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EDITORIAL COMMENT

# Polypill Opens a Path for Improving Adherence*

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In September 2011, the United Nations called for concerted efforts to reduce global mortality from chronic noncommunicable diseases (NCDs) (1). In the hopes of achieving this goal, the World Health Organization adopted 9 targets in May 2013 for prevention and control of NCDs to be reached by 2025 in comparison with the rates of mortality and risk factor prevalence estimated for 2010. The overarching target was a 25% reduction in NCD-related mortality in those 30 to 70 years of age, yielding the catchy slogan of "25 × 25" (2). Cardiovascular diseases (CVDs) are the leading contributors to these preventable premature deaths but also have the most proven lifesaving therapies among the NCDs. Thus, the "25 × 25" goal can be attained only if primary and secondary prevention of CVD is effectively provided to those at risk in the decade ahead.

A recent study, which modeled the potential impact of evidence-based interventions targeting 6 risk factors (smoking, alcohol, salt intake, obesity, blood pressure, and blood glucose level) (3), supports this hypothesis. The study found that the goal of "25 × 25" is attainable for CVD if the target related to each of those risk factors is reached. However, that goal will not be accomplished for the larger group of NCDs unless tobacco consumption is reduced by 50% (3). Although lipid-lowering interventions and drug therapy for secondary prevention of CVD were not included in this model, effective delivery of these clinical interventions is essential for reaching the NCD goal.

This message is especially pertinent for low- and middle-income countries (LMICs), which contribute to 80% of all NCD-related deaths and 90% of NCD-related deaths that occur in those younger than 60 years of age. A multicountry cohort study observed that these countries have a higher age standardized incidence of CVD-related events and mortality than high-income countries despite having lower levels of risk factors (4). The importance of efficient health systems, capable of effectively delivering proven drugs and revascularization procedures to people who can benefit from them, was stressed as a major explanatory factor that high-income countries have lower mortality rates despite higher risk factor levels.

Despite the obvious case for prioritized action on secondary prevention, global practice patterns reveal low levels of prescription and adherence (5,6). This is an inexcusable failure of the health care system anywhere but is particularly tragic in LMICs, where many young lives that could be saved are lost because the "lifeguard" of secondary prevention was not deployed. To move secondary prevention from evidence (efficacy) to action (effectiveness), we need to improve practice patterns of providers, enable uptake and adherence by patients, and, crucially, reconfigure health systems to reliably deliver chronic continuous care (7), starting with the primary health care setting.

SEE PAGE 2071

The 2-part FOCUS (Fixed Dose Combination Drug for Secondary Cardiovascular Prevention) study, published in this issue of the *Journal* by Castellano et al. (8), addresses one of the vexing issues of long-term care of patients with CVD: low levels of adherence to multidrug therapy. The initial cross-sectional component of this 5-country study (phase 1) sought to elucidate the determinants of adherence to therapy and identify barriers to continued consumption of lifesaving drugs by patients. The second component

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(phase 2) involved an open-label, randomized, controlled trial to evaluate the effect of a polypill (combining 3 drugs in a single tablet) on both patient adherence to treatment and cardiovascular risk factors, apart from assessing safety and tolerability (8).

The study was conducted in 3 South American countries (Argentina, Brazil, and Paraguay) and 2 European countries (Italy and Spain) with widely varying health systems. Italy and Spain have government-financed universal health coverage and low levels of private health insurance, whereas the 3 South American countries have varying levels of patient co-payments and higher levels of private health insurance as a feature of their mixed health systems. The affordability of CVD drugs also varies widely. The study population comprised men and women 40 years of age and older who survived a myocardial infarction in the previous 2 years.

In phase 1, adherence to 4 prescribed cardiovascular drugs (aspirin, statin, angiotensin-converting enzyme inhibitor, and beta-blocker) was assessed in 2,118 patients. The investigators used a previously validated Morisky-Green questionnaire (with a higher than usual cutoff score of 20 to define "good adherence"). Several patient characteristics were identified as having an adverse influence on adherence: younger than 50 years of age, intake of more than 10 pills per day, complex drug regimens involving nonoral administration of some medications, current smoking, sedentariness, and depression. In addition, sociodemographic determinants (lower levels of education, social support, and insurance coverage) and provider features (general practitioner rather than cardiologist, private clinic rather than public health facility) also had an adverse effect. Although some of these variables were clustered and interactive, an independent negative association with good adherence was observed with younger age, depression, and a complex treatment regimen, whereas a positive association was noted with higher levels of insurance coverage and social support. The average baseline measure of good adherence was 45.5% and ranged widely, from 17% to 50%, across countries.

The trial in phase 2 attempted to address some of these determinants by using a simplified drug regimen of 3 CVD drugs combined in a single polypill. This contained aspirin 100 mg, simvastatin 40 mg, and ramipril in variable doses (2.5 mg, 5 mg, or 10 mg). It did not include a beta-blocker. The polypill was provided to the intervention group, with the dose of ramipril titrated by the physician. The control group was provided the 3 drugs separately. Across the 5 countries, 695 participants from the phase 1 study were drawn for random allocation to the 2 groups.

A critical feature of the trial is that all the drugs were "provided" free of cost and not merely "prescribed" to patients in both groups. This was essential, because the primary research question related to whether the polypill would result in better adherence than is now achieved with separate pills. To answer this, the potential impact of vagaries such as affordability and variable insurance coverage had to be removed from the trial design. If the polypill indeed improves adherence due to greater patient acceptance, unencumbered by issues of affordability, the health system can then devise other methods to eliminate or minimize those barriers through universal coverage, price control, or other effective market interventions. To measure good adherence, the trial used the Morisky-Green questionnaire score of $\geq$20 (as in phase 1) and, in addition, a pill count.

The FOCUS trial found that the 3-drug polypill improved adherence on 9-month follow-up (50.8% vs. 41% on an intention-to-treat analysis and 65.7% vs. 55.7% in a per-protocol comparison). However, no significant differences were observed between the 2 trial arms in either the measured values of mean systolic blood pressure and low-density lipoprotein cholesterol (LDL-C) or rates of adverse events and death. Thus, while the primary endpoint of better adherence was met, the impact of that on improved health outcomes (intermediary risk factors or definitive CVD events) could not be shown in a trial of this size and duration. A double-blind trial of a polypill (Polycap, Cadilla Pharmaceutical Ltd., New Delhi, India) also had earlier shown an improvement in CVD risk factors equivalent to active separately administered drugs, except in the case of LDL-C, where the polypill had a lower effect than the separately administered simvastatin (9).

Previously, improved adherence to a polypill strategy for prevention of CVD was shown in the UMPIRE (Use of a Multidrug Pill in Reducing Cardiovascular Events) trial (33% higher than usual care). This trial, which randomized 2,004 participants with established CVD or at a high risk for CVD, used a 4-drug fixed combination in 2 variants: one containing 75 mg aspirin, 40 mg simvastatin, 10 mg lisinopril, and 50 mg atenolol and the other a combination of 75 mg aspirin, 40 mg simvastatin, 10 mg lisinopril, and 12.5 mg hydrochlorothiazide. At 15 months of follow-up, small but statistically significant differences were observed in systolic blood pressure and LDL-C level. Again, no significant differences were observed in serious adverse events or cardiovascular events (10). In this study, the intervention group had a free supply of either polypill, whereas the control group encountered affordability barriers under usual

care. Methodologically, the FOCUS trial provides a better test of the effect of a polypill on adherence, independent of the impact of affordability.

What are the implications for clinical practice? The polypill, on its own, improves adherence. If other barriers to adherence also are removed or lowered (through improved affordability and social support as well as treatment of comorbidities such as depression), there are likely to be even higher benefits. While a fixed-dose combination is attractive for ease of prescription, an opportunity for dose titration would be appealing to the physician. The FOCUS trial has attempted to provide both features in its polypill. The UMPIRE trial tested 2 polypills, with potential for choice customized for different types of CVD (with beta-blocker for post-myocardial infarction patients and diuretic substituted for post-stroke/transient ischemic attack patients). It appears that a family of polypills will soon emerge for reducing high CVD risk. This has to be kept small if physician practice is to be aided by clarity and not eroded by confusion. Meanwhile, larger trials will need to be conducted in relatively homogeneous populations to show an impact on risk factors as well as CVD events.

The implications for health systems are even more obvious. All efforts must be made to ensure that people with CVD or at high risk for CVD are covered by lifesaving CVD drugs and that adherence is promoted through multiple complementary interventions. The polypill is a useful contribution that can enhance the success of those efforts. Pooled public procurement by the health systems of LMICs of quality-assured, generically produced, price-controlled polypills will improve their availability and affordability, especially when distributed at no cost or low cost at public health care facilities. This is already happening for human immunodeficiency virus/acquired immunodeficiency syndrome, tuberculosis, and malaria. Given the huge health, economic, and social burdens imposed on LMICs by preventable CVD-related death and disability, the World Health Organization and LMICs must now accord the same status to the provision of lifesaving CVD drugs (11–13). Along with multisectoral policies that act at the population level to prevent the acquisition or augmentation of CVD risk factors ("poly-policy"), the polypill can help us reach the "25 × 25" goal.

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