

Chapter

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Polypill for the Prevention of Cardiovascular Disease

BRIAN PINTO, SUSHANT PATIL, ANAND RAO

The incidence of cardiovascular disease (CVD) is rising at an alarming rate across the world. 15.3 million deaths have been reported due to CVD in 1996 and it is considered as a leading cause of mortality amongst adults worldwide¹.

Table 1: Deaths in million due to various diseases in the world

| <i>Disease</i> | <i>Million deaths</i> |
|-------------------------|-----------------------|
| Coronary artery disease | 7.2 |
| Cancer | 6.3 |
| Cerebrovascular disease | 4.6 |
| Acute RTI | 3.9 |
| Tuberculosis | 3.0 |
| COPD | 2.9 |
| Diarrhea | 2.5 |
| Malaria | 2.1 |
| AIDS | 1.5 |
| Hepatitis B | 1.2 |

During the past 30 years, CVD rates have halved in the US, Australia, Canada, France, Finland and Japan, however they have more than doubled in India during the same period. It is estimated that CVD will be the leading cause of mortality and morbidity in the developing world by the year 2015².

Western diet and lifestyle have increased the population levels of several of the causal risk factors and their combined effects have made CVD common. CVD can be avoided or delayed, but the necessary changes to western diet and lifestyle are not practicable in the short term. Randomized trials have shown that drugs to lower the three most prevalent risk factors, i.e. low density

lipoprotein cholesterol³, blood pressure⁴⁻⁸ and platelet function^{9,10} reduces the incidence of ischemic heart disease (IHD) and stroke.

Drug treatment is usually targeted at single risk factor and that too restricted to a small group of individuals who have high abnormal levels in order to bring them to average population levels. This approach will lead to modest reduction in risk of CVD in a population. As is known that the risk factors for CVD leads to atherothrombosis. Atherothrombosis reduces life expectancy by approximately 8-12 years¹¹.

Table 2: Average remaining life expectancy at age 60 (men)

| | <i>Average remaining life expectancy at age 60 (men)</i> |
|-------------------|----------------------------------------------------------|
| Healthy | 20 yrs |
| History of CVD | - 7.7 yrs |
| History of AMI | -9.2 yrs |
| History of Stroke | -12 yrs |

Wald and Law have proposed in 2003 that a large preventive effect would require intervention in every one at increased risk irrespective of the risk factor levels, intervention on several reversible causal risk factor levels and reducing these risk factors by as much as possible^{12,13}. Thus was introduced the concept of a polypill.

They have proposed a polypill to target four potential risk factors: hypercholesterolemia, high blood pressure, increased platelet activation and hyperhomocystinemia in all people more than 55 years of age and all patients with cardiovascular disease¹².

The composition of polypill suggested was a statin, low dose aspirin, three anti hypertensives (angiotensin

converting enzyme inhibitors, beta blockers and diuretics) and folic acid. This strategy when given to all specified people and or patients without measuring the risk factors would reduce the risk of IHD and stroke by almost 80%¹². It is proposed that on an average, people without known coronary artery disease will gain about 11-12 years of life free from heart attack or stroke. The gain in life is substantial at all ages studied.

However the concept of polypill has been contested by some¹⁴. The issues brought out are:

1. Many people more than 55 years old will have one or more than one risk factor and most of their CHD event is attributed to the elevated levels of that risk factor.
2. These elevated risk factor needs to be treated aggressively.
3. Polypill concept will not prevent those with premature CAD.
4. Risks may be high in low risk patients.
5. The benefit of low dose combination therapies administered regardless of risk factor level are proven.

The underlying belief of the polypill that combination therapy is better than monotherapy is true particularly with regards to secondary prevention of CVD and is proved by various studies. In terms of primary prevention, the rationale seems to be logical particularly in the context of assessment of global cardiovascular risk¹⁵.

Thus polypill can be viewed from two perspectives

1. Blanket primary prevention in groups with high rate of disease or those with one risk factor.
2. As a strategy for secondary prevention using a combination pill approach to enhance patient compliance.

The concept of polypill is relevant in the Indian scenario but may have to be modified based on the characteristics of the Indian population and the patients.

The recent SHARE study which evaluated the differences in risk factors, atherosclerosis and cardiovascular factors between ethnic groups in Canada showed a CAD prevalence of 10.7% among south Asians compared to 4.6% among Europeans¹⁵.

CAD risk in Indians is 2-4 times higher at all ages and 5-10 times higher in young (under 40) irrespective of gender and social class¹⁶.

In 2020, India will have the highest CVD burden in the world¹⁷. The impact of urbanization and westerni-

Table 3: Prevalence of CVD in India

| Year | % Prevalence (age > 20 yrs) |
|------|-----------------------------|
| 1959 | 1.0% |
| 1975 | 4.5% |
| 1996 | 7.9% |
| 2001 | 9.0% |

zation appear to be greater in Indians than in other populations due to a genetic predisposition of CVD. The prevalence of heart disease has increased by almost nine times in the last 40 years. The prevalence of CVD is fast approaching the figures reported in migrant Indians¹⁸.

The concept of a polypill therefore is extremely attractive to reduce the cardiovascular burden in India.

Issues that need to be debated and discussed are:

1. Are hypertension and hypercholesterolemia, the only risk factors that we need to worry about?
2. Do all people more than 50 years of age require a polypill?
3. Does the threshold of age need to be reduced?
4. Will one poly pill fit all?

Of the 200 risk factors for CVD that have been identified or have been postulated world wide, intervention to reduce blood pressure, low density lipoprotein cholesterol and smoking have been reported to definitely reduce the cardiovascular risk. However targeting these risk factors may not provide complete benefit to the Indian population.

Two other risk factors for CVD that need to be intervened are diabetes and impaired glucose tolerance (IGT). It has been reported that the insulin levels in Indians whether diabetic or non diabetic are significantly higher than in the Europeans¹⁹.

Moreover IGT which is the result of insulin resistance is highly prevalent in India (18% in the age group of 40-49 years). About 132 million people are expected to have IGT by the year 2025 in India²⁰. It is reported that the prevalence of IGT is more than that of diabetes in the age group less than 40 years of age. These early stages of glucose intolerance are not only the forerunners of diabetes but also carry high risk for CVD. As it is well known that diabetes is now considered to be a cardiovascular equivalent. This has important implications in the light of the fact that India is projected to be the diabetes capital of the world by the year 2025. Thus it is imperative to prevent diabetes and if present, to prevent the CVD complications.

The Diabetes Prevention Program have reported a 58% and 31% reduction in the incidence of diabetes with intensive lifestyle modification and metformin respectively²¹.

Polypill for Indians should have a component that reduces insulin resistance.

It has been observed in the retrospective analysis of people in India with CAD and without CAD, that 82.2% females and 32.5% males had premature CAD (males < 55 years and females < 45 years)²². It is well known fact that CVD/Diabetes occurs at least a decade earlier in the Indians as compared to the Caucasians.

In order that polypill is directed to the people who would benefit the most, all those people (>40 years) who have a family history of premature CVD should be the group to whom a preventive pill of low dose aspirin and metformin should be indicated. The use of these two essential agents will help prevent the first CVD event^{9,10} and delay the onset of diabetes²¹ without the side effects of the polypill as proposed by Wald et al¹².

For the patient group who have one risk factor or with metabolic syndrome, a preventive pill containing low dose aspirin, metformin, low dose statin and an ACEI should be indicated. However the prevalent risk factor needs to be treated more aggressively. For people with diabetes, to prevent cardiovascular disease events, professor Rizza has recommended 1000 mg metformin, 40mg generic statin, low dose aspirin and 10 mg generic ACEI. This strategy will reduce the total serious diabetes complications by 23%²³.

For secondary prevention of CVD events, along with diet and cardiac/stroke rehabilitation, low dose aspirin, high dose statin, low to standard doses of antihypertensive therapy and omega-3 fatty acids is suggested by Robinson et al. This strategy has been found to reduce events by upto 97% over 5 years²⁴.

For the high risk group of patients who have had a coronary intervention including coronary artery bypass grafting, the preventive therapy will also include clopidogrel 75 mg.

Polypill is necessity for reducing the burden of CVD in the Indians especially to enhance compliance for secondary prevention and to reduce the risk in the population for CVD as primary prevention strategy, especially for people with family history of premature CVD. Apart from hypercholesterolemia and hypertension, type 2 diabetes and IGT are the major challenges that increase the risk of CVD in India which need to be prevented.

One polypill will not fit the needs of different patient groups.

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