Erectile dysfunction (ED) is defined as the inability to reach or maintain an erection satisfactory for sexual performance. It is present in up to 100 million men worldwide. In the Massachusetts Male Aging Study (MMAS), ED has been found to some degree in 52% of adult men between the ages of 40 and 70 years. The risk of ED is directly influenced by age, number of risk factors, and presence of cardiovascular disease. Moreover, high prevalence of ED has been reported in conjunction with vascular abnormalities, such as coronary artery disease (CAD), hypertension, cerebrovascular disease, and peripheral arterial disease. Despite these studies suggesting that ED should be classified as a vascular disease, little is known about potential mechanism(s) by which ED and CAD may be associated.

The Artery Size Hypothesis

The artery size hypothesis is a pathophysiologic mechanism recently proposed to address this association (Figure 1). Given the systemic nature of atherosclerosis, all major vascular beds should be affected to the same extent. However, symptoms rarely become evident at the same time. This is likely the result of larger vessels being able to better tolerate the same amount of plaque compared with smaller ones. Findings in a patient with >50% obstruction of the penile artery are shown in Figure 1A. Coronary circulation will not be critically affected because of its larger size, suggesting a mechanism for the theoretical lack of concomitant CAD in early-stage ED. Findings in a patient with a >50% obstruction of the coronary artery are shown in Figure 1B. Because of its smaller diameter, the penile artery will be severely narrowed, suggesting a mechanism for the frequent coexistence of sexual and anginal symptoms. If this hypothesis is valid, then: (1) ED and CAD should be considered as 2 different aspects of the same disease, (2) prevalence of occult CAD in ED should be low, (3) prevalence of ED in patients with CAD should be high, and (4) ED should precede the onset of symptoms of CAD in the majority of cases. Available clinical evidence appears to support this hypothesis (Table 1).
Erectile Dysfunction and Coronary Artery Disease as Different Clinical Manifestations of the Same Disease

Several findings support this hypothesis. First, common risk factors for atherosclerosis have been frequently found in patients with ED, and the severity of ED has been related to the number and severity of risk factors. The classic study by Virag and Bouilly showed that smoking, lipid abnormalities, and diabetes mellitus were more common in patients with ED than in the general population. Also, 1, 2, or ≥3 risk factors for atherosclerosis were detected in 78%, 96%, and 100% of patients with organic ED compared with 22%, 4%, and 0%, respectively, of those with nonorganic ED. Second, an increased prevalence of ED has been reported in association with common vascular diseases, such as hypertension (30%), diabetes (42%), CAD (58%), cere-
brovascular disease (65%), and peripheral arterial disease (73%). Finally, similar early impairment of endothelium-dependent vasodilatation and late obstructive vascular changes has been found in both ED and other vascular disorders.11,12

**Low Prevalence of Coronary Artery Disease in Patients with Erectile Dysfunction**

Some studies have been published on this topic.13–17 Patients enrolled in these studies had ED, ≥1 risk factors, and no clinical evidence of CAD. Coronary reserve was usually tested by means of standard exercise stress testing (EST). Prevalence of positive results ranged from 5% to 56% (mean, 22.5%). Excluding the reports by Pritzker13 and Curkendall and Glasser14 (both available in abstract form only) the prevalence of CAD is reduced to 17%. This proportion is similar to that found in large studies conducted in the 1970s and 1980s that evaluated the rate of positive response to EST (12%) in asymptomatic middle-aged men,18–23 limiting the role of ED as an independent marker or predictor of occult CAD. However, comparison between these studies may be misleading because of significant differences in the number and selection of patients, clinical characteristics, and criteria used to diagnose CAD. Moreover, because no systematic analysis of sexual function was performed in the earliest studies, it is uncertain if they represent a true reference population for comparison.

From a clinical perspective, given the low rate of detectable CAD in patients presenting with ED, further diagnostic assessment should be focused on those at high risk according to clinical criteria (ie, age, risk factor background, duration of ED) or noninvasive testing (ie, dynamic penile Doppler evaluation). Among the clinical predictors, diabetes is a well-known risk factor for both ED and CAD. Gazzaruso et al24 recently described the relation between ED and silent ischemia in uncomplicated type 2 diabetes. Those with silent ischemia had greater ED prevalence rates than those without. After adjusting for other confounding variables, ED appeared to be a significant independent predictor of silent CAD. Supporting the role of unfavorable risk factor profiling, Pritzker13 reported 56% prevalence of positive EST response in patients with ED and “aggressive” risk factor background (≥2 risk factors in 80% and diabetes in >20%). Based on coronary angiography results, patients in this study with multiple risk factors and ED had extensive coronary atherosclerosis (2- or 3-vessel disease).

Among the noninvasive tests, the role of dynamic penile Doppler evaluation as a tool to identify patients with ED at high risk for occult CAD has been found to be valuable.15–17 Reduced vasodilator response in penile circulation (so-called “nonresponders”) is defined as peak systolic velocity <35 cm/sec after pharmacologic stimulation. Although drug doses and time of peak systolic velocity measurement were different between studies, results were generally comparable. All patients but 1 with positive EST results (33 of 34) were classified as nonresponders, whereas nearly half of all cases with negative EST results (88 of 161) were classified as having a normal vasodilator response on the penile Doppler study. Test sensitivity and specificity was 97% and 55%, respectively. Negative predictive value was 98% (positive predictive value, 31%), indicating that a normal Doppler response virtually excludes occult CAD.

**High Prevalence of Coronary Artery Disease in Patients with Erectile Dysfunction**

ED prevalence rates have ranged from 42% to 75% in several clinical studies published over 4 decades. The wide range of ED prevalence in these studies may be explained by several general and specific factors. General factors include differences in population characteristics, definitions of ED, sensitivity and specificity of tests used to diagnose CAD, and concomitant treatment with drugs that can interfere with sexual function. Specific factors include the placebo effect and acute coronary syndromes (ACS).

**Placebo effect:** Several randomized studies comparing new drugs for ED versus placebo have been published. In these studies, ED diagnosis and symptom severity was typically assessed by means of the International Index of Erectile Function (IIEF), a self-administered, validated 15-item questionnaire.29 Placebo responders were defined as those patients who improved their erectile function without receiving the drug. Interestingly, as many as 25% of placebo responders actually showed a normalization of IIEF score after treatment in some studies.30 This finding, mainly caused by psychological factors (ie, being part of a study evaluating drugs for sexual function), which limits the role of IIEF in ED diagnosis, will definitively influence the prevalence of ED among patients with CAD.

**ACS:** Acute myocardial infarction (AMI) is the first manifestation of CAD in 60% to 70% of patients and is caused by acute thrombosis superimposed on a noncritical lesion.31,32 Moreover, the infarct-related artery occlusion is the only detectable lesion in 60% to 70% of AMI cases submitted to coronary angiography soon after the acute event.33 This suggests that in most cases, AMI occurs in the setting of a modest coronary atherosclerotic burden. Consequently, as suggested by the artery size hypothesis, penile circulation might not be significantly obstructed, accounting for a low prevalence of ED in this subset of patients with CAD. We found 18% ED prevalence in patients with recent AMI and single-vessel disease compared with 67% in patients with chronic angina pectoris with multivessel disease (p <0.001).34 Thus, it is likely that patients with CAD have a different ED prevalence according to clinical (acute or
chronic coronary syndrome) or angiographic data (single-vessel or multivessel disease).35

Erectile Dysfunction as a Marker for Coronary Artery Disease

The issue of the temporal relation between symptoms of ED and CAD has been addressed by 2 recent retrospective studies4,6 in which patients were enrolled with different types and degrees of CAD. ED symptoms were found to precede CAD symptoms in 58% to 67% of patients. Montorsi et al6 calculated a mean time interval of 39 months (range, 1 to 165 months) between ED onset and the occurrence of CAD symptoms. After a mean time interval of 32 months, 40% of patients had ACS as the first manifestation of CAD, whereas the remaining 60% had stable effort angina as the initial presentation after a mean time interval of 48 months. We recently confirmed our previous findings, showing that 71% of patients with chronic ischemic syndromes and ED had sexual symptoms preceding the onset of CAD symptoms.34 If confirmed, these findings suggest that in keeping with the slow progression of atherosclerosis, the time interval between ED and CAD onset is expected to be long enough to allow physicians to set up specific diagnostic evaluations and interventions, especially in high-risk patients. Prospective studies in selected CAD populations are warranted to confirm this finding.

Conclusion

Erectile dysfunction is essentially an atherosclerotic disease because of progressive or concomitant microvascular (ie, endothelial dysfunction) and macrovascular (vascular obstruction) alterations. The artery size hypothesis is a recently proposed pathophysiologic mechanism to address the relation between onset of symptoms of ED and CAD. Because this hypothesis is based on relatively slight differences in the diameter of arteries supplying various vascular beds, exceptions are likely to occur. So far, available clinical evidence, although scanty, appears to support this hypothesis. Clinical implications have been discussed.18

### Table 1

<table>
<thead>
<tr>
<th>Uncovered Issues About the Link Between ED and CAD</th>
<th>Artery Size Hypothesis</th>
<th>Clinical Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are ED and CAD different diseases or 2 different clinical manifestations of the same disease?</td>
<td>ED and CAD are different clinical manifestations of the same disease</td>
<td>ED and CAD are different clinical manifestations of the same disease</td>
</tr>
<tr>
<td>Which of the 2 comes first?</td>
<td>ED should come first</td>
<td>ED first in ≤71% of patients (retrospective studies)</td>
</tr>
<tr>
<td>What is CAD prevalence in ED patients?</td>
<td>Should be low</td>
<td>Low: mean 22.5% (5%–56%)</td>
</tr>
<tr>
<td>What is ED prevalence in CAD patients?</td>
<td>Should be high</td>
<td>High: mean 54% (42%–75%)</td>
</tr>
<tr>
<td>Is ED prevalence similar in all types of patients with CAD?</td>
<td>No</td>
<td>ACS with 1 VD: low ED prevalence</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CCS with 2–3 VD: high ED prevalence</td>
</tr>
</tbody>
</table>

ACS = acute coronary syndrome; CCS = chronic coronary syndrome; VD = vessel disease


