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Opinion

A New Horizon in Primary Prevention of Cardiovascular Disease, Can We Prevent Heart Attack by "Heart Polypill"?

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The problem of ischemic heart disease

"We will spend anything to save a little girl who fell down the well, but we will not spend money to build fences around the wells to prevent it!"[1]

Cardiovascular disease includes coronary heart disease and stroke. Together they are major causes of morbidity and mortality in many countries. In Iran, cardiovascular disease accounts for 45.7% of deaths.[2] Cardiovascular disease is the well down which many Iranians will fall. Because cardiovascular disease is more common in older populations, it will become an increasing problem as the Iranian population ages. Is there anything we can do to mitigate the problem? The answer must be yes.

Much of the epidemiology of cardiovascular disease is well understood. As a result we have a good understanding of how we could use this knowledge to prevent cardiovascular disease. This article will explain some of the most recent thoughts about how to prevent cardiovascular disease and how we could implement this in Iran.

Treatments to prevent cardiovascular disease

Cholesterol and cardiovascular disease

The relationship between total cholesterol levels and coronary heart disease is well known.[3] Higher cholesterol levels are associated with higher risk of coronary heart disease. The relationship between cholesterol level and cardiovascular risk is continuous.[4] Compared to individuals with average cholesterol levels, those with lower cholesterol levels have a lower risk. This suggests that cholesterol lowering is effective at any initial cholesterol level and that the effectiveness of cholesterol lowering in reducing cardiovascular risk is proportional to the reduction in cholesterol.

Meta-analyses of the effects of statins on the risk of coronary heart disease and stroke confirm this.[5–7] Cholesterol lowering reduces risk of coronary heart disease and stroke in patients with normal or high cholesterol levels.[8] The greater the reduction in cholesterol levels, the greater the reduction in risk of coronary heart disease.[9 – 11]

Taken together, all this supports the hypothesis that cholesterol lowering is effective at any initial cholesterol level and that the effectiveness of cholesterol lowering in reducing the risk of cardiovascular disease is proportional to the reduction in cholesterol. A meta-analysis indicates that a 1 mmol/L reduction in LDL cholesterol results in a relative risk of coronary heart disease of 0.67 and a relative risk of stroke of 0.94.[12]

Blood pressure and cardiovascular disease

We know that blood pressure is linked to the risk of coronary heart disease and stroke.[13] There is no optimum blood pressure; individuals with lower than average blood pressures have less risk of cardiovascular disease than those with average blood pressures. There is strong evidence that blood pressure lowering with antihypertensive drugs reduces risk of coronary heart disease and

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stroke. Treatment is equally effective in those over 60 and under 60, in both men and women.[14–16] A meta-analysis indicates that a 12 mmHg reduction in systolic blood pressure would result in a relative risk of coronary heart disease of 0.80 and a relative risk of stroke of 0.60.[17]

Aspirin and cardiovascular disease

It has long been known that aspirin reduces the risk of cardiovascular disease in those with existing cardiovascular disease.[18] There is also evidence that aspirin is effective in primary prevention of cardiovascular disease. Relative risk of coronary heart disease on aspirin is 0.72 and the relative risk of cerebrovascular accident does not significantly change (1.02).[19] The same meta-analysis also found that the incidence of serious bleeding from aspirin was very low: about 0.3% per year.

Folic acid and cardiovascular disease

It is not always possible to infer from epidemiological evidence that treatments will work. There is evidence that elevated plasma homocysteine is associated with cardiovascular disease.[20,21] However, there is yet no evidence that treatment with folic acid to reduce plasma homocysteine levels has any effect on cardiovascular disease.[22]

Secondary prevention of cardiovascular disease

In patients who have suffered myocardial infarction, both beta-blockers and angiotensin converting enzyme inhibitors (ACE-I) improve prognosis.[23–27]

Summary of evidence of effectiveness

We can summarize this information as follows: in primary prevention, we know three important drug treatments that will reduce risk of cardiovascular disease: aspirin, statins, and antihypertensives. We know that these treatments act in different ways. Therefore we can assume that their effects are independent. In other words, a patient taking aspirin can also benefit from a statin. We know that the initial cholesterol or blood pressure level does not matter, and it is better to be lower. In secondary prevention we also know that there are specific benefits from using ACE-I and beta-blockers. How has all this influenced the development of clinical guidelines?

Evolution of the philosophy of prevention

It is clear from the above discussion that treatments can reduce the risk of cardiovascular disease. Who should we treat? Logically, those at highest risk of cardiovascular disease have the greatest potential to benefit from treatment. It has taken the medical profession many years to reach this conclusion.

We can observe the evolution of the philosophy of prevention through changes in clinical guidelines. Antihypertensive treatment was first recommended for treatment of malignant hypertension (accelerated hypertension).[28] In the 1960's clinical trials recommended treating hypertension at a lower level.[29,30] At this time, the paradigm of hypertension was to think of it as an illness. Patients were diagnosed as either ill (hypertensive) or not ill (normotensive) and treated accordingly. Hypertension was determined by deviance of blood pressure from the population norm and the goal of treatment was to restore blood pressure to that population norm. This paradigm has a number of implications. Since mean blood pressures are higher in older persons, this meant that the threshold for diagnosing and treating hypertension should logically be higher. Guidelines from this era show reluctance to diagnose or treat hypertension in older persons. Over time, further clinical trials demonstrated that blood pressure lowering reduced cardiovascular disease even at lower risk levels and as a result the threshold for treating hypertension declined.[31,32]

In 1983, WHO-ISH guidelines continued to recommend treatment of hypertension at a higher threshold in persons over 70.[33] It was known from 1960's that risk of coronary heart disease was predicted by multiple risk factors.[34,35] However it was not until 1993 when the first guidelines for prevention made full use of this information. In that year, The New Zealand Guidelines Group published a discussion document on the management of raised blood pressure.[36] The guidelines introduced risk tables based on the Framingham risk equations to determine a patient's risk of cardiovascular disease from a combination of risk factors.[37] These risk factors include age, sex, diabetic status, smoking status, total cholesterol, HDL cholesterol and blood pressure. Because cardiovascular risk is the best predictor of benefit, they used these tables to calculate individual patients' risk of cardiovascular disease. Cardiovascular risk became the main indication for treatment. The patient's blood pressure is only part of the reason for offering antihypertensive treatment. This is a complete change in the

approach to hypertension. The goal of treatment is to reduce risk, not to normalize blood pressure. Patients are offered treatment because of its effect on their risk of cardiovascular disease, not because of its effect on their blood pressure. The concept of hypertension has become less important than the concept of cardiovascular risk. One immediate effect of this is to change the focus of treatment from younger to older patients, since it is older patients who are at higher risk of cardiovascular disease.

Early hypercholesterolemia guidelines have evolved in a similar way. At first treatment was recommended for cholesterol levels above a specific threshold, with a lower threshold in younger patients.[38,39] More recently, guidelines began to recommend using tables to calculate cardiovascular risk in order to determine which patients should be offered treatment.[40,41]

Since both hypertension and hyperlipidemia guidelines have moved towards using calculated cardiovascular risk to determine eligibility for treatment, there has been a convergence of hypertension and hyperlipidemia guidelines. A number of countries have produced combined guidelines for treatment of multiple cardiovascular risk factors in patients at high risk of cardiovascular disease. New Zealand has taken this trend to its furthest conclusion.[42] U.K. and European guidelines have followed this trend towards using formal estimates of cardiovascular risk to determine eligibility for treatment with aspirin, antihypertensives and statins.[43,44] U.S. guidelines have evolved in a different direction, making little use of the concept of cardiovascular risk and continuing to produce separate hypertension and hyperlipidemia guidelines.[45,46]

Practical effects of changes in clinical guidelines

The effect of the changes in clinical guidelines is that in many countries, patients at high risk of cardiovascular disease are eligible for multiple treatments: aspirin, antihypertensive treatment, and statins. The majority of older patients are eligible for treatment, and the majority of those eligible for treatment are eligible for more than one treatment. For example, a non-smoking, non-diabetic man of 60 whose blood pressure is 140/90 mmHg is likely to be at a greater than 20% ten-year cardiovascular risk. He is therefore eligible for aspirin, antihypertensive treatment, and a statin.

The future of prevention

Secondary prevention with a polypill

We can see from the preceding discussion that patients at a high risk of cardiovascular disease can benefit from multiple treatments to reduce their risk. Patients with existing cardiovascular disease are at high risk. It is already recommended that patients with coronary heart disease are treated with aspirin, beta-blockers, ACE-I, and statins. In patients who have suffered a cerebrovascular event, there is evidence for the benefits of blood pressure lowering irrespective of pretreatment blood pressure.[47] There are benefits from the use of statins,[7,48] and there is evidence to support the use of aspirin in ischemic stroke, but not in hemorrhagic stroke.[49]

As early as 2001, a joint WHO-Wellcome Trust meeting discussed the possibility of using fixed-dose combination therapy for secondary prevention of cardiovascular disease in low and middle-income countries.[50] A subsequent report concluded that secondary prevention might be cost-effective in low and middle-income countries.[51]

Different polypills could be used for secondary prevention: one for coronary heart disease incorporating aspirin, beta-blockers, ACE-I, and statins; one for nonhemorrhagic stroke, incorporating aspirin, thiazide, ACE-I, and statins; one for hemorrhagic stroke, incorporating, thiazide, ACE-I, and statins.

Primary prevention with a polypill

Some individuals without cardiovascular disease are at high risk because of their age and sex alone—for example a man of 65. Such an individual can benefit from antihypertensive drugs to reduce his blood pressure, statins to reduce his cholesterol, and from aspirin, even if his blood pressure and cholesterol levels are average for his age. The future of prevention will be about treating overall risk in such a man, not treating individual risk factors.

How can we reduce risk? Statins are well tolerated, with adverse effects reported less frequently on treatment than placebo.[12] Low dose aspirin is as effective as higher doses.[18] Since adverse effects are likely to be less frequent with lower doses we should use low dose aspirin. Antihypertensive therapy at half standard dose has about 80% of the effect on systolic blood pressure. The frequencies of adverse effects with ACE-I and ARB are low at all doses. Thiazides and calcium channel blockers have a much lower incidence of adverse effects at half standard than standard

doses.[52] The effects of additional drugs on blood pressure are additive and the combination of either a calcium channel blocker or a thiazide with an ACE-I or ARB is pharmacologically rational. This suggests that several antihypertensive drugs at low dose are likely to be better tolerated and more effective than one drug at a standard or high dose.

Following this rationale, in 2003, it was proposed that fixed dose combination therapy including low dose aspirin, more than one low dose antihypertensive drug and statins could greatly reduce incidence of cardiovascular disease in middle aged and older adults without cardiovascular disease.[53] The original proposal included aspirin, three antihypertensives at half dose, simvastatin and folic acid. The treatment was named the polypill. The most novel aspect of this proposal has been to completely abandon the concepts of hypertension and hyperlipidemia and to offer treatment to individuals whose blood pressure and cholesterol levels are at average levels but who are at high risk of cardiovascular disease because of their age and sex alone.

Potential advantages of a polypill

The polypill strategy has a number of key advantages. Firstly, it is simple to administer. Secondly, it does not require complicated diagnostic algorithms, since the treatment is given to all those above a certain age. Thirdly, it is likely to have a low incidence of adverse effects because all of the drugs are well tolerated in the doses in which they will be prescribed.

Since then, the idea of a polypill has been refined. There is insufficient evidence to include folic acid and three antihypertensive drugs may reduce blood pressure enough to cause symptoms in some.

Analysis of prevention based on a four drug polypill (two antihypertensives, aspirin and a statin) shows that it may be cost-effective, in low and middle-income countries.[54–56] The most logical combination is a thiazide diuretic and an ACE inhibitor.

Effectiveness of a polypill strategy

Relative risks with aspirin, beta-blocker, statin, and ACE-I in secondary prevention are shown in Table 1.[54] In Iran, about 80% of cardiovascular events are coronary heart disease and about 20% are cerebrovascular events. [Source: Personal Correspondence with Nizal Sarrafzadegan. Data supplied by Isfahan Cardiovascular Research Centre in 2007] The weighted effects of treatment and the effects of combined treatment are shown in Table 1. Overall, we would expect the relative risk on treatment to be 0.28. In secondary prevention a polypill could prevent almost three quarters of cardiovascular events. This analysis is consistent with evidence from the U.K., France, and Germany that patients with coronary heart disease treated with multiple therapies have improved survival compared to those treated with only one or two drugs.[57,58] Underuse of preventive treatment of patients in secondary prevention is common in middle-income countries. In Iran, following a diagnosis of coronary heart disease, 80% of patients receive aspirin, 70% a beta-blocker only 30% an ACE inhibitor, and 30% receive statins.[59] The polypill offers the potential to substantially improve prognosis in these patients.

The effectiveness of a polypill strategy in primary prevention can be calculated. With full compliance either atorvastatin 10 mg or simvastatin 40 mg would reduce LDL by about 1.8 mmol/L.[12] We expect that compliance with treatment in primary prevention may be poor: with 60% compliance this will result in a relative risk of 0.65 for coronary heart disease ($0.65=0.67^{(1.8 \times 0.6)}$) and 0.94 for cerebrovascular disease ($0.94=0.94^{(1.8 \times 0.6)}$). With full compliance a half-dose thiazide would reduce systolic blood pressure by about 7.4 mmHg.[52] Therefore, with 60% compliance a thiazide will result in a relative risk of 0.92 for coronary heart disease ($0.92=0.8^{[(7.4 \times 0.6) \div 12]}$) and 0.83 for cerebrovascular disease ($0.83=0.6^{[(7.4 \times 0.6) \div$

Table 1. Effects of multiple treatments for secondary prevention of cardiovascular disease.

Drug	Relative Risk			Relative Risk of combined therapy
	Coronary Heart Disease	Cerebrovascular Disease	Cardiovascular disease*	
Aspirin	0.66	0.78	0.68	0.28
Beta-blocker	0.73	0.71	0.73	
Statin	0.80	0.68	0.78	
ACE-I	0.71	0.81	0.73	

* Assumes that 80% of cardiovascular disease is coronary heart disease and 20% is cerebrovascular disease.

12]).[12] A half-dose ACE inhibitor by reduces systolic blood pressure by 6.9 mmHg and results relative risk of 0.93 for coronary heart disease and 0.84 for cerebrovascular disease. With 60% compliance aspirin will result in a relative risk of 0.82 for coronary heart disease ($0.82=0.72^{0.6}$) and 1.01 for cerebrovascular disease ($1.01=1.02^{0.6}$).[19] The overall effectiveness of a polypill in primary prevention is shown in Table 2. Even with 60% compliance, fixed dose combination therapy with four drugs could prevent half of cardiovascular disease.

Researching the polypill

The polypill has been the subject of a great deal of debate.[60–65] The consensus is that while the polypill offers great promise, as yet there is no evidence from randomized controlled trials that the treatment would be effective. But, before we can investigate effectiveness, there are many questions to be answered about its design and synthesis, pharmacokinetics, pharmacodynamics, bioequivalence, interactions, evidence of clinical efficacy, adverse effects, and safety.[56,66,67]

Studies have already begun to address questions about the effects of combination therapy on blood pressure and cholesterol levels and adverse effects. In Canada, the pharmaceutical industry evaluated combination therapy with a calcium channel blocker and a stain.[68] Initial results indicate that this successfully lowered both cholesterol levels and blood pressure.[69] In 2007, an Indian pharmaceutical company started a trial of a four component polypill consisting of aspirin, lisinopril, simvastatin, and atenolol in secondary prevention of cardiovascular disease.[70] The University of Auckland began a pilot placebo-controlled trial of a polypill for primary prevention containing aspirin 75 mg, simvastatin 20 mg, lisinopril 10 mg, and hydrochlorothiazide 12.5 mg in 2007.[71] This will recruit 400 patients in Australia, Brazil, India, New Zealand, the U.S., and the U.K. St. John's Research Institute in Karnataka, India is recruiting subjects for a clinical trial to test the efficacy and safety of a five component polypill (aspirin, thiazide, ramipirl, atenolol, and simvastatin) in comparison to each of its components given alone.[72] The World Health Organization is planning a pilot study of a four component polypill consisting of aspirin 75 mg, simvastatin 10 mg, lisinopril 5 mg, and hydrochlorothiazide 12.5 mg.[73] At present, a collaboration between Tehran University of Medical Sciences and University of Birmingham is leading the clinical evaluation of a polypill.[74] In 2006 and 2007, the Kalaleh Polypill Study recruited and randomized 500 patients to a polypill consisting of aspirin 75 mg, atorvastatin 20 mg, enalapril 2.5 mg, and hydrochlorothiazide 12.5 mg or an identical placebo. This study is approaching completion and is expected to report results soon.

If the results of pilot studies are encouraging, researchers in Iran, India, and the World Health Organization will soon be planning studies to investigate the effectiveness of the polypill in preventing cardiovascular events. These will need to follow up many thousands of subjects. In order to convincingly demonstrate the effectiveness of simvastatin, the Heart Protection Study randomized and followed up 20,000 subjects for five years.[8] There are three separate groups in whom we might consider using a polypill: those with cardiovascular disease, those without cardiovascular disease but eligible for preventive treatment with antihypertensives or statins under current guidelines, and those not eligible for any treatment. Because patients with existing cardiovascular disease are already eligible for multiple treatments, the polypill is not a radical change in philosophy. For patients who are currently eligible for antihypertensive or statin treatment, reducing additional risk factors with a polypill is a significant change in philosophy. But in patients currently not eligible for any treatment, a polypill is a revolutionary change in philosophy. Clinical researchers in Iran may have the

Table 1. Effects of multiple treatments for primary prevention of cardiovascular disease.

Drug	Relative Risk with 60% compliance			Relative Risk of combined therapy
	Coronary Heart Disease	Cerebrovascular Disease	Cardiovascular disease*	
Statin	0.65	0.94	0.71	0.50
Aspirin	0.82	1.01	0.86	
Half dose thiazide	0.92	0.83	0.90	
Half dose ACE-I	0.93	0.84	0.91	

* Assumes that 80% of cardiovascular disease is coronary heart disease and 20% is cerebrovascular disease.

opportunity to lead this revolution.

Conclusions

Decisions on treatment or prevention do not rest on evaluation of effectiveness alone. We must consider the costs of a polypill in relation to its effectiveness. Initial signs are that this should be a cost-effective strategy.[54] Finally the individual patients must choose whether they consider the benefits of treatment to be worth the inconvenience of medicalisation and taking tablets. Nevertheless, these are exciting times for cardiovascular disease prevention. Within the next few years, researchers will understand whether fixed-dose combination therapy will be a useful strategy to prevent cardiovascular disease. The polypill is not a long-term solution to the problem of cardiovascular disease. In the long term, prevention requires reductions in levels of smoking, changes in diet and levels of physical activity. However, for the generation of middle aged and older people alive today it may be the most important development in prevention for many decades.

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