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# Pharmaco-disparities in heart failure: a survey of the affordability of guideline recommended therapy in 10 countries

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## Abstract

**Aims** Heart failure with reduced ejection fraction (HFrEF) is treatable but guideline-directed medical therapy (GDMT) may not be affordable or accessible to people living with the disease.

**Methods and results** In this cross-sectional survey, we investigated the price, affordability, and accessibility of four pivotal classes of HFrEF GDMT: angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB) or angiotensin-neprilysin inhibitors (ARNI); beta-blockers; mineralocorticoid receptor antagonists (MRA); and sodium glucose co-transporter 2 inhibitors (SGLT2i). We sampled online or community pharmacies in 10 countries across a range of World Bank income groups, assessing mean 30 day retail prescription prices, affordability relative to gross national income per capita per month, and accessibility. We reported median price ratios relative to the International Reference Standard. We performed a literature review to evaluate accessibility to GDMT classes through publicly funded drug programmes in each country. HFrEF GDMT prices, both absolute and relative to the international reference, were highest in the United States and lowest in Pakistan and Bangladesh. The most expensive drug was the ARNI, sacubitril/valsartan, with a mean (standard deviation, SD) 30 day price ranging from \$11.06 (0.81) in Pakistan to \$611.50 (3.54) in United States. The least expensive drug was the MRA, spironolactone, with a mean (SD) 30 day price ranging from \$0.18 (0.00) in Pakistan to \$12.32 (0.00) in England. Affordability (SD) of quadruple therapy—ARNI, beta-blockers, MRA, and SGLT2i—was best in high-income and worst in low-income countries, ranging from 1.49 (0.00)% of gross national income per capita per month in England to 232.47 (31.47)% in Uganda. Publicly funded drug programmes offset costs for eligible patients, but ARNI and SGLT2i were inaccessible through these programmes in low- and middle-income countries. Price, affordability, and access were substantially improved in all countries by substituting ARNI for ACEi/ARB.

**Conclusions** There was marked variation between countries in the retail price of HFrEF GDMT. Despite higher prices in high-income countries, GDMT was more accessible and affordable than in low- and middle-income countries. Publicly funded drug programmes in lower income countries increased affordability but limited access to newer HFrEF GDMT classes. Pharmaco-disparities must be addressed to improve HFrEF outcomes globally.

**Keywords** Accessibility; Affordability; Cost; Equity; Heart failure; Pharmaco-disparities; Pharmacotherapy

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## Background

Heart failure (HF) has substantial morbidity, mortality, and healthcare expenditure.<sup>1,2</sup> The global burden of HF is estimated at 56.2 million patients, with approximately half having reduced ejection fraction (HFrEF).<sup>3</sup> Advances in the pharmacologic care of patients with HFrEF have led to improved outcomes.<sup>3</sup> Pivotal classes of evidence-based HFrEF pharmacological treatments include angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB) or angiotensin-neprilysin inhibitors (ARNI); beta-blockers (BB); mineralocorticoid receptor antagonists (MRA); and sodium glucose co-transporter 2 inhibitors (SGLT2i).<sup>3</sup> However, these four pivotal classes of guideline-directed medical therapy (GDMT) are often underutilized, depriving patients of life-saving treatments.<sup>4</sup>

Access to GDMT is an important barrier to HFrEF care, particularly in low and middle-income countries (LMICs) where a majority of people with HF live.<sup>2</sup> In a prior study that explored worldwide availability of medications for cardiovascular disease, significant disparities were noted between higher and lower income countries in the availability of generic ACEi and ARB in public health facilities.<sup>5</sup> Among patients with a self-reported coronary event, a substantially greater proportion in high-income countries reported taking BBs (four-fold greater) and ACEi or ARBs (10-fold greater) relative to those in low-income countries, likely a reflection of disparities in access to healthcare, including pharmacological treatments.

The uptake of medications can be limited by price. In comparison with other cardiovascular diseases such as hypertension, where patients may be treated with one or two drugs, HFrEF treatment requires multiple medications with frequent need to escalate doses to optimize therapy. Prices can vary substantially, and a World Health Organization/Health Action Initiative study of countries across income levels revealed that the median price ratio (MPR; ratio of the public sector procurement price to the international reference price) of captopril, an ACEi, ranged from 0.2 to 12.7.<sup>6</sup> In the same study, the affordability of generic antihypertensive medications was lower in low-income than high-income countries.<sup>6</sup>

Given the high and rising clinical burden of HFrEF, understanding variation in the price, affordability, and accessibility of GDMT across countries of different income levels is critically important and could inform public health and policy strategies to address treatment gaps. Therefore, in this study, we assessed the price, affordability, and accessibility of HFrEF GDMT across 10 high-, middle-, and low-income countries.

## Methods

### Study population

In this cross-sectional sampling survey, we aimed to include 12 low, lower-middle, upper-middle, and high-income countries, with income groups established by the World Bank.<sup>7</sup> The United States, Canada, and United Kingdom were forced in the sample, with other countries chosen randomly. When data could not be obtained, we selected another country in the income level for analysis. We aimed to achieve a balance in the number of countries in each income level.

### Data collection

We examined retail prices for ACEi (enalapril, ramipril, and perindopril), ARB (candesartan and valsartan), BBs (bisoprolol, carvedilol, and metoprolol), MRA (spironolactone and eplerenone), ARNI (sacubitril/valsartan), and SGLT2i (dapagliflozin and empagliflozin). For metoprolol, we included metoprolol succinate; if unavailable, we included metoprolol tartrate. The medications chosen were those with a class I indication for use in contemporary HFrEF guidelines based on a reduction in mortality or the composite of mortality and readmission.<sup>3</sup>

Online drug repositories such as those accessed via the World Health Organization do not include data on contemporary HFrEF therapies. Thus, we collected retail price data from three online pharmacies per country, chosen by convenience sampling. When online pharmacies were not available, we contacted community pharmacies in the capital city of each country via e-mail or through local investigators. Community pharmacies were limited to private pharmacies, defined as independent or chain pharmacies that charge patients for prescriptions. Public government-run or government-funded pharmacies were not included as they typically dispense medications free of charge to a limited, eligible population. Responses from community pharmacies were received between 2 November 2021 and 21 April 2022. Among the community pharmacies, we included both chain and independent pharmacies. We used the retail prices quoted for generic medications. When a generic was not available in the class, the brand-name medication was selected. Information about public programmes for drug coverage in each of the countries was obtained from literature reviews.

## Statistical analysis

We reported the mean (standard deviation, SD) 30 day retail price of each drug to the patient purchasing the product before applying insurance or other subsidies. The quoted retail prices may not reflect the out-of-pocket expense to patients because of differences in insurance or government coverage. We selected the dose of each drug based on the recommended starting dose for HF. For the price of each drug, we used the lowest price quoted by the pharmacy among options listed and the price for the specified dose, rather than as a fraction of a larger dose. For example, for valsartan, the price was quoted for a 40 mg tablet, rather than half the price of an 80 mg tablet.

To assess prices relative to the international standard, we reported the MPR, defined as the price of a drug divided by its international reference price, as established by the Management Services for Health.<sup>8</sup> We estimated the affordability by assessing price relative to the gross national income (GNI) per capita per month using World Bank 2021 data. We assessed whether the GDMT classes could be accessed via the online/community pharmacies or the publicly funded programmes, reporting the number and proportion (%) of pharmacies in which each drug was in stock at the time of each query. We reported all prices in USD, with conversion rates as of 21 April 2022.

## Results

### Countries included in survey

The analysis included four high-income (United States of America Canada, England, and Norway), three upper-middle income (Peru, South Africa, and Iran), two lower-middle income (Pakistan and Bangladesh), and one low-income country (Uganda). Syria, Togo, and Equatorial Guinea (low-income countries) were randomly and sequentially chosen for inclusion in the survey but had to be excluded as online data were not available and no responses were received from community pharmacies. Online pharmacies were available in all included countries other than Iran and Uganda, where data were obtained from community pharmacies. In South Africa, one online pharmacy and two community pharmacies were included as only one online pharmacy was available.

### Price of heart failure with reduced ejection fraction guideline-directed medical therapy

The mean (SD) retail price of each HFREF drug is reported in *Table 1*. Among high-income countries, retail prices were highest in the United States, second highest in Canada, and lowest in Norway and England. The price of most HFREF med-

ications across all GDMT classes (perindopril, enalapril, valsartan, candesartan, bisoprolol, empagliflozin, dapagliflozin, and sacubitril/valsartan) were highest in the United States (*Table S1*). Among the lower income countries, prices were highest in Uganda and Peru and lowest in Pakistan and Bangladesh.

In England, there was a fixed price for each item prescribed regardless of the agent; however, for low-income patients and patients over the age of 60, the prescription fee was waived; this meant that the prices of HFREF drugs were the lowest in England regardless of pharmacy for eligible patients. The most expensive drug was sacubitril/valsartan, with the lowest 30 day mean (SD) price in Pakistan (\$11.06 [0.81]) and the highest price in the United States (\$611.50 [3.54]). The least expensive drug was spironolactone, with the lowest 30 day price quoted in Pakistan (\$0.18 [0.00]) and the highest in Canada (\$7.06 [2.36]). The least expensive ACEi was enalapril, with the lowest 30 day price in Bangladesh (\$0.35 [0.11]), and the highest in the United States (\$15.40 [1.40]). The least expensive ARB was candesartan, with the lowest 30 day price in Bangladesh (\$1.99 [0.10]), and the highest in the United States (\$52.90 [13.08]). The least expensive beta-blocker was metoprolol, with the lowest 30 day price in Bangladesh (\$0.61 [0.07]), and the highest in Canada (\$17.63 [4.79]). The least expensive SGLT2i was empagliflozin, with the lowest 30 day price in Pakistan (\$2.91 [0.20]), and the highest in the United States (\$555.93 [32.70]).

Bangladesh and Pakistan had consistently lower prices for each drug queried (*Figure 1*), while the highest prices overall were in the United States (*Table S1*).

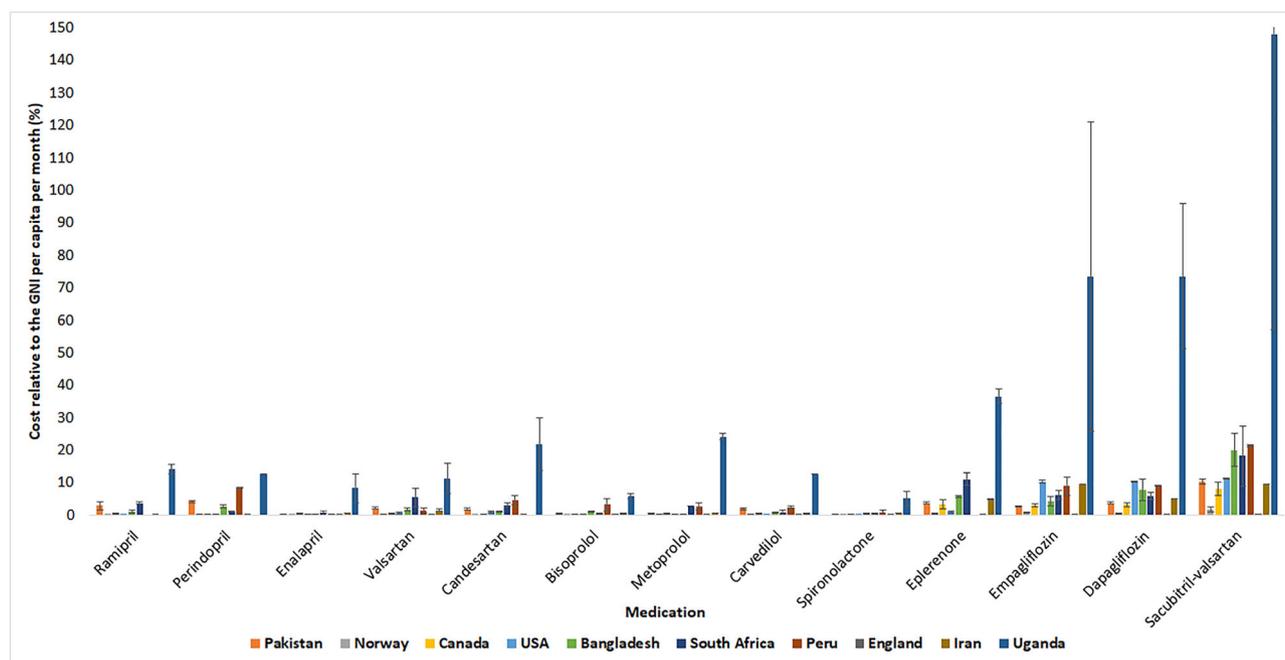
### Price relative to international reference standard

Relative to the international reference price, drug prices were highest in the United States and Canada and lowest in Pakistan and Bangladesh. The US and Canadian MPR (SD) for enalapril (50.83 [4.62] and 44.08 [14.68], respectively) and metoprolol (22.92 [5.95], 26.47 [7.19], respectively) were substantially higher than the international reference standard. By comparison, MPR in Pakistan and Bangladesh were closer to the reference standard for enalapril (1.17 [0.35] and 1.19 [0.22], respectively) and metoprolol (2.05 [0.08] and 1.82 [0.11], respectively). Among the LMICs, prices relative to reference standard were highest in Uganda, with an MPR for enalapril of 18.48 [9.80] and for metoprolol of 48.35 [1.94]. There was no international reference price available for SGLT2i and ARNI.

### Price relative to monthly gross national income per capita

The lowest possible 30 day mean price [SD] as a percentage of the monthly GNI per capita of quadruple

**Figure 1** The price of a 30 day prescription of select guideline-directed medical therapy for heart failure with reduced ejection fraction. All prices are in US dollars. Prices were highest in the United States and Canada. The most expensive agents were sacubitril/valsartan, dapagliflozin, and empagliflozin.



therapy—consisting of an ARNI, BB, MRA, and an SGLT2-i at the recommended starting doses was in England (1.49 [0.00]%), whereas the highest was in Uganda (232.47 [31.47]%) (Table 1). In the United States, prices relative to the monthly GNI per capita were low for BB, ACEi/ARB, and MRA [ranging from 0.05 [0.01]% to 0.29 [0.03]% for the cheapest drugs in these classes (Figure 2) but high for SGLT2i and ARNI (10.34 [0.61]% and 11.38 [0.07]%, respectively). The least affordable drug among HFREF GDMT across countries was sacubitril/valsartan, with the highest price relative to income (lowest affordability) in Uganda, Peru, and Bangladesh (147.84 [90.84]%, 21.4 [0.41]%, and 20.50 [5.00]% respectively) (Figure 3).

### Guideline-directed medical therapy accessibility and coverage

With some exceptions, medications across all pivotal classes were available at the pharmacies surveyed in the 10 countries (Table 1). The least commonly available drug was ramipril (available in 20 of 27 pharmacies, 70.83%), while the most commonly available drugs were bisoprolol, valsartan, and enalapril (27 of 27 pharmacies, 100.00%).

All 10 countries had a public programme for drug coverage for eligible patients, either at the federal or provincial/state level (Table 2). Among the low-income, lower-middle, and upper-middle income countries surveyed (Pakistan, Bangladesh, Uganda, South Africa, and Peru), drug coverage was

usually limited to public pharmacies via prescriptions provided by physicians in the public system (Table 2), but the newer classes of GDMT—ARNI and SGLT2i—were not typically accessible or covered via these programmes.

In contrast, high-income countries placed no pharmacy-related restrictions on public drug coverage, although there were other restrictions. In England, there were restrictions based on provider, such that private prescriptions were not covered. In Canada and the United States, public drug coverage was offered based on age and income, such that older adults and those with low-income could access publicly funded drugs. In Canada, people eligible for publicly covered drugs were required to make a small co-payment and there was no deductible. Among high-income countries, the United States was an outlier in that older adults enrolled in Medicare part D (the drug benefit plan for Medicare) generally bore the majority of the prices of medications until the deductible was reached. After the deductible was reached, there were often tiers of coverage and a decrease in copayment after each threshold was reached; once catastrophic coverage was reached, medications were nearly or entirely covered by the insurance plan. Patients who qualified for Medicaid on the basis of income, however, bore a minority of the price, with copayment ranging from \$0.50 to \$8 per item, depending on which state the patient resided in.<sup>46</sup> Coverage for patients on both Medicare and Medicaid was different from either programme, reflecting the complexity of publicly funded drug programmes in the United States.

**Table 1** The price and affordability of select guideline-directed medical therapies for heart failure with reduced ejection fraction worldwide

Country Pharmacy source	England (high-income)			USA (high-income)			Canada (high-income)			Norway (high-income)			Peru (upper-middle income)		
	Community			Online			Online			Online			Online		
	Price per capita (SD)	Price relative to GNI per capita (SD)	Median price ratio (SD)	Price per capita (SD)	Price relative to GNI per capita (SD)	Median price ratio (SD)	Price per capita (SD)	Price relative to GNI per capita (SD)	Median price ratio (SD)	Price per capita (SD)	Price relative to GNI per capita (SD)	Median price ratio (SD)	Price per capita (SD)	Price relative to GNI per capita (SD)	Median price ratio (SD)
Enalapril	12.34 (0.00)	0.37 (0.00)	40.51 (0.00)	15.40 (1.40)	0.29 (0.03)	50.83 (4.62)	13.36 (4.45)	0.37 (0.12)	44.08 (14.68)	6.16 (0.04)	0.09 (0.00)	20.34 (0.13)	0.85 (0.65)	0.17 (0.13)	2.82 (2.13)
Candesartan	12.34 (0.00)	0.37 (0.00)	N/A	52.90 (13.08)	0.98 (0.24)	N/A	12.50 (1.91)	0.34 (0.05)	N/A	5.19 (1.56)	0.08 (0.02)	N/A	22.62 (7.14)	4.50 (1.42)	N/A
Bisoprolol	12.34 (0.00)	0.37 (0.00)	9.07 (0.00)	8.82 (2.88)	0.16 (0.05)	6.48 (2.11)	6.12 (3.07)	0.17 (0.08)	4.49 (2.25)	6.40 (0.03)	0.10 (0.00)	4.70 (0.02)	16.15 (9.80)	3.21 (1.95)	11.86 (7.19)
Spironolactone	12.34 (0.00)	0.37 (0.00)	20.34 (0.00)	2.51 (0.57)	0.05 (0.01)	4.13 (0.94)	7.06 (2.36)	0.19 (0.07)	11.63 (3.89)	1.91 (0.01)	0.03 (0.00)	3.14 (0.01)	3.97 (3.60)	0.79 (0.72)	6.54 (5.93)
Empagliflozin	12.34 (0.00)	0.37 (0.00)	N/A	555.93 (32.7)	10.34 (0.61)	N/A	109.47 (21.69)	3.02 (0.60)	N/A	58.02 (7.37)	0.89 (0.11)	N/A	45.16 (14.51)	8.99 (2.89)	N/A
Sacubitril/ valsartan	12.34 (0.00)	0.37 (0.00)	N/A	611.50 (3.54)	11.38 (0.07)	N/A	295.23 (70.58)	8.14 (1.95)	N/A	111.69 (53.45)	1.71 (0.82)	N/A	107.52 (2.04)	21.40 (0.41)	N/A

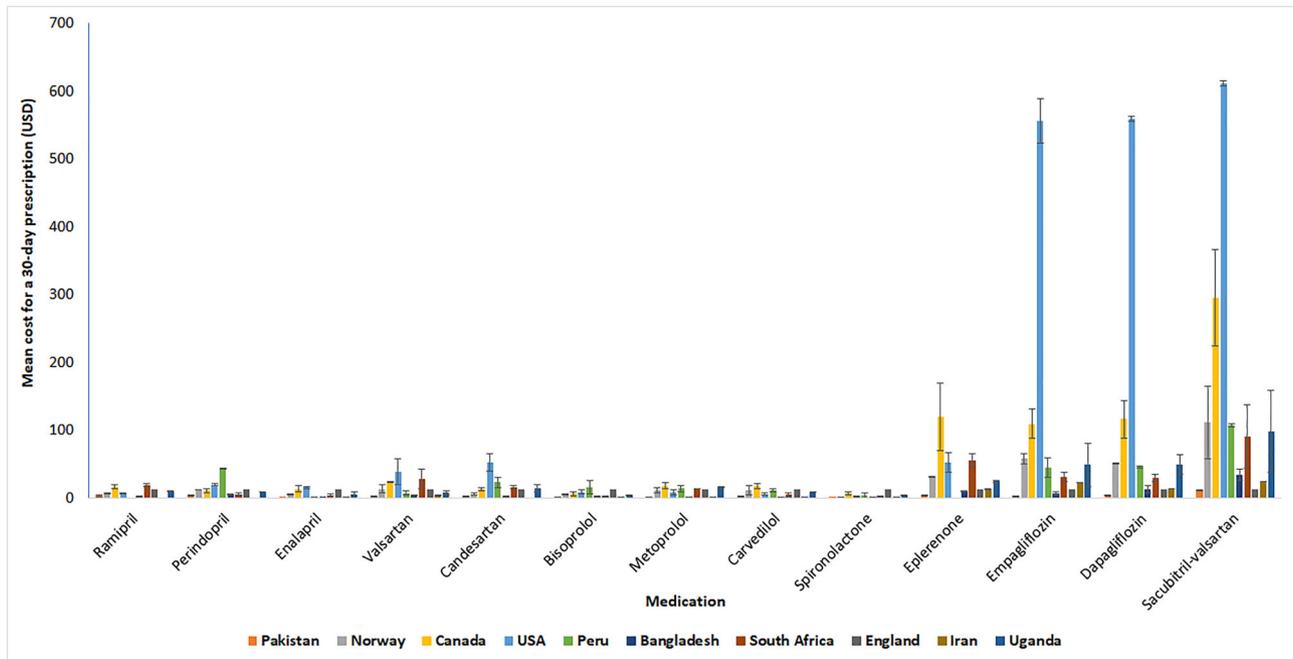
All prices listed are in USD and represent mean (SD) price per 30 day prescription. The medications shown represent the lowest cost medication within each class.

**Table 1** (continued)

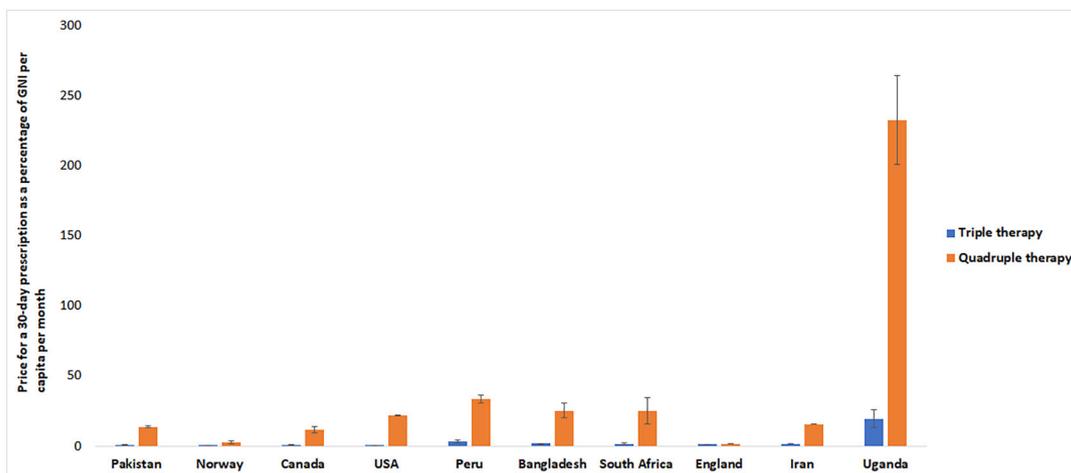
Country Pharmacy source	South Africa (upper-middle income)			Pakistan (lower-middle income)			Bangladesh (lower-middle income)			Iran (lower-middle income)			Uganda (low-income)		
	Online (1/3) and community (2/3)			Online			Online			Community			Community		
	Price per capita (SD)	Price relative to GNI per capita (SD)	Median price ratio (SD)	Price per capita (SD)	Price relative to GNI per capita (SD)	Median price ratio (SD)	Price per capita (SD)	Price relative to GNI per capita (SD)	Median price ratio (SD)	Price per capita (SD)	Price relative to GNI per capita (SD)	Median price ratio (SD)	Price per capita (SD)	Price relative to GNI per capita (SD)	Median price ratio (SD)
Enalapril	4.01 (1.60)	0.80 (0.32)	13.22 (5.28)	0.35 (0.11)	0.33 (0.10)	1.17 (0.35)	0.36 (0.07)	0.21 (0.04)	1.19 (0.22)	1.23 (0.00)	0.50 (0.00)	4.04 (0.00)	5.60 (2.97)	8.40 (4.46)	18.48 (9.80)
Candesartan	15.54 (2.86)	3.10 (0.57)	N/A	1.99 (0.35)	1.88 (0.33)	N/A	1.99 (0.10)	1.18 (0.06)	N/A	N/A	N/A	N/A	14.56 (5.44)	21.84 (8.16)	N/A
Bisoprolol	2.36 (0.60)	0.47 (0.12)	1.73 (0.44)	0.44 (0.11)	0.42 (0.10)	0.33 (0.08)	1.99 (0.11)	1.18 (0.06)	1.46 (0.08)	1.74 (0.03)	0.71 (0.01)	1.28 (0.02)	5.88 (0.49)	8.82 (0.730)	4.32 (0.36)
Spironolactone	2.11 (0.70)	0.42 (0.14)	3.48 (1.15)	0.18 (0.00)	0.17 (0.00)	0.30 (0.01)	0.83 (0.05)	0.49 (0.03)	1.37 (0.07)	1.28 (0.00)	0.52 (0.00)	2.12 (0.00)	3.50 (1.49)	5.25 (2.23)	5.76 (2.45)
Empagliflozin	31.42 (7.08)	6.27 (1.41)	N/A	2.91 (0.20)	2.75 (0.19)	N/A	7.24 (2.20)	4.28 (1.30)	N/A	23.29 (0.00)	9.44 (0.00)	N/A	49.00 (31.75)	73.50 (47.62)	N/A
Sacubitril/ valsartan	91.10 (46.53)	18.19 (9.29)	N/A	11.06 (0.81)	10.45 (0.76)	N/A	33.92 (8.46)	20.05 (5.00)	N/A	23.43 (0.00)	9.50 (0.00)	N/A	98.56 (60.56)	147.84 (90.84)	N/A

All prices listed are in USD and represent mean (SD) price per 30 day prescription. The medications shown represent the lowest cost medication within each class.

**Figure 2** The price of a 30 day prescription of heart failure with reduced ejection fraction pharmacotherapy relative to the GNI per capita per month. The proportional price of heart failure with reduced ejection fraction pharmacotherapy was highest in lower-middle and upper-middle income countries. The most expensive medications relative to GNI per capita per month were empagliflozin, dapagliflozin, and sacubitril/valsartan. GNI, gross national income.



**Figure 3** The price of a 30 day supply of triple and quadruple therapy as a percentage of GNI per capita per month. Triple therapy refers to the combination of angiotensin-converting enzyme inhibitors/angiotensin receptor blocker (whichever is less expensive), beta-blocker, and mineralocorticoid receptor antagonists. Quadruple therapy refers to the combination of angiotensin-neprilysin inhibitors, beta-blocker, mineralocorticoid receptor antagonists, and sodium glucose co-transporter 2. GNI, gross national income.



In high-income countries, the covered formulary included all pivotal HFrEF drugs, whereas low-income and middle-income countries omitted eplerenone, SGLT2i and

ARNI. England was the only high-income country where the price of the medication was entirely covered with a dispensing fee. The price of medications to the English government

**Table 2** Public coverage of guideline-directed medical therapy by country

Country	Publicly-funded drug coverage (yes/no)	Who qualifies	Degree of coverage	Which HFREF drugs are covered
Canada	Yes	Province dependent, generally only low-income (variably defined) and patients >65	Full for eligible patients with variable co-pay	All
England	Yes	All patients. Patients <60 and those receiving income support are exempt from dispensing fees	Full coverage with a \$12.34 dispensing fee per item. Patients can pre-pay for 3 months (\$36.62) or 12 months (\$130.85)	All
Norway	Yes	All patients	15% of medication cost is paid out of pocket	All
USA	Yes	Medicare: Patients >65, or with disabilities and/or ESRD Medicaid: Low-income patients up to 133% of the federal poverty level	Medicare: Variable, increases once deductible paid, up to 75% once catastrophic coverage limit reached Medicaid: full coverage with variable copay	All
Iran	Yes	Government employees, Residents in rural areas and cities less than 20,000 population, Self-employed, Students, patients with disabilities, families with injured persons during the war, private sector employees, and Military personnel and their families	Coverage of 70–90% of the cost of medication	Enalapril, valsartan, metoprolol, and spironolactone
Peru	Yes	EsSalud: All patients who are formally employed Seguro Integral de Salud: Very low-income patients	EsSalud: Full coverage with variable copay Seguro Integral de Salud: Full coverage with no co-pay	EsSalud: Enalapril, carvedilol, bisoprolol, valsartan, and spironolactone
South Africa	Yes	Patients who use public health facilities	Full if through a public health facility	Enalapril, carvedilol, and spironolactone
Bangladesh	Yes	All patients using public clinics and the outpatient department of public hospitals	Full coverage without co-pay, however informal payments often required	All essential medicines list (2008): enalapril, spironolactone
Pakistan	Yes	All patients using public primary health clinics	Full coverage without co-pay	Enalapril, bisoprolol, and spironolactone
Uganda	Yes	All patients using public health facilities	Full coverage without co-pay	Enalapril, candesartan, carvedilol, bisoprolol, and spironolactone

Sources: references (9–45).

ESRD, end-stage renal disease; HFREF, heart failure with reduced ejection fraction.

EsSalud refers to Seguro Social de Salud del Peru, the social health insurance of Peru.

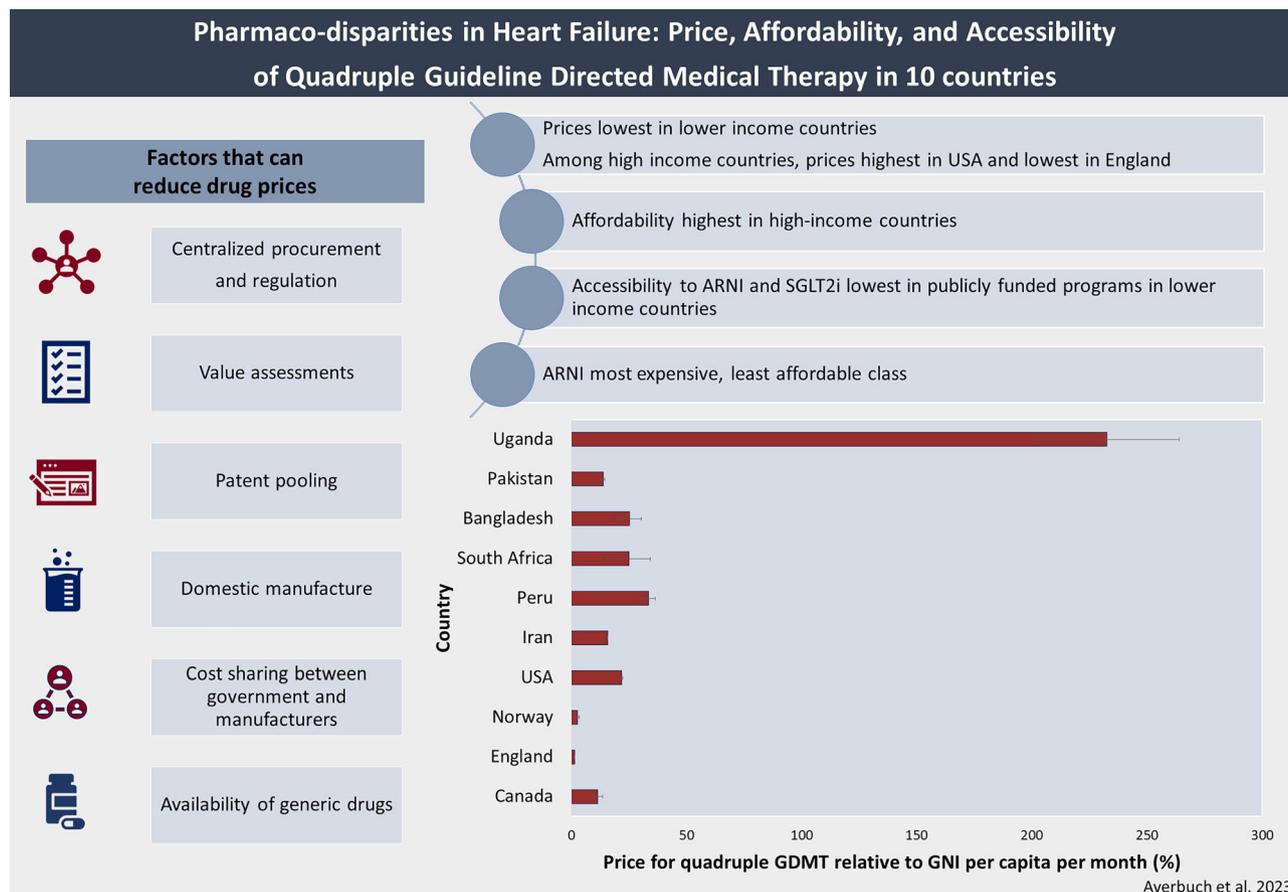
Seguro Integrale de Salud refers to the comprehensive health insurance program of Peru.

was higher than price to patients for SGLT2i and ARNI (Table 1) but lower than the price to patients for ACEi, ARB, BBs, and MRAs. By contrast, in Norway, the price to the government was greater than the price to the patient for all agents in our study, with 85% of the price of all medications covered (Table 2).

## Discussion

In this cross-sectional sampling survey of 10 countries across the world, we found variation in pricing relative to the international standard and pharmaco-disparities in access to and

affordability of GDMT, particularly with newer classes (Central Illustration). The retail price of HFREF pharmacotherapy and price relative to the international standard were highest in high-income countries, most notably in the United States, and lowest in low-income and lower-middle income countries. However, price relative to the GNI per capita was highest (i.e. affordability was lowest) in lower income countries, most notably, Uganda. While the four pivotal GDMT classes were available in private pharmacies in all the countries surveyed, newer classes (including ARNI and SGLT2i) were not covered by publicly funded programmes in LMIC. Our study adds insight into the global variations in the price of contemporary HFREF medications and the pharmaco-disparities in access and affordability across the world.



**CENTRAL ILLUSTRATION:** Factors that influence the price of HFREF pharmacotherapy. In our study, we found that while the price of HFREF pharmacotherapy was highest in high-income countries, the affordability was worse in middle- and low-income countries. Several factors influence the affordability of medications, including procurement costs, purchasing power, price regulation, domestic manufacture, and the availability of public and generic options. Potential solutions to high drug costs include centralized procurement, price negotiation as a criterion for approval, transparency in drug pricing, and federal insurance/subsidies to reduce patient costs.

## Price

The price of HFREF pharmacotherapy relative to the international standard was higher in high-income countries, with the highest retail prices in the United States. The high price of pharmacotherapy in the United States relative to other countries may be related to the regulatory framework regarding drug pricing and the size and negotiating strength of each payer.<sup>47</sup> The system by which drugs are priced is opaque, involving multiple parties with competing interests: pharmaceutical manufacturers; public and private insurers; pharmacy benefit managers, and pharmacies.<sup>48</sup> Federal drug pricing legislation is largely absent, and Medicare has historically been forbidden from negotiating prices with drug manufacturers and implementing a price structure as a condition for reimbursement.<sup>49</sup> The passage of the Inflation Reduction Act now allows Medicare to negotiate prices for 10 medications by 2026; however, it is not yet known whether this will apply to HF GDMT.<sup>50</sup> In addition, there are multiple avenues for costs to be passed back to the patient, including insurance authorizations, deductibles, co-insurance (a proportion of the drug list price), and co-payments (a fixed price per prescription). The high prices in the United States may allow pharmaceutical companies to recover their investments.<sup>48</sup> It is possible that the high prices in the United States subsidize the price of medications in other countries<sup>48</sup> but translate to disparities within the United States.

Several factors influence price variation across countries (Central Illustration). Similar to high-income countries other than the United States, Peru, South Africa, Bangladesh, Pakistan and Iran have federal regulation on drug pricing<sup>51–55</sup>; in contrast, drug pricing is not regulated in Uganda and procurement of medications involves multiple stakeholders, leading to low purchasing power in Uganda.<sup>56</sup> The domestic manufacture of drugs is another factor, explaining the lower prices in Pakistan and Bangladesh rel-

ative to Peru, South Africa, and Uganda.<sup>21</sup> The domestic market share is 80% in Bangladesh, and only 10% in Uganda.<sup>57,58</sup> Governments could promote domestic drug manufacture by subsidizing the cost of imported pharmaceutical ingredients and lifting import restrictions, which remain barriers to affordable domestic production.<sup>59</sup> Another barrier is patent law, particularly for agents without a generic equivalent (e.g. ARNI and SGLT2is); this can be mitigated by patent pooling, whereby sub-licences are granted to manufacturers in low- and middle-countries to allow manufacture and sale without royalties. The Medicines Patent Pool, a United Nations-backed organization, has led to significant reductions in drug prices for HIV and hepatitis C.<sup>60</sup>

### Affordability and accessibility

Affordability of contemporary HFREF quadruple GDMT at retail pricing was greatest in England, Norway, and Canada, and worst in Uganda, Peru, Bangladesh, and South Africa; and improved with use of an ACEi/ARB instead of ARNI in all countries sampled. Our findings are consistent with studies of ischemic heart disease that demonstrated greater affordability of medication (price <20% of the household income) in high versus lower income countries.<sup>61</sup> The lower affordability of HFREF pharmacotherapy in LMICs may contribute to their lower uptake; in a global registry, patients in lower-middle income countries were less likely than those in high-income countries to use an ACEi or ARB, BB, or MRA 6 months following hospitalization for HFREF.<sup>62</sup>

Public or private drug insurance may improve affordability, but accessibility to newer classes via these programmes remains a limitation in lower income countries. In a study in Peru, 26% of patients covered through the public drug plan for low-income patients had to incur out of pocket expenses for medications.<sup>9</sup> Public facilities in both Pakistan and Bangladesh were found to have poor availability of essential medications, with frequent stock-outs and reliance on private pharmacies.<sup>63,64</sup> Similarly, a study of Ugandan rural households found that 77% of respondents preferred using private health facilities due to unavailability of medications via public health services.<sup>65</sup> As a result, Ugandan patients face high out-of-pocket costs. South Africa has an established public healthcare network that is constrained by medication shortages and inadequate staffing.<sup>66</sup> As an alternative to two-tiered systems of pharmacotherapy, federal/state governments could subsidize GDMT in both public and private settings, as is being considered in Pakistan<sup>67</sup>; such a model could also be applied to outpatient prescriptions. In the United States, insurance and Medicaid plan D may reduce out of pocket expenses, but the need for prior authorizations or approvals and complex policies regarding coverage, deductibles, and copayments

limit access to GDMT and shift costs to patients. Programmes that include vouchers, discounts, and copayment cards can improve affordability and medication adherence.<sup>68</sup> Pragmatic clinician-level solutions such as drug or class substitutions, prescribing a larger dose that can then be divided to minimize the daily price and providing free samples, may also be considered in select cases.<sup>69</sup>

The affordability of HFREF GDMT is important not only to patients but also to healthcare systems. In healthcare systems where pharmacotherapy is subsidized, the prices borne by patients may be far lower than the prices to the healthcare system. For example, in England, the mean (SD) 30 day price charged to patients for empagliflozin, dapagliflozin, and sacubitril/valsartan was \$12.35 (0.00), whereas the prices charged to pharmacies by their suppliers were 4 to 10 times higher (Table 1), although this amount was later reimbursed to the pharmacy by the National Health Service.<sup>70</sup> Measures such as price controls, domestic manufacture, and centralized procurement may facilitate sustainability. One potential avenue for governments to reduce or limit pharmaceutical expenditures is to require a cost-effectiveness analysis prior to approval, as is done in some countries.<sup>71</sup> Countries in which the federal government procures medications may be better able to negotiate pricing to ensure cost-effectiveness. Cost-sharing agreements between the government and manufacturers may also improve the affordability of HF therapy for both governments and patients.

### Limitations

Our sample was restricted to 10 countries. We only listed prices for the lowest doses of each agent and our analysis focused on retail prices paid by patients; the prices do not represent the cost incurred by pharmacies or amounts paid by patients enrolled in publicly funded or private insurance programmes. While we used data from online pharmacies, the additional physical pharmacies surveyed in each country were from the capital city; prices may have been higher and access to drugs poorer in rural locales. Our survey of prices was limited to private pharmacies, as price data from public pharmacies were unavailable. Although we adjusted for the dose of medication in our cost analysis, not all pharmacies queried offered the same dosages of medication. Our analysis of affordability relied on the GNI per capita rather than household or disposable income as an established reference. Our analysis may overestimate affordability as we could not account for patients' non-medical expenses or disposable income. Low-income countries were underrepresented within our study, with only one low-income country included (Uganda), due to unavailability of data. Lastly, our results are reflective of cost and affordability at the time of sampling.

## Conclusions

The retail price of HF medication varies markedly between countries, with greater accessibility and affordability in high-income countries despite higher prices. Among high-income countries, prices were the highest in the United States. Public programmes increased affordability of GDMT but limited access to newer HFrEF classes in low- and lower-middle income countries. In LMICs, a 30 day supply of contemporary quadruple HFrEF GDMT at starting doses cost one-quarter to twice the GNI per capita per month. At current prices, ACEi/ARBs may represent greater value than ARNI particularly in low resource settings. The variation in price of HFrEF therapy is likely multifactorial but culminates in pharmaco-disparities that must be reduced to improve uptake of effective therapies and improve HFrEF outcomes globally.

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## Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Table S1.** The price of heart failure guideline-directed medical therapy in 10 countries.

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