Pfizer Pharmaceuticals – Don't Ignore Mother Nature

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(02/2007)

Published by
Healthy Choices for Mind and Body
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Pfizer Pharmaceutical Company announced in December 2006 that they were halting development of their much anticipated HDL-cholesterol raising drug. The mega-drug maker's stock value plunged 11% overnight, losing billions of dollars. Pfizer is now slashing their work force by 2000 employees to compensate for the 800 million dollars they spent on the drug's development and loss of anticipated revenue.

The drug, torcetrapib, would have debuted as the first drug aimed at preventing heart disease by boosting HDL-cholesterol, known as the 'good' cholesterol (see Cholesterol Basics article). Pfizer pulled the plug on it after a massive, 15,000 patient trial of a combination torcetrapib/atorvastatin pill showed that patients who took the drug were 60% more likely to die than those who didn't. I would argue that problems with torcetrapib were predictable, given that some naturally occurring states of high HDL-cholesterol don't automatically guarantee long life and good health.

Don't get me wrong, I'm not saying that HDL-cholesterol has been masquerading under false pretenses of beneficence. Since the 1970's *population* studies have shown that higher HDL-cholesterol levels generally predict less risk of having a heart attack. Also, medications that both lower LDL-cholesterol and raise HDL-cholesterol confer greater benefit with greater HDL-cholesterol elevation.

In spite of man's efforts to compartmentalize people's heart disease risk according to their HDL-cholesterol levels, nature continues to defy the 'rules'. Population studies do not guarantee that every individual in the population fits the pattern.
Desirable HDL-cholesterol levels have been set at >45 mg/dl for men and >55 mg/dl for women, but no level ensures a coronary-risk-free life. Some people with HDL-cholesterol levels higher than 95 mg/dl have heart attacks. Most do not.

On the other end of the spectrum, some people with HDL-cholesterol levels as low as 20 mg/dl have no heart disease. Certain human genetic mutations cause very low HDL-cholesterol levels. One might think that they would have early and severe vascular disease. Most do, but a few of these mutations induce premature heart disease only if LDL-cholesterol levels are high.

We can breed animals with a variety of mutations affecting HDL-cholesterol levels. Some follow the 'rules', but one such mutation induces very low levels of HDL-cholesterol without associated atherosclerosis. Another variant dramatically elevates HDL-cholesterol levels, but has *more* clogged blood vessels, not less. **These variant animals and humans are telling us that there is something we don't know about HDL-cholesterol that determines whether or not it is beneficial.**

Now let's consider Pfizer's drug. Torcetrapib works by blocking an enzyme (CETP) that moves cholesterol out of HDL particles into VLDL. From there, VLDL particles either get stuck in blood vessel walls or convert to LDL, both of which are bad. The promise of torcetrapib was that, by blocking CETP, cholesterol would stay in HDL and out of VLDL and LDL. HDL-cholesterol levels would rise, which has always been thought to be good.

Individuals with a genetic deficiency of CETP exist, giving us a natural example of what might torcetrapib might accomplish. These people all have very high levels of CETP. In Japan, one cluster of CETP-deficient individuals live long, heart disease-free lives, but most of these people have normal coronary risk. Some even have heart attacks at younger ages than usual.

Bottom line in the middle: Nature told us that CETP deficiency didn't necessarily protect against heart disease and, in some individuals, might increase risk. Science and medicine have repeatedly proved that we don't know as much as we think we do about the body's complex mechanisms. Pfizer should have heeded these lessons. It takes arrogance and blind faith to think that replicating a defect (knocking out CETP) that in nature does not uniformly confer benefit would result in benefit when we do it with a drug.

In individuals with low HDL-C levels, high dose torcetrapib induces HDL-cholesterol elevation by up to 54%. It affects both the number and size of circulating HDL particles. It lowers LDL-cholesterol slightly, but only in people with normal triglyceride levels. Because of the inconsistent effect on LDL-cholesterol, Pfizer proposed that torcetrapib be administered with a statin, in order to assure LDL lowering. Offering torcetrapib as a combination pill with soon-to-be-generic Lipitor would also guarantee Pfizer an ongoing share of the Lipitor market. Torcetrapib also raises some people's blood pressure, and it's not clear how that

happens. **What is clear is that we can't predict the fall-out of blocking CETP**.

CETP, one of HDL's proteins, transfers cholesterol out of HDL and into VLDL, in exchange for triglyceride moving the opposite direction. Pfizer and others decided that this is bad, but the body must have some reason for doing it this way. Blocking CETP also blocks the movement of triglycerides (fat) from VLDL particles into HDL particles. Once in HDL particles, any triglycerides that have been damaged get fixed and cleared out of the blood. Perhaps blocking this clean-up mechanism is counter-productive.

An HDL-cholesterol level is just that, a level. The level of *anything* in the blood represents a balance between how much is entering and how much is leaving, and at any given time tells us only what is present at that moment. It tells us very little about how it got to that level. Think of a bathtub you are trying to fill while the drain is open: The water level reflects the relative contributions of faucet flow and the size of the drain opening. A high level may result from either huge inflow or measly outflow. A low level might mean very little gain or excessive loss. A median level can represent the balance of large flux in both directions *or* not much happening in either. **A high HDL-cholesterol level could mean the cholesterol loading mechanisms are exceptionally active or suffering from bloated inertia.**

Many years ago probucol, also known as Lorelco, was pulled from the U.S. market by its maker, Hoechst-Marion-Roussel, under pressure from Food and Drug Administration. Probucol lowered total cholesterol levels and had an anti-oxidant effect, but also had the unfortunate side-effect of lowering HDL-cholesterol levels. The fear of any HDL reduction verged on phobia.

In spite of lower HDL-cholesterol levels, animals prone to clogged arteries that were given probucol cleaned up their arteries. Outcomes of patients on probucol improved, in spite of their lower HDL-cholesterol levels. There had been no deaths. The bias against low HDL-cholesterol levels was so strong that probucol got the ax, in spite of evidence that it cleans out clogged arteries.

Probucol is still available in Canada, where doctors continue to study the drug's mode of action. They report that probucol cuts the need for repeat angioplasties in half. Probucol works by blocking a protein, ACAT, that transports cholesterol from cells to HDL, not only does it reduce HDL particle cholesterol but it increases tissue cholesterol. The potential fall-out of letting cholesterol languish in tissue is not known and necessitates much more study before probucol returns to the U.S. market.

For now, people at risk of vascular disease will have to raise their HDL-cholesterol with exercise, niacin and nuts, and hope that the HDL particles they have are oxidizing, esterifying and transporting their lipids in the healthiest possible way.