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Assessment of the Cost Differences and Variability of Medicines for the Treatment of Heart Failure in India

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Authors' contributions

This work was carried out in collaboration among all authors. All authors designed the study. Authors CK, RK and AKR did the data acquisition. Authors CK, RK, SKS and SS did the study analysis and interpretation of data. Authors SKS, SS and AKR prepared and revised the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Introduction: Heart failure, a global health concern affecting millions, has varying prevalence, classifications, and treatments. Standard therapy includes ACE inhibitors, beta blockers, and diuretics. Newer options like ARNIs and sinoatrial node modulators are recommended. There is no previous research on cost disparity in heart failure medication in India. The objective of this

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research, which aims at reducing treatment costs, increasing adherence to therapy and using medicines more carefully, is to assess the differences in cost between various medicinal products.
Methods: The maximum and minimum price of each brand of the drugs given in Indian rupees (INR) was noted by using 'Drug Today' (January to April 2023, volume II). The cost range, cost ratio, and the percentage cost variation for individual drug brands were calculated. The cost of tablets/capsule was calculated and the cost ratio and percentage cost variation of various brands was compared.
Results: After calculation of cost ratio and percentage cost variation for each brands of drug used in the management of Heart failure, tab Propranolol (40 mg) had a maximum percentage cost variation of 678% and a cost ratio of 7.78 while tab Candesartan (8 mg) had a minimum percentage cost variation of 006% and cost ratio of 1.06. Ideally we use the drug which cost ratio less than 2 and percentage cost variation less than 100.
Conclusions: There is a wide variation in the price of different brands of drug used in the management of Heart failure available in India. The clinicians prescribing these drugs should be aware of these variations to reduce the financial burden of drug therapy and improve compliance.

Keywords: Heart failure; cost ratio; percentage cost variation.

1. INTRODUCTION

"Heart failure represents a major public health issue and is associated with considerable morbidity and mortality. Globally, heart failure (HF) affects an estimated 26 million people and is responsible for 1%–2% of hospitalizations in the USA and Europe" [1]. "The burden of HF in India appears high, and estimates of prevalence range from 1.3 million to 4.6 million, with an annual incidence of 491 600–1.8 million" [2]. "The incidence and prevalence estimates of heart failure (HF) are unreliable in India because of the lack of surveillance systems to adequately capture these data. This lack of HF surveillance is not unique to India. In 2001, Mendez and Cowie found no population-based HF studies in all developing countries,making global prevalence estimates difficult" [3]. "Estimating the burden of HF is further hampered by the lack of a standard definition. In fact, the WHO Global Burden of Disease study places HF in several categories within cardiovascular disease, including ischemic, hypertensive, inflammatory and rheumatic heart disease (RHD)" [4].

"The 2013 guidelines of the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) defined two types of HF: preserved ejection fraction (HFpEF) and reduced ejection fraction (HFrEF). A preserved ejection fraction (EF) is 50% or greater, while reduced EF was defined as 40% or less. Patients with an EF of more than 40% but less than 50% represent an intermediate group whose treatment is similar to HFpEF" [5].

"In addition to HF type, patients can be assigned a class and/or stage of HF. The New York Heart Association (NYHA) defines four classes of HF" [5].

- Class I: No physical limitation; ordinary physical activity does not cause HF symptoms
- Class II: No symptoms at rest, but ordinary physical activities cause HF symptoms
- Class III: No symptoms at rest, but less-than-ordinary physical activities cause HF symptoms
- Class IV: Symptoms of HF at rest

The ACCF/AHA also defines four stages of HF [5].

- Stage A: At high risk for HF but without structural heart disease or symptoms of HF
- Stage B: Structural heart disease but without signs or symptoms of HF
- Stage C: Structural heart disease with prior or current symptoms of HF
- Stage D: Refractory HF requiring specialized interventions

"First-line drug therapy for all patients with HFrEF(HF with reduced ejection fraction) should include an angiotensin converting enzyme (ACE) inhibitor and beta blocker while diuretics for chronic heart failure. These medications have been shown to decrease morbidity and mortality" [6,7]. A study found "valsartan/sacubitril to be superior to the ACE inhibitor when added to standard therapy, including a beta blocker and diuretics, in reducing the risk of death and hospitalization" [8].

However, the 2016 "Focused Update on New Pharmacological Therapy for Heart Failure" from

the ACCF, AHA, and Heart Failure Society of America (HFSA) changed how patients are managed in stage C with HFrEF. The new guidelines focused on two new classes of medications: an angiotensin receptor neprilysin inhibitor (ARNI) (valsartan/sacubitril and a sinoatrial node modulator (ivabradine).

"Beta blockers and ACE inhibitors have been proven to reduce morbidity and mortality in a wide range of HFrEF patients" [9-12]. "These proven benefits warrant the use of these agents in all patients with HF. MRAs such as spironolactone and eplerenone have also been shown to reduce morbidity and mortality in addition to ACE inhibitors and beta blockers in patients with HFrEF, depending on the NYHA class and EF. Therapy should always be individualized, but one of these agents can be added to base therapy for additional benefits" [13].

"Vasodilators show morbidity and mortality benefit in African-American patients in specific situations and can be added to therapy" [14,15]. "To help reduce morbidity in patients, additional agents may be added for symptomatic relief. In patients with signs and symptoms of fluid overload, diuretics should be used to help mobilize and excrete the excess fluid. Specifically, loop diuretics are seen as the first-choice agents, but thiazides may be added to overcome loop resistance" [16,17]. "Digoxin may be added for symptom relief and to decrease morbidity. Though it does not show mortality reduction, it has demonstrated utility in decreasing hospitalizations for worsening HFrEF" [18,19].

"Ivabradine may be added to treatment in patients on beta blockers who have persistently elevated heart rates or who cannot tolerate beta blockers. The addition of ivabradine will further reduce morbidity, mortality, and hospitalizations in these patients, because increased rates of cardiovascular death, hospitalization for HF and myocardial infarction, and coronary revascularization have been reported in patients with heart rates greater than 70 bpm" [20,21]. "Thus, ivabradine should be considered add-on therapy in select patients with persistently elevated heart rates despite beta-blocker therapy" [22].

ARB and neprilysin inhibitor combination products (such as sacubitril/valsartan) offer a new option for patients. These agents may have a role in patients who remain symptomatic despite reaching maximum doses of ACE inhibitors/ARBs and beta blockers.

A recent study found "valsartan/sacubitril to be superior to the ACE inhibitor enalapril when added to standard therapy, including a beta blocker and diuretics, in reducing the risk of death and hospitalization" [16]. "Ivabradine also reduced the risk of hospitalization for worsening heart failure and the risk of cardiovascular death" [7].

The study revealed that various drugs used in heart failure of different brands available in India have huge cost variations which lead to increase economic burden and decrease compliance. So we ideally use the drugs which cost ratio and percentage cost variation is minimal.

We found that for eligible patients with HFrEF, initiation of sacubitril-valsartan during hospitalization was cost saving compared with initiation 2 months after hospitalization and was cost saving or highly cost-effective compared with indefinite continuation of enalapril treatment. There may also be cost savings from a societal perspective.

For the treatment of heart failure, we have a wide range of medications created by several pharmaceutical companies. Therefore, we designed this study to identity cost variability in different drugs formulation developed by different pharmaceutical companies for treatment of heart failure to reducing treatment costs, increasing adherence to therapy and using medicines more carefully, is to assess the differences in cost between various medicinal products

There is no previous research on cost disparity in heart failure medication in India. This study will be useful to determine cost difference between various drugs to lower therapy costs, promote patient compliance, and use medications more judiciously.

2. METHODS

Price in INR of drugs used in the management of Heart failure manufactured by different pharmaceutical companies in India, in the different strengths was obtained by using Drug Today (January-April 2023, volume I) as they are a readily available source of drug information and are updated regularly. "The cost of 10 tablets/capsules was calculated. The costs of drugs were also cross-checked at a pharmacy or

retail drug store. The difference in the maximum and minimum price of the same drug formulation manufactured by different pharmaceutical companies and percentage variations in prices were calculated. The cost ratio, calculated as the ratio of the costlier brand to that of the cheapest brand of the same drug, is calculated as follows" [53].

2.1 Cost Ratio

Price of the costlier brand/ price of the cheapest brand

2.2 Percentage Cost Variation

[(Maximum cost-minimum cost)/minimum cost] ×100

Maximum and minimum percentage cost variation and cost ratio of a particular drug was noted down.

2.3 Inclusion Criteria

Drugs used in the management of Heart failure from branded manufacturing companies and drugs of the same and different strengths were included. Dosage forms were also included.

2.4 Exclusion Criteria

Drugs used in the management of Heart failure in combinations with other groups of drugs, fixed-dose combinations and drugs with no price information were excluded from the study.

We will also classify drugs used in management of heart failure with initial dose, targeted dose, adverse effects and contraindications. We collected data for this from drug label information from Food and Drug Administration & National Institutes of Health.

3. RESULTS

Different drug therapy used for management of heart failure classified in Table 1.

The costs of drugs used in management of heart failure available in 27 different formulations were analyzed and a substantial variation in cost was observed. Out of this drug formulations studied, the percentage cost variation of 18 drug formulations was more than 100% out of which 7 drug formulations had more than 200%. The cost ratio was also observed to be very high and 4 drug formulations had this ratio of more than 4. After calculation of cost ratio and percentage cost variation for each brand of drug used in the management of Heart failure, tab. Propranolol (40 mg) had a maximum percentage cost variation of 678% and a cost ratio of 7.78 while tab Candesartan (8 mg) had a minimum percentage cost variation of 006% and cost ratio of 1.06. Among ACE inhibitor Ramipril (2.5 mg) was more cost effective and Bisoprolol (5 mg), GTN (6.4mg) was more cost effective among beta blocker and nitrate respectively. Among ARBs and diuretics all generic form and strength was almost equally cost effective (Table 2).

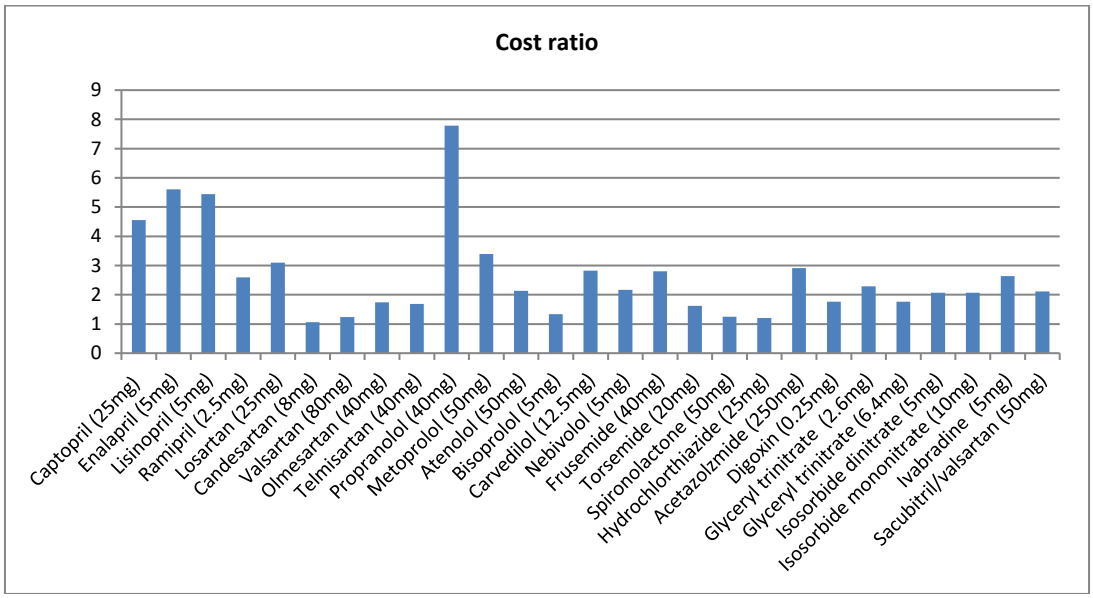

Fig. 1. Cost Ratio of different brands of drug used in heart failure

Table 1. Drug therapy used for the Treatment of Heart Failure

Medication	Initial Dose	Target Dose	Adverse Effects	Contraindications
Angiotensin-Converting Enzyme Inhibitors [5,23-30]				
Captopril	6.25–25 mg TID	50 mg TID	• Hypotension	• Hypersensitivity
Enalapril	2.5 mg BID	20 mg BID	• SCr/BUN increase	• Previous angioedema due to any ACE inhibitor
Fosinopril	5–10 mg daily	40 mg daily	• Hyperkalemia	
Lisinopril	2.5–5 mg daily	40 mg daily	• Cough	
Perindopril	2 mg daily	16 mg daily		
Quinapril	5 mg BID	20 mg BID		
Ramipril	1.25–2.5 mg daily	10 mg daily		
Trandolapril	1 mg daily	4 mg daily		
Angiotensin Receptor Blockers [31-33]				
Candesartan	4–8 mg daily	32 mg daily	• Hypotension	• Hypersensitivity
Losartan	25–50 mg daily	150 mg daily	• SCr/BUN increase	• Concomitant use with aliskiren in patients with diabetes
Valsartan	20–40 mg BID	160 mg BID	• Hyperkalemia	
Beta Blockers [34-37]				
Bisoprolol	1.25 mg daily	10 mg daily	• Hypotension	• Severe bradycardia
Carvedilol	3.125 mg BID	50 mg BID	• First-degree heart block	• Second- or third-degree heart block in the absence of a pacemaker
Carvedilol CR	10 mg daily	80 mg daily	• Edema	
Metoprolol	12.5–25 mg daily	200 mg daily	• Dizziness	• Cardiogenic shock
			• Abdominal pain/diarrhea	• Decompensated HFrEF
				• Sick sinus syndrome
Loop Diuretics [38-41]				
Bumetanide	0.5–1.0 mg daily	10 mg daily	•Hypotension/dizziness	• Hypersensitivity
Furosemide	20–40 mg daily	600 mg daily	• Fluid loss	• Anuria
Torsemide	10–20 mg daily	200 mg daily	• Hypokalemia, hypocalcemia, hypomagnesemia, hyponatremia	
Ethacrynic acid	25–50 mg daily	100 mg BID		
Thiazide Diuretics Used in Combination with Loop Diuretics [42]				
Metolazone	2.5–10 mg daily +loop diuretic	NA	• Hypotension • Dizziness	•Hypersensitivity • Anuria
Hydrochlorothiazide	25–100 mg daily or BID +loop diuretic	NA	• Gout attacks • Hypercalcemia • BUN increase	• Hydrochlorothiazide: Cr Cl ≤ 10 mL/min

Medication	Initial Dose		Target Dose		Adverse Effects	Contraindications
Aldosterone Antagonists [43,44]						
	CrCl < 50	CrCl > 50	CrCl < 50	CrCl > 50		
Spironolactone	12.5 mg daily or every other day	12.5–25 mg daily	12–25 mg daily	25 mg daily or BID	• Hyperkalemia • Diarrhea • Impaired renal function • Dizziness • Fatigue • Spironolactone: gynecomastia	• Spironolactone: acute renal insufficiency, anuria, or significant renal dysfunction • Eplerenone: serum potassium > 5.5 mEq/L at initiation, CrCl < 30 ml/min, concomitant use of strong CYP3A4 inhibitors
Eplerenone	25 mg every other day	25 mg daily	25 mg daily or BID	50 mg daily		
Vasodilators [5,45]						
Hydralazine	25–50 mg TID–QID		300 mg daily in divided doses		• Hypotension • Headache • Dizziness • Asthenia • Nausea	• Allergy to nitrates • PDE5 inhibitors • Riociguat
Isosorbide dinitrate	20–30 mg TID–QID		120 mg in divided doses			
Digoxin [46]						
Digoxin	0.125–0.25 mg daily		0.25 mg daily (may be lower in patients older than 70 years of age or patients with renal dysfunction		• Arrhythmias • Heart block • Nausea/vomiting • Diarrhea • Anorexia • Visual changes • Headache	• Hypersensitivity • Ventricular fibrillation
I(f) Inhibitor [47-49]						
Ivabradine	5 mg BID		7.5 mg BID		• Bradycardia • Atrial fibrillation • Phosphenes (transient enhanced brightness in restricted area of visual field) • Blurred vision	• Acute decompensated HFrEF • BP < 90/50 mm Hg • Sick sinus syndrome, sinoatrial block, or third-degree AV block without functioning demand pacemaker • Resting HR < 60 bpm prior to treatment

Medication	Initial Dose	Target Dose	Adverse Effects	Contraindications
				• Severe hepatic impairment • Pacemaker dependence • Concomitant use with strong CYP3A4 inhibitors
Angiotensin Receptor-Neprilysin Inhibitor [50-52]				
Sacubitril/valsartan	49 mg/51 mg BID	97 mg/103 mg BID	• Hypotension • Hyperkalemia • SCr increase • Dizziness • Cough	• Previous angioedema due to any ACE inhibitor or ARB • Concomitant use of ACE inhibitors or use within the previous 36 hours • Concomitant use of aliskiren in diabetic patients

Table 2. Cost ratio and percentage cost variation of drugs used in the management of heart failure in the Indian market

Drugs & strength/10 tab	No. of brands	Cost range (INR)	Cost ratio	Percent cost variation
Angiotensin-Converting Enzyme Inhibitors				
1.Captopril (25mg)	25	41.00-9.00	4.55	355
2.Enalapril (5mg)	27	50.57-9.00	5.61	461
3.Lisinopril (5mg)	20	136.00-25.00	5.44	444
4.Ramipril (2.5mg)	38	70.00-27.00	2.59	159
Angiotensin Receptor Blockers				
1.Losartan (25mg)	48	31.00-10.00	3.1	210
2.Candesartan (8mg)	4	48.00-45.00	1.06	006
3.Valsartan (80mg)	10	86.00-69.00	1.24	024
4.Olmesartan (40mg)	39	155.00-89.00	1.74	074
5.Telmisartan (40mg)	85	103.00-61.00	1.68	068
Beta Blockers				
1.Propranolol (40mg)	15	74.00-9.50	7.78	678
2.Metoprolol (50mg)	30	90-26.50	3.39	239
3.Atenolol (50mg)	27	32.00-15.00	2.13	113.3
4.Bisoprolol (5mg)	4	91.00-68.00	1.33	033
5.Carvedilol (12.5mg)	15	82.00-29.00	2.82	182
6.Nebivolol (5mg)	15	113.00-52.00	2.17	117
Diuretics				
1.Frusemide (40mg)	9	14.00-5.00	2.8	180
2.Torsemide (20mg)	24	120.00-74.00	1.62	062
3.Spironolactone (50mg)	5	35.00-28.00	1.25	025
4.Hydrochlorthiazide (25mg)	4	16.80-13.94	1.20	020
5.Acetazolzmide (250mg)	10	49.00-16.80	2.91	191
Digoxin				
1.Digoxin (0.25mg)	4	12.51-7.10	1.76	076
Vasodilators				
1.Glyceryl trinitrate (2.6mg)	5	31-71	2.29	129.03
2.Glyceryl trinitrate (6.4mg)	4	42-74	1.76	76.19
3.Isosorbide dinitrate (5mg)	3	3.80-7.90	2.07	107.89
4.Isosorbide mononitrate (10mg)	7	10.52-21.78	2.07	107.03
I(f) Inhibitor				
1.Ivabradine (5mg)	23	131-346	2.64	164.12
Angiotensin Receptor-Neprilysin Inhibitor				
1.Sacubitril/valsartan (50mg)	14	420.00-199.00	2.11	110.5

4. DISCUSSION

The analysis of 27 different drug formulations used in heart failure management unveiled a noteworthy discrepancy in costs. Among the formulations investigated, 18 displayed a percentage cost variation exceeding 100%, with 7 of them even surpassing 200%. Moreover, the cost ratio was found to be notably elevated, with 4 drug formulations exhibiting ratios surpassing 4. This study's exploration of the cost ratio and percentage cost variation for each drug brand utilized in heart failure management revealed striking differences. For instance, Propranolol (40 mg) exhibited a remarkable maximum percentage cost variation of 678% alongside a cost ratio of 7.78, in stark contrast to Candesartan (8 mg) which showcased minimal variation at 0.06% and a 1.06 cost ratio. Notably, among ACE inhibitors, Ramipril (2.5 mg) emerged as a cost-effective option, while among beta blockers and nitrates, Bisoprolol (5 mg) and GTN (6.4 mg) proved to be more economical, respectively. In contrast, generic forms and strengths of ARBs and diuretics demonstrated nearly equivalent cost-effectiveness.

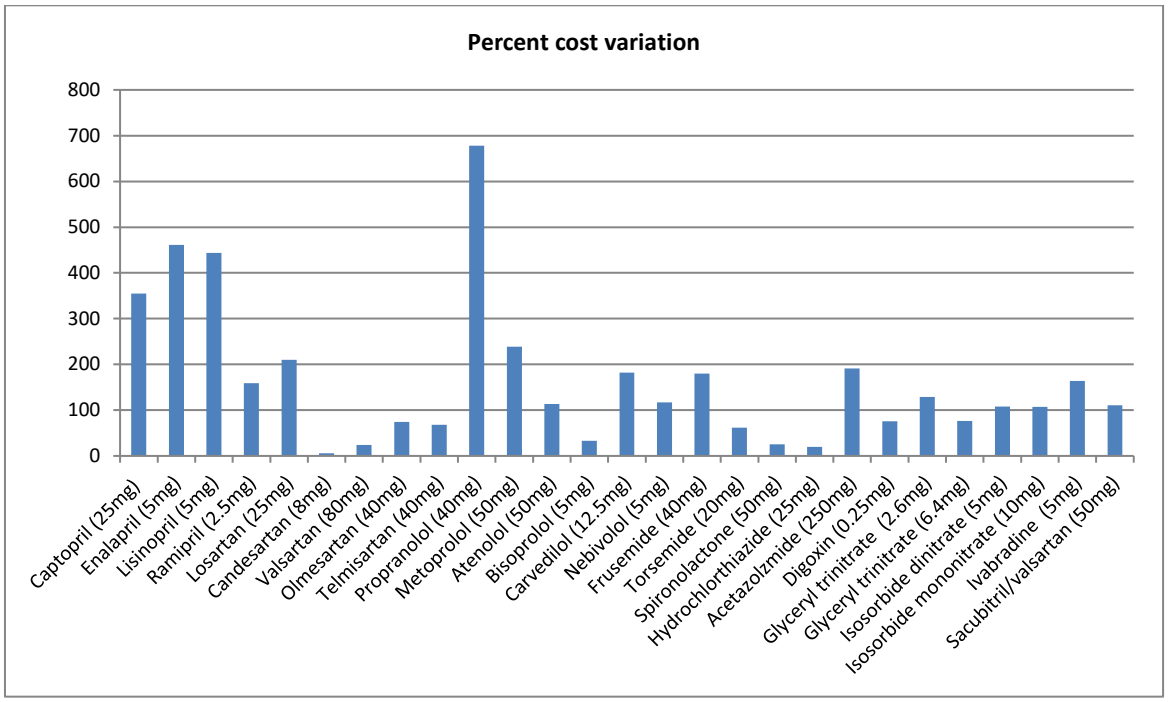

Fig. 2. Percentage cost variation of different brand of drugs used in heart failure

These findings underline the substantial cost variations within heart failure drug formulations, which could have significant implications for both patients and healthcare systems. Cost-effective drug selection and prescription practices are paramount in enhancing patient outcomes while minimizing the economic burden. Strategies that promote the use of more economical yet equally effective options, particularly in the case of generic formulations, could play a pivotal role in optimizing heart failure management and resource allocation.

There are some limitations in this study. We only evaluated price from drug today and cross checked from pharmacy store. We didn't evaluated price from other sources due to lack of sources. We were also not able to collected data from heart failure patients to collect data of overall cost of heart failure treatment.

5. CONCLUSION

In India, the prices of different brands of medications for heart failure varied greatly. The cost of a drug is an equally significant consideration for reasonable drug use, although it is frequently overlooked when prescribing. As a result, research like this that compare the prices of several brands of a class of drugs can aid in the prescription of medications that are affordable to the common person. Patients' medicine costs can be reduced and compliance increased when generic medications are prescribed. The cost and quality of medications should be adequately disclosed to the physicians. The physician should constantly keep in mind that treating patients with a specific medication only because it is expensive is not the right course of action. Instead, the doctor should balance his or her therapeutic decisions when prescribing a specific medication by taking the patient's socioeconomic status into consideration. There is a strong need to create awareness about this huge price variation among the general public, healthcare providers, healthcare payers, government agencies, policymakers, and pharmacists for appropriate intervention to reduce the economic burden on patients as well as the healthcare system.

CONSENT

It is not applicable.

ETHICAL APPROVAL

The study was approved by the Institutional Ethics Committee by AIIMS Patna (Ref. No. AIIMS/Pat/IEC/2022/980

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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