Peripheral Vascular Disease and Dilated Aorta

Peripheral arterial disease (PAD) affects more than 8 million adults in the United States, many of whom have one or more coinciding cardiovascular disease risk factors [D Lloyd-Jones. *Circulation* 2010]. It is associated with high mortality rates, poor outcomes, and is often undetected due to a lack of symptoms [Mukherjee D et al. *Am J Cardiol* 2007; Saw J et al. *J Am Coll Cardiol* 2006; Aboyans V et al. *J Am Coll Cardiol* 2005]. Jonathan L. Halperin, MD, Mt. Sinai Medical Center, New York, NY, discussed prognostic and management strategies for this prevalent disease.

Ankle brachial index (ABI), which evaluates the presence of lower extremity PAD in patients with symptoms of intermittent claudication or rest ischemia, may provide information that is needed for early detection in asymptomatic patients. In a meta-analysis that included 480,325 patient-years of follow-up, subjects (24,955 men and 23,339 women) with no previous history of coronary heart disease, a low ABI (≤0.90) was associated with approximately twice the rate of 10-year all-cause mortality, cardiovascular mortality, and major coronary events compared with the overall rate in each Framingham Risk Score (FRS) category. Authors found that addition of ABI to the FRS would result in reclassification and modification of treatment recommendations in 19% of men and 36% of women [ABI Collaboration. *JAMA* 2008]. Studies that focused on PAD detection in the primary care setting revealed similar findings that suggested that ABI may be a valuable diagnostic tool prior to PAD symptom manifestation [Diehm C et al. *Circulation* 2009; Hirsch AT et al. *JAMA* 2001]. ABI measurement is simple, inexpensive, and accurate, and it is a powerful biomarker that merits further consideration, concluded Dr. Halperin.

Thoracic aortic aneurysm (TAA), which is often found in heritable diseases, such as Marfan Syndrome (MFS), is also associated with high rates of morbidity and mortality, due in major part to increased risk of thoracic aortic dissection (TAD). Valentin Fuster, MD, PhD, FACC, Mt. Sinai Medical Center, New York, NY, discussed recent data concerning TAA and various treatment approaches.

Genetic mutations and aortic wall abnormalities have been shown to contribute to TAA and TAD [Tadros TM et al. *Circulation* 2009; Fedak PW et al. *Circulation* 2002; El-Hamamsy et al. *Nat Rev Cardiol* 2009]. Fibrillin-1 and transforming growth factor-β (TGF-β) play key roles in the development of TAA, TAD, and MFS. Fibrillin-1 mutations have been found to lead to aortic wall stiffening, increased TGF-β activity, inflammation, matrix metalloproteinase (MMP) upregulation, elastolysis, cell disarray, and loss of structural integrity of the matrix [Tadros TM et al. *Circulation* 2009; Fedak PW et al. *Circulation* 2002; El-Hamamsy et al. *Nat Rev Cardiol* 2009].

Recent studies have investigated the use of angiotensin II receptor blocker (ARB) therapy for the treatment of MFS. In a study by Dietz and colleagues, aortic aneurysm in a mouse model of MFS was associated with increased TGF-β. When treated with the ARB losartan, noncardiovascular manifestations of MFS were partially reversed [Dietz HC et al. *Science* 2006]. Additionally, a correlation was observed between circulating TGF-β1 and aortic root diameters in mice ($p<0.002$). In humans, circulating total TGF-β1 concentrations were elevated in MFS patients compared with control ($p<0.0001$). MFS patients who were treated with losartan or β-blockers showed significantly lower total TGF-β1 concentrations compared with untreated MFS patients ($p<0.05$) [Matt P et al. *Circulation* 2009]. In a study by Ahimastos and colleagues, MFS patients who were treated with perindopril, an angiotensin-converting enzyme inhibitor (ACEi), had reduced aortic stiffness and aortic root diameter compared with placebo, possibly through attenuation of TGF-β signaling [Ahimastos AA et al. *JAMA* 2007]. Larger studies are needed to evaluate the efficacy of these therapies for the treatment of MFS.

Surgery may be indicated, depending on the size of the aneurysm, rate of expansion, and the presence of symptoms and comorbidities (Table 1). However, in the case of type A intramural hematoma (IMH), a variant form of TAD, timely surgery is suggested to avoid progression to typical dissection and is associated with favorable outcomes compared with medication alone [Kitai T et al. *Circulation* 2009; Estrera A et al. *Circulation* 2009; Song JK et al. *Circulation* 2009]. The predictive role of aortic diameter and hematoma thickness in IMH remains controversial and requires further investigation. Though there are many potential treatment approaches for TAA, additional studies are needed before definitive strategies can be established.

Table 1. Surgery is Indicated for TAA Under the Following Conditions:

Diameter (in mm)	Location/ Situation
≥ 55	Ascending Aortic Aneurysm
≥ 60	Descending Aortic Aneurysm
≥ 70	High-Risk Comorbidities
≥ 10 accelerated growth rate per year	Original Size of Aneurysm <55

Table modified from Ince H & Nienaber CA. *Nature Cardiovasc Med* 2007.