

# Cardiology at Concorde

Specializing in Non-Invasive Cardiology



## Raising HDL

The Holy Grail for cardiologists is to find a medication which would shrink or remove the fatty cholesterol deposits from the coronary arteries. These deposits or “plaques” cause obstruction to blood flow and produce angina and heart attacks. Patients often ask whether there is some form of “Drano®” which can flush away these deposits. Researchers are getting closer to this goal every day.

Unfortunately, the plaques containing cholesterol are not just sitting on the inner lining of the arteries like sludge. The cholesterol is actually taken into the inner layers of the artery wall and then surrounded with inflammatory cells, which react to the cholesterol deposit as if it were an invader. This invader or irritant produces more and more reaction resulting in severe narrowing of the artery or even rupture of the plaque. In order to reduce the risk of plaque growth and rupture, we use blood cholesterol lowering drugs to reduce growth of the plaque and inflammation in the artery wall.

Cholesterol is transported in the blood stream on carrier proteins known as lipoproteins. The most widely known lipoproteins are HDL and LDL. Low density lipoprotein, LDL or “bad” cholesterol moves cholesterol into the artery walls and “HDL” or “good” cholesterol moves it out of the artery wall. Until now, the most effective approach for treating patients with cholesterol blocked arteries has been to lower the LDL cholesterol with statins. Recent research suggests that a more effective strategy would be to raise HDL levels. Until recently, the only strategies for raising HDL have been exercise, weight loss, modest amounts of alcohol and drugs like niacin or the fibrates.

Until today, Pfizer® had been working on a drug called torcetrapib which reportedly raises HDL more effectively than the other drugs mentioned. The trial has been terminated and the drug withdrawn because of an increase in the number of deaths in patients taking the active drug compared with those on placebo. In spite of this disappointing trial, there is ample evidence that raising HDL levels is a promising approach.

We know from past medical studies that patients with low HDL levels (less than 40 in males and less than 50 in females) have a higher risk of heart attack and stroke than those with normal HDL levels. What has been lacking has been a “proof of concept” experiment that shows actual shrinkage of the plaque when HDL elevating or mimicking drugs are used. Enter Dr. Steven Nissen, Chairman of the Department of Cardiovascular Medicine at the Cleveland Clinic and current President of the American College of Cardiology. Using a technique known as IVUS or Intravascular Ultrasound, Dr. Nissen

and his coworkers showed that the intravenous injection of an artificial HDL like lipoprotein every week for 5 weeks produced definite shrinkage of plaque over the 5-week period. This is especially astonishing because the best LDL lowering drugs on the market today produce very small or no plaque reduction over periods of months or years.

IVUS is an invasive procedure performed by passing a special catheter from the groin and into the heart arteries and then making sonogram grey scale images of multiple sites along the coronary artery lining. Grey scale images are familiar to many families when they see the first pictures of their unborn baby by abdominal ultrasound. Although invasive, IVUS can evaluate drugs in development much more rapidly and at less cost than the multicenter, randomized, placebo controlled trials that require years of follow-up before a difference in heart attack or stroke between patient groups makes new drug benefits obvious (see the article on this site called "Evidence Based Medicine").

How do you go about creating an HDL like substance? In the 1980's researchers at the University of Milan found that 40 residents of a small town in Northern Italy had an HDL protein in their blood which although present in low levels (low HDL) was associated with increased longevity dating back to common ancestors from the year 1780. These residents share a genetic mutation in one of the cholesterol carrying lipoproteins now called apo A-1 Milano. Using gene to protein producing tools, an artificial version of Apo-1 Milano (named ETC-216) was created. Further experiments by Dr. P.K. Shah at Cedars-Sinai Hospital in Los Angeles showed favorable effects of ETC-216 in animal models of cholesterol build up. In 2001, Dr. Sanjay Kaul showed that direct injection of ETC-216 into stents placed in pig coronary arteries dramatically reduced the build up of scar tissue in the stent.

In 2003, Dr. Nissen and his colleagues at 10 hospitals in the United States reported results in 47 patients studied by IVUS after 5 weekly infusions of the artificial form of Apo A-1 Milano. Plaque reduction was seen after 5 weeks in the patients who received the active drug whereas plaque build up was seen in patients treated with placebo. ETC-216 may never reach pharmacy shelves, because of the high cost and lengthy process required to produce it and the possibility that continued benefit may require continued intravenous infusions. Nevertheless, cardiologists are very enthusiastic about the anticipated trial and release of HDL raising therapies in the near future.

Parts of this article were abstracted from the Cedars-Sinai Medical Center Newsletter. For more information on HDL raising therapies in development see the USA Today site: [http://www.usatoday.com/news/health/2006-01-08-heart-disease-cover\\_x.htm](http://www.usatoday.com/news/health/2006-01-08-heart-disease-cover_x.htm)

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