Resource Effective Strategies to Prevent and Treat Cardiovascular Disease

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Abstract—Cardiovascular disease (CVD) is the leading cause of global deaths, with the majority occurring in low- and middle-income countries. The primary and secondary prevention of CVD is suboptimal throughout the world, but the evidence–practice gaps are much more pronounced in low- and middle-income countries. Barriers at the patient, healthcare provider, and health system level prevent the implementation of optimal primary and secondary prevention. Identification of the particular barriers that exist in resource-constrained settings is necessary to inform effective strategies to reduce the identified evidence–practice gaps. Furthermore, targeting modifiable factors that contribute most significantly to the global burden of CVD, including tobacco use, hypertension, and secondary prevention for CVD, will lead to the biggest gains in mortality reduction. We review a select number of novel, resource-efficient strategies to reduce premature mortality from CVD, including (1) effective measures for tobacco control, (2) implementation of simplified screening and management algorithms for those with or at risk of CVD, (3) increasing the availability and affordability of simplified and cost-effective treatment regimens including combination CVD preventive drug therapy, and (4) simplified delivery of healthcare through task-sharing (nonphysician health workers) and optimizing self-management (treatment supporters). Developing and deploying systems of care that address barriers related to the above will lead to substantial reductions in CVD and related mortality. **(*Circulation*. 2016;133:742–755. DOI: 10.1161/CIRCULATIONAHA.115.008721.)**

Key Words: cardiovascular disease ■ healthcare system ■ ischemic heart disease ■ stroke

The 2013 Global Burden of Disease study showed that, despite a 39% decrease in age-specific death rates, global deaths from cardiovascular disease (CVD) have risen by 41% between 1990 and 2013.[1] Ischemic heart disease has risen to become the leading cause of global deaths, up from fourth position in 1990 (41% increase), and stroke has risen to third position from fifth (50% increase).[1] As outlined in Figure 1, the incidence of major and fatal CVD events is lowest in high-income countries (HIC).[2] It is predicted that, by 2020, nearly three quarters of the global mortality and 80% of the CVD burden (as measured by disability life-years lost) will occur in low- and middle-income countries (LMIC), where 85% of the world's population now live.[2,3] These changes have been driven largely by population growth and ageing.[1,3,4]

HIC have experienced large reductions in the incidence and mortality of CVD, with mortality declines averaging 50% since the 1970s, and as much as 75% in countries such as the United Kingdom, United States, and Finland.[5,6] The precise contribution of different factors varies among countries, in part reflecting differences in the initial pattern of risk factors and strategies used, but they include healthier diets, lower rates of smoking, improved management of risk factors such as hypertension, better management of acute CVD events, and greater use of secondary prevention.[5,7] Despite these impressive gains in HIC, morbidity and mortality associated with cardiovascular diseases remain very high, particularly among poor countries and in marginalized populations.[8]

In September 2011, the United Nations made a political declaration to adopt a global target of a 25% reduction in premature (<70 years) mortality from CVD, cancer, diabetes mellitus, and chronic respiratory disease by 2025, which subsequently translated into a noncommunicable disease (NCD) action plan.[9] This action plan has designated eight indicators to measure progress toward the overall "25×25" goal, including (1) decreasing raised blood pressure, (2) decreasing tobacco use, (3) increasing physical inactivity, (4) decreasing sodium intake, (5) decreasing the harmful use of alcohol, (6) halting the rise of diabetes and obesity, (7) improving access to drug therapy and counseling to prevent CVD, and (8) increasing availability of the affordable basic technologies and essential medicines to manage NCDs.[10] However, none of these targets will likely be met unless the many existing barriers to evidence-based and efficient CVD management are addressed. This review focuses on ischemic heart disease and stroke, along with related risk factors, given that these two conditions are the leading contributors to the global burden of

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Circulation **is available at http://circ.ahajournals.org** **DOI: 10.1161/CIRCULATIONAHA.115.008721**

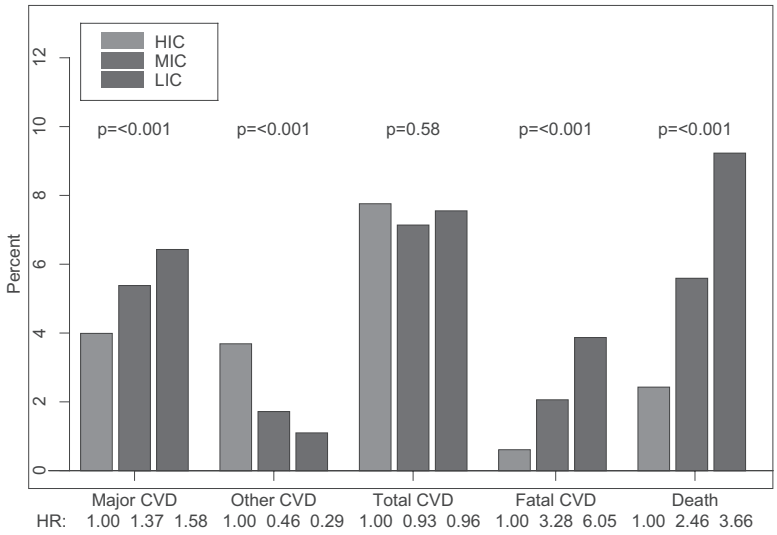

Figure 1. Cardiovascular disease (CVD) events and death by country income strata. HIC indicates high-income countries; LIC, low-income countries; and MIC, middle-income countries. Adapted from Yusuf et al[2] with permission of the publisher. Copyright ©2014, Massachusetts Medical Society.

CVD.[1] This article reviews the current gaps in the prevention and management of CVD compared with the evidence (evidence–practice gaps), barriers to closing evidence–practice gaps, and targets for resource-effective interventions. Finally, we review a select number of novel, resource-efficient population, individual, and health system strategies to overcome identified barriers.

Evidence–Practice Gaps in the Prevention and Management of CVD

The extent of evidence–practice gaps in the prevention and management of CVD can be demonstrated by data from the Prospective Urban Rural Epidemiology (PURE) Study, a longitudinal cohort study being conducted in 630 urban and rural communities from 17 high-, middle-, and low-income countries, with expansion underway to include 800 communities in 25 countries.[8] Unbiased and systematic, community screening of individuals was undertaken to achieve a representative sample of adults aged 35 to 70 years.[8] Standardized questionnaires, physical measurements including blood pressure, and laboratory investigations were completed to capture baseline demographics, medication use, and clinical events.[8] Data from PURE demonstrate that the management of hypertension is suboptimal throughout the world, but especially in LMIC (Figure 2).[11] First, approximately half of PURE participants who have hypertension are unaware of their diagnosis. Second, although the majority of individuals who are aware of their diagnosis of hypertension receive treatment, only a minority (< 20%) achieves adequate blood pressure control, defined as a systolic blood pressure (SBP) less than 140 mm Hg and a diastolic blood pressure less than 90 mm Hg. Third, most participants (77%) who receive blood pressure lowering treatment use only 1 medication[11]; however, it is widely acknowledged that at least 2 antihypertensive medications are needed to control blood pressure.[12] Gaps in hypertension awareness, treatment, and control are evident in all countries within the

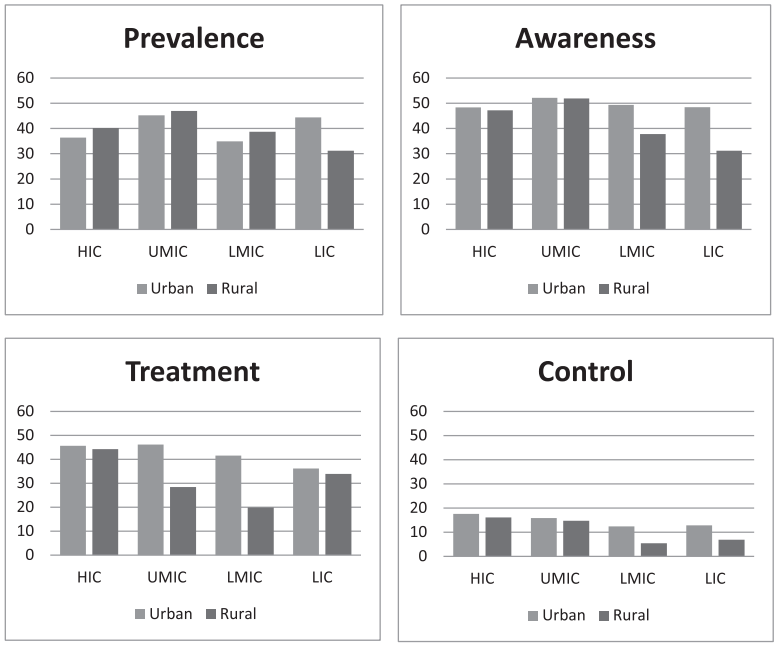

Figure 2. Prevalence, awareness, treatment, and control of hypertension by country economic status. HIC indicates high-income countries; LIC, low-income countries; LMIC, low-middle income countries; and UMIC, upper-middle income countries. Adapted from Chow et al[11] with permission of the publisher. Copyright ©2013, American Medical Association.

PURE study, but larger gaps are present in LMIC.[11] These data demonstrate the need for broader and more efficient blood pressure screening coupled with more effective blood pressure control. Similar evidence–practice gaps are evident in the management of lipids, with suboptimal use of statins.[8] Many of those with known CVD continue to be exposed to major risk factors, with 19% continuing to smoke, only 35% participating in high levels of physical activity, and only 39% following a healthy diet, with the greatest problem, again, in low-income countries (LIC).[13] Given the consistent evidence–practice gaps in the management of CVD risk across multiple risk factors, there is a need for comprehensive programs to tackle the structural determinants of CVD, case finding and, where shown to be effective, risk factor screening for CVD prevention and management.

There are also important, modifiable differences in the acute management of patients with CVD between HIC and LMIC. For instance, patients from HIC with a previous acute myocardial infarction (MI) are more likely to receive evidence-based medications, including aspirin, clopidogrel, and statin, at discharge (odds ratio [OR], 2.3; 95% confidence interval [CI], 1.2–4.5) and are more likely to receive percutaneous coronary intervention (OR, 19.7; 95% CI, 10.5–37.0), in comparison with LMIC.[14]

The PURE study also found suboptimal secondary prevention drug therapy in patients with established CVD (Figure 3).[8] More than 75% of participants in LIC with previous ischemic heart disease or stroke were not taking any medications for secondary prevention of CVD, compared with <10% among participants in HIC.[8] Similar gaps have been identified by other research. For example, a 2005 World Health Organization–led study of patients visiting healthcare facilities in LMIC found that, of those with ischemic heart disease, only 81% had been prescribed aspirin, 48% β-blockers, 40% angiotensin-converting enzyme (ACE) inhibitors, and 30% statins. Even lower medication rates were demonstrated among patients with cerebrovascular disease.[15] Collectively, these studies and others demonstrate the global magnitude of the evidence–practice gaps in the prevention and management of CVD, particularly in LMIC.[16,17]

Barriers to Evidence-Based and Efficient CVD Management

Closing these evidence–practice gaps in the prevention and management of CVD requires overcoming barriers that prevent the uptake of best practices. Systematic evaluations of barriers to effective CVD care in LMIC have received relatively little attention from researchers to date, but this is now changing.[18,19] For example, Khatib and colleagues performed a systematic review of barriers to hypertension awareness, treatment, and follow-up by evaluating both quantitative and qualitative reports. This review outlined that barriers occur at the patient, healthcare provider, and health system or policy level (Table 1).[18,20–22] Further research is required to elucidate the way in which these barriers combine and how they can be overcome, using methods that allow the researcher to determine which changes are necessary and which are sufficient to bring about desired changes.[23]

Although some barriers to optimal CVD management can be found in many countries at varying income levels, some

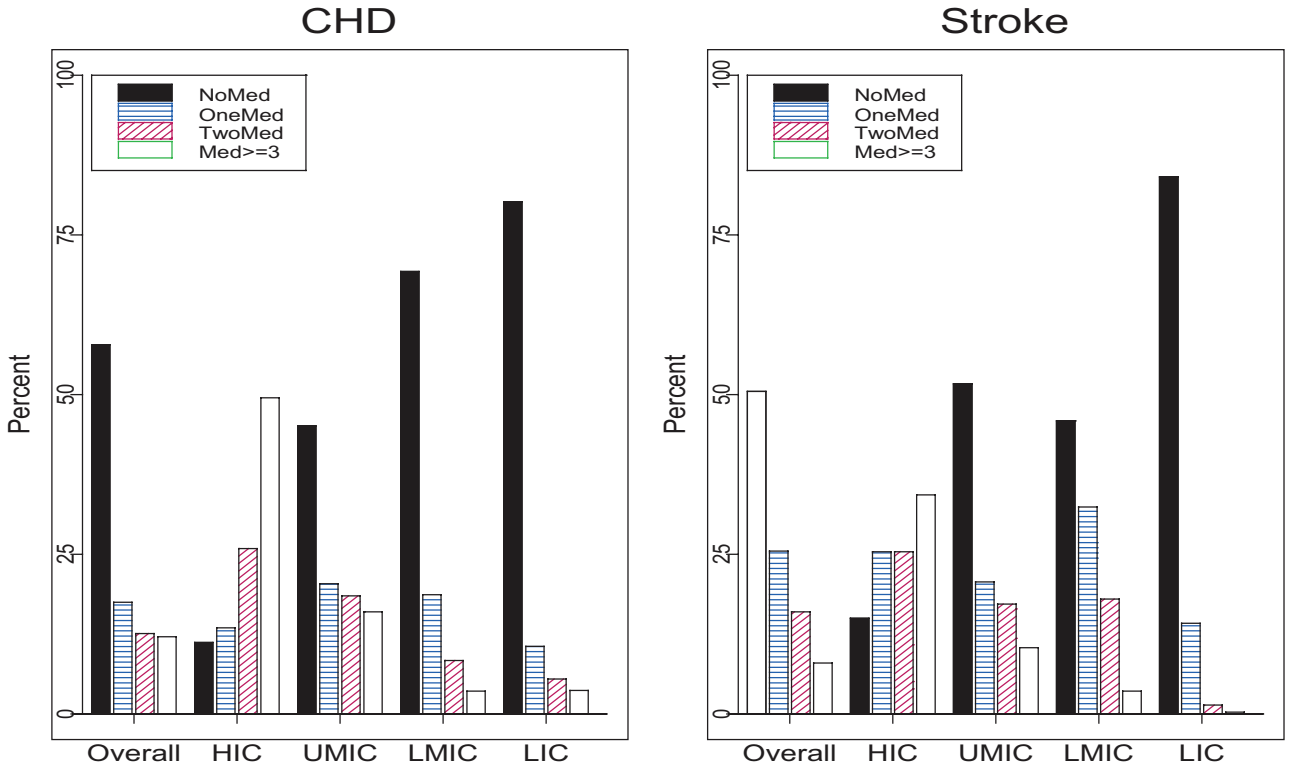

Figure 3. Number of drugs taken by individuals with previous stroke or ischemic heart disease by country economic status. CHD indicates coronary heart disease; HIC, high-income countries; LIC, low-income countries; LMIC, low-middle income countries; and UMIC, upper-middle income countries. Adapted from Yusus et al[8] with permission of the publisher. Copyright ©2011, Elsevier.

Table 1. Barriers to Evidence-Based Cardiovascular Disease Healthcare at the Patient, Healthcare Provider, and Health System/Policy Level, Prioritized by Country Income Strata

Barrier	Example	Country Income Strata
Patient[18]:		
Availability, access, and costs (External)	Lack of health insurance	Both HIC and LMIC
Knowledge (Internal)	Asymptomatic thus question need for ongoing treatment	Both HIC and LMIC
Beliefs (Internal)	Alternative/traditional medicine	LMIC > HIC
Memory (Internal)	Affects adherence to recommended therapies	Both HIC and LMIC
Side effects to medications (Internal)	Whether real or perceived (myalgia, cough, etc)	Both HIC and LMIC
Healthcare provider[18,21]:		
Knowledge	Familiarity and awareness of management options	LMIC: Standards of education, ongoing options for continued medical education
Attitudes	Lack of agreement with guidelines, outcome expectancy, self-efficacy, motivation and treatment inertia	LMIC: Conflicting opinions regarding alternative medicine
Behavior	External or environmental factors limiting management (time, resources, reimbursement)	LMIC>HIC
Health system/policy[22]:		
Healthcare financing system	Low priority in national budgets: competing political agendas (military, other medical conditions such as HIV, etc). Limited universal healthcare coverage.	LMIC>HIC
Medical products and technologies	Lacking infrastructures for stocking pharmacies with evidence-based generic medications. Poor affordability of essential medications, even when they are generic.	LMIC>HIC
Leadership/governance	Low priority for cardiovascular disease prevention: lack of effective screening programs, smoking cessation programs, safe environments for exercise, high costs for healthy foods	Both HIC and LMIC
Health workforce	Limited number of adequately trained physicians and healthcare professionals	LMIC>HIC
Health information system and research	Limited health system infrastructures to ensure monitoring of health determinants, performance and health status	LMIC>HIC
Service delivery	Efficient delivery of effective and safe interventions	Both HIC and LMIC

HIC indicates high-income countries; HIV, human immunodeficiency virus; and LMIC, low- and middle-income countries.

barriers are specific to certain contexts. It must also be noted that barriers to primordial prevention overlap with barriers identified primarily at the patient and health system level.[24] Ideal cardiovascular primordial prevention targets include never smoking, healthy diet, adequate physical activity, optimal blood pressure, glucose, and lipids, and a normal body mass index.[24] Barriers to achieving such targets are often related to limited patient knowledge, motivation, and an unfavorable environment that is not supported by appropriate health policy and government leadership that promote cardiovascular health in younger populations.

Patient-Level Barriers

There are two important barrier categories at the patient level that impact best practice with respect to CVD prevention and management. First, internal barriers that prevent optimal adherence to medications and lifestyle modification have been well documented.[25] These barriers include lack of awareness of their condition (ie, hypertension or a need for secondary prevention), reluctance to take medications for conditions that are asymptomatic or which cause side-effects, and difficulties in remembering to adhere to treatment regimens, especially if they are complex. It has been found that some patients harbor beliefs that pills are unnatural and that taking pills reminds them they are "unhealthy".[25] In some LMIC, medication use and adherence may be negatively impacted by beliefs derived from alternative or traditional medicine, which sees disease literally as "dis-ease," or discomfort and that medicines should only be used during acute illness, rather than prevention.[26] The second type of patient-level barriers are external, including lack of availability of appropriate healthcare resources, lack of the necessary financial resources to access care, either directly (eg, purchasing medications) or related costs (eg, transportation costs or fees to consult health practitioners).[27]

Healthcare Provider–Level Barriers

At the healthcare provider level, barriers have been classified according to knowledge, attitudes, and behavior.[21] Knowledge barriers include limitations relating to the large volume of health information that healthcare professionals must synthesize, inadequate training of healthcare providers in the evidence-based management of CVD and related risk, and inappropriate risk stratification.[21,28] Attitude barriers include unwillingness to accept evidence-based guidelines, lack of motivation to change current practice patterns, described as inertia, and beliefs that the guidelines are difficult to implement and/or will not result in the desired outcomes.[21] Behavioral barriers include environmental and external factors that prevent behavior change, thus limiting best practices. Some examples include limited time and resources to

implement guideline recommendations, coupled with misaligned financial incentives. Low health worker-to-patient ratios in LMIC reduce the time available to see and counsel patients.[29] The complexity of guidelines has been described as another factor that can affect behavior change.[28,30–32] Current guidelines for the diagnosis and management of cardiovascular risk and disease are complex and may be impractical to implement in resource-constrained settings.[33–36] For instance, the US Joint National Committee (JNC) 8 outlines a detailed evidence-based guideline for the identification and management of individuals with hypertension.[36] However, this algorithm is complex and varies according to age, comorbidities, and race.[36] Furthermore, it includes 3 separate drug treatment titration strategies, which involve up to 6 steps and require many visits to a clinic to diagnose hypertension, initiate treatment, and ultimately to control blood pressure at recommended levels. Such features limit the use of guidelines by primary care physicians in the HIC where they are developed and are even less practical in LMIC.[21]

In HIC, even when primary care physicians are supported by multifaceted quality improvement interventions comprising automated risk assessment, computerized decision support, and audit and feedback tools to improve guideline implementation, it has been difficult to demonstrate improvements in processes and outcomes.[37] Even if such complex interventions were effective, their implementation within infrastructures seen in LMIC can be challenging.

Health System–Level Barriers

The World Health Organization Health Systems Framework can help classify barriers at the health system level.[22] It comprises 6 building blocks: (1) leadership/governance, (2) healthcare financing, (3) health workforce, (4) medical products and technologies, (5) information and research, and (6) service delivery (Table 1).[22] Examples of barriers related to these building blocks include limited numbers of adequately trained physicians and allied health professionals, lack of financing or prepayment mechanisms to reduce point of service costs, and payment structures that disincentivize prevention.[38] Access to affordable generic evidence-based CVD medications is frequently a much greater problem in LMIC than HIC, with statins and ACE inhibitors often not being available in many hospitals, health clinics, and community pharmacies in LMIC.[39] Even when available, these evidence-based medications are often unaffordable in LMIC.[39] For example, whereas the cost of CVD medications (statins, ACE inhibitors, β-blockers, and aspirin collectively) is <1% of the average monthly income in HIC, in rural India, the cost of a statin or an ACE inhibitor approaches 50% and 20%, respectively, of a household's median monthly income.[39]

Barriers relating to healthcare financing can be seen in countries at all income levels, but are more pronounced in LMIC. Typically 1% to 2% of a much smaller gross domestic product is committed by governments to health expenditures in LMIC compared with around 12% on average in HIC.[40] Moreover, in LMIC a much greater share of health expenditure is out of pocket, leading to catastrophic health spending and distress financing, which affects the poor and uninsured disproportionately.[41] This microeconomic burden is exacerbated by the limited progress that many LMICs have made toward universal health coverage.[42] Although several MICs, including India (lower-middle income) and Brazil, China, and South Africa (upper-middle income), are making progress, significant challenges have been identified, including unwillingness or inability to collect the necessary funds, which can be coupled with a lack of political will.[42] Many LMIC have also made less progress in developing leadership and governance, as exemplified by generally weak tobacco control policies, reflecting low priorities, limited capacity to develop and implement healthy public policies, as well as corruption and susceptibility of governments to pressure from international tobacco corporations.[43,44]

Identification of the particular barriers at the patient, healthcare provider, and health system level that exist in resource-constrained settings is necessary to inform effective strategies to reduce the identified evidence–practice gaps.[45]

Targets for Resource-Effective Strategies

Just as it is important to understand the barriers that impede the uptake of the evidence-based management of CVD, it is important to understand the modifiable factors that contribute most significantly to the global burden of CVD. It has long been recognized that the greatest health gains will be achieved by shifting the overall distribution of risk factors. Where the goal is to reduce exposure to hazardous products, be they tobacco, alcohol, or energy dense food, this requires a combination of actions on price, availability, and marketing at population levels, something examined in more detail below. However, such a strategy should be complemented by 1 designed to identify and manage those with the ability to benefit from more interventions targeted at specific high risk strata, especially as they relate to metabolic risk factors.

Identification of high-risk individuals can be informed by research such as the INTERHEART study, which included 28 000 people in 52 countries,[46] and the INTERSTROKE study, with 26 000 participants from 33 countries.[47] These studies identified the most important modifiable risk factors for ischemic heart disease and stroke worldwide. Smoking, lipids, hypertension, and diabetes mellitus account for 80% of the population attributable risk for both ischemic heart disease and stroke.[46] Among these, reducing the first 3 has been demonstrated clearly to reduce major adverse cardiac events. First, tobacco kills ≈6 million people and causes more than half a trillion dollars of economic damage each year.[43] Tobacco control using a population-wide strategy is acknowledged to be important and cost-effective. Second, the Cholesterol Treatment Trialists' Collaboration meta-analysis of >90 000 people in 14 RCTs of statins showed that for each 1 mmol/L reduction in low-density lipoprotein over 5 years there was 12% reduction in relative risk for total mortality, 23% for major CVD events, 26% for MI, 24% for coronary revascularizations, 17% for strokes, and 21% for major vascular events.[48] Effects were seen even in those at low risk and those with low average low-density lipoprotein levels.[48] Third, the Blood Pressure Lowering Treatment Trialists' Collaboration meta-analysis, with >160 000 participants in 29 trials, showed that lowering SBP by 5 mm Hg over 4 to 5 years with most drugs reduced the risk of ischemic heart disease by 20%, stroke by

Table 2. Number (%) of Major CVD Events Over 4-Year Follow-Up for the Different Subgroups in the Population Urban Rural Epidemiology (PURE) Study (n=152 609), Highlighting That the Majority of Events Occur in Current Smokers, Those With Hypertension, or Documented History of CVD[50]

Baseline Condition	Number in PURE Cohort With a Condition at Baseline (%)	Follow-Up Major CVD Events N=3488 (2.2%)
Cardiovascular disease	7743 (5.1)	673 (19.3)
Hypertension (history or blood pressure >140/90 mm Hg)	62 034 (40.7)	2317 (66.4)
Current smoker	31 397 (20.6)	1021 (29.4)
CVD, hypertension, or current smoker	84 078 (55)	2822 (80.9)
Diabetes mellitus (history or FPG >7 mmol)	16 071 (10.5)	905 (26.0)
CVD, hypertension, smoker, or diabetes mellitus	88 326 (57.9)	2929 (84.0)

CVD indicates cardiovascular disease; and FPG, fasting blood glucose.

28%, and major CVD events by 22%, but this benefit is most clear in those with SBP >140 mm Hg.[49] Thus, a strategy that focuses on population (for tobacco) and individual measures (blood pressure and lipid reduction in high-risk populations or those with elevated levels) can yield very large benefits in terms of reducing CVD.

The PURE study (Table 2) indicates that over a 4-year follow-up, 20% of the CVD events that occur are in the 5% of individuals who have a history of previous MI or stroke. Furthermore, 66% of events derive from the 41% of individuals with hypertension (those with a history of hypertension or those with SBP >140 mm Hg on a measurement at a single time). It was also noted that 29% of CVD events occur in the 21% who are current smokers.[50] Collectively 81% of major CV events (CV deaths, MI, stroke, and hospitalizations for heart failure) occur in the 55% of the population who are either smokers, have hypertension, have a history of CVD, or a combination thereof. Although diabetes mellitus is undoubtedly an important risk factor and has been associated with a hazard ratio of 2.32 (95% CI, 2.11–2.56) for death from vascular causes,[51] its addition to tobacco, hypertension, and previous CVD only increases future CVD events from 81% to 84%.[50] Given the overlap in CVD risk factors in patients with diabetes mellitus, the evidence for managing blood sugars beyond aggressive management of tobacco use, blood pressure control, and secondary prevention is less clear. A 30% reduction in tobacco use, 30% improved hypertension control, and 30% improvement in secondary prevention over 10 to 15 years can collectively reduce incident CVD events by 25% globally.[12] In addition, in-hospital and postdischarge use of aspirin, statins, ACE inhibitors, and β-blockers can reduce case-fatality rates from acute coronary syndromes by >80%.[12] Therefore, collectively, these measures could have an important impact on global CVD mortality and are the basis of the CVD Road Maps developed by the World Heart Federation.[50,52–54] Similar findings have been described in a US population, where 87% to 92% of patients experiencing a fatal or nonfatal MI had ≥1 antecedent major CV risk factor.[55] Approaching risk assessment with these 3 factors in mind, tobacco use, hypertension, and documented CVD, makes screening for those who should be targets for primary and secondary prevention potentially simple and inexpensive. Although adding lipids improves the discrimination of CVD risk assessment, these investigations may be cost-prohibitive in resource-constrained settings. Adding a statin, without lipid assessment, in those with documented CVD, self-reported diabetes mellitus, or a high-risk nonlaboratory-based risk score, has been estimated to be a cost-effective strategy.[46,56]

Resource-Effective Strategies to Prevent and Manage CVD

Strategies to prevent and manage CVD should be based on (1) evidence of benefit and cost effectiveness, (2) feasibility of implementing such strategies in settings with different levels of resources, (3) ability to scale and sustain them, and (4) sociopolitical acceptability.[57] The following examples illustrate resource-effective and evidence-based interventions to address (1) population health, (2) primary and secondary prevention, and (3) deficiencies in health systems to prevent and manage CVD. Table 3 summarizes the quality of the evidence supporting the strategies outlined below.

Population Health Strategies

Tobacco Prevention and Control Policies

Despite a reduction in cigarette smoking rates in HIC over the last 3 decades, global sales of cigarettes continue to rise as a result of increased consumption in LMIC.[79] This requires a 2-pronged strategy. In the short term, the most effective way to reduce tobacco-related health concerns is to help current tobacco users quit because the majority of the tobacco-related morbidity and mortality in the next 2 to 3 decades will arise from those >30 years of age who currently use tobacco. However, in the longer term, over the next 30 to 60 years, it will be necessary to prevent adolescents and young adults from

Table 3. Evidence Supporting the Major Resource-Effective Strategies to Prevent and Treat Cardiovascular Disease

Resource Effective Strategies	Level of Evidence*	References
Tobacco prevention and control policies (WHO MPOWER)	A	58–60
Improving price, availability and marketing of healthy foods	C	61–65
Simplified CVD-risk screening and management algorithms	B	66
Availability of combination therapy for CVD	A	12,67–71
Task-sharing with NPHWs and treatment supporters	B	72–78

CVD indicates cardiovascular disease; MPOWER, monitoring tobacco use and prevention policies, warning about the dangers of tobacco, protecting people from tobacco smoke, enforcing bans on tobacco advertising, promotion and sponsorship, offering help to quit tobacco use, raising tobacco taxes; NPHWs, nonphysician health workers; and WHO, World Health Organization.

*Level-A body of evidence = multiple populations have been evaluated, or data are derived from multiple randomized, clinical trials or meta-analyses. Level-B body of evidence = limited populations have been evaluated, or data are derived from a single randomized trial or nonrandomized trial. Level-C body of evidence = very limited populations have been evaluated or only the consensus opinions of experts, case studies, or standards of care support the recommendation.

Table 4. The WHO MPOWER Measures for Tobacco Reduction[58]

Monitor tobacco use and prevention policies
Protect people from tobacco use
Offer help to quit tobacco use
Warn about the dangers of tobacco
Enforce bans on tobacco advertising, promotion and sponsorship
Raise taxes on tobacco

MPOWER indicates monitoring tobacco use and prevention policies, warning about the dangers of tobacco, protecting people from tobacco smoke, enforcing bans on tobacco advertising, promotion and sponsorship, offering help to quit tobacco use, raising tobacco taxes; and WHO, World Health Organization.

initiating tobacco use. The World Health Organization has identified 6 evidence-based tobacco control strategies, known as "MPOWER" (Table 4),[58] that address both approaches. The MPOWER strategies correspond to provisions included in the World Health Organization Framework Convention on Tobacco Control (FCTC), which outlines policy measures for tobacco control (Table 5).[59] It has been estimated that full implementation of the FCTC in 23 LMIC could avert >5 million deaths over a decade.[60] The measures set out in the FCTC are considered cost-effective for reducing tobacco use and would cost only US$0.14 in China to US$0.49 in Russia per person per year.[57] However, despite the FCTC having been signed by almost all countries, ratification of the FCTC lags behind, and tobacco marketing remains widespread in LMIC.[80–82] This demonstrates the need for countries to not only promulgate but to also enforce laws that control tobacco marketing. Unfortunately, as countries such as Uruguay and Jamaica have discovered, those enlightened politicians seeking to implement comprehensive tobacco control face challenges from powerful transnational tobacco corporations exploiting international trade agreements.[83]

Dietary Policies

Data from HIC countries suggest that increased fruits and vegetables, reduced saturated fats, and elimination of trans fats in the diet are associated with lower risk of ischemic heart disease.[61,62] However, similar data are not widely available from LMIC. Consequently, large studies conducted in LMIC, where diet patterns substantially differ from HIC, are urgently needed. Until such studies are available, as with tobacco control, population-based strategies are the most effective measures,[63] with a focus on price, availability, and marketing. Unfortunately, healthy foods are often unaffordable, in part because fruits and vegetables are very expensive in LMIC[64,65] (Mente unpublished 2015), and in part because of agricultural subsidies for products such as high fructose corn syrup in the HIC.[84] Again, as with tobacco, the spread of energy dense food is being driven by trade liberalization.[85]

Individual Strategies for the Prevention and Management of CVD

Simplified CVD-Risk Screening and Management Algorithms

Given the limitations of current diagnostic and management algorithms for patients at risk of CVD, simple cost-effective strategies are required to tackle the 3 modifiable risk factors (ie, hypertension, smoking, and secondary prevention) that are found in 55% of the population ≥35 years of age and account for 81% of major CVD events in the PURE study (Table 2). Unfortunately, as noted above, many guidelines for hypertension detection and management recommend that multiple elevated blood pressure readings should be documented before initiating treatment, and some recommend multiple investigations to assess CVD and medication-related complications.[33–36] These recommendations can create barriers to early initiation of effective treatments. The PURE study data show that approximately 90% of individuals with an initial SBP >160 mm Hg (Stage 2 hypertension), based on an average of 3 measures on 1 occasion, had a sustained high SBP (>140/90 mm Hg) on repeat visits within 1 year, so meeting existing criteria for hypertension (Table 6)[66] (Yusuf, unpublished 2015). Furthermore, 74% of patients with a single SBP between 140 and 159 mm Hg and another cardiac risk factor or documented CVD had an SBP of >140 mm Hg on follow-up visit. These data support a simplified screening process (eg, initiate antihypertensive treatments in those with an SBP >160 mm Hg on a single occasion) to diagnose and initiate treatment for hypertension.

Diagnostic and management strategies that can be adopted without expensive risk stratification tests, as recommended by the World Health Organization, can be cost-effective.[86] Thus, the strategy recommended by the World Health Organization incorporates the use of basic technologies (stethoscopes, sphygmomanometers, blood glucose test strips etc.), simple nonlaboratory-based risk assessment scores relevant to the population being assessed, and a core list of recommended generic CVD medications (Table 6).[86] This simplified approach to cardiovascular risk assessment and management may help reduce current evidence–practice gaps by targeting and simplifying the approach to modifiable risk factors including hypertension, smoking, and secondary prevention of CVD, including the management of dyslipidemia. Furthermore, this simplified approach can overcome many commonly identified barriers, including time constraints, cost, complexity, and confusion with existing guidelines.

Table 5. Core Provisions of the World Health Organization Framework Convention on Tobacco Control[59]

Core demand reduction provisions	Price and tax measures to reduce the demand for tobacco
	Nonprice measures to reduce the demand for tobacco: • Protection from exposure to tobacco smoke • Regulation of the contents of tobacco products • Regulation of tobacco product disclosures • Packaging and labeling of tobacco products • Education, communication, training and public awareness • Tobacco advertising, promotion and sponsorship • Demand reduction measures concerning tobacco dependence and cessation
Core supply reduction provisions	Control illicit trade in tobacco products
	Ban sales to and by minors
	Provision of support for economically viable alternative activities

Table 6. Proportion of Participants With No History of Hypertension but With Systolic Blood Pressure >140 mm Hg on Repeat Visit in the PURE Study Population Based on Various Criteria at Enrollment (Yusuf, unpublished PURE Data, 2015).

Population at Baseline Visit	Baseline (N)	SBP > 140 mm Hg at 1-Year Follow-Up Visit (N, %)
SBP > 180 mm Hg	686	634, 92.4%
SBP > 160 mm Hg	2512	2263, 90.1%
SBP >160 mm Hg and history of MI, stroke/TIA, angina, participant reported-DM	223	203, 91.0%
SBP >160 mm Hg and no history of MI, stroke/TIA, angina, self-DM	2289	2059, 90.0%
SBP 140–159 mm Hg and history of MI, stroke/TIA, angina, self-DM	576	424, 73.6%
SBP 140–159 mm Hg and no history of MI, stroke/TIA, angina, self-DM	6124	4072, 66.5%
SBP <140 mm Hg	29007	6538, 22.5%

BP was measured using an Omron automated device with 3 readings obtained during a single visit. The average of the 3 readings is used. DM indicates diabetes mellitus; MI, myocardial infarction; PURE, Prospective Urban Rural Epidemiology Study; SBP, systolic blood pressure; and TIA, transient ischemic attack.

Resource-Efficient Management of Acute Presentations of CVD

The significant reduction of CVD mortality in HIC by 50% to 75% since the 1970s has been attributed to different factors, including better management of acute ischemic heart disease events.[5–7] Although the widespread implementation of primary percutaneous coronary intervention for acute MIs or a thrombolytic program for acute strokes (with computed tomography scans within 4 hours of symptom onset) may not be feasible or resource-efficient options in many LMICs, other acute interventions are needed. The use of aspirin and streptokinase for the acute, in-hospital management of ST-segment–elevation MI is considered to be cost-effective and could avert 335 000 DALYs among patients 30 to 69 years of age in LMIC.[87] Furthermore, clopidogrel, β-blockers, ACE inhibitors, diuretics, and statins for the management of acute coronary syndromes, stroke, and acute heart failure are considered essential medicines by the World Health Organization (Table 7).[88] Ensuring that these evidence-based medications are available post-MI and keeping the costs to the patient low through the elimination of copayments results in improved medication adherence and rates of first major vascular events, without increasing overall health costs.[89]

Expanding Management Options by Appropriate and Affordable Combination Therapy for CVD

Fixed-dose combination drug therapy has transformed the treatment of infectious diseases (eg, human immunodeficiency virus [HIV] and tuberculosis).[90] In principle, the same strategy could be applied to CVD risk management.[12] Current strategies require multiple pills for the adequate treatment of CVD risk factors, which often leads to low adherence and poor clinical effectiveness.[91] Because a single drug is frequently insufficient to control blood pressure, control can be better achieved using fixed-dose combinations of blood pressure–lowering drugs, an approach endorsed in European and US hypertension guidelines.[34,36,92] Such a "polypill," containing evidence-based medications including aspirin (for high-risk patients and secondary prevention), statin, and blood pressure–lowering drugs could result in a cumulative risk reduction of 75% in CVD events.[93] Modeling based on the effect on risk factors observed in The Indian Polycap Study (TIPS) 1 and 2 study, such a preparation is estimated to reduce CHD risk by 62% and stroke risk by 48% in moderate-risk populations who are free of CVD.[67,68] A crossover randomized, controlled trial by Wald et al[69] indicated that, in individuals enrolled in a risk factor control program, the risk factor reduction achieved through use of a fixed-dose combination pill is of sufficient magnitude to result in a 60% to 70% relative risk reduction for CVD. The Use of a Multidrug Pill In Reducing cardiovascular Events (UMPIRE) trial has demonstrated that fixed-dose combination therapy significantly improves adherence compared with usual care with individual medications.[70] Finally, a recent publication suggested that lifestyle modification combined with the Polycap could reduce CVD events by as much as 80%, as long as adherence is high (>90%).[12] A 2014 systematic review highlighted improved risk factor control and adherence with a fixed-dose combination cardiovascular medication as compared with placebo or a single drug.[71] Ongoing randomized, clinical trials evaluating the impact of a "polypill" on clinical events are underway.[12] However, the evidence to date supports a combined approach including combination drug therapy, lifestyle modification, and adherence-improvement strategies.

The provision of affordable generic combination therapies containing evidence-based cardiovascular agents could simplify the management of CVD risk and address 2 of the

Table 7. Core List of Medications Required for Implementing Essential Cardiovascular Disease Prevention Interventions in Primary Care, Based on the World Health Organization List of Essential Medicines[88]

Medication	Indication
Aspirin	Primary and secondary prevention (IHD and ischemic stroke)
Clopidogrel	Secondary prevention (IHD and ischemic stroke)
Thiazide diuretic	Hypertension
Calcium channel blocker	Hypertension
Statin	Primary and secondary prevention (IHD and ischemic stroke)
Angiotensin converting enzyme (ACE) inhibitor	Hypertension, primary and secondary prevention (IHD and ischemic stroke), heart failure
β-blocker	Hypertension, secondary prevention (IHD), heart failure
Furosemide	Heart failure
Spironolactone	Hypertension, heart failure, secondary prevention (IHD)
Isosorbide dinitrate, glyceryl trinitrate	IHD
Glibenclamide	Diabetes mellitus
Metformin	Diabetes mellitus
Insulin	Diabetes mellitus

IHD indicates ischemic heart disease.

identified modifiable targets, including hypertension and secondary prevention. Affordable combination drugs are currently unavailable in public health systems in most countries (except in some regions of India and a few Central American countries). This situation limits therapeutic options and complicates prescribing practices. Furthermore, there are increased costs to the patient and health system because more visits to healthcare providers are required to achieve adequate risk factor control. Implementation of a multi-drug strategy has been demonstrated to be cost-effective in LMIC.[94–96] A regimen including a statin, aspirin, and 2 blood pressure–lowering medications to at risk populations in 23 LMIC over 10 years has been estimated to prevent 18 million deaths from CVD at a cost per head of US$1.08 ($0.75–1.40).[94] However, the true costs of the combined medications are higher than previously modeled (ie, US$3.90–7.80 per month in India). This cost is still much less than the costs to patients for purchasing the individual components of the combined medications (ie, US$28.4 in India) and would still be considered cost-effective.[97]

Health System Strategies

Task Sharing With Nonphysician Health Workers, Community Health Workers, and Treatment Supporters

Given the enormous burden of CVD (and the relative simplicity of identifying those with elevated blood pressure or those with known vascular disease) and limitations of current health systems, task sharing with nonphysician health workers (NPHWs) or community health workers (CHWs) may be an effective strategy to achieving the World Health Organization "25×25" goal. Experience in LMIC countries shows that elements of basic chronic disease management can be shifted to NPHW, often with improved outcomes.[98] A systematic review of task-shifting for HIV care in Africa demonstrated that NPHWs offer cost-effective and high-quality care to a higher volume of patients than a physician-centered model.[99] Furthermore, task-shifting has been shown to be a potentially effective and affordable strategy for improving access to healthcare for NCDs.[72] Such a strategy is supported by the World Health Organization Task Shifting-Global Recommendations and Guidelines.[100]

Task shifting or task-sharing has also been used successfully in HIC. It has been demonstrated that nurse-practitioner, nurse, or community health worker-led programs can improve blood pressure, lipids, and HbA1c,[73–75] as well as the management of some chronic conditions.[76] Not only would task sharing be of benefit in LMIC, but it may also be useful in high-risk/low–socioeconomic position areas in HIC because of the increased burden of CVD, vulnerable populations, and limited resources.[3,101] With the use of simplified algorithms for CVD assessment and management as outlined above, combined with appropriate physician oversight and readily available, fixed-dose combination cardiovascular medications, it is likely that task-sharing with NPHWs can be implemented reliably, safely, and effectively in diverse community health settings in LMIC.[86,102,103] Yet, for this to succeed, there is a need to address those factors that prevent their widespread implementation, including concerns regarding safety, clear benefits in health outcomes, difficulties with staff retention, a need

Table 8. Current Gaps in Knowledge Relating to Resource-Effective Strategies to Prevent and Treat Cardiovascular Disease and Suggested Next Steps

Gaps in Knowledge	Next Steps
A. Evidence–practice gaps	
Evidence–practice gaps relating to the prevention and management of CVD in LMIC.	Continued follow-up and further analyses of data from the PURE study and other longitudinal cohort studies in LMICs, expansion and deepening of country/community-based registries, such as those in the INDEPTH Network,[107] strengthening of vital registration systems, and design and implementation of intervention studies in LMIC.
B. Barriers to care	
Barriers to evidence-based and efficient CVD prevention and management in LMIC.	Systematic assessments of barriers to care at the patient, healthcare provider, and health system level in different countries to identify the important contextual factors and to inform resource effective strategies to prevent and manage CVD.
C. Interventions	
Evidence supporting the impact of dietary policies on CVD health in LMIC.	Large-scale studies conducted in LMIC, including descriptive, etiologic, and interventional, where diet patterns substantially differ from HIC, complemented with research on the food environment and food policy, including the effects of trade liberalization.
Strategies to support the implementation of tobacco prevention and control policies (ie, FCTC).	Promulgation and enforcement of laws that control tobacco cultivation, manufacturing, trade, distribution, marketing, taxation, and treatment.
Impact of contextually appropriate, simple, and cost-effective risk stratification and management tools on community-based populations.	Large scale studies across low-, middle-, and high-income countries to evaluate the implementation of WHO-recommended diagnostic and management strategies.
Clinical benefit of fixed-dose combination therapy for the prevention and management of CVD.	Randomized clinical trials evaluating the impact of a "polypill" on clinical events.
Appropriate clinical responsibilities of NPHWs in the prevention and management of CVD.	Large randomized, controlled trials evaluating the effectiveness and efficiency of NPHWs and LHWs in the prevention and management of CVD, with additional studies evaluating the safety of NPHWs prescribing first-line CVD evidenced-based medications.

CVD indicates cardiovascular disease; FCTC, Framework Convention on Tobacco Control; HIC, high-income countries; LHWs, lay health workers; LMIC, low and middle income countries; NPHWs, nonphysician health workers; PURE, Prospective Urban Rural Epidemiology Study; and WHO, World Health Organization.

to re-engineer the health workforce that includes contextualized training of NPHWs to receive a core set of skills in the screening and management of CVD, and policy limiting the NPHW's ability to prescribe from a restricted list of medications. The latter is a significant limitation in many countries.[72] Despite these barriers to implementation, NPHWs could be a cost-effective strategy to overcome identified barriers to best-practice and help achieve the World Health Organization "25×25" goal through improved screening of at risk individuals, counseling, and medical management.

As described above, patient adherence to guideline-recommended medications and lifestyle modification remain barriers to optimal care. However, mechanisms to improve adherence utilized in other chronic conditions (eg, HIV treatment strategies in South Africa) are likely also applicable to CVD risk management. For example, the use of treatment supporters, defined as uncompensated, patient-nominated friends or family who help ensure optimal adherence to recommended therapies and clinic appointment schedules, has been demonstrated to be effective in patients with HIV.[77] Treatment supporters, coached by NPHWs or healthcare providers, could help promote an effective self-management program for patients with or at risk of CVD, thus proving to be an effective strategy in resource constrained settings.[78]

The task-sharing and task-shifting roles, as described above, are only a few suggested components of a more comprehensive strategy toward widening the experience and training of health system personnel. Moving beyond primary-care physicians and specialists to nurses, pharmacists, NPHWs, CHWs, village volunteers, treatment supporters, and community groups is essential to overcome the financial and human resource limitations that plague current health systems. Government policies that move toward universal healthcare, with coverage of essential medications, diagnostic tests, and interventions for CVD care, are essential in minimizing inequities in healthcare.

Finally, although not specific to CVD, a comprehensive health system strategy will also consider the financing of healthcare. Although many of the interventions and policies described in this review will be cost saving, some will require additional revenue. Universal health coverage is now firmly on the international agenda, in particular as a result of its inclusion within the Sustainable Development Goals and the growing recognition of its contribution to international obligations on the right to health.[104] Those advocating for improved prevention and treatment of CVD must therefore necessarily address the issue of healthcare financing, drawing on evidence such as that in a recent study of progress toward universal health coverage that highlighted the crucial role of effective systems of progressive taxation.[105]

Finally, the inclusion of a target for NCDs in the Sustainable Development Goals has provided a powerful stimulus to measure and respond to the so far largely hidden burden of CVD in the poorest countries, in particular those being left behind, as countries such as Pakistan and Bangladesh move from low-income to lower–middle-income status. The PURE Study does include 2 countries still classified in the World Bank's LIC category, Tanzania and Zimbabwe, but further progress will be limited by the simple lack of research capacity, especially in rural areas, in many of these countries, an issue that should now be a priority for research funders.[106]

Summary

CVD accounts for the majority of NCD deaths around the world, with ≈80% occurring in LMIC. A large body of evidence supports the findings in this review. However, there are gaps in knowledge, particularly relating to LMIC. Table 8 outlines the gaps in knowledge relating to resource effective strategies to prevent and treat CVD and suggested next steps to minimize these gaps. Using the evidence available to date, this review has demonstrated that significant evidence–practice gaps in the prevention and management of CVD exist, particularly in LMIC. Targeting key modifiable factors, including tobacco use, hypertension, and secondary prevention of CVD with resource-efficient strategies in at-risk populations within LMIC, coupled with population-level policies, could help achieve and even exceed the projected target of 25% reduction in premature mortality from CVD by 2025 in some countries. Strategies include (1) effective measures for tobacco control, (2) implementation of simplified screening and management algorithms for those with or at risk of CVD, (3) increasing the availability and affordability of simplified and cost-effective treatment regimens including combination CVD preventive drug therapy, and (4) simplified delivery of healthcare through task-sharing (NPHWs) and optimizing self-management (treatment supporters).

Disclosures

Dr Yusuf conducts research on single-pill, fixed-dose cardiovascular combination pharmacotherapy for which the Population Health Research Institute has received grant support from the Canadian Institute for Health Research, the Heart and Stroke Foundation Canada, Wellcome Trust, Cadila Pharmaceuticals Ltd, and Astra Zeneca. Dr Huffman receives support from the World Heart Federation for its Emerging Leaders program, which is supported by AstraZeneca, Boehringer Ingelheim, and Bupa. The other authors report no conflicts.

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