



Has the Polypill finally proven its worth?

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Has the Polypill finally proven its worth?
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Polypills, fixed dose tablets containing combinations of drugs for cardiovascular prevention, enjoyed much hype in the early 2000s including one projection of a possible 88% relative risk reduction in ischaemic cardiac events.¹ However, as DTB noted in 2009², evidence was lacking on their effect on hard outcomes, despite short term trials showing improvements in surrogate markers such as blood pressure and cholesterol.³ The results of the first long-term randomised controlled trial were published in August this year prompting media headlines about a “four-in-one pill to prevent a third of heart problems”.⁴ So has the polypill’s time come at last?

The PolyIran trial⁵, a collaboration between the universities of Tehran and Birmingham, compared a once daily polypill (hydrochlorothiazide 12.5mg, aspirin 81mg, atorvastatin 20mg and enalapril 5mg) plus lifestyle advice with lifestyle advice alone. The setting was a rural province of Iran that has a high burden of cardiovascular disease: nearly half of all premature deaths are from ischaemic heart disease or stroke and two-thirds of these occur in people under the age of 70 years. The study, which began recruitment in 2011 and had a mean follow up of five years was conducted to high standards and employed cluster randomisation by village to avoid potential contamination by pill sharing. A total of 6838 people were enrolled across 236 villages - 80% were aged over 65 years, half were women and 10% had heart disease, 50% had hypertension and 15% had type 2 diabetes. Exclusion criteria included bleeding risk, active asthma and severe chronic kidney disease. Participants in the control group who had hypertension continued to have this treated by their community physicians.

The finding for the primary outcome of major cardiovascular events at 5 years, pooled for all participants, was 5.9% in the polypill group and 8.8% for the control group (an absolute and relative risk reduction of 2.9% and 33% respectively). This was statistically significant and represented a number needed to treat of 35 over

5 years. Median adherence to medication was 80% and in a sub-group with high adherence ($\geq 70\%$), benefits of the polypill were greater with a 5-year NNT of 21. Statistically significant reductions were also observed for fatal ischaemic heart disease (0.6% polypill v. 1.2% control) and fatal stroke (0.2% polypill and 0.6% control). No statistically significant difference was shown in overall mortality. Interestingly, no increase in intracranial or gastrointestinal bleeding was seen in the polypill group. We might view this last finding with caution as the application of careful exclusion criteria in the trial may limit its generalisability to patients with risk factors for bleeding. Overall, the frequency and type of adverse event was similar between the two groups.

So, what does this mean for the polypill, long touted as an ideal intervention for use in low and middle income countries where individual monitoring and titration of treatments for cardiovascular risk factors is unfeasible? On the one hand, this is a large, high quality trial showing a statistically significant effect on hard outcomes. However, the effect size is not much greater than that seen in other settings for statins alone and certainly way below optimistic early speculations. The authors acknowledge some limitations: the ongoing treatment of hypertension via usual care in the control group and the possibility of increased health-care seeking behaviour in the control group leading to improved outcomes. They speculate that the majority of the effect may have come from the statin and aspirin component (both groups had similar blood pressure levels at the end of the trial). In addition, in the time period during which the trial was conducted, there was a national health care improvement programme underway, aiming to improve identification and treatment of cardiovascular risk which is likely to have reduced the impact of the polypill.

The debate will continue, the focus perhaps being on local context and the level of healthcare provision available in whatever setting a polypill might be used. Its benefit is likely to be larger for populations where alternative care is less available and this trial does not add any insight regarding the use of the polypill in a setting such as the UK. It seems the exact place of the polypill in the prevention of cardiovascular disease still remains elusive.

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