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## Review – Sexual Medicine

# Association between Erectile Dysfunction and Coronary Artery Disease: Matching the Right Target with the Right Test in the Right Patient

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### Abstract

**Introduction:** Evidence is accumulating in favour of a link between erectile dysfunction (ED) and coronary artery disease (CAD). This review attempts to identify which patients, among those with ED and no cardiovascular (CV) disease, should be screened for early, subclinical CAD, which coronary targets should be investigated, and which tests should be used.

**Materials and methods:** A comprehensive evaluation of available published data included analysis of published full-length papers that were identified with Medline and Cancerlit from January 1988 to January 2006.

**Results:** Initial screening of patients with ED may adopt risk assessment office-based approaches to score patients into low, intermediate, or high risk of future cardiovascular events. Attention should be drawn to patients at intermediate risk. Targets for the assessment of subclinical CAD in this subset of patients should include both obstructive (flow-limiting) and nonobstructive (non-flow-limiting) CAD. Some tests address obstructive atherosclerosis by directly assessing coronary flow reserve (i.e., standard exercise stress test, rest/stress myocardial scintigraphy or echocardiography). Other tests are general measures of atherosclerosis burden (not necessarily obstructive) either in the coronary circulation (i.e., coronary calcium score by electron-beam computed tomography), or in extracoronary vessels (i.e., ankle brachial index, carotid intima-media thickness by B-mode ultrasound) as surrogate markers of CAD. Although a systematic use of these measures of nonobstructive atherosclerosis burden has not yet been recommended in the guidelines for coronary risk assessment, their use is progressively being extended from the research area to clinical practice.

**Conclusions:** ED is definitely a vascular disorder and all men with ED should be considered at risk of CV disease until proven otherwise. Available risk assessment charts should be used to stratify (low, intermediate, and high) the coronary risk score in each patient with ED.

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## 1. Introduction

Erectile dysfunction (ED) is defined as the inability to reach or maintain erection sufficient for satisfactory sexual performance. Evidence is accumulating in favour of ED as a vascular disorder in the majority of patients. Common risk factors for atherosclerosis are prevalent in patients with ED and the extent of ED has been related to the number and severity of risk factors themselves [1,2]. Besides, the prevalence of ED is increased in patients with vascular diseases such as coronary artery disease (CAD) [3–5], diabetes [2,6], cerebrovascular disease [7], hypertension, and peripheral arterial disease [8,9]. Finally, ED and vascular diseases share a similar pathogenic involvement of nitric oxide pathway leading to impairment of endothelium-dependent vasodilatation (early phase) and structural vascular abnormalities (late phase) [10–12]. Thus, ED may be considered as the clinical manifestation of a vascular disease affecting penile circulation; likewise angina pectoris is the clinical manifestation of a vascular disorder affecting coronary circulation. Moreover, there is growing opinion that ED may be an index of subclinical coronary disease. This review focuses on this clinically relevant aspect of the ED–heart association, in an attempt to identify which patients, among those with ED and no cardiovascular (CV) disease, should be screened for early, subclinical CAD, which coronary targets should be investigated, and which tests should be used.

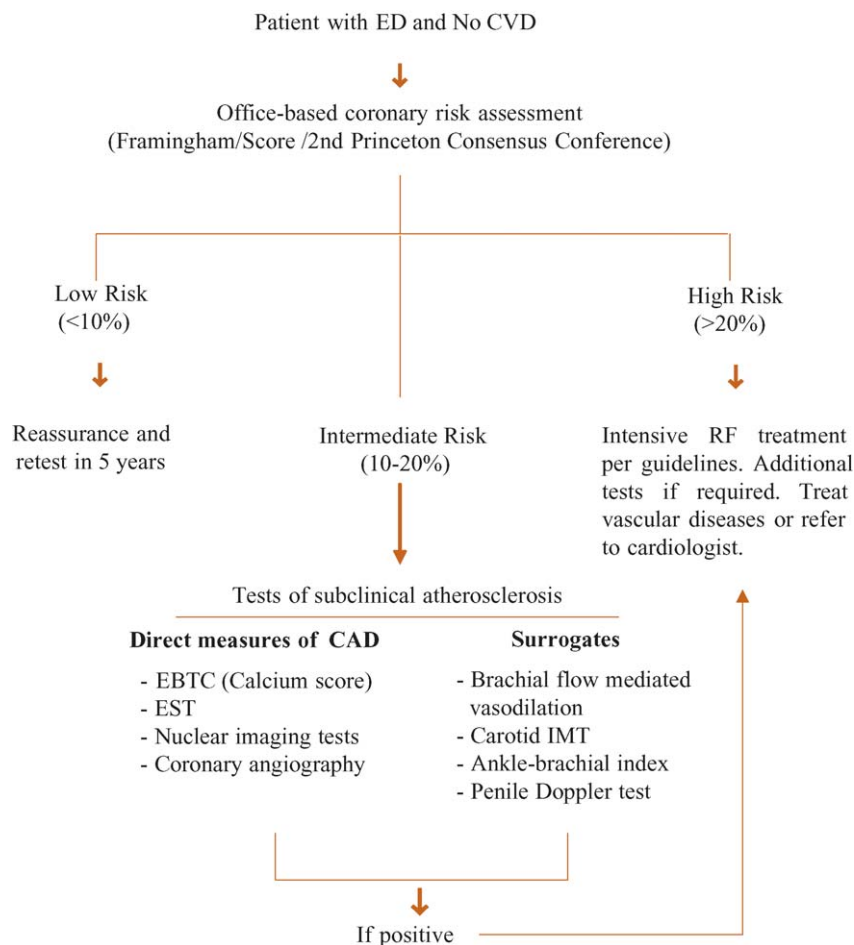
## 2. Link between penile and coronary circulation: the “artery size” hypothesis

We recently proposed a pathophysiologic mechanism, named the “artery size” hypothesis, to explain the association between ED and CAD [13–15]. The concept is based on the conceptual model that exposure to common risk factors leads sequentially and uniformly across all vascular beds to endothelial dysfunction, intima-media thickening and, lastly, vascular obstruction and flow-limiting stenoses. The reason why symptoms rarely become clinically evident in different arterial districts at the same time in a given patient may be the result of larger vessels (i.e., coronary arteries) being able to better tolerate the same amount of plaque as compared to smaller ones (i.e., penile arteries) without inducing flow-limiting stenosis. According to this putative mechanism, ED and CAD should be considered as two different aspects of the same disease, with an expected temporal relationship (i.e., ED should become manifest earlier than CAD). Consequently,

men with ED as the first complaint should rarely complain of significant CAD, whereas men with overt CAD should frequently suffer concomitant ED.

## 3. ED as a marker of subclinical CAD: which patients should be screened?

ED is now beginning to be considered as an early manifestation of a largely subclinical systemic vascular disorder. Whether ED is only a risk marker or may even be considered a “CAD risk equivalent” is not yet fully clarified; yet, there is consensus to consider all men with ED at risk of CV disease until proven otherwise [16,17]. However, given the high prevalence of ED in the middle-aged population, a systematic cardiologic screening would not be cost effective. Therefore, it is crucial to identify ED patients at high risk for occult CAD or acute coronary events or both. A reasonable first step is to estimate, through one of many risk assessment office-based approaches, the subject’s own relative and absolute risk of a CV event (usually in the following 10 yr). Although none of these tools is yet considered ideal, the Framingham Risk Score [18] and the European System Coronary Risk Evaluation (SCORE) [19] are popular and widely used in the United States and in European countries, respectively. The recently released Second Princeton Consensus Conference recommendations addressed this topic more specifically in patients with sexual dysfunction and heart diseases [16]. According to the presence or severity of conventional risk factors subjects are divided into categories at different risk: low (<10%), intermediate (10–20%), and high (>20%). Low-risk patients should be reassured and retested in about 5 yr. Medications for ED can be prescribed without need for additional tests. High risk patients—defined as those with overt CAD, diabetes, extracardiac atherosclerosis (peripheral arterial disease, symptomatic carotid stenosis, abdominal aortic aneurysm) or asymptomatic subjects with multiple risk factors conferring a 10-yr risk of CAD >20%—should undergo further cardiologic assessment and should receive aggressive treatment for the risk factors. In this group of patients, treatment for ED should be deferred until a full cardiologic assessment is performed. Men at intermediate risk, representing almost 40% of the US population, may benefit from additional noninvasive tests aimed to better define the presence and the extension of subclinical coronary atherosclerosis [20–22]. Some tests address obstructive atherosclerosis by directly assessing coronary flow reserve (i.e., standard exercise stress test, rest/stress myocardial scintigraphy or echocardiography). Other tests are



**Fig. 1 – Flow chart of coronary risk assessment in patient with erectile dysfunction and no cardiovascular diseases.**

general measures of atherosclerosis burden (not necessarily obstructive) either in the coronary circulation (i.e., coronary calcium score by electron-beam computed tomography [EBCT]), or in extracoronary vessels (i.e., ankle brachial index [ABI], carotid intima-media thickness [IMT] by B-mode ultrasound) as surrogate markers of CAD. Although a systematic use of these measures of nonobstructive atherosclerosis burden has not yet been recommended in the guidelines for coronary risk assessment, their use is progressively being extended from the research area to clinical practice (Fig. 1).

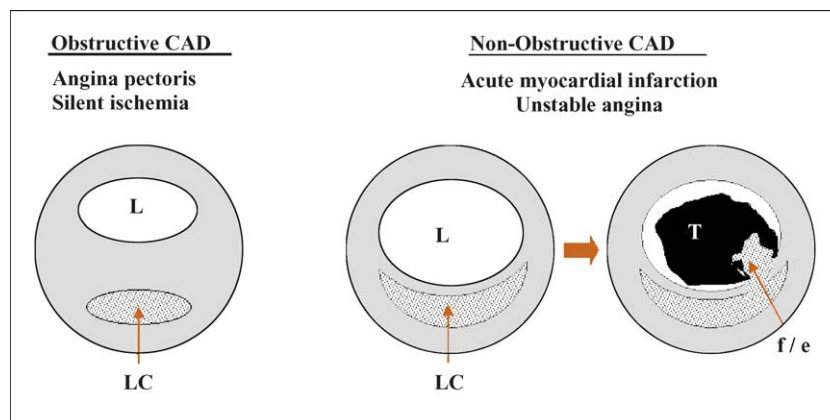
#### 4. ED as a marker of subclinical CAD: which target should be searched for?

Two subclinical forms of CAD should be considered in a man with ED: *obstructive* CAD (i.e., significant coronary artery narrowing that leads to stress-induced myocardial ischaemia) and *nonobstructive* CAD (i.e., functional [endothelial dysfunction] and

nonobstructing [vulnerable plaques] coronary narrowing that may lead to acute coronary events). Although both types of CAD may coexist in the same patient, according to which target is addressed specific diagnostic tests may be required.

##### 4.1. Obstructive versus nonobstructive CAD: anatomic and clinical correlates

CAD basically encompasses two clinical manifestations: stable angina pectoris and acute myocardial infarction (AMI). A flow-limiting coronary obstruction is the anatomic substrate of stable angina pectoris. The artery lumen is narrowed to a certain extent, either concentrically or eccentrically, by a well-developed atheroma, in which the lipid core is separated from the lumen by a thick fibrous cap (Fig. 2). Conversely, a nonobstructing coronary lesion is the more frequent anatomic substrate responsible for AMI. The artery lumen is wide open and is separated from a large lipid core by a thin fibrous cap (the so-called “vulnerable” plaque). These type of



**Fig. 2 – Anatomic and clinical correlates in chronic (left) and acute (middle and right) coronary syndromes. L = lumen; LC = lipid core; T = thrombus; f/e = fissuration/erosion.**

lesions are prone to fibrous cap fissuration/erosion and rupture in specific “weak sites.” This process promotes intraluminal thrombosis and myocardial infarction and sudden death (Fig. 2) [23].

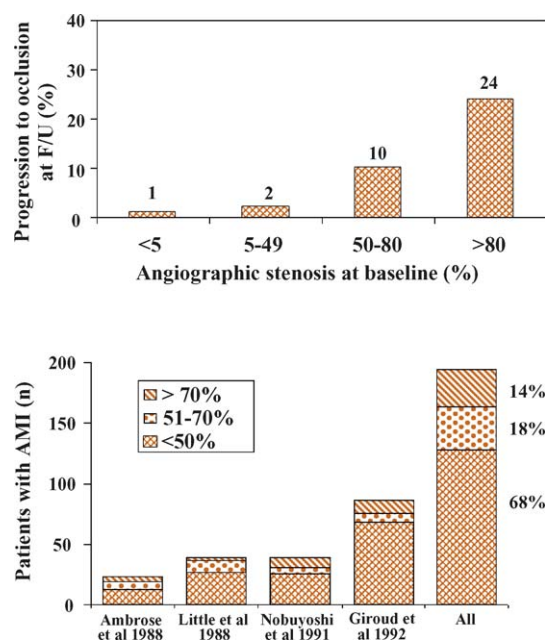
#### 4.2. ED as marker of obstructive CAD

Significant coronary stenosis is the subclinical form of CAD most frequently investigated in ED patients. This is likely the result of a general thinking, especially among noncardiologists, which links the evidence of CAD with the evidence of a critical coronary stenosis. In fact, it is intuitive that a coronary obstruction could progress over the time to occlusion and AMI and that its documentation might prevent acute coronary events. However, two main considerations do not fully support this assumption. First, CAD is basically a slowly progressive disease. The Coronary Artery Surgery Study (CASS) showed a low 5-yr rate of progression to occlusion of coronary stenosis, ranging from 1% for those patients with no stenosis to 24% in those with 85–99% narrowing at study entry (Fig. 3) [24]. Second, AMI is due to the abrupt occlusion of a noncritical coronary stenosis (<50%) in 70% of cases (Fig. 3) [25–27]. Thus, prevention of AMI should be preferentially addressed towards identification of nonobstructive, “vulnerable” plaques rather than towards obstructive, slow-progressing CAD. However, because half of patients with chronic coronary syndromes also harbour “vulnerable” plaques in their own coronary circulations, AMI may still occur as abrupt occlusion of a nonstenotic vessel in 20–30% of patients [28].

##### 4.2.1. ED as marker of obstructive CAD: which tests for this target?

The first-line diagnostic tool to screen a patient for obstructive CAD is standard electrocardiographic

stress test (EST). It is easy to do, reproducible, and inexpensive. The test is defined as “positive” when typical electrocardiographic (ECG) changes (>1 mm ST-segment depression) occur during exercise. Average test sensitivity and specificity are 66% (ranges from 40% to 90% for one- or three-vessel coronary disease) and 84%, respectively [29]. Test accuracy (i.e., is the capacity of a test positive/negative result to truly predict/deny CAD) is influenced by the disease prevalence and by pretest patient probability of



**Fig. 3 – Coronary lesions (%) that progressed to occlusion according to initial angiographic diameter stenosis (upper graph; adapted from Alderman EL et al. [24]). Severity of infarct-related coronary stenoses before acute myocardial infarction in four studies. The majority of stenoses that caused infarction had a <50% obstruction (lower graph, adapted from Welt and Simon [27]).**

**Table 1 – Results of cardiologic work-up in patients with ED and no clinical CAD**

	No. of patients	Age, yr	+EST n, (%)	ED duration, months	≥2 RF (%)	Significant coronary stenosis n, (%)
Pritzker et al. [30]	50	40–60	28 (56)	NA	80 <sup>a</sup> ; D 20	20/20 (100)
Kim et al. [32]	97	56 (45–75)	8 (8.2)	NA	41; D 31	2/3 (67)
Kawanishi et al. [31]	58	56 (25–78)	8 (13.7)	NA	NA	NA
Curkendall et al. [33]	980	NA	49 (5)	NA	NA	NA
Shamloul et al. [34]	40	>40	12 (30)	>3	NA	NA
Vlachopoulos et al. [35]	50	59 ± 11 (41–74)	12 (24)	25 ± 21	78; D 20	9/10 (90)

ED = erectile dysfunction; CAD = coronary artery disease; D = diabetes; +EST = positive exercise stress test; NA = not available; RF = risk factor.  
<sup>a</sup> Patients defined as having multiple risk factors.

disease. Age, sex, risk factors, and the character of chest pain (if present) determine the pretest patient probability risk. The higher the pretest patient likelihood of having CAD and the greater the prevalence of CAD among the population, the better the test accuracy. The typical ED patient has an intermediate pretest likelihood of CAD.

A few reports investigating the EST response in asymptomatic ED patients have been published [30–35] (Table 1). The typical patient enrolled in these studies is an asymptomatic middle-aged man with ED and multiple risk factors, including diabetes in about 25% of the cases. The overall rate of positive EST response was as low as 22% (range: 5–56%; Table 1). Interestingly, in those patients with positive EST who were further investigated by coronary angiography, a high rate of significant CAD (31 of 33 [94%] pooled data) was detected. It is worth noting that almost 50% of these patients were diabetics.

These data confirm that a minority of ED subjects do actually have underlying significant coronary artery stenosis. However, the wide range of positive EST response likely reflects patient populations with different coronary risk scores. Thus, it is mandatory to look for clinical or noninvasive tests that may help to further stratify patients at high risk of subclinical obstructive CAD.

#### 4.2.2. ED as marker of obstructive CAD: role of penile Doppler test

Penile blood flow by colour duplex ultrasound has been proposed as additional diagnostic test to identify ED patients at risk of latent CAD [31,32,34,36]. Conventionally, patients who showed peak systolic velocity (PSV) <35 cm/s after intracavernosal injection with a vasoactive agent (generally prostaglandin E<sub>1</sub> [PGE<sub>1</sub>]) are thought to have a nonspecific, endothelium-independent vascular impairment of penile circulation. These patients have been further evaluated with cardiologic tests to verify whether this finding could be predictive of

occult obstructive CAD (Table 2). Although both drug dosages and time of PSV measuring were somewhat different between studies, pooled studies showed consistent results. Nearly half the patients with positive EST response were classified as non-responders (sensitivity 67%), whereas three fourths of those with negative EST were classified as responders (specificity 59%). This turned into negative/positive predictive values of 84% and 32%, respectively. In other words, the finding of normal Doppler response in a patient with ED makes obstructive CAD unlikely. Conversely, an abnormal Doppler response indicates a generic vascular cause of ED (latent obstructive CAD) in only 30% of cases.

#### 4.2.3. ED as marker of obstructive CAD: role of diabetes and ED duration

Diabetes is by far the most important variable causing both ED and CAD. Sairam et al. showed a 15% rate of undiagnosed diabetes or impaired fasting glucose in 129 consecutive subjects presenting with ED by using fasting blood glucose (ED as “sentinel” of diabetes) [37]. In established type 2 diabetes, approximately 35–75% of men have ED. Furthermore, diabetes is associated with a 2- to 4-fold increase in the risk of myocardial infarction and death due to more severe and diffuse CAD,

**Table 2 – Results of Doppler penile test according to EST response (pooled studies<sup>a</sup>)**

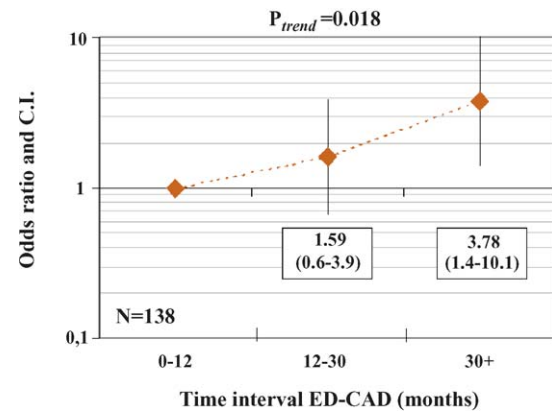
	Positive EST (n = 129)	Negative EST (n = 369)
Responders (PSV > 35 cm/s)	42	218
Non-responders (PSV < 35 cm/s)	87	151

EST = exercise stress test; PSV = peak systolic velocity; PGE<sub>1</sub> = prostaglandin E<sub>1</sub>.  
<sup>a</sup> Kawanishi et al. [31]: 20 µg PGE<sub>1</sub>; Kim et al. [32]: 10 µg PGE<sub>1</sub>; Shamloul et al. [34]: 60 mg papaverine + 2 mg phentolamine; El Sakka and Morsy [36]: 10 µg PGE<sub>1</sub>.

independent of age and other CV risk factors [38,39]. A recent European survey showed that among 4196 patients with CAD admitted to the hospital on either an acute or elective basis, 31% had known diabetes. In the remaining patients, oral glucose tolerance tests unveiled impaired glucose regulation and newly detected diabetes in 35% and 18%, respectively, averaging up to 65% of CAD patients with some form of glucose metabolism alteration [40]. Finally, Gazzaruso et al. first reported the relationship between ED, silent ischaemia, and uncomplicated type 2 diabetes [6]. They found those patients with silent ischaemia and angiographic evidence of significant coronary heart disease (CHD) had greater ED prevalence (33.8% vs. 4.7%,  $p = 0.001$ ) than those without silent ischaemia. After adjusting for other confounding variables, ED appeared to be the most efficient independent predictor of silent CAD.

Although the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) guidelines considered diabetes as “CAD risk equivalent” [21], the American Diabetes Association consensus guidelines recommended CAD screening in asymptomatic subjects only when more than two risk factors are present [41]. However, the Detection of Ischemia in Asymptomatic Diabetic (DIAD) study showed similar rate of positive myocardial scintigraphy among 1123 type 2 diabetics aged 50–75 yr with or without more than two risk factors, reflecting the potential inaccuracy of counting the number of risk factors present in this category of patients [42]. It is unknown whether ED, like diabetes, should be considered a “CAD risk equivalent”; if true, the association of diabetes and ED in otherwise asymptomatic patients should prompt an “ultra” aggressive assessment for CV risk and occult systemic vascular disease [16,17,20].

Duration of ED may be an important although less investigated variable to investigate. Most patients with ED seek medical attention after a mean time interval of almost 2 yr. In theory, the longer the ED duration the longer the time exposure to risk factors and the greater the risk of subclinical CAD. Although no systematic data are reported in the literature, we recently investigated this issue in 138 patients admitted to hospital because of acute coronary syndromes who reported ED prior to CAD onset (mean interval,  $32 \pm 26$  mo). As shown in Fig. 4, there was a significant trend towards a progressive increase in the relative risk of having multivessel disease as ED duration increased after adjusting for age, common risk factors, and body mass index [43]. In other words, long-standing ED ( $>30$  mo) in patients with a first episode of acute coronary syndrome was frequently linked to three-vessel disease.



**Fig. 4 – Relative risk of coronary multivessel involvement according to the duration of erectile dysfunction in 138 patients with first episode of acute coronary syndrome.**

#### 4.3. ED as a marker of nonobstructive CAD

Identification of nonobstructive CAD means individuation of patients at high risk of acute coronary syndromes despite the lack of flow-limiting coronary stenoses. These patients harbour coronary “vulnerable” plaques and may be at risk of acute coronary events and sudden death. Enormous efforts have been put forth in cardiovascular research to identify diagnostic tools that might improve the prediction of acute coronary events beyond the role of classical risk factors. These tools include both measures of atherosclerosis burden (coronary EBCT, carotid IMT, ABI) and indexes of vascular function (endothelial dysfunction) or vascular inflammation (high-sensitivity C-reactive protein [hsCRP]). The biologic and clinical significance of these markers and their link with ED are depicted in the following paragraphs.

##### 4.3.1. EBCT

EBCT is a new, noninvasive method to assess coronary atherosclerosis. Recent work suggests that EBCT can yield incremental risk stratification information. Particularly, the extent of coronary calcification was correlated with angiographic and pathologic findings and was predictive of future cardiovascular events [44]. Chiurlia et al. [45] investigated the prevalence of occult CAD in 70 consecutive patients with vascular ED (positive penile Doppler test) compared to 73 controls without ED. They used brachial artery flow-induced vasodilation to assess endothelium integrity, hsCRP as marker of inflammation, and EBCT to evaluate coronary atherosclerotic burden. They concluded that prevalence and extent of asymptomatic

atherosclerosis is higher in asymptomatic ED patients as compared to patients without ED.

#### 4.3.2. Carotid IMT

The IMT of the carotid artery by ultrasound has been found to be a reliable surrogate of systemic atherosclerosis, including CAD. An increased IMT was associated with an increased risk of myocardial infarction and stroke in adults older than 65 yr without a history of CV disease over a median follow-up of 6.2 yr [46]. Moreover, decreasing cholesterol levels, increasing high-density lipoprotein cholesterol (HDLc) levels, and reducing blood pressure values have been found to slow carotid IMT progression and acute CV events [47]. Recently, Bocchio et al. found that, among men with ED and no clinical evident atherosclerosis, those with increased carotid IMT (>1.0 mm) had a more severe ED, were older, and had higher hsCRP levels than those without ED ( $p < .05$ ) [48]. Caretta et al. reported a trend towards a more severe impairment of erectile function tests according to carotid IMT (<0.9, >0.9–1.29, and >1.3 mm) in a selected older

patient population with no risk factors [49]. No tests to detect underlying CAD were performed in that study.

#### 4.3.3. ABI

The ABI is the ankle-to-arm systolic blood pressure ratio originally used to identify peripheral artery disease (defined as any value <0.90). The test is quick and easy to perform even in the office setting and has been shown to be an accurate and reliable marker of generalised atherosclerosis [50]. In a long-term prospective study asymptomatic men and women with an ABI ratio <0.90 had a relative risk of 6.3 for all CV disease mortality and 3.1 for all-cause mortality, even after adjusting for conventional CV risk factors [51]. The more recent Edinburgh artery study confirmed the initial results showing that a low ABI is an independent predictor of the risk of fatal AMI after adjusting for prevalent CV disease, diabetes, and conventional risk factor score [52]. Thus, an ABI value <0.90 in an asymptomatic subject (with ED) provides independent prognostic information especially if the man is older than 60 yr.

**Table 3 – Studies addressing endothelial function in asymptomatic ED**

	Yavuzgil et al. [57]		Kaya et al. [59]		Kaiser et al. [58]		Chiurla et al. [45]	
Patients enrolled	ED	No ED	ED	No ED	ED	No ED	ED	No ED
No. of patients	36	39	32	25	30	27	70	73
Age, yr	54 ± 9	53 ± 7	55 ± 10	57 ± 7	46 ± 2.4	47 ± 1.2	51 ± 6.7	50 ± 6.2
Test for ED	?		IIEF-5 (ED < 22)		IIEF-15 (ED < 26)		IIEF-5 (ED < 22)	
IIEF score	14.8 ± 3.5	26.8 ± 2.3	9.1 ± 3.1	22.3 ± 2.9	13.7 ± 1.2	21.3 ± 1.2	12.7 ± 1.5	22.1 ± 1.4
Penile Doppler PSV (cm/s)	–	–	NA	–	28 ± 3	–	27.5 ± 3.5	–
Test for endothelium	BAFMD (upper arm)*		BAFMD (forearm)*		BAFMD (wrist)*		BAFMD (forearm)*	
FMD, %	3.2 ± 3	6.0 ± 4	6.0 ± 2.9	12.3 ± 3.5	1.3 ± 0.3	2.4 ± 0.3	2.36 ± 1.8	3.92 ± 2.2
	$p < 0.0001$		$p < 0.001$		$p = 0.014$		$p < 0.001$	
Post-NTG 0.4 mg/isosorbide dinitrate 5 mg sublingually, %	12.1 ± 6	15.4 ± 8	12.8 ± 4.2	17.8 ± 5.2	13 ± 1.4	17.8 ± 1.4	8.36 ± 3.3	9.50 ± 3.5
	$p = 0.032$		$p < 0.001$		$p < 0.05$		$p = 0.09$	
Comments	Data as mean ± SD Age-matched patients		Data as mean ± SE Low risk factor score in both groups. Some patients in the No ED group had IIEF scores below the cut-off.		Data as mean ± SEM No risk factors in both groups. Age-matched patients. Some patients in the No ED group had IIEF scores below the cut-off.		Data as mean ± SD Similar risk factors score in both groups.	
	31% CAD	21% CAD						
	25% Diab	15% Diab						
	22% Rx D	13% Rx D						
	17% Rx BB	10% Rx BB						
	Unclear type of IIEF used.							

\* Cut-off values to define a normal response (peak values): upper arm: 7.4%; forearm: 4.4%; wrist: 2.5%. From Betik AC, et al. Am J Physiol Heart Circ Physiol 2004;286:H442–8.

ED = erectile dysfunction; IIEF = International Index of Erectile Function; PSV = peak systolic velocity; NA = not available; FMD = flow-mediated dilation; BAFMD = brachial artery flow-mediated dilation; NTG = nitroglycerin; CAD = coronary artery disease; Diab = diabetes; Rx D = treatment with diuretics; BB = beta-blocker; sl = sublingual.

#### 4.3.4. Endothelial dysfunction

Endothelial dysfunction is a key variable in the pathogenesis of atherosclerosis and its complications, including ED and CAD. It is a contributing factor in the genesis of myocardial ischaemia and acute coronary syndromes in patients with either angiographically proved CAD or normal coronary vessels [53]. Moreover, it has been shown to be an independent predictor of future CV events providing valuable prognostic information additional to that derived from traditional risk factors [54]. Because endothelial tests for coronary circulation are invasive and impractical to use on a wide scale, noninvasive evaluation of endothelial function has been introduced. Results similar to those obtained from invasive studies have been reported, confirming endothelial dysfunction as a systemic disorder [55,56]. So far, four studies addressing endothelial function in asymptomatic ED subjects have been published (Table 3) [45,57–59]. Despite differences in the clinical characteristics of the patient populations, including age and risk factor scores, tests used for ED and endothelial dysfunction diagnosis, results consistently showed blunted endothelium-dependent vasodilation response in patients with ED as compared to controls. Interestingly, Kaiser et al. [58] showed an impaired vascular response in patients with ED and no CV disease, without major risk factors or detectable cardiac and vascular abnormalities. These results lend support to the concept of ED as marker of an early vascular defect that is, at least in part, not related to traditional risk factors and occurs well before the development of other overt functional or structural systemic vascular disease. Moreover, in three of four studies, an impairment of endothelium-independent vasodilation was detected, suggesting a systemic disorder of vascular smooth muscle cells. Endothelium-independent impairment, however, has not been found to predict long-term coronary events [53,54].

#### 4.3.5. hsCRP

Although debate persists regarding the precise physiologic role of hsCRP, the prognostic value of hsCRP as a marker of CV risk is now firmly established. Although hsCRP predicts future CV events in many clinical conditions, including healthy subjects without CV disease [60], epidemiologic studies of general populations unselected for CV disease condition have found a poor correlation with results of tests that quantify the extent of atherosclerosis, such as carotid IMT measured by Doppler ultrasound or coronary calcification measured by EBCT. These observations have led some to suggest that elevated hsCRP levels may primarily

reflect an increased tendency for plaque rupture rather than a high atherosclerotic burden. The relationship between hsCRP and severity of vascular ED was evaluated in 137 impotent subjects with no CV disease. Severity of ED was scored according to penile Doppler test. Plasma level of hsCRP was significantly associated with the severity of ED ( $p < 0.05$ ) after adjusting for age [61]. Giugliano et al. evaluated the association between ED, endothelial function (blood pressure decrease to L-arginine infusion), and markers of vascular inflammation in 40 obese men with and without ED. Circulating hsCRP levels were significantly higher in obese men with ED as compared to those without ED ( $p < 0.05$ ). Multivariate analysis identified BMI, mean blood pressure response to L-arginine, and hsCRP as independent predictors of ED score (the higher the hsCRP plasma level, the more severe the ED score) [62].

### 5. ED as predictor of future CV events: clinical evidence

The issue whether patients with ED do have a higher long-term risk of CV events as compared to general population without ED is yet to be resolved. A well-planned prospective study is still lacking. Available data come primarily from retrospective investigations. One of these reviews examined 2115 men with several risk factors at a large primary care clinic [63]. Those who had ED when first seen were three times more likely to have had an AMI in the past. By contrast, the overall association between ED and subsequent AMI was greater (OR = 4.9; CI, 1.9–12.7), but statistical significance was lost when adjusted for age (OR = 2.2; CI, 0.7–6.6) in part due to the small number of events (17 of 1844) in the 2 yr follow-up. Blumentals et al. [64] examined a large cohort of patients ( $n = 12,825$ ) with diagnosis of ED recruited by an administrative database compared with a similar number of controls without ED. The ED group had a 2-fold increase (OR = 1.99; CI, 1.17–3.38) in the risk of AMI as compared to non-ED patients after adjusting for age at ED diagnosis, smoking, obesity, use of medications such as angiotensin-converting enzyme (ACE) inhibitors,  $\beta$ -blockers, and statins. Study limitations were mainly inherent to the type of database used, which included only patients with established ED and AMI (probably the most severe cases) and lacked information about potential comorbidity and diabetes. Conversely, Ströberg et al. [65] sent a questionnaire about sexual function to 160 patients who suffered AMI 2 yr earlier. Among 100 who responded (mean age, 59 yr), ED prevalence

was 34%, duration was <3 yr in the majority, and the score was severe in <10%. Interestingly, a control group of similar age without previous AMI had an ED rate of 30%, raising doubts about ED as a predictive marker of acute coronary syndromes.

Finally, a very recent paper by Thompson et al. [66] made a substantial step forward in this issue. Among men enrolled in the Prostate Cancer Prevention Trial (finasteride vs. placebo) 4247 subjects, 55 yr of age or older, had no ED at study entry and were followed up for 5 yr. Onset of both ED and CV events was monitored. Over time, 57% of subjects developed ED. After adjusting for all covariates, men with incident ED had a significantly increased risk of AMI or angina as compared to those without incident ED (HR = 1.37; CI, 1.06–1.76,  $p = 0.02$ ). ED had an equal or greater effect on subsequent CV events of the same magnitude as family history of premature CAD, smoking, or hypercholesterolaemia.

## 6. Conclusion

ED is definitely a vascular disorder and all men with ED should be considered at risk of CV disease until proven otherwise. Available risk assessment charts should be used to stratify (low, intermediate, and high) the coronary risk score in each patient. Many ED patients carry an intermediate risk of CAD. Those patients should undergo additional noninvasive tests to “enrich” prevalence of CAD and further stratify risk. Targets should include both obstructive and nonobstructive CAD. The overall prevalence of occult flow-limiting stenoses is low, although it strictly depends on risk factor background and presence of diabetes. Nonobstructive CAD is a much more important target to look at although it is more difficult to assess by clinical criteria alone. Information from emerging noninvasive tests, such as ultrasound imaging of carotid IMT, hsCRP, and EBCT, could be integrated as biomarkers to assess the risk of acute coronary syndromes, but more information is necessary before widespread clinical application is possible. The risk of acute coronary syndrome in the overall ED patient population is yet poorly quantified although it seems to be higher than in the normal population without ED.

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