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Access to Heart Failure Medicines in Low- and Middle-Income Countries: An Analysis of Essential Medicines Lists, Availability, Price, and Affordability

Anubha Agarwal, MD, MSc,

Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL

Muhammad Jami Husain, PhD,

Global Noncommunicable Diseases Branch, Division of Global Health Protection, Centers for Disease Control and Prevention, Atlanta, GA

Biplab Datta, PhD,

Department of Population Health Sciences, Medical College of Georgia, Augusta University

Sandeep P. Kishore, MD, PhD,

Department of Medicine, University of California San Francisco

Mark D. Huffman, MD, MPH

Department of Medicine, Washington University in St. Louis, MO

The George Institute for Global Health, University of New South Wales, Sydney, Australia

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Heart failure (HF) is a leading global public health problem with >64 million prevalent cases globally. Patients with HF with reduced ejection fraction (HFrEF) from low- and middle-income countries experience a 22% to 58% higher 1-year mortality rate than those in high-income countries.¹ Guideline-directed medical therapy (GDMT) consisting of ACE (angiotensin-converting enzyme) inhibitors or ARB (angiotensin receptor blockers) or ARNI (angiotensin receptor-neprilysin inhibitors), β -blockers, MRA (mineralocorticoid receptor antagonists), and SGLT2 (sodium-glucose cotransporter 2) inhibitors substantially reduces mortality among patients with HFrEF. These medicines are among the most cost-effective interventions and are thus included as the highest priority health system interventions recommended by the Disease Control Priorities Project.² Despite this high-quality evidence, GDMT remains widely underutilized in low- and middle-income countries resulting in widespread undertreatment of patients with HFrEF due to health system-, provider-, and patient-level barriers.¹ National essential medicines lists (EMLs) promoted by the World Health Organization (WHO) guide countries on which medications to purchase in the setting of limited resources and have resulted in higher procurement and availability of essential

medicines in the public sector.³ We provide a cross-sectional analysis of national EMLs in 53 low- and middle-income countries, and availability, price, and affordability of GDMT in select countries to identify potential barriers to access to these essential medicines for patients with HFREF.

The data that support the findings of this study are available from the corresponding author upon reasonable request. We used the WHO online repository of country EMLs and limited our analyses to 53 low- and middle-income countries that published national EMLs in English representing 5 WHO regions, including Africa, Eastern Mediterranean, Americas, South-East Asia, and Western Pacific. The available HFREF medications in the national EMLs included in this analysis are ACE inhibitor (enalapril), β -blockers (carvedilol and metoprolol), MRA (spironolactone), and loop diuretic (furosemide). We extracted data on inclusion of HFREF medications within each included country EML into 1 spreadsheet for data analysis on variations in frequencies between individual GDMT drugs and therapeutic drug classes. We used the WHO Essential Drugs and Medicine Policy Department and the Health Action International project on Medicine Prices and Availability to assess availability (% of facilities), price (median price ratio: median local unit price divided by the international unit reference price), and affordability (number of days of income to afford the cost of 30 days of medication) of GDMT for patients with HFREF (enalapril, losartan, carvedilol, metoprolol, spironolactone, and furosemide) in select countries depending on data availability in the WHO/Health Action International surveys. We have published additional details on these methods.⁴

Among the 53 countries with national EMLs published in English, 47% included all 4 drug classes. β -Blockers indicated for patients with HFREF including metoprolol and carvedilol were on the fewest number of national EMLs (32% and 42%; Table). In contrast, MRA (spironolactone, 89%) and loop diuretics (furosemide, 94%) were included in most national EMLs. Availability of GDMT is higher for generic than originator brand medicines and higher in the private sector than the public sector. Patient price for GDMT is lower for generic compared with originator brand medicines and lower in the public sector compared with the private sector. Public sector procurement prices are markedly lower than patient prices. Of the limited affordability data available, generic furosemide 40 mg was the most affordable in the public sector.

This analysis demonstrates less than half of national EMLs in this analysis included all 4 drug classes of GDMT for patients with HFREF. There was wide variability in availability, price, and affordability of GDMT in both public and private sectors, which is a barrier to access to these essential HFREF medicines in low- and middle-income countries. Similarly, the PURE study (Prospective Urban Rural Epidemiology) demonstrated medicines for primary and secondary cardiovascular disease prevention were unavailable and unaffordable for large proportion of households in low- and middle-income countries and associated with increased risk for major adverse cardiovascular events and mortality.⁵ Limitations of this analysis include data scarcity in both national EMLs in English and WHO/Health Action International surveys, which limited a comprehensive analysis of GDMT components, such as bisoprolol as well as newer agents, such as sacubitril/valsartan and SGLT2 inhibitors. This data scarcity also resulted in low sampling of some outcomes. The data from this

analysis of WHO/Health Action International surveys were collected between 2002 and 2015, so it may not fully reflect current availability, price, and affordability of GDMT. However, this analysis demonstrates an important policy opportunity in national EMLs to potentially improve availability, affordability, and GDMT use to improve the care of patients with HFrEF in low- and middle-income countries.

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Disclosures

In the past 3 years, Dr Huffman received funding from the World Heart Federation to serve as its senior program advisor for the Emerging Leaders program, which has been supported by Boehringer Ingelheim, Novartis, Bupa, and AstraZeneca. Dr Huffman also received support from the American Heart Association, Verily, and AstraZeneca and American Medical Association for work unrelated to this research. The George Institute for Global Health's wholly owned enterprise, George Health Enterprises, has received investment funds to develop fixed-dose combination products containing aspirin, statin, and blood pressure-lowering drugs. Drs Huffman and Agarwal plan to submit patents for heart failure polypills. Dr Kishore has served as a consultant for Resolve to Save Lives for hypertension control and has previously led a partnership on multiple chronic conditions with the Icahn School of Medicine at Mount Sinai and Teva Pharmaceuticals. The findings and conclusions of this report are those of authors only and do not necessarily represent the official position of the Centers for Disease Control and Prevention. The other authors report no conflicts.

Nonstandard Abbreviations and Acronyms

ACE	angiotensin-converting enzyme
ARB	angiotensin receptor blockers
ARNI	angiotensin receptor-neprilysin inhibitor
EMLs	essential medicines lists
GDMT	guideline-directed medical therapy
HF	heart failure
HFrEF	HF with reduced ejection fraction
MRA	mineralocorticoid receptor antagonists
PURE	Prospective Urban Rural Epidemiology
SGLT2	sodium-glucose cotransporter 2
WHO	World Health Organization

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Table. Presence on National Essential Medicines Lists, Availability, Price, and Affordability of Guideline-Directed Medical Therapy for Patients With Heart Failure With Reduced Ejection Fraction

	Presence on National EML* N=53 (%)	Availability [†] (% of facilities; n=no. of surveys)				Patient price [‡] MPR (n=no. of surveys)				Procurement price [‡] MPR (n=no. of surveys)				Affordability, [§] no. of days of income (n=no. of surveys)			
		Originator brand		Lowest price generic		Originator brand		Lowest price generic		Originator brand		Lowest price generic		Originator brand		Lowest price generic	
		Public	Private	Public	Private	Public	Private	Public	Private	Public	Private	Public	Private	Public	Private	Public	Private
ACE inhibitor or ARB																	
Enalapril 10 mg	37 (69.8)	7.44 (n=15)	22.40 (n=16)	59.23 (n=18)	80.49 (n=19)	23.95 (n=4)	104.61 (n=7)	8.09 (n=17)	24.99 (n=19)	15.02 (n=3)	1.65 (n=12)	2.85 (n=2)	4.83 (n=7)	1.24 (n=7)	1.47 (n=13)		
Losartan 50 mg	//	6.98 (n=11)	38.50 (n=11)	53.69 (n=12)	77.00 (n=12)	74.32 (n=11)	293.94 (n=27)	56.41 (n=14)	110.38 (n=33)	3.52 (n=9)	1.18 (n=9)	7.32 (n=6)	9.34 (n=8)	3.11 (n=8)	3.40 (n=12)		
β-Blocker																	
Carvedilol 25 mg	22 (41.5)	2.85 (n=2)	76.65 (n=2)	19.03 (n=3)	41.10 (n=3)	0.00 (n=1)	24.62 (n=3)	0.00 (n=2)	15.81 (n=3)	2.12 (n=1)	1.14 (n=3)	//	//	//	//		
Metoprolol 100 mg	17 (32.1)	0.00 (n=1)	13.30 (n=1)	76.90 (n=1)	66.70 (n=1)	//	//	//	//	//	//	//	//	//	//		
Mineralocorticoid receptor antagonist																	
Spironolactone 25 mg	47 (88.7)	15.70 (n=2)	38.35 (n=2)	68.57 (n=3)	59.33 (n=3)	0.00 (n=1)	13.90 (n=1)	1.21 (n=4)	3.91 (n=3)	2.67 (n=1)	1.02 (n=3)	//	//	//	//		
Loop diuretic																	
Furose-mide 40 mg	50 (94.3)	7.34 (n=19)	50.31 (n=20)	71.36 (n=29)	76.29 (n=30)	10.42 (n=4)	68.02 (n=33)	3.99 (n=40)	11.52 (n=43)	6.28 (n=4)	1.74 (n=36)	//	//	0.20 (n=1)	0.45 (n=2)		

Prices are in MPR to international reference prices, and all MPRs were converted into a base year (2013). Countries included in the WHO/HAI survey analysis of availability, price, and affordability: Afghanistan, Armenia, Bolivia, Brazil, Burkina Faso, Burundi, China, Colombia, Congo, Democratic Republic of Congo, Ecuador, Egypt, El Salvador, Ethiopia, Fiji, Ghana, Haiti, India, Indonesia, Iran, Jordan, Kazakhstan, Kenya, Kuwait, Kyrgyzstan, Lao PDR, Lebanon, Malaysia, Mali, Mauritius, Mexico, Moldova, Mongolia, Morocco, Nicaragua, Nigeria, Oman, Pakistan, Peru, Philippines, Russia, Sao Tome en Principe, Saudi Arabia, South Africa, Sri Lanka, Sudan, Syria, Tajikistan, Tanzania, Thailand, Tunisia, Uganda, Ukraine, United Arab Emirates, Uzbekistan, and Yemen. ACE indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; EML, essential medicines list; MPR, median price ratio; and WHO/HAI, World Health Organization/Health Action International.

* Presence on national EML is defined as the inclusion of the specific drug (irrespective of drug dose specified) in the number of national EMLs of the countries included in this analysis: Afghanistan (EML year 2007), Algeria (2006), Angola (2008), Bhutan (2012), Botswana (2012), Burundi (2012), Central African Republic (2009), Chad (2007), Congo (2013), Cote d'Ivoire, Democratic Republic of Congo (2010), Djibouti (2007), Egypt (2006), Eritrea (2010), Ethiopia (2015), Ghana (2010), Guyana (2010), Honduras (2011), India (2011), Indonesia (2008), Iran (2009), Kenya (2016), Lebanon (2010), Lesotho (2005), Malaysia (2008), Mali (2008), Mauritania (2007), Mexico (2009), Morocco (2008), Myanmar, Namibia (2008), Nepal (2009), Nigeria (2010), Oman (2009), Pakistan (2007),

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Paraguay (2009), Peru (2010), Philippines (2008), Rwanda (2010), Senegal (2008), Somalia (2008), South Africa (2014), Sri Lanka (2009), Sudan (2007), Tanzania (2013), Thailand (2012), Timor-Leste (2004), Togo (2012), Tunisia (2008), Uganda (2007), and Zambia (2013).

⁷ Availability is defined as the percentage of facilities in which a particular medicine was available at the time of the survey. The availability of medicines corresponding to the exact forms and strengths are reported. The availability data refer to the day of data collection at each particular facility and may not reflect the average monthly or yearly availability of medicines at individual facilities. The data, survey methodology, and definitions are available on the Health Action International website (<https://haiweb.org/what-we-do/price-availability-affordability/collecting-evidence-on-medicine-prices-availability/>).

⁸ The median price data collected in the surveys are expressed as a summary measure in relation to a standard set of reference prices, defined as the MPR, which facilitates national and international comparisons. The medicine and dose-specific international reference prices are taken from the Management Sciences for Health International Drug Price Indicator Guide, which represents the median procurement prices offered by both not-for-profit and for-profit suppliers to low- and middle-income countries for multisource products. Prices are reported as MPR. The MPR is calculated as the median local unit price divided by the international unit reference price in local currency using the exchange rate on the first day of data collection. We report prices for (1) public-sector procurement, representing prices that the government and other purchasers pay to procure medicines, generally through a tendering process; (2) patient prices in the public sector that patients must pay in government, municipality, or other local authority health facilities, including clinics and hospitals, health centers, and pharmacies; and (3) patient prices in the private sector that patients pay in retail pharmacies and pharmacies in private clinics and hospitals. In countries where patients have a free provision of a medicine, the patient prices were assumed to be 0.

⁹ Affordability is measured by the patient cost of medicines relative to an income measure, which the WHO/HAI methodology defines as the daily wage of the lowest paid unskilled government worker in each country. Affordability is expressed as the number of days the lowest paid unskilled government worker would have to work to afford the cost of 30 days of medication.

// Insufficient data available.