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Association between erectile dysfunction and coronary artery disease. Role of coronary clinical presentation and extent of coronary vessels involvement: the COBRA trial

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Aims To investigate the prevalence of erectile dysfunction (ED) in patients with CAD according to clinical presentation, acute coronary syndrome (ACS) vs. chronic coronary syndrome (CCS), and extent of vessel involvement (single vs. multi-vessel disease).
Methods and results 285 patients with CAD divided into three age-matched groups: group 1 (G1, $n = 95$), ACS and one-vessel disease (1-VD); group 2 (G2, $n = 95$), ACS and 2,3-VD; group 3 (G3, $n = 95$), chronic CS. Control group (C, $n = 95$) was composed of patients with suspected CAD who were found to have entirely normal coronary arteries by angiography. Gensini's score used to assess extent of CAD. ED as any value <26 according to the International Index of Erectile Function (IIEF). ED prevalence was lower in G1 vs. G3 (22 vs. 65%, $P < .0001$) as a result of less atherosclerotic burden as expressed by Gensini's score [2 (0–6) vs. 40 (19–68), $P = 0.0001$]. Controls had ED rate values similar to G1 (24%). Group 2 ED rate, IIEF, and Gensini's scores were significantly different from G1 [55%, $P < 0.0001$; 24 (17–29), $P = 0.0001$; 21 (12.5–32), $P < 0.0001$] and similar to G3 suggesting that despite similar clinical presentation, ED in ACS differs according to the extent of CAD. No significant difference between groups was found in the number and type of conventional risk factors. Treatment with beta-blockers was more frequent in G3 vs. G1 and G2. In G3 patients who had ED, onset of sexual dysfunction occurred before CAD onset in 93%, with a mean time interval of 24 [12–36] months. In logistic regression analysis, age (OR = 1.1; 95% confidence interval (CI), 1.05–1.16; $P = <0.0001$), multi-vessel vs. single-vessel (OR = 2.53; 95% CI, 1.43–4.51; $P = 0.0002$), and CCS vs. ACS (OR = 2.32; 95% CI, 1.22–4.41; $P = 0.01$) were independent predictors of ED.
Conclusion ED prevalence differs across subsets of patients with CAD and is related to coronary clinical presentation and extent of CAD. In patients with established CAD, ED comes before CAD in the majority by an average of 2 up to 3 years.

Introduction

Erectile dysfunction (ED) is defined as the consistent inability to reach and maintain an erection satisfactory for sexual activity.[1] This condition has been reported to afflict, to some degree, 52% of male adults between the ages of 40 and 70 years in the USA and ≈322 million men worldwide[2,3] It has been found to be related to age, atherosclerosis risk factors, and heart disease.[3–6] Of great clinical importance is the potential link between ED and coronary artery disease (CAD). Prevalence of ED as high as 75% has been reported in the established CAD.[7–12] However, data from the previous studies are difficult to analyse and compare because of important differences in patient's selection, clinical (most age) and angiographic characteristics, criteria used to define ED (interview or validated test), test accuracy for CAD (non-invasive or angiographic), and presence of confounding factors such as medications or diseases known to negatively affect sexual function.

The aim of this study was to evaluate the prevalence of ED and its relationship with coronary atherosclerosis in a large, selected patient population with angiographically documented CAD. We tested the hypothesis that ED prevalence is related to coronary atherosclerotic burden that in turn is related to the type of clinical presentation—acute coronary syndrome (ACS) vs. chronic coronary syndrome (CCS). In fact, ACS, mainly acute myocardial infarction (AMI), is usually due to abrupt closure of a previous single, non-critical stenosis in an otherwise coronary tree without additional critical lesions (low atherosclerotic burden pattern). Conversely, CCS is usually due to significant

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coronary stenosis frequently involving multiple arteries and sites (high atherosclerotic burden pattern). As atherosclerosis is a systemic disorder, penile circulation might be involved to a similarly different extent as coronary circulation in ACS vs. CCS patients. If true, ED prevalence should be low in the former and high in the latter.[13,14]

Methods

Four groups of patients were defined according to clinical and angiographic results: group 1 (G1, $n = 95$) with patients with ACS and angiographic detection of one-vessel disease (1-VD). Group 2 (G2, $n = 95$) with patients with ACS and angiographic detection of two- or three-vessel disease (2- or 3-VD). Group 3 (G3, $n = 95$) included patients with CCS regardless the number of vessel involved and controls (C, $n = 95$) who were found to have an entirely normal coronary tree. A sample of 95 subjects per group was chosen in order to assess a variation of ED prevalence from 25 (control group) to 50% in any of the three patients' groups with an alpha error of 0.01 (accounting for multiple tests) and a power of 90%. Between May 2004 and July 2005, 3330 patients underwent coronary angiography for both ACS and CCS syndromes at the Institute of Cardiology of the University of Milan. Four-hundred and ten patients (12.4%) were found to have angiographically normal coronary arteries. Four-hundred and fifty (13.5%) were classified as ACS (i.e. first episode of acute ST-elevation myocardial infarction or non-ST elevation myocardial infarction or unstable angina),[15] whereas the remaining patients were classified as CCS (defined as clinical and non-invasive evidence of stable myocardial ischaemia lasting >2 months). The first 95 patients qualifying for G1 were enrolled in the study. Each subsequent patient qualifying for G2, G3, and C groups was enrolled, if his age was within 5-year class compared to corresponding patient of G1.

Patients with previous percutaneous or surgical myocardial revascularization procedures were excluded. All patients underwent complete routine laboratory tests, included lipid profile, fasting glucose, and total and free-plasma testosterone levels. Diagnostic coronary angiography was carried out in all patients by the Judkins standard technique. If required, percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass graft surgery was carried out during the hospital stay.

Risk factors (when not previously known) were defined according to the European Society of Cardiology guidelines as follows:[16] hypertension as blood pressure >140/90 mmHg in three consecutive readings, at rest; hypercholesterolemia as total and/or LDL cholesterol level >5 mmol/L (>190 mg/dL) and 3 mmol/L (>114 mg/dL), respectively; diabetes as fasting glucose level >7.0 mmol/L (>125 mg/dL); obesity as body mass index (BMI) >30 kg/m^2; and family history of CAD as parents with CAD at age <55 (father) or <65 (mother).

Ankle-brachial index was taken as an accurate and reliable marker of generalized atherosclerosis. It was calculated by dividing the ankle systolic pressure by the brachial pressure (both measurements taken by cuff manometers). The lower of the indexes obtained for the two legs was used as the measure of disease severity.[17]

The local medical committee approved the study protocol and each patient gave written informed consent.

Quantitative coronary angiography

Off-line qualitative coronary angiography analysis was performed by two experienced observers unaware of the patient's cardiological condition and the result of the patient's IIEF-EFD questionnaire, using ARTREK Quantum IC (Image Comm. System Inc, Sunnyvale, CA, USA).[18] The outer diameter of the contrast-filled catheter was used for calibration. The lesions were analysed in multiple projections, and reference vessel diameter, minimal lumen diameter, and percent diameter stenosis were measured from the 'worst' angiographic view. Significant angiographic narrowing was defined as >50% diameter stenosis involving either one major epicardial vessel at any site or any collaterals with >3 mm diameter. Patients were classified as having 1-VD, 2-VD, or 3-VD, if they had a single lesion in 1, 2, or 3 coronary vessels. For example, a single lesion on the left circumflex and anterior descending arteries was classified as 2-VD, as was a single lesion on the left circumflex artery (CX) and on a large first diagonal or postero-lateral branch. Lesions on each major epicardial vessel plus a lesion of a large diagonal branch was classified as 3-VD. Multiple lesions of the same vessel separated by at least >20 mm of normal artery segment was classified as 2-VD.

Gensini's score

Calculation of Gensini's score was carried as previously reported.[19] We modified the original scoring system by adding a specific score for acute total occlusion, as in the case of ACS. As acute coronary occlusion usually occurs in a previous angiographically non-critical lesion,[20] we scored acute total occlusion as a non-significant lesion (from 0 to 5 score) instead of true chronic total occlusion (from 32 to 172 score) (*Figure 1*).

Erectile function evaluation

Erectile function was evaluated by the erectile function domain of the International Index of Erectile Function (IIEF-EFD) a validated 15-item self-administered questionnaire.[21] Erectile function is specifically addressed by six questions that form the so called 'erectile function domain' of the questionnaire. Each question is scored 0 to 5. ED is defined as any value <26. In the case of ED, patient was asked to answer the following question: 'Did ED symptoms come before CAD symptoms?' If yes, 'how long before? (months)'. IIEF questionnaire was administered to patients after a mean time interval of 3 [2–5] days since the admission to the hospital. Patients with diseases that could alter sexual activity, such as liver cirrhosis, renal failure, thyroid disease (hypo- and hyperthyroidism on replacement treatment), major depression on long-term pharmacological treatment, and spinal cord injuries, and those with previous pelvic, penile, urethral, or prostate trauma or surgery were excluded.

Statistical analysis

In order to account for the data matching, comparisons between groups were performed stratifying patients into 95 independent sets, each including one patient per group with matched age. Quantitative variables were compared by repeated measures ANOVA, considering the 95 independent sets as 'subjects' and the differences between groups as within subjects effects. Qualitative variables were compared by CMH chi-square, stratifying for matching set.

IIEF-EFD and Gensini's scores were rank transformed before analysis because of their skewed distribution. When individual comparisons between groups were made, the Bonferroni correction for multiple comparisons was employed. Spearman coefficient was used to correlate variables.

The relationship among ED prevalence, clinical presentation, and extension of CAD was analysed by multivariable logistic regression adjusting for the following covariates: age; diabetes; hypertension; hypercholesterolemia; family history of CAD; smoking; BMI; treatment with beta-blockers, statins, diuretics, or antiplatelets. Adjusted odds ratios (OR) and 95% CI were estimated. The area under the ROC curve was used as a measure of prediction ability. The relation of time interval between ED and CAD onset was evaluated by the analysis of covariance after Log transformation of data.

Data are presented as mean $\pm$ SD, unless otherwise stated. A two-tailed *P*-value <0.05 was considered as significant.

Results

Clinical characteristics of study population are reported in *Table 1*.

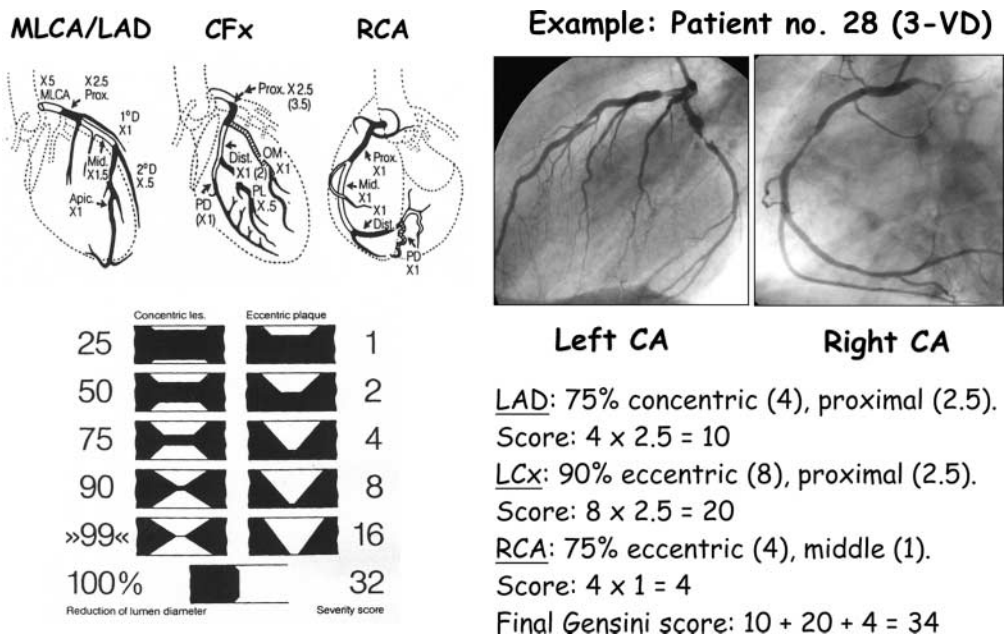

Figure 1 Schematic drawing of the GENSINI score (Left). The method assigns a different severity score depending on the degree of stenosis, its location (proximal, middle or distal tract) along the target vessel and the type of coronary vessel involved (left anterior descending, left CX or RCA). An example of Gensini score calculation is shown on the right part of the figure. MLCA, main left coronary artery; LAD, Left anterior descending; CFx, Left circumflex; RCA, right coronary artery.

Table 1 Clinical characteristics of study population ($n = 380$)

	Controls ($n = 95$)	Group 1 ($n = 95$)	Group 2 ($n = 95$)	Group 3 ($n = 95$)	*P*-value
Age (years)	53.6 ± 8.6	53.7 ± 8.5	54.7 ± 6.7	55.4 ± 5.7	0.26
BMI (kg/m^2)	26 ± 3	26.6 ± 3.1	26.8 ± 3.3	26.8 ± 3.3	0.96
IIEF-EFD score	27 (26–28)	27 (26–29)	24 (17–29)	24 (15–27)	<0.0001
Modified Gensini's score	0 (0–2)	2 (0–6)	21 (12.5–32)	40 (19–68)	<0.0001
Involved coronary vessels, *n*	0	1 ± 0	2.4 ± 0.5	2.2 ± 0.8	–
Number of risk factors	1.97 ± 1.16	2.41 ± 0.94	2.53 ± 1.05	2.52 ± 1.07	0.65
Smoking, *n* (%)	34 (36)	63 (66)	68 (73)	51 (54)	=0.08
Family history, *n* (%)	8 (8)	20 (36)	17 (32)	15 (29)	=0.005
Diabetes (type I-II), *n* (%)	9 (9)	7 (7)	13 (14)	21 (22)	=0.08
Hypertension, *n* (%)	56 (59)	40 (42)	39 (42)	52 (55)	0.12
Hypercholesterolemia, *n* (%)	64 (67)	76 (80)	72 (77)	79 (83)	0.60
Obesity, *n* (%)	14 (15)	14 (15)	20 (21.5)	16 (17)	0.71
>3 risk factors, *n* (%)	28 (29)	44 (46)	46 (48)	48 (50.5)	0.56
Type of CAD onset (*n*,%)					
STEMI	–	63 (66)	67 (70.5)	–	0.52
NSTEMI	–	12 (13)	16 (17)	–	0.45
UA	–	19 (20)	11 (11.6)	–	0.10
SA	–	–	–	95 (100)	–
Therapy on admission					
Diuretics, *n* (%)	20 (21)	8 (8)	8 (8)	15 (16)	0.10
Beta-blockers, *n* (%)	20 (21)	16 (17)	29 (31)	48 (50.5)	<0.0001
Calcium-antagonists, *n* (%)	26 (27)	7 (7)	7 (7)	21 (22)	=0.0019
ACE-I & ARB, *n* (%)	37 (39)	25 (26)	25 (26)	30 (32)	0.19
Oral antidiabetic drugs, *n* (%)	4 (4)	4 (4)	6 (6.5)	13 (14)	=0.02
Statins, *n* (%)	9 (9)	20 (21)	24 (26)	38 (40)	=0.004
Acetylsalicylic acid, *n* (%)	26 (27)	0 (0)	19 (36)	24 (45)	<0.0001
Total testosterone (ng/mL)	4.7 ± 1.8	4.1 ± 1.5	4.3 ± 1.5	4.3 ± 1.5	0.75
Free testosterone (pg/mL)	10.9 ± 4.5	10.9 ± 6.4	10.9 ± 5.6	9.7 ± 4.4	0.22
Brachial-ankle index	1.13 ± 0.1	0.98 ± 0.10	0.95 ± 0.10	0.80 ± 0.29	=0.001

Data are given as mean (SD) except for IIEF-EFD and modified Gensini's score data given as median [interquartile range]. Differences between G1 vs. G2 vs. G3 on measurement outcomes was made through two-way ANOVA accounting for matching groups (except IIEF-EFD and modified Gensini's score by rank transformed before analysis) and categorical outcomes through χ^2. ACE-I, ACE-inhibitors; ARB, angiotensin-receptor blockers; NSTEMI, non-ST elevation myocardial infarction; SA, stable angina; STEMI, ST-elevation myocardial infarction; UA, unstable angina.

There was no difference in age between groups. Risk factors were uniformly distributed between groups, except for smoking and diabetes that were significantly more frequent in G2 and G3 when compared with G1, respectively. Noteworthy, almost 50% of patients in each group had >3 risk factors. Overall, G3 patients received more cardiovascular drugs than G1 and G2. Use of diuretics was similar between groups, whereas beta-blockade was significantly more used in chronic angina pectoris.

Figures 2 and *3* show ED prevalence, IIEF-EFD score, and modified Gensini's score in the three groups of patients with CAD and in controls. Overall ED prevalence was 47% (135/285). When separately considered, ED prevalence was 22 (21/95), 55 (52/95), and 65 (62/95) in G1, G2, and G3, respectively ($P = <0.0001$ for G1 vs. G2 and G1 vs. G3; $P = 0.45$ for G2 vs. G3). Controls ED prevalence was 24% (23/95). Corresponding IIEF-EFD scores were (median and interquartile range): 27(26–29), 24(17–29), and 24(15–27) in G1, G2, and G3, respectively ($P = 0.0004$ for G1 vs. G2, $P < 0.0001$ for G1 vs. G3, and $P = 0.48$ G2 vs. G3) and 27(26–28) in controls. Extent of coronary atherosclerosis as assessed by modified Gensini's score was significantly different within each group and between each group and controls. Systemic atherosclerosis, as reflected by the ankle-brachial index, was greater in G3 when compared with G1 (0.80 ± 0.280 vs. 098 ± 0.10, $P < 0.0001$).

Severe ED (a score <10) was present in 35/135 (26%) of the CAD patient population and was significantly more frequent in 2,3-VD when compared with 1-VD (31 vs. 12.5%, $P < 0.01$). *Figure 4* shows ED prevalence and IIEF-EFD score according to the extent of coronary atherosclerosis. IIEF-EFD score was significantly lower in multi-vessel disease when compared with single-vessel disease [18 (11.5–23) vs. 21 (16–24), $P = 0.0069$]. An inverse relationship was found between modified Gensini's score and IIEF score: $R = -0.312$, $P < 0.0001$.

In G3 patients who complained of ED, symptoms appeared prior to CAD detection in 58/62 (93%) of cases, with a mean time interval of 24 (12–36) months (*Figure 5*). The remaining four patients had ED on the basis of IIEF score (24 in two and 25 in the remaining two patients), although they denied symptoms. Time intervals in 1-, 2-, 3-VD patients were 12 (9.5–24), 24 (16,5–36), and 33 (21–47), respectively. There was a significant relationship between length of

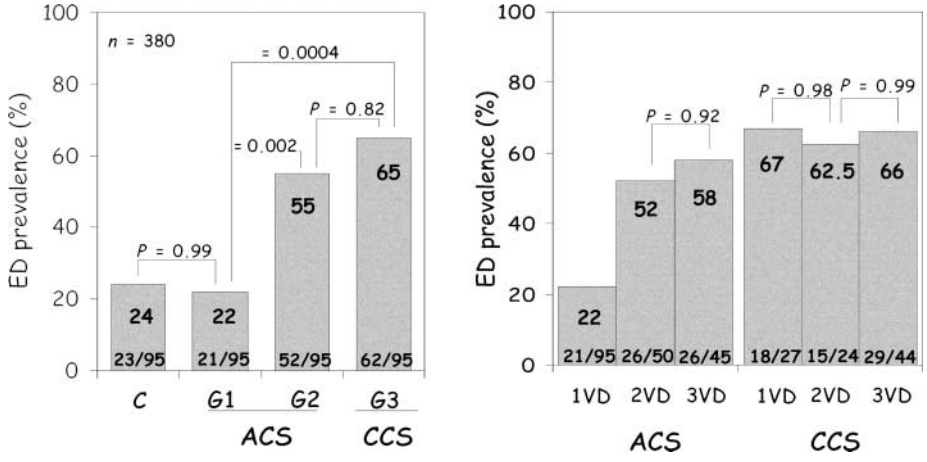

Figure 2 Prevalence of ED in the four groups of patients (Left). Prevalence of ED in ACS and in CCS according to CAD extension as expressed by the number of vessels involved (Right). Among both ACS and CCS patients, ED rate was not influenced by the number of vessels involved. Since ACS patients with 1-VD set apart from those with multi-vessel disease, no statistical comparison was made between 1-VD vs. 2,3-VD.

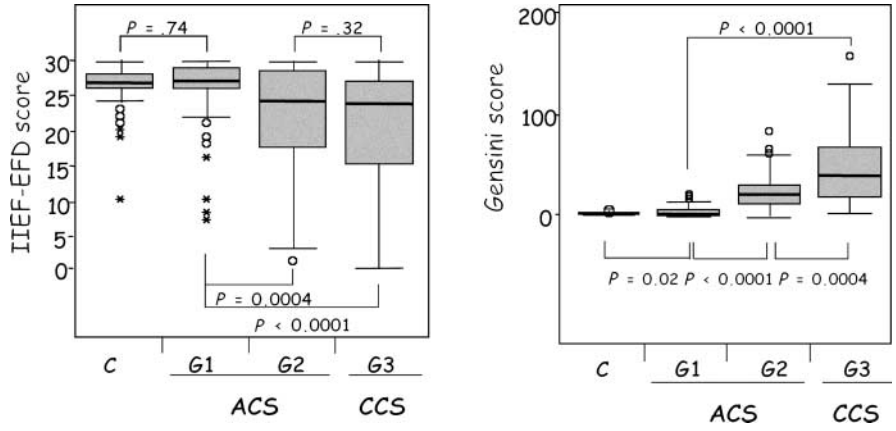

Figure 3 IIEF-EFD and modified Gensini's score in the study population.

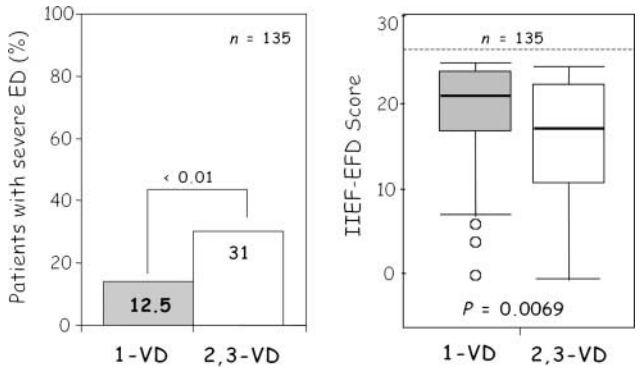

Figure 4 Prevalence of severe ED (IIEF score <10) in patients with 1 or 2,3 vessel disease. IIEF-EFD score in patients with ED and 1 or 2,3-vessel disease. Dotted line represents IIEF cut-off for ED (<26).

time interval between ED and CAD onset and the number of vessel involved after adjusting for the same covariates as for logistic regression ($P = 0.016$).

The results of logistic regression analysis are reported in *Table 2*. Age, multi-vessel coronary involvement, and CCS as clinical presentation were independent predictors of ED. Conversely, in patients with ACS (G1 and G2), we used the number of coronary vessels involved as the dependent variable and ED as a predictor. The presence of ED was associated with a four-fold increase (OR = 4.2, 95% CI, 2.26–8.00; $P < 0.0001$) in the risk of having 2- or 3-VD vs. 1-VD. Sensitivity, specificity, and positive and negative predictive values of ED vs. multi-vessel disease were 55% (95% CI: 0.35–0.55), 78% (95% CI: 0.68–0.85), 71% (95% CI: 0.59–0.81), and 63% (95% CI: 0.53–0.71), respectively. The area under the ROC curve was 0.663 (95% CI: 0.596–0.725).

Discussion

The key findings of this study are (1) ED rate significantly differs across patients with established CAD according to coronary clinical presentation and atherosclerosis burden: it is low in ACS and 1-VD and high in CCS. (2) ED severity but not ED prevalence is related to extent of CAD. (3) ED symptoms come prior to CAD symptoms in virtually all patients with a mean time-interval of 3 years.

AMI is the hallmark presentation of ACS. AMI is due to abrupt thrombotic occlusion of a coronary vessel.[22] Studies enrolling patients who underwent coronary angiography twice, before and soon after AMI, showed that in 60–70% of cases the infarct-related vessel (IRV) was not critically obstructed (<50% diameter stenosis) at the time of the first angiography.[19,23] The absence of a significant coronary artery narrowing likely accounts for the lack of chronic anginal symptoms in 70% of patients.[24] Moreover, Topol *et al*. reported that the infarct-related artery was the only diseased vessel in 65% of patients with AMI who underwent coronary angiography soon after thrombolysis.[25] All together these data suggest that, in the majority of cases, AMI occurs because an isolated non-critical stenosis in an otherwise modestly involved coronary tree (low atherosclerotic burden) abruptly occludes. Since atherosclerosis is a systemic disorder, a non-significant vascular obstruction as that found in coronary circulation might also be present in the penile circulation, despite the smaller artery size. If this holds true, ED rate should be expected to be low (i.e. due to endothelial dysfunction) in ACS.

Group 1 patients had typical clinical and angiographic features of ACS. Baseline angiogram showed acute thrombotic occlusion of a single major epicardial vessel in most cases. The absence of previous anginal symptoms and the lack of angiographically detectable collaterals to the culprit vessel suggested that the infarct-related artery was non-critically obstructed before the acute event. Thus, coronary atherosclerotic burden of these patients was actually slight as confirmed by the low modified Gensini's score. In this group, ED prevalence was 22%. This value was similar to that obtained in age-matched controls with normal coronary arteries (24%). Although subjects with suspected CAD could be not considered to be representative of the general 'healthy' population, ED rate of control group was similar to that found in general population with no heart disease ranging between 15 and 25%.[2,26] Thus, most patients with ACS and 1-VD do not complain of ED as result of an overall low coronary and penile atherosclerotic burden. Reasons for ED in group 1 may be either endothelial dysfunction (the early change in the atherosclerosis process) or coronary atherosclerosis undetected by angiography, such as diffuse concentric coronary disease without focal stenoses leading to a near-normal coronary artery appearance.[27] Whatever the cause for ED, this group represents one edge of the 'ED-coronary atherosclerosis' relationship.

Effort-induced angina pectoris is the hallmark of chronic coronary syndrome. It is usually the result of significant, multi-vessel disease (high coronary atherosclerotic burden). Opposite to ACS vascular scenario, penile vessels should be severely obstructed accounting for a high ED rate in these patients. Group 3 patients had typical clinical and angiographic features of CCS and represent the opposite edge of the 'ED-atherosclerosis' relationship. ED prevalence was significantly higher than in group 1 (65 vs. 22%, $P < 0.0001$) due to a much more evident atherosclerotic burden as reflected by the higher modified Gensini's score. The finding that patients with CCS and 1-VD had higher ED rate (67 vs. 22%, $P < 0.0001$) when compared with patients with ACS and 1-VD, confirms the role of different pathophysiological background and related atherosclerotic burden at work in CCS. Infact, multivariate analysis showed that patients with CCS presentation had a 2.3-fold increase in relative risk of ED when compared with those with ACS. The lower ankle-brachial index (0.98 ± 0.10 vs. 0.80 ± 0.28, $P < 0.0001$), an accurate and reliable marker of generalized atherosclerosis, supported a more advanced vascular involvement in CCS. Differences in age, risk factor profile, and medications between groups could have influenced ED prevalence. However, groups were matched for age and no major difference in number and prevalence of common risk factors were found. Diabetes was uniformly distributed among groups with a trend towards a greater prevalence in G3 and was found to approach ($P = 0.08$) statistical significance as independent predictor of ED. The lack of a more robust correlation between diabetes and ED is likely depending on the low disease prevalence in the study population. A recent European survey showed that a high prevalence of undiagnosed glucose intolerance (12.5%) or true diabetes (22%) in CAD patients with normal

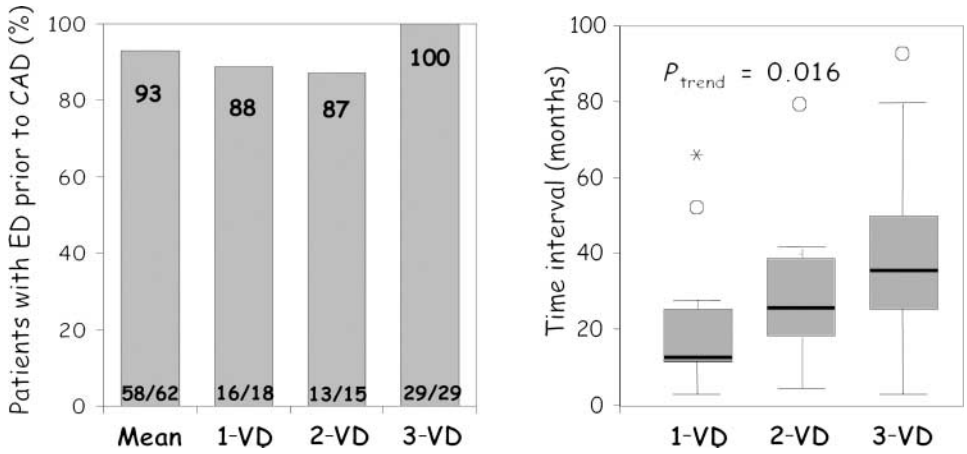

Figure 5 Group 3 patients who had ED symptoms prior to CAD symptoms and time interval (months) between ED and CAD symptom onset in CCS according to number of vessels involved (1,- 2,- 3-VD).

Table 2 Logistic regression analysis ($n = 285$, ED = 135)

	OR	95% Wald confidence limits	*P*-value
Hypertension	0.84	0.47–1.51	0.57
Hypercholesterolemia	1.19	0.598–2.37	0.62
Smoke (yes vs. no)	0.89	0.484–1.64	0.71
Family history of CAD	1.63	0.866–3.07	0.13
Rx statins	1.56	0.78–3.11	0.21
Rx beta-blockers	1.23	0.612–2.46	0.57
Rx diuretics (thiazides)	0.80	0.321–2.01	0.64
Rx acetilsalicylic acid	0.59	0.28–1.25	0.17
BMI	1.08	0.99–1.18	0.09
Age	1.10	1.05–1.16	<0.0001
Diabetes	2.12	0.93–4.82	0.06
Multi-vessel vs. single-vessel	2.53	1.43–4.51	0.0002
CCS vs. ACS	2.32	1.22–4.41	0.01

fasting glucose level can be unmasked by systematic oral glucose tolerance test.[28] This finding confirms the leading role of diabetes as cause of both ED and CAD and suggests the systematic use of additional tests to detect glucose abnormality.[5,28–31] Patients with CCS were more frequently taking cardiovascular drugs, especially beta-blockers, than patients in G1. Although the negative effect of beta-blockers on sexual function has not been fully confirmed,[32] logistic regression analysis showed that no treatment, included beta-blockers, had significant impact on ED when adjusted for other confounding variables.

Group 2 patients represent an intermediate step of the 'ED-coronary atherosclerosis' relationship. Although clinical presentation was similar to that of group 1, both ED prevalence (55 vs. 22%, $P < 0.0001$) and modified Gensini's score were significantly higher and similar to CCS. Thus, as far as ED rate is concerned, the 'favourable' pathophysiologic background of group 1 patient was offset by an advanced (silent) atherosclerosis involvement. According to this finding, we evaluated whether ED may predict coronary artery involvement in ACS. Interestingly enough, ED was associated with a four-fold increased risk (OR = 4.2; 95% CI, 2.1–8.4; $P < 0.0001$) of having multi-vessel disease and vice versa independently of other conventional risk factors. This suggests that the IIEF questionnaire may be a useful 'bedside' test to predict the extension of CAD in ACS: according to positive predictive value seven out of 10 patients with ED turned out to have angiographic multivessel disease. If confirmed, a different diagnostic and/or therapeutic strategy may be adopted according to the presence/absence of ED, especially in patients with AMI treated with systemic thrombolysis in which coronary anatomy is not known.

We further evaluated the 'ED-coronary atherosclerosis' relationship by assessing ED rate according to CAD extension. Interesting enough, having 2- or 3-VD did not significantly increased ED prevalence as compared to 1-VD in both ACS and CCS patients with similar age (*Figure 2B*), suggesting ED as a sort of 'on-off' phenomenon that we hypothesized takes place when >50% angiographic obstruction of at least one major coronary vessel occurs.[13] At this time, in fact, the same amount of coronary plaque would be severely obstructing penile circulation due to its smaller artery size. If true, having 2- or 3-VD would not add to ED prevalence.

An important although still unresolved issue is why almost 30% of patients with proved CAD did not complain of ED. Age may be an explanation. The Massachussets Male Aging Study (MMAS) indicated age as the variable most strongly associated with ED.[3] We found age to be independent predictor of ED in the whole study patient population, with a 10% per patient increase in the yearly relative risk of ED. *Figure 6* shows the relationship between age and ED rate after having stratified patients for CAD extension. ED significantly increased over time being 30% under 50 years and close to 100% over 60 years of age. At any age ED rate was similar regardless extent of CAD, confirming the 'on-off' phenomenon. Controls showed the expected increase of ED rate with age, although the time-course was significantly lower than in CAD, confirming the importance of atherosclerosis. Moreover, a significant group interaction between age and CAD was found as indicated by slope divergence as age increased. Reasons why, given the same amount of CAD, younger patients seem to be protected from ED as compared to older ones are not easily understood. Age-related hormonal, metabolic and inflammatory

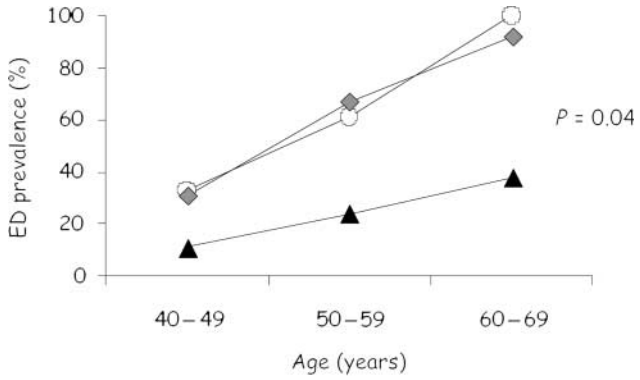

Figure 6 ED prevalence in CAD patients with 1-VD ($N = 27$, full diamonds) or 2,3-VD ($N = 68$, empty circles) and controls ($N = 95$, full triangles) according to three age decades. Value of ED rate at different age decade was significantly different within each group ($P = 0.033$, $P = 0.001$, $P = 0.027$, for 1-VD CAD, 2,3-VD CAD and Controls, respectively). ED rate was significantly higher in both CAD groups as compared to Controls at any age decade.

changes may be potential mechanisms.[33] Further studies are warranted to clarify this point.

Misunderstood questions, wrong interpretation, and psychological issues related to completing a questionnaire about sexual function are problems commonly found and could influence ED rate.[34] However, if true this methodological bias should be uniformly distributed in all age decades.

Severity of ED has been found to be related to the degree of atherosclerosis.[7,35] Greenstein *et al*. reported that patients with 1-VD had more and firmer erections than men with 2- and 3-VD. However, a non dichotomy test for sexual dysfunction was used in that study and differences in age, risk factors between groups were poorly analysed.[35] We found that severe ED (a score <10) was more frequent in patients with multi-vessel as compared to single-vessel disease (31 vs. 12.5%, $P < 0.01$). Moreover, IIEF-EFD score was significantly lower in the former than in the latter group and significant inverse relationship between IIEF-EFD and modified Gensini's score were found indicating more severe ED in patients with more diffuse coronary artery involvement. Thus, severe ED in patients with stable CAD should raise questions about multi-vessel coronary involvement.

ED has been described as a potential marker of sub-clinical CAD in asymptomatic subjects. We previously investigated 300 consecutive unselected patients, both ACS and CCS, with angiographically documented CAD. ED was found in 149/300 (49%). Among those with ED, 67% reported that sexual symptoms preceded anginal symptoms by a mean interval of 34 months (range 1–168).[8] In the present study, 93% of patients with CCS reported ED symptoms before angina pectoris onset, with a mean interval of 24 (12–36) months. The higher percentage of patients with ED prior to CAD in the present study is likely the result of patient selection and experience of the investigator asking the appropriate question. Although 'recall bias' should be taken into consideration, time interval between ED and CAD onset was related to the number of coronary vessel involved. In other words, the longer the ED duration the higher the number of coronary vessel involved when first CAD diagnosis was made. All together these data fuel the concept of ED as 'sentinel of the heart'. Although this study does not address the issue whether asymptomatic subjects with ED are at higher risk of future ACS/CCS as compared to those without ED, the relative and absolute risk of cardiovascular event(c)s in each patient with ED and no CV symptoms should be estimated through one of many risk assessment office-based approaches and treat consequentially. While waiting for further prospective, long-term studies, a strict medical surveillance program should be mandatory in patients with ED, multiple risk factors, and no clinical CAD.

Some study limitations need to be addressed. Anatomical and functional evaluation of penile circulation through ultrasound evaluation and dynamic Doppler test were not systematically carried out in this patient population. Coronary angiography was considered as the 'gold-standard' technique to detect CAD. However, this technique detects only lumen artery change and not true plaque volume extension. Thus, a uniform lumen artery reduction caused by concentric disease will result in an angiographically normal small vessel, despite a diffuse atherosclerotic burden. Coronary intravascular ultrasound or multi-slice CT scan represent more appropriate techniques to quantify atherosclerotic involvement of coronary arteries, even at an early stage. Gensini's score was originally proposed to quantify coronary artery involvement in patients with CAD. As ACS has a different atherosclerotic background, we added an arbitrary score for acute coronary occlusion.

In conclusions, the COBRA trial shows for the first time that ED rate in patients with angiographically established CAD differs according to type of clinical presentation and related atherosclerotic background. The rate is low in ACS with 1-VD and high in CCS with diffuse disease. Severity (not prevalence) of ED is related to severity of CAD. In CCS, ED frequently comes before the onset of CAD symptoms, representing an early marker for latent ischaemic heart disease.

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Appendix

IIEF-EFD questionnaire for ED (questions 1-5 and 15)

(1) Q: how often were you able to get an erection during sexual activity? A: no sexual activity (0), almost never/never (1), a few times (much less than half of the time) (2), sometimes (about half of the time) (3), most times (much more than half the time) (4), almost always/always (5).
(2) Q: when you had an erection with sexual stimulation, how often were your erections hard enough for penetration? A: no sexual activity (0), almost never/never (1), a few times (much less than half of the time) (2), sometimes (about half of the time) (3), most times (much more than half the time) (4), almost always/always (5).
(3) Q: when you attempted sexual intercourse, how often were you able to penetrate your partner? A: no sexual activity (0), almost never/never (1), a few times (2), sometimes (about half of the time) (3), most times (much more than half the time) (4), almost always/always (5).
(4) Q: during sexual intercourse, how difficult was it to maintain your erection after you had penetrate your partner? A: no sexual activity (0), almost never/never (1), a few times (2),

sometimes (about half of the time) (3), most times (much more than half the time) (4), almost always/always (5).

(5) Q: during sexual intercourse, how difficult was it to maintain your erection to completion of intercourse? A: did not attempt intercourse (0), extremely difficult (1), very difficult (2), difficult (3), slightly difficult (4), not difficult (5).

(6) Q: how do you rate your confidence that you could get and keep an erection? A: very low (1), low (2), moderate (3), high (4), very high (5).

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