The polypill in cardiovascular prevention: evidence, limitations and perspective – position paper of the European Society of Hypertension

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Antihypertensive, lipid lowering, antidiabetic and antiplatelet treatments all substantially reduce the risk of cardiovascular morbid and fatal events. In real life, however, effective implementation of these treatments is rare, and thus their contribution to cardiovascular prevention is much less than it could be, based on research data. This article reviews the pros and cons of cardiovascular prevention by the polypill approach. It is argued that the high prevalence of individuals with a multifactorial risk profile provides a strong rationale for a therapeutic strategy based on the combination in a single tablet of drugs against different risk factors. It is further argued that other important favourable arguments exist. First, in real-life adherence to all above treatments is very low, leading to a major increase in the incidence and risk of cardiovascular outcomes. Second, although a large number of factors are involved, adherence is adversely affected by the complexity of the prescribed treatment regimen and can be considerably improved by treatment simplification. Third, recent studies in patients with a history of manifest cardiovascular disease have documented that different cardiovascular drugs can be combined in a single tablet with no loss of their individual efficacy or unexpected inconveniences and this does favour adherence to treatment and multiple risk factor control, supporting use of the polypill in secondary cardiovascular prevention. It is finally also mentioned, however, that the polypill may have some drawbacks and that at present no evidence is available that this approach reduces cardiovascular outcome to a greater degree than standard treatment strategies. Trials are under way to provide an answer to this question and thus allow the therapeutic value of this approach to be known.

Keywords: antihypertensive treatment, cardiovascular risk, polypill

Abbreviations: BP, blood pressure; CV, cardiovascular; MI, myocardial infarction

HISTORICAL BACKGROUND

The concept of cardiovascular polypill is aged more than 15 years. It was originally proposed in 2001 by a WHO and Welcome Trust expert group [1] which thought that the combination in a single tablet of four drugs, each with a documented ability to prevent cardiovascular disease [a beta-blocker, an angiotensin-converting enzyme inhibitor (ACEI), a statin and aspirin] might reduce the risk of future events in patients with previous cardiovascular disease [2]. This was taken up 2 years later by Wald and Law [3] who claimed that a polypill containing six agents with proven or potential cardiovascular prevention ability (three antihypertensive drugs, a statin, aspirin and folic acid) would reduce the incidence of cardiovascular events by more than 80% in individuals aged more than 55 years, thereby implementing, if extensively adopted, primary and secondary cardiovascular prevention to an unprecedented degree. However, this 'vaccination approach' found strong opposition from the scientific community which thought that, in addition to being unproven, the extent of cardiovascular prevention claimed by Wald and Law [3] was unrealistic. Concern was also generated by the unknown consequences of medicalizing the entire population, the inconveniences and costs of potential adverse reactions to the high number of assumed drugs, the untoward psychological effects of lifetime treatment in healthy individuals and, last but not least, the possibility of favouring, via the belief of living in a drug-protected state, unhealthy life habits. Without suitable clinical studies demonstrating its efficacy, the polypill strategy did not go beyond an unsubstantiated hypothesis and was abandoned.

In the last few years, a large body of evidence has been obtained that adherence to antihypertensive, lipid lowering, antidiabetic and other drugs that improve

Journal of Hypertension 2017, 35:1546–1553

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Received 20 March 2017 **Accepted** 27 March 2017

DOI:10.1097/HJH.0000000000001390

cardiovascular risk profile is so low [4–12] as to make low adherence perhaps the most important factor opposing cardiovascular risk factor control in the general population. It has also been found that complex treatments, such as those based on multiple daily pills, adversely affect adherence, which can be considerably improved by treatment simplification [13–17]. As treatment simplification is the main characteristics of a polypill, this has revived this strategy as a means to improve the notoriously low efficacy of primary and secondary cardiovascular prevention at the population level [18–23].

The current article will review the arguments provided by epidemiology and treatment in favour of a polypill-based approach to cardiovascular prevention, the evidence that this approach is effective in risk factor control and cardiovascular protection obtained by recent research, and the inconveniences that may be associated with the lumping of several drugs in a single tablet. A conclusion will be reached that, despite some (perhaps ineliminable) cons the available documentation justifies use of the polypill in the context of secondary prevention whereas more evidence is needed to advocate this therapeutic approach in patients with no previous cardiovascular disease. Although touching cardiovascular prevention in general, the review will privilege information on hypertension because several aspects of this condition [high worldwide prevalence, common multifactorial risk profile, need of drug combinations to achieve blood pressure (BP) control and low adherence to the prescribed treatment regimens] may make hypertensive patients especially suitable candidates to a polypill-based therapeutic approach.

EPIDEMIOLOGICAL ASPECTS

A strong argument in favour of the polypill is that most hypertensive patients exhibit a multifactorial risk profile. In the Framingham study, for example, individuals in whom hypertension was the only risk factor were less than 20% of the overall hypertensive population [24], a finding in line with subsequent observations in both United States and elsewhere [25–27]. It is, in particular, well established that, at least in Western countries, the majority of patients with high BP also have abnormalities of the lipid profile, and that hypertension and diabetes, hypertension and dyslipidaemia, diabetes and dyslipidaemia, and the three conditions together, coexist in a noticeable number of patients [28,29]. Indeed, at the population level BP, lipid and glucose abnormalities appear to entertain a relationship not just of a qualitative but also of a quantitative nature, as documented by a progressive increase in the prevalence of hypercholesterolemia and diabetes (as well as of blood glucose, serum total cholesterol and serum triglyceride values) as office or out-of-office BP increases [30]. It has also been found that because of their multifactorial risk profile and the relatively high frequency of asymptomatic organ damage, no less than 30–40% of hypertensive patients can have a 10-year risk of a cardiovascular morbid or fatal event greater than 20% [28], thereby belonging to the high cardiovascular risk category and been thus candidates to antiplatelet treatment [31].

There is a general agreement that in real-life therapeutic control of risk factors by drug treatment is highly unsatisfactory. In hypertension, BP control (i.e. achieving values of $<$140/90 mmHg in the general or $<$150/90 mmHg in the elderly hypertensive population) is achieved in no more than 30–40% of individuals under BP lowering treatment, this being the case both in the context of primary and secondary prevention [21,22,32]. Furthermore, a large proportion of treated hypertensive patients exhibit a limited control of their additional cardiovascular risk factors [28]. Indeed, evidence has been obtained that the greater is the number of risk factors in need of treatment, the lower is the rate of their individual control, suggesting that treatment complexity may negatively affect the physicians' ability and/or willingness to cope with the treatment needs [33]. As a result, many treated hypertensive patients remain in a high cardiovascular risk state, no matter whether BP achieves or does not achieve control [34]. Failure to control additional risk factor is listed as one of the causes of the high residual cardiovascular risk that is persistently documented in hypertensive individuals in whom treatment reduces BP to the recommended target [35].

ADHERENCE TO TREATMENT

Poor control of cardiovascular risk factors has a multifold origin, that is deficiencies of the healthcare system in the area of cardiovascular prevention, failure of physicians to make use of the treatment strategies with documented efficiency, therapeutic inertia (i.e. lack of suitable treatment changes when risk factor control is not achieved) and low adherence to the prescribed lifestyle changes or drugs [36]. The last factor is unanimously regarded as so common as to probably represent the most important barrier against risk factor control. This is true for the treatment of all risk factors, including hypertension which has consistently shown to be associated with a high degree of permanent or prolonged treatment discontinuation as well as by other types of poor compliance to the prescribed therapeutic regimen (occasional failure to assume a prescribed drug, short term or 'week-end' drug discontinuation, drug 'holidays', totally irregular drug assumption etc.) [37], which make the time under BP-lowering treatment regimen often a small fraction of the overall prescription time.

Strong evidence is now available that low adherence to treatment is associated with many adverse consequences. Control of BP, for example, has been shown to bear a relationship with adherence to antihypertensive drug treatment, the same being the case for control of serum cholesterol and lipid profile by statins [38,39]. Poor medication adherence has been found to lead to a faster deterioration of vital organ function and reduction of quality of life [40]. Cost and use of expensive medical resources have been found to increase when adherence is poor [40–43]. Most importantly, several studies have now documented that a close inverse relationship exists between adherence to treatment and the incidence of hospitalization and cardiovascular events [7,8,40,44–52]. To cite some examples, in a meta-analysis of 21 studies, Simpson *et al.* [44] have reported years ago that good adherence to a beneficial drug therapy was accompanied by a 46% reduction of

mortality compared with bad adherence. Observational studies from the Lombardy region have found a better adherence (≥75 vs. <25% of the treatment time covered by prescription) to reduce hospitalization for myocardial infarction (MI), stroke by 24 and 23%, respectively [45], and hospitalization for heart failure by 34% [47]. Similar findings have been obtained in the elderly population [50], and the Lombardy and other data-bases have further shown that a similar marked increase of cardiovascular hospitalization accompanies poor adherence to statin treatment [8,48], and that the increase in the risk of cardiovascular outcome is particularly pronounced following prolonged discontinuation of treatment. In the ADVANCE trial, for instance, diabetic patients discontinuing antihypertensive treatment exhibited a nine-fold increase in the risk of death compared with those continuing treatment [53], whereas in the Lombardy population, discontinuation of antihypertensive treatment for 3 months or longer has been associated with an almost 40% increase in cardiovascular events [45]. Significantly, the association between adherence and treatment effects can be demonstrated also for treatment-related adverse events. A meta-analysis by Simpson *et al.* [44] showed that, in trials in which treatment turned out to be harmful rather than protective (e.g. administration of flecainide in patients surviving a MI), good adherence to the physician's prescription was accompanied by an increased mortality. Along the same line, in the Lombardy data-base, a progressively greater adherence to the prescription of statins was associated with a progressively greater incidence of a well known inconvenience of these drugs, that is new onset diabetes [54].

The factors involved in the adherence to drug treatment have been addressed by several studies and are by and large well established [55–61]. The asymptomatic context in which cardiovascular prevention operates does not favour adherence to medication because some patients fail to grasp the need for taking drugs in absence of any symptom or sign to remove or of any perceivable short-term advantage [55]. Adherence has also been reported to variably differ according to age, sex, ethnicity, educational level, coexistence of other risk factors or comorbidities such as depression (reduced adherence) and cardiovascular or renal disease (increased adherence) [57,59–61]. Perception of treatment inefficiency (i.e. failure to achieve risk factor control) and occurrence of side effects are major causes of low adherence to or discontinuation of treatment [62,63], which is probably why antihypertensive drugs with a better tolerability profile are associated with less treatment discontinuation rates than those with a greater side effect incidence [6,61].

Several additional factors shown to have a relationship with adherence bear a connection with the use of a polypill, that is treatment based on drug combination, reduction in the number of prescribed daily tablets and treatment cost. Combination of two or more antihypertensive drugs is notoriously more effective in lowering BP than monotherapy [64], which is why its use has almost invariably predominated in antihypertensive treatment trials and is currently recommended by guidelines in the majority of hypertensive patients [34]. More recently, population or patient-based observational studies have also shown that treatments based on drug combinations are accompanied by greater adherence to the prescribed therapeutic regimens [61,65], possibly due to the motivating effect of a better BP control on the patient, with a lower incidence and risk of events [66]. Adherence to treatment has also consistently been found to progressively improve as the number of daily tablets is reduced [13], combinations of drugs and complex dosing regimens being repeatedly reported to be associated with lower adherence rate (and BP control) than the simpler ones [14–17,67]. Finally, cost of medications has also been found to be a barrier to medical adherence. In a meta-analysis of studies on cardiovascular disease and diabetes, an 11% increased risk of nonadherence to drug prescriptions has been reported in publicly insured patients required to co-pay their medications [58] whereas in other studies increasing prescription coverage, and thus reducing the patient's financial contribution to treatment, improved medication adherence, with also a reduction in the rate of the first major vascular event [49]. All this argues in favour of combining drugs in a single tablet, allowing the required multiple drug treatment to be delivered in a simplified form. By reducing drug wasting, this can also reduce drug-related costs, a goal that is further promoted by the fact that the polypill components are generic and frequently provided at a price inferior to that of the same drugs given separately. Use of generics does not represent a clinical limitation because recent studies on large numbers of patients have shown antihypertensive drugs and statins to be similar to their brand-name counterparts with regard to both persistence on treatment and risk of cardiovascular outcomes [68,69]. A list of ways to improve adherence to treatment in hypertensive patients is shown in Table 1.

RISK FACTOR REDUCTION, ADHERENCE TO TREATMENT AND CARDIOVASCULAR PROTECTION

The polypill has been predominantly investigated in the context of secondary cardiovascular prevention, particularly in patients with a previous MI, for a number of reasons. First, in patients with established cardiovascular disease the efficacy of drug-related correction of several cardiovascular factors (antiplatelet, BP-lowering and lipid-lowering treatments) has been unequivocally proven by randomized trials [31,70,71], and a greater protective ability has usually been documented when these drugs are used in combination [72].

TABLE 1. Ways to improve adherence

Good doctor/patient relationship
Patient education (on the adverse consequences and benefits of treatment)
Cooperation with patients' relatives and other professionals
Patients' involvement in risk factors management (for hypertension also via self BP measurement) and use of combination of antihypertensive drugs as first step
Minimization of bureaucratic problems related to diagnostic examinations and treatment
Effective/well tolerated treatment
Simplification of the treatment regimen
Use of reminding devices for medical appointments and drug assumption)
Motivational strategies
Prescription of less expensive drugs

Two, compared with primary prevention, secondary prevention is characterized by a more favourable 'number needed to treat ratio' (NNT), that is by a greater number of hospitalizations and events saved for a given number of treated patients, with thus a more favourable cost–benefit ratio, at least over a mid-time treatment duration. Finally, despite its high economical burden for the healthcare system, in patients with cardiovascular disease control of cardiovascular risk factors is still largely ineffective [32] due to underprescription of a number of drugs with documented protective effects, low treatment compliance and, in developing countries, limited availability of medicaments and unaffordable treatment costs.

In the last 10 years, several studies have shown that the polypill strategy can favourably affect cardiovascular prevention in patients with established cardiovascular disease. The second Indian Polycap Study [73] made use of ramipril, atenolol, hydrochlorothiazide, simvastatin and aspirin (supplemented by potassium) in a single capsule (half-dose of the drugs) and compared its effects with the administration of two capsules (full doses of the drugs) for 8 weeks in more than 500 patients with cardiovascular disease or type 2 diabetes. Compared with one capsule, two Polycap capsules (Cadila Pharmaceuticals, Ahmedabad, India) significantly reduced BP by a further 2.8/1.7 mmHg, total serum cholesterol by 7.2 mg/dl and low-density lipoprotein (LDL)-cholesterol by 6.6 mg/dl, with a calculated reduction in the relative risk of coronary disease of 69% and stroke of 57%. Discontinuation of treatment was low and similar in the two groups (6.9 and 7.8%, respectively) showing that the Polycap had a good tolerability.

The use of a multidrug pill in reducing cardiovascular events (UMPIRE) trial [74] has assessed whether a polypill strategy lowered BP and serum cholesterol in several thousand patients with established or at high risk (>15% over 5 years) of developing cardiovascular disease, the primary goal being to determine whether this might be associated with an improved adherence to treatment. Two polypill types were used depending on the extent of baseline comorbidities, that is a polypill containing aspirin, simvastatin, atenolol and lisinopril and another containing aspirin, simvastatin, lisinopril and hydrochlorothiazide. Over a median follow-up of 15 months, the polypill group exhibited a significant improvement in adherence to treatment than the usual care group (86 vs. 65%, $P < 0.01$), an even larger improvement occurring in patients with lower adherence to treatment at baseline. The improved adherence was accompanied by a significantly greater reduction of systolic BP (−2.6 mmHg) and LDL-cholesterol (−4.2 mg/dl), whereas no significant differences in serious adverse or cardiovascular events between groups were observed.

The improving adherence using combination therapy (IMPACT) trial [75] has randomized more than 500 patients with established cardiovascular disease or a high cardiovascular risk (>15% risk of an event over 5 years) to usual care (free combinations) or two different polypill strategies (aspirin, simvastatin, lisinopril and atenolol or hydrochlorothiazide) according to an open-label study design and with self-measured adherence as the primary endpoint. BP and cholesterol reductions were nonsignificantly different between the two treatment groups and so were serious adverse and cardiovascular events. This was not the case for adherence, however, which after 12 months from randomization was 46% and 81% in the usual and polypill treatment strategy, respectively, the difference being statistically significant ($P < 0.001$). Similar observations were made in the Kanyini Guidelines Adherence with Polypill open-label trial [76] in which more than 600 patients with a risk profile and a polypill composition similar to those of the UMPIRE trial showed, after 1.5 years from initial randomization to treatment, a much greater adherence to the polypill-based strategy than to the usual free combination care (70% vs. 47%, $P < 0.0001$). This was unexpectedly not accompanied by a greater BP and serum cholesterol reduction, a finding possibly accounted for by the more limited power of the study compared with that provided by the much higher number of patients available for the UMPIRE trial.

Further significant evidence has more recently been obtained by research conducted in Spain from the Centro Nacional de Investigationes Cardiovasculares (CNIC) in collaboration with Ferrer international. A first polypill containing aspirin (100 mg), simvastatin (40 mg) and ramipril at various doses (2.5, 5 or 10 mg) was extensively tested in preclinical and clinical studies to document a similar efficacy with the free association of its individual components [77,78]. It was thereafter tested in a randomized study on about 700 patients with a history of MI [79]. Compared with a 9 months separate administration of the three drugs, the polypill group showed similar effects on BP (on-treatment systolic value 129.6 vs. 128.6 mmHg) serum LDL-cholesterol (89.9 vs. 91.7 mg/dl), serious adverse events (23% vs. 21%) and death (0.3% in either group). In line with other studies, however, adherence to treatment as measured by both self-reported questionnaire and by pill counting was significantly better in the polypill than in the group in which drugs were given separately, the difference amounting to 22% (50.8 vs. 41.0%, $P = 0.019$). Similar findings have been obtained with a second polypill also containing aspirin and ramipril at various doses, but replacing simvastatin with atorvastatin 20 mg, which has additionally documented the safety, tolerability and bioequivalence of all the polypill components by in-vitro and in-vivo studies [80]. This has led this polypill to receive in 2014 the approval of the European Medical Agency for use in secondary prevention of cardiovascular events in adult patients. The indication specifically mentions that use should consist of substitution therapy whenever patients are adequately controlled by the polypill components at equivalent doses. Table 2 shows the clinical situations in which use of the polypill may be considered.

TABLE 2. Clinical situations in which use of the polypill for secondary prevention of cardiovascular disease may be considered

Patients not adherent to one or more components of drug therapy recommended for secondary cardiovascular prevention
Patients with blood pressure or low-density lipoprotein cholesterol not at the recommended target with free drug administration who have a suspected low adherence to treatment
Patients with adequate control of BP and lipid profile with free antihypertensive and lipid lowering drug administration (substitution strategy)

POTENTIAL INCONVENIENCES

The polypill approach is not exempted by potential inconveniences whose impact can, in some instances, be minimized, whereas in other instances it may be not entirely avoidable. From a technical standpoint, the decision to include different compounds in a polypill must consider a number of problems, that is the chemical compatibility, physical stability and pharmacokinetic properties of each component vs. the others [81,82]. Combining components with different solubility and sensitivity to heat and moisture, for example, can reduce the availability of some drugs as well as, in part, their pharmacokinetic and pharmacodynamic characteristics [80]. Large differences in the concentration of some drugs vs. others, for example few milligrams of one compound vs. hundreds of another, may also modify the expected overall biological effect. Even if the original pharmacological characteristics of the drugs are retained, care should always be taken to only combine drugs with complementary mechanisms and a similar duration of action to ensure a balanced effect throughout the between-dose interval. The problems may of course increase steeply as the number of drugs in a polypill increases.

Several clinical inconveniences must also be taken into consideration. One, although minimized by the availability of polypills with different doses of drug components, titration to multiple risk factor control may sometimes be difficult, such as when the dose of statin to achieve the LDL-cholesterol target may need an increase whereas no increase of antihypertensive drugs is needed because target BP values have already been achieved. Two, a polypill cannot be used if there is contraindication to just one of the polypill components. Three, when serious side effects appear, the polypill has to be discontinued, leaving the patient unprotected against all risk factors before treatment is resumed on a free basis. A similar problem can materialize, when patients miss a polypill dose, an event that in real life remains common even when adherence improves. Finally, as recently suggested [83], pursuing cardiovascular risk factor correction by a comprehensive simple pharmacological approach might minimize, in the eye of the patient, the importance to pursue this goal by appropriate lifestyle changes as well. This can be minimized, however, by implementing patient's information and education.

ONGOING STUDIES AND OPEN QUESTIONS

The ability of a polypill to effectively control BP and lipid-related risks argues in favour of cardiovascular protection because antihypertensive and lipid-lowering treatment trials have shown protection to majorly depend on risk factor control 'per se' with less (and debatable) contribution of 'pleiotropic' drug properties [84,85]. Yet, the absence of outcome-based randomized trials represents a major limitation because it precludes information on the extent of cardiovascular protection achievable by combining multiple cardiovascular risk factor interventions with an improved adherence to treatment, thereby allowing calculation of the cost-utility of this approach. However, some of these trials are under way. The Polyran study [86] is seeking to determine the effects of a polypill containing antihypertensive medicaments, atorvastatin and aspirin on primary and secondary prevention of cardiovascular disease in Iranian patients aged more than 50 years. Three arms are planned: 3500 randomly selected participants will receive minimal preventive care and educational material, that is a pamphlet on cardiovascular risk reduction, biannual visits and BP measurements; 3500 patients will receive the above and the polypill once daily; and 24 000 participants will receive the standard primary health care, consistently with the current Iranian Healthcare System guidelines. Major cardiovascular events (death and hospitalizations) will be the endpoint.

The secondary prevention of cardiovascular disease in the elderly (SECURE) study [87] is a multicenter, randomized study funded by the European Union Horizon 2020 Research Program and designed to evaluate the new CNIC-Ferrer polypill (aspirin 100 mg; ramipril 2.5, 5 or 10 mg; and atorvastatin 40 mg) as a valid comprehensive strategy for secondary cardiovascular prevention. SECURE will enrol 3206 patients aged more than 65 years with a recent MI from several European countries. Patients under the polypill will be compared with those under usual care based on aspirin, an ACEI, and a statin administered in single pills, and the benefit will be assessed through the difference in major cardiac and extracardiac vascular events, including revascularization.

Several other aspects of the polypill use are in need of clarification. It would be important to know, for example whether a polypill approach may (1) substantially delay progression of chronic kidney disease, thereby including in its benefits patients that majorly contribute to the burden of the healthcare systems; and (2) can be profitably used in advanced renal disease as well in which treatment complexity is so high as to make its simplification a valid goal 'per se'. It would also be important to know whether the polypill approach should be limited to secondary cardiovascular prevention or it may be extended to patients without a history of cardiovascular disease, but with a high cardiovascular risk profile. This might appear as a reasonable option not only because these patients have already been included in some studies that have documented the potential therapeutic benefits of the polypill, but also because these patients share with patients who had a cardiovascular event a multifactorial risk profile, a low treatment adherence, and a similar BP target for antihypertensive treatment [34]. Last but not least, use of the polypill in patients at low-to-moderate cardiovascular risk should not be completely forgotten by research because these patients may also have a multifactoral risk profile, albeit with more modest risk factor abnormalities than those seen in high risk individuals. Furthermore, their adherence to cardiovascular risk correction is even lower than that of high-risk patients [61]. Finally, recent studies show that early correction of a mild or moderate increase of cardiovascular risk is a fundamental measure to prevent progression to a high-risk condition that is much less effectively reversible with treatment [88], leaving even well treated patients at a high residual risk.

TABLE 3. Optimal composition of a polypill – questions

Less or more potent drugs
Lower or higher drug doses
Two or three antihypertensive drugs
Should aspirin be a regular component?
Should antidiabetic agents be included?
Other components: drugs, vitamins?

A final issue is the optimal composition of a polypill (Table 3) [89,90]. One, whether preference should be given inclusion of (1) less or more potent drugs such as simvastatin rather than atorvastatin or rosuvastatin, hydrochlorothiazide rather than chlorthalidone; (2) lower vs higher drug doses (e.g. simvastatin 20 or 40 mg/day) and (3) three or two antihypertensive drugs. In each case, the former choice would more easily achieve the rigorous risk factor control required in secondary prevention whereas the latter would guarantee a better tolerability and safety, which is an equally important clinical goal, particularly in the elderly in whom side effects, may have far reaching adverse consequences [91]. Two, whether aspirin should be a regular component of a polypill or its bleeding effects may make it desirable for this drug to be included only in polypills to be used in patients with a very high cardiovascular risk, in which the benefit of antiplatelet interventions clearly exceeds their inconveniences [31]. And three, whether the polypill represents a valuable approach also for the treatment of type 2 diabetes, because in this condition BP-lowering and lipid-lowering treatments account for an important portion of the overall protective effect of treatment against diabetes-dependent macrovascular and microvascular complications [92,93]. A polypill to be used in diabetes might in principle also include antidiabetic agents selelcted among those friendly to use and with evidence of cardiovascular protection. Thus, several options may have a clinical justification, and indeed the availability of polypills with different numbers, types and doses of drugs will probably be developed in the future to make the approach suitable to many patients, and effective for both less and more demanding therapeutic targets.

ACKNOWLEDGEMENTS

Conflicts of interest

GM has received speaker's or consultation fees from: ACTAVIS, AMGEN, ASTRA ZENECA, BOEHRINGER, FERRER, MEDTRONIC, MENARINI, NOVARTIS, RECORDATI, SANOFI, SERVIER.

AC has received honoraria for eductional activities sponsored by Menarini International, Ferrer International, Servier and Sanofi.

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