New, Emerging and Controversial Risk Factors for Atherosclerotic Vascular Disease

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C-Reactive Protein (CRP)

CRP is a marker of systemic inflammation that can increase 1,000-fold in response to major infection or trauma. Levels are remarkably stable over long periods of time when measured in asymptomatic adults. CRP appears in the serum before the erythrocyte sedimentation rate begins to rise, approximately 24-48 hours after the onset of inflammation (Lyon 2003). CRP may also be impacted by visceral adipose tissue. IL-6 is expressed in adipose tissue, released into systemic circulation, and leads to CRP production in the liver. Therefore, elevated CRP status in patients may be an integration of signals from the artery, adipose tissue, and possibly other inflamed tissues (Anty 2006).

Chronically elevated low-grade CRP has been associated with vessel damage and vascular disease (Anty 2006). More specifically, high sensitive CRP (hs-CRP) levels are a strong predictor of cardiac events, even after adjustment for traditional risk factors (e.g. smoking, hypertension, and hyperlipidemia).

This effect was initially described in the Physicians Health Study in which middle aged men deemed healthy were monitored for more than eight years for the development of first ever MI, stroke or venous thrombosis. Baseline hs-CRP levels were found to be higher among men who developed MI or stroke than among those who remained free of disease. Moreover, the men in the quartile with the highest CRP values had three times the risk of MI of the men in the lowest quartile, whereas the risk of stroke was approximately doubled. These results were independent of other lipid and non lipid risk factors (Ridker 1997). Numerous other trials have suggested similar findings to that of the Physicians Health Study (Burke 2002, Pradhan 2002, Ridker 2000, Sakkinen 2002).

CRP - Periodontal disease

Periodontal disease is a chronic infection in humans caused by pathogenic bacteria that colonize as oral biofilms. Periodontitis, its severe form, induces chronic inflammation and immune reactions that result in the loss of the bone and soft tissues that support the teeth in the jaws. Observational studies have shown that periodontitis is associated with an increased risk of myocardial infarction and stroke, although a causal link has not yet been proven (Scannapieco 2003). The effect may be due to the direct action of periodontal pathogens or their products on endothelial cells via transient bacteremia or indirectly via products of the inflammatory response, such as CRP (Choi 2002).

Full-mouth tooth extraction among individuals with periodonitis was recently shown to reduce CRP by 34% (Taylor 2006). Elevation of CRP in those with periodontitis has been verified by other studies (Ebersole 1997, Wu 2000).

Lipoprotein A

Lp(a) has a structure nearly identical to LDL cholesterol. A variation occurs when a disulfide bond attaches Apo(a) to the LDL lipoprotein: LDL + Apo(a) = Lp(a). Several plausible mechanisms have been proposed to explain the association between Lp(a) and vascular disease. First, it has been suggested that Lp(a) plays a part in the initiation, progression, and subsequent rupture of atherosclerotic plaque (Linden 1998). Second, because of the structural homology of apoprotein(a) and plasminogen, Lp(a) may compete with, bind, and inhibit the thrombolytic activity of tissue plasminogen (Linden 1998). Third, Lp(a) lipoprotein has been associated with endothelial dysfunction (Linden 1998). Fourth, Lp(a) activates monocytes, colocalizes with plaque macrophages, stimulates smooth-muscle cells, and could induce inflammation (Linden 1998).

Various population-based prospective studies have reported positive associations between Lp(a) levels and coronary heart disease (CHD) risk (Bostom 1994, Bostom 1996, Cantin 1998, Cambillau 1992, Loscalzo 1990, Ridker 1993, Schaefer 1994).

In one of the largest community based cohort studies of 9,936 men and women, it was found that men in the highest Lp(a) quintile had a three fold risk of stroke, but no reported association between Lp(a) and stroke was made in women in the highest quintile for Lp(a) (Nguyen 1997).

The same finding was reported in a prospective study of 5,888 community-dwelling older adults (65 years of age or older - 2375 women and 1597 men). Elevated level of Lp(a) was found to be an independent predictor of stroke, death from vascular disease, and death from any cause in men but not in women (Ariyo 2003).

Continued on page 39.

Homocysteine

Homocysteine as a predictor of CVD risk was first proposed by Kilmur McCully, MD, over 40 years ago (McCully 1969). Several years later, a report highlighted that 50% of children with the genetic disorder homocysteihoria (cystathionine-synthase deficiency) died prematurely from vascular disease (Wilcken 1976).

The Physician's Health Study, a large prospective study of 14,916 male physicians with no prior myocardial infarction or stroke, provided baseline plasma samples of HCY and were followed for five years (Stampfer 1992). Results indicated that the 271 subjects, who later had MI, displayed significantly higher mean baseline levels of Hcy than matching paired controls who remained free of MI. Subjects whose Hcy levels were in the highest 5% had approximately three times the risk of MI compared with those having lower Hcy levels, even after adjustment for a variety of coronary risk factors.

In a cross-sectional study (Framingham Heart Study) of 1,041 elderly subjects (418 men and 623 women; aged 67-96 y), a clearly graded increase in the prevalence of carotid-artery stenosis with increasing plasma levels of Hcy was observed. The individuals in the group having the highest levels of Hcy had twice the risk of severe stenosis when compared with the group with lowest Hcy levels (Selhub 1995).

A recent meta-analysis (Humphrey 2008) identified 26 studies published from 1966-2006. The outcome of the analysis stated that the risk of coronary heart disease increases approximately 20% for each 5 umol/L of homocysteine. Medications that may cause an elevation of plasma homocysteine requiring supplementation of Betaine (trimethylglycine) B12, and folate) include:

- Fenofibrate— (Dierkes 1999).
- Niacin— Above 1000mg (Garg 1999)
- Metformin— (Carlsen 1997).
- Antiepileptic drugs— (Schwaninger 1999).
- Levodopa— (Muller 1999).
- Methotrexate—(Haagsma 1999).

Frank's Sign — Earlobe crease

In 1973, a physician first described findings of a bilateral or unilateral prominent ear crease in the lobule of the earlobe in a large proportion of his patients who had one or more risk factors for coronary heart disease (Frank 1973). Subsequently, several clinical studies have examined the association of the diagonal ear crease with coronary atherosclerotic heart disease (Haines 1977, Jorde 1984, Kaukola 1979, Lichstein 1974, Mehta 1974, Shoenfeld 1980).

Data from an autopsies series (Cumberland 1987, Kirkham 1989) have indicated a higher prevalence of ELCs in patients with CAD at death (Cumberland 1987). One such study found a significantly higher rate of cardiac death in both men and nondiabetic women with ELCs (Tsunoda 1982).

The literature after the late 1980's was scarce for ELC and cardiovascular disease association until a recent study looking at ELC and carotid intima-media thickness (IMT), an index of subclinical atherosclerosis. The groups consisted of 65 subjects (38 men, mean age 57) with earlobe creases and a second group of 65 age and gender matched subjects without earlobe creases (Celik 2006).

The results indicated that subjects with ELC had significantly higher Carotid IMT as compared to control subjects without ELC. There was no statistically significant difference between the groups in terms of gender, age, smoking, diabetes, prevalence of family history for CAD, total cholesterol, HDL and LDL cholesterol, triglycerides and cardiovascular medical therapy. Hypertension was significantly more prevalent in ELC cases than in controls. In addition, body mass index (BMI) was significantly higher in ELC subjects than controls (Celik 2006).

The study suggests that ELC may be the earliest manifestation of a generalized vascular disease in apparently healthy subjects and that these subjects may be at an increased risk of later developing CVD. The limitations of this study are obvious. The small sample size and the cross-sectional study design need to be confirmed by additional studies. From the available data Frank's sign cannot be ignored, although it is clear that the sensitivity and specificity of Frank's sign is low; 62% and 67% respectively (Celik 2006).

Vertex baldness

The possible relationship between hair loss and coronary heart disease has attracted some interest over the past 30 years. A quarrel among various research groups has focused around the following questions: 1) Is any baldness, regardless of which type of baldness pattern, meaningfully associated with myocardial infarction (MI) or atherosclerotic burden? 2) Is there a difference between frontal baldness and vertex baldness in that respect? 3) What extent of vertex baldness matters?

In 1993, the highly controversial paper (Lesko 1993) published the data collected from a large, hospital-based, case-control study of male pattern baldness and myocardial infraction. The researchers examined the relationship between male pattern baldness and the risk of myocardial infarction in men under the age of 55 years. Cases were men admitted to a hospital for a first nonfatal myocardial infarction (n = 665); controls were men admitted to the same hospitals with noncardiac diagnoses (n = 772).

Extent of baldness was assessed using the 12-point modified Hamilton Baldness Scale.

For severe vertex baldness there was a three-fold increase in MI among those with vertex baldness. More specifically, the data revealed male pattern baldness involving the vertex scalp is associated with coronary artery disease in men under the age of 55 years. Vertex baldness, not frontal baldness, was strongly associated with MI in a "dose-response" fashion. The greater the extent of vertex baldness, the greater the risk of MI.

The Physicians' Health Study (PHS) of 22,071 apparently healthy men at baseline provided a unique opportunity to evaluate whether different patterns of male baldness at age 45 years were associated with future risk of coronary events, including nonfatal MI, angina, and coronary revascularization. 22,071 U.S. male physicians aged 40 to 84 years in 1982, with no history of MI, stroke, transient ischemic attack, or cancer were followed for 11 years.

Compared to men with no hair loss, those with frontal baldness had a relative risk of CHD of 1.09 (9% increase risk) while those with mild, moderate, or severe vertex baldness had relative risks of CHD of 1.23 (23% increased risk). Vertex baldness was more strongly associated with CHD risk in the subgroup of men with hypertension or high cholesterol levels (Lotufo 2000).

A plausible explanation for an association between baldness and CHD may be elevated androgen levels. Men with severe baldness seem to have a greater number of androgen receptors in the scalp. Higher levels of dihydrotestosterone may directly accelerate atherosclerosis by stimulating the proliferation of vascular smooth muscle cells (Fujimoto 1994).

Other notable risk markers
The list provided in this article is a sample from an exhaustive directory of markers in the scientific literature. Other notable markers for cardiovascular risk assessment include:

Fibrinogen – Fibrin may stimulate cell migration and adhesion and smooth muscle proliferation causing occlusion of the vessel.
Iron overload – Excess serum iron is a modifiable risk factor for atherogenesis.
Testosterone – Low levels in men associated with premature heart disease.
Vitamin K - Vitamin K is required to inhibit calcium accumulation in the arteries.
Uric acid – Independent relation of hyperuricemia with myocardial infarction risk.
Serum Bilirubin – Low Bilirubin as a risk marker for CAD. Via its antioxidant potential, bilirubin has antiatherogenic properties, and that an inverse relationship exists between circulating bilirubin concentrations and risk of CAD.

Clinical Key note Summary of Cardiovascular risk markers

C-Reactive Protein (CRP)	• Patient CRP status is an integration of signals from the artery, adipose tissue, and possibly other inflamed tissues (Periodontal). • CRP levels are a strong predictor of cardiac events, even after adjustment for traditional risk factors (e.g. smoking, hypertension, hyperlipidemia). • Periodontitis elicits a mild acute-phase response with elevation of CRP. • Periodontal treatment results in lowered CRP levels.
Lipoprotein A	• Men in the highest Lp(a) quintile had a three-fold risk of stroke, but no reported association between Lp(a) and stroke was made in women in the highest quintile.
Homocysteine	• The risk of coronary heart disease increases approximately 20% for each 5umol/L of homocysteine. • Various medications may increase plasma homocysteine.
Frank's Sign - Earlobe Crease	• The presence of an ELC may be an early sign of vascular disease and suggests the need for more aggressive medical monitoring.
Vertex Baldness	• Vertex baldness was more strongly associated with CHD risk in the subgroup of men with hypertension or high cholesterol levels. • Higher levels of dihydrotestosterone (DHT) may directly accelerate atherosclerosis by stimulating the proliferation of vascular smooth muscle cells.

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