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Original Research Article

Cost analysis of drugs used in management of heart failure with reduced ejection fraction and marketed in India

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ABSTRACT

Background: Heart failure is characterised by significant morbidity, mortality, poor functional capacity, reduced quality of life, and high cost of lifelong medications. No studies have been performed yet on cost analysis of oral drugs used in management of HFrEF (Heart Failure with Reduced Ejection Fraction). So, we analysed cost variations of different brands of such drugs which are marketed in India.
Methods: It was an analytical study in which maximum and minimum costs in rupees per 10 tablets/capsules of each drug in same strength, manufactured by different pharmaceutical companies in India, were obtained from "Current Index of Medical Specialties" (CIMS) January to April 2023, Indian Drug Review (IDR 2023) and Drug Today (January– April 2023 Cost ratio and % cost variation were calculated for each drug. % Cost variation= Maximum cost-Minimum cost × 100/ Minimum cost. Cost ratio= Price of the costliest brand/ Price of the least costly brand.
Results: Totally 652 brands of HFrEF management drugs from different classes were evaluated. Telmisartan 80 mg had highest cost ratio of 44 and 4300% cost variation, while Spironolactone 25 mg had lowest cost ratio of 1.29 and 31.11% cost variation.
Conclusions: Our study showed significant cost variation in different brands of the same drugs that are used in the management of HFrEF. To lessen economic burden and to improve adherence to treatment, also considering the demographics, it is desirable for doctors to prescribe least costly brands/ generic drugs, to meet the health-care needs of such patients.

Keywords: Cost Analysis, Cost Variation, Cost ratio, HFrEF

INTRODUCTION

Heart failure is a complex clinical syndrome in which there is breathlessness or exertional limitation due to impairment of ventricular filling, ejection of blood, or a combination of both.[1] The syndrome is divided into subtypes based on left ventricular ejection fraction (LVEF). When the LVEF is below 40% this is termed heart failure with reduced ejection fraction (HFrEF).[2] HFrEF is identified as the over activation of the neurohormonal axis mainly of the sympathetic nervous system and the renin–angiotensin–aldosterone system. In the beginning it is an adaptive response but later it becomes maladapive and results in salt and water retention and then a cascade of deleterious consequences related to hemodynamic effects and fibrosis. Patients with reduced ejection fraction have a significantly higher mortality than patients with preserved ejection fraction (HFpEF).[2] It is a life-threatening syndrome characterised by significant morbidity and mortality, poor functional capacity and quality of life, and high costs. Therefore, attempts to decrease its social and economic burden have become a major global public health priority.[3]

Epidemiology

Heart Failure (HF), one of a major cause of hospitalisation in the High-Income Countries (HIC), represents 1% to 2%

of the total hospital admissions. HF is a disease associated with significant mortality, which is higher than many common cancers like breast or colon. It is also associated with high morbidity, and accounts for a significant share in the healthcare expenditures in the developed world.[4] Based on the NHANES (National Health and Nutrition Examination Survey) data, the 2017 heart disease and stroke update shows that 6.1 million Americans 20 years of age have HF. These projected figures estimate that the prevalence of HF in US will increase by 46% from 2012 to 2030 and the estimated medical costs related to HF will increase almost by 127% to $69.7 billion in 2030.[5]

A preliminary estimate in the adult population in India on the community-level prevalence of HF is about 1%.[6] Based on these estimates (where US prevalence data is extrapolated to Indian population), the prevalence of HF in India is estimated approximately 23 million.[5] Prevalence of HF is likely to be proportionate to the risk factor levels in the society. India is said to be having the "double burden". On one side there is rise in prevalence of conditions like hypertension, diabetes, and coronary artery disease and on the other side, there is persistence of other conditions like rheumatic heart disease. There are also other specific conditions which are unique to India, like aortoarterits, endomyocardial fibrosis, untreated congenital heart disease, high prevalence of chronic obstructive pulmonary disease (COPD) which can contribute to the burden of HF. According to the INDUS study, the estimated prevalence of HF in India in 2016 was 1% of the total population; that is about 8 to 10 million patients.[6,7]

Trivandrum Registry IHD and the INTER-CHF registry showed 71% of heart failures are due to CAD and shows various other aetiologies in patients. The Trivandrum Heart Failure Registry (THFR) suggests HF with preserved ejection fraction represents 25% of the total HF burden, which means that HF with reduced ejection fraction is more predominant.[8] Therefore, this type of heart failure was chosen for our study. For patients who have been diagnosed with HFrEF, randomized clinical trials demonstrate constant mortality benefit from angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, direct-acting vasodilators, beta blockers, and aldosterone antagonists.

Additionally, some data show benefits from two new classes of drugs: angiotensin receptor blocker/ neprilysin inhibitor and sinus node modulator. Disease management and monitoring can reduce hospitalisations and mortality, especially for patients who have previously been hospitalised for heart failure.[9] In India, most of the health-care costs are borne by the patient. Healthcare is largely provided by the private sector (76%) and paid for out of pocket (67%).[10] The management of HFrEF is lifelong for the patients, and most of the patients are elderly who might be dependent on someone else for financial support. To the best of our knowledge, no studies have been performed yet on cost analysis and variation of different oral drugs used in management of HFrEF marketed in India. We have only considered tablets and capsules dosage forms and not others as single manufacturer was mentioned in our sources. Hence, this study was performed with the objective of comparing the cost differences among different brands of drugs. The knowledge of this study can be applied for making treatment regimens more economical which in turn will improve patient compliance and decrease the failure rates of therapy.

METHODS

The study was performed in the Department of Pharmacology of tertiary care hospital in Mumbai with the inclusion criteria being all oral branded drugs used in the treatment of HFrEF available in Indian market was included in the study. FDCs of drugs used in the treatment of HFrEF guideline available as capsules and tablets was included in this study. Drugs of dosage forms other than tablets or capsules and those drugs which had only one manufacturing brand were excluded from this study.

Price of drugs used in the treatment of HFrEF in Indian rupees (INR) manufactured by different pharmaceutical companies in India, in the same strength was obtained from "Current Index of Medical Specialties" (CIMS) January-April 2023, and Indian Drug Review (IDR 2023), Drug Today (January-April 2023) as they are a readily available source of drug information and are updated regularly. Difference in the maximum and minimum price of the same drug formulation manufactured by different pharmaceutical companies and percentage variation in prices was calculated. Percentage variation in price was calculated as follows.

$$Cost\ variation = \frac{Maximum\ cost - Minimum\ cost \times 100}{Minimum\ cost}$$

$$\text{Cost ratio} = \frac{Price\ of\ the\ most\ costly\ brand}{Price\ of\ the\ least\ costly\ brand}$$

Maximum and minimum percentage cost variation as well as cost ratio among all FDCs were noted.

Ethical declaration

Study was started after obtaining permission from the Institutional Ethics Committee of the hospital.

Statistical analysis

The findings of this study have been expressed as absolute numbers and percentages.

RESULTS

We analysed total of 652 brands of heart failure management drugs in different classes available in Indian market. Significant cost variations were observed among

different brands of same class of drugs. We have analysed drug formulations in tablet form with different strengths. A price variation is significant when the cost ratio is more than 2 and percentage cost variation is more than 100.

Table 1: Drug costs, cost ratio, and percentage cost variation of drugs that are used in the management of HFrEF available in Indian market.

Drugs	Strength (mg)	No. of brands	Maximum cost (per 10 tablets/ capsules in rupees)	Minimum cost (per 10 tablets/ capsules in rupees)	Cost ratio	Percentage cost variation
ACE inhibitors						
Captopril	12.5	2	24.50	15.78	1.55	55.25
Captopril	25	3	35.00	9.07	3.85	285.9
Enalapril maleate	2.5	24	81.00	6.00	13.5	1250
	5	26	225.00	9.00	25	2400
	10	18	252.00	12.00	21	2000
Lisinopril	2.5	19	56.00	13.50	4.15	314.8
	5	23	136.30	25.00	5.45	445.2
	10	19	229.70	39.00	5.89	489
Pindopril	2	6	111.00	56.25	1.97	97.33
	4	7	130.00	85.25	1.52	52.49
Ramipril	1.25	15	69.75	14.91	4.68	367.8
	1.5	5	69.75	33.00	2.11	111.36
	2.5	41	270.00	25.23	10.70	970.15
	5	40	490.00	37.86	12.94	1194.24
	10	14	185.79	63.00	2.94	194.90
ARBs						
Telmisartan	20	31	349.00	15.00	23.26	2226
	40	60	769.00	18.00	42.7	4172
	80	17	1100.00	25.00	44*	4300*
Losartan	25	22	269.00	10.00	26.9	2590
	50	27	475.00	19.00	25	2400
Irbesartan	150	2	129.00	78.56	1.64	64.2
Candesartan	4	6	34.95	20	1.74	74.75
Valsartan	40	3	672.00	45.00	14.93	1393
	80	6	1148.00	69.00	16.63	1563.7
	160	4	1400.00	130	10.77	976.92
Olmesartan	10	6	89.05	77.30	1.15	15.20
	20	16	890.00	44.50	20.22	1900
	40	13	890.00	63.80	13.94	1295
Combination of ACEI and ARBs						
Losartan+Ramipril	1.25+50	2	55.50	47.50	1.18	16.84
	2.5+50	3	162.75	56.80	2.87	186.5
	5+50	2	138.69	69.99	1.98	98.6
Telmisartan+Ramipril	40+2.5	4	175.50	69.65	2.51	151.97
	40+5	6	202.50	85.80	2.36	136.01
ARNI						
Sacubitril+Valsartan	24+26	3	977.50	439.00	2.22	122.66
Sacubitril+Valsartan	49+51	2	1061.30	482.78	2.19	119.83
Beta blockers						
Bisoprolol	2.5	4	64.54	46.50	1.39	38.8
	5	5	96.32	40.00	2.4	140.8
	10	2	163.00	95.00	1.71	71.58
Carvidilol	3.125	5	40.00	9.00	4.44	344.44

Continued.

Drugs	Strength (mg)	No. of brands	Maximum cost (per 10 tablets/ capsules in rupees)	Minimum cost (per 10 tablets/ capsules in rupees)	Cost ratio	Percentage cost variation
	6.25	6	63.00	17.93	3.5	251.36
	12.5	6	111.00	30.00	3.7	270
	25	4	181.90	52.00	3.5	249.80
Metoprolol	12.5	2	44.40	33.23	1.33	33.6
	25	25	45.00	19.50	2.3	130.76
	50	27	77.50	28.60	2.70	170.98
	100	7	157.35	89.17	1.76	76.46
Nebivolol	2.5	7	127.25	32.00	3.98	297.65
	5	8	152.00	52.00	2.92	192.30
MRAs						
Spironolactone	25	2	29.00	22.50	1.29#	31.11#
Eplerenone	25	8	354.00	127.75	2.77	177.10
	50	7	507.50	290.00	1.75	75
Sodium- glucose co- transporter 2 inhibitors						
Dapagliflozin	10	10	802.00	99.00	8.1	710.10
Empagliflozin	25	2	570.00	570.00	1	0
	100	5	125.00	125.00	1	0
Diuretics						
Turosemide	40	2	13.60	7.90	1.72	72.15
Torsemide	10	4	53.00	33.95	1.56	56.11
Others						
Ivabradine	5	7	314.59	145.00	2.17	116.95
	7.5	2	329.00	155.00	2.12	112.25
Digoxin	0.25	4	12.51	7.10	1.76	76.19

*Costliest HFrEF drug available in Indian market. #Cheapest HFrEF drug available in Indian market

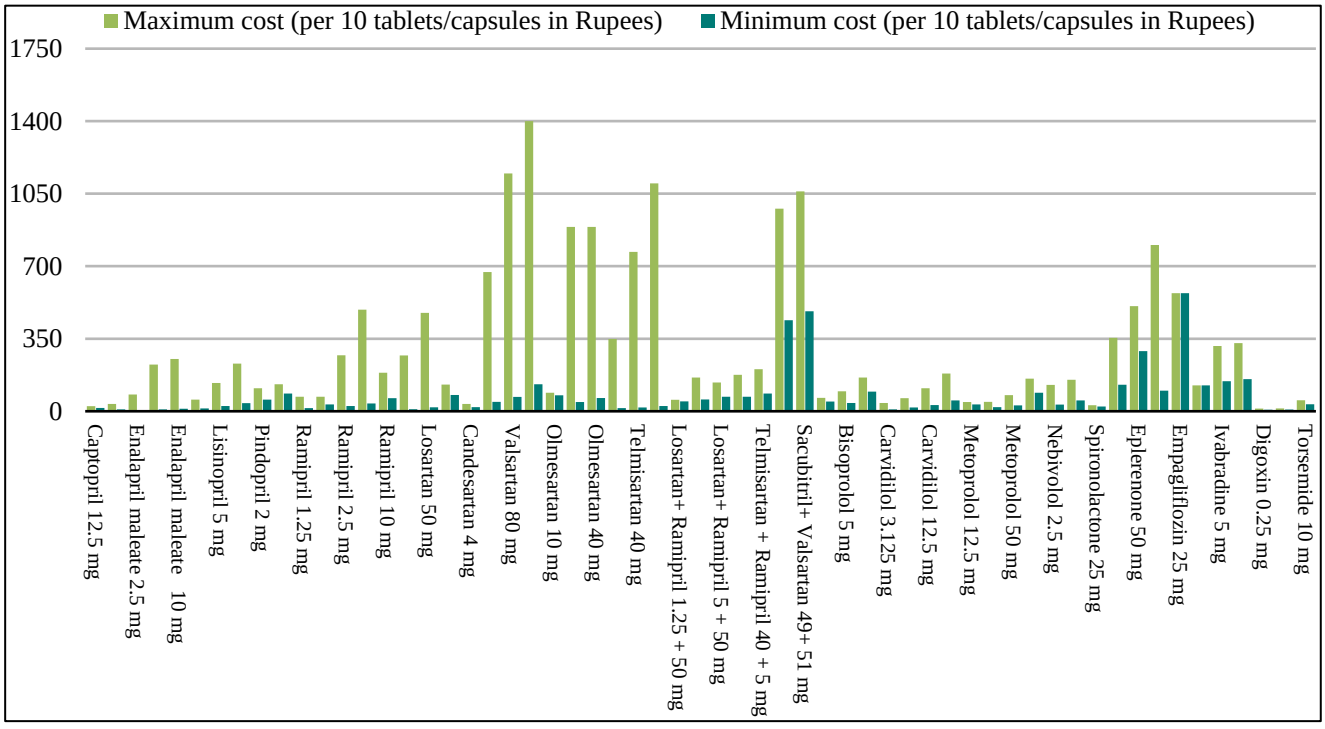

Figure 1: Maximum and minimum cost (per 10 tablets/capsules in rupees).

In this study, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), combination of ACEI and ARBs, angiontensin receptor neprilysin inhibitors (ARNIs), Beta blockers, mineralocorticoid receptor antagonists (MRAs), Sodium-glucose co-transporter 2 inhibitors (SGLT2i) and other groups as recommended by American Heart Association 2022 guidelines for the treatment of HFrEF were analyzed. Most of the heart failure drugs have percentage price variation above 100%.

Among single heart failure drugs, Tab. Telmisartan 80 mg shows highest percentage cost variation (4300%) and highest cost ratio (44). Most expensive formulation of this drug is 44 times costlier than least expensive formulation. Tab. Spironolactone 25 mg shows lowest percentage cost variation 31.11 and lowest cost ratio 1.29. Among fixed dose combinations, Tab. Losartan 2.5 mg+Tab. Ramipril 50 mg shows highest percentage cost variation 186.5% and highest cost ratio 2.87. Tab. Losartan 1.25 mg+Tab. Ramipril 50 mg shows lowest percentage cost variation 16.84% and lowest cost ratio 1.18.

DISCUSSION

Chronic heart failure is a progressive disease which is increasing in epidemic proportions and affecting both the developed and the developing world. Heart failure is associated with shorter life expectancy, increased frequency of hospitalisation and poor quality of life (QoL), and is a major public health challenge even in India.[15]

The findings of this study offer significant insights into the landscape of heart failure management drug pricing within the Indian pharmaceutical market, shedding light on notable variations in costs across different oral formulations and drug classes. Our analysis, encompassed a comprehensive evaluation of 652 brands, focusing on formulations of essential drug classes including ACEIs, ARBs, ARNIs, Beta blockers, MRAs, SGLT2i, and others. The observed disparities in drug pricing, characterised by a substantial cost ratio exceeding 2 and a percentage cost variation surpassing 100%, underscore critical challenges in ensuring equitable access to essential medications for heart failure patients. According to 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure in patients with HFrEF, inhibition of the renin-angiotensin system is advised to decrease morbidity and mortality. First-line therapy includes ARNI, ACEI, or ARB. In hospitalised patients with acute HF it is advised to start ARNI before they are discharged, due to the positive impact of ARNI on the health status of patients, reduction in the prognostic biomarker NT-proBNP, and improvement of LV remodelling parameters when compared to ACEI/ ARB. Alternative use of ARB in place of ACEI and ARNI is recommended for patients experiencing intolerable cough and angioedema. Transitioning patients from an ACEI to an ARNI or vice versa requires a minimum of 36 hours between doses. Beta blockers have also been shown to improve the left ventricular ejection fraction (LVEF), reduce HF symptoms, and enhance clinical status therefore lower the risk of death and hospitalisation. It is recommended that beta blockers be prescribed to all patients diagnosed with HFrEF, including in-hospital patients, unless there are contraindications to the medication. MRA, also referred to as aldosterone antagonists or anti-mineralocorticoids, have demonstrated consistent improvements in all-cause mortality, HF hospitalisations, and sudden cardiac death (SCD) among a diverse range of patients with HFrEF. However, patients who are at risk for renal dysfunction or hyperkalemia require careful monitoring. Additionally, MRA initiation is contraindicated for patients with eGFR $\leq$30 ml/min/1.73 m^2 or serum potassium levels $\geq$5.0 mEq/l. In the DAPA-HF and EMPEROR-Reduced trials, SGLT2i compared with placebo reduced the composite of cardiovascular death or HF hospitalisation by approximately 25%. The benefit in reduction of HF hospitalisation was greater (30%) in both trials.[11] Notably, Tab. Telmisartan 80 mg emerged as a striking example of extreme pricing discrepancies, with a staggering 4300% percentage cost variation and a cost ratio of 44, indicating a pressing need for regulatory interventions to address such disparities. This means that the most expensive formulation of this drug is 44 times more costly than the least expensive one. Given these findings, it's imperative to ensure that physicians are aware of more affordable alternatives. Conversely, Tab. Spironolactone 25 mg demonstrated a more consistent pricing structure, highlighting potential areas for improvement and standardisation within the pharmaceutical market. Furthermore, our analysis of fixed-dose combinations revealed significant variability in pricing, with implications for treatment affordability and accessibility. The identification of Tab. Losartan 2.5 mg+Tab. Ramipril 50 mg as exhibiting the highest percentage cost variation underscores the complexities in pricing strategies within this drug category.

A study conducted by Yan BW et al in USA investigated the cost-effectiveness of sequentially adding the SGLT2i and ARNi to form quadruple therapy as compared with the previous standard of care with ACE inhibitor/mineralocorticoid receptor antagonist/beta blocker. It concluded that when compared with the previous standard of care, the SGLT2i addition had an incremental cost- effectiveness ratio of $73000/QALY and weakly dominated the ARNi addition. The addition of both the ARNi and SGLT2i for quadruple therapy offered 0.68 additional discounted QALYs over the SGLT2i addition alone at a lifetime discounted cost of $66700, resulting in an incremental cost- effectiveness ratio of $98500/QALY.[12] A systematic review done by Urbich M et al of medical costs associated with heart failure in the USA included 87 studies, 41 of which allowed a comparison of cost estimates across studies. The annual median total medical costs for heart failure care were estimated at $24,383 per patient, with heart failure-specific hospitalisations driving costs (median $15,879 per patient). Analyses of subgroups revealed that heart failure-related costs are highly sensitive to individual patient

characteristics (such as the presence of comorbidities and age) with large variations even within a subgroup. Additionally, differences in study design and a lack of standardised reporting limited the ability to compare cost estimates.[13]

In countries such as India, where medical expenses are a major concern, drug non-compliance has emerged as a serious issue. Often, patients choose to discontinue their medication without consulting with their doctors as a means of cutting expenses. However, this can have catastrophic implications in HF, including acute pulmonary edema, stroke, SCD. To mitigate these risks, it is suggested that government agencies and sponsoring authorities provide financially underprivileged patients with free or subsidized daily medication to reduce the overall long-term financial burden.[14] In India, appropriate use of healthcare resources such as emergency departments, intensive care units, ventilator support, and timely interventions by heart failure experts can help lower overall costs.[15] Research shows that many treating physicians are not familiar with the costs of branded medicine, which can have a significant impact on their patients' financial well-being. To address this issue, doctors should consider adopting a shared decision-making approach when prescribing medications, taking into account the patient's financial situation.[16] A study performed by Mulakaluri and Phani Prasant has demonstrated that providing physicians with a manual containing comparative drug prices, including the majority of available brands in the country, can markedly decrease a patient's expenditure on medication.[17] In spite of all these factors, we could not find any study performed on cost analysis of oral drugs marketed in India to best of our knowledge. Therefore, the present study was undertaken to analyze the cost variations of different brands of heart failure drugs marketed as tablets or capsules. This study provides the comparison of cost of different group of the drug which are used for the management of HFrEF, and brings into the limelight, the immense differences in cost prevailing in them. A close study of these differences in cost and ensuring that the most economical medications are prescribed, if the pharmacodynamic properties and efficacy is matched, will ensure that the financial load on patients is relieved which in turn improves adherence to treatment. We analyzed oral drugs which are used for the management of HFrEF because to the best of our knowledge no other cost analysis studies of this type has been done in India.

Limitations of the study was that authors only considered only those brands of HFrEF drugs as mentioned in CIMS, IDR and Drug Today, though many different brands may be available in India but not mentioned in our source of information. Various generic drugs available in Indian market have not been considered in our study. We have only considered tablets and capsules dosage forms and not others since in CIMS, IDR and drug today only single manufacturer was mentioned.

CONCLUSION

This study showed wide price variation of drug which are used for the management of HFrEF available in Indian market. There should be combined efforts from the government, physicians, and pharmaceutical companies to reduce such a price variation and provide maximum benefits to patients. In India, not all patients are covered under insurance/ medi claim, and this factor should also be kept in mind while developing pricing policy. Large- scale studies of a similar nature will help in giving a better overview of drug price variation in the Indian market.

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REFERENCES

1. Murphy SP, Ibrahim NE, Januzzi JL. Heart failure with reduced ejection fraction: a review. Jama. 2020;324(5):488-504.
2. Haydock PM, Flett AS. Management of heart failure with reduced ejection fraction. Heart. 2022;108(19):1571-9.
3. Savarese G, Becher PM, Lund LH, Seferovic P, Rosano GM, Coats AJ. Global burden of heart failure: a comprehensive and updated review of epidemiology. Cardiovascular research. 2022;118(17):3272-87.
4. Census of India Website: Office of the Registrar General and Census Commissioner, India. Available at: censusindia.gov.in. Accessed on 28th March 2024.
5. Guha S, Harikrishnan S, Ray S, Sethi R, Ramakrishnan S, Banerjee S, Bahl VK, Goswami KC, Banerjee AK, Shanmugasundaram S, Kerkar PG. CSI position statement on management of heart failure in India. IHJ. 2018;70(1):1.
6. Pillai HS, Ganapathi S. Heart failure in South Asia. Curr Cardiol Rev. 2013;9:102-111.
7. Chaturvedi V, Parakh N, Seth S, Bhargava B, Ramakrishnan S, Roy A, et al. heart failure in India: The INDUS (INDia Ukieri Study). JPCS. 2016;2:28-35.
8. Harikrishnan S, Sanjay G, Agarwal A. One-year mortality outcomes and hospital readmissions of patients admitted with acute heart failure: data from the Trivandrum Heart Failure Registry in Kerala, India. Am Heart J. 2017;189:193-99.
9. Chavey WE, Hogikyan RV, Van Harrison R, Nicklas JM. Heart failure due to reduced ejection fraction: medical management. American Family Physician. 2017;95(1):13-20.
10. Asaria M, Mazumdar S, Chowdhury S, Mazumdar P, Mukhopadhyay A, Gupta I. Socioeconomic inequality in life expectancy in India. BMJ Global Health. 2019;4(3):1445.
11. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, Deswal A, Drazner MH, Dunlay SM, Evers LR, Fang JC. 2022 AHA/ACC/HFSA

guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol. 2022;79(17):263-421.
12. Yan BW, Spahillari A, Pandya A. Cost-effectiveness of quadruple therapy in management of heart failure with reduced ejection fraction in the united states. circulation: cardiovascular quality and outcomes. 2023;16(6):9793.
13. Urbich M, Globe G, Pantiri K, Heisen M, Bennison C, Wirtz HS, Di Tanna GL. A systematic review of medical costs associated with heart failure in the USA (2014–2020). Pharmacoeconomics. 2020;38:1219-36.
14. Singh A, Chauhan S, Devasia T, Karkala YR, Paramasivam G, Shetty PN, Uppunda D, Kareem H. Financial burden of heart failure in a developing country: cost analysis from Manipal Heart Failure Registry, India. JPH. 2021;29:585-94.
15. Mishra S, Mohan JC, Nair T, Chopra VK, Harikrishnan S, Guha S, et al. Management protocols for chronic heart failure in India. IHJ. 2018;70(1):105-27.
16. Ray A, Najmi A, Khandelwal G, Sadasivam B. A cost variation analysis of drugs available in the Indian market for the management of thromboembolic disorders. Cureus. 2020;12(5).
17. Mulakaluri PP: Generic medicines in the Indian scenario - what are we expecting? Telangana J Psychiatr. 2017;3:1-3.

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