

Advances in the Pharmacologic Treatment of Arteriosclerosis: What Does the Future Hold?

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The last 10 years has seen an explosion in our knowledge about atherosclerosis and its risk factors and management. Research initiatives are now being directed at lowering low-density lipoprotein (LDL), raising high-density lipoprotein (HDL), raising apolipoprotein A (apo A), and lowering atherosclerotic risk by polypharmacy. It is now conceivable that pharmacologic and preventive health measures may actually eradicate the disease that is the foundation of our specialty.

Lowering LDL

Statins are now the most commonly prescribed class of drugs in developed nations, and in the United Kingdom, simvastatin is now available as an over-the-counter medication. These drugs have made a major impact on cardiovascular mortality and may even benefit bypass patency and operative mortality. Other non-vascular benefits include prevention of osteoporosis, Alzheimer's disease, and possibly colon cancer. Current guidelines suggest using these drugs to lower LDL cholesterol below 100 mg/dL, and it is conceivable that we should try to lower cholesterol as low as possible. However, some patients cannot tolerate the medication because of side effects, which may be mild, such as vague muscle ache, lethargy, or memory "holes," or potentially serious and lethal, such as rhabdomyolysis and hepatic dysfunction. Future more powerful statins and medications that obviate the side effects are already in the pipeline. Also, current research suggests that we may need to use biologic markers such as C-reactive protein to determine who will benefit from these medications.

Raising HDL and Apo A: "Liquid Drano"

Like LDL, HDL is a lipoprotein consisting of fatty acids combined with a protein, in the case of HDL, apo A and A-I. This apolipoprotein regulates the lipid-scavenging effect of the HDL particle. It is now well established that HDL is important in reverse cholesterol transport from the periphery (and the vasculature) to the liver. HDL also has an antioxidant and anti-inflammatory effect. Cholesteryl ester transfer protein (CETP) transfers oxidized lipids from LDL to HDL. Once these oxidized lipids are in HDL, they are reduced by HDL apolipoproteins. It has also been shown that the liver takes up reduced lipids from HDL more rapidly than from LDL. Therefore, HDL reduces the oxidized lipids in LDL, a further anti-inflammatory effect of HDL. Whether these actions are the actual methods by which high levels of HDL appear to be atheroprotective is still not clear. However, these findings have prompted exciting research activity directed at the genes and proteins that regulate HDL metabolism, which portends major benefits for the future treatment and prevention of atherosclerosis.

Multiple approaches to increasing apo A-I production are in development in preclinical animal models, and some are in early clinical trials. Perhaps the most desirable approach would be a small molecule that up-regulates apo A-I gene transcription. Another approach is the intravenous infusion of a recombinant apo A-I protein. Finally, the concept of using somatic gene transfer of apo A-I deoxyribonucleic acid (DNA) to a tissue in which apo A-I could be made and secreted is attractive and is being piloted in animal studies.

A further method could be delaying the catabolism of HDL, using the finding that HDL metabolism involves a process of intravascular remodeling by which larger HDL particles are converted to smaller particles. These smaller particles are at a higher likelihood of being removed, at least in part, through the kidney. Inhibition of remodeling would be expected to lead to larger HDL particles and higher levels of both HDL and apo A-I. Hepatic lipase is the best established molecule responsible for intravascular remodeling. It converts the larger HDL₂ to the smaller HDL₃. In theory, inhibition of hepatic lipase would be expected to increase HDL and apo A-I levels. Genetic deficiency in CETP has also been shown to be associated with exceptionally elevated levels of HDL cholesterol and apo A-I owing to delayed catabolism of HDL. This led to the concept that inhibition of CETP might be a pharmacologic strategy for raising HDL. The impact of CETP inhibition on atherosclerosis in humans remains to be determined. However, CETP inhibitors are already in clinical trials (Torcetrapib).

Perhaps the most dramatic evidence that HDL modification can have clinical effects is based on a 25-year-old discovery that 40 residents of the northern Italian village of Limone Sul Garda had very low HDL levels yet, paradoxically, had low rates of coronary artery disease. It was subsequently found that all had a gene variation of apo A now known as apo A-I Milano. The variation contributed to larger than normal HDL particles, which are believed to make the HDL especially efficient at removing plaque. Recently, Nissen and colleagues published data demonstrating that a synthesized version of this variant (Esperion Therapeutics Inc., Ann Arbor, MI) in a phospholipid complex actually reduced coronary plaque within 5 weeks of infusion.¹ In the study, 36 patients who had had heart attacks or severe chest pain received weekly intravenous infusions of the substance for 5 weeks. Eleven patients received placebo treatments.

At 6 weeks, imaging tests showed that the patients receiving the synthetic protein had intravascular ultrasonographic evidence of a 4.2% reduction in plaque buildup in their coronary arteries. There was no significant change in the placebo group. Trial limitations include a lack of any apparent dose response and a lesser degree of atherosclerosis in the placebo group at baseline.

PolyPill

A wonder pill that could slash the rate of deaths from heart attack or stroke by over 80% is being proposed by UK researchers. The “PolyPill” would contain a cocktail of a low dose of six existing drugs and would be given to everybody over the age of 55 years. It could potentially save 200,000 lives every year in the United Kingdom alone, they say. The pill would combine different drugs to try to lower the four key risk factors for heart disease: cholesterol, high blood pressure, high homocysteine blood levels, and blood platelet function. A statin would reduce high levels of LDL cholesterol, slashing the risk of cardiovascular disease, whereas three blood pressure-lowering drugs would reduce the risk of stroke. Folic acid in the pill would cut high homocysteine levels, which can encourage the buildup of plaque. Finally, aspirin would be added to regulate the function of platelets.

The proposal is underpinned by a massive analysis of earlier trials of drugs that can lower different aspects of the risk of cardiovascular disease. Over 750 trials involving 400,000 people were assessed. However, the PolyPill has yet to be tested in any clinical trials.

Naturally, there are concerns with the concept of packaging six drugs in a single, one-size-fits-all pill. Such a pill would carry the twin dangers of unnecessary side effects for people at low risk and, conversely, undertreating those who need more aggressive care. The availability of such a pill might also deter people from the lifestyle changes (such as losing weight and stopping smoking) that can do the same thing at no cost and have other benefits as well.

References

1. Nissen SE, Tsunoda T, Tuzcu EM, et al. Effect of recombinant apoA-I Milano on coronary atherosclerosis in patients with acute coronary syndromes: a randomized controlled trial. *JAMA* 2003;290:2292–300.
2. Wald NJ, Law MR. Strategy to reduce cardiovascular disease by more than 80%. *BMJ* 2003;326:1419.

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