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Combination Therapy to Prevent Cardiovascular Disease

Slow Progress

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CARDIOVASCULAR DISEASE IS THE MAJOR CAUSE OF mortality and morbidity globally and affects half of all individuals over their lifetimes.[1] The burden of cardiovascular disease in developing countries is increasing substantially, and cardiovascular disease is becoming the leading cause of death.[1] The concept of combining antihypertensive drugs, a statin, and aspirin into a single, fixed-dose, combination pill to prevent myocardial infarction and stroke is now a dozen years old, but still no such pill is licensed in most countries.

Only a small proportion—perhaps fewer than 10%—of individuals in the world who have, or are at high risk of developing, cardiovascular disease receive appropriate drugs for preventing future myocardial infarction or stroke.[2] Many people at high risk are not identified because of a lack of systematic screening. Of those who are diagnosed, many are not treated because of unavailability or unaffordability of drugs, cumbersome treatment regimens, and lack of well-functioning health systems. Even patients who do receive treatment often have poorly controlled risk factor profiles[3] because of an emphasis on treating individual conditions like hypertension or diabetes rather than the overall risk of cardiovascular disease. Moreover, adherence is universally poor, with less than half of those patients who are prescribed antihypertensive, lipid-lowering, or antidiabetic drugs continuing treatment beyond 1 year.[4]

These issues lead to a massive treatment gap and an opportunity for reducing cardiovascular disease. Actions like reducing tobacco consumption within the population are essential, but including the key medications necessary to reduce the risk of cardiovascular disease into a single pill could increase use of effective and inexpensive medications, thereby lowering costs and improving treatment adherence. In most low- and middle-income countries it will also be necessary to strengthen health systems with systematic screening and follow-up through greater use of nonphysician health workers and innovative and simple communication technologies.

Different fixed-dose combination pills are now available in India, Mexico, and Central and South America. At least 6 randomized trials have shown that the combination of several antihypertensive agents, a statin, and aspirin can substantially reduce blood pressure and lipid levels and, when aspirin is included, inhibit platelet aggregation.[5] The pills are well tolerated and have low rates of adverse effects and discontinuation. The trials have shown high adherence, although most have been of short duration. However, a recent large trial analyzing patients from 12 to 18 months showed that compared with usual care and separate drugs, combination pills produced a greater reduction in blood pressure and lipid levels.[6]

However, none of the trials as yet has included clinical outcomes, and there is debate among researchers and regulators over the importance of large outcome studies. Most will want trials with clinical outcomes to consider a combination pill for use in primary prevention. At least 2 large international trials (TIPS-3 and HOPE-3) are currently under way testing a combination pill (or its concept) against placebo, but it will be several years before results are available. While showing that each component of a combination pill contributes to the overall benefit is theoretically optimal, such trials are simply not practical given the necessary size and follow-up time that will be needed. As discussed during panel sessions held at the Global Summit on Combination Polypharmacy for Cardiovascular Disease in Hamilton,[7] Canada, in 2012, regulators might not insist on this type of study if there is convincing evidence that a combination pill leads to a substantial reduction in cardiovascular disease (40% or 50% more than usual care), a level of benefit that cannot be expected from using any single agent.

Licensing is an essential step for developing combination therapy, but these treatments present new problems for regulators. Both the US Food and Drug Administration and the European Medicines Agency have approved 2- and 3-drug combinations, but neither has approved combinations of 4 or 5 drugs. An emerging opinion among researchers and some regulators is that outcome studies are not needed (nor practical nor ethical) for licensing of fixed-dose combination pills for secondary prevention as long as the expected effects on

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blood pressure and lipids and good tolerability can be demonstrated. Regulators at the Hamilton meeting agreed that they are likely to accept pharmacokinetic, pharmacodynamic, and safety studies to approve combination pills for secondary prevention.

The pandemic of deaths from cardiovascular disease cannot, however, be addressed simply through secondary prevention. Data from the United States demonstrated that only 4% of the adult population has a history of cardiovascular disease, and these individuals account for only 11% of major acute cardiac events (Peter Alperin, MD, Archimedes Inc, September 20, 2012, written communication). Most major cardiac events occur in individuals with average or moderate risk, simply because they are most of the population.

Another barrier to widespread availability of combination pills is the attitude of physicians, particularly cardiologists, who commonly perceive fixed-dose therapy as inferior to titrating each of several drugs individually according to blood pressure and lipid levels. This perception is an example of "the perfect being the enemy of the good" because such an approach provides little marginal benefit but incurs substantial extra costs. Concerns about the efficacy of using multiple antihypertensive drugs in combination should be allayed by a meta-analysis of the fixed-dose combination pill trials that demonstrated reductions in blood pressure (−9.2 mm Hg systolic pressure and −5.0 mm Hg diastolic pressure compared with placebo),[5] which are likely to be sufficient to achieve a substantial reduction in cardiovascular disease events. Titration of medications by specialists is simply not practical in most health systems in low- and middle-income countries and is a barrier to the effective control of blood pressure.

What about the concept of giving the combination pill at low doses to everyone aged 55 years or older? There is a strong theoretical rationale for such an approach, as screening, which is imperfect and expensive, is avoided, and this group includes most of those who will experience cardiovascular disease. However, there appears to be little support for such a radical approach at least at present. Perhaps if primary prevention trials involving moderate-risk individuals show a clear benefit with few adverse effects, the idea of offering treatment to everybody older than 55 years might be reconsidered.

The other major barrier to widespread availability of a combination pill is the development of a business model that enhances access to many individuals (especially those in resource-limited settings) by keeping costs low and simultaneously provides adequate incentives to pharmaceutical companies to invest in research, manufacturing, licensing, and distribution. Large, research-intensive pharmaceutical companies have thus far been reluctant to develop (or sublicense) a combination pill, presumably because doing so does not fit their traditional business model of developing new patented drugs with higher profit margins.

The current available combination pills are manufactured by manufacturers of generic pharmaceuticals with little experience in getting drugs licensed in developed countries and few marketing resources. Perhaps a different model could be adopted, a model wherein the combination pill could be sold in large volumes at low cost to large health care organizations. This approach would substantially reduce the costs of distribution, packaging, and marketing, could make a combination pill affordable, and would allow the manufacturer to gain a fair profit. This has not happened so far, although Kaiser Permanente has encouraged the use of combination therapy with multiple pills copackaged in blister packs.[8]

Considerable barriers remain in the widespread use of fixed-dose combination therapy, but some progress has occurred in the last decade. On average, it takes 20 years for important innovations to achieve widespread acceptance and be incorporated into health systems—so history is still on the side of eventual implementation of this approach.

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