those with no TR, even after adjusting for age, LVEF, IVC size, RV function, and RV size. Unfortunately, the cause of death in these patients is not defined.

The authors attempt to determine why the severity of TR leads to a worse prognosis independent of the parameters mentioned above. They speculate that the presence of TR may be a more sensitive marker of RV dysfunction than is qualitative inspection on echocardiography, or that TR may "mask the decreased contractility of the RV analogous to the effect of mitral insufficiency on the ability to estimate LV contractility from LVEF." Further study is needed in this very large patient population to determine why TR severity has a negative effect on both mortality and morbidity. Indeed, it may be that a more aggressive approach to these patients with surgery such as tricuspid annuloplasty may have a positive effect on the natural history of TR and lead to an improvement in patient survival and quality of life. ■

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# Atherosclerosis

## Bigger Is Better: High-Density and Low-Density Lipoprotein Particle Size

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Atherosclerosis was previously thought to be an irreversible process and an inevitable part of aging. Although modern lipid-lowering therapy has resulted in a significant reduction in the risk of cardiac events, this reduction in adverse clinical events has been associated with only modest degrees of angiographic plaque regression. The salutary effect of lipid-lowering therapy with hydroxymethyl glutaryl coenzyme A inhibitors (statins) on morbidity and mortality is thought to be at least in part conferred by suppression of atherosclerotic plaque inflammation, which results in increased plaque stability. Statin therapy is associated with an average 30% reduction in adverse cardiovascular events. Despite this unquestionable and remarkable beneficial effect, statins still fail to prevent the majority of cardiac events. Other pathogenetic mechanisms, such as local angiogenesis and vascular remodeling, might result in plaque rupture even in the absence of demonstrable inflammation. Indeed, patients with acute coronary syndromes might present with normal levels of C-reactive protein, a marker for vascular inflammation. Further reduction in atherothrombotic events in individuals with established atherosclerosis might require not only plaque stabilization and restoration of normal endothelial function (which can be largely achieved with statin therapy), but also a significant regression in the total atherosclerotic plaque burden. Currently available treatment modalities result in only modest angiographic regression of atherosclerotic arterial obstruction. To achieve more significant regression, not only a reduction in cholesterol influx but also cholesterol efflux from the plaque must be achieved. The key to plaque regression seems to reside in high-density lipoprotein (HDL) size.

In a small village in northern Italy lives a family with a naturally occurring variant of apolipoprotein A-I, known as ApoA-I Milano. Individuals with ApoA-I Milano are characterized by very low levels of HDL, ranging from 10 to 30 mg/dL. Life expectancy, however, is not adversely affected, and atherosclerosis is uncommon. ApoA-I Milano is characterized by a substitution of cysteine for arginine in position 173, thus allowing HDL dimerization and the formation of large HDL particles, which are particularly active in reverse cholesterol transfer. Esperion Therapeutics (Ann Arbor, MI) has formulated recombinant ApoA-I Milano into a complex (ETC-216) with naturally occurring phospholipids to mimic the properties of nascent HDL. Preliminary data derived in animals demonstrated objective plaque regression as quickly as 48 hours after a single infusion.[1]

### Effect of Recombinant ApoA-1 Milano on Coronary Atherosclerosis in Patients with Acute Coronary Syndromes—A Randomized Controlled Trial

Nissen SE, Tsunoda T, Tuzcu EM, et al.
*JAMA.* 2003;290:2292-2300.

The preliminary evaluation of ApoA-1 Milano in humans involved 57 patients with acute coronary syndrome who underwent cardiac catheterization.[2] A non–infarct-related artery with 20% to 50% luminal diameter narrowing in a segment of at least 30 mm length was selected for intravascular ultrasound (IVUS) interrogation. Patients were randomly assigned to one of three treatment groups: placebo or low- or high-dose ETC-216. Study medication was administered as an intravenous infusion at weekly intervals for a total of five doses. Intravascular ultrasound was repeated after the last infusion. The primary efficacy parameter evaluated was the change in percent atheroma volume (from baseline to follow-up). Prespecified secondary efficacy measures included the change in total atheroma volume and the average maximal atheroma thickness. The results of ETC-216 treatment (compared with placebo) were quite impressive and included a 1% reduction in percent atheroma volume and a 4.2% reduction in total atheroma volume after only 5 weeks of therapy. For comparison, Brown and colleagues[3] administered the combination of simvastatin and niacin to patients with coronary atherosclerosis and observed a 0.4% reduction in angiographic percent diameter stenosis after 3 years of treatment. However, angiography might not represent a true measure of plaque regression, because negative remodeling of the vessel lumen might occur as plaque burden decreases. Nevertheless, therapy with an HDL mimetic (ETC-216) seems to achieve more rapid and more extensive benefits by increasing reverse cholesterol transfer than can be achieved by conventional lipid-lowering therapy, which decreases the influx of cholesterol into the vessel wall.

*In the United States, we have a less uniform system for emergency medical services, and many in the population are unfamiliar with CPR.*

Although these preliminary data are promising, several important questions remain. First, will the plaque volume reduction achieved with ETC-216 be sustained, or will plaque volume "relapse" after discontinuation of therapy? Will periodic "booster" infusions at predetermined intervals be required? Last, although intuitive, will a reduction in adverse clinical events accompany the IVUS-determined decrease in plaque volume? These questions will need to be answered before this potentially important therapy can be implemented into practice.

Large particle size of both low-density lipoprotein (LDL) and HDL is associated with exceptional longevity. Barzilai and coworkers[4] investigated 213 Ashkenazi Jewish probands with an average life expectancy of 98.2 years. Particle size of HDL and LDL was significantly larger than those observed in controls, independent of plasma levels of HDL or LDL cholesterol and apolipoprotein A1 and B. Genetic analysis revealed a high frequency of isoleucine-to-valine substitution for the codon 405 in the cholesteryl ester transfer protein, which resulted in decreased enzymatic activity. In addition to longevity, the prevalence of hypertension, cardiovascular disease, and metabolic syndrome were all much lower in the probands than in matched controls. Interestingly, both HDL and LDL particle sizes are significantly larger in women than in men, which might in part explain why women have a lower incidence of atherosclerosis and a longer life expectancy.

It seems that HDL level alone might not be as important prognostically as HDL particle size, a situation similar to that observed for LDL. Smaller HDL particle size has been demonstrated in patients with atherosclerotic cardiovascular disease (ACVD). In addition, HDL was recently demonstrated to have proinflammatory properties in patients with ACVD. Statin therapy is associated with a shift to larger HDL particle size and induces anti-inflammatory effects.[5]

How do we translate the results of the above-noted studies into clinical practice? ApoA-I Milano is quite attractive as a therapeutic agent, given its dramatic effect on plaque burden. Larger studies are necessary to confirm clinical efficacy and to identify the patient populations most likely to derive benefit. Synthetic HDL therapy is unlikely to become as prevalent as statin therapy, owing to both the need for intravenous administration and the projected very high cost (Pfizer acquired Esperion for a cost of more than 1 billion dollars).

In addition, drugs that modulate HDL levels might be closer to market. For example, torcetrapib is a cholesterol ester transfer protein inhibitor that increases both HDL size and levels. A combination atorvastatin/torcetrapib pill is about to enter phase 3 clinical trials.

In the context of our aging population and the reduction in cardiovascular mortality achieved by innovative technologies over the past 2 decades, the prevalence of individuals with chronic cardiovascular disease has increased dramatically. Furthermore, the veritable epidemic of obesity, diabetes, and the metabolic syndromes in the U.S. population will likely exaggerate the prevalence of ACVD. With the advent of HDL mimetic therapy, we are entering a new era of "reversibility" in the treatment of atherosclerosis. Although the concept is appealing, the cost might be appalling and will need to be justified by objective measures of clinical benefit. ■

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# Vascular Disease

## Vascular Disease and Erectile Dysfunction

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[*Rev Cardiovasc Med.* 2005;6(2):127-128]



### Impaired Brachial Artery Endothelium-Dependent and -Independent Vasodilation in Men with Erectile Dysfunction and No Other Clinical Cardiovascular Disease.

Kaiser D, Billups K, Mason C, et al.
*J Am Coll Cardiol.* 2004;43:179-184.

### Erectile Dysfunction: The Earliest Sign of Generalized Vascular Disease?

Cheitlin M.
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It is quite common during the course of taking a thorough cardiovascular history that male patients will describe symptoms consistent with erectile dysfunction (ED). Often these symptoms are attributed to either adverse effects of medication, particularly antihypertensive treatments, or life stresses. ED is present in approximately 30 million American men, with vascular causes, particularly endothelial dysfunction, responsible for the vast majority of cases. Penile erection occurs through neural stimulation of the endothelial lining of penile vessels and the lacunae of the corpus cavernosum. This stimulation results in the release of nitric oxide (NO), which activates guanylate cyclase, leading to the conversion of guanosine triphosphate into cyclic guanosine monophosphate (cGMP), resulting in smooth muscle relaxation, arteriolar vasodilation, relaxation of the corpus cavernosum lacunae, filling of the lacunae with arterial blood under arterial pressure, and swelling of the penis. The erection resolves as a result of the cGMP's hydrolysis to GMP by the enzyme phosphodiesterase-5 (PDE-5). Compounds such as sildenafil (Viagra®; Pfizer, Inc., New York, NY), a PDE-5 inhibitor, prolong the action of cGMP, resulting in maintenance of smooth muscle relaxation and an erection.

*ED is present in approximately 30 million American men, with vascular causes, particularly endothelial dysfunction, responsible for the vast majority of cases.*

Kaiser and colleagues studied vascular structure and function in 30 patients with ED with no other cardiovascular disease compared with 27 age-matched controls. They measured a variety of vascular parameters, including carotid and brachial artery diameters, intima-media thickness, compliance and distensibility, aortic pulse wave velocity, coronary calcification, and brachial artery endothelium-dependent and -independent vasodilation. In comparing these two populations, there were no differences in baseline laboratory studies including lipids, glucose, and homocysteine levels, nor in coronary calcium scores, carotid and brachial artery diameters, intima-media thickness, brachial and carotid artery compliance and distensibility, and aortic pulse wave velocity. Brachial artery endothelium-dependent flow-mediated vasodilation and endothelium-independent vasodilation were reduced in patients with ED compared with normal subjects. ED patients did have lower than normal penile Doppler peak systolic velocities. Most patients with ED had abnormalities in the penile NO-cGMP system, as sildenafil treatment resulted in significant symptomatic improvement.

The investigators conclude that despite the similarity in coronary risk score, measures of vascular compliance and distensibility, and coronary calcium score, "abnormalities in the peripheral vascular NO-cGMP vasodilation system may result in ED as the first clinical manifestation of cardiovascular disease." The next step will be to show whether patients with ED, no manifestations of cardiovascular disease, and abnormal NO-cGMP–mediated vasodilation will go on to develop cardiovascular events.