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INVITED EDITORIAL
Prevention and epidemiology

Reaping the rewards of a simplified dosing regimen

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The recent history of cardiovascular medicine has been an outstanding success. Ferrari and Luscher have described how the reduction of cardiovascular disease (CVD) risk with new drugs is responsible for extending average expectancy by 6 years out of a total of 8 years for all medical interventions.[1] This remarkable achievement has been enacted through the systematic identification of risk factors (hypertension, apo-B-containing lipoproteins, smoking, hyperglycaemia, obesity) and the rational design of therapeutics to target each, in addition to addressing suboptimal lifestyle factors.[2]

Such approaches are clearly effective—the best evidence collated from multiple trials of different agents demonstrates that each 5 mmHg reduction in systolic blood pressure reduces the risk of major cardiovascular events (MACE) by 10–20% in adults aged less than 85 years.[3] Similarly, each 1 mmol/L (40 mg/dL) reduction in low-density lipoprotein cholesterol (LDL-C) reduces risk of MACE by approximately one-quarter.[4] Nevertheless, such undoubted success is not without complications.

The multifactorial causes of CVD and their amelioration by multiple specific treatments can result in patients having a substantial medication burden. Moreover, looking at the ongoing trials with new drugs for residual CVD risk factors e.g. associated with lipoprotein(a) or inflammation, it seems the optimal approach to CVD risk factor might be even more a challenge.[2] The polypharmacy often results in poor adherence and persistence of therapy and, therefore, poor outcomes for patients. Such effects are amplified in a manner which is not always apparent to prescribers, owing to the unrecognized substantial prevalence of adults (without physical cause) who have an aversion to swallowing tablets and capsules.[5] Whilst patients can be taught to swallow tablets more effectively,[5] however increased consideration has been especially given in recent years to reducing pill burden via combination therapies [often called fixed-dose combinations (FDC) or single pill concept (SPC)]—dosage forms (typically tablets or capsules) that contain more than one active ingredient.

Whilst antihypertensive combination therapies have been available in some regions for many years, great interest in this field was provoked by the promotion, by Wald and Law in the early 2000s of the 'polypill' concept of a single dosage form containing multiple agents, which had been demonstrated to significantly reduce cardiovascular risk.[6] Initially, much of the focus of this approach was on combining tried-and-tested off-patent drugs to produce a cheap and effective formulation.[7] The approach has been recognized as having a great value, and the European Society of Cardiology (ESC) Guidelines for the management of hypertension recommend initial combination therapy using a fixed-dose combination approach.[8] The same approach of upfront lipid lowering combination therapy (preferably as FDC) was recommended by the International Lipid Expert Panel in 2021 for very high CVD risk patients,[9] and next in the ESC Acute Coronary Syndrome Guidelines 2023.[10] Currently, the novel lipid-lowering agent, bempedoic acid, is available in a fixed-dose combination with ezetimibe,[11] and other drugs under development will be available as FDC with ezetimibe from the beginning (e.g. obicetrapib).

In light of these developments, the article by Weisser *et al.* 'Effect of a single pill concept on clinical and pharmacoeconomic outcomes in cardiovascular diseases'[12] published in this issue of *European Heart Journal—Cardiovascular Pharmacotherapy* is a most welcome addition to the literature. The authors sought to test the hypothesis that a SPC is superior to a multi-pill concept (MPC) in reducing CVD events, all-cause death, and costs in CVD patients. The authors used anonymized medical claims data between 2012 and 2018 from a population of patients with hypertension, dyslipidaemia, and CVDs, who started drug therapy either as SPC or an identical drug regimen delivered as an MPC. In order to reduce the bias inherent in such an observational study, 1:1-Propensity Score Matching (PSM) was employed. They found that the SPC approach was associated with a lower risk of all-cause mortality [incidence rate ratio (IRR)=0.62; 95% CI 0.57–0.68; $P < 0.001$], stroke [IRR = 0.77; 95% confidence interval (CI) 0.67–0.88; $P < 0.001$], myocardial infarction (IRR = 0.76; 95% CI 0.63–0.90; $P = 0.0016$), heart failure (IRR = 0.59; 95% CI 0.54–0.64; $P < 0.001$), and a range of additional outcomes.[12] The also noticed that mean time to first events and time to death were also in favour of SPC. Importantly, what was many times raised as an argument against polypills, mean total costs were 4708€ for SPC

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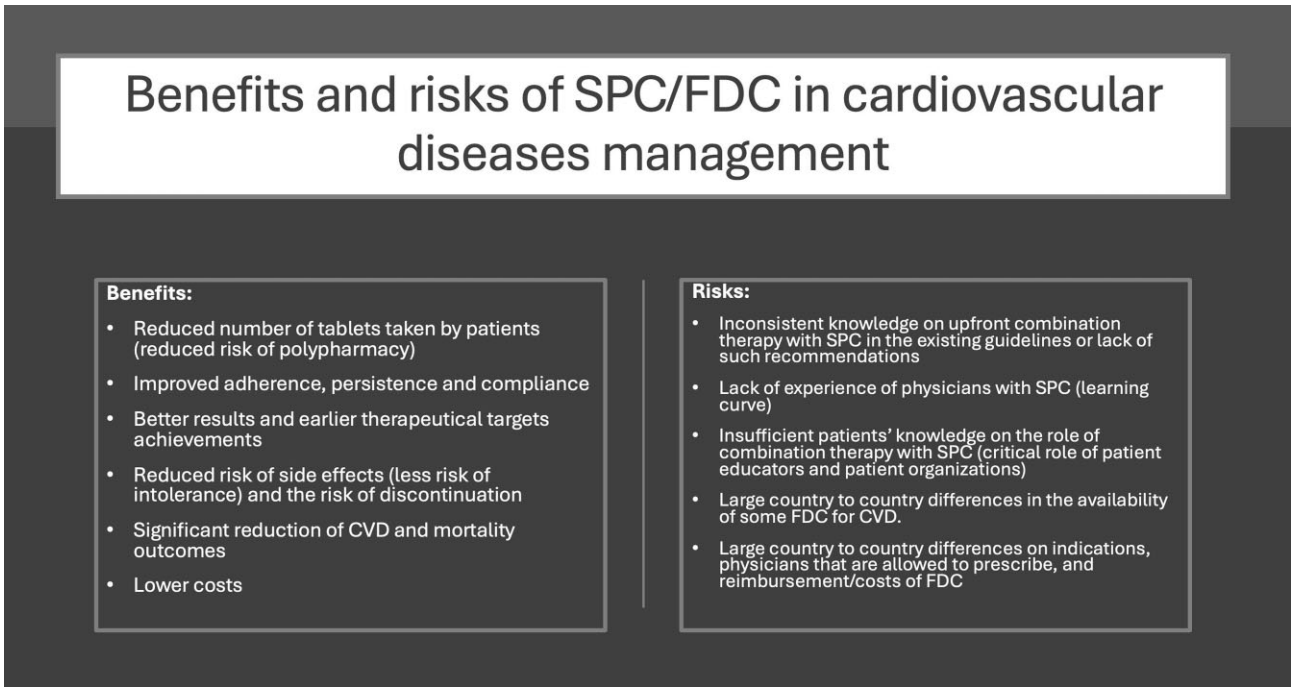

Figure 1 Benefits and risks of single pill combination/fixed-dose combinations in cardiovascular diseases management.

vs. 5.669€ for MPC, respectively ($P < 0.001$). The authors conclude that, therefore, the SPC approach should become the (gold) standard of care in the treatment of hypertension, dyslipidaemia, and the secondary prevention of CVD.[12]

Whilst these conclusions seem rational and in line with the findings of other studies, it is important to consider some limitations of the study. The study included a very heterogeneous population, and whilst it may be argued that this improves the external validity of the study, it may complicate the interpretations of some findings. Of particular note, in the propensity-matched population, approximately 95% of patients had hypertension, whereas less than half had hyperlipidaemia, which does not reflect the population data. Whilst any extent of lipid (LDL-C) lowering appears to be effective, with no lower limit observed in studies,[13,14] whereas excessive blood pressure lowering may result in adverse effects. Therefore, an analysis of this type with a majority of hypertension patients may in fact underestimate the potential benefit which could be achieved in a population whose cardiovascular risk was driven to a greater extent by dyslipidaemia. Furthermore, the study necessarily treats all types of fixed-dose combinations equally in the analysis when they vary substantially in their composition and the effectiveness of the drugs included within them for the deduction of cardiovascular events. As with any observational study, residual confounding cannot be entirely eliminated, even after PSM, and it is important to note that the choice of treatments given to patients will have been made on clinical grounds in each case, potentially allowing for confounding by indication. Finally, it is also notable that the data in this study stopped in 2018. Since then, access and availability e.g. of injectable therapies for LDL-lowering (such as inclisiran[15] and monoclonal antibody PCSK9 inhibitors[16]) afford us new opportunities to improve the long-term management of cardiovascular risk factors even without the need for daily tablets.

Despite these limitations, the paper nevertheless adds to the body of knowledge already available from randomised controlled trials. By including a large number of patients (approximately 50 000) and following up over years, the study has sufficient statistical power to evaluate the effect of fixed-dose combination therapy on mortality outcomes—and the findings appear to be very promising. It is always reassuring when hard clinical data support common-sense clinical practice, and based on these data, it does indeed seem that fixed-dose combination therapy can improve compliance and, crucially, outcomes for patients at risk of CVD, and should be recommended in all guidelines for CVD management (*Figure 1*).

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Data availability

No new data were generated or analysed in support of this research.

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