Benefits, challenges, and registerability of the polypill

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Introduction

Cardiovascular disease (CVD) is the most common cause of death in Western countries and will continue to be so in 2020.1 A correlation has been demonstrated between CVD, stroke, and renal failure and a number of modifiable risk factors, including hypertension,2 dyslipidaemia,3–5 platelet function,6 and homocysteine levels,7,8 although the risks associated with the latter now seem to be of less importance.9 As cardiovascular (CV) risk factors commonly co-exist,10 high-risk patients with hypertension, obesity, and diabetes may well benefit from a combination of aspirin, antihypertensive agents, lipid-lowering drugs, and possibly folic acid. This led Professor Wald’s group to propose a six-component polypill for the primary prevention of CVD in everyone over the age of 55 years.11–13 We support the polypill concept, however, we suspect that both the healthcare professionals and the public will need a long period of education and consultation before this is accepted and suggest that it might be better to first target secondary prevention. As the most suitable drug combination depends on a patient’s characteristics and co-morbidities, it may also be better to be less ambitious and consider a series of polypills comprising three or four components.

Although the expectation might be that patients who receive numerous therapies for secondary prevention will be at higher risk than those who receive fewer therapies, unpublished results from the Maximal Individual Therapy in Acute Myocardial Infarction (MITRA) registry14 (n = 6067) demonstrate that post-myocardial infarction (MI) survival is significantly improved in patients who receive four medications [aspirin, beta-blocker, angiotensin-converting enzyme (ACE) inhibitor, and statin] when compared with those who receive zero, one, or two agents (unpublished results) (Figure 1). Similarly, a survey carried out in French hospitals demonstrated consistently better 1-year survival rates in patients with acute MI (n = 2320) receiving triple-combination therapy than in those receiving single medications, irrespective of whether the treatment comprised antiplatelet, lipid-lowering, or antihypertensive agents (Figure 2).15 Increasing the number of medications, however, can have a negative impact on compliance and/or adherence to therapy16,17 and, as a result, multiple-target, fixed-combination pills are being developed, which have the potential to alter the delivery of CV treatment.

The CV polypill

In their controversial article published in 2003, Wald and Law18 proposed that a single daily pill combining half-doses (to minimize toxicity) of a beta-blocker, thiazide diuretic, and an ACE-inhibitor, together with a statin, folic acid, and aspirin, and taken by everyone aged >55, could reduce the incidence of CVD by over 80%. Furthermore, the authors claimed that approximately one in three people would gain an average of 11–12 years of heart attack- and/or stroke-free life. The objective of the polypill was to improve four key CV risk factors simultaneously: LDL-cholesterol, blood pressure (BP), serum homocysteine levels, and platelet function. The proposed benefits are based on a series of meta-analyses, which suggest that statin use lowers mean LDL-cholesterol levels by 1.8 mmol L\(^{-1}\) (69.7 mg dl\(^{-1}\)), thereby decreasing the risk of ischaemic heart disease (IHD) and stroke by 60 and 17%, respectively. Furthermore, half-doses of multiple
antihypertensive drugs can significantly lower BP with fewer side effects than the full dose and can reduce the risk of IHD by 46% and stroke by 63%. Importantly, Wald and Law estimated that adverse events would only warrant discontinuation of the pill in 1–2% of patients and that fatal side effects would occur in less than one in 10,000 users.

Despite these findings, the concept of multiple-target combination products has met with numerous challenges, and their development is still in its infancy.

Challenges and requirements for success

The success of any new agent, including a fixed-dose, multiple-action combination pill, depends on several factors, including the following.

Physician acceptability

Physicians like to have the flexibility to titrate individual agents and, as a result, are often hostile to the concept of fixed-dose combination pills. In practice, however, physicians often manage unresponsive patients by prescribing an alternative agent rather than titrating the dose. Considerable re-education of both primary care and specialist physicians will, therefore, be required to improve physician acceptance of the polypill.

Pharmaceutical/formulation issues

Not all drugs are suitable for use in combination products. Candidate agents should be safe, well tolerated, effective in sub-maximal doses, and physicochemically compatible with the other components of the pill. The potential for drug–drug interactions that affect the bio-availability and/or efficacy of the individual agents must also be considered.

Cost

The eventual costs of a polypill are likely to be much greater than the simple addition of the generic components. Although combining multiple generic drugs in a single packaging should, in theory, be cost-effective, the individual agents are often substantially more expensive than might be expected. Furthermore, the pharmaceutical costs of development and registration will not be trivial, and as each additional component can cause a logarithmic increase in the workload required to prove the safety and efficacy of a product, cost-effectiveness is likely to decrease as the number of components increases. The predicted return on investment might, therefore, be surprisingly small.

Registration

If a combination product comprises drugs that are already available, evidence of its likely efficacy and safety can largely be obtained from existing large-scale clinical trials and meta-analyses. Although the regulatory authorities will require, at the very least, a demonstration of pharmacodynamic/pharmacokinetic efficacy using surrogate markers, they will hopefully not require hard endpoint data. Large-scale morbidity and mortality trials would be both prohibitively expensive and ethically challenging.

Patient acceptability

This partly depends on the ease with which a treatment can be administered—the number of pills, the dosing time and interval, and whether the pill is easy to swallow and can be taken with food and drink—and the occurrence of side effects. In the case of Wald and Law’s hypothetical ‘polypill’, the inclusion of aspirin (the uncoated form of which is associated with dyspepsia) has the potential to cause side effects that might lead to treatment discontinuation and hence loss of benefit from the other drugs. Similarly, the inclusion of a beta-blocker can cause severe side effects in patients with unrecognized (or forgotten) bronchospasm or asthma. The use of beta-blockers in elderly patients with hypertension (except for post-MI patients) is now increasingly questioned because of adverse effects on glucose metabolism as well as poorer effectiveness when compared with newer antihypertensive agents.19,20

Table 1 summarises the pros and cons of multiple-action, fixed combination medication.
Committee for Proprietary Medicinal Products (CPMP), 22 matters further, the ‘A plus B’ rule is only really appropriate for fixed-combination products, such as amlodipine besylate/benazapril hydrochloride (HCl), which have a single therapeutic aim (reducing BP). The effects of combining agents with different therapeutic targets, such as lipid and BP (atorvastatin/amlodipine, for example) or lipid and platelet aggregation (pravastatin/aspirin), are harder to assess unless wider endpoints, such as CV morbidity and/or mortality, are used. One hopes, however, that the regulatory authorities will be less demanding, as the cost of a complex bio-equivalence study would effectively rule out the development of any polypill and, in any case, too many dose combinations would defeat the object of developing a simplified combination therapy.

According to old guidelines from the FDA and CPMP,22,21 fixed-combination products should not change medical practice simply because they are convenient—they must also provide health benefits. Three types of product labelling are available according to whether a product is indicated in first-line therapy, second-line therapy, or as a convenience for patients who require simplified therapy.

First-line therapy
For a fixed-combination product to be indicated in first-line therapy, a low-dose combination of Drugs A plus B must be more effective than the respective high-dose monotherapies and have a similar side-effect profile or be similarly effective but have fewer side effects. Examples are amiodipine besylate/benazapril HCl and telmisartan/hydrochlorothiazide.23,24

Second-line therapy
Fixed-combination products can be indicated in second-line therapy in patients who fail to achieve a satisfactory benefit/risk ratio with monotherapy and require additional agents or dose titration. In such cases, fixed-dose combination products are recommended if one or more of the components diminishes the dose-related side effects of the other(s). For example, the ACE-inhibitor benazapril reduces the incidence of ankle oedema in patients treated with the third-generation calcium-channel blocker amlodipine besylate.25

Convenience therapy
A fixed-combination product can be indicated for convenience if it has the potential to simplify therapy by improving the dosing strategy or pill burden. If a product achieves this without providing additional health benefits, the convenience claim should be restricted to non-prescription (over-the-counter) products, which are fraught with problems. For example, the recent UK case of over-the-counter licensing of a low dose of statin has been questioned in an authoritative critique from the independent and highly respected Drugs and Therapeutic Bulletin.26 Furthermore, as reducing the pill burden has the potential to improve compliance to therapy, it may be necessary for regulatory authorities to relax their former guidelines and rethink their current restrictions on product labelling.

The burden of proving the safety and efficacy of a combination product lies with the applicants rather than with the regulatory authorities. Applicants must provide proof that each product contains the appropriate drug ratios and

Table 1  Pros and cons of multiple-action, fixed combination medication

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<td>Concerns that such a pill be too big to swallow</td>
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Regulatory guidelines for multiple-target, fixed-dose combination products
Before approving (registering) monotherapies, some believe that the regulatory authorities, such as the American Food and Drug Administration (FDA)21 and the European Committee for Proprietary Medicinal Products (CPMP),22 will continue to require appropriately analysed data from randomized, controlled clinical trials, which demonstrate clear benefit vs. placebo or another effective drug in terms of quality and/or quantity of life. One hopes, however, that this restrictive attitude will change. Once approved, the authorities have little control over the doses prescribed or whether a drug is taken alone or in combination with additional agents. In contrast, by registering a fixed-dose combination product, the regulatory authorities are effectively advocating both the dose and the combination of two or more drugs. As a worse case scenario, for such products to be approved, each active component must contribute to the therapeutic effect of the combination product, e.g. the benefits of specific doses of Drug A plus Drug B must be greater than the effects of either drug alone. In the case of a two-drug combination, a factorial trial testing five doses per agent might require a minimum sample size greater than 800. To complicate matters further, the ‘A plus B > A or B’ rule is only really

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minimal doses, that the product is safe and effective in a significant proportion of the target population, that the benefit/risk ratio is at least as good as that of the individual agents, and pharmacodynamic and pharmacokinetic data to assess drug–drug interactions. The applicant is also required to assess any clinically beneficial pharmacokinetic interactions in healthy subjects, patients, and high-risk subgroups (such as the elderly and those with diabetes and/or renal disease). Thus, although drug–drug interactions are a major concern for the development of combination products, thorough assessments have the potential to improve the safety of these medications when compared with more traditional single therapies, which are often used in combinations that have not been formally tested.

For products that combine established drugs, often used concomitantly (such as antihypertensive agents and statins), well-founded bibliographic data can be used to provide a rationale for the proposed doses, thereby minimizing the number of new studies that must be carried out.

Justification for fixed-combination products

Justification for combining various active components in a single pill must be based on valid therapeutic principles, which take into account the potential advantages and disadvantages. The advantages of a combination product might include simplification of therapy leading to improved patient compliance and an improvement in the benefit/risk assessment due to the following.

(i) The addition or potentiation of a therapeutic benefit, i.e. a combination product is as effective as higher doses of the individual components but has a better safety profile or is more effective than a single substance with an acceptable safety profile.

(ii) An improvement in the side-effect profile of one drug due to an interaction with another. This is only considered a valid benefit, however, if the side effect that is counteracted is serious or common and was not created to discourage drug abuse. (The addition of an antinausea agent to morphine, for example, is unlikely to meet the approval of the regulatory authorities.)

The degree of acceptance of fixed-combination medications varies from country to country, with America and Europe leading the field, followed by countries such as Canada and Australia, and then Japan. In the USA, numerous single-target combination products have been approved, as well as two mixed-target combination pills, atorvastatin/amiodipine and pravastatin/amlodipine and pravastatin/aspirin. In contrast, the Japanese regulatory authority will not, at present, consider applications for multiple-target combination pills and has yet to approve any of the single-target combinations that are registered in almost every other country. It is hoped, however, that this attitude may change as a result of current discussions.

Although it is agreed that most patients (even the simplest cases or those having only hypertension without any other disease) require more than one drug, the implicit notion that it is known, or has been demonstrated, that having all of the medications in one pill have a measurable effect on compliance and therefore would benefit public health is still a matter for debate.

A number of other challenges are still to be addressed. The need for separate titration of individual ingredients may be important in a number of situations. This may require the design of pills of different strengths in order to cover all of the possible doses of each of the titrated ingredients. Deciding on how many of such pills should be made available is also an important challenge.

Discussion

It is estimated that ~50% of all patients discontinue their prescription medication within 1 year of initiation, and an additional 35% discontinue their treatment after 2 years. Furthermore, because of poor adherence, 30–50% of prescriptions fail to produce the desired therapeutic results in patients with chronic medical conditions. Although it is generally accepted that reducing the pill burden improves adherence and/or compliance to therapy, very few data are available to support this theory. This is largely because adherence and compliance are difficult to quantify in normal clinical practice. Data from clinical trials may not be applicable because of improved monitoring and more compliant patients. In a retrospective cohort study evaluating 10,526 participants in a US-managed care plan, patients receiving two or more medications in addition to their BP- and lipid-lowering agents were up to 45% less likely to adhere to their therapy than those receiving zero to one additional medications (Figure 3). Similarly, a retrospective claims analysis using data from several managed-care organizations during 1999–2000 demonstrated that the percentage of patients adhering to concomitant BP- and lipid-lowering therapies was significantly less than the percentage adhering to either BP- or lipid-lowering therapy alone [32.9 vs. 54.7% (P < 0.005) and 42.0% (P < 0.005), respectively, after 9–10 months]. If future studies are able to demonstrate a significant relationship between the simplification of therapy and compliance, guidelines that currently exclude convenience as sufficient justification for combination products may need to be revised. Many elderly patients are confused and take their pills haphazardly and/or in the wrong dosage. A polypill would be expected to help this group of patients considerably.

Figure 3 Adherence to lipid- and BP-lowering therapy decreases as the number of additional medications increases.16
In addition to reducing the pill burden, combination products have the potential to improve compliance by allowing some patients to achieve their therapeutic goals more quickly than they might with monotherapy. This is especially important in patients with asymptomatic conditions, such as hypertension and dyslipidaemia, who may be tempted to discontinue their medication unless a measurable benefit is achieved within the first few months of treatment. Furthermore, the recent Valsartan Antihypertensive Long-Term Use Evaluation trial demonstrated a significant CV benefit of more rapid BP control. 19

Multiple-target combination products can also improve CV risk management by encouraging physicians to treat global risk, rather than individual risk, factors. This is essential because CV risk factors, such as hypertension and dyslipidaemia, frequently co-exist and interact in a multiplicative, rather than additive, manner. 20 On the basis of this knowledge, many large-scale CV outcome trials, such as the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial–Lipid-Lowering Arm 30 (n = 10,359) and the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid-Lowering Arm 31 (n = 10,305), have included both antihypertensive agents and statins. Although some argue that additional studies are required to determine the optimal dose combination and the exact indications for each product, others believe that existing large-scale clinical trials are sufficient proof of safety and efficacy and that the development of combination pills should focus on drug delivery and packaging.

In terms of safety, potential risks are associated with ‘hiding’ active components in a single pill. If the name of the combination product does not reflect its active components, users may not be aware which drugs they are taking. As a result, they are less likely to inform their physician or pharmacist of their current medication(s) and are more likely to take additional agents that interact with their combination drug and lead to adverse effects. The hidden inclusion of beta-blockers in a combination product, for example, may be of concern for any patient with bronchospasm. Thus, detailed product labelling is essential to ensure that all patients are adequately informed about their combination products.

Conclusions

Guidelines for the management of CVD stress the importance of treating global risk, rather than individual risk, factors. 22–24 Patients at high CV risk, for example, benefit from a combination of aspirin, antihypertensive, and lipid-lowering agents. 35,36 As the number of medications increases, however, adherence and compliance to therapy are likely to decrease. 16,17 The use of multiple-target, fixed-combination products, such as atorvastatin/amlodipine and aspirin/pravastatin, which concomitantly reduce multiple risk factors without increasing the pill burden or the risk of adverse effects, has the potential to improve CV risk factor management, thereby reducing the incidence of CVD. Discussions with regulatory bodies are required in order to obtain some ‘balance’ between an overcautious registration approach and the potentially large public health benefits that would arise from affordable combinations of well-proven therapies.

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