Erectile Dysfunction and Cardiovascular Risk

Prediction of Cardiovascular Events With Aortic Stiffness in Patients With Erectile Dysfunction

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Abstract—Erectile dysfunction confers an independent risk for cardiovascular events and total mortality. Aortic pulse wave velocity (PWV) is an important predictor of cardiovascular events and all-cause mortality. We investigated whether PWV predicts major adverse cardiovascular events (MACEs) in patients with erectile dysfunction beyond traditional risk factors. MACEs in relation to PWV were analyzed with proportional hazards models in 344 patients (mean age, 56 years) without established cardiovascular disease. During a mean follow-up of 4.7 years (range, 1–8.5 years), 24 of 344 participants (7.0%) experienced a MACE. Subjects in the highest PWV tertile (>8.8 m/s) had a 4-fold higher risk of MACEs compared with those in the lowest PWV tertile (<7.6 m/s; adjusted hazard ratio, 3.97; P=0.035). A PWV value of 7.81 m/s was associated with a negative predictive value (ability to rule out MACE) of 98.1%. Addition of PWV to standard risk factor model yielded correct patient reclassification to higher or lower risk category by 27.6% (P=0.0332) in the whole cohort. Our results show that higher aortic stiffness is associated with increased risk for a MACE in patients with erectile dysfunction without known cardiovascular disease. Aortic PWV improves risk prediction when added to standard risk factors and may represent a valuable biomarker of prediction of cardiovascular disease risk in these patients. (Hypertension. 2014;64:672-678.)

Key Words: erectile dysfunction ■ pulse wave analysis ■ vascular stiffness

Erectile dysfunction (ED) is a highly prevalent disorder that affects, to a varying severity, 1 of 2 men aged 40 to 70 years.1,2 Erectile disorders are common in patients with subclinical or symptomatic coronary artery disease (CAD).3-6 Importantly, ED is considered an early manifestation of a generalized vascular disease3-8 and predicts an all-cause mortality9-11 and cardiovascular events, including CAD,12-15 stroke,13 and peripheral artery disease.16 Therefore, within the context of the collectively increased risk that ED confers, identification of those ED patients who are truly at high risk for future cardiovascular events has the potential to reduce their risk through lifestyle modification or pharmacological interventions targeted at management of both risk factors and the disease itself.17,18

Established and novel biomarkers are particularly useful in primary or secondary prevention, and because ED is primarily a vascular disease, arterial biomarkers are particularly appealing.17-19 Aortic pulse wave velocity (PWV), the gold standard index of aortic stiffness,20-22 is increased in ED patients.23 PWV is an important predictor of future cardiovascular events and all-cause mortality both in the general population and in patients with disease states.24-29 It has also emerged as a potential target for intervention and improvement of patient outcome.30 Importantly, it has been integrated in recommendations for the assessment and management of specific populations such as patients with hypertension.31

The predictive role of aortic PWV has not been investigated in ED patients. Accordingly, we sought to investigate whether PWV predicts cardiovascular events in patients with ED and whether such an ability is independent of classic risk factors. An important aim of our investigation was to assess whether PWV can meaningfully reclassify patients who have been characterized with classical risk scores such as the Framingham risk score to higher or lower risk categories, a feature of principal clinical importance.

Study Population
From January 2004 to June 2011, we enrolled consecutive patients who were referred to the Cardiovascular Diseases and Sexual Health Unit of our department. These patients had ED symptoms of recent onset, but they were neither symptomatic of cardiovascular disease nor had they documented cardiovascular disease. All patients were evaluated comprehensively with noninvasive tests (exercise stress test and stress echocardiography: 65 [15%] were positive for one or both of the 2 noninvasive procedures) and coronary angiography,
Aortic Stiffness and Events in Erectile Dysfunction

Follow-Up
Information on major adverse cardiac events (MACEs) up to February 2012 was obtained by visits to our unit, phone interview, or mail. Each subject or a family member completed the questionnaire on MACEs, current medication, and health status. MACEs analyzed as the end points of this study included cardiovascular death, CAD, stroke, and peripheral arterial disease. All MACEs included in analysis were validated by research doctors who were unaware of the patient’s arterial stiffness tests using source data, including death certificates, hospital record forms, and interview.

Statistical Analysis
Sample size calculation was based on the hypothesis that patients with high PWV would have a relative risk of ≥2.5 for MACEs compared with patients with low PWV for a median follow-up of 3 years. Therefore, we estimated that 334 subjects in total would provide 80% power at the 5% level of significance to detect a MACE difference corresponding to a relative risk of ≥2.5 between groups (high PWV and low PWV).

We assessed differences in normal variables by the Student t test and differences in non-normal variables by the Mann–Whitney U test. The Pearson χ² test was used for frequency comparison. Survival curves of PWV tertiles were estimated by use of the Kaplan-Meier method and compared by using the Mantel (log-rank) test. The primary analysis used the unadjusted Cox proportional hazards estimates to evaluate the risk ratios of cardiovascular risk factors. All unadjusted significant covariates of MACEs with a P<0.10 on univariate analysis were incorporated into the stepwise Cox regression models. The robustness of the estimated hazard ratios (HRs) was evaluated using bootstrap resampling method of 1000 data sets. A bias of the estimate <0.01 was considered adequate for the performance of the calculated HR. We evaluated the discriminatory capability of PWV or PP and traditional risk factors using C statistics, which is an extension of the traditional receiver operating characteristic curve analysis to survival analysis.

We also assessed the ability of PWV to reclassify risk in our population. Because we had only 4.7 years of follow-up in our study, for the reclassification analysis we did not use standard risk categories based on 10-year Framingham risk score—predicted risk cutoff points (<10%, 10%–20%, >20%). Instead, we computed the predicted risk for all patients using a Cox regression model that included only the standard risk factors used for calculation of Framingham risk score (global cardiovascular risk; age, BP, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, diabetes mellitus, smoking). Then we defined cutoff points for risk groups according to the tertiles of the predicted risk in patients who experienced an event during the 4.7-year follow-up (33rd percentile of risk=4%, 66th percentile=7%), which resulted in a uniform distribution of events across risk categories. Then we cross-classified groups of risk (<4%, 4%–7%, >7%) based on a model that included standard risk factors against groups of risk based on a model where PWV was added. Cross-classification was evaluated separately in patients who did or did not experience an event. We then calculated the net reclassification index (NRI), which quantifies the ability of PWV to predict risk when added to the classical risk factors. The NRI was calculated as the sum of (1) the difference in proportions of patients reclassified into a higher risk group minus the proportion reclassified into a lower risk group among men who developed events, plus (2) the difference in the proportion of patients reclassified into a lower risk category minus the proportion reclassified into a higher risk group among men who did not develop events. The significance of the NRI was assessed with an asymptotic test as described by Pencina et al.

To identify PWV that gave optimal sensitivities and specificities, receiver operating characteristic curves were drawn by plotting sensitivity versus 1-specificity. Cutoff values were determined using individual data collected prospectively during the first visit after January 2004. Sensitivity, specificity, positive predictive value, and negative predictive value were calculated to determine the predictive power of PWV in distinguishing between MACE and non-MACE. Their corresponding 95% confidence intervals (CI) correspond to a sensitivity of >90%, thus allowing only 10% of false-negative results.

Evaluation of ED
ED of vasculogenic origin was diagnosed according to (1) comprehensive medical and sexual history, (2) score of the 5-item form of the international index of erectile function, the sexual health inventory for men (≤21 indicates ED), (3) comprehensive medical examination (performed by cardiologists, urologists, psychotherapists, and allied health professionals), (4) hormonal testing (total testosterone and prolactin), and (5) dynamic penile Doppler ultrasound (with intracavernous injection of alprostadil). Through these evaluations, patients were excluded if their ED was secondary to hormonal, psychological, neurological, or anatomic abnormalities, pelvic surgery, or trauma. Vasculogenic ED is diagnosed when the peak systolic velocity is ≤35 cm/s and/or when the end-diastolic velocity is >5 cm/s.

PWV Measurement Protocol
Pulse travels at a higher velocity in a stiff aorta. Carotid–femoral PWV, an established index of aortic stiffness, was calculated from measurements of pulse transit time and the distance traveled between 2 recording sites (PWV=distance in meters divided by transit time in seconds) with a validated noninvasive device (Complior, Artech Medical), as previously described. Two different pulse waves were obtained simultaneously at 2 sites (at the base of the neck for the common carotid and over the right femoral artery) with 2 transducers. Distance was defined as the distance from the suprasternal notch to femoral artery minus the distance from the carotid artery to the suprasternal notch. Subjects had fasted for 26 hours and had abstained from caffeine, ethanol, and flavonoid-containing beverage intake for ≥12 hours before each session. Arterial stiffness measurements were performed in the morning between 8 and 10 AM in a quiet, temperature controlled room at 23°C. After a 20-minute rest period, measurements for evaluation of aortic stiffness were taken in the supine position controlled room at 23°C. After a 20-minute rest period, measurements for evaluation of aortic stiffness were taken in the supine position. Pulse pressure (PP) was calculated as femoral artery minus the distance from the carotid artery to the suprasternal notch.

Figure 1. Flow chart of study participants. CAD indicates coronary artery disease; and ED, erectile dysfunction.

Patients with recent onset of ED without known CAD
referred to our Unit for ED N=416

Lost to follow-up N=34

Patients analyzed N=382

CAD N=58

noCAD N=336

Figure 1. Flow chart of study participants. CAD indicates coronary artery disease; and ED, erectile dysfunction.
Clinical Characteristics and Arterial Stiffness

The mean age of participants at entry was 56 years. Thirty-four patients were lost to follow-up (Figure 1). Compared with patients included in analysis, patients who were lost to follow-up were older (62 versus 56 years; \( P < 0.001 \)), and they had higher systolic pressure (141 versus 134 mm Hg; \( P = 0.018 \)), PP (58 versus 51 mm Hg; \( P = 0.005 \)), and a higher PWV (8.9 versus 8.4 m/s; \( P = 0.041 \)). The prevalence of hypertension, diabetes mellitus, hypercholesterolemia, and smoking was not different between participants and patients lost to follow-up.

The mean follow-up time was 4.7±1.9 years, during which 24 subjects developed MACEs (20 nonfatal, 4 fatal). Of those MACEs related to CAD (n=15), 3 were CAD deaths, 3 were ST-segment-elevation myocardial infarction with survival beyond 1 day, 6 were non–ST-segment-elevation acute coronary syndromes, and 3 were coronary revascularization after documented angina pectoris and positive stress test. Other MACEs were stroke (n=5) or transient ischemic attack (n=1) and new onset of peripheral arterial disease (n=3, 1 fatal).

The baseline clinical and ED characteristics of the 344 participants are given in Table 1. Compared with patients who did not experience MACEs, subjects who developed MACEs were older (\( P = 0.007 \)) and had a higher PWV (\( P < 0.001 \)). Patients with MACEs more frequently had diabetes mellitus (\( P = 0.02 \)) and arterial hypertension (\( P = 0.05 \)). The prevalence of hypercholesterolemia and smoking was not different between groups.

According to a multivariable regression analysis, PWV was positively associated with age (\( P < 0.001 \)), PP (\( P < 0.001 \)), hypertension (\( P = 0.035 \)), and diabetes mellitus (\( P = 0.010 \)).

Outcome and Prognostic Impact of PWV

ED population was divided into tertiles according to the PWV values (low tertile, <7.6 m/s; middle tertile, 7.6–8.8 m/s; high tertile, >8.8 m/s). Kaplan–Meier survival curves for MACEs by tertiles of PWV at baseline are shown in Figure 2. The differences across tertiles remained significant after exclusion of soft (transient ischemic attack and angina pectoris that underwent coronary revascularization) cardiovascular events (log-rank Mantel–Cox=14.785; \( P < 0.001 \)). Kaplan–Meier survival curve analysis showed that PWV was associated with MACEs, and the difference between the tertiles was significant (Mantel log-rank test, 11.161; \( P = 0.004 \)). A Cox proportional hazard model adjusting for age, body mass index, hypertension, hyperlipidemia, diabetes mellitus, and smoking, subjects at the highest tertile of PWV (HR, 3.97, 95% CI, 1.23–12.54; \( P = 0.035 \)) but not those with the middle tertile (HR, 1.82; 95% CI, 0.78–7.41; \( P = 0.402 \)) had significantly increased risk for MACEs compared with those with the lowest tertile.

Using PWV as a continuous variable in a Cox proportional hazard model showed strong associations with the occurrence of MACEs (\( P < 0.001 \)). The unadjusted Cox analysis also identified age (\( P = 0.005 \)) and fasting blood glucose (\( P = 0.05 \)) as being significantly associated with MACEs (Table 2). In a Cox model adjusting for continuous confounders with a \( P < 0.10 \) on univariate analysis (Table 2), PWV was independently associated with the occurrence of MACEs (adjusted HR, 1.52; 95% CI, 1.14–1.97; \( P = 0.011 \)). The bootstrap procedure showed that the bias of the HR as regards the PWV was low (ie, 0.008), indicating robustness of the estimated HR.

Kaplan–Meier survival curves showed that PP was also associated with a higher rate of MACE, and the differences between PP tertiles (<45, 45–55, 55 mm Hg) were significant (Mantel log-rank test, 9.512; \( P = 0.007 \)). However, in the Cox analysis the association between PP and MACEs was not significant (\( P = 0.880 \)).

Discrimination

The \( C \) statistic for the multivariate model, including classical risk factors (age, smoking, diabetes mellitus, systolic BP, total

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**Table 1. Baseline Characteristics of Patients With and Without MACEs**

<table>
<thead>
<tr>
<th>Variable</th>
<th>MACE (n=24)</th>
<th>No MACE (n=320)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>61±7</td>
<td>56±10</td>
<td>0.007</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>28.7±4</td>
<td>27.5±3</td>
<td>0.18</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>140±18</td>
<td>137±19</td>
<td>0.38</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>83±8</td>
<td>85±10</td>
<td>0.56</td>
</tr>
<tr>
<td>Pulse pressure, mm Hg</td>
<td>57±13</td>
<td>52±13</td>
<td>0.08</td>
</tr>
<tr>
<td>Pulse wave velocity</td>
<td>9.2±1.5</td>
<td>8.2±1.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>210±38</td>
<td>209±36</td>
<td>0.65</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>45±9</td>
<td>45±9</td>
<td>0.72</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>106 (80–147)</td>
<td>104 (78–122)</td>
<td>0.13</td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>109 (92–124)</td>
<td>107 (95–119)</td>
<td>0.24</td>
</tr>
<tr>
<td>hsCRP, mg/L</td>
<td>1.8 (1.3–2.2)</td>
<td>1.7 (1.2–2.0)</td>
<td>0.41</td>
</tr>
<tr>
<td>Total testosterone, ng/mL</td>
<td>4.1±0.8</td>
<td>4.9±1.2</td>
<td>0.021</td>
</tr>
<tr>
<td>Erectile function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doppler PSV, cm/s</td>
<td>29±10</td>
<td>33±9</td>
<td>0.035</td>
</tr>
<tr>
<td>Doppler EDV, cm/s</td>
<td>5.3±2.5</td>
<td>6.2±3.0</td>
<td>0.25</td>
</tr>
<tr>
<td>SHIM score</td>
<td>12±4</td>
<td>13±4</td>
<td>0.10</td>
</tr>
<tr>
<td>Duration of ED, y</td>
<td>2.3±2.0</td>
<td>2.2±1.9</td>
<td>0.96</td>
</tr>
<tr>
<td>Risk factors, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>19 (79)</td>
<td>193 (60)</td>
<td>0.05</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>12 (50)</td>
<td>195 (61)</td>
<td>0.20</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>8 (33)</td>
<td>51 (16)</td>
<td>0.02</td>
</tr>
<tr>
<td>Smoking</td>
<td>13 (54)</td>
<td>172 (54)</td>
<td>0.74</td>
</tr>
<tr>
<td>Drug therapy, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antihypertensive therapy</td>
<td>15 (63)</td>
<td>144 (45)</td>
<td>0.10</td>
</tr>
<tr>
<td>Statins</td>
<td>7 (30)</td>
<td>90 (28)</td>
<td>0.57</td>
</tr>
</tbody>
</table>

Categorical variables are presented as absolute (relative) frequencies; continuous variables are presented as mean±SD or median (interquartile range). BMI indicates body mass index; BP, blood pressure; ED, erectile dysfunction; EDV, end-diastolic velocity; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; MACE, major adverse cardiovascular event; PSV, peak systolic velocity; and SHIM, sexual health inventory for men.
cholesterol, high-density lipoprotein), was 0.767. Addition of PWV to this model offered a statistically significant improvement in the resulting C statistic to 0.795 (P=0.0335, for comparison between the areas under the curve), indicating the ability of PWV for MACE discrimination beyond the classical risk factors in our population. However, addition of PP to this model offered only a small improvement in the resulting C statistic to 0.780 (P=0.215).

Reclassification
In the whole study population, addition of PWV to the standard model, including the risk factors, resulted in upward reclassification (correct reclassification into a higher risk group) of 6 (25%) patients who experienced a MACE, as well as upward reclassification (wrong reclassification into a higher risk group) of 31 (10.3%) patients who did not experience an event. Furthermore, addition of PWV resulted in downward reclassification (wrong reclassification into a lower risk group) of 3 (12.5%) patients who experienced a MACE, as well as downward reclassification (correct reclassification into a lower risk group) of 81 (25.4%) patients who did not experience an event (Table 3). The overall NRI was 27.6% (z=2.13; P=0.0332). When only intermediate-risk patients (4%–7% risk group) were evaluated, the respective reclassifications were 16.7%, 7.8%, 4.2%, and 13.8%, resulting in an NRI (clinical NRI) of 18.5%.

Prognostic Performance of PWV
In receiver operating characteristic curve analysis, a PWV value of 7.81 m/s corresponded to a sensitivity of ≈90%. This cutoff value was associated with a negative predictive value (ability to rule out MACE) of 98.1% (95% CI, 93.3%–99.8%), indicating that a patient with PWV <7.81 m/s has a 0.981 probability of being free of MACEs during follow-up. This enhanced negative predictive value was, however, traded off with a low specificity (37.1%; 95% CI, 31.5%–43.1%) and low positive predictive value (10.5%; 95% CI, 6.7%–14.2%).

Discussion
Our study is the first to investigate the prognostic role of aortic stiffness in patients with vasculogenic ED. The principal findings of our study are (1) increased aortic PWV predicts MACEs independently in long-term follow-up. This predictive ability is independent of classic risk factors that are often present in such patients. (2) When added to standard risk models, such as the Framingham risk score, PWV reclassifies correctly a considerable percentage of patients to a higher or lower risk category. (3) An ED patient with PWV value <7.81 m/s has a probability of 0.981 to be free of events in the follow-up.

Clinical Implications
Our results justify inclusion of aortic PWV in the recommendations of scientific societies29 and suggest extension to other population groups such as ED patients. The clinical implications of our findings stem from the high prevalence of ED across ages1,2 and from the facts that ED is associated with clinical implications of scientific societies29 and suggest extension to other population groups such as ED patients. The clinical implications of our findings stem from the high prevalence of ED across ages1,2 and from the facts that ED is associated with
occult CAD and it carries in itself an independent risk for future cardiovascular events. Identification of those ED patients who are truly at high risk for future cardiovascular events is of paramount importance. Such patients may require a comprehensive evaluation to reveal occult CAD and are candidates of aggressive management of the risk factors to reduce their cardiovascular disease risk and concomitantly improve their sexual function. Finally, treatment of ED itself by phosphodiesterase type 5 inhibitors may also reduce cardiovascular disease risk. Because improvement of aortic stiffness may per se be a target of therapy by mediating a benefit in prognosis our results imply that treatment of risk factors should be directed at strategies that preferentially improve aortic stiffness. A particular strength of our study is the stringent tests that we used to validate PWV, such as reclassification; thus, PWV fulfills most of the required criteria for a biomarker to enter the clinical arena.

Although PWV is principally influenced by age and BP and less by other traditional risk factors, the predictive ability of PWV is independent of these parameters. This is particularly important because CAD and ED share many risk factors such as age, hypertension, diabetes mellitus, hyperlipidemia, and smoking. Although most studies have shown that ED predicts cardiovascular risk independently of risk factors, this has been questioned. The fact that the predictive ability of PWV is independent of classic risk factors implies that the risk that ED carries for future cardiovascular events is on top of that conferred by these factors.

Arterial stiffness, although principally both a measure and a result of atherosclerosis, is also associated with the extent of coronary and extracoronary atherosclerosis. In this context, our findings are in accordance with the artery size hypothesis, according to which atherosclerosis is widespread throughout the arterial tree, but it is clinically manifest initially as ED because the same amount of atherosclerotic burden compromises flow first through the smaller lumen of the penile arteries. However, it should be noted that arterial stiffness is also a predictor of acute coronary events, which in their majority occur in the presence of nonobstructive atherosclerotic disease. This is particularly important because a significant proportion of, especially younger, ED patients present with acute coronary syndromes in the absence of extensive atherosclerotic coronary burden. In such patients, the combined use of PWV with multiple detector computed tomography, which can detect subclinical plaques not limiting flow enough to influence the exercise stress test, may help to improve cardiovascular prediction.

Patients with PWV values <7.81 m/s have a high likelihood to be free of events at follow-up. For a frequent disease such as ED, it is particularly cost-effective to have a simple noninvasive test such as PWV that can save further testing for patients.

Mechanisms

The predictive value of aortic stiffness is based on its pathophysiological importance for arterial and overall cardiovascular performance. A stiff aorta increases left ventricular afterload and disturbs myocardial blood flow, thus unbalancing coronary perfusion/myocardial demand equilibrium. Increased PWV within ED patients may identify subjects with accelerated arterial aging. In addition, aortic PWV is influenced by the complex interplay among endothelial dysfunction, subclinical inflammation, and testosterone deficiency, a prominent pathogenetic milieu in ED.

Limitations

Phosphodiesterase type 5 inhibitors have the potential to reduce the risk for events in ED patients, whereas they also reduce aortic stiffness. However, treatment with phosphodiesterase type 5 inhibitors is unlikely to have influenced our results because they were equally distributed between groups with and without MACEs. A limitation of our study is the nonavailability of data regarding hemoglobin A1c or physical activity, which have been shown by some studies to be associated with aortic stiffness. Although the proportion of patients lost to follow-up was <10%, this may be a study limitation. Nevertheless, compared with patients included in analysis, PWV was significantly higher in patients lost to follow-up; therefore, the predictive value of high PWV, if different from the reported, may be actually underestimated and not overestimated.

Perspectives

Although the presence of ED per se increases cardiovascular risk, it is also important to determine within ED which patients are at higher risk. A growing body of evidence supports the potential use of several easily measured vascular or circulating biomarkers to further characterize risk for cardiovascular events in men with ED, but few have been evaluated in this population. Our analysis confirms the previous body of evidence in favor of the predictive role of aortic stiffness in various populations and extend this ability to reclassify risk of ED patients when added in a traditional risk model. Additional studies are needed to assess whether PWV when used as a treatment target can reduce further cardiovascular risk in the context of ED.

Disclosures

None.

References


What Is New?
• Our study is the first to investigate the prognostic role of aortic stiffness in patients with vasculogenic erectile dysfunction.

What Is Relevant?
• Aortic pulse wave velocity is increased in patients with erectile dysfunction.

Summary
Increased aortic pulse wave velocity independently predicts cardiovascular events in long-term follow-up and improves risk prediction when added to standard risk prediction models in erectile dysfunction patients.
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