

## Is the Polypill Empty? Chronicle of an Illusion

Atherosclerosis affects older adults from almost all over the world. It is characteristic of our socio-cultural education, largery due to changes in diet and physical activity over the past 200 years. Although in clinical practice risk factors are approached as problems that each patient has to face with their own personal effort –and in many cases they are considered secular sins (sedentarism, obesity, smoking)–, a broader view helps us understand that risk factors reflect a lifestyle that is typical of our culture. (1)

Years ago, Geoffrey Rose developed a conceptual model which demonstrated that small quantitative changes in the whole population would have a great impact on global health. (2) For example: a mean systolic blood pressure reduction of 5 mm Hg in the population reduces the prevalence of high blood pressure values by 25%, and an average weight reduction of 1 kg (2.2 pounds) in the population also reduces the incidence of obesity by 25%. It is worth noting the contrast between the usual approach to medicine (to detect individuals with high risk factors –potentially ill– in order to correct them) and this proposal (society is ill). (3) The task is oriented towards changing population habits related to atherosclerosis; this change might have a major impact on risk reduction. “A large number of people at a small risk may give rise to more cases of disease than the small number who are at high risk.” Behind this recognition, there were proposals from large-scale community interventions on correctable factors: increase number of hours of physical activity in schools, reduce the access to the so-called junk food, particularly for children, reduce the sodium content in diets with control of food production, eliminate dangerous lipids, replace animal fats with vegetables, etc. Yet, we know these changes are very difficult to implement.

Campaigns aiming at individual changes on the basis of advertising and educational strategies have also failed to bring about the expected results. A recent review of The Cochrane Collaboration analyzed 55 published trials on population interventions with campaigns lasting 12 months on average (between 6 months and 12 years). It resulted in small reductions in risk factors,

and none of them impacted on cardiovascular morbidity or mortality. In this regard, it has been proposed to concentrate efforts on validated strategies, and in case of applying resources for campaigns, to strictly evaluate their local impact, particularly in developing countries with increasing incidence of these diseases. (4)

An alternative to this cultural change in diet and exercise is the proposal of a universal polymedication, which has shown in clinical trials that it prevents mortality and cardiovascular events.

### THE POLYPILL PROPOSAL

In the year 2002, Salim Yusuf reviewed the contributions of a series of drugs on secondary prevention. (5) In his calculations, mortality had been reduced by 75% or life had lasted several years with the combination of aspirin, beta blockers, statins, and angiotensin-converting enzyme inhibitors. Based on this concept, in 2003, Wald and Law published the proposal of a superpill that could reduce cardiovascular disease by 80% and prolong life expectancy by 11 years if it was prescribed massively among people over 55 years of age in primary prevention. (6) The proposal was based on Rose’s analysis and Yusuf’s projection, which together generated some key concepts:

1. There is a continuous risk-factor distribution among the population (blood pressure, cholesterol, glycemia, weight), and any threshold considered as the basis of hyperfactor is arbitrary. A massive low reduction of the values in the population could induce a quantitatively predictable reduction in cardiovascular morbidity and mortality, at least with cholesterol and blood pressure. For instance, a systolic blood pressure lower than 20 mm Hg is associated with half the risk for cardiovascular death, whatever the baseline considered up to 100 mg Hg.
2. There are several drugs in primary prevention that have proved useful in risk prevention when administered in patients with high cardiovascular risk criteria.
3. Prescribing combined low doses of these drugs massively with a single pill could contribute to

**Table 1.** . Estimate based on risk reduction in Wald and Law’s proposal. Effects of the polypill on the risk of ischemic heart disease and stroke at two years, in individuals aged between 55 and 64.

Risk factors	Agent	Factor reduction	% Reduction	
			Ischemic heart disease	Stroke
Homocysteine	Folic acid	3 µmol/L	16 (11-20)	24 (15-33)
Platelet function	Aspirin	Unmeasured	32 (23-40)	16 (7-25)
Diastolic pressure	3 drugs – Low doses	11 mm Hg	46 (39-53)	63 (55-70)
All			88 (84-91)	80 (71-87)

proper observance and mean reduction of the desired parameters and resulting risk.

*The most important doctrinal statement of this proposal is that it could be performed with no need for controls or early measurements or dosages, and there would be no thresholds for indications.*

The miracle pill, whose proposed name is “polypill”, combined six drugs: a low dose of aspirin to reduce platelet aggregation, folic acid to lower homocysteine levels, three low doses of antihypertensive drugs (the suggested combination included low doses of hydrochlorothiazide, angiotensin converting enzyme inhibitors, and beta-blockers), and atorvastatin 10 mg or simvastatin 40 mg (Table 1).

### THE SCIENTIFIC COMMUNITY: APOLOGY AND CRITICISM

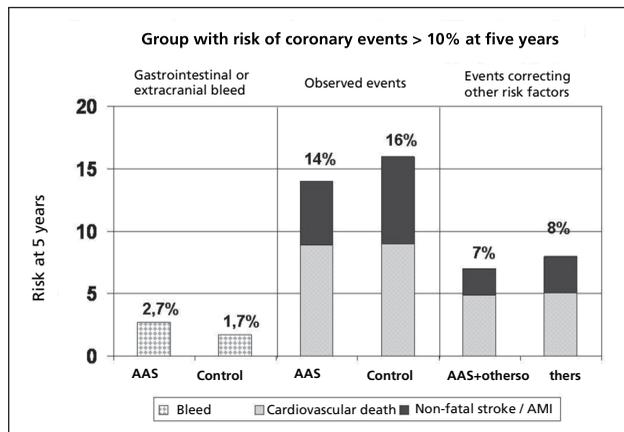
As expected, community reactions were very different.

Some criticism:

1. From an epidemiological point of view, criticism was focused on the reduction of risk factors with active community policies, and pointed at the illusory expectation of an improvement through medicating the whole of the healthy population with six active drugs for years.
2. Five of the six drugs in the polypill had been validated in controlled trials, which will be discussed later in this paper; no trials on the fifth drug –the folic acid– were available at that time, and it was included on the basis of epidemiological projections. Taking advantage of this license from the authors, other researchers tried to satirize the proposal by replacing the polypill by the polymeal, (7) a combination of dietary measures that promised a 75% risk reduction, and had also “better tasting”. The diet included red wine, fish, dark chocolate, fruit, vegetables, garlic, and almonds, all of them associated with lower cardiovascular mortality in epidemiological studies.
3. Clinicians who see patients were also moved by this proposal, which suggested that measurements and controls for prevention were almost irrelevant and could be replaced by an almost fixed-dose pill.
4. Those who were against medicalisation considered this proposal of prescribing six drugs to the whole of the adult population over 55 years of age a foolish attempt. This led to the need for quaternary prevention, i.e. preventing patients from being harmed by the intake of six associated medications.

In other groups, however, the proposal aroused great enthusiasm:

1. Limitations in the ability of medicine to influence on dietary and physical habits make it unfeasible to have an impact through them in a reasonable time. The polypill was then an immediate solution.
2. Concentration in a single pill would surely have a great impact on adherence and compliance, so it suggested a real possibility of community impact.
3. The pill could include low-cost, off-patent drugs, which made it ideal for low-income populations. The emerging socio-economic groups at high



**Fig 1.** Aspirin in primary prevention. Incidence of events at 5 years in a subgroup of patients with an estimate for coronary risk higher than 2% per year, depending on age, sex, diabetes, hypertension, and dyslipidemia. Aspirin increased in absolute 1% the incidence of major bleeding at 5 years, and reduced in absolute 2% the incidence of cardiovascular events, with no impact on cardiovascular mortality. With the current strategies for additional prevention (blood pressure monitor and statin therapy), expected reduction of cardiovascular events will be 1%, on the same magnitude as bleeding increase with aspirin.

cardiovascular risk from India and China were considered.

### STROKE BY STROKE ON THE COMPONENTS OF THE POLYPILL

Since Wald and Law’s publication, new information has been generated, particularly about the pharmacological spectrum of the components, which invites to reflect upon the authors’ original projections.

### The miracle pill begins to get empty: the failure of the folic acid

The controlled trials designed in the nineties and ended in the first decade of the new century were conclusive. As it was known, folic acid was effective in reducing blood homocysteine levels, but it had no impact on the reduction of heart disease.

In a recent meta-analysis that included the CHAOS 2, VISP, WAFACS, HOST, HOPE 2, WENBIT, NORVIT and SEARCH studies on 37,485 participants, there were no advantages in major cardiovascular events (RR 1), major coronary events (1.03), or stroke. (8) In one of the trials, the group that was administered folic acid and vitamin B complex increased its risk of morbidity and mortality. (9) Although the topic still remains open to debate, (10) most of the scientific community considered these results as a definite failure. This first defection consolidated the conviction that no observational epidemiological analysis can ensure what will happen when projected to therapeutics. In some cases, the model works, and thus lowering blood pressure with most of the drugs and cholesterol with statins reduces the risk as it was predicted. In other cases, it does not: lowering cholesterol with estrogens, ezetimibe, or torcetrapib

has provided no benefits or has been harmful, as well as lowering homocysteine levels with folic acid has not been useful.

### **Second fall: aspirin for primary prevention in low-risk groups**

The least questioned component of the multipill met its Waterloo in the meta-analysis on individual participants carried out by the group that had made research on it prospectively. (11) Aspirin had no impact on mortality, but it did show a one-third reduction of the incidence of myocardial infarction. Something that had not been considered was found in this new analysis: the risk of (gastrointestinal and extracranial) bleeds increased in parallel with cardiovascular risk. Thus, the clinical impact of risk-reduction is very low for low-risk patients, and gastrointestinal risk is also reduced. But for moderate- and high-risk patients, the benefit in terms of reduction of myocardial infarction with no impact on mortality is balanced with the increased risk of gastrointestinal and extracranial bleeds (Figure 1).

The resulting recommendation is not to use aspirin in primary prevention massively, but restrict it to populations at high risk of myocardial infarction and with control of possible gastrointestinal bleeding. It excludes aspirin from the polypill used on a massive basis.

*The problems with the antihypertensive complex, and the question of whether lowering blood pressure is always healthy*

Wald and Law proposed a combination of three antihypertensive drugs in low doses for their polypill, selected among the five drug groups: diuretics, beta-blockers, ACE inhibitors, angiotensin II receptor blockers, and calcium blockers, with no initial preferences. For reasons of cost and patents, they suggested that the combination of diuretics, ACE inhibitors and beta-blockers could be feasible. In practice, angiotensin converting enzyme inhibitors and diuretics were combined in all planned trials, as we will discuss later.

### **And now for the third one: ACE inhibitors in primary prevention**

Based on the observation that ACE inhibitors evaluated in trials on heart failure were associated with reduced incidence of myocardial infarction, the antiatherosclerotic action of these agents and their potential role in cardiovascular prevention were postulated. This was initially evaluated in the HOPE study, (12) which proved that administering 10 mg of ramipril to patients at high cardiovascular risk and with normal blood pressure was associated with reduction of major cardiovascular events. Since the effect on systolic blood pressure was reduced, these data consolidated the idea of an antiatherosclerotic effect, which was strongly supported by basic research. Later on, several trials that challenge this assumption were carried out, in particular, the VALUE (13) and ONTARGET trials. (14, 15)

The VALUE trial compared amlodipine –an

antihypertensive drug with no “reological” properties– against valsartan, with the idea that, in case of a similar reduction in blood pressure levels, the AT-II inhibitor would contribute to a reduction of cardiovascular events. The study was adverse to valsartan because it showed better antihypertensive efficacy of amlodipine at baseline, and even a greater reduction in the incidence of myocardial infarction.

The ONTARGET trial had several arms that comparatively assessed with non-inferiority hypotheses the value of telmisartan versus ramipril, the combination versus ramipril and telmisartan versus placebo, in patients who had intolerance to angiotensin converting enzyme inhibitors. The study concluded that telmisartan was equivalent to ramipril, and that the combination of the two drugs was not superior to ramipril alone. The most striking result was that telmisartan was not superior to placebo, in a clinical context similar to that of the HOPE study. This result suggests that, being telmisartan equivalent to ramipril, it is conceivable that the benefit observed with ramipril in the HOPE study is not maintained due to changes in current medication (increased use of statins, etc.), or simply due to regression toward the mean. The effectiveness of inhibitors in preventing the development of diabetes has not been consolidated when they were evaluated prospectively in the DREAM study. (16)

The current feeling about these drugs is that their preventing action is restricted to the effect of reducing systo-diastolic blood pressure, and not to specific antidiabetic or anti-atherosclerotic properties.

### **The fourth one got jammed: diuretics, and the case of hydrochlorothiazide**

Thiazide diuretics are currently recommended in the guidelines as initial treatment of choice in hypertension. This topic has been heavily discussed in recent years, and I will point out just some details of the arguments and interests at stake. One of the sources for that reconsideration has been the results of the ACCOMPLISH trial, (17) which included 11,506 patients to compare two combination therapies: benazepril in both groups, plus amlodipine or hydrochlorothiazide (HCTZ). Blood pressure lowered slightly more in the amlodipine group, 131.6/73.3 mm Hg versus 132.5/74.4 mm Hg in the HCTZ group. There was an absolute risk reduction of 2.2% of the incidence of combined cardiovascular event, a relative risk reduction of 19.6%, and HR was 0.8 (95% CI, 0.72-0.9). Although this is the first study in which the combination with diuretics is overtaken by another one, and it consists of a comparison between combinations –which can lead to infinite possible designs–, it aimed at a new reading of the available information on thiazides, which I will summarize below, in perspective of analyzing their inclusion in the polypill.

### **Hydrochlorothiazide, chlorthalidone, or indapamide**

The recommendation of the JNC VII guidelines (18) refers to the group of thiazides, without distinguishing among the different agents. In practice, over 97% of the

prescription is restricted to hydrochlorothiazide in low doses, 12 to 25 mg in the American and Argentinian markets. It is used most often in combination with other antihypertensive drugs. On the basis of comparative clinical trials, it has been argued that both chlorthalidone and indapamide have impacted on morbidity and mortality, while the effects of hydrochlorothiazide have always been lower. In an editorial that argues “Why chlorthalidone may replace hydrochlorothiazide”, (19) a leading figure in hypertension like Norman Kaplan points out that:

- a) In different trials, it has been shown that the antihypertensive efficacy of chlorthalidone doubles that of the hydrochlorothiazide at the same dose, with similar effects on potassium levels. The nighttime ambulatory blood pressure is 7 mm Hg lower with chlorthalidone than with HCTZ at equal doses. (20)
- b) In several trials, chlorthalidone, in doses from 12 to 25 mg, has been shown to reduce cardiovascular morbidity and mortality, which has never confirmed with HCTZ at low doses.

In that editorial, Kaplan advocates the combination of chlorthalidone 12.5 mg and spironolactone 25 mg. Both are generic drugs, and are available at low cost in the U.S. market, at approximately 30 ARS (Argentine pesos) monthly for the combination.

Among the great achievements of diuretics in clinical trials over the past ten years, the two victorious drugs have been chlorthalidone and indapamide. Chlorthalidone, in the ALLHAT trial, (21) in which it showed the advantages against lisinopril, amlodipine, and doxazosin over morbidity and mortality. Indapamide, with its great impact in the PROGRESS study, (22) in which it reduced the incidence of stroke and cardiovascular morbidity and mortality either alone or in combination with perindopril in hypertensive patients with a history of cerebrovascular disease.

For the purposes of the polypill, it is possible that the inclusion of hydrochlorothiazide in low doses may be challenged because of its limited effectiveness and the similar risk of hypokalemia. To give an idea of the attack against this drug, we have failed in our attempt to publish a controversy in our RAC (Argentine Journal of Cardiology), in which the topic for discussion is whether or not the HCTZ should continue as first-line treatment of hypertension, because we have not found a panelist to defend it.

### Out-of-control diuretics

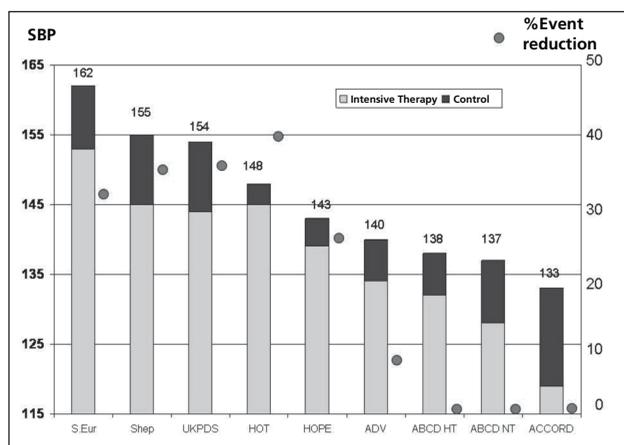
One of the illusions about the polypill, as pointed out by its inventors, is that there is no need to measure cholesterol or blood pressure in individuals who receive it. It is expected to reduce each parameter in order to impact on the population and assume a very low rate of adverse effects, so that no additional measurements are needed. However, even low doses of thiazide diuretics reduce 0.25 to 0.5 mEq/L mean blood potassium levels, and levels below 3.5% are observed in 10%, which may be associated with severe arrhythmias and sudden

death. (23) Potassium levels were measured in all studies using diuretics, and were corrected with potassium supplements or by adding potassium-sparing diuretics.

### Third and fourth ones together: Is blood pressure lowering always beneficial? Or is it reasonable to expect that blood pressure lowering with drugs –irrespective of its baseline– will have the same effect as that observed in the population curves?

#### In favor

Based on the prediction of epidemic curves, each rise of 20 mmHg in systolic blood pressure is associated with doubled mortality rate. This duplication occurs in a similar way both between 110 and 130 mm Hg, and between 130 and 150 mm Hg, although the absolute risk increase is much greater in higher ranks. In a comprehensive review of a large number of trials with drugs that have an impact on blood pressure in different clinical contexts (primary prevention, post-infarction, heart failure, post-stroke), the authors showed that risk reduction is proportional to blood pressure, regardless of baseline blood pressure levels. (24) This would suggest that what was observed in the epidemic curves works similarly under a drug therapy. One of the major questionings on this analysis is that it mixes up very different problems: It is not the same to show that lowering 10 mm Hg with ramipril after an anterior myocardial infarction with ventricular impairment reduces mortality even if the patient has a baseline



**Fig 2.** Studies on drug therapies that reduce blood pressure in patients with diabetes: the relationship between blood pressure in the control group (dark column) and in the intensive-therapy group (light column), and its relationship with cardiovascular event reduction are represented in the chart. In the studies on the left, with higher mean blood pressure, the benefit (indicated by circles) was highly significant. By contrast, in the studies in which mean blood pressure was lower, even when systolic blood pressure lowering was significant –as in the case of the ACCORD trial (14 mm Hg reduction)–, there was little or no benefit. Reproduced with the authorization of Zanchetti A. Blood pressure targets of antihypertensive treatment: up and down the J-shaped curve. Eur Heart J 2010; 31: 2837-40.

blood pressure of 120 mm Hg, than lowering 10 mm Hg in hypertensive patients from 160 mm Hg but with no heart disease. Although the percentage of reduction was identical, there is no way to argue that the mechanisms are similar, and we are working on the same population epidemic curve. In fact, there are no published trials on antihypertensive drugs on normotensive individuals without multiple cardiovascular risk factors, who would be the candidates for the polypill in its original proposal.

### **Against**

Several authors have shown that the benefits from clinical trials are very limited when baseline blood pressure is not high, and that trying a more pronounced reduction in high-risk patients, particularly in diabetic patients, does not provide the expected benefits. Even, a J-shaped behavior –that is, increased risk when blood pressure is lowered even more– can be observed in some trials.

### **No benefits from intensive blood pressure-lowering for diabetic patients**

The Task Force of the European Society of Hypertension (25) has reviewed the evidence from the clinical trials and has concluded that there is no proof that high-risk patients require blood pressure levels lower than 130 mm Hg, and that there is no reason to lower blood pressure in normotensive patients, ie. with levels not above the range currently considered normal. The idea of lowering blood pressure levels was based on observations of clinical trials, and aimed particularly at diabetic patients. However, its evaluation in the ADVANCE (26) and ACCORD (27) trials did not confirm that expectation. The prospective, controlled ACCORD study assessed the relative benefits of targeting lower mean blood pressure in patients with diabetes. A significant difference was achieved: the mean systolic blood pressure was 119 mm Hg in the intensive-therapy group and 133 mm Hg in the standard-therapy group. Despite the difference of 14 mm Hg in blood pressure levels, no clinical benefit was achieved in cardiovascular morbidity and mortality. Zanchetti (28) summarizes all this information from trials on diabetes in a chart, which shows that the impact of blood pressure reduction is much greater when baseline levels are high, and that almost no benefits are obtained in several trials in which baseline was 140 mm Hg or less (Figure 2).

### **Is there a J-curve behavior of blood pressure?**

In an analysis of blood pressure on 10,001 patients with coronary artery disease enrolled in the TNT trial, the authors reported that there was an increased risk in the J-curve relationship: the best point of blood pressure was 146/81 mm Hg, and the risk of cardiovascular events above and below that level was higher. (29) Stroke was the only event that decreased with lower levels of blood pressure. In patients with coronary artery disease, this observation is unrelated to the level of blood pressure treatment –which was not a target of this trial– but questions the idea that the lower the BP the better –which

can be extended to the elderly, with high prevalence of coronary artery disease. This observation was identical to that referred to by the authors of the ONTARGET study, (30) in this case under antihypertensive therapy in different branches: the only event that was reduced in parallel with systolic blood pressure was the stroke, while it had a neutral effect on the incidence of myocardial infarction. What caused concern was the J-curve effect on cardiovascular mortality, which increased with more pronounced systolic blood pressure reduction.

No controlled trials have considered three levels of blood pressure to compare this possible behavior, and evidence from the reviews of clinical trials is flawed and contradictory.

At present, the problem of blood pressure lowering in all the individuals regardless of their baseline levels should be considered a hypothesis to assess and not a solid evidence emerged from treatment trials. Again, extrapolating the population criteria of Geoffrey Rose with community interventions to pharmacological interventions should be considered only a hypothesis to be analyzed.

### **The least expected fifth one: questioning of statins in primary prevention**

Statins for primary prevention have been evaluated in patients at high cardiovascular risk, estimated by sum of risk factors, high levels of C-reactive protein, or hypercholesterolemia –defined by high levels of cholesterol. No studies were focused on the general population, regardless of cholesterol levels, history or risk factors, as the polypill proposes. Over the past two years, several meta-analyses have been published on this topic, with conflicting results. One of the key problems is the inclusion criteria of trials in the meta-analysis, particularly in the last one, carried out by the Cochrane, which arrives at a very curious interpretation.

### **In favor**

Meta-analysis by Baigent et al.: (31) they included 90,056 patients from 14 controlled trials, with access to individual data, and tried to project the magnitude of the event reduction associated with LDL cholesterol reduction. Mean reduction was 1.09 mmol (about 40 mg/dl), and mortality reduction at 5 years was 12% per mmol reduction [RR 0.88 (CI 95% 0.84-0.91;  $p < 0.0001$ )], with reduced incidence of myocardial infarction (23%), stroke (17%), and need for coronary artery bypass (24%). Overall, global cardiovascular events are reduced 21% per 40 mg/dl cholesterol reduction. The absolute impact was much greater in patients with a history of heart disease than in primary prevention, but the percentage reduction was similar. No increased adverse effects or cancer were induced [RR 1 (CI 95% 0.95-1.06)].

Along the same line, a meta-analysis involving 170,000 participants was published, in which statins versus placebo or high versus low doses were compared in order to achieve a more intensive LDL cholesterol reduction. LDL cholesterol levels under intensive

therapy were 0.51 mmol (about 20 mg/dl) lower, which was associated with reductions in cardiovascular events, 15% in major events, 19% in coronary artery bypass, 16% in ischemic stroke, in the range observed with similar reductions against placebo. (32)

Each mmol reduction (40 mg/dl) lowers the risk of major events by 20% and mortality rate by 10%. No increased incidence of cancer with the intensive treatments was observed either.

### **Against**

Ray et al. (33) published a meta-analysis on 11 trials in primary prevention, involving 65,229 participants. Their main conclusion was that statins do not reduce mortality [RR 0.91 (0.83-1.01),  $p = ns$ ]. This study was published in a very special issue of *Archives of Internal Medicine*, which was accompanied by a destructive analysis of the JUPITER study (34) and other adverse opinions about the use of statins in primary prevention. It is worth noting that the conclusion is not held just the way it is expressed: statins were associated with a 9% mortality reduction, from a 17% chance of reduction to an increase of 1%. It does not mean that it has no impact on mortality, but that it was statistically at the limit, largely determined by trial selection.

### **In favor, but against**

The Cochrane Collaboration published a meta-analysis of 14 trials involving 34,272 participants, whose inclusion criteria was that less than 10% of randomised patients had a history of heart disease. (35) Selection criteria were based primarily on hypercholesterolemia or other risk factors: diabetes, hypertension, microalbuminuria. They observed statistically significant reductions in mortality of 17% (RR 0.83, CI 95% 0.73 to 0.95), reduction in fatal and non-fatal cardiovascular events of 30% (RR 0.70, CI 95% 0.61-0.79), and reduced need for revascularisation of 34% (RR 0.66, CI 95% 0.53-0.83). After a detailed analysis, there were no adverse effects or harm caused by statin prescription. The conclusion deserves to be transcribed literally:

*Although reductions in all-cause mortality, composite endpoints and revascularisations were found with no excess of adverse effects, there was no evidence of selecting reporting of outcomes, failure to report adverse events and inclusion of people with cardiovascular disease. Only limited evidence showed that primary prevention with statins may be cost effective and improve quality of life. Caution should be taken in prescribing statins for primary prevention among people at low cardiovascular risk.*

Conceptual translation: Statins reduce mortality and cardiovascular events in these trials, but we do not believe in the results. In the discussion, they refer that precisely the two studies that reported no beneficial effects on mortality were those not included because 14% and 17% of their patients had a history of cardiovascular disease (remember that

inclusion criteria were less than 10%). They also reported humorously to have excluded the JUPITER study because it was published on a date that had not been considered for inclusion. Since it is almost two years now since this study was published, it could have been included without any effort, and the real reason for its exclusion was the strength of its positive outcomes, probably exaggerated by the fact that it was stopped at a time in which reduction in mortality and cardiovascular events was considerable. This report caused a stir and the emergence of several editorials and letters in the past weeks, because it has questioned the use of statins in primary prevention, unfortunately not on the basis of the meta-analysis results, but of the particular interpretation expressed in the conclusion.

### **CONCLUSIONS ABOUT STATINS IN THE POLYPILL**

In their guidelines, scientific societies recommend that the use of statins should be restricted to individuals at high risk of cardiovascular events. The latest recommendation of the European Society is 20% risk of disease at 10 years, according to Framingham score, or 5% of mortality using the European score. (36)

There is no evidence of its usefulness in low-risk groups, but the lack of risk allows for prospective assessment in large population groups, as required by the polypill.

### **POLYPILL TRIALS WITH DIFFERENT DESIGNS**

Several trials with different designs have been addressed –some of them already finished in their preliminary stages of Phase II– aiming at assessing the feasibility and safety of different formulations and their general comparison with the normal patterns (Table 2).

### **The Indian Polycap Study (TIPS)**

It was designed by Salim Yusuf, and sponsored by the Indian pharmaceutical laboratory Cadila. He compared what was called the Polycap, composed of 12.5 mg hydrochlorothiazide, 50 mg atenolol, 5 mg ramipril, 20 mg simvastatin, and 100 mg aspirin per day, with another eight treatment groups in which each drug was tested individually or in different progressive combinations. The study time frame was 12 weeks of follow up, and reported a number of very interesting data:

- a) The combination of the five agents in a capsule did not reduce the effect of individual agents: Reductions in heart rate using Polycap and other groups using atenolol alone were similar (–7 beats), reductions in platelet aggregation were similar to those with aspirin alone, reductions in blood pressure were similar to taking the three blood pressure-lowering drugs separately (7.4 mm Hg systolic and 5.6 mm Hg diastolic BP), and LDL was reduced as if using simvastatin (0.7 mmol, approximately 28 mg/dl).

- b) Overall tolerability was similar, assessed by the need for suspension and the report of adverse effects. Permanent suspension was observed in 9.7% to 22.5% with different combinations, and in 16% with the Polycap.
- c) Reductions in blood pressure increased when baseline systolic blood pressure exceeded 140 mm Hg,  $-8.3$  mm Hg, while reduction was  $-6.1$  mm Hg,  $p < 0.08$  in the group with less than 140 mm Hg. Similarly, the percentage reduction of cholesterol was independent from baseline, but absolute reduction was greater when LDL-C exceeded 130 mg/dl. (37)

### SPACE Collaboration

#### GAP Trials - Kanyini-GAP - UMPIRE - IMPACT

SPACE Collaboration (Single Pill to Avert Cardiovascular Events) comprises a series of clinical trials from Australia, New Zealand and India –also sponsored by British groups– about the use of the Red Heart Pill made by Dr. Reddy's Laboratories in India. It is targeted to patients with cardiovascular risk criteria (15% events estimated at 5 years according to the Framingham score, that is, 3% per year), in primary or secondary prevention, when physicians consider that this medication should be prescribed. The aim is to evaluate the impact of concentrating all the drugs in a single pill on the adherence, against the individual use of drugs, as well as its effects on comparable parameters: blood pressure, heart rate, total cholesterol and LDL-C. It uses two combinations, depending on the cardiovascular history: Atenolol with cardiovascular history, and hydrochlorothiazide with no cardiovascular history. The UMPIRE trial will recruit 2,000 patients, 1,000 from India and 1,000 from Great Britain. The Kanyini-GAP trial will recruit 1,000 participants from indigenous populations in New Zealand. The IMPACT trial will recruit 600 patients.

#### The PILL Study: Program to Improve Life and Longevity

This study will recruit 400 patients from various countries (India, Brazil, New Zealand, Great Britain, Australia) with 7.5% risk at 5 years (1.5% per year) according to the Framingham score, who are not receiving adequate treatment. It will compare the polypill from Dr. Reddy's Laboratories, commented above, against placebo. The endpoint will be the adherence and modification of the parameters of blood pressure, lipids, and platelet activity.

#### The Iranian Study

It included 475 patients who were followed up for 8 months; the study compared a pill with four components against placebo. The study had poor adherence: 76/241 participants in the active group and 51/234 in the placebo group stopped taking the medication or did not return for consultation.

Systolic-diastolic blood pressure was reduced by 8 mm Hg/4 mm Hg compared to the placebo group, and cholesterol was reduced by 25 mg/dl.

### Spanish National Center for Cardiovascular Research (CNIC) Project

The CNIC, working in partnership with the Spanish laboratory Ferrer-International, has devised a pill; the project is led by Valentín Fuster and Ginés Sanz. It combines 100 mg aspirin, 40 mg simvastatin, and three different doses of ramipril: 2.5, 5 and 10 mg. The project includes patients in secondary prevention after myocardial infarction, and it will be compared with the usual medication in terms of adherence.

### BALANCE OF RESULTS AND STRATEGIES OF TRIALS

Most of ongoing trials are carried out in populations with poor health care and from low-income countries or population segments. As opposed to Wald and Law's early proposal for the polypill, only populations at high cardiovascular risk or with a cardiovascular history have been included. In most cases, trials compare the usual medication concentrated in a single pill, and only a few of them have been compared against placebo –even in patients at high cardiovascular risk–, but for very short periods of time.

The completed studies have shown good tolerability and greater adherence to the single medication than to the medication separately, with effects on blood pressure and cholesterol, and a similar antiplatelet action.

### CONCLUSIONS ABOUT THE POLYPILL PROJECT STATUS

The evolution of the 'polypill' concept has not followed the direction of the initial proposal. Wald and Law's idea was to apply it as universal indication for the entire population over 55 years of age, with no need for measurements. It was implicit that those individuals with high blood pressure, significant dyslipidemia, diabetes, heart diseases or at high risk due to different criteria would be managed also by their general practitioners. The big bet was to treat groups with no history and at estimated medium or low risk.

The information obtained from clinical trials in recent years has undermined the hope of a health impact through multiple interventions in healthy individuals at low cardiovascular risk. In that regard, we have reviewed the studies on folic acid, aspirin, antihypertensives on the basis of normal blood pressure, the problem of hydrochlorothiazide, the doubts about ACE inhibitors, and finally the controversy on statins for primary prevention and their prescription. Their point in common is that subjects at low cardiovascular risk and with low parameters for current standards should not receive treatment.

In practice, the design of the trials on the polypill has focused on subjects at high cardiovascular risk in primary prevention, with indication of

**Table 2.** Ongoing clinical projects with polypill

Study	Polypill components	Design	Number of patients (n) and follow-up	Conclusion
TIPS	HCT 12.5 mg, atenolol 50 mg, ramipril 5 mg, simvastatin 20 mg, aspirin 100 mg	Phase II Primary prevention Comparison: individual and combined drugs	12 weeks	Effective drug combinations, with good tolerability
SPACE Collaboration (38)	Two formulations: With a CV history	Phase III Parameter and adherence endpoints	n = 1,000 18 months in the GAP trial;	In progress
IMPACT, UMPIRE, Kanyini-GAP Trials (39)	aspirin 75 mg, simvastatin 40 mg, lisinopril 10 mg, atenolol 50 mg With no history: the same, except for HCTZ 12.5 mg instead of atenolol		n = 600 in the IMPACT trial	
PILL Pilot (40)	Same as the previous ones for patients with no history	Phase III Against placebo Effects on parameters	n = 400	In progress
WHO (41) Feasibility	Aspirin 75 mg, simvastatin 20 mg, lisinopril 10 mg, and HCTZ 12.5 mg	Phase II	n = 286 3 months	Good tolerability and acceptance from doctors and patients
CNIC (42)	Simvastatin 40 mg, aspirin 100 mg, and three doses of ramipril (2.5, 5, 10 mg)	Adherence compared with usual post-infarction treatment		In progress
Wake Forest - Irán (43)	Atorvastatin 20 mg, aspirin 81 mg, enalapril 2.5 mg, hydrochlorothiazide 12.5 mg	Compared with placebo	n = 475 at 8 months	Finished: High loss of patients. Acceptable effects on parameters

therapies according to current guidelines, or in secondary prevention. The idea was to assess whether bioavailability and biological effects are preserved when combining four drugs, and also to analyze whether adherence increases, particularly in disadvantaged socio-economic groups.

The approach of combining all the chronic drugs in a single pill is a useful and low-cost contribution, and –as Sanz states in the CNIC project– with significant potential to improve adherence in chronic patients. However, this approach is unrelated to the original project concept of treating the total of the healthy population –regardless of their blood pressure levels, cholesterol or cardiovascular risk– as public health intervention. Trying to simplify the administration of the medication currently indicated by using low-cost components is like a dream for physicians and patients (and perhaps a nightmare for the pharmaceutical industry). If one tried to individualize it, pharmacists should have to prepare prescription drugs, which is currently an almost obsolete practice, except in alternative medicine. This is a topic for discussion, especially among hospital population, but it is part of traditional clinical medicine.

The illusion of medicating the whole of the healthy

population with a single pill has been emptying: each of its components has been questioned for this population, and the original concept has neither been probed nor it is planned to do so in the coming years.

It seems more logical to work on measures through educational interventions like those proposed by Geoffrey Rose (physical activities at schools, intervention on food production, anti-smoking campaigns, etc.), and ideally support, through a universal primary care system, the creation of an interpersonal physician-patient-family dialogue that promotes the adoption of proper strategies according to individual conditions and preferences. But it still remains another illusion.

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