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One pill, four questions: what we still need to know about reducing cardiovascular risk with combination therapy

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The benefits of combination therapy were originally described more than a century ago.[1] Combining drugs with a common therapeutic target and disparate off-target effects allows improved efficacy with fewer or less severe adverse effects. This strategy has been employed widely in chemotherapy for infections, hypertension, diabetes, psychiatric disorders, respiratory diseases, and cancer.

The combination of fixed doses of drugs may also offer additional advantages in terms of simplicity, scalability, patient acceptability, and adherence, with potential for substantial cost savings and task shifting.[2] Use of fixed-dose combinations (FDCs) also has a long history, having been used for the treatment of high blood pressure since the 1950s.[3]

Cardiovascular disease is now the single greatest threat to global health. Adverse trends in smoking, nutrition, obesity, and diabetes are expected to impose an increasing health burden in low- and middle-income countries. Could FDCs play a larger role in primary and secondary prevention of cardiovascular events?

Over a decade ago, Wald and Law proposed that an FDC consisting of half-therapeutic doses of statin, two antihypertensive agents, aspirin, and folate would be well tolerated and might reduce cardiovascular disease by 80%.[4] In view of the risk-benefit balance they advocated that this 'polypill' might be prescribed to everyone over the age of 55 without screening. This proposal for population-level drug therapy received wide attention and comment - some hyperbolic,[5] some more cautious.[6] The prospect that a cheap FDC might be particularly useful for secondary prevention of cardiovascular events in low- and middle-income countries was also recognised.[7,8] However, the gap between concept and reality can often be large: unpleasant facts have frequently murdered beautiful theories, so extensive testing of a cardiovascular FDC or polypill was always going to be required. That process has begun.

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Declarations of interest

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A new systematic review and meta-analysis by de Cates and colleagues summarises the current state of knowledge regarding some aspects of efficacy and disutility of cardiovascular FDCs from nine phase II randomised trials ($n = 7047$), largely conducted in higher-risk populations.[9] It is important to note that the FDCs included in the analysis were single pills of diverse composition and doses (although all contained a statin and at least one antihypertensive agent) and had a range of comparators (placebo, single drug active component, or 'usual care'). The authors found no convincing evidence of either benefit or risk for FDCs in terms of all-cause mortality or cardiovascular events, but the data are too limited (only two studies reported these outcomes) and the duration of follow-up too short to draw meaningful conclusions. This is unsurprising given that these phase II trials were primarily designed to evaluate changes in cardiovascular risk factors and adherence.

The authors also found that the average effect size of FDCs on cardiovascular risk factors were considerably smaller than those predicted by Wald and Law, indicating the importance of empirical data from randomised trials as the basis of a realistic estimate of the benefit from a FDC approach, rather than one based on a modelling strategy. It is highly likely that these estimates derived from randomised trials still exaggerate effects compared with use in 'real-world' circumstances.[10] FDCs were also associated with a modest increase in reported adverse events and an increase in discontinuation, factors which may need to be set against any anticipated improvement in adherence.[11]

So where do we stand with FDCs or polypills for cardiovascular disease? FDCs improve cardiovascular risk factors, but not as much as was hoped. The widespread use of polypills in the unscreened community seems doubtful at present, and there is substantial resistance to mass medication.[12] The case for the use of FDCs in global secondary prevention is persuasive, but several questions remain. Firstly, if FDCs are to be used for secondary prevention should they contain low or half doses of active agent? Higher doses would seem more rational for secondary prevention. Secondly, how much gain in terms of adherence will be achieved when a single cardiovascular pill has to be combined with other therapies in older people with multiple pathologies (e.g. diabetes, osteoarthritis, and psychological illness)? Perhaps a wider range of FDCs needs to be developed that is appropriate for common disease combinations, not just cardiovascular disease. However, and this is the third question, it is not clear who will develop them – enthusiasm from the pharmaceutical industry has been predictably muted for a pill with such low profit margins. Inclusion of cardiovascular FDCs in the WHO Model Lists of Essential Medicines might be helpful in this regard.[13] Finally, and perhaps most importantly, the cardiovascular benefits of cheap effective FDCs will only be fully realised through properly functioning universal healthcare systems with good engagement of practitioners and patients. There is a risk that FDCs could distract from investment in public health,[14] or worse, like many strategies targeted at high-risk individuals, exaggerate inequities in health care.[15] Even in the absence of universal health coverage, further studies are needed to evaluate how best to deliver FDCs in an equitable and sustainable manner in local healthcare systems if they are to make a useful contribution to global health.

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