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Longitudinal Risk of Developing Cardiovascular Diseases in Patients With Erectile Dysfunction—Which Patients Deserve More Attention?

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ABSTRACT

Background: Erectile dysfunction (ED) is widely considered as an early manifestation of cardiovascular diseases (CVDs), sharing similar risk factors.

Aim: Assess rates and predictors of developing CVD and/or hypertension (HTN) over a long-term follow-up period using user-friendly and clinically reliable tools in men presenting with ED but without CVD/HTN or known vascular risk factors at baseline.

Methods: Data from 108 patients presenting between 2005 and 2011 with ED were analyzed. All patients were free from CVD and/or HTN (CVD/HTN) at baseline. Patients completed the International Index of Erectile Function (IIEF) at baseline and were followed up every 6 months with clinical assessment or phone interview. Kaplan-Meier analyses estimated the probability of developing CVD/HTN over time. Cox-regression models tested the association between patient baseline characteristics (for example, age, Charlson Comorbidity Index, baseline IIEF-EF, ED severity, alcohol intake, smoking), response to phosphodiesterase type-5 inhibitors (PDE5is), and the risk of developing CVD/HTN.

Results: Of all, 43 (40%) patients showed IIEF-EF scores suggestive of severe ED; 37 (39%) and 59 (61%) were nonresponders and responders to PDE5i, respectively. Median (interquartile range) age was 51 (41, 61) years. Median (interquartile range) follow-up was 95 (86-106) months. Overall, the estimated risk of developing CVD/HTN was 15% (95% confidence interval [CI]: 9-27) at 10-year assessment. Men with baseline severe ED had a higher risk of developing CVD/HTN (34%; 95% CI: 17-59, $P = .03$) at 10 years than patients with mild to moderate ED (5% [95% CI: 2-14]). At the Cox regression analysis, severe ED (Hazard ratio [HR], 4.62; 95% CI: 1.43, 8.89; $P = .01$) and baseline IIEF-EF score (HR, 0.92; 95% CI: 0.86, 0.99; $P = .02$) were associated to the risk of CVD/HTN overtime. Conversely, age and nonresponders to PDE5is (HR, 0.92; 95% CI: 0.32, 2.68; $P = .9$) were not associated to a risk of CVD/HTN over time.

Clinical Implications: The use of an easy and user-friendly tool, as the IIEF-EF domain score, would allow to reliably assess which men with ED at first presentation may deserve a different, more specific and detailed cardiologic investigation to prevent inauspicious CV events.

Strengths & Limitations: A single-center-based, observational longitudinal study, raising the possibility of selection biases are the main limits.

Conclusions: Patients with severe ED and lower baseline IIEF-EF but no vascular risk factors at first presentation have more than 30% risk of developing CVD/HTN in 10-year time. Those patients may benefit from medical preventive strategies to lowering the risk of CV events and HTN. **Pozzi E, Capogrosso P, Boeri L, et al. Longitudinal Risk of Developing Cardiovascular Diseases in Patients With Erectile Dysfunction—Which Patients Deserve More Attention?. J Sex Med 2020;XX:XXX–XXX.**

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INTRODUCTION

The association between erectile dysfunction (ED) and onset of cardiovascular diseases (CVD) has been extensively demonstrated in several studies over the last decades.[1−4] In this context, common risk factors (eg, diabetes mellitus [DM], smoking, obesity, hypercholesterolemia, hypertension [HTN]) and pathophysiological mechanisms have been found to be shared among the 2 conditions.[5] Recently, ED has been even added as an independent clinical risk factor able to help doctors to identify patients at most risk of heart disease and stroke.[6] Of relevance, vasculogenic ED, widely considered the most common type among organic variants of ED, has been demonstrated to significantly increase the risk of further CV events.[5]

Over time, different hypotheses have been postulated to explain this relationship. Of those, endothelial dysfunction (EDy) together with artery size hypothesis would easily explain why ED usually precedes CVD onset.[7−9] Accordingly, it has been demonstrated that symptoms of ED can precede even by 3 to 5 years the onset of a CV event, thus allowing and making cardiovascular prevention fundamental in terms of overall men's health.[4,5,10,11] The time-span between the onset of ED and a potential life-threatening CV event emerged to become crucial to identify patients that are at sufficient risk of developing CVD and that would benefit further cardiological investigations.[1,12]

In this context, some studies found a correlation between the severity of ED and the probability of developing CVD. Schouten et al,[13] for instance, assessed ED severity using a single question on erectile rigidity; the group found that patients with reduced penile rigidity had higher probability of experiencing coronary artery disease (CAD) than those with normal penile rigidity. Banks et al[14] found that risk of developing CVD was directly proportional to ED severity in men with or without a history of cardiovascular events at baseline. Moreover, ED has been found to be highly prevalent in patients with HTN (and vice versa) because of increased vessel rigidity, EDy, and systemic vascular alterations.[14−16]

Overall, published data would support the concept that preventive strategies toward a number of CVD may be developed also through a personalized approach in terms of cardiovascular risk factors modification. To this aim, the identification of a clinically relevant and effective predictive symptom, such as ED, could allow earlier and effective cardiovascular prevention. Therefore, the goal of the present study was to depict those patients at higher risk of further developing CVD and/or HTN over time, after an initial diagnosis of ED. In this context, we sought to follow up a cohort of patients seeking first medical help for ED as their primary compliant and without any known CVD/HTN at baseline, to depict whether ED per se could act as a reliable and effective preventive clinical marker in the everyday clinical setting.

METHODS

Data from a cohort of 120 patients presenting for ED as their primary complaint at a single outpatient clinic between 2005 and 2011 entered this analysis. All patients were assessed with a comprehensive medical history. Health significant comorbidities were scored with the Charlson Comorbidity Index (CCI)[17] (CCI was categorized as 0 or $\geq$1). For the specific purpose of the study, all selected patients were free from CVD/HTN (any type) at first outpatient-clinic assessment; conversely, patients with a previous diagnosis of either any cardiovascular comorbid condition or HTN were excluded from the analyses to avoid unnecessary selection bias. CVD were defined as follows: acute myocardial infarction and/or surgical treatment of CAD; angina; cerebrovascular accidents (ie, stroke, transient ischemic attack); congestive heart failure; aortic aneurysm; and, nonfatal cardiac arrhythmias, defined as a minimum of an arrhythmia requiring treatment. HTN was defined as office systolic blood pressure values $\geq$ 130 mmHg and/or diastolic blood pressure values $\geq$ 90 mmHg. Patients were also comprehensively assessed in terms of sociodemographic characteristics, thus including recreational habits (ie, smoking history, alcohol use) and regular physical exercise (defined as at least 2 hours/week) at the time of first assessment. Smoking habits were assessed as pack-year history and then categorized into 2 groups as follows: no smokers (never smoked); ex-smokers/active smokers. Similarly, alcohol consumption was categorized as abstainers (no alcohol consumption) or drinkers (any amount per week). Measured body mass index, defined as weight in kilograms by height in square meters, was obtained for every patient. All patients completed the International Index of Erectile Function (IIEF)[18] at baseline. We used the IIEF-EF to more specifically segregate ED severity to further stratify those patients at greater risk of having future CV events, with a potentially superior and more tailored CVD prevention strategy. Severity of ED was interpreted according to Cappelleri's criteria, with severe ED defined for IIEF-EF $<$ 11.[18] Patients' response to initial phosphodiesterase type 5 inhibitors (PDE5is) trials (any type) was also assessed. For the specific purposes of the study, patients without any reported IIEF-EF improvement after PDE5i therapy (any) were categorized as nonresponders.

Hence, the cohort of patients has been longitudinally followed up every 6 months with either outpatient clinical assessments or dedicated phone interviews. Overall, 12 patients (10%) have been lost to follow-up and were eventually excluded; a convenience sample of 108 ED patients (90%) was included in the final analysis. Of 108, 99 patients (91.7%) attended the follow-up outpatient clinic in person, whereas 9 (8.3%) only answered to the phone call updating the physicians with their clinical data.

Data collection followed the principles outlined in the Declaration of Helsinki. All patients signed an informed consent agreeing to share their own anonymous information for other future studies. The study was approved by the local ethic committee (IRCCS OSR Prot. 2014 − Pazienti Ambulatoriali).

Statistical Analysis

Univariate Cox proportional hazards regression models identified the association between patient baseline characteristics

(eg, age, CCI, baseline IIEF-EF, recreational habits), PDE5is response, and the risk of developing CVD/HTN over time. Kaplan-Meier analysis was used to estimate the probability of developing CVD/HTN over time of the whole cohort and in patients with nonsevere (IIEF-EF $\geq$ 11) vs severe ED (IIEF-EF $<$ 11) at baseline assessment. Statistical analyses were conducted using Stata 14.0 (StataCorp, College Station, TX), with a 2-sided significance level set at $P < .05$.

RESULTS

Table 1 shows patients' characteristics. Median (IQR) age at first presentation was 51 (41-61) years. Median (IQR) follow-up duration was 95 (86-106) months. Of all, 74% of the whole cohort was free of comorbidities at first assessment; 26% had CCI $\geq$ 1 (neurologic disease, COPD, type 1 DM, type 2 DM, chronic kidney diseases, solid tumors, and peripheral vascular disease).

Table 2 depicts IIEF-EF scores at baseline. Overall, 43 (40%) patients had IIEF-EF scores suggestive for severe ED.

Overall, the estimated risk of developing CVD/HTN was 15% (95% CI: 9-27) at 10-year assessment.

Table 3 reports univariate cox regression hazard models predicting the risk of developing CVD/HTN over time. Severe ED (HR, 4.62; 95% CI: 1.43, 8.89; $P = .01$) and baseline IIEF-EF score (HR, 0.92; 95% CI: 0.86, 0.99; $P = .02$) were associated to higher risk of CVD/HTN overtime. No further univariable association has been observed.

As represented in Figure 1, those patients with severe ED at baseline had a higher risk of developing CVD/HTN (estimated risk of developing CVD/HTN: [34%; 95% CI: 17-59, $P = .03$]) at 10 years than patients with mild and moderate ED (estimated risk of developing CVD/HTN: 5% [95% CI: 2-14]). The estimated risk of CVD/HTN in nonsevere and severe ED groups, according to Kaplan-Meier analysis, is depicted in Table 4.

Table 1. Clinical characteristics of the entire cohort (N = 108)

Age, years; median (IQR)	51 (41, 61)
Charlson Comorbidity Index, N (%)	
0	80 (74)
≥1	28 (26)
Body mass index, median (IQR)	24.9 (23.2, 26.9)
Smoking history, N (%)	
Never smoked	76 (70)
Current/ex-smoker	32 (30)
Alcohol use, N (%)	
No	21 (19)
Yes	87 (81)
Regular physical activity, N (%)	
No	62 (58)
Yes	45 (42)
Type 1 diabetes mellitus, N (%)	
No	105 (97)
Yes	3 (2.8)
Type 2 diabetes mellitus, N (%)	
No	98 (91)
Yes	10 (9.3)
Newly developed HTN, N (%)	
0	96 (91)
1	9 (8.6)
Newly developed CVD, N (%)	
No	102 (94)
Yes	6 (5.6)

CVD = cardiovascular disease; HTN = hypertension; IQR = interquartile range.

DISCUSSION

Potential user-friendly and easy to be clinically collected predictors of CVD and/or HTN have been analyzed over a long-term follow-up in a cohort of patients presenting with ED and no history of CVD/HTN at the time of their first assessment. The aim was to identify those patients at actual higher risk of developing future CV events to offer them more specific and comprehensive cardiological primary prevention strategies. Our findings suggest that baseline IIEF-EF score (ie, ED severity at presentation) acts as a predictor of CVD/HTN development over time; in particular, severe ED at baseline (eg, IIEF-EF $<$ 11) emerged to be associated with almost 30% risk of CVD/HTN over time. Conversely, age and being nonresponder to PDE5i as a first-line treatment did not emerge as predictors of future development of CVD/HTN.

Over the last decades, several studies have been carried out to assess and confirm the association between ED and CVD.[19] Among the first, Montorsi et al clearly demonstrated the link between the 2 conditions.[1,5,9,20] Indeed, of the historical cohort of 300 consecutive patients presenting for acute chest pain and angiographically documented CAD, almost 70% had reported that ED onset had preceded the CV event itself.[1] Clinically speaking, of paramount importance was the mean time interval of 38.8 months between the onset of ED and CAD, and even more relevant the complete absence of significant differences in terms of risk factors distribution and clinical and angiographic characteristics between patients with the onset of ED before vs after CAD diagnosis.[1] All these results sound even more appealing at the light of our current findings, where ED severity

Table 2. Baseline erectile function severity according to IIEF-EF domain scores

Baseline IIEF-EF, median (IQR)	N (%)
ED severity	
Severe	43 (40)
Moderate	18 (17)
Mild to moderate	17 (16)
Mild	30 (28)

IIEF-EF = International Index of Erectile Function—Erectile Function; IQR = interquartile range; ED = erectile dysfunction.

Table 3. Univariate cox regression analysis predicting risk of developing CVD/HTN over time

Characteristics	Hazard ratio (HR)	95% CI	*P* value
Age	1.02	0.98, 1.06	.4
CCI 0 vs CCI ≥1	1.73	0.57, 5.19	.3
Smoking	0.69	0.19, 2.47	.6
Alcohol use	0.56	0.18, 1.80	.3
Regular physical activity	0.50	0.16, 1.59	.2
Total testosterone	1.02	0.78, 1.33	.8
Dyslipidaemia	0.51	0.12, 2.18	.3
Baseline IIEF-EF	**0.92**	0.86, 0.99	**.02**
Severe ED	**4.62**	1.43, 14.89	**.01**
PDE5i responder vs nonresponder	0.92	0.32, 2.68	.9

CCI = Charlson comorbidity index; CI = confidence interval; CVD = cardiovascular disease; ED = erectile dysfunction; HTN = hypertension; IIEF-EF = International Index of Erectile Function—Erectile Function; PDE5i = phosphodiesterase type 5 inhibitors.
Bold values indicate statistically significant *P* value ≤ .05.

per se emerged as a stand-alone predictor associated with the long-term development of CVD and/or HTN.

Thereafter, a number of evidences had confirmed ED as a vascular disorder and a warning sign of future CVD.[5,21,22] For instance, using the placebo group cohort of the Prostate Cancer Prevention Trial, Thompson et al[23] showed that among those men without ED at study entry, as many as 57% reported incident ED after 5 years; incident ED emerged to be associated with a 1.25 HR for subsequent CVD during study follow-up. The authors also found that the association was in the range of risk associated with smoking or a family history of acute myocardial infarction.

In this context, different theories have been tested to deeply understand the linkage between the 2 conditions. In this regard, common risk factors for atherosclerosis were found to be highly prevalent in patients with ED.[22,24–26] Moreover, vasculogenic

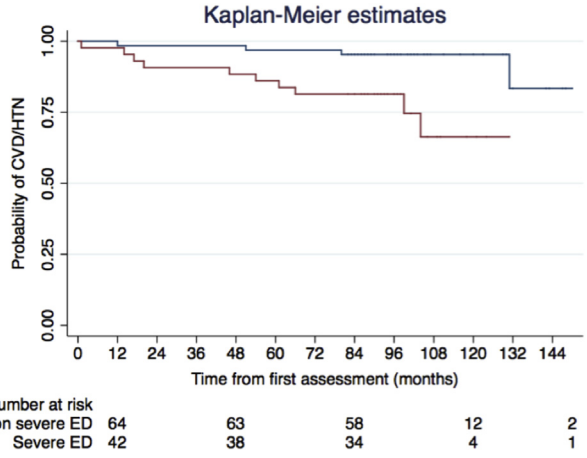

Figure 1. Kaplan-Meier estimates. Figure 1 is available in color online at www.jsm.jsexmed.org.

Table 4. Estimated risk of CVD/HTN among patients with nonsevere and severe ED, according to Kaplan-Meier analysis (median follow-up = 95 [86-106] mo)

Time	KM estimate, 95% CI
Nonsevere ED	
12 mos	2% (0, 11)
48 mos	2% (0, 11)
84 mos	5% (2, 14)
120 mos	5% (2, 14)
Severe ED	
12 mos	2% (0, 15)
48 mos	12% (5, 26)
84 mos	19% (10, 34)
120 mos	34% (17, 59)

CI = confidence interval; CVD = cardiovascular disease; ED = erectile dysfunction; HTN = hypertension; KM = Kaplan Meier.

ED was demonstrated to share pathophysiological mechanisms with other common systemic vascular diseases. Among those, EDy with deficient nitric oxide pathway achieved great interest over the last 2 decades; indeed, EDy leads to malfunctional endothelium-dependent vasodilatation owing to structural vascular abnormalities, penile artery atherosclerosis, and flow-limiting stenosis.[19] In addition to this, artery sized hypothesis had been proposed to find a rational explanation of why symptoms of ED can precede by even 3 to 5 years the onset of a CV event. The theory stated that common risk factors shared between ED and CVD gradually and uniformly affect all vascular beds leading to EDy, intima thickening, and eventually flow-limiting stenosis; chronologically, penile arteries are first to be affected in respect to coronary vessels which explains why ED precedes CVD.[9,27] Although the association between ED and CVD is well known and extensively discussed, only few studies have investigated which patients—mostly among men with ED—are actually at a higher risk of harboring a silent cardiological disorder.[28,29] Historically, Greenstein et al, for instance, identified a correlation between prevalence of multivessel involvement at coronary angiography and ED severity[30]; patients with severe ED (as defined with a single question upon penile rigidity) had higher probability of experiencing CAD than those with normal penile rigidity. Likewise, Banks et al found that among men without previously diagnosed CVD, those with severe ED were more likely to develop ischemic heart disease (risk 1.60), heart failure (risk 8.00), peripheral vascular disease (risk 1.92), and other causes of CVD (risk 1.26) in respect to men without ED at presentation.[14] As a major flaw, this group did not use the IIEF-EF domain to attempt and standardize ED severity assessment.[14] This approach has been extensively followed throughout times.[31] More recently, studies have shown that ED is not only correlated with CV events but can be also considered as a proxy of general health status.[32,33]

Our current data come together and therefore confirm the latter broad number of studies that have widely analyzed both the pathophysiological and the clinical correlations between ED and

CVD, along with the simultaneous presence of common risk factors, and the relevant possibility that ED anticipates, even well in advance, the subsequent development of CVD and/or HTN. What is clinically important of these new observations at a relatively long-term follow-up is the fact that the use of a validated questionnaire (ie, IIEF), the most known and widely investigated instrument in this setting, may allow to understand which ED men deserve a different, more specific and detailed cardiologic investigation, so as to implement strategies to prevent even inauspicious events, or at least to reduce their risk and severity.[5] Even more relevant, this long-term prediction could be obtained with a user-friendly, easy, poorly inquisitive, but sufficiently reliable, approach.[5,28] In this sense, further studies are needed to corroborate our longitudinal long-term findings and to investigate also the relationship between ED severity and the development of other specific comorbidities. This will give physicians proper tools to offer more personalized and tailored medical assessment in terms of prevention and screening strategies to patients presenting with ED as their primary complaint.

Our study is certainly not devoid of limitations. First, despite the fact that we analyzed a homogeneous, same-ethnicity cohort of men presenting with ED as their primary compliant, this was a single-center-based observational longitudinal study, raising the possibility of selection biases. In this context, in spite of the merit of being homogeneous for patients enrollment and meticulous in terms of the longitudinal evaluation of the enrolled patients themselves, the absence of age as a predictive factor may suggest that a single-center analysis could not derive final conclusions; indeed, with larger numbers and a longer follow-up period, we cannot exclude age to become a significant predictor for CVD/HTN.[34] Thereof, larger cohort studies across different centers and populations are needed to validate our findings. Second, our study did not prospectively include and follow up over time a control group of healthy men without ED and CVD at baseline. Third, a multivariate analysis was not performed because the number of events did not allow to include all covariates in a single model. Nevertheless, our results indicate that an accurate investigation of the presence of severe ED at the baseline may be important in the everyday diagnostic workup of men with sexual function impairment.

CONCLUSIONS

Findings from this longitudinal observational cohort study showed that severe ED per se was associated with a risk not less than 17% of developing CVD and/or HTN in 10-year time in men without any known CVD at baseline. The IIEF-EF domain may act as a user-friendly and clinically effective tool to develop preventive strategies to lowering the risk of CV events and HTN in the everyday clinical practice even in this subset of relatively healthy men at baseline.

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