

Evaluation of Optimization of Drug Therapy in Heart Failure Patients with reduced ejection Fraction in the Outpatient Department and Emergency Department of a Central Hospital

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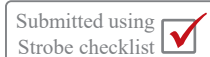
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Abstract

Background: Heart failure with reduced ejection fraction (HFrEF) is a significant global healthcare burden. However, limited data exists on management patterns and outcomes in heart failure in the Nepalese healthcare context. This study aimed to evaluate the baseline characteristics, guideline-directed medical therapy (GDMT) utilization, shortcomings and treatment outcomes in HFrEF patients at a tertiary care center in Nepal.

Methods: This was a prospective observational study conducted on 96 consecutive patients diagnosed with HFrEF. Demographic characteristics, clinical presentation, drug prescriptions, dosing patterns and treatment outcomes were systematically analyzed. Optimal dosing was defined according to current international guidelines.

Results: The study population had a mean age of 61.6 ± 12.9 years (range 20-90 years) with male predominance (64.6%). Most patients were middle-aged (41.7%) or elderly (41.7%), with 69.8% residing outside Kathmandu metropolitan area. Atrial fibrillation was present in 13.5% of patients. Two-thirds had been receiving treatment for heart failure for more than three months. The majority of patients presented in NYHA functional class II and III.

GDMT prescription rates were high: beta-blockers 97.9% (metoprolol succinate 80.2%), RAAS inhibitors 81.25% (ARBs preferred over ACEi, 38.5% vs 24%), mineralocorticoid receptor antagonists 79.2% (spironolactone exclusively), and SGLT-2 inhibitors 73.9% (dapagliflozin 51%, empagliflozin 22.9%). Loop diuretics were prescribed in 77% of patients (furosemide 64.6%). Anticoagulation with NOACs was used in 9.3% of patients, with no warfarin prescriptions.

Despite high prescription rates, optimal dosing was achieved in a minority of patients. No patient received optimal doses of all GDMT components. Only 51% of patients achieved optimal dosing of two medications, while 30.2% achieved optimal dosing of one medication. Spironolactone demonstrated the highest optimal dosing rate (75%) followed by SGLT-2 inhibitors. Beta-blockers showed universal suboptimal dosing. Primary barriers to optimization included ongoing uptitration process (45.8%), hemodynamic unsuitability (16.6%), and physician inertia (10.4%).

Clinical improvement was observed in 72.9% of patients, while 19.7% experienced clinical deterioration. The remaining patients maintained stable clinical status throughout the treatment period.

Conclusions: This study unveils a paradox in HFrEF management in Nepal: excellent GDMT prescription rates coupled with universal suboptimal dosing. High utilization of evidence-based therapies, including rapid adoption of SGLT-2 inhibitors, is commendable. The systematic underdosing represents a critical quality gap prompting the healthcare system for its rectification. The favorable clinical outcomes in nearly three-quarters of patients suggest substantial potential for further improvement through systematic medication optimization strategies. These findings indicate the gravity of need for structured heart failure management programs that includes physician education initiatives and systematic uptitration protocols to bridge the gap between guideline recommendations and clinical practice in the Nepalese healthcare setting.

Keywords: Heart failure, reduced ejection fraction, guideline-directed medical therapy, medication optimization, Nepal, clinical outcomes

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Introduction

Heart failure (HF) is a major health burden in every corner of the world. It is characterized by the heart's inability to pump blood effectively that results in compromised systemic perfusion and substantial morbidity and mortality¹. This chronic cardiovascular condition stands out as a growing global health challenge, affecting an estimated 64 million people worldwide in 2017, and the projections indicate continued increase due to better survival rates and aging populations². An estimated 8-10 million people in India were affected by heart failure in 2019, with an annual incidence ranging from 1.5 to 2 million³. Although the exact data are lacking, the estimated prevalence of heart failure in Nepal was 211.86 per 100,000 population in 2019⁴.

Evidence-based pharmacotherapy, as advocated by the major International Heart Failure Guidelines, forms the cornerstone of management for patients with reduced ejection fraction⁵. Major clinical trials have consistently proved the life-saving benefits of guideline-directed medical therapy (GDMT). ACE inhibitors' mortality benefit was validated by the CONSENSUS and SOLVD trials^{6,7}, while CHARM Alternative established ARBs as effective alternatives⁸. The efficacy of Beta-blocker was established through COPERNICUS, CIBIS-II, and MERIT-HF trials- all showing significant reductions in all-cause mortality⁹⁻¹¹. Mineralocorticoid receptor antagonists showed their value in RALES, EPHESUS, and EMPHASIS-HF trials, proving their role on reducing cardiovascular death and hospitalizations¹²⁻¹⁴. Most recently, SGLT-2 inhibitors have emerged as transformative additions, with DAPA-HF and EMPEROR-Reduced trials establishing significant benefits in cardiovascular outcomes¹⁵⁻¹⁶.

Despite robust evidence favoring optimal medical therapy, treatment inertia remains a significant barrier. Studies have shown that target dose achievement is limited (10-30%), with high discontinuation rates (24-55%) within one year¹⁷. Post-hoc analyses from STRONG-HF demonstrate that patients receiving at least 90% of the maximally recommended doses experience better outcomes and quality of life¹⁸. The disparity between evidence and practice underscores the critical need for systematic approaches to optimize HF pharmacotherapy and thereby improve cardiovascular outcomes in heart failure patients.

Methods

This is a hospital-based prospective observational study. The study enrolled heart failure patients with reduced ejection fraction (HFrEF) who presented to cardiology and emergency departments at Bir Hospital, Kathmandu, Nepal.

The sample size of 96 participants was calculated based on the population proportion formula, taking the reference of the study by Rao et.al. where 50% of the total HFrEF patients were on optimal treatment¹⁹, with a confidence interval at 95% and margin of error at 10%. The study involved all consenting adults over 18 years receiving heart failure drug therapy, enrolling both acute and stable cases. Minors, non-consenting individuals, patients with primary diagnoses other than heart failure, those with significant cognitive or mental health impairments, pregnant women, and terminally ill patients with less than six months of life expectancy were excluded from the study.

The study examined patient demographics (age, gender), guideline adherence, prescribing patterns, and clinical outcomes. The data were collected by cardiologists and cardiology fellows during

routine examination and from medical records. Age was categorized according to World Health Organization classifications: Adults (18-44 years), Middle-aged (45-64 years), Elderly (65-79 years), and very elderly (≥ 80 years). Geographic residence was classified as either within the Kathmandu metropolitan area or outside Kathmandu to assess referral patterns and patients' preference for tertiary centers. Statistical analysis utilized SPSS version 23. Categorical variables were summarized using frequencies (n) and percentages (%), and continuous variables were summarized using the mean and standard deviation (SD). Ethical clearance was obtained from the Institutional Research Board (IRB) at the National Academy of Medical Sciences, Bir Hospital, with written informed consent taken from all participants after a clear explanation of study objectives, ensuring informed consent, confidentiality, and voluntary participation with freedom to withdraw at any time.

Results

The study included 96 patients with a mean age of (61.6 ± 12.9) years and an age range of 20 – 90 years. The middle-aged and elderly population was equal in number and outnumbered other age groups. Males were more common (62%), and most of the patients were from out of Kathmandu valley, reflecting the tendency of patients from different parts of the country to come to the tertiary centers for complex diseases (Table 1)

Table 1: Baseline Clinical Characteristics of Study Population

Parameter		Value (n = 96)
Mean Age (years) $\pm$ SD		61.6 $\pm$ 12.9
Age range (Years)		20 - 90
Age Groups (Years)	Adults (18 -44)	11 (11.5%)
	Middle-Aged (45 -64)	40 (41.7%)
	Elderly (65 -79)	40 (41.7%)
	Very Elderly (>80)	5 (5.2%)
Gender	Male, n (%)	62 (64.6%)
	Female, n (%)	34 (35.4%)
Residency	Kathmandu	29 (30.2%)
	Out of Kathmandu	67 (69.8%)

Around one-tenth of patients (13.5%) had atrial fibrillation, and two-thirds were already on treatment for more than 3 months (Table 2).

Table 2: Presence of Atrial Fibrillation and Duration of Treatment of Heart Failure in the Patient Population

Particulars	Numbers (%)	
Atrial fibrillation	Yes	13 (13.5%)
	No	83 (86.5%)
Duration of treatment	<3 months	32 (33.3%)
	>3 months	64 (66.7%)

Many of the patients were in New York Heart Association (NYHA) functional class II followed by NYHA class III (Figure-1).

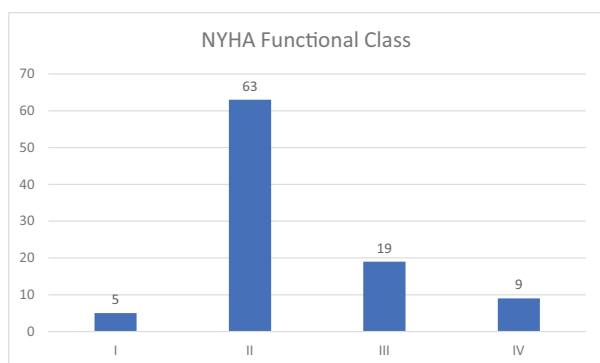


Figure 1: NYHA Functional Class of Patients

Nearly all patients (97.9%) got β -blockers, metoprolol succinate being the most common prescription drug. RAAS inhibitors and MRAs were prescribed in around 80% of the patients. ARBs were preferentially prescribed among RAAS inhibitors, while spironolactone was the only MRA utilized. SGLT-2 inhibitors were fourth in the row, with dapagliflozin being the common drug in the group. Furosemide was the common diuretic; above 60% of patients got the drug. Almost one-tenth of patients were on anticoagulants-NOACs, and surprisingly, none of them got coumadin (Table 3)

Table 3: Drug Prescription Pattern among Patient Population

Drugs used	Number	Total	
RAAS Inhibitors	ACEi	23 (24%)	78 (81.25%)
	ARB	37 (38.5%)	
	ARNI	18 (18.8%)	
β -Blockers	Metoprolol Succinate	77 (80.2%)	94 (97.91%)
	Carvedilol	15 (15.6%)	
	Bisoprolol	2 (2.1%)	
MRAs	Spironolactone	76 (79.2%)	76 (79.16%)
	Eplerenone	0	
SGLT-2i	Empagliflozin	22 (22.9%)	71 (73.95%)
	Dapagliflozin	49 (51%)	
Diuretics	Furosemide	62 (64.6%)	74 (77%)
	Torsemide	12 (12.5%)	
Anticoagulants	Rivaroxaban	4 (4.2%)	9 (9.37%)
	Apixaban	5 (5.2%)	

None of the patients were on optimal doses of all guideline-directed medical therapy. More than half (51.0%) of the patients were on optimal doses of two drugs. This was followed by one optimal drug group (30.2%). None of the drugs were at an optimal dose in one-tenth of the patients (11.4%) (Figure 2).

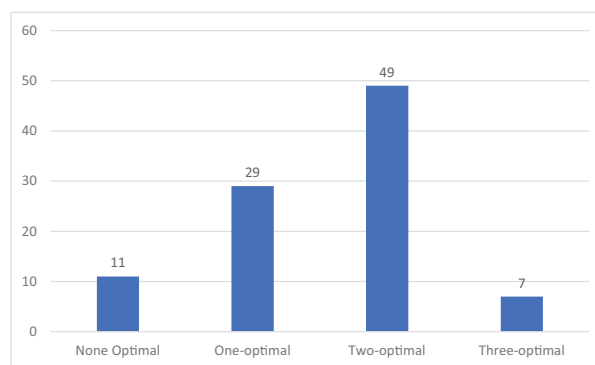


Figure 2: Patient Distribution as per GDMT

Most of the patients (72.9%) had improvement in symptoms and clinical and laboratory parameters as assessed by comparative symptomatology (NYHA functional class), clinical examination (decrease or absence of basal crepitations) and laboratory findings (change in renal parameters) based on his/her medical records. Almost one-fifth (19.7%) of patients deteriorated during the course of treatment, while the remaining patients were symptomatically static (Figure-3).

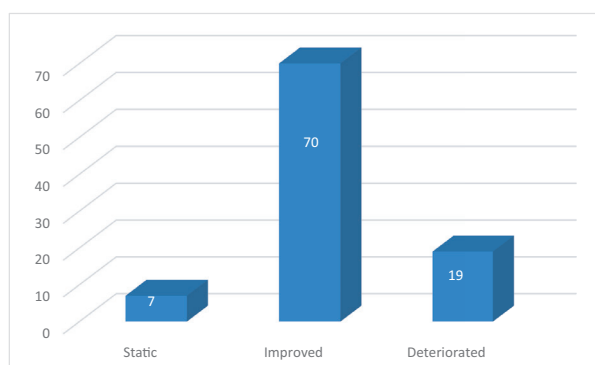


Figure 3: Outcomes of Patient Treatment

Many of the patients were on the process of uptitration of GDMT (45.8%). Some of the patients (16.6%) were hemodynamically unsuitable for optimizing therapy. Drug inertia on the part of doctors was seen in 10.4% of patients. Intolerance to drugs and cost issues were other barriers to drug optimization (Figure 4).

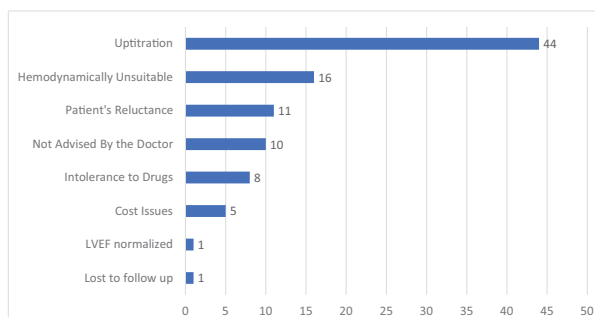


Figure 4: Causes of Sub-optimal GDMT in the Patient population

Among the RAAS inhibitors, only 9.3% of the patients got the optimal dose, losartan and ARNI being the choices of prescribers. The most commonly prescribed drug was also losartan at a dose of 25mg (21.9%) (Supplementary Table 1).

None of the β -blockers was at an optimal dose. Metoprolol succinate at a dose of 25mg was the most common prescription (32.3%) followed by 12.5mg of the same drug in about one-fourth of the patients (26%). In overall prescriptions, carvedilol followed metoprolol succinate (80.2% vs 15.6%) (Supplementary Table 2).

Spironolactone was the only MRA prescribed. Surprisingly, three-fourths of the patients got an optimal dose of the drug (75%). None of the patients was advised Eplerenone (Supplementary Table 3).

SGLT-2 inhibitors were the drugs advised at optimal doses in above seventy percent of the patients. Dapagliflozin was prescribed at above twice the rate of Empagliflozin (Supplementary Table 4).

Less than one-tenth of patients were on anticoagulants, exclusively on NOACs. Rivaroxaban and apixaban were the only NOACs that the patients were put on (Supplementary Table 5).

Furosemide was the most commonly prescribed diuretic (64.6%); 10mg was the most commonly prescribed dose (Supplementary Table 6).

Discussion

Demographic Profile and Clinical Characteristics

This single-center prospective observational study provides a valuable understanding of the demographic profile and management patterns in HFrEF patients in the Nepalese healthcare context. The mean age of 61.6 ± 12.9 years in our cohort resembles contemporary heart failure registries from South Asian populations²⁰. However, this is notably earlier than in Western cohorts, where the mean age typically ranges from 65-70 years²¹. This age difference may reflect the earlier onset of hypertension, cardiovascular diseases, and diabetes mellitus in developing countries, mostly attributed to the epidemiological transition and westernized lifestyle patterns²².

The predominance of heart failure in middle-aged (45 – 64 years) and elderly (65 -79 years) populations in our cohort demonstrates similarity in this respect with the findings of Western research²³.

The male predominance (64.6%) in our study aligns with the common epidemiological patterns of HFrEF, where men are disproportionately affected in comparison to women²². The substantial proportion of patients from outside Kathmandu (69.8%) underpins the centralized nature of specialized cardiac care in Nepal and highlights the potential needs of accessible and trustworthy healthcare services across the country. The tertiary care centers in developing countries are overburdened, where specialized services are limited and concentrated in metropolitan areas.

Functional Status and Clinical Presentation

The predominance of patients in NYHA functional class II and III reflects the typical presentation pattern of HFrEF patients seeking medical attention. In AMERICCAASS- Registry, ambulatory patients were mostly in NYHA functional class II, and admitted patients were mostly in NYHA functional class III²⁴. The relatively lower proportion of NYHA class IV patients in our research suggests that most patients might have been diagnosed and managed in the outpatient settings before developing advanced symptoms.

The prevalence of atrial fibrillation is lower (13.5%) in our study than reported in major international heart failure registries (25-40%)²⁵. This difference could be attributed to underdiagnosis secondary to limited access to continuous cardiac monitoring or ECG screening.

It may, however, possibly reflect genuine population differences in AF prevalence among Nepalese heart failure patients.

Guideline-Directed Medical Therapy Implementation

The optimal doses of drugs used in heart failure with reduced ejection fraction were based on the 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure.

Beta-blocker Therapy

The near-universal prescription of beta-blockers (97.9%) shows excellent adherence to guideline recommendations, which is well above the beta-blocker utilization rates in many international registries, ranging from 85-95%²⁶. Metoprolol succinate was the preferred choice (80.2%), likely due to its widespread availability, once daily dosing, and familiarity among clinicians. However, the alarming revelation that none of the patients achieved optimal beta-blocker dosing reflects our position well behind in guideline adherence.

RAAS Inhibitor Therapy

The high utilization of RAAS inhibitors (81.25%) is appreciable, with ARBs being preferred over ACE inhibitors (38.5% vs 24%). This preference pattern contradicts Western research findings and international guidelines, where ACE inhibitors are typically first-line therapy²⁶. This trend possibly reflects concerns about ACE inhibitor-induced cough in the Nepalese population or physician preferences based on tolerability profiles and prescribing behavior. The inclusion of ARNI (sacubitril/valsartan), a new member in the basket in Nepalese drug houses, in 18.8% of patients is also satisfactory and indicates progressive adoption of newer therapeutic options.

Mineralocorticoid Receptor Antagonists

The prescription rate of MRAs (79.2%) is outstandingly higher than many international cohorts, pointing towards good awareness among physicians of their mortality benefits in HFrEF²⁷. The exclusive use of spironolactone, with 75% of patients receiving optimal doses, is remarkably noteworthy in the management approach; however, the lack of eplerenone utilization may reflect cost considerations and limited availability.

SGLT-2 Inhibitors

The remarkable use of SGLT-2 inhibitors (73.9%) with optimal dosing in over 70% of patients illustrates a good adoption of evidence-based therapy. This high guideline adherence rate exceeds many developed healthcare systems²⁸ and points towards proactive implementation of contemporary recommendations despite resource constraints.

Anticoagulation Patterns

The exclusive use of NOACs (9.3% of the total population) without any warfarin prescription highlights the modern anticoagulation trend in our context. It was likely driven by the convenience of fixed dosing, the absence of interaction with foods and drugs, physician awareness, and the needless monitoring requirements. The overall anticoagulation rate, however, appears way lower considering the 13.5% prevalence of atrial fibrillation, compared to 57% in the Swedish Heart Failure Registry²⁹. However, it is quite close to the prevalence of atrial fibrillation as observed in the Chinese Heart Failure Registry (17.6%)²⁰.

Treatment Optimization Challenges

The finding that no patient achieved optimal dosing of all GDMT components represents a significant quality gap. It highlights a critical gap between clinical practice and heart failure management recommendations. Only 51% of patients were on optimal doses of two drugs. Optimal doses of all four pillars of heart failure therapy were in 50% of the HFrEF cohort in a US-based study. The primary barriers for suboptimal dosing were the ongoing up-titration process (45.8%) and hemodynamic unsuitability (16.6%). Physician inertia in 10.4%, however, suggests the need for enhanced educational initiatives and regular CMEs.

Despite near-universal prescription, the underdosing of beta-blockers is astonishing. International registries show better clinical outcomes with higher beta-blocker doses, emphasizing the importance of aggressive up-titration when hemodynamically tolerated³⁰.

Clinical Outcomes

The clinical improvement seen in 72.9% of patients is encouraging. This highlights the fact that a multi-drug approach provides clinical benefits despite suboptimal dosing. The deterioration rate of 19.7% is still lower than in other international studies³¹, which could be mainly because of a less severe threshold for admission in our part of the world. Even then, this figure underscores the need for more aggressive optimization strategies to minimize adverse outcomes.

Healthcare System Implications

This study points out both strengths and weaknesses in heart failure management within the Nepalese healthcare system. High prescription rates of evidence-based medications and rapid adoption of newer therapies like SGLT-2 inhibitors and ARNI are the strengths in the study. However, weakness in our part of management lies in the suboptimal dosing of guideline-directed drugs, which needs to be rectified soon with various modalities.

The geographic distribution pattern, highlighting a higher number of patients from outside Kathmandu, emphasizes the need for capacity building in peripheral centers and the development of heart failure networks to ensure equitable access to specialized care across the country.

Study Limitations

Several limitations warrant acknowledgment.

1. The single-center cross-sectional design may limit generalizability to other healthcare settings in Nepal.
2. The absence of objective measures like ejection fraction, other laboratory parameters, viz. BNP, NT-ProBNP, and long-term follow-up data limit comprehensive outcome assessment.
3. The study period and selection criteria may introduce temporal and selection biases.

Recommendations

This study establishes a foundation for quality improvement initiatives in heart failure management. The following are the recommendations-

1. Promotion of systematic up-titration protocols
2. Establishment of dedicated heart failure clinics across the country
3. Development of regional healthcare networks for ensuring accessibility and affordability

4. Larger prospective studies, including objective measures of cardiac function, biomarkers, and long-term outcomes, to comprehensively evaluate the effectiveness of current management strategies

Conclusion

This study points out both progress and persistent challenges in heart failure management in Nepal. Medication prescription rates are encouraging, but the universal suboptimal dosing represents a critical quality gap requiring immediate attention. The findings indicate the need for systematic approaches to medication optimization, enhanced educational initiatives, and the development of specialized heart failure management programs that include regional healthcare networks to improve patient outcomes in the Nepalese healthcare context.

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