DEBATE

Polypill *Is* an Important Strategy for the Prevention of Cardiovasacular Disease Risk

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Cardiovascular disease burden and polypill

While the cardiovascular disease (CVD) burden has decreased in developed countries, it has exponentially increased in low- and middle-income countries (LMICs). It is estimated that by 2020, 80% of the burden of CVD will occur in LMICs (1). The decrease in developed countries has been attributed to reduction in risk factors, early detection and effective care. The increase in LMICs is largely due to rapid urbanization and poor health care systems.

The polypill, a multiconstituent combination pill containing blood pressure lowering agents, a statin, antiplatelet agent, and folic acid, was hypothesized to prevent 80% of cardiovascular events (2). Nine modifiable risk factors accounted globally for over 90% of the total population attributable risk (PAR) for an acute myocardial infarction (3) or stroke (4). Importantly, CVD risk factors are ubiquitous. In the INTERHEART study (3) conducted in 52 countries in all regions of the world, 99% of the controls had at least one CVD risk factor. To contain this global pandemic, a revolutionary strategy is called for.

Approaches to Prevention

There are two approaches to prevention: at the individual and at the population levels (5). In the *individual level approach*, individuals at risk are screened and if needed treated. The advantage is a favorable benefit–risk ratio, but involves costs for screening, and has limited potential for the population at large. This strategy is less likely to be successful in the long run, as "at risk" individuals need to change their behavior in contrast to those around them.

The *population level approach* involves the shift of the mean levels of risk factors exposure of entire populations in a favorable direction. This radical strategy has large potential for change in the population and is considered behaviorally appropriate. A good example is the change effected in the diet in North Karelia in the 1970s in Finland (6). This strategy, although radical, is acceptable to all and does not exert pressure on individuals to change.

The Impact of CVD Risk Factor Modification

There is a clear graded relationship between blood pressure (BP) and serum cholesterol with CVD. Therefore reducing BP and serum cholesterol from *any* level has potential benefits, which is more pronounced in those at higher risk (advancing age or in individuals with multiple risk factors) (7).

The currently accepted strategy is to start treatments [lifestyle modification (LSM) or drugs] only over a predetermined threshold for a risk factor. The average "normal" BP and serum cholesterol have shifted considerably compared to known values in the past (7). This shift is clearly due to the environments people are living in and the prevalent lifestyle. Mortality from IHD and strokes doubles with every 8 years of increasing age. There is a strong case to reduce risk factor levels well below the "normal values." Preventive strategies must therefore be implemented at an early age irrespective of risk factor threshold or presence of disease.

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CVD Risk Factor Modification with Lifestyle Intervention

Present approaches to LSM even among motivated people are unlikely to bring about the required reductions in risk factors at the population level (8). Moreover physician's knowledge and skills on how to implement sustained changes in lifestyle are inadequate, even in developed countries (9).

Do lifestyle interventions work?

In the Nurses' Health Study (8) at the end of follow-up, only 3% of the 84,129 women were in the low-risk category. A systematic review and meta-analysis (10) evaluated the effects of LSMs through individual counseling and education. The absolute reductions (95% confidence interval) in systolic and diastolic BP and blood cholesterol were -3.6 mmHg (-3.9, -3.3 mmHg), -2.8 mmHg (-2.9, -2.6 mmHg), and 0.07 mmol/L (-0.8, 0.06 mmol/L), respectively. The pooled odds ratio for risk reduction of total mortality was 0.96 (0.92, 1.01) and that for CHD mortality was 0.96 (0.89, 1.04). This review suggests that lifestyle interventions through counseling or education produces only modest changes in risk factors and has a limited effect on mortality.

We therefore need to explore more effective strategies to implement LSM. On a more urgent basis, to contain the burgeoning epidemic of CVD, especially in developing countries, we must explore more effective alternative approaches (i.e., drug therapy) for primary and secondary prevention.

Drugs for CVD prevention

Three categories of drugs namely BP-lowering, lipid-lowering, and anti-platelet drugs have been well proven in reducing CVD events in secondary prevention while the former two demonstrate benefits in primary prevention as well. In spite of strong evidence for a few decades now, the use of these therapies is suboptimal even in high-income countries (11–13) and even lower rates in LMICs (14).

For primary and secondary prevention of CVD, individuals must take several drugs lifelong. Adherence is a significant problem especially in LMICs and for those without universal health insurance coverage. A fixed dose combination (FDC) is a strategy that could improve adherence by reducing costs and the pill burden. Combining drugs that act by different mechanisms to modify the same physiological parameter is an attractive option. This is because lower doses of multiple drugs that act through different mechanisms will have greater effect with lower rates of adverse events as seen with for BP-lowering drugs (2). A systematic review demonstrated that FDCs improved adherence that in turn improved outcomes in a range of settings (15). Thus it is clear that taking all proven therapies in appropriate patients can result in greater reduction in CVD events and death than utilizing only some of these agents.

The polypill concept for CVD prevention

For secondary prevention, Yusuf proposed a four-drug combination of aspirin, beta-blocker, statin, and ACEI and estimated that their use would result in a cumulative risk reduction of 75% in CVD events (16). Wald and Law in 2003, after a more extensive analysis (2), proposed a polypill involving a six-drug combination that could potentially reduce IHD events by 88% and stroke by 80%. The six-drug combination contained three BP-lowering drugs at half doses (thiazide, beta-blocker, and ACEI), aspirin, a statin, and folic acid. They argued that this pill could be given to anyone over 55 years without measurement or monitoring of risk factors as well as to all individuals with a CVD event. They estimated that adverse effects with this polypill would occur only in about 8% of treated subjects, with most due to aspirin. Importantly all the drugs used in the proposed polypill have been in use for over a decade with acceptable rates of adverse effects at standard doses.

International health authorities and funding agencies such as the World Health Organization, Centers for Disease Control, the Wellcome Trust, and the National Institutes of Health have encouraged the testing of the polypill. In response, several groups around the world are in different stages of research (17).

Secondary prevention

The Prospective Urban Rural Epidemiologic (PURE) cohort study (14) included over 150,000 subjects from 17 countries of whom 5650 had coronary heart disease event and 2292 had stroke. Overall, few individuals with CVD took antiplatelet drugs (25.3%), beta-blockers (17.4%), ACE inhibitors or ARBs (19.5%), or statins (14.6%). Use in high-income countries was as follows: antiplatelet drugs 62.0%, beta-blockers 40.0%, ACE

inhibitors or ARBs 49.8% and statins 66.5%. The use in low-income countries was abysmally low at 8.8%, 9.7%, 5.2% and 3.3%, respectively. Other studies (18,19) also recorded less than optimal use of EBMs in different regions of the world. The reduction in the burden of CVD in developed countries is largely attributed to the use of EBMs. The polypill is certainly a clear strategy to improve the use of EBMs in secondary prevention.

Primary prevention

The use of the polypill for primary prevention is presently arguable. Let us consider primary prevention from two perspectives: high-risk primary prevention and moderate- to low-risk primary prevention. Wald and Law argued against stratifying people by risk factor levels and recommended using just age (above 55years) as sufficient indication for life-long use of a polypill (2). The polypill cannot be recommended for use in low- to moderate-risk primary prevention as evidence on long-term effectiveness is as yet unavailable.

There is a growing and ongoing body of research establishing the efficacy and safety of polypills. We recently completed a 12-week trial in a primary prevention population and demonstrated efficacy on physiological parameters and very good safety (20). In a secondary prevention population too we demonstrated similar findings (World Congress of Cardiology, April 2012; abstract number P-282). In both of these trials we estimated about a 50% reduction in clinical events. Presently we are evaluating the impact of a polypill strategy in moderate risk population on hard clinical events over 5 years (TIPS-3; 7500 patients, 5–10 countries, 5 year follow-up; funded by the Wellcome Trust, UK). Other groups around the world too are in different stages of evaluating different versions of the polypill (17). We are shortly completing the HOPE-3 trial with over 12,000 patients globally and over 1800 in India. In this trial we are evaluating rosuvastatin and candesartan/ hydrochlorothiazide in a factorial design in those with average BP and cholesterol levels and without vascular disease. The outcomes are major CVD events and effects on cognition and renal parameters over 5 years.

Given the rapidly rising burden of CVD globally and especially in developing countries, what should be our approach to the use of a polypill in primary prevention? With the evidence already available, a polypill must be used in a high-risk primary prevention population. On the other hand, in low- to moderate-risk primary prevention, it must be more carefully considered and not as yet widely used until clinical trial evidence is available. We can consider it for those who are unlikely to be adherent to multiple drugs (forgetfulness), without support for regular doctor visits and prescription refills and for whom cost for multiple drugs is a constraint.

More importantly, use of the polypill must be an integral part of an overall strategy for CVD prevention. From the patients' perspective, education on LSM and the need for regular medications is essential. From a larger perspective that should involve caregivers and the government, we must address comprehensive prevention strategies. These should include wider educational efforts, environmental modifications, and governmental level health policy changes.

Issues with the polypill

One objection is the fear that the polypill will be used instead of LSM and the community will be unnecessarily "medicalized." It has always been clear that LSM remains an essential part of a strategy for prevention of CVD. The polypill is an important complement to LSM. The time saved in prescribing and explaining about one pill instead of four or five will give physicians more time to counsel the patient on issues like LSM and adherence to medications.

Can one size fit all, and should we not carefully choose the drugs and titrate the doses for each patient? This is traditional thinking and applies to many clinical situations. Considering what we are presently facing with CVD, an innovative strategy must be seriously planned and carefully implemented. We agree that there will not be just one polypill for all patients. Eventually different versions of a polypill will be available for those with uncontrolled hypertension, diabetes, asthma, etc., with appropriate drug combinations, e.g., higher dose of an anti-hypertensive, adding a calcium channel blocker in place of a beta-blocker for hypertension or metformin for diabetes, or avoiding a beta-blocker for those with

asthma. But at the same time we should not have myriad combinations that will take away the simplicity of the polypill strategy.

A major limitation that the polypill strategy faces is the inherently low profit margin for pharmaceutical companies. This is because all the drugs in a polypill should be off-patent to make it affordable and large pharmaceuticals do not see appropriate profits in this strategy. The enthusiasm for aggressive marketing and persistent lobbying with the government and regulators is lacking. We therefore need academicians and well-meaning physicians to take a fresh look at this issue.

Conclusions

In summary, to adequately deal with the largest killer in the world, especially in LMICs, we need a comprehensive and a radical strategy. This year marks a decade since this revolutionary concept was mooted. Research to date has provided evidence on the feasibility, physiological efficacy, and importantly the safety in short-term studies. Presently there is a clear case to widely use the polypill in secondary and high-risk primary prevention. Pragmatic trials are ongoing to evaluate the role of the polypill in low- to moderate-risk primary prevention and in secondary prevention.

Diseases that have reached epidemic proportions globally need revolutionary and comprehensive approaches. Polypill is one such approach. Critics of this strategy need to consider that a polypill is not just a bunch of drugs in a FDC, but rather as an important and comprehensive strategy for CVD prevention that cannot be ignored anymore.

Conflicts of interest

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