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ORIGINAL PAPER

# Reassessing cardiovascular risk stratification in men with erectile dysfunction

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**Summary** ***Background and objectives: Erectile dysfunction (ED) is an independent and strong marker of cardiovascular disease (CVD) risk. The Princeton Consensus aimed to evaluate and manage cardiovascular risk in men with ED and no known cardiovascular disease, focusing on identifying those requiring additional cardiologic work-up. It has recently been updated to the American population demographics, but European recommendations are needed.***
***Methods: It was developed a cross-sectional investigation including erectile dysfunction patients. Data were collected from hospital registries. Two risk stratification models were employed and compared: Princeton Consensus Criteria (PC) and European Society of Cardiology (ESC) CVD Risk Criteria. The objective was to stress the importance of the changes in IV Princeton Consensus recommendations in stratifying CVD risk in men with erectile dysfunction using a model validated in European men.***
***Results: A total of 137 patients with ED, with a mean age of 57.1 years old, were included. According to the PC criteria, 39.7% of the patients were "Low Risk". When using ESC criteria, the proportion of "Low Risk" patients were significantly lower (12%, p < 0.05). Among "Low Risk" patients according to the PC, 52.5% and 20% were classified as High and Very high risk according to ESC criteria, respectively. One myocardial infarction was reported. The patient was classified as "Low Risk" according to the PC, but the ESC criteria categorized him as "high risk".***
***Conclusions: PC is less sensitive than ESC recommendations detecting CVD. It raises concerns that Urologists could be overlooking patients with undiagnosed CVD, consequently missing out on opportunities for prevention of major cardiovascular events (MACEs) and premature deaths.***

KEY WORDS: *Erectile dysfunction; Cardiovascular disease; IV Princeton consensus.*

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## INTRODUCTION

*Erectile dysfunction* (ED), defined as a man's consistent or recurrent inability to attain and/or maintain penile erection enough for successful vaginal intercourse (1), is a common problem in men as they age. Epidemiological data shows a high prevalence and incidence of ED worldwide (2). It is estimated by the year 2025, 322 million men will suffer from ED (3). In a European study of men aged 30-80 years, the prevalence of ED was 19.2%, with a steep age-related increase from 2.3% to 53.4% (4).
*Cardiovascular disease* (CVD) is a leading cause of death and disability in men (5). In Europe, deaths from CVD in those aged < 70 years old are a particular concern, with > 60 million potential years of life lost to CVD annually (6).
The link between ED and CVD has been previously characterized primarily by shared risk factors (7-9). However, an emerging set of data indicates that ED is in fact an independent and strong marker of CVD risk (10-22). As we know, both diseases are consequences of systemic vascular disease and shared common risk factors.
Furthermore, they share the same pathological process: endothelial dysfunction (18). Knowledge of this association justified the introduction in 2021 in the *European Society of Cardiology* (ESC) guidelines on cardiovascular disease prevention in clinical practice of the recommendation to assess cardiovascular risk in men with evidence of erectile dysfunction, with recommendation level IIa and evidence C (23). Because of the *quality of life* (QoL) burden it carries, ED may drive men to seek medical attention in the absence of other cardiovascular symptoms. Thus, the presence of ED may provide the opportunity for CVD assessment and mitigation of its risks. The importance of evaluating cardiovascular risk in men with ED is now a critical factor for overall early stage management of CVD, especially in younger men (7, 9).
In accordance with the *European Association of Urology* (EAU) guidelines, sexual rehabilitation should only commence after a meticulous evaluation of the cardiovascular risk, alongside with an assessment of the individual's capabilities to engage in physical activity (7). Despite these recommendations, recent research highlighted a deficiency in the evaluation of CVDs in patients with ED by urologists: alarmingly, fewer than half of these clinicians undertook a combined assessment encompassing both CVD and ED (24).
The Princeton consensus (Expert Panel) Conference, is a multispecialty collaborative tradition dedicated to optimizing sexual function and preserving cardiovascular health (9). The III Princeton consensus (Princeton 3) were published over a decade ago (9), and since then, several

alternative risk models have been revised and validated for the prediction of cardiovascular risk in individual patients, according to their demographic background. The IV Princeton consensus (Princeton 4) were recently updated, addressing this disparity (25). The Princeton 4 recommends the use of *Atherosclerotic Cardiovascular Disease* (ASCVD) model introduced by the *American College of Cardiology/American Heart Association* (AHA/ACC) in 2013 (26) to estimate the CVD risk in all patients with organic vasculogenic ED. However, the ASCVD score is not validated to the European population. Of particular interest is the SCORE2/SCORE2-OP developed by the ESC, that was last updated in 2021 and is distinct for being the developed and validated for the European population (27).
The present study aimed to stress the importance of the changes in Princeton 4 recommendations in stratifying CVD risk in men with erectile dysfunction using a model validated in European men.

## Methods

This study was designed as a cross-sectional study to evaluate the adequacy of the *Princeton consensus* (PC) for stratifying men with ED based on their CVD risk. The study drew upon a clinical series of patients with ED to conduct a comprehensive review. The study included all patients referred to the andrology department at a *Central Hospital in Portugal* for the assessment and treatment of erectile dysfunction within the designated study timeframe (three-year period, from December 2019 to December 2022). All patients included in the analysis were diagnosed with organic ED according to the clinical data and all of them were interviewed by the same expert in andrological care to ensure consistency in data collection and evaluation.
We collected demographic data, medical history, and CVD risk factors recorded in the hospital registries during a minimum follow-up period of 12 months. The proportion of positive stress test results and subsequent invasive cardiac procedures was documented. The occurrence of *major adverse cardiovascular events* (MACEs) was monitored during the study period.
Two risk stratification models were employed: Classic *Princeton criteria* (PC) and ESC CVD Risk Criteria. To facilitate meaningful comparisons and clinical applicability, patients were subsequently categorized into "*low risk*" and "*Non-low risk*" groups for all risk assessments. Specifically, PC and ESC Lowest risk categories, PC low risk and ESC Low to Moderate risk patients, respectively, were placed in the "*low risk*" category, whereas the leftovers were grouped under "*non-low risk*". For a visual representation of the risk groups recommended by the ESC CVD Risk Stratification Criteria, please refer to Figure 1 (23).
The ESC guidelines (23) served as the basis for patient stratification in this study. Following the ESC panel's recommendations, individuals with a history of CVD were automatically categorized as not being at low risk for future MACEs, as depicted in Figure 1. Consequently, all patients with documented CVD were classified as "*non-low risk*" for the analysis. Those without previous CVD were stratified based on the SCORE2/SCORE2-OP system. We utilized the HeartScore calculator available on the ESC online platform (*https://www.heartscore.org/*), which necessitates input regarding patients' age, sex, blood pressure, total HDL and LDL cholesterol levels, and smoking status. All relevant data were extracted from hospital registries.

| Patient Category | Subgroups | Risk Categories | CVD Risk Model |
|---|---|---|---|
| Apparently healthy patients | | | |
| Persons without established CVD, DM, CKD, Familial Hypercholesterolemia | <50 years | Low- to Very High-Risk | 10-year CVD risk estimation (SCORE2) |
| | 50-69 years | Low- to Very High-Risk | 10-year CVD risk estimation (SCORE2) |
| | >70 years | Low- to Very High-Risk | 10-year CVD risk estimation (SCORE2) |
| Patients with CVD | | | |
| CKD without DM or Atherosclerotic CVD | Moderate CKD | High-Risk | SCORE2 not applicable |
| | Severe CKD | Very High-Risk | SCORE2 not applicable |
| Familial Hypercholesterolemia | | | |
| Associated with markedly elevated cholesterol levels | N/A | High Risk | SCORE2 not applicable |
| Patients with DM | | | |
| DM type II or Type I if above 40 years old | Well controlled, without target organ damage (TOD) and no other CVD risk factors | Moderate-Risk | SCORE2 not applicable |
| | Patients not categorized as moderate- or very high-risk | High-Risk | SCORE2 not applicable |
| | DM patients with CVD and/or severe TOD | Very High-Risk | SCORE2 not applicable |
| Patients with established CVD | | | |
| Documented atherosclerotic CVD, clinical or unequivocal on imaging. | N/A | Very High-Risk | SCORE2 not applicable |

***Figure 1.***
*Patients' categories and associated CVD risk according to ESC guidelines.*

The data were managed on and analysed using SPSS for Windows. All values were expressed as mean (± standard deviation) or as percentages. Standard descriptive analysis was performed to analyse the baseline characteristics of the study population. The categorized risk estimates derived from the different risk scores were compared using McNemar test (as the risk scores were dichotomized as "*low risk*" or "*high risk*"). A p value < 0.05 was considered statistically significant.
The study was conducted following the principles outlined in the Declaration of Helsinki. Approval from the Institutional review board were obtained.

## Results

Our study included 137 patients with ED with a mean age of 57.1 ± 10.5 years old. The average *Body mass index* (BMI) was 27.7 ± 4.1 kg/m$^2$, and each patient had a median of 3 CVD risk factors. Of the total population, 28.5% had *diabetes mellitus* (DM), 12.4% had *chronic kidney disease* (CKD), 6.6% had a previous stroke and 4.4% had a *myocardial infarction* (MI). Baseline characteristic of the population are summarized in Table 1. Table 2 presents the categorization of patients based on various risk models, and Table 3 provides a comparison between these models. Figure 2 gives a visual representation of the distribution according to the model applied.
According to the PC, approximately 39.7% of patients were classified as "*low risk*". However, when using alternative risk scores (ESC criteria), the percentage of patients classified as being at the lowest risk group was significantly lower (12%, p < 0.05). Within the "*low risk*" group according to the PC, 52.5% and 20% were classified as high and very high risk according to the ESC criteria, respectively.
Patients without previously known CVD showed a mean 10-year risk of CVD events of 6.5% ± 3.5% according to the SCORE2/SCORE2-OP. Moreover, Low, Intermediate and high-risk patients according to PC showed a 10-year risk calculated with the SCORE2/SCORE2-OP formula of 5.4% ± 3.2%, 7.6% ± 3.6% and 8.5% (n = 1), respectively.
To address arbitrary cutoff values used for categorization in the SCORE2/SCORE2-OP model, we utilized a ROC curve (Figure 3). Our analysis pinpointed a 5% 10-year CVD risk threshold from the SCORE2/SCORE2-OP model, offering

***Table 1.***
*Patients' characteristics.*

| Variables | | Mean ± SD |
|---|---|---|
| Variables | | Mean ± SD |
| Age (years) | | 57.1 ± 10.5 |
| BMI (kg/m$^2$) | | 27.7 ± 4.1 |
| Mean blood pressure (mmHg) | | 97.1 ± 13.3 |
| Total cholesterol (mg/dL) | | 175.8 ± 39.5 |
| HDL cholesterol (mg/dL) | | 51.2 ± 18.5 |
| LDL cholesterol (mg/dL) | | 103.7 ± 46.4 |
| Cardiovascular risk factors (%) | ≤ 2 | 41.9% |
| | ≥ 3 | 58.1% |

***Table 2.***
*Patients' distribution according to the risk models applied.*

| Risk model | | N% |
|---|---|---|
| III Princeton consensus | Low | 39.7 |
| | Intermediate | 55.1 |
| | High | 5.1 |
| ESC Guidelines | Low to moderate | 12 |
| | High | 53.8 |
| | Very high | 34.2 |
| SCORE2/SCORE2-OP (Patients apparently healthy) | Low to moderate | 25.9 |
| | Intermediate | 57.4 |
| | High | 16.7 |

***Table 3.***
*Patients' distribution according to the risk models applied.*

| Risk models | | III Princeton consensus (n%) | | P |
|---|---|---|---|---|
| | | Low risk | Non-low risk | |
| ESC model for patients with type 2 diabetes mellitus, CKD, FH or established ASCVD (n%) | Low risk | 27.5% | 3.9% | < 0.05 |
| | Non-low risk | 72.5% | 96.1% | |
| ESC model for apparently healthy patients (SCORE2/SCORE2-OP) (n%) | Low risk | 40.7% | 11.1% | < 0.05 |
| | Non-low risk | 59.3% | 88.9% | |

***Figure 2.***
*Patient distribution according to the models applied.*

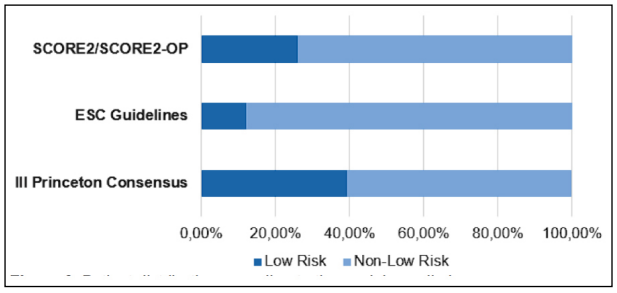


***Figure 3.***
*ROC curve.*

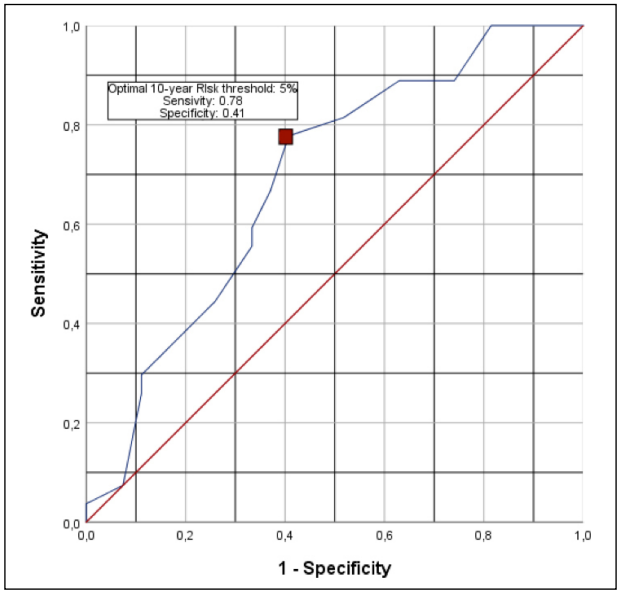

***Table 4.***
*Characteristics of patients who underwent a cardiac procedure or a major adverse cardiovascular event (MACE).*

| Patients | MACE | Cardiac intervention | III Princeton consensus | ESC guidelines |
|---|---|---|---|---|
| 1 | Not ocurred | Angioplasty | Non-low risk | Non-low risk |
| 2 | Ocurred MI | Bypass | Low-risk | Non-low risk |
| 3 | Ocurred VT | ICD | Non-low risk | Non-low risk |
| 4 | Not ocurred | MitraClip | Non-low risk | Non-low risk |
| 5 | Not ocurred | Valvuloplasty | Non-low risk | Non-low risk |

the optimal balance of sensitivity and specificity when compared to the PC. Of the men without CVD, 40.7% showed a 10-year risk below 5%, aligning with the proportion classified as "*low risk*" by the PC (39.7%). Notably, within the PC "*low risk*" group, 40.7% still exhibited a 10-year MACE risk surpassing this threshold.
Among men who underwent stress testing, 10 patients (21.7%) tested positive for ischemia and were referred to the Cardiology department. During follow-up, two MACEs were reported: 1 *myocardial infarction* (MI) and 1 *ventricular tachycardia* (VT). Out of the 137 included patients, five underwent cardiac interventions (1 angioplasty, 1 bypass, 1 *implantable cardioverter defibrillator* (ICD), 1 MitraClip and 1 valvuloplasty). The sole MI reported occurred in a patient classified as "*low risk*" according to the PC. However, the 47-year-old male with DM, according to the ESC guidelines, was categorized as "*high risk*".
Nevertheless, there was no significant difference in the MI rate between the two models ($p < 0.05$). Further information on these patients can be seen in Table 4.

## Discussion

The association between ED and undiagnosed CVD has been extensively investigated since its initial recognition as an independent risk factor. A meta-analysis encompassing 12 prospective cohort studies identified ED as a predictive indicator for various cardiovascular outcomes: cardiovascular events (HR 1.44, 95% CI 1.27-1.63), cardiovascular mortality (HR 1.19, 95% CI 0.97-1.46), myocardial infarction (HR 1.62, 95% CI 1.34-1.96), cerebrovascular events (HR 1.39, 95% CI 1.23-1.57), and all-cause mortality (HR 1.25, 95% CI 1.12-1.39) (28). Another comprehensive literature review highlighted that ED precedes cardiac events by a period of 3 to 5 years, which responds to an important window of opportunity in the prevention of cardiovascular events (21). An umbrella review of systematic reviews and meta-analyses underscored the consistent finding that ED frequently precedes symptomatic CVD. This recognition equips healthcare practitioners with the opportunity to screen and identify high-risk patients at an early stage, ultimately contributing to prevent morbidity and mortality (27). Similarly, Gandaglia et al. found that ED patients with cardiovascular risk factors should be considered high risk, warranting comprehensive cardiovascular evaluations due to potential silent coronary artery disease (30). Raheem et al. emphasized the responsibility of urologists, general practitioners, and primary care physicians to identify high-risk patients and refer them to cardiologists for assessment (31).
Due to the robust association between ED and CVD, major urological associations such as EAU, AUA and, more recently, ESC advocate for systematic assessment of ED patients regarding their CVD risk (7, 23, 32). This approach recommends sexual rehabilitation exclusively for patients categorized as low risk, while those at higher risk require further cardiologic evaluation. This evaluation does not primarily focus on the patient's ability to tolerate pro-erectile medication, given the generally safe nature of these therapies (33). Instead, it aims to determine the patient's physical capability to sustain the exercise intensity demanded by sexual activity. Sexual activity between couples in a longstanding relationship equates to approximately 3 Mets (metabolic equivalent of task), therefore completing 4 minutes of the standard Bruce treadmill protocol (5-6 Mets) without symptoms, arrhythmias, or a fall in systolic *blood pressure* (BP) confirms the safety of sexual activity (7, 9).
The Princeton 3 underscored that intermediate risk patients should undergo stress test to gauge exercise capacity prior to initiating proerectile therapy. High-risk patients are advised to undergo a thorough cardiologist assessment and optimization before embarking on rehabilitation (7, 32). A limitation of the Princeton 3 was its insufficient consideration of varying degrees of severity associated with specific risk factors, such as age, DM, and lipid profile. While uncontrolled hypertension designates individuals as high risk, the Consensus overlooked the progressive impact of aging, current lipid profile and glycaemic status, regarding them to mere contributors within the cumulative risk factor count. In contrast, the ESC criteria (as shown in this study) and the ASCVD score (as proposed in the Princeton 4) demonstrates a more comprehensive, personalized and sensitive approach.
As recently published (25), the Princeton 4 suggests assessing all vasculogenic ED patients based on their 10-year risk of CVD using the ASCVD score. If the 10-year risk is 5-20%, *coronary artery calcium* (CAC) testing is recommended before initiating pro-erectile treatment. Patients with an abnormal CAC test or an initial risk over 20% should be referred to preventive cardiology for rigorous risk factor control. Our study supports and reinforces this new recommendation.
The ESC criteria encompass the exact age, blood pressure, lipid profile in risk evaluation, CKD stage and current glycaemic control. For instance, under the PC, a 40-year-old smoker with hypertension and dyslipidaemia is classified as intermediate risk (owing to the presence of three risk factors, excluding sex). Conversely, a 75-year-old smoker without comorbidities is labelled low risk. However, considering both individuals show normal lipid profile and blood pressure, the SCORE2/SCORE2-OP model presents divergent outcomes. The first patient is designated low risk with a 2% 10-year cardiovascular event risk, while the second patient faces a substantially higher risk of 18% over the same period. However, the clinical significance of these disparities remains uncertain. While it is accepted that patients classified as Intermediate Risk by the PC should undergo a physical capacity assessment, there hasn't been a direct compari-

son with other risk models, nor has a definitive threshold for the 10-year CVD event risk, needing stress testing, been explored. Yet, this approach appears the most patient-focused method for evaluating these patients.

Notably, there was only one reported case of myocardial infarction, and it occurred in a patient classified as "*low risk*" according to the PC criteria. In contrast, the ESC criteria categorized that patient as "*high risk*". However, despite the different risk stratifications, the study did not find significant differences in the risk of MACEs between the "*low risk*" and "*non-low risk*" groups. This can be attributed to the infrequency of these events during the relatively brief study period, or, to a lesser extent, to a well-timed preventive intervention.

Using ROC curves helped us pinpoint a 5% 10-year CVD risk threshold from the SCORE2/SCORE2-OP model, which struck a balance between sensitivity and specificity when compared to the PC. However, we observed that for "*low risk*" patients defined by the PC, 40.7% of patients still exhibited a 10-year MACE risk surpassing 5%. This finding underscore, again, the significant differences between these two models and the importance of selecting the appropriate model and cutoff values when assessing cardiovascular risk.

This study possesses some limitations. Firstly, its retrospective design renders it susceptible to potential biases in data collection. Nonetheless, it's important to note that all patients underwent interviews conducted by the same Urologist, and the quality of registries was classified as highly reliable. Secondly, while the collected risk factors were considered dependable, the reference to the presence of family history of premature coronary artery disease were inconsistent and was consequently excluded from the analysis as a potential risk factor. Finally, the limitations stemming from the sample size, potential data loss during follow-up, and its duration proved inadequate for comprehensively assessing the clinical implications regarding the incidence of MACEs between the models.

Ultimately, alternative risk models like the ESC recommendations may enhance the assessment of patients with CVD. This stresses the pertinence of the updates in Princeton 4, from the previous Princeton 3.

## Conclusions

The study underscores that the PC exhibits lower sensitivity compared to the ESC recommendations to stratify the CVD risk of European men. This disparity raises concern that Urologists could be overlooking patients with undiagnosed cardiovascular disease, thereby missing critical opportunities for timely prevention of MACEs and premature deaths. This underscores the relevance of the updates in Princeton 4 compared to the previous Princeton 3. The EAU guidelines should be revised accordingly, taking into account the optimal risk model for the European patient population.

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