A Polypill Strategy to Improve Global Secondary Cardiovascular Prevention
From Concept to Reality

José M. Castellano, MD, PhD,* Ginés Sanz, MD, PhD,† Antonio Fernandez Ortiz, MD, PhD,‡ Ester Garrido, BSc,§ Sameer Bansilal, MD, MS,∗ Valentin Fuster, MD, PhD*†

ABSTRACT

The prevention of cardiovascular disease (CVD) by using a polypill has gained increasing momentum as a strategy to contain progression of the disease. Since its initial conception just over a decade ago, only a handful of trials have been completed assessing the efficacy and safety of this innovative concept. The results of these trials have supported the viability of the polypill in CVD prevention and management, albeit with a few caveats, essentially related to the lack of evidence on the effect of the polypill to effectively reduce cardiovascular events. The polypill has the potential to control the global health epidemic of CVD by effectively reaching underdeveloped regions of the world, simplifying healthcare delivery, improving cost-effectiveness, increasing medication adherence, and supporting a comprehensive prescription of evidence-based cardioprotective drugs. Major trials underway will provide definitive evidence on the efficacy of the polypill in reducing cardiovascular events in a cost-effective manner. The results of these studies will determine whether a polypill strategy can quell the burgeoning public health challenge of CVD and will potentially provide the evidence to implement an effective, simple, and innovative solution to restrain the global CVD pandemic. (J Am Coll Cardiol 2014;64:613–21) © 2014 by the American College of Cardiology Foundation.

Noncommunicable diseases have surpassed communicable diseases as the world’s major disease burden, with cardiovascular disease (CVD) remaining the leading global cause of death, accounting for 17.3 million deaths per year, a figure that is expected to grow to 23.6 million by 2030 (Fig. 1) (1,2). The overall aging population (projected to almost double by 2060 in Europe and the United States) (3) and improving survival of patients with coronary heart disease (CHD) have created a large pool of patients eligible for secondary prevention.

The administration of cardiovascular (CV) medications (e.g., statins, antihypertensive agents, antithrombotic agents) remains the most common medical intervention for secondary prevention of CVD, estimated to be responsible for one-half of the overall 50% observed reduction in mortality from coronary artery disease over the past 20 years in some Western countries (4). This tremendous reduction in mortality has been achieved despite patients not receiving the most comprehensive, proven benefit of contemporary medical therapies.

Recent data highlight the massive treatment gap and room for improvement in secondary prevention on a global scale. The PURE (Prospective Urban Rural Epidemiology) study showed that among participants with a history of CHD or stroke, only 25% were taking antiplatelet drugs, 17% were taking beta-blockers,
20% were taking angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, and 15% were taking statins 5 years after their event (5). In low- and middle-income countries (LMIC) within the same study, the use of these drugs was as low as 3%. A recent meta-analysis of >375,000 patients estimated adherence to CV medications at 2 years at 57% (6,7).

Rates of compliance with lifestyle modification and adherence to prescribed medications are alarming. More than 50% of patients, on average, decide to abandon their prescribed treatment, and the objectives to improve habits (quit smoking, lose weight, or engage in physical activity) are met by an equally low or lower percentage (8). Beyond the impact non-adherence has on individual health, it carries a huge economic cost because it is associated with a failure to achieve therapeutic goals, higher rates of hospitalization, and greater incidence of death. Reasons for nonadherence to pharmacological therapy are complex and have been studied in-depth (8-10). Most of the reasons for suboptimal adherence can be grouped into 4 categories: patient-, illness-, provider-, and system-related factors (Central Illustration, Table 1).

Taken together, these considerations lead to ineffective CV prevention and a missed opportunity for reducing CVD. One novel strategy seeking to address adherence is the use of a fixed-dose combination (FDC) polypill. Incorporating the key medications necessary to reduce CV risk into a single, once-daily dose pill could increase use of an effective, inexpensive therapy, thereby lowering costs and improving treatment adherence (11). The concept of the polypill approach was introduced more than a decade ago and has slowly progressed from a conceptual debate to a therapeutic reality. Some of the scientific community’s initial skepticism was due to the sweeping proposal from Wald and Law (12), who claimed that a polypill including 6 active components administered to every individual older than 55 years of age would reduce the incidence of CVD by >80%. This “vaccination approach” has never been tested in a large population, and its efficacy, potential adverse effects, and cost-effectiveness would need to be assessed. Subsequently, the indication of the polypill has been suggested in primary prevention, specifically in individuals without previous CVD, with no indication for statins or blood pressure (BP)-lowering drugs, but who are at an overall high risk of CV events. The efficacy of this strategy is currently being tested in 2 large randomized trials. Finally, this third approach, the so-called “substitution approach,” would use the polypill in patients already taking cardioprotective drugs for secondary prevention. The rationale is straightforward: by improving adherence to treatment, availability, and efficiency, the polypill might serve as a strategy to improve risk factor control and ultimately decrease CV events on a global scale (13). Several trials have tested the effect of this adherence approach, with promising results. To date, however, no large randomized controlled trial (RCT) has been conducted to study the effect of the polypill strategy on event recurrence.

Evidence is available on the efficacy, safety, tolerability, and affordability of FDC polypills for the primary and secondary prevention of CVD.

**PRIMARY PREVENTION.** Several pilot studies have demonstrated the feasibility of the primary prevention strategy (14-17). The large, Phase II randomized TIPS-1 (Indian Polycap Study-1) assessed the effects of different pills containing either single agents or combinations of drugs to measure their effect on risk factors, such as BP and low-density lipoprotein cholesterol (LDL-C) (18). The Phase II study also evaluated the feasibility and tolerability of administering a single pill to a relatively unselected group of patients (characterized by having at least 1 CV risk factor). Patients randomized to the polypill group exhibited BP reductions similar to those assigned to 3 BP-lowering drugs and lower LDL-C reductions compared with those receiving simvastatin alone. Of interest, tolerability of the polypill was similar to that of other treatments, regardless of the number of active components in the 1 pill.

The PILL (Program to Improve Life and Longevity) study reported similar findings in 378 subjects with no indication for any component of the polypill and an estimated 5-year Framingham risk score of >7.5%; they were randomized to receive a polypill containing aspirin 75 mg, lisinopril 10 mg, hydrochlorothiazide 12.5 mg, and simvastatin 20 mg or placebo for 12 weeks (16). Over 12 weeks, polypill treatment reduced systolic BP by 9.9 mm Hg and LDL-C by 0.8 mmol/l, translating to a 60% long-term reduction in risk for both CHD and ischemic stroke. However, adverse effects (58% in the treated group vs. 42% in the placebo group) and a drug discontinuation (23% in the polypill arm vs. 18% in the placebo arm) were concerning.

Wald et al. (19) tested a polypill containing half-standard doses of 3 antihypertensive agents (amlodipine 2.5 mg, hydrochlorothiazide 12.5 mg, and losartan 25 mg) and a standard 40-mg dose of