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ORIGINAL ARTICLE

ASSESSMENT OF PHYSICIAN ADHERENCE TO GUIDELINE RECOMMENDED MEDICATION IN HEART FAILURE WITH REDUCED EJECTION FRACTION AT OUTPATIENT CARDIAC CLINIC; RETROSPECTIVE CROSS- SECTIONAL STUDY AT TIKUR ANBESSA SPECIALIZED HOSPITAL

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ABSTRACT

Background*-Heart failure (HF) is a burden for the healthcare system. There is clear evidence from landmark studies that optimal uses of Angiotensin-converting-enzyme inhibitors (ACEI), Angiotensin receptor blockers (ARBs), Beta-blockers (BB), and Mineralocorticoid receptor antagonists (MRAs) to achieve target dose used in RCTs improves survival and reduce morbidity in patients with HF with reduced ejection fraction (EF).*
The objective of this study is to evaluate physicians' adherence to guideline-recommended medications for treatment of heart failure with reduced ejection fraction (HFrEF)
Method*-Retrospective cross-sectional study was conducted and the medical record of 364 patients with HFrEF treated at TASH from 2012 to 2018 was reviewed. Global class adherence score (GCA) was used to evaluate the use of ACEI, BB, ARB, and MRAs according to the international guideline by physicians. SPSS 20 software was used for data entry and analysis.*
Result*-GCA score among physicians was good in 36%, moderate in 47%, poor in 17% of the study patients. Class adherence for the individual drug was 67% for ACEI, 48.7% for MRA, and 73.6% for Beta-blockers. The proportion of patients at target dose (100%) was 7.6% for ACEI, 0.8% for Beta-blockers, and 1% for MRA. Use of more than 50% target dose was 36.7 % for ACEI, 6.6% for beta-blocker, 49% for MRA. Duration of heart failure > 5 years was associated with a good GCA (P=0.003). Diabetic patients were prescribed higher doses of ACEI, compared to non-diabetics (p=0.001).*
Conclusion *In this study use of all indicated medication as per guideline by physicians was low (36%) and the majority of patients received less than 50% target dose, especially for beta-blocker and ACEIs.*
Keywords*: Global class adherence (GCA), physician guideline adherence, Heart failure with reduced ejection fraction (HFrEF), Target dose,*

INTRODUCTION

Heart failure (HF) is a complex clinical syndrome that results from structural or functional impairment of ventricular filling or ejection of blood. It is a major public health problem affecting more than 20 million people worldwide (1). Heart failure has been classified into three subtypes, namely HF with reduced ejection fraction, HF with preserved ejection fraction, HF with mid-range ejection fraction.(2) ACEIs, ARBs, Beta-blockers & MRAs constitute the cornerstone of pharmacotherapy for HFrEF . These drugs are known to slow and retard the progress of heart failure by addressing the deleterious effect of neurohormonal stimulation.(5) International guidelines recommend the use of these classes of drugs intending to achieve target doses used in the RCTs (2).

There is clear evidence from landmark studies of disease-modulating and survival-promoting benefits of ACEI/ARB, BB, and MRA for HFrEF (6).

Optimal uses of these drugs in patients with HFrEF reduce mortality and morbidity in clinical practice. (5,6). Despite this, data from large observational studies suggest that these drugs are under prescribed in HFrEF patients. (7)

Putting guideline recommendations into practice is not optimally practiced in most of clinical practice, and surveys suggest that the implementation of guidelines remains suboptimal, particularly regarding use of beta-blockers and their dosage (8).

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Global surveys like QUALIFY survey(7) MAHLER survey,(9), HART trial(10) as well as SUGAR survey from Korea(11), USA(12), Indonesia (13), Nigeria (14), South Africa (15) shows moderate to poor adherence of physician to this international guidelines. Several reasons have been associated with the suboptimal implementation of this guideline: patient-related factors, like age, and co-morbidities leading to intolerance or contraindications; physician-related factors, including lack of awareness of treatment goals, reluctance to use newly recommended drugs or multiple therapies, focus on symptom relief rather than reduction of mortality, and fear of adverse effects; non-medical factors, including affordability such as cost of medications and inadequate access to healthcare systems, were attributed to poor adherence to the international guidelines. (7)

What is already known about this subject?

The last decades have witnessed interest in physician adherence to evidence-based guidelines directed at the management of heart failure. This has led to several publications from Europe, the USA (12), Japan (16), Nigeria (14), and South Africa (15). These international studies have shown several differences in the degree of adherence and perceived barrier to adherence. Real-life physician adherence studies are scanty in Africa. A study from Nigeria shows physician-adherence to evidence-based Heart failure drugs was variable (14) and another study from South Africa (15,17) reports comparable adherence from other countries, with a low rate of beta-blockers and MRAs prescription. The Sub- Saharan Africa survey of heart failure also showed most patients were treated with renin-angiotensin-aldosterone system blockers but not with B-blockers at discharge (18).

What does this study add?

Even though, Ethiopia has a comparable cardiovascular disease burden as other developing countries, a study on the practice of this international guideline adherence is limited. The prevalence of HFrEF is increasing with the aging of the population and the rise of multiple comorbidities. Therefore, it is necessary to reassess physicians' adherence to the latest guidelines.

How might this impact clinical practice?

This study assesses the practice of physicians in adhering to evidence-based international guideline recommendations, in prescribing these life-saving medications in a patient with HFrEF. This lays a foundation to further study the perceived barrier in practicing evidence-based HF treatment in our setup and encourages clinicians to work on the gap identified, which benefits patients.

The objective of this study is to evaluate physicians' adherence to guideline-recommended medications for treatment of Heart failure with reduced ejection fraction (HFrEF).

METHODS

Study design

This is a retrospective cross-sectional study; medical records of patients with HFrEF treated at Tikur Anbessa specialized hospital from 2012- 2018 were reviewed.

Study area /setting

Tikur Anbessa specialized Hospital is a tertiary-level, teaching public hospital. It is located in the capital city of Ethiopia, Addis Ababa. It is the largest Hospital in Ethiopia. The hospital serves as a top referral hospital for patients coming from all over the country. The cardiology unit in the department of internal medicine is staffed with cardiologists, cardiology fellows, internists, and internal medicine residents. It is currently serving more than 6000 patients with different cardiac conditions on an outpatient base.

The source population for this study was all patients who are diagnosed to have heart failure with reduced ejection fraction and on follow-up at the outpatient cardiac clinic.

The study populations were patients who were diagnosed to have HFrEF fulfilling the inclusion criteria and included in this study

Inclusion criteria:

- Patients > 18 years old,
- Patient who had at least 4 regular follow-ups at the outpatient cardiac clinic,
- Patients with impaired left ventricular function with an ejection fraction of < 40 % in recent echo done at least within the last 2 years
- Heart Failure (HF) medication prescription ordered by physicians.

Exclusion criteria;

- Unavailable echocardiography results for classifying the type of HF as reduced ejection fraction versus preserved ejection fraction.

Sample size and sampling technique

Sample size determination:

According to previous year's recordings, it is anticipated that over the study period a total of 4500 patients are seen at the cardiac follow-up clinic. A sample size of 383 patients was calculated based on a previous study: Janet *et .al* a retrospective study from Nigeria, on physician adherence to pharmacotherapy guidelines for chronic heart failure, where ACEIs/ARBs were prescribed in 83% of patients, beta-blockers were used in 48% and aldosterone antagonists in 41% of patients. Confidence interval of 95% and degree of freedom of 0.05 was used.

Data collection procedures
Data were collected from the medical records of patients using a checklist. To keep the data quality, data collectors were trained. The investigators supervised the data collection process.

Data Quality control
Data were checked for completeness and consistency before data entry by the principal investigator and entered into EPI info version 3.5.1 and exported into SPSS for data analysis. After data entry, data cleaning was made by running frequencies of each variable to check for accuracy, outliers, and consistencies.

Statistical analysis
The data were analysed using SPSS statics version 20. Continuous parameters were recorded as means ± SD. Descriptive data were given in percentages & table. A Chi-square test was done to see the association between categorical variables. P-values of less than 0.05 and a confidence level of 95% by the two-sided test were considered to indicate statistical significance.

OPERATIONAL DEFINITIONS

Global Guideline Adherence Score
Global class adherence score was defined as a performance measure on basis of the three pharmacologic class, ACEIs/ ARBs, beta-blockers, and MRAs to evaluate physician guideline adherence.
A global guideline adherence score was constructed based on physicians' adherence to guidelines regarding the following three classes of medications; ACEIs/ ARBs, beta-blockers, & MRAs.
The adherence score was the ratio of the treatment prescribed to the treatment that should theoretically have been prescribed. The theoretical treatment score was calculated for every patient, taking into account treatment eligibility criteria and the existence of contraindications to drugs or treatments based on international guidelines on the management of HFrEF.
The score was calculated for each patient by summing the points attributed as follows: one point for non-prescription in the absence of specified indications and one point each for the use of ACEIs or ARBs, beta-blockers, MRAs (if indicated),. Non-administration of recommended drugs because of specific contraindications or intolerance was scored as adherence to guidelines.

The score ranges from 0 (poor) to 1(excellent), and three levels of adherence were defined:

- **GOOD ADHERENCE (**use of all indicated medications in eligible patients; score=1); I.e. Based on the ratio of the treatment prescribed to the treatments that should have been prescribed, E.g.: 3:3=1
- **MODERATE ADHERENCE** (use of more than half of **indicated** medications in eligible patients; score>0.5−<1); and
- **POOR ADHERENCE** (use of ≤50% of indicated **medications** in eligible patients; score ≤0.5).
- **ADHERENCE-** relates solely to physicians following guidelines and not to patient compliance to drugs.
- **TARGET DOSE:** -Recommended maximal tolerable drug dose in HFrEF according to previous landmark trials.
- **ACEIs Target dose**: -lisinopril, enalapril, and fosinopril 20 mg/day, captopril1 50-100 mg/ day and ramipril 10 mg/day
- **ARBs Target dose:** - Valsartan 320 mg/day, losartan100 mg/day and Candesartan 32 mg/ day
- **Beta-blockers Target dose**- Metoprolol 200 mg/day, carvedilol 50 mg/day, carvedilol phosphate extended-release 80 mg/day, bisoprolol 10 mg/day, Atenolol 100 mg
- **MRA Target dose**- Spironolactone 50 mg/ day

STUDY VARIABLES

Dependent variables:
- Physician Guideline Adherence (Global class adherence)

Independent variable
- Residence, Sex, Age, Marital Status, Educational Status, Occupation
- Comorbidity, duration of heart failure, time since the last hospitalization

.Research checklist

We used the STROBE reporting guidelines. Cuschieri, Sarah (2019). The STROBE guideline, Saudi Journal of Anaesthesia. 13. 31. 10.4103/sja.SJA_543_18.

RESULT

Description of the study participants
A total of 364 patient's charts were reviewed. The baseline characteristics of the study participants are described in *Table 1*. The mean age of the patients was 48.7. Majority of the patients were male (60.4 %). For those who had previous hospitalization, the mean time since the last hospitalization was 8.5 months. The majority of patients, 64.6% were in New York Heart Association (NYHA) class II, and 23.6% of patients were NYHA class III in their most recent outpatient visit.

Table 1: Socio-demographic characteristics of heart failure patients with reduced ejection fraction in Tikur Anbessa Hospital, Addis Ababa, Ethiopia 2012-2018 (n=364)'

Variable	Response category	Frequency	Percent
Sex(%)	Male	220	60.4
	Female	144	39
Residency (%)	Urban	222	60.9
	Rural	142	39.1
Mean Age(year)+/- SD	Mean	48.7 year +/- 14.07	
	Medical History		
Smoking status	Current smoker	11	3
	Ex-smoker	84	23.1
	Non-smoker	269	73.9
Duration of Heart failure	Less than 5 years	308	84.6
	Greater than 5 years	56	15.4
Mean time since Hospitalization	Less than 6 month	78	21.4
	6 month to 1 year	126	34.6
	Greater than 6 month	140	38.5
	Never hospitalized	20	5.5
Co-morbidities	Atrial fibrillation	40	11
	Stroke	9	2
	DM	84	23.1
	Dyslipdemia	40	11
	Hypertension	143	39.3
	Asthma	8	2.2
	AKI/CKD	8	2.2
	Other	32	8.8
Average SBP(MMHG)	Mean	122.37	
Resting heart rate (BPM)		81.55 (Average)	
NYHA class	1.Class I	38	10.4
	2.Class II	235	64.6
	3.Class III	86	23.6
	4.Class IV	5	1.4
Left ventricular Ejection fraction	EF= 30-40%	43.3%	
	EF=15-30%	51.7%	
	EF<15%	5%	
Etiology of Heart failure	Ischemic Heart disease	53.6%	
	Cardiomyopathy	35.7%	
	Valvular heart disease	10%	
	Other	1%	

Comorbidities frequently seen include; Hypertension (39.3%) diabetes mellitus (23.1%) atrial fibrillation (11%) CKD (2.2), Asthma/COPD, (2.2%) & stroke (2%). Mean heart rate of the patients was 81.55 .b.p.m. and 89 % of the patients were in sinus rhythm. Among patients in sinus rhythm 87%.had a heart rate ≥70 b.p.m.

ACEIs (Angiotensin-converting enzyme inhibitors)

Among patients who have indication for ACEI, 70.6 % of patients were on ACEI. Among non-prescribed patients, 9.3 % were on ARBs and 20.3 % of patients were not on ACEIs/ARBs when indicated. Enalapril was the most commonly prescribed ACEIs (69.8%). The mean dose of ACEIs (enalapril) prescribed was 8.14 mg. Thirty-six patients had contraindication for ACEIs due to AKI, Hyperkalaemia, and ACEIs induced Cough. Those with ACEIs induced cough (32 patients) were put on ARBs. A total of 33 patients were on ARBs. Among these patients, all of them were in less than 50% target dose. Physician class adherence to ACEIs alone was 67.6%.

BETA-BLOCKER

Among the 97% of patients who had an indication for beta-blockers, 79.4 % of the patients used beta blockers, the most common reasons for not prescribing beta -blockers were intolerance and hypotension. Among patients who were on Beta-blocker, 57 % were on Metoprolol followed by Atenolol (31%). The rest were on carvedilol & bisoprolol.

Among patients on Beta-blocker, the majority (45.05%) were on less than 25% of the target dose and two-third of patients was on less than 50% of the target dose. Only 7 % of patients were prescribed above 50% of the target dose. Eleven patients had contraindication for beta-blocker; all of them were due to hypotension and intolerance.

Among patients for whom metoprolol was prescribed, 37% were on Metoprolol succinate and 14% on Metoprolol Tartrate. The type of metoprolol prescribed for the remaining 49% was not documented. Physician class adherence to Beta-blockers was 73.6%.

MINERALOCORTICOID RECEPTOR ANTAGONISTS

Among the 95% of patients who had an indication for MRAs, 49.18% were on mineralocorticoid receptor antagonists (spironolactone). The mean dose of Spironolactone used was 24.9 mg /dl. Among those who were not on MRAs, 12(3.3%) patients had contraindication (Hyperkalaemia and Acute renal failure) and few patients were on class I heart failure with no strong indication for MRAs.

Among patients on MRAs, 87% were on 50 % target dose. Physician class adherence to MRAs alone was 48.7%.

Table 2: Physician Class Adherence for individual drugs used

Drugs	Physician class adherence		Target dose used			
			<25%	25-50%	50-75%	100%
			N (%)			
ACEI/ARB	N	%				
Yes	290	79.8	27.3	8.2	36.7	7.6
No	74	20.3				
Beta blockers						
Yes	289	79.4	50.9	21.1	6.6	0.8
No	75	20.6				
MRA						
Yes	179	49.3	0	0	48.3	1
No	185	50.7				

ACEI-Angiotensin-converting enzyme inhibitors, ARB- angiotensin II receptor blockers, MRA-mineralocorticoid receptor antagonists.

FACTORS ASSOCIATED WITH PHYSICIAN GUIDELINE ADHERENCE

Longer duration of heart failure was associated with good guideline adherence (P=0.003), whereas longer duration since the last hospitalization for heart failure was not associated with good guideline adherence (P value=0.157). Patients with diabetes were prescribed a higher dose of ACEIs compared to non-diabetics (*P* =0.000). There was no association between having multiple cardiometabolic comorbidities and good guideline adherence (P value=0.422).

According to underlying heart failure, dilated cardiomyopathy followed by ischemic heart disease was associated with better use of all indicated medications (51.5% vs. 35.9 %) (P = 0.001). Guideline adherence was low in those with valvular heart disease (26.2%), (P=0.001)

Most patients received diuretic agents (88.0%) and the majority were on antiplatelet agents (54%), statins (64.4%), digoxin (25.7%), and nitrates (6.8%). Few patients were also on HAART, anti-coagulant, oral hypoglycaemic agents & insulin.

Table 3- Factors associated with physician guideline adherence

Variable	N(%) (Prescribed all indicated medications)		P- Value
Duration since last hospitalization for heart failure	Greater than 6 month	37.8%	0.157
	Less than 6 month	30.8%	
Duration of heart failure	Greater than 5 years	53%	0.003
	1-5 years	33.1%	
	Less than 1 year	33.3%	
Multiple Comorbidity	Yes	36.9%	0.422
	NO	36.3%	
Underlying causes of heart failure	Dilated cardiomyopathy	51.5%	0.001
	Ischemic heart disease	35.9%	
	Valvular heart diseases	21%	

Global Class Adherence

Good adherence, as defined as the use of all 3 indicated drugs, was seen only in 36.2% of the patients. Adherence class was moderate in 46.9 % of patients, use of 2 of the indicated medication. In 16.7 % of the time physicians, guideline adherence was poor (only 1 or none of the indicated medication was used)

Not using a specific medication when it was not indicated/ when there was a contraindication was scored as guideline adherence for the individual drug. Class Adherence for individual drug use despite dosage used was 48.7% for MRA, 73.6% for Beta-blocker, 67.6 for ACEI.

The proportion of patients at target dose (100%) and >50% of target dose was low for most drugs (7.6% and 36.7% for ACEI,) (0.8% and 6.6% for Beta Blocker) and (0.3 % and 49 % for MRA), respectively.

DISCUSSION

This hospital-based cross-sectional study done in Ethiopia included 364 participants' to evaluate physicians' adherence to guideline-recommended medications for the treatment of chronic heart failure (CHF) with reduced ejection fraction adherence to the four classes of medication recommended for HFrEF according to international guidelines like ESC. Overall physician adherence to international guidelines when treating heart failure patients with low EF was low. Physicians used all indicated medications 36% of the time with Good global class adherence, used half of all the indicated medication with moderate GCA 46.8% of the time and global class adherence was poor in 16.76% of the time (only one or none of the indicated medication used).

Compared to guideline adherence study from Nigeria, where good guideline adherence was seen, 51 % of the time, finding from this study showed guideline adherence was low (14). In another multicentre study from Europe, MAHLER study; good GCA was seen in 63% of the physician. Compared to our study where guideline adherence was assessed for residents, internists, cardiology fellows, and Cardiologists, the MAHLER study was done only among cardiologists which probably contributed to the improved guideline adherence. (15)

Class Adherence for individual drug use despite dosage used was 48.7% for MRA, 73.6% for Beta-blocker, 67.6% for ACEI which is comparable to adherence study from Nigeria (14) and South Africa (15). Proportion of patients at target dose and >50% of target dose was low for most drugs (7.6% and 36.7% for ACEI, 0.8% &6.6% for Beta Blocker, and 0.3 % and 49 % for MRA, respectively.

Compared to other studies on international guideline adherence like QUALIFY-HF in which ACEIs were used in 73.2%, Beta-blockers used 84.6% of the time and MRA used - 78.9% of the time, guideline adherence in this study was low for individual drugs(9).

Especially the mean dose of beta-blockers used was very low (34.4 mg/dl for metoprolol). In addition to the use of a low dose of beta-blockers, a significant proportion of the patients were on metoprolol tartrate which has limited data from studies on its benefit on HF patients. The mean dose of ACEIs used in this study (8.2 mg/dl) was relatively lower than what was seen in many adherence studies. The use of MRA was lower but the average dose used was (24.4 mg/dl), which approached 50% of the recommended dose for MRA (Spironolactone). The reason behind the lower target dose use for all individual drugs class may be physician-related, patient-related, or system-related which were not addressed in this study.

Duration of Heart failure greater than five years was associated with a good global class adherence (p-value -0.03), those with a duration of heart failure greater than 5 years were more likely to be prescribed all the indicated medication than those with shorter duration since diagnosis of heart failure. Among those with heart failure diagnosed more than 5 years ago, in 53% of the patient all indicated medication was used. Even though having co-morbidity (DM, HTN) in comparison with those with no comorbidity or co-morbidity with little cardio-metabolic risk was associated with better guideline adherence in the QUALIFY-HF study, this is not seen in this study(P =0.422) (7). Longer duration since the last hospitalization (greater than 6 months) was not associated with a better /good global class adherence.(P-value 0.157). According to underlying causes of heart failure, patients with dilated cardiomyopathy are more likely to be prescribed all the indicated drugs; good global class adherence was seen in 51.7 % of the patients (P-value =0.001) followed by the patient with Coronary artery disease. Patients with valvular heart disease were more likely not to be in all indicated medications with lower guideline adherence. Only 21 % of patient with valvular heart disease was prescribed all indicated medication, P= 0.001
The presence of DM was associated with a higher dose of ACEIs use (15-20 mg Enalapril) with P-value (0.001). Majority of patients with DM were prescribed above 50% target dose of ACEIs. This is due to the indication of ACEIs in DM patients to prevent and delay the progress of diabetic nephropathy in addition to its cardiovascular use.

In this study, physician adherence to the international guideline for treatments of heart failure with reduced ejection fraction was low. In addition, physicians were less likely to use target doses of these indicated drugs. A longer duration of heart failure was associated with better physician guideline adherence but longer duration since the last hospitalization, having multiple comorbidities was not associated with better guideline adherence.

CONCLUSION AND RECOMMENDATION

In this study use of all indicated medications as per international guideline recommendation for HFrEF was low. Only 36% of patients were prescribed all the indicated drugs. The dose used for individual drug class was sub-optimal, and less than 50 % of the target dose. Especially, the beta-blockers dose was very sub-optimal.
This finding emphasizes the importance of physician adherence to international guidelines when treating patients with HFrEF. A HFrEF patient has to be on all indicated medications as per guidelines, and their dosage has to be optimized on their follow-up with the aim of achieving target dose as per recommendation by guidelines.
Further research is recommended to investigate the common factors behind physician failure to adhere to guideline recommendations. Whether patient, physician, or system-related factors are the reason behind low adherence has to be studied. In addition, quality improvement programs aiming at improving the care of heart failure patient both in inpatient and outpatient setup need to be worked on, including improving physician adherence to guideline-recommended medication. In long run, Physician adherence to international guideline when treating HFrEF patients will improve survival and minimize recurrent hospitalization.

LIMITATION

This is a single hospital-based study and the reason for physicians' non-adherence to guidelines was not studied. Because of the nature of the study, most of the information is collected from secondary data, information inconsistency and incompleteness may be there.

GENERALIZABILITY

This study sample is representative of the population. In this study physician adherence to guideline -recommended medication was low. Since Tikur Anbessa specialized hospital is among fewer hospitals equipped with cardiologists & Internists in Ethiopia we can safely speculate physician guideline adherence can even be lower in the hospitals where there are no cardiologists & fewer internists which is the case in the majority of Ethiopian hospitals.

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CONTRIBUTORSHIP

Authors were involved in planning, conducting, and reporting this work. There is no additional contributor to this work.

ETHICAL CLEARANCE

This research was conducted after passing through ethical clearance from Addis Ababa university institutional ethical review board. As the study is conducted by reviewing individual patient documents, data were collected anonymously and kept confidential. No personal identifiers were used on the data collection form. Collected data were only accessed by the investigators. We claim that this research was conducted following the declaration of Helsinki.

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