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VIEWPOINT

Polypills

Essential Medicines for Cardiovascular Disease Secondary Prevention?

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In 1977, the World Health Organization (WHO) developed its first Model List of Essential Medicines to guide countries in the creation of national formularies and policies for access, quality, and use of essential medicines as part of achieving the right to health. In 2012, the WHO announced its goal of reducing the number of premature deaths (<70 years) due to noncommunicable chronic diseases by 25% by the year 2025, including the indicator that 50% of eligible people receive drugs to prevent myocardial infarction and stroke. Despite the large body of evidence supporting the use of pharmacological treatment for the secondary prevention of cardiovascular diseases (CVD), substantial gaps in coverage of secondary interventions for prevention of CVD are widespread globally. Fixed dose combination, or polypill, therapy has been shown to improve adherence by 33% compared with usual care in CVD secondary prevention and has been recommended as a "best buy" by the WHO. In November 2012, along with 5 other scientists, we submitted an application to the Model List of Essential Medicines to include polypill therapy for secondary CVD prevention. In July 2013, the updated 18th Model List of Essential Medicines was released without inclusion of polypill therapy for secondary CVD prevention. In this article, we argue that polypill therapy meets the criteria for essential medicines and that inclusion in the Model List of Essential Medicines will facilitate its access and has the potential to avoid a few million premature deaths and related morbidity from CVD at low cost.
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Background to the World Health Organization Model List of Essential Medicines

Access to essential medicines is considered an integral component of the "universal right to the highest attainable standard of health" according to the World Health Organization (WHO) constitution (1946) (1). Medicines defined as essential are "those that satisfy the priority health care needs of the population based on disease prevalence, evidence on safety and efficacy and comparative cost effectiveness" (2). In 1977, the WHO developed its first Model List of Essential Medicines to guide countries in the creation of national formularies and policies for access, quality, and use of essential medicines as part of achieving that right. Access is measured by a combination of price, availability, and affordability with the goal that these medications are "available within the context of functioning health systems at all times in adequate amounts, in the appropriate dosage forms, with assurance quality, and at a price the individual and community can afford" (2). Despite the declaration and acceptance of this right by the international community for more than 35 years, access to essential medicines remains low. In a 2009 analysis of 36 low- and middle-income countries, access to essential medicines for prevention and control of noncommunicable chronic diseases (NCDs) was limited to 36% and 55% in public and private sectors, respectively, compared with 54% and 66% that had access to medications for acute diseases, respectively (3).

WHO "25 × 25" Goal

In 2012, the WHO announced its goal of reducing the number of premature deaths (<70 years) due to NCDs by 25% by the year 2025 (4). This target was preceded by other WHO goals of reducing the burden of premature death and of disability from NCDs, which were formalized as a result of the Political Declaration from the 2011 United Nations High Level Meeting on NCDs. Because cardiovascular diseases (CVD) are the leading causes of mortality in the world and because more than 80% of CVD deaths occur in low- and middle-income countries, CVD treatment and control are crucial for reaching these WHO goals. If current

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trends continue, CVD morbidity and mortality are projected to increase substantially in the coming decades. The CVD secondary prevention with fixed-dose combination, or polypill, therapy has been deemed a "best buy" by the WHO (5), given its efficacy, adherence, scalability, and cost-effectiveness. More than one-half of patients with prior ischemic heart disease or stroke receive no secondary medications, and <10% receive all 3 of the 4 proven medications (antiplatelet agents, statins, beta-blockers, and blood pressure–lowering drugs) (6). This situation is much worse in low-income countries, where more than 3 of every 4 patients with CVD take zero medications (6). Yet the WHO recent indicators to reach its "25 × 25" target include the provision that 50% of eligible people receive drugs to prevent myocardial infarction and stroke.

A large amount of evidence supports the use of pharmacological treatment for the secondary prevention of cardiovascular death in patients with prior CVD events. Antiplatelet agents, beta-blockers, lipid-lowering agents, and angiotensin-converting enzyme inhibitors have all individually demonstrated improvements in mortality and morbidity and are recommended for secondary prevention of CVD by a diverse group of professional organizations. However, substantial gaps in coverage of secondary interventions for prevention of CVD are widespread globally (6). There are numerous reasons for these substantial gaps, which include lack of their value and the importance of lifelong therapy perceived by both physicians and patients, lack and costs of access to health practitioners, lack of availability (stock-outs) of key medications, poor adherence, unaffordable costs of even generic drugs compared with local incomes, and inadequate prescription of medicines. Fixed-dose combination therapy that combines CVD secondary preventive medicines seems to overcome many of these barriers. In particular, fixed-dose combination therapy has been shown to improve adherence by 33% compared with usual care in CVD secondary prevention (7), thus meeting the Model List recommendation that fixed-dose combination therapies should have "a proven advantage in therapeutic effect, safety or compliance over single compounds administered separately" (2). Furthermore, fixed-dose combinations can be less expensive, thereby making them more affordable.

Fixed-Dose Combination, or Polypill, for Secondary CVD Prevention as an Essential Medicine?

In November 2012, we and 5 scientists submitted an application with support from 51 colleagues from 19 countries to the WHO 18th Expert Committee on the Selection and Use of Essential Medicines to recommend that fixed-dose combination, or polypill, therapy be added to the WHO Model List of Essential Medicines for the secondary prevention of CVD (ischemic heart disease and thrombotic stroke). Our application was not accepted on the basis of the recommendations from 2 expert reviewers, 1 of whom suggested that the "Committee needs to decide whether it is willing to make a largely symbolic gesture now, by including one or all of the proposed combinations, while knowing that global access will be slow and that sufficient evidence of efficacy, safety and cost-effectiveness are not as yet at hand" (2).

Abbreviations and Acronyms

CVD = cardiovascular disease

NCD = noncommunicable chronic disease

WHO = World Health Organization

Although fixed-dose combination therapy per se has not been tested for efficacy in secondary prevention of CVD, each of the components has individually demonstrated reduction of mortality and morbidity when given against a background of other proven drugs. Therefore, the benefits of the drugs are additive, and all 4 are recommended by numerous guidelines to be used together. However, these medicines individually and when used in combination have also been shown to be well tolerated. Recent trials indicate that fixed-dose combination therapy reduces lipid levels (through which statins are thought to exert their beneficial effects) and blood pressure (a marker of the effects of angiotensin-converting enzyme inhibitors, beta-blockers, and diuretics) to the same extent as giving each drug separately (an additive effect on the surrogate markers of efficacy), the effects of aspirin on suppression of markers of thromboxane A2 are similar when it is given separately or in combination with the other components of the polypill, and they are well-tolerated (8). Similar or improved efficacy, tolerance, and adherence have been demonstrated both in individuals with prior CVD (compared against the individual components given separately) (7) and in individuals without prior CVD (compared against placebo) (8). Furthermore, the efficacy of fixed-dose combination therapy with other medicines has been demonstrated in populations of patients with other conditions such as acquired immune deficiency syndrome, tuberculosis, and hypertension, thereby supporting the general concept that using drugs in fixed-dose combinations has merit.

Each individual component of fixed-dose combination therapy for CVD prevention has been proven to reduce death, myocardial infarction, or stroke in patients with ischemic heart disease or stroke. The existing data on fixed-dose combination therapy show the combinatorial formulation reduces risk factors to the extent expected if the components were given individually (8–10). Therefore, the current consensus is that the fixed-dose combination therapy should be considered for use in CVD secondary prevention. This conclusion is based on the existing data and the high-risk profile for CVD events in patients eligible for secondary prevention.

Conclusions

Approval for inclusion of the polypill will not just be a symbolic gesture. Instead, it will emphasize to a broad set of

stakeholders the benefits of combination therapy; it could stimulate pharmaceutical manufacturers to commit the necessary resources to develop and test various polypills, and equally importantly, it would encourage regulators in being more flexible in developing a practical pathway to approvals of a polypill. Inclusion of fixed-dose combination therapy in the Model List of Essential Medicines will facilitate its access and has the potential to avoid a few million premature deaths and related morbidity from CVD at low cost. Fixed-dose combination therapy meets the aforementioned criteria for essential medicines, namely priority health care need, safety, efficacy, and cost-effectiveness, and should be included in the WHO Model List of Essential Medicines as part of a comprehensive effort to help achieve the WHO "25 × 25" goal.

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