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Erectile dysfunction links to cardiovascular disease—defining the clinical value

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ABSTRACT

Despite many advances over the last few decades, cardiovascular disease (CVD) remains the leading cause of death globally, with men afflicted at an earlier age than women. In a bid to reduce the global burden of morbidity and mortality due to CVD, emphasis has been placed on prevention, particularly on widespread promotion of ideal cardiovascular health behaviors and advancing strategies to identify and treat high-risk individuals who may benefit from aggressive preventive therapy.

Erectile dysfunction is a highly prevalent condition that has been demonstrated to share the same risk factors as clinical CVD, and to have independent predictive value for future CVD events. Importantly, subclinical atherosclerosis appears to precede vascular ED by a decade or longer, with ED preceding clinical CVD such as myocardial infarction and stroke in temporal sequence by about 2–5 years. Crucially, since ED may represent the first presentation of otherwise "healthy" men to care providers, a clinical diagnosis of vascular ED may represent a unique opportunity to identify high risk individuals, intervene, and thus prevent progression to clinical CVD.

This review summarizes up-to-date evidence of the relationship between ED and subclinical and clinical CVD, and details the position of current guidelines and clinical recommendations on the role of ED assessment in CVD prevention. Finally, this review proposes a clinical framework for the incorporation of ED into standard CVD risk assessment in middle-age men.

Introduction

Erectile dysfunction (ED) is defined as "the consistent or recurrent inability to attain and/or maintain penile erection for sufficient sexual satisfaction" [1]. Globally, ED affects an estimated 150 million men, and up to 30 million men in the United States [1]. Of this large number of individuals, the majority have vasculogenic ED, which is thought to represent a distinct manifestation of the same systemic disease that leads to clinical cardiovascular disease (CVD) [2,3]. Furthermore, ED has been strongly associated with subclinical and clinical CVD in several cross-sectional and prospective studies [4–6], and is deemed to have independent predictive value for clinical CVD outcomes [6].

Current CVD prevention is guided by a risk-based approach in which probability-based risk scores are used to determine appropriateness of preventive therapy [7]. Given documented limitations of these risk scores, including their inability to reclassify individuals deemed to be at intermediate risk and their limited predictive power among younger individuals, there exists an urgent need for further improvement. Additionally, there remains a need to identify low-cost, easily detectable, early markers of future CVD that can trigger comprehensive risk factor modification in men who would not have ordinarily presented for CVD risk assessment.

The shared risk factors between ED and CVD [8], its strong association with both subclinical and clinical CVD [4,6], the biological plausibility of the "artery-size hypothesis" (a pathobiological basis for the predictive value of ED for CVD) [9], and the strength of epidemiologic evidence demonstrating the value of ED for CVD prediction makes a compelling argument for its potential utility in clinical CVD risk prediction, and for guiding the initiation and intensity of preventive therapy.

The plausible utility of ED in risk prediction and guidance of preventive therapy has encouraged a significant push in certain clinical and research circles to systematically evaluate ED symptoms as part of standard clinical cardiovascular risk assessment [10,11]. The third Princeton Consensus Conference (an expert panel dedicated to optimizing sexual function and cardiovascular health),

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for example, named ED as a "marker of increased risk of CVD, which provides an opportunity for CVD risk reduction" [12]. Similarly, assessment of ED status has been incorporated into the United Kingdom QRISK-3 calculator and is now a standard risk factor for the estimation of 10-year CVD risk in men [13].

While the UK QRISK calculator includes the assessment of ED status, standard risk prediction tools in the United States, such as the Pooled Cohort Equations and the Framingham Risk Scores, do not recognize ED as an important risk factor in CVD risk prediction modeling. Additionally, there are no clear US cardiovascular guidelines or recommendations on the clinical assessment or evaluation of men who present with ED.

This review aims to: (1) synthesize high-quality evidence of the relationship between ED and CVD risk; (2) discuss the potential value of ED screening as a cardiovascular risk stratification tool; (3) identify prohibitive gaps in current knowledge limiting the inclusion of ED in US guidelines; and (4) provide clinical perspectives regarding the work-up of ED patients from a CVD standpoint.

Current evidence of the relationship between ED and CVD

Shared risk factors, endothelial dysfunction and atherosclerosis

In 1985, Virag et al. published a report in the *Lancet*, drawing attention to the distribution of "four main arterial risk factors", including hypertension, diabetes, smoking, and hyperlipidemia in men with erectile dysfunction [14]. In this important study, the authors grouped patients into broad categories of organic ED (including ED due to arterial, venous, endocrine or neurological causes) and non-organic ED. They found that the frequency of organic ED increased from 49% in the absence of any of these arterial risk factors, to 100% in patients with 3 or 4 arterial risk factors [14]. These findings formed the foundations for the "shared risk factor" approach to understanding the relationship between ED and CVD, and have been replicated in many studies, including contemporary studies [11]. It is now generally accepted that ED and CVD share similar risk factors and that they may represent different manifestations of the same pathogenetic mechanisms of endothelial dysfunction and atherosclerosis which develop as a direct consequence of these risk factors on penile and ASCVD-related vascular supplies (coronary and cerebrovascular), respectively (Fig. 1) [11].

The artery-size hypothesis and the nitric oxide-cyclic GMP vasodilator system: two pathobiological explanations for ED preceding clinical CVD in temporal sequence

A risk marker is only valuable if it precedes, in temporal sequence, the predicted event. While earlier studies showed that men with ED have a high prevalence of CVD and vice versa, more recent studies have been geared toward disentangling the temporal sequence of ED, subclinical CVD, and CVD [15]. Based on epidemiologic and clinical evidence, ED has been reported to predate the occurrence of CVD symptoms by about 2–5 years [16,17]. The "artery-size hypothesis" is a pathophysiologic mechanism proposed by Montorsi et al. to explain this temporal relationship from a macrovascular perspective, and is based upon the following primary assumptions [9]:

(1) Atherosclerosis is a systemic disease that should, in theory, affect all major vascular beds to a similar degree.
(2) The rate of occurrence of atherosclerotic symptoms in these vascular beds is dependent on differences in the size of the supplying arteries.
(3) Larger vessels can better tolerate the same degree of plaque deposition compared to smaller vessels.

The artery size hypothesis thus suggests that the epidemiologic and clinical evidence of the occurrence of ED before CAD, stroke, or peripheral vascular disease is dependent on differences in arterial diameter, with penile arteries having a smaller artery diameter (1–2 mm) compared to coronary (3–4 mm), internal carotid (5–7 mm) or femoral (6–8 mm) arteries [9].

In addition to the artery-size hypothesis, another pathobiological explanation for the occurrence of ED before clinical CVD is a differential functional impact of early atherosclerosis-related impairment in the nitric-oxide-cyclic guanosine-3′5'–monophosphate (NO-cGMP) signaling pathway on the penile vasculature versus classical CVD-related vascular supplies. Compared to other arteries that dilate up to about 15% during flow-mediated dilation tests, the smaller arteries that supply the penile trabecular tissues and sinusoids need to dilate up to 80% to provide blood flow necessary for sufficient venous compression to sustain penile erection [18]. Since the attainment and maintenance of penile erection is thus significantly dependent on the degree of vasodilation of cavernosal supplies, a reduction in the maximum attainable flow occasioned by impairment of this critical NO-cGMP signaling pathway may significantly impair penile erection far in advance of the occurrence of classical CVD events, which are more likely to result from structural atherosclerotic changes like atherosclerotic plaques.

The relationship between ED and subclinical CVD

Cross-sectional studies of the relationship between ED and subclinical CVD have found significant associations [19,20]. A recent systematic review and meta-analysis demonstrated significant associations between ED and markers of subclinical disease such as flow mediated dilation (FMD) and carotid intima-media thickness (cIMT) [21]. However, the temporal sequence of subclinical CVD and ED has remained less clear. The assessment of temporal sequence has taken on great importance as there is significant interest in understanding if the presence of subclinical CVD, as measured using novel cardiovascular markers like coronary artery calcium scoring, can predict incident ED. Since ED is known to predate clinical CVD, the assessment of markers of risk that may precede the occurrence of ED symptoms, and therefore trigger early risk factor modification, is deemed crucial from a CVD prevention standpoint.

This relationship between subclinical CVD and future ED was most thoroughly investigated by Feldman et al. in the Multi-Ethnic Study of Atherosclerosis [4]. In their study of 1862 men free of known CVD (mean age 59.5 ± 9 years), Feldman et al. showed increased odds of future ED (assessed 9 years after initial testing) when advanced coronary artery calcium (CAC) and carotid plaque were present at baseline, suggesting that early detection of subclinical atherosclerosis may provide opportunities for predicting the onset of vascular ED (Fig. 2).This study however had significant limitations in that the study was not formally longitudinal and the prevalence of ED in the study population at baseline was not known [4]. Evidence of the temporal relationship of ED and subclinical CVD is therefore suggestive but inconclusive, and more studies exploring this relationship are needed.

The relationship between ED and clinical CVD

While the relationship of ED and subclinical CVD less certain, there is a wealth of evidence demonstrating that ED is an independent risk factor for CVD [6,22–24]. In a meta-analysis of 12 prospective studies, Dong et al. reported evidence of the independent association of ED with increased risk of CVD, CHD, stroke and even all-cause mortality. Compared to men without ED, they

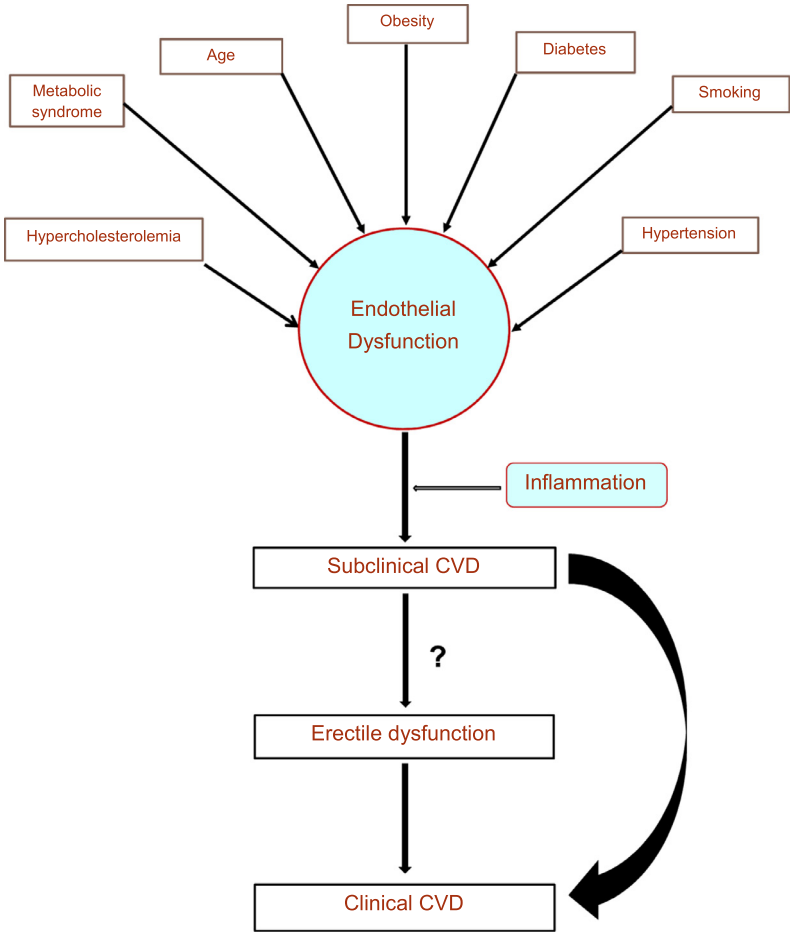

Fig. 1. Schema of the temporal sequence of disease progression from traditional risk factors to clinical CVD.

reported that men with ED experienced a significantly increased risk of 48% for CVD, 46% for CHD, 35% for stroke, and 19% for all-cause mortality [25]. More recent studies, which aimed to more thoroughly account for the effects of possible confounders such as depression and use of beta-blockers, have found similar associations between ED and CVD [6]. In the most recent of these studies, Uddin et al. [6] assessed the utility of self-reported ED for predicting CVD events in 1914 male participants (mean age, 69 ± 9.2 years) of the Multi-Ethnic Study of Atherosclerosis (MESA), followed over a 3.8-year period. They found self-reported ED to be a significant predictor of hard CVD events (hazard ratio, 1.9; 95% CI 1.1–3.4) even after adjustment for traditional cardiovascular risk factors, depression, and beta blocker use (Fig. 2). The predictive value of a simple assessment of self-reported ED, rather than the more definitively imaging-based diagnosis of vasculogenic ED, reflects the strength of this relationship and further highlights the potential value of ED as a low-cost risk stratification tool.

Importantly, the relationship between ED and CVD has been shown to be stronger in the intermediate risk group and among younger men [26]. This is potentially important from a guideline perspective, as current risk tools are limited in predicting risk in these groups.

Current place of ED screening in CVD prevention: a clinical practice guidelines perspective

Despite general agreement on the high prevalence of ED in individuals at risk of CVD, and the potential utility of ED for CVD risk stratification [27], ED is not mentioned in US risk prediction guidelines [28]. Furthermore, the assessment of cardiovascular risk factors and CVD signs or symptoms in men with ED carries a moderate class IIa recommendation in the 2016 European guidelines on CVD prevention, which argues that “the benefit of routine screening for ED and the most effective tool to assess it are still unclear” [29]. In line with these reservations, neither the European SCORE risk chart nor the ACC/AHA Pooled Cohort Equations include ED as a variable to include in the calculation of global CVD risk. Of the common CVD risk calculators, ED status is only included in the recently updated United Kingdom QRISK-3 10-year CVD risk prediction algorithm, where its presence was shown to be associated with a 25% increased risk of CVD (see example case in Fig. 3) [13].

The absence of ED in risk prevention guidelines may offshoot from controversies surrounding its *independent* incremental value, particularly when added to existing variables of the Framingham risk scores or the Pooled Cohort Equations. For example, in a prospective study of the incremental value of ED assessment over the Framingham Risk Scores in 1057 men aged 40–70 years from the Massachusetts Male Aging Study (MMAS), the addition of ED only yielded a small increase in CVD risk discrimination (c-statistics, 0.6910 versus 0.6953) over the Framingham risk scores alone [23].

While the inclusion of ED in global multivariable risk prediction models may be a subject of controversy, ED assessment may have potential utility when adopted as a risk-enhancing factor whose presence may signal the need for more detailed assessment or ag-

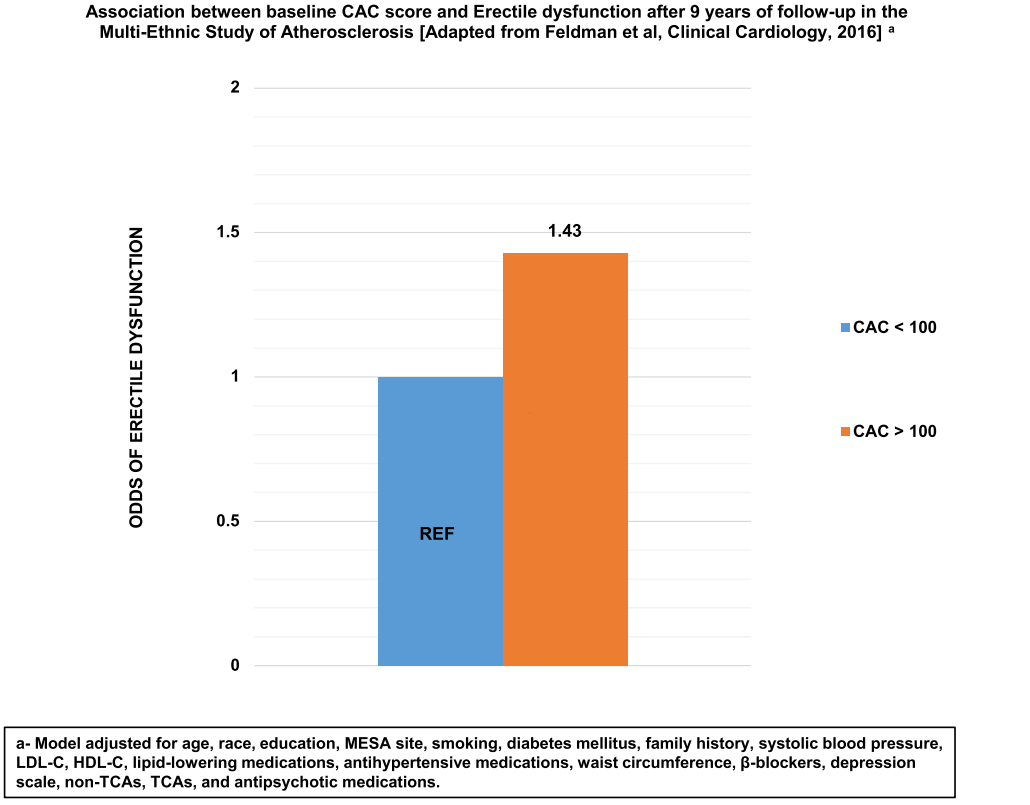

Fig. 2. Relationship between subclinical CVD, ED and clinical CVD as demonstrated in the Multi-Ethnic Study of Atherosclerosis (MESA).

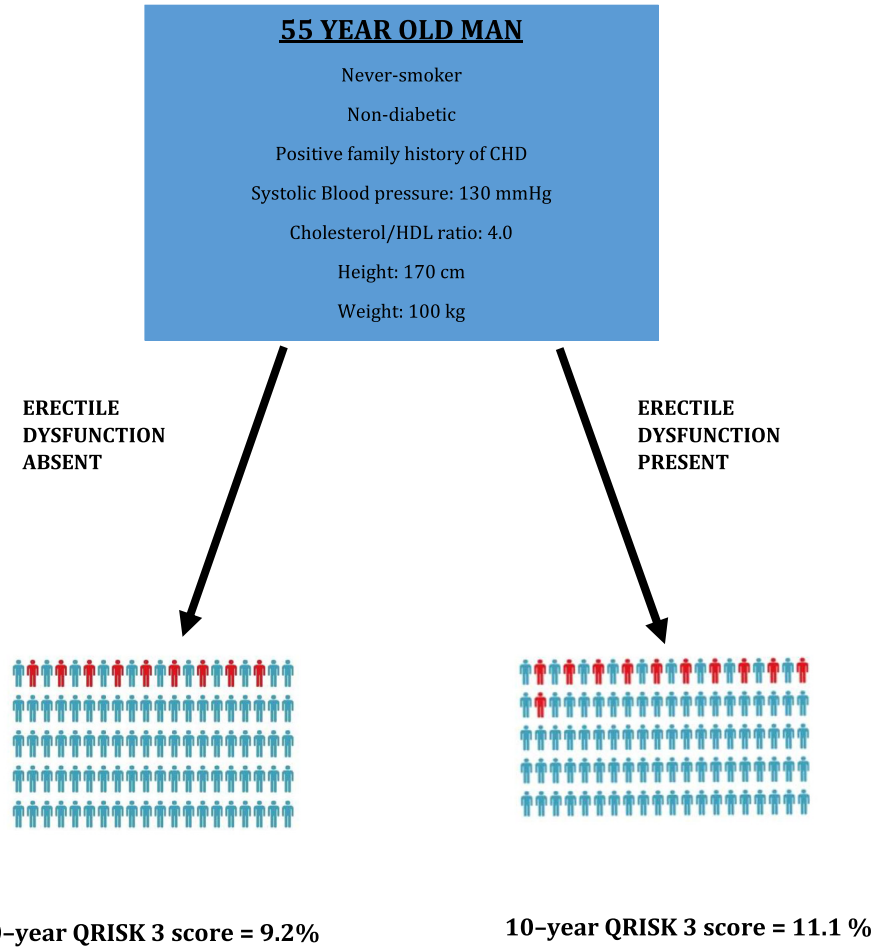

Fig. 3. QRISK 3 CVD risk calculator simulation highlighting differences in 10-year ASCVD risk based on ED status, in a model 55-year old man with metabolic syndrome. *Estimates were calculated using the QRISK®3-2018 calculator https://qrisk.org/three.

gressive therapy, independent of these risk scores. Certain expert and guideline committees such as the Princeton consensus III and more recently, the 2018 American Urological Association guidelines on ED, have adopted this approach, highlighting the presence of ED as an important risk marker for underlying CVD that may warrant further evaluation and treatment [1,12].

Clinical value of the relationship between ED and CVD

With significant improvements in CVD prevention through early detection and risk reduction, individuals at risk of CVD are suffering fewer adverse outcomes [30]. However, while the decision to treat aggressively with preventive therapy is often very clear for individuals at very high (>20%) 10-year ASCVD risk as defined by the Pooled Cohort Equations, many men fall into an "intermediate" (5%–20%) risk category for which this decision is not as clear. For this group, further risk stratification is needed to appropriately balance therapeutic risks and benefits. It is in this intermediate risk setting that CAC has demonstrated significant utility for risk reclassification and therapeutic decision-making [31]. CAC is a low-radiation (~1 mSV) cardiac-gated non contrast CT derived quantification of coronary atherosclerotic burden which is a widely-available, quick (10–15 min), and low-cost ($75–$175) advanced cardiovascular risk stratification tool with proven ability to improve cardiovascular risk assessment across race/ethnicity groups [31].

We believe that similar to CAC, the assessment of ED will have maximal utility for further stratifying risk in intermediate risk men, and that the presence of ED may serve as a male-specific risk-enhancing factor which when present, indicates the need for further testing or initiation of preventive therapy (similar to early menopause or prior history of pre-eclampsia in women).

Based on our clinical experience and strong evidentiary support from the literature, we propose that ED screening is important in CVD prevention, especially in combination with CAC scoring, for the following reasons: first, the assessment of erectile function in men during a typical outpatient visit is a noninvasive, quick and cost-effective way to gather insight into an individual-level endothelial dysfunction and inflammation, which are both strongly correlated with CVD risk and outcomes [27]. Importantly, men commonly first visit a doctor to discuss ED, not necessarily their CVD risk. Second, ED can provide clinical evidence to support reclassification of risk if an individual does not initially meet current thresholds for therapeutic initiation (i.e. falls in the intermediate risk zone) as it is independently associated with CVD risk and outcomes [32]. Third, ED can serve as one of the most motivating factors for men to reduce CVD risk because aggressive lifestyle modifications and adherence to optimal medical therapy not only decreases CVD risk but also improves erectile function and quality of life [33].

Linking with the new 2018 ACC/AHA Risk Assessment guidelines, we therefore suggest the following stepwise recommendations for combining existing risk prediction scores, ED status, and CAC for CVD risk prediction in the clinical setting, modifying an illustration by Greenland et al. [31] to include ED screening (Table 1).

Table 1
Proposed decision-making approach incorporating ED assessment into CVD prevention.

Proposed decision-making approach to using 10-year ASCVD risk estimate plus ED status to guide CAC testing and statin therapy			
Patient's 10-year ASCVD risk estimate:	**<5%**	**5-20%**	**>20%**
Consulting ASCVD risk estimate alone	Statin not recommended	Consider for statin	Recommend statin
Consulting ASCVD risk estimate + ED status			
If ED present	Consider CAC scoring	Recommend statin, corroborate with CAC	Recommend statin
Consulting ASCVD risk estimate + ED status + CAC			
CAC score = 0, ED present	Statin not recommended	Confirm vasculogenic nature of ED, Patient-physician discussion, strongly consider statin initiation	Recommend statin
CAC score > 0, ED present	Recommend statin*	Recommend statin	Recommend statin
Does ED + CAC score modify treatment plan?	✓ ED and CAC can reclassify risk up for this population	✓ ED and CAC can reclassify risk up or down for this population	✖ ED and CAC cannot reclassify risk for this population

*In this case, it is reasonable to first consider aggressive risk factor modification before initiating statin. In all other situations where statins are recommended, we are assuming that aggressive lifestyle modification was already initiated.

Abbreviations – ED: erectile dysfunction; CAC: coronary artery calcium; ASCVD: atherosclerotic cardiovascular disease

Step 1: Calculate the 10-year AHA/ACC atherosclerotic cardiovascular disease risk

Using the AHA/ACC online or mobile risk calculator, a 10-year ASCVD risk score should be calculated, which determines the direction of standard guideline-based recommendations regarding management decisions in the setting of primary prevention. In the majority of patients who fall into either the high (>20%) or low (<5%) risk group, the decision to prescribe intensive lifestyle and pharmacologic intervention or to proceed with standard management [2], respectively, is quite clear. However, for men in the borderline and intermediate risk categories (5%–20%), additional evaluation is required, and these individuals may benefit from ED assessment and further CVD risk stratification. Additionally, individuals who are in the low-risk group (<5%) but have concerning "risk-enhancing factors"—such as ED—may benefit from additional screening.

Step 2: Assess erectile dysfunction status

Following evaluation of ASCVD risk, the presence of ED in low to intermediate risk men may be viewed as a risk-enhancing factor that should trigger downstream advanced risk assessment or treatment modification. The initial clinical evaluation of ED can be completed using a single "*how able are you to keep an erection good enough for sexual intercourse?*" question, which is validated in both research studies and general practice settings [34]. Responses to this question are "*Always able*", "*Usually able*", "*Sometimes able*" and "*Never able*", and thus capture both the presence and severity of ED. Although this is clearly a basic evaluation of erectile function, it has driven much of the literature linking ED and CVD, and therefore may be sufficient for initial CVD risk assessment in clinical practice. Secondary causes of ED such as uncontrolled depression/anxiety, endocrine causes, history of prostate cancer, heavy alcohol consumption, beta-blocker use, or anti-depressant

use [35] should additionally be ruled out, and a vasculogenic nature of the ED should be documented.

Importantly, guidelines suggest that clinicians should counsel symptomatic individuals that they should temporarily refrain from sexual activity, which is a form of strenuous activity and may be associated with acute cardiovascular events [36], until adequate evaluation is completed for example with stress testing.

Step 3: Provide personalized subclinical cardiovascular disease evaluation

Based on a cost analysis by Pastuszak et al., if all men with ED were evaluated for CVD one could identify ~6 million men with unknown CVD risk factors during a 20-year period. Despite the additional costs of testing, if the screening and treatment yields a 20% reduction in CVD outcomes over two decades, 1.1 million CVD outcomes would be avoided and $21.3 billion would be saved [37].

Given its superiority to other biomarkers of subclinical disease in terms of risk prediction and risk reclassification, CAC scoring represents the test of choice for intermediate risk men with ED to guide the physician-patient risk discussion. Additionally, low-risk (<5% 10-year ASCVD risk) men who have ED could also consider clinical CAC scoring, especially when a vasculogenic nature of ED is strongly suspected.

This is in line with the 2017 guideline recommendations of the Society of Cardiovascular Computed Tomography (SCCT) which recommends CAC scoring in the context of shared decision making for additional risk stratification in the 5%–20% risk category, and suggested its use in the low risk (<5%) category when "risk markers" like erectile dysfunction are present [38].

Step 4: Begin a patient–physician discussion regarding appropriate management decisions based on personalized risk status

The preventive management of men with ED should be titrated to CVD risk status. In those individuals with vasculogenic ED who are at low risk for CVD (for example have no evidence of subclinical disease), lifestyle-based interventions are appropriate first-line options. There is strong evidence linking increased physical activity and adherence to a heart-healthy diet with improved erectile function in all men, especially those with metabolic syndrome [39]. In men with ED who are at intermediate risk for CVD, and have a CAC score >0, it is reasonable to engage in a patient–physician discussion about the possible pleiotropic effects of statin therapy. While statin therapy significantly reduces CVD risk, there is also growing evidence linking statin therapy to possible improvement in erectile function [40]. Additionally, according to SCCT guidelines, men with CAC >100 may benefit from aspirin therapy.

Conclusion

Multiple studies assessing the relationship between ED and CVD have established common risk factors and pathophysiologic pathways, the temporal precedence of ED in relation to CVD, and the independent predictive value of ED for clinical CVD, pointing to ED as a potentially useful tool in CVD risk assessment and prevention. While the incremental value of including ED status in global multivariable models for 10-year CVD risk prediction may be unclear, the assessment of ED status in a sequential approach to cardiovascular risk assessment may have significant utility in clinical practice for individual patients, as it serves as a risk-enhancing factor signaling the need for advanced CVD screening in borderline to intermediate risk patients. Importantly, since the incidence of vasculogenic ED in young, otherwise healthy individuals may herald future CVD, ED assessment may help to identify a special group of at-risk individuals who otherwise would not have been selected for advanced risk characterization and targeted disease prevention. While current US and European guidelines do not include ED assessment, we anticipate that future guideline recommendations will adopt a variation of our approach.

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