"Polypill" for Cardiovascular Disease Prevention

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STUDY

Wald NJ, Law MR: A strategy to reduce cardiovascular disease by more than 80%. *BMJ* 326:1419–1424, 2003

SUMMARY

Objective. To assess the components of, and potential benefit and adverse effects of, a single daily pill (a theoretical "polypill") to prevent cardiovascular disease (CVD) by simultaneously reducing four CVD risk factors (LDL cholesterol, blood pressure, platelet function, and serum homocysteine).

Design. Meta-analyses of published randomized trials and cohort studies.

End points. Proportional reduction in fatal and nonfatal ischemic heart disease (IHD) and stroke events, life years gained, and prevalence of adverse effects.

Results. A polypill composed of a statin; three pressure-lowering drugs, each at half of its standard dose; aspirin, 75 mg; and folic acid, 0.8 mg, was estimated to potentially reduce IHD events by 88% (95% CI 84–91%) and stroke by 80% (71–87%). One-third of those taking this polypill from age 55 years or from diagnosis of diabetes or CVD would potentially benefit, gaining on average about 11 years of life free from IHD event or stroke. Such a polypill would cause adverse symptoms in 8–15% of those taking it, depending on the specific components in the formulation.

Conclusion. The polypill strategy could prevent IHD and stroke if taken by everyone (without contraindications) aged 55 years and older and everyone with existing CVD or diabetes regardless of their age. This potentially new and different strategy merits further consideration and careful evaluation.

COMMENTARY

People with diabetes have two to three times the risk of CVD of those without diabetes.[1] There is evidence of benefit of single-factor interventions, including lipid therapies, blood pressure control, and use of regular aspirin.[2–4] The control of CVD risk factors among people with diabetes, however, remains suboptimal.[4] For example, only about 7% of people with diabetes achieve recommended control of lipid, blood pressure, and glucose levels.[5]

Wald and Law propose a new strategy to prevent CVD. Their strategy, which is still only theoretical, involves three new principles: *1*) simultaneously lower several causal and reversible CVD risk factors; *2*) intervene on everyone at risk of CVD regardless of risk factor level (e.g., all people with diabetes or everyone over 55 years of age); and *3*) reduce the risk factors by as much as possible.

Wald et al.[6–8] have assessed the components of, and the potential benefits and adverse effects of, a single daily pill (a theoretical "polypill") to prevent CVD by simultaneously reducing four CVD risk factors (LDL cholesterol, blood pressure, platelet function, and serum homocysteine). As described above, they estimate that such a polypill could reduce IHD events by 88% and stroke by 80% and that one-third of those taking it would potentially benefit, gaining on average about 11 years of life free from IHD event or stroke. They predict that their polypill would cause adverse symptoms in 8–15% of those taking it.

There are, however, important gaps in knowledge about the real benefits and risks of such a polypill.[6]

Evidence exists for lipid and blood pressure control and for use of aspirin to reduce the risk of CVD.[2–4] But CVD benefits from routine use of folic acid have not been established, and their inclusion in a multifactorial intervention to prevent CVD is premature.

The strategy proposed by Wald et al.[6–8] is based on the results of a rigorous meta-analysis of a very large number of trials. However, the data were from trials of single risk factor intervention, and direct empirical evidence is lacking for simultaneous intervention for several risk factors.

One small trial in Denmark directly tested the effectiveness of altering all known CVD risk factors, compared to standard care, among people with diabetes, and it found a 47% reduction in CVD[9]—considerably less than what Wald et al. have estimated.[6] Part of the reason for the possible overestimation of potential benefit by Wald et al. may be because they compared the polypill to no treatment, whereas many people over 55 years of age or with diabetes would already be on some treatment.

The authors estimated that 8–15% of people taking the polypill would be expected to have symptoms attributable to one or more of the six components of the pill. But again, we do not have direct

empirical evidence of the side effect profile of a polypill with six components.

In the absence of direct evidence of the benefits and risks, the polypill strategy is only an idea at this time. However, it is an intriguing idea that raises issues of potential interest for improving the effectiveness, efficiency, and delivery of high quality preventive care among people with diabetes. Who would benefit most from screening and monitoring of CVD risk factors? What are the advantages and disadvantages of combination drug therapy for control of CVD risk factors?

The polypill idea also reinforces the importance of aggressive multifactorial intervention to lower CVD risk. Indeed, the Steno study[9] demonstrated that multifactorial risk reduction can lower the risk of CVD among people with diabetes by about 50%.

REFERENCES

[1]Saydah SH, Eberhardt MS, Loria CM, Brancati FL: Age and the burden of death attributable to diabetes in the United States. *Am J Epidemiol* 156:714–719, 2002

[2]Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, Brown L, Warnica JW, Arnold JM, Wun CC, Davis BR, Braunwald E: The effect of pravstatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med* 335:1001–1009, 1996

[3]Hansson L, Zanchetti A, Carruthers SG, Dahlof B, Elmfeldt D, Julius S, Menard J, Rahn KH, Wedel H, Westerling S: Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomized trial. *Lancet* 351:1755–1762, 1998

[4]Narayan KM, Benjamin E, Gregg EW, Norris SL, Engelgau MM: Diabetes translation research: where are we and where do we want to be? *Ann Int Med* 140:958–963, 2004

[5]Saydah SH, Fradkin J, Cowie CC: Poor control of risk factors for vascular disease among adults with previously diagnosed diabetes. *JAMA* 291:335–342, 2004

[6]Wald NJ, Law MR: A strategy to reduce cardiovascular disease by more than 80%. *BMJ* 326:1419, 2003

[7]Law MR, Wald NJ, Morris JK, Jordan RE: Value of low dose combination treatment with blood pressure lowering drugs: analysis of 354 randomized trials. *BMJ* 326:1427, 2003

[8]Law MR, Wald NJ, Rudnicka AR: Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. *BMJ* 326:1423, 2003

[9]Gaede P, Vedel P, Larsen N, Jensen GVH, Parving H, Pedersen O: Multifactorial interventions and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med* 348:383–393, 2003

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