THE POLYPILL – IS THIS AN EFFECTIVE APPROACH TO PREVENTION OF CARDIOVASCULAR DISEASE?

The past 2 or 3 years have seen increasing interest, overseas at least, in the idea of a polypill – one combination pill that will take care of all aspects of cardiovascular disease. When first put forward as an idea by Wald and Law in 2003, the intention was to combine lipid-lowering medication, antihypertensive medication and antiplatelet therapy with folic acid. They proposed this as an approach not only to secondary prevention but for primary prevention as well, targeting those with pre-existing cardiovascular disease as well as everyone over the age of 55. The underlying assumption concerning the efficacy of this strategy is that the 6 individual ingredients of the polypill (thiazide diuretic, angiotensin-converting enzyme inhibitor, β-blockers, statin, aspirin, and folic acid) when combined together have synergistic treatment effects – calculated by multiplying the relative risk reductions on each class of treatment. The idea has definitely generated interest around the world, although some critics have questioned the assumption that the effects of these drugs will be synergistic and multiplicative.

Julia Hippisley-Cox and Carol Coupland, writing in a recent British Medical Journal, decided to look at the effect of combinations of statins, aspirin, β-blockers and angiotensin-converting enzyme inhibitors in the secondary prevention of all-cause mortality in patients with ischaemic heart disease. Using a database of 1.18 million patients registered with general practices across 23 health areas in Britain, they examined all patients with a first diagnosis of ischaemic heart disease between January 1996 and December 2003. Cases were patients with ischaemic heart disease who died. Controls were patients with ischaemic heart disease who were matched for age, sex and year of diagnosis and were alive in the year that their matched case died.

Hippisley-Cox and Coupland found 13 029 patients with a first diagnosis of ischaemic heart disease. A total of 2 266 cases were matched to 9 064 controls. The drug combinations that were associated with the greatest reduction in all-cause mortality were statins, aspirin and β-blockers; β-blockers and angiotensin-converting enzyme inhibitors; and statins, aspirin and angiotensin-converting enzyme inhibitors. The treatments that were associated with the least reduction in all-cause mortality were β-blockers alone, angiotensin-converting enzyme inhibitors alone, and combined statins and angiotensin-converting enzyme inhibitors. This trial is the first large-scale, long-term community-based study to report the effect of different combinations of drugs in the secondary prevention of all-cause mortality in patients with ischaemic heart disease. They included patients with multiple comorbidity, elderly people and women – who may have been excluded from previous trials.

Their findings were that combinations of statins, aspirin and β-blockers improve the survival of high-risk patients with ischaemic heart disease. They also found that adding an angiotensin-converting enzyme inhibitor did not have any additional benefit, even for those patients with congestive cardiac failure. This latter finding is consistent with the results of another recent trial. The evidence is compelling that a combination of these drugs, but not with an angiotensin inhibitor, does play a role in the secondary prevention of ischaemic heart disease. But what of primary prevention? This trial does not address this issue and there are still many concerns about what has been called a scatter-shot approach to primary prevention. There is already evidence that the effects of aspirin are different in men and women. The role of folic acid in the proposed polypill is far from established, particularly with the conflicting evidence of the proposed efficacy of antioxidants in preventing cardiovascular disease.

Difficult ethically perhaps, but in a situation where health care costs are escalating alarmingly, possibly a more practical approach than yet more pills.


MORE ON THE MILLION WOMEN STUDY

The Million Women Study hit the headlines in 2003 when it was published in the Lancet and changed the prescribing habits of doctors treating postmenopausal women. Many people feel that the study was flawed, unrepresentative of all women, did not provide consistent follow-up and used an inaccurate classification of hormone replacement therapy (HRT). There was also the issue of the public’s understanding of what constitutes risk – highlighted by what became a generally accepted idea that using HRT increases the absolute, rather than the relative, risk of developing breast cancer. However, the fact remains that fewer people are currently willing to prescribe HRT and certainly not for long periods of time.
Now results from another arm of the study have been published, again in the *Lancet*. Study collaborators, writing in a recent issue, point out that it is known that postmenopausal women who use HRT containing unopposed oestrogen are at increased risk of endometrial cancer. To minimise this risk many HRT users who have not had a hysterectomy use combined oestrogen-progestogen preparations or tibolone. Investigators recruited 716,738 postmenopausal women in the UK who had no previous cancer or previous hysterectomy between 1996 and 2001. They provided information about their use of HRT and were followed up for an average of 3.4 years. During this time 1,320 endometrial cancers were diagnosed. The results showed that different types of HRT had sharply different effects on the overall risk of endometrial cancer. Compared with women who had never used HRT, risk was reduced with the use of continuous combined preparations, increased with last use of tibolone and oestrogen only, and not significantly altered with the use of cyclic combined preparations. The women’s body mass significantly affected these associations, with the adverse effects of oestrogen-only and tibolone greatest in non-obese women, and the beneficial effects of combined HRT greatest in obese women. The increasing incidence of endometrial cancer in obese women who do not use HRT is well known and believed to be due to the proliferation of the endometrium caused by increased levels of oestradiol and other related circulating hormones that are produced by adipose tissue.

The investigators conclude that oestrogens and tibolone increase the risk of endometrial cancer and that progestogens counteract the adverse effect of oestrogen, the effect being greater the more days every month that they are added to the oestrogen and the more obese the women are. However, they refer to previous findings that combined oestrogen-progestogen HRT causes a greater increase in breast cancer than the other therapies do. They state that when endometrial and breast cancer are added together, there is a greater increase in total cancer incidence with the use of combined HRT, both continuous and cyclical, than with use of the other therapies.

So, where are we with HRT? Various well-designed, randomised trials have failed to show that HRT reduces the risk of the various diseases that it was at one time assumed to do. Hormones effectively reduce the risk of fractures, but do not reduce the risk of most coronary, cerebrovascular and cognitive events. There is also accumulating evidence that hormones might increase the risk of ovarian cancer. HRT is definitely the most effective treatment for menopausal symptoms – which is what they were first marketed for. So, how should hormones be prescribed to allow women to benefit without risk? The consensus seems to be that women should take the lowest possible dose for the shortest possible time. But what is the shortest possible time? As yet, no-one knows. What is becoming evident is that people are looking at alternatives to hormone treatment to deal with the various physiological changes women experience as they get older. Local oestrogens can relieve urogenital symptoms. Some of the serotonin inhibitors can relieve hot flushes. We know that regular exercise, weight bearing and otherwise, can maintain cardiovascular health, bone strength and prevent, or mitigate, the effects of obesity. A balanced diet, possibly supplemented by calcium and vitamin D, can prevent osteopenia and osteoporosis. Keeping mentally active can ward off dementia. There are definitely other options. For those women whose menopausal symptoms are severe though, HRT with very careful monitoring may be the only answer.


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