The Future of Metabolic Syndrome and Cardiovascular Disease Prevention: Polyhype or Polyhope? Tales from the Polyera

Abstract

Recently society has been witnessing the rise of a new era in the prevention and treatment of the metabolic syndrome and cardiovascular disease: the Polyera. This new era started when a promising concept – the Polypill – was introduced by Wald et al. in 2003. The Polypill is a theoretical combination of six pharmacological compounds (a statin, three different antihypertensives, aspirin, and folic acid) that in combination could reduce cardiovascular disease by more than 80%. Although the Polypill could theoretically be a highly effective intervention, it is not yet available in the market and its effectiveness remains unproven. In the population at large, cheap prizes may come at prohibitive costs. With frail elderly and population prevalences of co-morbidity far higher than in drug trials, rare adverse effects may be frequent. In December 2004, a more natural, safer, and probably tastier alternative to the Polypill – the Polymeal – was introduced. Contrary to the Polypill, the Polymeal combined 6 different foods (fruits and vegetables, almonds, chocolate, wine, fish, and garlic) that taken together in a regular basis could cut cardiovascular disease risk by over 75%. Polyproducts from the polyera in true populations might hide unexpected polyinteractions. In the polyera, polytrials will need to establish benefits, harms, and costs.

“Unless current trends are halted or reversed, over a billion people will die from cardiovascular disease in the first half of the 21st century. The large majority will be in developing countries and much of the life years will be lost in middle age. This would be an enormous tragedy, given that research in the last half of the 20th century showed that cardiovascular disease was largely preventable.”

Anthony Rodgers, Clinical Trials Research Unit, University of Auckland, New Zealand, 2004.

From Opulence to Aching Hearts

Economic transition, urbanization, industrialization, and globalization promote the adoption of a sedentary lifestyle and diet. This has increased the population levels of the metabolic syndrome and of additional risk factors for cardiovascular disease (CVD) progressively and has made these two conditions common [1,2]. The epidemic is not only rising, but also disseminating from developed to developing countries, partly as a result of increasing life expectancy and lifestyle changes. CVD – the primary clinical outcome of metabolic syndrome [3] – can no longer be seen as an exclusive problem of rich societies. Almost 75% of all CVD deaths occur in developing nations [4]. While the prevalence of metabolic syndrome in “western” populations range between 12–25% [5,6], CVD now ranks as the world’s number one cause of morbidity and mortality causing one third of all deaths globally. Approximately 17 million people die each year of CVD worldwide and this number is expected to increase up to 24 million by 2030 [4].

A Battle being Lost

Cardiovascular disease risk management as well as the treatment of metabolic syndrome is a combination of interventions oriented to a positive modification of different risk factors [7]. Although effective therapy is available to treat metabolic syndrome and almost all types of CVD, due to high costs, low compliance, and poor identification of those at risk, many patients who could benefit from treatment remain untreated, or inadequately treated. It is evident that new
and innovative strategies are indispensable to control the global epidemic of heart disease.

**June 28, 2003: Genesis of an Era**

Wald and Law proposed the Polypill concept as a population prevention strategy by mass treatment [2]. They posited that everyone is at increased risk irrespective of their risk factors levels, and that reducing several modifiable risk factors together would yield a large preventive effect of CVD. On June 28th 2003, the BMJ published the innovative theories of Wald et al. and a new era in CVD prevention was born: the Polyera, where simultaneously combined rather than isolated individual interventions are offered and designed for the population as an effective alternative to prevent and treat disease.

**What is the Polypill?**

The Polypill is a theoretical combination of six pharmacological compounds that combined and through concomitant modification of four different risk factors for metabolic syndrome and/or CVD (cholesterol modification with statins, blood pressure lowering with three different antihypertensives, antiplatelet aggregation with aspirin, and reduction of hyperhomocysteinemia with folic acid) could reduce CVD by more than 80% (Table 1) [2].

**Evidence Based Medicine and Multiplicative Models**

To find the right formula for the Polypill, the authors used basic principles of evidence based medicine and by thoroughly revising the published literature were confident to have found the ideal mixture [2,8–10]. However, as the Polypill is still a theoretical principle and such a pill does not exist yet, Wald and Law used a multiplicative model to integrate the effects of the different components and to calculate the potential effect of the Polypill. With this mathematical model Wald et al. combined the effects of the six drugs by multiplying the individual reduction effects (relative risks) on CVD events of each one of the ingredients assuming complete independency of action from one another.

**Potential Effect of the Polypill**

The authors calculated that the Polypill given daily to populations aged 55–64 years, could theoretically reduce coronary heart disease (CHD) by 88% (95% CI 84–91%) and stroke by 80% (95% CI 71–87%) (Table 1) [2]. Although the authors did not calculate the potential effect of the Polypill on the prevention of metabolic syndrome, it could be expected to be large as the ingredients of the Polypill will also target some of the components and risk factors of the metabolic syndrome. When these hypothetical levels of risk reduction were applied to life-table models built with data from populations free from CVD studied in the Framingham studies, treating 1000 participants with the Polypill during 10 years would represent large gains in terms of years of life saved (YLS) that ranged between 50–215 [11]. In terms of events prevented, 10 years of giving daily the Polypill to 1000 people would theoretically prevent 76–179 CHD events and 11–33 strokes [11]. The actual gains in YLS and events prevented would depend on the age and level of risk of the population. The highest gains were observed when the Polypill was given to the total population from the age of 60 years, irrespective of their level of risk [11]. According to the Polypill authors, “about a third of people taking the Polypill would benefit. On average each will gain 11–12 years of life free from a heart attack or stroke. The gain in life is substantial at all ages” [2].

**A Pill for Every Ill and the End of Screening for CVD**

Since approximately 50% of cardiovascular deaths occur in subjects with previous history of CVD and 96% of cardiovascular deaths occur in people aged 55 or over, Wald and Law recommended to give a Polypill daily to everybody with and older than 55 years of age and everybody aged less than 55 years who have previously suffered a CVD event [2]. Furthermore Wald and Law assert: “There is no need to measure the four risk factors before starting treatment, because intervention is effective whatever the initial levels of the risk factors, nor to monitor the effect of the treatment, because fluctuations within individuals tend to mask variations between individuals in the systematic effects of the interventions”. In other words the strategy proposed by Wald et al. is a true mass chemoprevention strategy, which would make individual screening and treatment of CVD risk a superfluous intervention destined to disappear. Finally the authors conclude: “no other preventive method would have so great an impact in public health in the Western world” [2].

**Every Rose has its Thorn**

Although the Polypill concept is very promising, medicalising a large sector of society appears to be a risky strategy. You come in ethically deep waters when as much as 15% of the people taking the Polypill could suffer adverse effects [2]. It is not the population but the individual who takes a pill, and the harm of the one is not necessarily balanced by the benefit of the other. Pharmacological prevention of CVD among populations free of the disease should be very safe, inexpensive and have considerable benefits to ensure a proper balance between adverse effects, costs and effects. If future implementation of the Polypill would target large sections of the global population, the cost of the medication is a

---

**Table 1** Risk reduction effect of ingredients of Polypill in the prevention of cardiovascular disease

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Percentage reduction (95 % CI) in risk of CHD</th>
<th>Percentage reduction (95 % CI) in risk of stroke</th>
<th>Source of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>A Statin</td>
<td>61 (51–71)</td>
<td>17 (9–25)</td>
<td>Law et al. (MA) [8]</td>
</tr>
<tr>
<td>three antihypertensives</td>
<td>46 (39–53)</td>
<td>63 (55–70)</td>
<td>Law et al. (MA) [9]</td>
</tr>
<tr>
<td>folic acid</td>
<td>16 (11–20)</td>
<td>24 (15–33)</td>
<td>Wald et al. (RCT) [10]</td>
</tr>
<tr>
<td>aspirin</td>
<td>32 (23–40)</td>
<td>16 (7–25)</td>
<td>Wald et al. (RCT) [2]</td>
</tr>
<tr>
<td>combined effect</td>
<td>88 (84–91)</td>
<td>80 (71–87)</td>
<td></td>
</tr>
</tbody>
</table>

CHD: coronary heart disease; MA: meta-analysis; RCT: Randomized controlled trials

*Atorvastatin 10 mg/day, or simvastatin or lovastatin 40 mg/day taken in the evening or 80 mg/day taken in the morning

---

relevant issue if we do not want to exhaust the health budget in a single effort. Furthermore, none of the ingredients of the Polypill target relevant conditions such as insulin resistance, obesity, and smoking, which generate heavy burdens to the health status of the population and are important risk factors or components of the metabolic syndrome and cardiovascular disease.

**What is Reasonably Affordable?**

As the Polypill has not been tested yet by clinical trials nor is available on the market, the future cost of the Polypill remains unknown and its potential cost-effectiveness for treating populations free of disease, a subject of debate. When the potential cost-effectiveness of the Polypill was evaluated using data from the Framingham studies and a Dutch scenario for costs, it was found that in order to be cost-effective in populations free of CVD, the annual cost of the medication should not exceed €300 at age 50 and €400 at age 60 [11]. These costs are 10 times the cost of aspirin therapy but three quarters the cost of statin treatment [12–14]. Since aspirin and statins are two of the constituents of the Polypill, it could be expected that the medication’s costs for the Polypill could be in this price range or even higher. When compared with aspirin in an incremental cost-effectiveness analysis, the maximum costs of the Polypill medication should not be over €157 and €268 for cost-effectively treating populations free of CVD at age 50 and 60, respectively [11]. Although the Polypill could theoretically be a highly effective intervention, the costs of the medication and its potential adverse effects could be the caveats for implementing the Polypill in the primary chemoprevention of cardiovascular disease.

**December 18, 2004: Consolidation of the Polyera**

With the objective to demonstrate that using nonpharmacological ingredients and the same assumptions and methods as the Polypill authors, could potentially lead to similar risk reduction effects with theoretically less adverse effects than the Polypill, we set to find a more natural, safe and probably tastier alternative to the Polypill: the Polymeal. The Polymeal study was published in the traditionally tongue-in-cheek Christmas’ edition of the BMJ the 18th of December 2004 [15]. With a touch of irony, we proposed the Polymeal concept following the framework set by the Polypill concept for the Polyera: simultaneous combination – rather than isolated individual – interventions as an alternative to prevent and treat disease.

**What is the Polymeal?**

The Polymeal is a theoretical combination of six food ingredients (wine, chocolate, fish, fruits and vegetables, almonds and garlic) that combined and through concomitant modification of different risk factors for cardiovascular disease could reduce CVD by more than 76% (Table 2) [15].

**Evidence Based Recipes and Multiplicative Models**

To find the right recipe for the Polymeal, we searched Pubmed for nonpharmacological ingredients with individually reported effects on reduction in CVD events or modification of risk factors for CVD and with evidence levels 1 or 2 (randomized controlled trials, meta-analyses of randomized controlled trials, and meta-analyses of observational studies) [16–22]. To calculate the potential effect of the Polymeal we used multiplicative models similar to the ones used by Wald and Law for the analyses of the Polypill.

**Too Good to be True?**

The Polymeal given daily (fish 2–4 times a week) to populations aged 50 years and over could in theory reduce CVD by 76% (95% CI 63–84) (Table 2). In terms of potential gains in life expectancy – calculated with data from the Framingham studies, – taking the Polymeal daily could represent an increase of 6.6 years in total life expectancy and 9 years in life expectancy free from CVD for men at age 50. For women at the same age, taking the Polymeal daily could mean an increase of 4.8 years in total life expectancy and 8.1 years in life expectancy free from CVD [15].

**Potential Effect of the Polymeal on Metabolism**

Diet high in fruits and vegetables are associated with lower incidence of chronic diseases such as CVD, diabetes, and osteoporosis. Fruits and vegetables are a rich source of antioxidants as well as dietary fiber, and have a lower glycemic index (GI). Higher intakes of fruits and vegetables are associated with lower plasma inflammatory markers [23]. A review of epidemiological studies found a lower risk of metabolic syndrome with higher consumption of fruits and vegetables [24]. Moderate red wine consumption is associated with a reduced risk of CVD. Key components of red wine, phenolic compounds and alcohol are thought to be responsible for the protective effect. Chronic consumption of red wine improved fasting lipid levels [25]. In an intervention trial, wine supplementation reduced monounsaturated fatty acid (MUFA) and increased polyunsaturated fatty acid (PUFA) [26]. Consumption of flavanol-rich dark chocolate has been shown to decrease blood pressure and increase insulin sensitivity in healthy subjects as well as in patients with essential hypertension [27,28]. Dietary chocolate forms the third highest daily per

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Percentage reduction (95% CI) in risk of CVD</th>
<th>Source of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>wine (150 ml/day)</td>
<td>32 (23–41)</td>
<td>Di Castelnuovo et al. (MA) [17]</td>
</tr>
<tr>
<td>fish (114 g four times/week)</td>
<td>14 (8–19)</td>
<td>Whelton et al. (MA) [22]</td>
</tr>
<tr>
<td>dark chocolate (100 g/day)</td>
<td>21 (14–27)</td>
<td>Taubert et al. (RCT) [21]</td>
</tr>
<tr>
<td>fruit and vegetables (400 g/day)</td>
<td>21 (14–27)</td>
<td>John et al. (RCT) [19]</td>
</tr>
<tr>
<td>garlic (2.7 g/day)</td>
<td>25 (21–27)</td>
<td>Ackermann et al. (MA) [16]</td>
</tr>
<tr>
<td>almonds (68 g/day)</td>
<td>12.5 (10.5–13.5)</td>
<td>Jenkins et al. (RCT) [18], Sabate et al. (RCT) [20]</td>
</tr>
<tr>
<td>combined effect</td>
<td>76 (63–84)</td>
<td></td>
</tr>
</tbody>
</table>

CVD: cardiovascular disease; MA: meta-analysis; RCT: Randomized controlled trials
capita source of antioxidants in the US [29]. Recently, studies have shown an increase in HDL cholesterol concentration [30] as well as a reduction in LDL oxidation susceptibility [31] after consumption of dark chocolate.

Reducing postprandial glucose excursions is one of the most important strategies for prevention of the metabolic syndrome, diabetes and CVD. It is important to limit postprandial oxidative damage to lipids and proteins. Along with their capacity to significantly reduce total and LDL cholesterol [32], almonds may also reduce the glycermic impact of carbohydrate foods with which they are eaten [33]. Almonds have been shown to decrease postprandial oxidative protein damage [34].

Garlic has been used in herbal medicine for centuries for various conditions. Studies have shown LDL and total cholesterol lowering effect of garlic in individuals with hyperlipidemia [35] and in patients with type 2 diabetes [36]. Consumption of fish or fish oils rich in n-3 long chain PUFA decrease the risk of CVD. A systematic review of the effect of omega-3 fatty acids on serum markers of CVD risk reported beneficial effect on triglycerides and HDL cholesterol [37]. Small doses of fish oil inhibit platelet aggregation [38, 39]. However, very high consumption of fish must be balanced against possible consumption of high levels of mercury, which may be present in certain types of fish. Therefore, although we did not calculate the potential effect of the Polymeal on the prevention of the metabolic syndrome, it could be expected to be substantial as its ingredients also target the majority of components and risk factors of the metabolic syndrome.

Avoiding Unpleasant Situations

Except for those allergic to the components, if taken with moderation, no adverse effects could be expected from taking the Polymeal. However, the Polymeal should not be combined with additional consumption of alcohol, in order to avoid intoxication and deleterious consequences that high consumption of alcohol may exert in other tissues [22]. Furthermore, garlic could cause flatulence, halitosis and body odor, the consequences of which must be considered at the level of the individual and in the social context [15].

Costs and Quality of Life

Just like the Polypill, the characteristic ingredients of the Polymeal are not offered in the market as a combination. The exact price of the Polymeal would depend on the local prices and the specific brand and type of the items selected. If the potential price of the Polymeal could be calculated based on prices from a local supermarket in Rotterdam, the Netherlands, the price of the Polymeal could add up to € 21 per week [15]. Although no particular brands are recommended, spending more – for example, on your favorite wine or chocolate – might be rewarded by an improved quality of life [15].

Considering that the price per year of the Polymeal could be equivalent to the price per month of the Polymeal, it is inferable that the Polymeal is more cost-effective than the Polypill. Nevertheless, the investment required for the Polymeal is already considered for societal implementation. Hype or hope? Only confirmatory evaluations will tell. If the hypothetical premises would hold true in experimental evidence, a new era of prevention might arise: the Polyera, splitting the history of prevention into two periods BP and AP (Before and After the Polyera). The morbidity consequences of a complex life style might be treated

Every Rose has its Thorn: Polymeal is not the Exception

Although the Polymeal appears to be an effective, natural, probably safer and tastier alternative to the Polypill, the validity level of the source evidence affects the Polymeal study. Although only levels 1 and 2 of evidence were included, some of the RCTs selected were of a small sample size. This is particularly the case for chocolate and almonds. Evidence-based medicine is explicit about the level of evidence but not about additional definers of quality in the studies (e.g., sample size, correction for confounding). "Evidence" should not be a bureaucratic decision based on study designs, but of informed debate about the strengths and weaknesses of the presented facts.

Compared with the Polypill, there is less evidence available on the potential interaction of the ingredients of the Polymeal, nonetheless there is certainly far more information for the ingredients of the Polymeal as humankind know and have used these elements for centuries while the ingredients of the Polypill only for decades. Finally, some of the ingredients of the Polymeal are rich in calories, particularly chocolate and overindulgence is a cause of concern.

The Future of Cardiovascular Disease Prevention: the Polyera is here to stay!

Although the metabolic syndrome and in general atherosclerotic cardiovascular disease is largely preventable, they have become common, and CVD nowadays constitute the number one killer in the world. In Western societies and soon also in most developing countries, we all have high levels of metabolic syndrome and other risk factors for CVD, hence everybody is at risk of developing and suffering from the deleterious consequences of developing a myocardial infarction, a stroke or other atherosclerotic disease events. Current efforts oriented to prevent metabolic syndrome and to control the global epidemic of CVD have been successful, but to a limited degree. A potentially effective alternative would be “mass treatment”, irrespective of risk factors levels, modifying several modifiable risk factors together. In this sense, a set of “Polyinterventions” could provide comprehensive means to modify the levels of risk of the population at a wider scale and at levels above 90% reduction of CVD as suggested by Robinson et al. in the Polyportfolio publication [40]. The future of the treatment and prevention of these conditions lies on “polyinterventions” oriented first to positively modify the risk profile of the population including weight control, increasing physical activity, and an adequate diet designed to reduce the risk of these morbidities and pharmacological interventions reserved for those at high risk of developing metabolic syndrome and/or CVD. For example, after the daily consumption of the Polymeal, additional interventions to prevent CVD such as walking half an hour or taking the Polypill – for those with history of CVD – could aid to lower the metabolic syndrome and CVD further. However, both the Polypill and the Polymeal are successes of simulation models – and simulation models are but quantified opinions. Empirical testing is mandatory before they could be considered for societal implementation. Hype or hope? Only confirmatory evaluations will tell. If the hypothetical premises would hold true in experimental evidence, a new era of prevention might arise: the Polyera, splitting the history of prevention in two periods BP and AP (Before and After the Polyera). The morbidity consequences of a complex life style might be treated
by complex interventions. The ensuing paradoxes of consumerism fighting the consequences of consumerism might be left to individual choice of a desirable lifestyle.

Guarantor Statement

Oscar H. Franco as guarantor of this paper accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

Ethical Approval Statement

Ethical approval was not required as this was a secondary data analysis.

Parts of this manuscript has been published previously (December 2006) in Dutch in the journal "Tromnibus". All authors have no competing interest to declare. Both Oscar H. Franco and Kavita Karnik work for Unilever, which is a multinational Fast Moving Consumer Goods (FMCG) company.

References

2. Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80%. BMJ 2003; 326: 419
15. Franco OH, Bonneux L, de LC, Peeters A, Steyerberg EW, Mackenbach JP. The Polyplem: a more natural, safer, and probably tastier (than the Polypill) strategy to reduce cardiovascular disease by more than 75%. BMJ 2004; 329: 1447–1450
40. Robinson JC, Mashehwar N. A “poly-portfolio” for secondary prevention: a strategy to reduce subsequent events by up to 97% over five years. Am J Cardiol 2005; 95: 373–378