DEBATE

Polypill for Primary Prevention: Against the Basic Tenet of Evidence-based Medicine!

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Science is facts; just as houses are made of stones, so is science made of facts; but a pile of stones is not a house and a collection of facts is not necessarily science.
Henri Poincare
French mathematician & physicist (1854–1912)

A pill refers to anything small and round for a specific dose of medicine. The term is used colloquially in several ways. A polypill is a medication that is a combination drug of multiple active ingredients, and that is aimed to be consumed widespread in the population, even currently healthy ones, as a means of preventive medicine. It usually contains three or more active ingredients, with the intention of reducing the number of tablets or capsules (generally orally administered) that need to be taken, which in turn may facilitate handling and administration of the drug. The dosages are usually relatively low compared to what is administered to people already having disease or significant risk factors. The concept of polypill is not new and debates have taken place for long to manufacture polypills for a variety of disorders like tuberculosis, hypertension, and dyslipidemia. Reduced cost, convenience, and compliance have been the major factors driving this concept. Some proposers have claimed incremental synergy among components than mere addition of benefits. Two-drug combinations have gained significant popularity for management of hypertension, dyslipidemia, and diabetes. Even several three-drug combinations have been approved world-over for management of hypertension and FDA in United States has approved triple-drug combos.

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Primary prevention by controlling risk factors reduces myocardial infarction (MI), stroke, and heart failure, decreases the need for coronary revascularization procedures, and extends and improves the quality of life. Primary prevention by use of a polypill in a high-risk population is as innovative as a vaccine to prevent outbreaks of epidemics long for prevention of multifactorial vascular disease in a population with variable risk. Theoretically, the concept is appealing but there is no single large outcome trial to show that the idea works in the population at large and that too on a long-term basis, although the trials are on way. Several polypill formulations have been developed and have demonstrated the short-term feasibility, safety, and efficacy (in reducing risk factor levels) of a polypill in individuals at moderate risk but there are no data for hard end-points and long-term safety and efficacy. In science, mechanistic approach does not always work and sometimes surprising results are seen for a very plausible and rational approach. Thus, proof of concept is not proof of evidence and evidence-based medicine is what we practice in modern times. Primary prevention needs a systematic, comprehensive, multidisciplinary approach and not a quick-fix. Here is a somewhat contrarian critique with regard to use of polypill as a population-based strategy to prevent and control the epidemic of cardiovascular diseases and why this may not succeed.

Cardiovascular disease accounts for nearly one-third of all adult deaths in India (1–2). Population-based studies indicate that stroke as the cause of death is as prevalent as coronary heart disease at least in rural area (1). Prevalence of stroke is nearly twice in rural India compared to the Western world. Dyslipidemia accounts for majority of cases of coronary heart disease (3) while arterial hypertension is the single-most important risk factor for stroke (4). Premature vascular disease

is preventable. Dyslipidemia and high blood pressure are largely responsible for vascular risk. Hemorrhagic stroke is more prevalent in India compared to the Western world and this has implications with regard to use of aspirin for primary prevention (5). Use of cardio-protective agents for secondary prevention in India is dismal (1). Polypharmacy, cost, and complexity of regimen could be reasons for such data. Knowing the prevalence of risk factor profile of the population is necessary to design primary preventive strategies. Direction of trends in India is unfavorably poised toward worsening. Recent trends of risk factor prevalence in India are sparse. The Indian Sentinel Surveillance Study (ISSS) of industrial workers (6) has shown that nearly 30% of the subjects above the age of 50 years have short-time high risk while 70% of the subjects had life-time high risk. Limited epidemiological studies also show progressive deterioration in the blood pressure profile although near-static values for various lipid parameters (7–9). Such data are in line with that reported from the Western world and hence population-targeted strategy for primary prevention of vascular events cannot be very different for the Indians. Threshold of age beyond which primary preventive strategies need to be implemented has to be lower in India in view of higher prevalence of vascular disease (1). There is huge potential to lower cardiovascular mortality and morbidity in the society. There is a persuasive argument that those who are unfortunate enough to be unable to reduce their risk burden by lifestyle modification deserve convenient pharmacotherapy to do so. However ISSS also states that nearly one-third of subjects above the age of 50 years have low short-term as well as life-time risk and would be treated unnecessarily by a polypill were that become a reality.

Origin of this one-in-all polypharmacy for prevention of omnipresent vasculopathy is less than a decade old. In 2003, Nicholas Wald and Malcolm Law coined the term "polypill" and proposed the concept of combining six medications that have been used for decades to treat cardiovascular disease and providing this to all people with cardiovascular disease and those in Western countries aged 55 years or more (10). The basic idea behind the proposal was to reduce LDL-C (with a statin) and systolic blood pressure (with diuretic, beta-adrenergic receptor blocker, and an ACE-inhibitor) which are both suboptimal in vast majority of subjects above the age of 55 years and contribute significantly to cardiovascular mortality and morbidity. In addition, they proposed (without any reasonable and valid data) that aspirin as antiplatelet therapy and folic acid as antioxidant therapy would reduce vascular events significantly. They combined the numerical results from several meta-analyses of the individual effects of these medications to produce an estimate of the overall combined effect on morbidity and mortality. In their paper A strategy to reduce cardiovascular disease by more than 80% (10), Wald and Law postulated that by using a combination of these well-known, cheap medications in one pill (the "polypill") would be a particularly effective treatment against cardiovascular disease. They presented a statistical model which suggested that widespread use of the polypill could reduce mortality due to heart disease and strokes by up to 80%. The treatment is potentially cheap, with few side-effects (in perhaps 10–15% of recipients) and the research was based on data from many trials relating to the individual components. This was a hypothesis whose time obviously had come. Feasibility and safety studies have been done in small populations with somewhat positive results (11,12). Subsequent studies have cast doubts on the primary preventive efficacy of aspirin (13–15), folic acid (16–18), and beta-blockers in apparently healthy persons (19) but with one or more risk factors and hence the renewed debate. Several meta-analyses have shown relatively weak effect of beta-blockers to reduce stroke and the absence of an effect on coronary heart disease when compared to placebo (20). Recent evidence argues against universal cardio-protective properties of beta-blockers but attest to their usefulness for specific cardiovascular indications. Folic acid was quickly dropped off the list for lack of evidence. Aspirin, however, still constitutes an important component of polypill and hence its role needs to be examined in greater detail. Dropping it off altogether may not be such a bad idea.

Several meta-analyses have focused on determination of the effectiveness of aspirin in primary prevention of vascular disease. Nine randomized trials have evaluated the benefits of aspirin for the primary prevention of CV events: the British Doctors' Trial (BMD), the Physicians' Health Study (PHS), the Thrombosis Prevention Trial (TPT), the Hypertension Optimal Treatment (HOT) study, the Primary Prevention Project (PPP), the Women's Health Study (WHS), the Aspirin for Asymptomatic Atherosclerosis Trial (AAAT), the Prevention of Progression of Arterial Disease and Diabetes (POPADAD) trial, and the Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes (JPAD) trial (14,15). The combined sample consisted of about 90,000 subjects divided approximately evenly

between those taking aspirin and subjects not taking aspirin or taking placebo. A meta-analysis of these nine trials assessed six CV end-points: total coronary heart disease, nonfatal MI, total CV events, stroke, CV mortality, and all-cause mortality. The meta-analysis suggested superiority of aspirin for total CV events and nonfatal MI ($p < 0.05$ for each), with nonsignificant results for decreased risk for stroke, CV mortality, and all-cause mortality. Thus, primary prevention with aspirin modestly decreased the risk for total CV events and nonfatal MI, but there were no significant differences in the incidences of stroke, CV mortality, all-cause mortality, and total coronary heart disease. Hemorrhagic stroke shows an upward trend and this has implications in India. However most recent meta-analysis casts doubt on the use of aspirin for primary prevention of MI (15). At least, women seem not to benefit unless at very high risk (13). There are other unresolved issues that cast doubts on its eligibility as a component of polypill like aspirin resistance, the COX-2 inhibitor risk controversy, and possible adverse aspirin-ACE-inhibitor interaction.

Several polypill concoctions contain hydrochlorthiazide (HCTZ). However, there is no evidence that HCTZ in its usual dose of 12.5–25 mg daily reduces MI, stroke, or death (21). In fact, Messerli and his group have called it more of a fad or folly to use hydrochlorthiazide as an anti-hypertensive agent. Indapamide or chlorthalidone probably could be better partner for this multicomponent strategy. Statins are beneficial in high-risk subjects and these have the most convincing data. However, the benefits are smaller in low-risk subjects with greater uncertainty regarding adverse effects and quality of life due to mild chronic myositis. Of all the components of polypill, statins provide relatively consistent proof of risk reduction but there are inconsistencies and gaps in our knowledge in several subgroups and also the effects are demonstrable only for modest duration of therapy. Will the favorable effects taper off or magnify with time is anybody's guess. ACE-inhibitors were shown to be of value for high-risk primary prevention in an era wherein use of statins was limited. Many secondary prevention trials like PROGRESS for stroke recurrence prevention and PEACE (stable CAD) showed very modest benefits of ACE-I in well-treated subjects. It does appear that benefits of ACE-inhibitors may have been overestimated by Wald and Law and the statistical model may be flawed.

To an inquisitive mind, there are more questions than answers in this simple strategy. From past experience, one can say that simple, neat, and plausible approaches are usually wrong but not always. Recommending a polypill for the entire older adult population would, however, include many individuals without the multiple risk factors targeted by its components, putting them at risk for drug-related side-effects and responsible for the costs of a medication from which they would not derive benefit. However, we cannot dismiss an idea which has the potential to change our lives. Such an approach needs thread-bare discussion with critical analysis of every aspect. I have following questions in my mind, which would need to be answered over time:

1. Composition of polypill keeps varying. What should be the ideal polypill?
2. Should it be full-dose or half-dose with regard to ramipril (or anyother ACE-I) and a statin? Larger doses have incremental benefits but small doses may be ineffective.
3. Is aspirin in primary prevention an effective strategy?
4. Are there data to suggest that beta-receptor blocking drugs and diuretics work in primary prevention?
5. Is not hydrochlorthiazide a paltry antihypertensive with no outcome data even in secondary prevention trials?
6. Will the benefits stack-up? Are there imponderables which shall not allow additive beneficial effects?
7. What shall be the long-term compliance, given the increased incidence of cough with ramipril among orientals?
8. What shall happen to flexibility if a given risk factor is not adequately controlled by a polypill? Should you be happy with less than ideal blood pressure or LDL-C level in a middle-aged person who is on this polypill?
9. As the polypill contains three antihypertensive drugs, should all patients whose blood pressure is still above 140/90 mmHg on polypill be labeled "resistant hypertension"?
10. Which statin shall be used in those whose LDL-C is still above the target ¬– the same as in polypill or a different one?
11. In light of JUPITER trial, can an effective statin in

modest doses be an ideal monopill discarding the idea of a ploypill if the goal is to achieve about 60% reduction in vascular events in primary prevention?

12. Is it a correct approach for 80% risk reduction? Polypill does not target many major and minor risk factors like smoking, diabetes mellitus, obesity, poor nutritional practices and sedentary behavior.

13. What about super-additive diabetogenic effects of beta-blockers and diuretics in the long run in a highly insulin-resistant population as in India?

14. Is risk reduction by a polypill overestimated, since a threshold is currently not existing in all drugs and side-effects and interactions are possible?

15. Is age alone an effective and a simpler means of selecting people for preventive treatment using the polypill? In that case why bother about risk stratifying and just medicalize the preventive strategy for all above a certain age.

16. Are we sure about the acceptability of multi-component pill by the patient, physician, society and regulatory bodies?

17. Should we pit a polypill against a polymeal as suggested by Franco and colleagues to reduce cardiovascular disease by as much as 76%? The authors hypothesized that the polymeal promises to be an effective, nonpharmacological, safe, cheap and tasty alternative to reduce cardiovascular morbidity and increase life expectancy in the general population.

18. Will poypill convert a high-risk population to low-risk one (from an epidemic to an endemic)? Are there known unknowns and unknown unknowns in the prevention of cardiovascular disease?

19. Do we understand all the challenges of healthy individuals taking a preventive medication for nearly 30 years? Are not there issues of stigma, anxiety or inconvenience?

20. Data from rural Andhra Pradesh (1) suggest similar or higher prevalence of cardiovascular mortality as in Urban USA adults but in India vascular disease antedates by 10 years. Hence, should polypill be started at age 45 years in countries like India? This would put a much larger population on medication with important economic and societal consequences.

References

1. Joshi R, Chow CK, Raju PK, Raju R, Reddy KS, Macmahon S, Lopez AD, Neal B. Fatal and nonfatal cardiovascular disease and the use of therapies for secondary prevention in a rural region of India. Circulation. 2009; 119(14):1950–1955.
2. Srinath Reddy K, Shah B, Varghese C, et al. Responding to the threat of chronic diseases in India. Lancet. 2005; 366:1744–1749.
3. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, McQueen M, Budaj A, Pais P, Varigos J, Lisheng L; INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): Case-control study. Lancet. 2004; 364(9438):937–952
4. O'Donnell MJ, Xavier D, Liu L, et al. Risk factors for ischemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): A case-control study. Lancet. 2010; DOI:10.1016/S0140-6736(10)60834-3.
5. Banerjee TK, Das SK. Epidemiology of stroke in India. Neuroloy Asia. 2006; 11:1–4.
6. Jeemon P, Prabhakaran D, Huffman MD, Ramakrishnan L, Goenka S, Thankappan KR, Mohan V, Joshi PP, Mohan BV, Ahmed F, Ramanathan M, Ahuja R, Chaturvedi V, Lloyd-Jones DM, Reddy KS; Sentinel Surveillance in Industrial Populations Study Group. Distribution of 10-year and lifetime predicted risk for cardiovascular disease in the Indian Sentinel Surveillance Study population (cross-sectional survey results). BMJ Open. 2011 Jan 1; 1(1):e000068.
7. Gupta R, Guptha S, Gupta VP, Agrawal A, Gaur K, Deedwania PC. Twenty-year trends in cardiovascular risk factors in India and influence of educational status. Eur J Cardiovasc Prev Rehabil. 2011 Sep 26.
8. Gupta R, Guptha S, Agrawal A, Kaul V, Gaur K, Gupta VP. Secular trends in cholesterol lipoproteins and triglycerides and prevalence of dyslipidemias in an urban Indian population. Lipids Health Dis. 2008; 7:40.
9. Gupta R, Kaul V, Bhagat N, Agrawal M, Gupta VP, Misra A, Vikram NK. Trends in prevalence of coronary risk factors in an urban Indian population: Jaipur Heart Watch-4. Indian Heart J. 2007; 59(4):346–353.
10. Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80%. BMJ. 2003; 326(7404):1419.
11. Indian Polycap Study (TIPS), Yusuf S, Pais P, Afzal R, Xavier D, Teo K, Eikelboom J, Sigamani A, Mohan V, Gupta R, Thomas N. Effects of a polypill (Polycap) on risk factors in middle-aged individuals without cardiovascular disease (TIPS): A phase II, double-blind, randomised trial. Lancet. 2009; 373(9672):1341–1351.
12. PILL Collaborative Group, Rodgers A, Patel A, Berwanger O, Bots M, Grimm R, Grobbee DE, Jackson R, Neal B, Neaton J, Poulter N, Rafter N, Raju PK, Reddy S, Thom S, Vander Hoorn S, Webster R. An international randomised placebo-controlled trial of a four-component combination pill ("polypill") in people with raised cardiovascular risk. PLoS One. 2011; 6(5):e19857.
13. Dorresteijn JA, Visseren FL, Ridker PM, Paynter NP, Wassink AM, Buring JE, van der Graaf Y, Cook NR. Aspirin for primary prevention of vascular events in women: Individualized prediction of treatment effects. Eur Heart J. 2011; 32(23):2962–2969.

14. Kappagoda CT, Amsterdam EA. Trials of primary prevention of cardiovascular events using aspirin. Am J Cardiol. 2011; 108(8):1198–1200.

15. Kappagoda T, Amsterdam E. Aspirin for primary prevention of myocardial infarction: What is the evidence? J Cardiopulm Rehabil Prev. 2011 Sep 22.

16. Wald DS, Morris JK, Wald NJ. Reconciling the evidence on serum homocysteine and ischaemic heart disease: A meta-analysis. PLoS One. 2011; 6(2):e16473.

17. Miller ER 3rd, Juraschek S, Pastor-Barriuso R, Bazzano LA, Appel LJ, Guallar E. Meta-analysis of folic acid supplementation trials on risk of cardiovascular disease and risk interaction with baseline homocysteine levels. Am J Cardiol. 2010; 106(4):517–527.

18. Lee M, Hong KS, Chang SC, Saver JL. Efficacy of homocysteine-lowering therapy with folic Acid in stroke prevention: a meta-analysis. Stroke. 2010; 41(6):1205–1212.

19. De Caterina AR, Leone AM. The role of Beta-blockers as first-line therapy in hypertension. Curr Atheroscler Rep. 2011; 13(2):147–153.

20. Bangalore S, Sawhney S, Messerli FH. Relation of beta-blocker-induced heart rate lowering and cardioprotection in hypertension. J Am Coll Cardiol. 2008; 52(18):1482–1489.

21. Messerli FH, Bangalore S. Half a century of hydrochlorothiazide: Facts, fads, fiction, and follies. Am J Med. 2011; 124(10):896–899.

Erratum:

Images in Issue 1, Number 1, January 2012, page number 15.
Correct “Figure 4 (a) and (b)” are as follows:

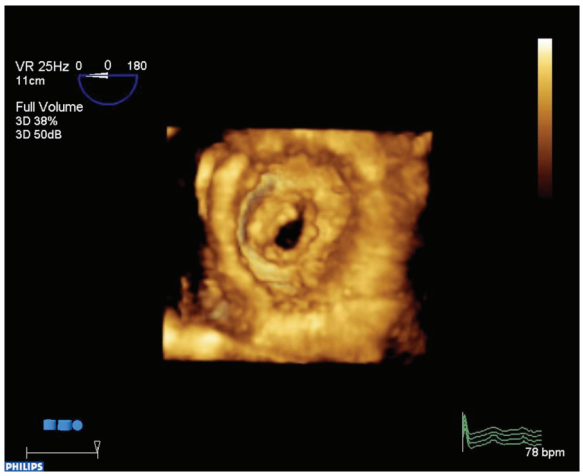

Figure 4 (a)

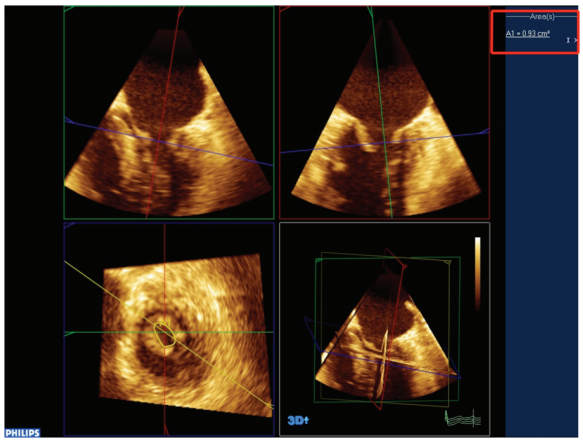

Figure 4 (b)