patients with congestive heart failure to relieve congestive symptoms. However, various complications like electrolyte abnormalities, worsening renal function and resistance can arise from chronic use, hence the use of safer alternatives like

the 4 classes of GDMT. [18] The use of Beta-blockers in this study was found to be significantly associated with a lower NYHA class despite its low usage among studied patients.

5. Conclusion

Despite the knowledge of the overwhelming benefits of the use of GDMT in heart failure and the need for regular up-titration to optimal maximal doses, there is still inertia by managing physicians/cardiologist in up titrating medications to recommended doses. The need to manage patients in a specialized heart failure clinic for focused care with regular training of doctors and nurses involved in management is essential. The use of remote optimization to guideline recommended doses can also be explored in our setting for better outcomes in heart failure patients.

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