JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 71, NO. 5, 2018

PUBLISHED BY ELSEVIER

REVIEW TOPIC OF THE WEEK

Modernizing the World Health Organization List of Essential Medicines for Preventing and Controlling Cardiovascular Diseases

Sandeep P. Kishore, MD, PhD,[a] Evan Blank, MD,[b] David J. Heller, MD, MPH,[a] Amisha Patel, MD, MPH,[c] Alexander Peters, MD,[d,e,f] Matthew Price,[g] Mahesh Vidula, MD,[h] Valentin Fuster, MD, PhD,[i] Oyere Onuma, MD,[j] Mark D. Huffman, MD, MPH,[k] Rajesh Vedanthan, MD, MPH[i]

ABSTRACT

The World Health Organization (WHO) Model List of Essential Medicines (EML) is a key tool for improving global access to medicines for all conditions, including cardiovascular diseases (CVDs). The WHO EML is used by member states to determine their national essential medicine lists and policies and to guide procurement of medicines in the public sector. Here, we describe our efforts to modernize the EML for global CVD prevention and control. We review the recent history of applications to add, delete, and change indications for CVD medicines, with the aim of aligning the list with contemporary clinical practice guidelines. We have identified 4 issues that affect decisions for the EML and may strengthen future applications: 1) cost and cost-effectiveness; 2) presence in clinical practice guidelines; 3) feedback loops; and 4) community engagement. We share our lessons to stimulate others in the global CVD community to embark on similar efforts. (J Am Coll Cardiol 2018;71:564–74) © 2018 by the American College of Cardiology Foundation.

According to 2015 World Health Organization (WHO) data, mortality from cardiovascular disease (CVD) is estimated at 17,867,000 deaths (31% of all-cause mortality) (1). The WHO Global Action Plan for noncommunicable diseases identifies targets to achieve the global goal of

From the [a]Arnhold Institute for Global Health, Department of Medicine/Health System Design & Global Health, Icahn School of Medicine at Mount Sinai, New York, New York; [b]Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, New York; [c]Department of Medicine-Cardiology, Columbia University/New York Presbyterian Hospital, New York, New York; [d]Department of Surgery, Weill Cornell Medicine, New York, New York; [e]Program in Global Surgery and Social Change, Harvard Medical School, Boston, Massachusetts; [f]Department of Plastic and Oral Surgery, Boston Children's Hospital, Boston, Massachusetts; [g]Independent Consultant, Baltimore, Maryland; [h]Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts; [i]Zena & Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York, New York; [j]Department for Management of Noncommunicable Diseases, Disability, Violence and Injury Prevention, World Health Organization; and the [k]Department of Preventive Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois. Dr. Kishore leads a partnership on multiple chronic conditions supported by the Arnhold Institute for Global Health and Teva Pharmaceuticals. Dr. Heller has been supported by the Fogarty International Center of the National Institutes of Health (award number R21 TW 010452-01); and has received research support from Teva Pharmaceuticals. Dr. Price has served as a consultant for Last Mile Health, which receives funding from Pfizer, Johnson & Johnson, and Medtronic. Neither Last Mile Health nor these funders played any role in this work. Dr. Huffman has been supported by the National Heart, Lung, and Blood Institute of the National Institutes of Health (award number R00 HL107749-05); and has received travel support from the World Heart Federation to attend a polypill meeting and to serve as its senior program advisor for the Emerging Leaders Programme, which is supported by Boehringer Ingelheim and Novartis and has been supported by AstraZeneca and Bupa. Dr. Vedanthan has been supported by the National Heart, Lung, and Blood Institute of the National Institutes of Health (award number 1R01HL125487-01A1). The content is solely the responsibility of the authors and does not necessarily represent the views of the National Institutes of Health. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Gerald S. Bloomfield, MD, MPH, served as Guest Editor for this paper.

Manuscript received August 22, 2017; revised manuscript received November 30, 2017, accepted November 30, 2017.

Listen to this manuscript's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

ISSN 0735-1097/$36.00 https://doi.org/10.1016/j.jacc.2017.11.056

reducing the risk of premature mortality from noncommunicable diseases by 25% by 2025. It also includes a health system target of 80% for essential medicine availability in both public and private sectors. In 2016, the WHO and the CDC (Center for Disease Control), with support from the World Heart Federation (WHF), launched the Global Hearts initiative to support countries in scaling up CVD prevention and control, including increased access to essential medicines and technologies (2). Further, the WHF Roadmap for secondary prevention of CVD outlines strategies for overcoming barriers to availability, affordability, and adherence to essential medicines for the prevention and control of CVD (3).

Despite the political interest, medication access, including availability and affordability, remains low (4) in many low- and middle-income countries (LMICs). For example, in 2011, availability of statins for hyperlipidemia was only 36% in the public sector (vs. 54% in the private sector) in 2,779 medicine outlets in 40 LMICs (4). In high-income countries (HICs), the availability of essential medicines is far higher, estimated at 90% or greater in both urban and rural settings (4). According to the PURE (Prospective Urban Rural Epidemiology) study, availability of essential medicines for CVD prevention in low-income countries varied according to per-capita income, ranging from 25% in urban settings to 3% in rural (5). Essential medicines were unaffordable (i.e., cost >20% of a household's nonsubsistence income) for approximately 60% of households in LMIC settings (5). The lack of available and affordable treatments has been associated with poor outcomes for CVD (4).

Reducing gaps in availability, affordability, and access to essential medicines for CVD requires a broad range of solutions and tools. The WHO Model List of Essential Medicines (EML) is a key tool for improving global access to medicines for CVD, particularly in LMICs. Initiated in 1977 with 204 products, the EML has grown to 433 products in 2017 with biennial reviews of and updates to the list. The EML is used primarily by member states to determine their national EMLs and policies, and secondarily by United Nations agencies to guide drug donations. Medicines on the EML have been found to be more affordable and available (6).

We identified a global gap of missing or outdated medicines for CVD on the EML and, as a collective, sought to fill the gap through evidence-based applications to modernize the EML. In this report, we describe our shared efforts to modernize the WHO EML for global CVD prevention and control through applications to add, delete, and change indications for CVD-related medications in keeping with clinical practice guidelines, and summarize key lessons learned. Recognizing that the EML is an important tool for improving access to essential drugs in LMICs, the global CVD community should consider themselves stewards of the EML. Periodic evidence synthesis and revision ensure that the EML is modern and that we share our iterative learnings over the past decade to guide others to pursue these revisions.

THE WHO EML: BACKGROUND

According to the WHO, essential medicines satisfy the priority health care needs of member states and are selected based on disease prevalence; public health relevance; and evidence of clinical efficacy, safety, and relative cost-effectiveness (7). The EML is no longer intended for low-income settings alone. Instead, the EML aims to create a common, global standard—a model list. Since the first WHO EML was published in 1977, the number of national EMLs has steadily increased. Today, at least 34 countries have national EMLs, and 94% of those countries report using the WHO EML as their basis for public procurement (6). Therefore, it is important to ensure that the EML is updated to reflect contemporary worldwide medical practice.

An updated EML is built within the framework of human rights and should not be dependent on the price or cost of a medicine (8,9), as affirmed by the WHO Medicines and Health Products Programme Strategic Framework 2016-2030 (9). Consistent with previous decisions by the WHO, including the addition of patented, relatively expensive drugs for the treatment of cancer and hepatitis C virus, affordability can be a consequence rather than a precondition of adding a medicine to the EML (8). An early example of this arose in 2002, when antiretroviral drugs (ARVs) for human immunodeficiency virus (HIV) were added to the EML despite their high cost and existing patent status. This approach, among other strategies, led to a 90% reduction in the price of ARVs and led toward international and regional pooled procurement to improve access (10).

Medicines on the EML are more likely to be available than medicines not on the list. According to Bazargani et al. (6), the median rate of availability of a wide range of drugs on the EML worldwide is 62%, whereas the availability of drugs not on the list is 27%. This difference is greater among the most vulnerable populations in the lowest-income countries, in which the mean rate of availability of

ABBREVIATIONS AND ACRONYMS

ACE = angiotensin-converting enzyme

ARB = angiotensin receptor blockers

ARV = antiretroviral drug

DOAC = direct oral anticoagulant

EML = List of Essential Medicines

FDC = fixed-dose combination

HIC = high-income country

LMIC = low- and middle-income countries

NOAC = novel oral anticoagulant

NSAID = nonsteroidal anti-inflammatory drugs

medicines on the EML in the public sector is 40% compared with 7% availability for nonessential medicines. In the private sector, the differences remain but are attenuated (78% availability for essential medicines and 57% availability for nonessential medicines) (6). Although some may argue that these medicines are on the EML due to their widespread use and consequent "essential" nature as defined by the WHO, we contend that EML status also subsequently improves access and lowers cost. Therefore, "essential" status is not simply a marker of such drugs' prior frequency of use.

Over the past decade, the process by which medicines are added to the EML has also been revised. Inclusion of a drug on the EML now depends on applications supported by high-quality systematic reviews, complemented by an assessment of the quality of the evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology. This process has contributed to more transparent and reproducible methods of evidence synthesis, as demonstrated within clinical practice guidelines developed by professional organizations such as the American College of Cardiology and the American Heart Association (11,12), as well as the WHO itself. The WHO Expert Committee also explicitly aims to align with WHO or other global, high-quality guidelines. The WHO ensures transparency in the selection process by including a period of public comment for all applications, posting reviewers' unedited comments online, inviting the public to make statements ahead of the Expert Committee meeting, and publishing a publicly available summary of decisions.

The WHO Expert Committee is comprised of pharmacologists, clinical pharmacologists, methodologists, and physicians (13). Membership of the 21st Expert Committee (May 2017) consisted of 15 members from Australia, Brazil, China, Egypt, Finland, India, Italy, Morocco, South Africa, Sri Lanka, Switzerland, the United States, and the United Kingdom. The Expert Committee includes members of an Expert Advisory Panel and meets biennially to review applications consisting of systematic literature reviews to revise and update the WHO EML through additions and deletions to the list—these applications are judged based on the rigor, depth, and timeliness of their review of existing published data on the medication's efficacy, toxicity, and cost-effectiveness. The Expert Committee can recommend that the medication alone or that a medication serve as a representative of a pharmacological class. Representatives of a class of medications are denoted on the EML by a square box (7).

UPDATING THE WHO MODEL LIST OF ESSENTIAL MEDICINES: EXAMPLE OF CARDIOVASCULAR DISEASES

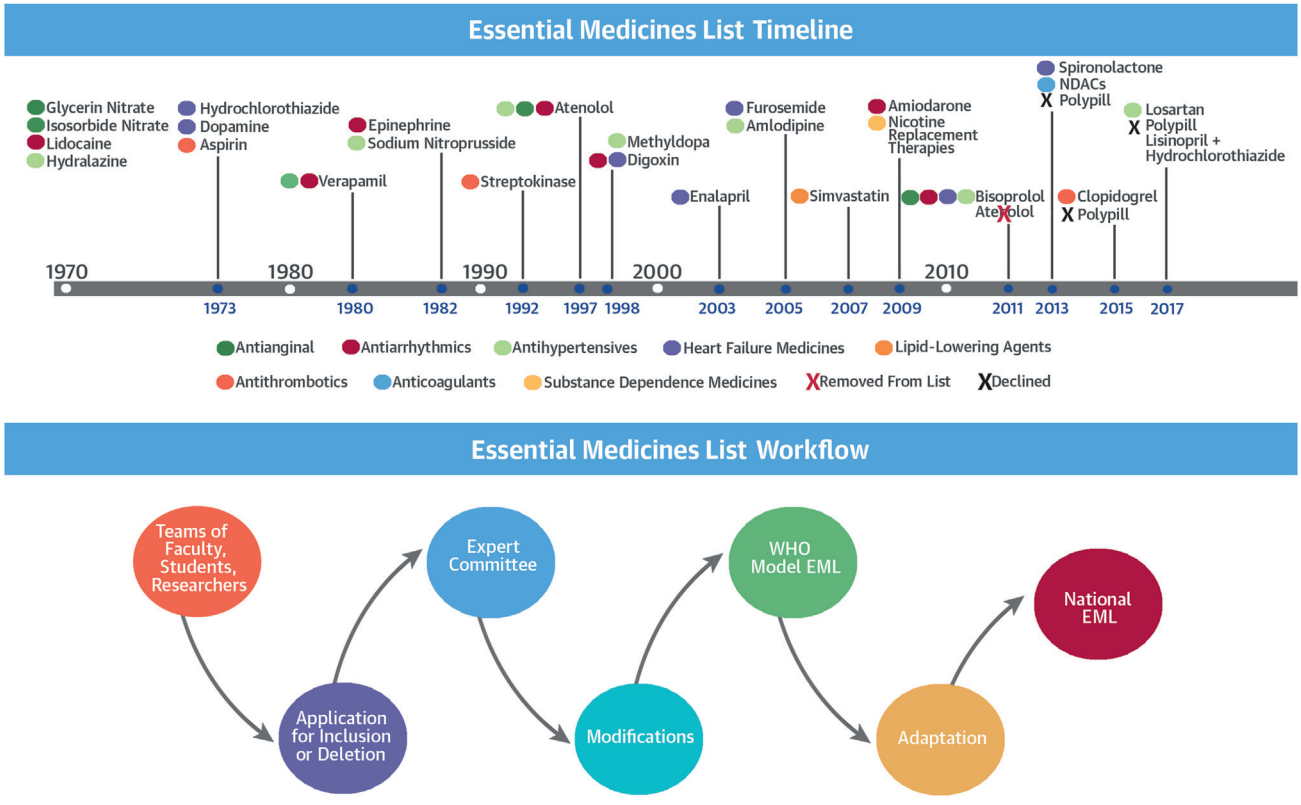
Anyone can petition for a medicine to be added to the EML. Over the past 10 years, we and others have initiated a process of modernizing the EML for CVD medications by submitting evidence-based petitions to the WHO. Starting with the application for simvastatin in 2007, led by a medical student–trainee–faculty consortium at multiple academic medical centers, our approach has evolved to include biennial petitions to modernize the EML for CVD medications (**Central Illustration**). We have adopted a rational approach: target medicines aligned with contemporary, guideline-directed, global cardiovascular care. In the following text, we briefly summarize the rationale and content behind our applications to the EML (**Table 1**).

ADDITIONS. Statins (2007). The principal motivation to add lipid-lowering agents to the WHO EML was to reduce the substantial burden of atherosclerotic CVD. Elevated cholesterol, particularly low-density lipoprotein cholesterol, causes atherosclerotic CVD across all ethnic groups (14). High-quality evidence supports the use of statins for the primary (15,16) and secondary (16) prevention of atherosclerotic CVD across a wide range of populations (17).

The U.S. patent for simvastatin held by Merck expired on June 23, 2006, which catalyzed a large generic drug launch, with firms from India and Israel ramping up production (18). Costs fell from $1,200 to $40/patient/year, as priced by the Management Sciences for Health International Medical Products Price Guide (19). This reduction helped make statins cost-effective by WHO standards, and in 2007, statins were added to the EML as a therapeutic class. Given its lower cost and off-patent status, we proposed simvastatin as the representative example of the therapeutic class of statins. In 2007, statins were added to the EML with simvastatin as the representative (20).

Beta-blockers: atenolol to bisoprolol (2011). Although atenolol is a commonly prescribed and relatively low-cost beta-blocker, there is no high-quality evidence to support its use for treatment of patients with heart failure, and accordingly, clinical practice guidelines have recommended against it for this condition. By contrast, at the time of our application, several next-generation, off-patent beta-blockers, including carvedilol, bisoprolol, and metoprolol succinate, were indicated for improving outcomes among individuals

CENTRAL ILLUSTRATION **Essential Medicines List—Timeline of Additions, Deletions, and Modifications**



Kishore, S.P. et al. J Am Coll Cardiol. 2018;71(5):564–74.

This timeline prepared by the authors indicates the classes of cardiovascular medicines on the Essential Medicines List (EML). Teams that include faculty, students, and trainees develop an application for inclusion or deletion to the World Health Organization (WHO) Expert Committee for the Selection and Use of Essential Medicines, which decides on modifications to the WHO EML. The EML is then adapted at the national level.

with heart failure with reduced ejection. In this work, we petitioned the WHO to switch the representative beta-blocker from atenolol to bisoprolol.

The most contemporary Cochrane systematic review evaluating the effect of beta-blockers on patients with heart failure highlighted the benefit and safety profiles of cardioselective beta-blockers (e.g., bisoprolol) over nonselective agents in patients with chronic obstructive pulmonary disease (21). Of the 3 beta-blockers that are appropriate for all indications (carvedilol, metoprolol succinate, and bisoprolol), we proposed that bisoprolol would be the best representative of the class, because of its cost-effectiveness, demonstrated efficacy for heart failure, simple once-daily dosing, and relative safety in patients with comorbid chronic obstructive pulmonary disease. We recommended carvedilol or metoprolol succinate as alternatives. In 2011, atenolol was removed from the EML, and beta-blockers were added to the list as a therapeutic class for the treatment of heart failure with reduced ejection fraction, with bisoprolol as the representative.

Spironolactone (new indication) (2013). Prior to our application, spironolactone was listed on the EML solely as a potassium-sparing diuretic agent for the treatment of hypertension. Given the strong recommendations from clinical practice guidelines from the American College of Cardiology, American Heart Association, Heart Failure Society of America, and European Society of Cardiology for the use of aldosterone antagonists in patients with heart failure with reduced ejection fraction (22–25) (Class I, Level of Evidence: A), we proposed that the WHO EML Expert Committee: 1) add aldosterone antagonists as a therapeutic class of medicines for the treatment of patients with heart failure with reduced ejection

TABLE 1 Summary of Our Experience Modernizing the WHO Essential Medicines List for Cardiovascular Disease

Year	Medication	Square Box	Indication	Rationale and Summary
			Additions	
2007	Simvastatin	Yes	Lipid-lowering agents	Reduce atherosclerotic burden; generic production reduced costs significantly • Cost • Clinical practice guidelines
2011	Bisoprolol	Yes	Antihypertensive Medicines used in heart failure	Remove substandard medication (atenolol) • Clinical practice guidelines • Feedback loops and continual improvement
2013	Spironolactone	No	Medicines used in heart failure	Add new indication—heart failure • Clinical practice guidelines
2015	Clopidogrel	No	Antithrombotic	Address rise in percutaneous coronary interventions worldwide • Clinical practice guidelines
2017	Losartan	Yes	Antihypertensive	Alternative to ACE inhibitors, overcoming side effects • Clinical practice guidelines
			Rejections	
2013	Fixed-dose combination	Yes	N/A	Secondary prevention of atherosclerotic disease, improved "polypill" adherence • Clinical practice guidelines
2015	Direct oral anticoagulants	Yes	Antithrombotic	Prevention of stroke in patients with nonvalvular atrial fibrillation; clinically superior to warfarin and cost-effective given less monitoring • Cost • Clinical practice guidelines
2017	Lisinopril-hydrochlorothiazide	Yes	Antihypertensive	Dual-agent blood pressure regimen superior to single agent • Clinical practice guidelines

This table summarizes the additions, deletions, and modifications of medicines for the World Health Organization (WHO) Essential Medicines List and our rationale for each.

fraction with a New York Heart Association functional class of II and above; and 2) specify spironolactone as the representative of the aldosterone antagonist class.

The indication of heart failure with reduced ejection fraction was added to spironolactone in 2013.

Clopidogrel (2015). Antiplatelet medications, including aspirin and clopidogrel, have an independent mortality benefit in patients with acute coronary syndrome (26–29). Clopidogrel is also a safe and cost-effective medication that reduces cardiovascular and total mortality in patients with acute coronary syndrome and following percutaneous coronary interventions. Given the rising burden of acute coronary syndromes and the increasing number of percutaneous coronary interventions performed globally, the need for and use of clopidogrel have been rising (30–32). Clopidogrel was also the subject of the first instance of a compulsory license issued for a cardiovascular medicine, by Thailand in 2006 and 2008, which permitted the medication to be produced off patent (33).

Although short-term case-fatality rates for acute coronary syndrome in HICs have fallen dramatically in the current era because of a combination of medical therapy, reperfusion, and better overall intensive care (34–37), treatment of patients with acute coronary syndrome in LMICs is highly variable and frequently suboptimal, with increased symptom-to-presentation (pain-to-door) times and increased presentation-to-treatment (door-to-drug) times compared with HICs and decreased adherence to evidence-based therapies, including clopidogrel (38,39). Furthermore, the availability of cardiac catheterization laboratory services is increasing globally, including in LMICs (40). The number of people in whom dual antiplatelet therapy is indicated is thus similarly increasing (33). In 2015, we successfully petitioned for clopidogrel to be added to the WHO EML as an antiplatelet agent.

Losartan (2017). Angiotensin-converting enzyme (ACE) inhibitors are highly effective for treating and improving outcomes in hypertension, heart failure with reduced ejection fraction, and chronic kidney disease (41,42), leading to their addition to the EML in 2002 (43). However, many patients cannot tolerate ACE inhibitors due to cough, angioedema, and other adverse side effects (41,44). Moreover, these side effects are more common in certain subpopulations in LMICs: up to 44% of persons of Chinese ancestry experience cough associated with ACE inhibitors, compared with 20% or less in the general population, and rates of angioedema are up to 4.5× more common in persons of African ancestry than in the general population (45,46). Angiotensin receptor blockers (ARBs) significantly lower rates of respiratory effects

compared with ACE inhibitors, namely, a 74% lower incidence of cough and a 66% lower incidence of angioedema (41,42). Moreover, ARBs are low cost (losartan averages U.S. $0.02 per tablet) (47). High-quality randomized controlled trials demonstrate noninferiority to ACE inhibitors for the treatment of hypertension, heart failure with reduced ejection fraction, and chronic kidney disease (48–50).

We, therefore, petitioned the WHO EML for a square-box addition of ARBs to the EML in 2016, with losartan as the class exemplar. In 2017, losartan was added to the EML with a square box as the exemplar for ARBs.

REJECTIONS (2013, 2015, AND 2017). There have been 3 notable, recent rejections to petitions for inclusion on the EML: novel oral anticoagulants; combination of dual antihypertensive therapy; and fixed-dose combination (FDC), or polypill, therapy.

Direct oral anticoagulants (2015). Direct oral anticoagulants (DOACs), alternatively known as novel oral anticoagulants (NOACs), specifically apixaban, dabigatran, and rivaroxaban, were petitioned to be added to the EML in 2015 for the prevention of stroke in individuals with nonvalvular atrial fibrillation. Worldwide prevalence of nonvalvular atrial fibrillation is increasing, and these patients have an increased risk of stroke that can be substantially reduced with anticoagulants (51). The EML includes warfarin, which is characterized by frequent monitoring of blood coagulability, dose adjustments to maintain therapeutic levels, diet modifications, and multiple drug-drug interactions. The petitioning authors conducted a meta-analysis of the landmark DOAC trials and argued that DOACs were clinically superior to warfarin and more cost-effective (52) because they do not require frequent monitoring (53).

The Expert Committee did not recommend the addition of DOACs to the EML in 2015 (54). The committee raised concerns that the patients included in the previously mentioned trials may not represent the global population that would use DOACs. The committee argued that the absolute risk reduction in all-cause mortality, stroke, and systemic embolization seen in patients taking DOACs was of marginal clinical significance. The committee also highlighted evidence suggesting that patients taking DOACs receive no benefit compared with patients taking warfarin with a high therapeutic International Normalized Ratio range, usually considered 80% or greater (55). Furthermore, the committee noted that inexpensive antidotes exist for patients who experience bleeding while taking warfarin, whereas antidotes for DOACs were emerging and not widely available at the time of the application. Finally, the committee felt that the clinical benefit of DOACs over warfarin did not justify the significant difference in cost and cost-effectiveness.

Lisinopril-hydrochlorothiazide combination (2017). Because hypertension is the leading risk factor for mortality worldwide (56) and because many medications have demonstrated efficacy in achieving blood pressure control (57), multiple blood pressure–lowering drugs have long been featured on the WHO EML. However, most people with hypertension require more than 1 medication to achieve control (58,59). High-quality evidence demonstrates that combination therapy decreases blood pressure 60% to 80% more than single-agent therapy does, with a commensurate reduction in cardiovascular events (60,61). For this reason, single tablets combining 2 or more blood pressure–lowering drugs are increasingly used and prescribed (62).

We petitioned the WHO to add the combination of lisinopril and hydrochlorothiazide to the EML as an exemplar of combination blood pressure–lowering therapy. The Expert Committee did not recommend the addition of the lisinopril-hydrochlorothiazide combination to the EML in 2017 (63).

Polypills (2013, 2015, and 2017). In 2013, 2015, and 2017 (64–66), applications were submitted to add FDC, or polypill, therapy to the EML for secondary prevention of atherosclerotic CVD (ischemic heart disease and thrombotic stroke). The components for each application included aspirin, statins, and blood pressure–lowering drugs, which increase adherence by 44% compared with usual care (67). The applications emphasized FDC therapy for secondary prevention of CVDs to avoid the more controversial strategy of mass treatment for primary prevention. The Expert Committee did not recommend the addition of a polypill to the EML in 2013, 2015, or 2017. The committee raised different concerns during each review, including the lack of clinical outcomes from phase 2 polypill trials; uncertainty about the availability, price, and regulatory approval of different polypills; and uncertainty about the effects of polypills on low-functioning health systems. FDC therapy for HIV, tuberculosis, and malaria had been added to the EML in previous years without similar data, although these combinations have the added potential benefit of reducing antimicrobial resistance. Nevertheless, the committee noted in the 2017 EML:

TABLE 2 Summary of Lessons Learned for Modernizing the Essential Medicines List for Cardiovascular Medicines

Domain	Lesson Learned	Specific Example
Cost and cost-effectiveness	• Cost is not always a barrier to entry; generic competition can lower drug prices • A listing on the WHO Model List of Essential Medicines can help focus attention on making treatments more affordable	Addition of simvastatin, clopidogrel following generic production
Clinical practice guidelines	• The absence of systematic reviews and practice guidelines in low- and middle-income countries is not always a barrier to entry • Adaptation of the guidelines (e.g., WHO PEN) will continue to strengthen the evidence base	Addition of new indication of heart failure for spironolactone Addition of losartan as alternative to ACE inhibitors
Feedback loops and continual improvement	• Modification of the list by removing inferior or obsolete medications based on new data is as important as the addition of novel medications	Removal of atenolol as the representative of beta-blocker; Addition of modern beta-blocker (bisoprolol) with the indication of heart failure
Community and next-generation engagement	• Anyone, from any country, can apply successfully with a compelling, data-driven argument • The global cardiovascular community, including next-generation health professionals, can actively contribute to modernizing the Essential Medicines List	Simvastatin, bisoprolol, spironolactone, clopidogrel, and losartan applications by medical students, residents and faculty

ACE = angiotensin-converting enzyme; PEN = Package of Essential Noncommunicable; WHO = World Health Organization.

Fixed-dose combinations for non-communicable diseases may have advantages over the single medicines given concomitantly, including increased adherence and reduced pill burden. The potential value of fixed-dose combinations of currently listed essential medicines, with regulatory approval and demonstrated bioavailability for the management of chronic non-communicable diseases, is recognized (7,68).

These statements are supportive of the polypill concept. However, the benefits of EML listing, such as tariff exemption and faster registration and delivery through prequalification, will not be afforded to polypills. The Expert Committee also noted that additional guidance on FDCs is required: "The Expert Committee also recommended that the existing WHO guidance documents on FDCs urgently need updating, as well as development of a guidance document outlining key criteria for differentiating the role and need for FDCs in different therapeutic indications (e.g., acute, chronic, communicable and non-communicable diseases)" (7,68).

LESSONS LEARNED AND FUTURE DIRECTIONS

We have observed 4 key factors that affect inclusion of medicines on the WHO EML (Table 2) and will likely influence the outcomes of future applications summarized in Table 2.

1. COST AND COST-EFFECTIVENESS. One issue we have repeatedly encountered is the central tension among clinical effectiveness, drug costs, and cost-effectiveness. The application for DOACs, for example, was rejected largely due to cost despite favorable cost-effectiveness analyses:

Despite some cost-effectiveness analyses suggesting that the NOACs are "cost-effective", replacing warfarin with an NOAC will require significant investment of a country's health-care funds, which might be better spent on alternative treatments for other diseases or health-care facilities. In making judgments regarding health-system expenditure on high-price medicines, countries will therefore need to have methods in place for estimating likely utilization of new medicines and for monitoring their use in practice (68).

However, the addition of medicines to the EML can catalyze substantial price reductions and improve cost-effectiveness. For example, in the case of antiretroviral therapy for the treatment and control of HIV, the addition of ARVs to the EML was part of broader political advocacy and social pressure to lower the prices of therapeutics that are considered truly essential (10). The Expert Committee has resolved to lead a discussion on high-priced medicines from the perspective of public health, facilitate research on the effectiveness of implementing policies on medicine prices (including intellectual property), update WHO guidelines on pricing policies, gather data on per-country experiences of various price-setting mechanisms, collect country-level data on the use of medicines added to the EML, and work with individual countries to develop strategies and the capacity to manage high-priced medicines. Although we acknowledge that there may not always be a direct association between a medication being listed on the EML and a subsequent cost reduction, we argue that, as seen with medicines used to treat cancer, hepatitis C, and HIV/acquired

immunodeficiency syndrome (8,69), the EML can be an effective political tool for advocating for increased access to affordable essential therapies. The pricing of essential medicines following the addition to the EML is an important area of future investigation.

2. CLINICAL PRACTICE GUIDELINES. The WHO requires high-quality systematic reviews to support applications to the EML. A key barrier to the treatment of CVD appears to be the lack of consistent, consensus clinical practice guidelines on the prevention, treatment, and control of CVD in LMICs. Adapting clinical practice guidelines from HIC settings to the LMIC context is 1 approach. One example is the WHO PEN (Package of Essential Noncommunicable) guidelines for the treatment of acute myocardial infarction, stroke, heart failure, and raised blood pressure in LMICs. The Global Hearts initiative is another example of adapting global guidelines and protocols to national contexts (70). A further example is the systematic, evidence-based efforts to improve the impact and quality of hypertension guidelines specific to LMIC contexts by the COUNCIL (Control Unique to Cardiovascular Diseases in Low and Middle Income Countries) initiative (71).

To implement clinical practice and other guidelines across broad settings, the WHF has developed a series of CVD roadmaps for secondary prevention of CVD, raised blood pressure, and tobacco control. The roadmaps are designed to "translate existing knowledge of best practices, barriers and solutions into practical strategies for improvement in cardiovascular health" (3,72). Further work to adapt CVD guidelines holds the promise of not only strengthening future EML applications, but also ensuring access to essential medicines.

3. FEEDBACK LOOPS AND CONTINUAL IMPROVEMENT. Just as the medical community can help ensure that the EML is modernized by adding new medications, so too can it modernize the EML by submitting petitions to delete medicines from the list when they are ineffective or harmful. For example, as modern beta-blockers, with a strong base of evidence for the treatment of heart failure with reduced ejection fraction, became widely used by clinicians, we recognized the need to substitute them for atenolol.

Translating changes to the EML at the national level, particularly by changing or removing drugs, is another related, important step. The example of nonsteroidal anti-inflammatory drugs (NSAIDs) highlights this issue. Although the 19th EML includes acetylsalicylic acid and ibuprofen as NSAIDs for pain control, McGettigan and Henry (73) found that other less effective NSAIDs, such as diclofenac, were present on 74% of national EMLs for 100 countries in 2012. In contrast, whereas acetylsalicylic acid (88%) and ibuprofen (90%) were commonly listed on these national EMLs, naproxen was listed on only 27% of national EMLs despite a superior cardiovascular safety profile (73). Feedback loops and continual improvement of the relation between the WHO EML and national EMLs remain important for ensuring modernization (74).

4. COMMUNITY AND NEXT-GENERATION ENGAGEMENT. The global CVD community can benefit from enhanced engagement with a diverse array of stakeholders, including the next generation of health workers, patients, and advocates. Many applications appear to come from HIC settings (including ourselves) rather than from individual LMICs. Although reasons for the paucity of EML applications from LMIC authors are unclear, possibilities include the lack of knowledge about the EML and its potential implications, lack of mentorship, and lack of training to create compelling applications. To address this gap, the Young Professionals Chronic Disease Network has initiated a Next Generation Leaders program on evidence-based technical petitions to WHO and National EML committees. Modernizing national EMLs to the WHO EML based on country needs is an important area of focus.

National-level analyses demonstrate that the WHO EML modernization process has not always reached national EMLs. For example, 43% of low-income countries, 75% of lower-middle-income countries, and 69% of upper-middle-income countries have statins on their national EML. However, only 30% of low-income countries, 57% of LMICs, and 50% of upper middle-income countries include the 4 medication classes of aspirin, beta-blockers, statins, and ACE inhibitors (75). Brazil, China, India, Indonesia, Kenya, Malawi, the Philippines, South Africa, and Tanzania indicate increasing alignment of medications on the national EML to the WHO EML (76). Reconsideration of polypill therapy for CVDs and reviews of cardiovascular medicines/therapeutics for in-patient or hospital use and diagnostics are future areas of focus.

CONCLUSIONS

The global burden of CVD is substantial, and insufficient access to CVD medicines perpetuates and accentuates this problem. The WHO EML is 1 important mechanism and tool for improving access to CVD medicines. Here, we have outlined the rationale for and recent efforts to modernize the WHO EML across the spectrum of cardiovascular care. We build on previous published data by highlighting the substantial changes to the CVD medicines on the EML over the past

decade, including debates about newer medicines, such as polypills and DOACs. We note in particular that the translation to national EMLs remains incomplete.

WHO and national EMLs represent a collective opportunity and responsibility toward improving access to essential medicines and improving cardiovascular health. We believe that the clinical CVD community has a key role to play as petitioners, advisors, and advocates. Our work represents our collective, iterative, and expanding set of lessons learned—individually and as a group—over the past decade to modernize the WHO EML and advocate for expanded access to CVD medications worldwide. We hope to socialize and disseminate these lessons to stimulate others to embark on similar efforts to modernize WHO EML and national EMLs. We believe—and have demonstrated—that anyone can contribute to improve the accessibility, availability, and affordability of essential medicines for the prevention and control of CVD and to improve cardiovascular health.

ADDRESS FOR CORRESPONDENCE: Dr. Sandeep P. Kishore, Arnhold Institute for Global Health, 1216 Fifth Avenue, New York, New York 10029. E-mail: sandeep.kishore@mssm.edu.

REFERENCES

1. Wang H, Naghavi M, Allen C, et al. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 2016;388:1459–544.

2. World Health Organization. Global Hearts Initiative: working together to beat cardiovascular diseases. Available at: http://www.who.int/cardiovascular_diseases/global-hearts/GHI_Brochure.pdf?ua=1. Accessed January 3, 2017.

3. Perel P, Avezum A, Huffman M, et al. Reducing premature cardiovascular morbidity and mortality in people with atherosclerotic vascular disease: the World Heart Federation Roadmap for secondary prevention of cardiovascular disease. Glob Heart 2015;10:99–110.

4. Cameron A, Roubos I, Ewen M, et al. Differences in the availability of medicines for chronic and acute conditions in the public and private sectors of developing countries. Bull World Health Organ 2011;89:412–21.

5. Khatib R, McKee M, Shannon H, et al. Availability and affordability of cardiovascular disease medicines and their effect on use in high-income, middle-income, and low-income countries: an analysis of the PURE study data. Lancet 2016;387:61–9.

6. Bazargani YT, Ewen M, de Boer A, Leufkens HGM, Mantel-Teeuwisse AK. Essential medicines are more available than other medicines around the globe. PLOS ONE 2014;9:e87576.

7. World Health Organization. Essential medicines and health products. Available at: http://www.who.int/medicines/services/essmedicines_def/en/. Accessed January 3, 2017.

8. World Health Organization. WHO moves to improve access to lifesaving medicines for hepatitis C, drug-resistant TB and cancers. May 8, 2015. Available at: http://www.who.int/mediacentre/news/releases/2015/new-essential-medicines-list/en/. Accessed January 3, 2017.

9. World Health Organization. Towards access 2030: WHO essential medicines and health products strategic framework 2016–2030. Available at: http://www.who.int/medicines/publications/Towards_Access_2030_Final.pdf?ua=1. Accessed June 13, 2017.

10. Hoen E, Berger J, Calmy A, Moon S. Driving a decade of change: HIV/AIDS, patents, and access to medicines for all. J Int AIDS Soc 2011;14:15.

11. Anderson JL. Evolution of the ACC/AHA clinical practice guidelines in perspective: guiding the guidelines. J Am Coll Cardiol 2015;65:2735–8.

12. Jacobs AK, Anderson JL, Halperin JL. The evolution and future of ACC/AHA clinical practice guidelines: a 30-year journey: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;64:1373–84.

13. World Health Organization. Members of the 20th Expert Committee on the Selection and Use of Essential Medicines. Available at: http://www.who.int/selection_medicines/committees/expert/20/experts/members-committee/en/. Accessed January 3, 2017.

14. Ounpuu S, Negassa A, Yusuf S. INTER-HEART: a global study of risk factors for acute myocardial infarction. Am Heart J 2001;141:711–21.

15. Taylor F, Huffman MD, Macedo AF, et al. Statins for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev 2013;1:CD004816.

16. Cholesterol Treatment Trialists' (CTT) Collaborators. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. Lancet 2012;380:581–90.

17. Yusuf S, Bosch J, Dagenais G, et al. Cholesterol lowering in intermediate-risk persons without cardiovascular disease. N Engl J Med 2016;374:2021–31.

18. CNN Money. Zocor and Zoloft face patent expiration. Available at: http://money.cnn.com/2006/06/15/news/companies/zoloft_zocor/index.htm. Accessed December 16, 2017.

19. Management Sciences for Health. International drug price indicator guide 2007. Available at: http://mshpriceguide.org/wp-content/uploads/2016/06/MSH-International-Drug-Price-Indicator-Guide-2007.pdf. Accessed June 21, 2017.

20. World Health Organization. Package of essential noncommunicable (PEN) disease interventions for primary health care in low-resource settings. Available at: http://www.who.int/nmh/publications/essential_ncd_interventions_lr_settings.pdf?ua=1. Accessed January 3, 2017.

21. Salpeter S, Ormiston T, Salpeter E. Cardioselective beta-blockers for chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2005;4:CD003566.

22. Dickstein K, Cohen-Solal A, Filippatos G, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur J Heart Fail 2008;10:933–89.

23. Jessup M, Abraham WT, Casey DE, et al. 2009 focused update: ACCF/AHA guidelines for the diagnosis and management of heart failure in adults. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Developed in collaboration with the International Society for Heart and Lung Transplantation. J Am Coll Cardiol 2009;53:1343–82.

24. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;62:e147–239.

25. Heart Failure Society of America. Executive summary: HFSA 2010 comprehensive heart failure practice guideline. J Card Fail 2010;16:475–539.

26. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;64:e139–228.

27. O'Gara PT, Kushner FG, Ascheim DD, et al. ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;61:e78–140.

28. Sabatine MS, Cannon CP, Gibson CM, et al. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. N Engl J Med 2005;352:1179–89.

29. Yusuf S, Zhao F, Mehta SF, Chrolavicius S, Tognoni G, Fox KK. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 2001;345:494–502.

30. Gao R. Current status of percutaneous coronary intervention in China. Heart 2010;96:415–8.

31. Hun Y. Current status and development of percutaneous coronary intervention in China. J Zhejiang Univ Sci B 2010;11:631–3.

32. Ramakrishnan S, Mishra S, Chakraborty R, Chandra KS, Mardikar HM. The report on the Indian coronary intervention data for the year 2011—National Interventional Council. Indian Heart J 2013;65:518–21.

33. Patel A, Vidula M, Kishore SP, Vedanthan R, Huffman MD. Building the case for clopidogrel as a World Health Organization essential medicine. Circ Cardiovasc Qual Outcomes 2015;8:447–51.

34. de Vreede JJ, Gorgels AP, Verstraaten GM, Vermeer F, Dassen WR, Wellens HJ. Did prognosis after acute myocardial infarction change during the past 30 years? A meta-analysis. J Am Coll Cardiol 1991;18:698–706.

35. Flynn A, Moscucci M, Share D, et al. Trends in door-to-balloon time and mortality in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention. Arch Intern Med 2010;170:1842–9.

36. Gillum RF. Trends in acute myocardial infarction and coronary heart disease death in the United States. J Am Coll Cardiol 1994;23:1273–7.

37. Krumholz HM, Normand SL, Wang Y. Trends in hospitalizations and outcomes for acute cardiovascular disease and stroke, 1999-2011. Circulation 2014;130:966–75.

38. Karthikeyan G, Xavier D, Prabhakaran D, Pais P. Perspectives on the management of coronary artery disease in India. Heart 2007;93:1334–8.

39. Yusuf S, Islam S, Chow CK, et al. Use of secondary prevention drugs for cardiovascular disease in the community in high-income, middle-income, and low-income countries (the PURE Study): a prospective epidemiological survey. Lancet 2011;378:1231–43.

40. Kaul U, Bhatia V. Perspective on coronary interventions and cardiac surgeries in India. Indian J Med Res 2010;132:543–8.

41. Yusuf S, Teo KK, Pogue J, et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. N Engl J Med 2008;358:1547–59.

42. Yusuf S, Teo K, Anderson C, et al., for the Telmisartan Randomised AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease (TRANSCEND) Investigators. Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: a randomised controlled trial. Lancet 2008;372:1174–83.

43. World Health Organization. WHO model list of essential medicines: 16th list (updated) March 2010. Available at: http://apps.who.int/iris/bitstream/10665/70643/1/a95060_eng.pdf. Accessed June 13, 2017.

44. Israili ZH, Hall WD. Cough and angioneurotic edema associated with angiotensin-converting enzyme inhibitor therapy. A review of the literature and pathophysiology. Ann Intern Med 1992;117:234–42.

45. Woo KS, Nicholls MG. High prevalence of persistent cough with angiotensin converting enzyme inhibitors in Chinese. Br J Clin Pharmacol 1995;40:141–4.

46. Brown NJ, Ray WA, Snowden M, Griffin MR. Black Americans have an increased rate of angiotensin converting enzyme inhibitor-associated angioedema. Clin Pharmacol Ther 1996;60:8.

47. Management Sciences for Health. International drug price indicator guide, 2014 edition. Available at: http://apps.who.int/medicinedocs/documents/s21982en/s21982en.pdf. Accessed December 19, 2016.

48. Li EC, Heran BS, Wright JM. Angiotensin converting enzyme (ACE) inhibitors versus angiotensin receptor blockers for primary hypertension. Cochrane Database Syst Rev 2014;8:CD009096.

49. Bangalore S, Fakheri R, Toklu B, Ogedegbe G, Weintraub H, Messerli FH. Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in patients without heart failure? Insights from 254,301 patients from randomized trials. Mayo Clin Proc 2016;91:51–60.

50. Ricci F, Di Castelnuovo A, Savarese G, Filardi PP, De Caterina R. ACE-inhibitors versus angiotensin receptor blockers for prevention of events in cardiovascular patients without heart failure—a network meta-analysis. Int J Cardiol 2016;217:128–34.

51. Chugh SS, Havmoeller R, Narayanan K, et al. Worldwide epidemiology of atrial fibrillation: a global burden of disease 2010 study. Circulation 2014;129:837–47.

52. Kansal AR, Zheng Y, Pokora T, Sorensen SV. Cost-effectiveness of new oral anticoagulants in the prevention of stroke in patients with atrial fibrillation. Best Pract Res Clin Haematol 2013;26:225–37.

53. Neumann I, Schünemann HJ. Novel oral anticoagulants—addition—EML. 2014. Available at: http://www.who.int/selection_medicines/committees/expert/20/applications/NOACs/en/. Accessed June 25, 2017.

54. World Health Organ Expert Committee. The selection and use of essential medicines. Report of the WHO Expert Committee, 2015. Available at: http://apps.who.int/iris/bitstream/10665/189763/1/9789241209946_eng.pdf?ua=1. Accessed June 21, 2017.

55. Canadian Agency for Drugs and Technologies in Health. CADTH therapeutic review recommendations: new oral anticoagulants for the prevention of thromboembolic events in patients with atrial fibrillation. June 2012. Available at: https://www.cadth.ca/media/pdf/tr0002_New-Oral-Anticoagulants_rec_e.pdf. Accessed August 18, 2017.

56. Lim SS, Vos T, Flaxman AD, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012;380:2224–60.

57. Paz MA, de-La-Sierra A, Sáez M, et al. Treatment efficacy of anti-hypertensive drugs in monotherapy or combination: ATOM systematic review and meta-analysis of randomized clinical trials according to PRISMA statement. Medicine 2016;95:e4071.

58. Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension 2003;42:1206–52.

59. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens 2013;31:1281–357.

60. Wald DS, Law M, Morris JK, Bestwick JP, Wald NJ. Combination therapy versus monotherapy in reducing blood pressure: meta-analysis on 11,000 participants from 42 trials. Am J Med 2009;122:290–300.

61. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. BMJ 2009;338:b1665.

62. Jarari N, Rao N, Peela JR, et al. A review on prescribing patterns of antihypertensive drugs. Clin Hypertens 2016;22:7.

63. World Health Organization. The selection and use of essential medicines: report of the WHO Expert Committee on Selection and Use of Essential Medicines, 2017 (including the 20th WHO Model List of Essential Medicines and the 6th WHO Model List of Essential Medicines for Children). Available at: http://www.who.int/medicines/publications/essentialmedicines/EML_2017_EC21_Unedited_Full_Report.pdf?ua=1. Accessed June 13, 2017.

64. Huffman MD, Yusuf S. Polypills: essential medicines for cardiovascular disease secondary prevention? J Am Coll Cardiol 2014;63:1368–70.

65. Huffman MD, Perel P, Castellano JM, et al. Essential medicines selection. Aspirin + statin + antihypertensive—addition—EML. 2014. Available at: http://www.who.int/selection_medicines/committees/expert/20/applications/aspirin_statin_antihyper_Ad/en/. Accessed June 21, 2017.

66. World Health Organization. Essential medicines selection. Aspirin + atorvastatin + ramipril (polypill)—EML. Available at: http://www.who.int/selection_medicines/committees/expert/21/

applications/aspirin_atorvastatin_ramipril_ad/en/. Accessed June 13, 2017.

67. Bahiru E, de Cates AN, Farr MRB, et al. Fixed-dose combination therapy for the prevention of atherosclerotic cardiovascular diseases. Cochrane Database Syst Rev 2017;3:CD009868.

68. World Health Organization. The selection and use of essential medicines: report of the WHO Expert Committee, 2015 (including the 19th WHO Model List of Essential Medicines and the 5th WHO Model List of Essential Medicines for Children). Available at: http://apps.who.int/iris/bitstream/10665/189763/1/9789241209946_eng.pdf?ua=1. Accessed June 25, 2017.

69. World Health Organization. WHO takes major steps to make HIV treatment accessible. April 22, 2002. Available at: http://www.who.int/mediacentre/news/releases/release28/en/. Accessed January 3, 2017.

70. World Health Organization. Cardiovascular disease. Global Hearts initiative. Available at: http://www.who.int/cardiovascular_diseases/global-hearts/en/. Accessed December 19, 2016.

71. Owalabi M, Olowoyo P, Miranda JJ, et al. Gaps in Hypertension Guidelines in Low- and Middle-Income Versus High Income Countries: A Systematic Review. Hypertension 2016;68:1328–37.

72. Perel P, Bianco E, Poulter N, et al. Adapting the World Heart Federation Roadmaps at the national level: next steps and conclusions. Glob Heart 2015;10:135–6.

73. McGettigan P, Henry D. Use of non-steroidal anti-inflammatory drugs that elevate cardiovascular risk: an examination of sales and essential medicines lists in low-, middle-, and high-income countries. PLOS Med 2013;10:e1001388.

74. Reddy KS, Roy A. Cardiovascular risk of NSAIDs: time to translate knowledge into practice. PLOS Med 2013;10:e1001389.

75. Wirtz VJ, Kaplan WA, Kwan GF, Laing RO. Access to medications for cardiovascular diseases in low- and middle-income countries. Circulation 2016;133:2076–85.

76. IMS Institute for Healthcare Informatics. Understanding the role and use of essential medicines lists. 2015. Available at: http://apps.who.int/medicinedocs/documents/s21980en/s21980en.pdf. Accessed October 26, 2017.

KEY WORDS cardiovascular disease, essential medicines, NCDs, WHO Essential Medicines List