Heart Metab. 2019;79:38-39

Will the polypill be the solution?

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Abstract: The polypill is a fixed-dose combination of individual drugs given to reduce the risk of future cardiovascular events. The idea is very attractive, but currently there are several unknowns that make it difficult to implement. These unknowns include the exact constituent drugs, the baseline cardiovascular risk at which treatment becomes acceptable, and the added value of titration of drugs to achieve risk factor targets. The debate regarding the individual and societal benefits of the polypill has been raging for the last 15 years and there are currently several ongoing trials. These may provide clearer future guidance. ■ *Heart Metab*. 2019;79:38-39

Keywords: cardiovascular risk; polypill

Introduction

"Will the polypill be the solution?" Before attempting to answer the question, we need to define the relevant treatment group and the precise contents of the polypill. These are needed to know the baseline cardiovascular risk and therefore the risk:benefit ratio of each drug in the polypill combination. The original idea proposed and modelled by Wald and Law in 2003 was that the pill was for primary prevention and contained six active ingredients.[1] The absolute benefit of the polypill was increased by selecting people thought to be at moderate risk based on age greater then 55 years. The original polypill contained a fixed-dose combination (FDC) of statin, three blood pressure-lowering drugs (a thiazide, a β-blocker, and an angiotensin-converting enzyme inhibitor [ACEI]), folic acid (0.8 mg) and aspirin (75 mg).[1] At the time this seemed reasonable since the evidence base for using statins, ACEIs, and β-blockers in patients following an acute coronary event was overwhelming; so, the case for secondary prevention was mandated in guidelines. On the other hand, the case for primary prevention was as controversial then as it is now.

The main problem is that the risk associated with a drug is often independent of its absolute benefit. So, whether a component of the polypill is "efficacious" will be determined by the baseline risk of events in the population being treated. A clear example that illustrates this is the use of aspirin against placebo, the subject of three recent large primary prevention trials (ASCEND, ARRIVE, and ASPREE).[2] In both covering Editorials and a timely meta-analysis, the conclusions were that the risk of major bleeding with aspirin was higher than the small but definite reduction in cardiovascular events (ischemic stroke and myocardial infarction); with a number needed to harm of 210 and number needed to treat of 265.[2,3] This balance in favor of harm occurred despite a moderately high 9.2% average risk of CV events over 10 years in the combined study populations (n=164 225).[3] One could therefore argue that if the baseline risk of events was just a bit higher aspirin would be of net benefit and should therefore be included in a polypill. However, baseline risk is largely driven by age and it is also age that drives the bleeding risk of aspirin![4] We can't therefore assume higher-risk patients will derive a net benefit. For this reason, the hypothesis that as-

pirin could be of net benefit for primary prevention in higher risk populations still needs to be tested prospectively.[4]

The example of aspirin reveals additional problems for the polypill idea. Once baseline cardiovascular risk exceeds 10% many guidelines, like those in the UK, recommend the use of a statin[5] and also the treatment of stage 1 hypertension. So these would have to be mandated as a background therapy. In addition, these recommendations can be very pragmatic, those in the UK being for 20 mg of atorvastatin.[5] This reduces the flexibility of the FDC in the polypill and also introduces difficulties for once-daily dosing (statin at night versus diuretic in the morning).

The aspirin illustration above demonstrates how the original proposal by Law and Wald has to be updated by evidence. It would be difficult to argue for the inclusion of aspirin in today's polypill. Similarly, the supposed benefit of folic acid has not been realised and that of β-blockers questioned. On the other hand, some newer medications that have come off patent merit further study (eztimibe, for example) as do some old medications based on new evidence (metformin, for example). The constituents of the FDC of the polypill are therefore in a constant state of flux. Furthermore, it is not possible to assume that just because an individual constituent drug has a benefit when compared with placebo that this benefit will endure when added to another active constituent of the polypill. Similarly, the risks associated with the coadministration of drugs maybe higher than the additive risk of each constituent alone (diuretics and ACEIs on renal function, for example). It is therefore necessary to determine the risk:benefit ratio of the actual FDC proposed in the polypill. However, trials of the polypill still need to allow an estimate of the contribution to risk:benefit for each individual component. To achieve this, by necessity, their design is complex often involving serial 2 x 2 factorial randomizations that can cloud data interpretation.[6]

The debate continues as to whether we should adopt a "fire and forget" or "treatment to target" philosophy in primary prevention. On the basis of SPRINT, there seems to be merit in titrating antihypertensive patients to achieve lower blood pressure targets.[7] The same maybe true of LDL-cholesterol in primary prevention. Adopting an agile and personal approach to primary prevention does not sit well with the "one size fits all" polypill approach; despite the latter being less demanding on health care resources.

The title of this Hot Topic poses a simple question; the simple answer is "no," at least for the moment. The main drawbacks are that we still don't know the ideal components of the polypill. Furthermore, the very nature of medicine is that it is in a constant state of evolution and the inflexibility of the polypill reduces the room for change in the face of new evidence. The FDC doesn't offer the flexibility to personalize treatment to individual patient characteristics whether this is baseline cardiovascular risk, side effects, response to treatment and/or achievement of targets. Despite this view, the outcome of a number current polypill trials[8] is awaited which may change the balance of the argument. ■

Disclosure/Acknowledgments: *The author has no conflict of interest to disclose.*

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