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Vascular Erectile Dysfunction and Subclinical Cardiovascular Disease

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Abstract

Purpose of review—We review the recent literature on the hypothesized temporal relationship between subclinical cardiovascular disease (CVD), vascular erectile dysfunction (ED), and clinical CVD. In addition, we combine emerging research with expert consensus guidelines such as The Princeton Consensus III to provide a preventive cardiologist's perspective toward an ideal approach to evaluating and managing CVD and ED risk in patients.

Recent findings—Development of ED was found to occur during the progression from subclinical CVD to clinical CVD. A strong association was observed between subclinical CVD as assessed by coronary artery calcium (CAC) and carotid plaque and subsequent ED, providing evidence for the role of subclinical CVD in predicting ED. ED is also identified as a substantial independent risk factor for overt clinical CVD, and ED symptoms may precede CVD symptoms by 2–3 years.

Summary—Given the body of evidence on the relationship between subclinical CVD, ED, and clinical CVD we recommend that all men with vascular ED should undergo cardiovascular risk assessment. We further recommend using CAC scores for advanced risk assessment in patients at

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Compliance with Ethical Guidelines

Conflict of Interest

Zain Gowani, S M Iftekhar Uddin, Mohammadhassan Mirbolouk, Dawar Ayyaz, Kevin L. Billups, Martin Miner, David I. Feldman each declare no potential conflicts of interest.

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Human and Animal Rights and Informed Consent

All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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low-intermediate to intermediate risk (5–20% CVD risk), with risk driving subsequent lifestyle and pharmacologic treatment decisions.

Keywords

erectile dysfunction; cardiovascular disease; subclinical disease; coronary calcium score; risk assessment; Princeton III Consensus

Introduction

Common risk factors shared between cardiovascular disease (CVD) and vascular erectile dysfunction (ED) have piqued interest in their similar pathogenesis, their temporal relationship, and the potential for a diagnosis of vascular ED to predict future coronary events. However, these relationships between ED and CVD have been challenging to elucidate, given their bidirectional relationship. For example, while data suggest ED may predict subclinical/overt CVD, existing CVD is a well-known risk factor for ED [1]. In clinical practice, despite patients with ED being commonly seen by primary care providers, men's health specialists, and cardiologists alike, few national or internationally-endorsed guidelines exist to inform clinicians about the best approach to evaluating and managing cardiovascular risk in ED patients.

The relationship between vascular ED and clinical CVD was originally developed based on a shared clinical risk factor model (including hypertension, smoking, and diabetes) and the presumed overlap in pathophysiological mechanisms including inflammation, endothelial dysfunction, and atherosclerosis [2]. In the early 2000s, longitudinal studies on CVD and ED began to reveal the two-way relationship; they suggested patients with CVD are more likely to have ED and that patients with ED are more likely to develop future CVD, even when adjusted for shared risk factors [3–6]. The Princeton Consensus Conference, an inter-specialty meeting centered on preserving cardiac function and optimizing sexual health, has addressed this issue in multiple iterations; and most recently in 2012, they identified ED as a substantial independent risk factor for CVD [7]. As of 2017, the QRISK group published one of the first risk scores to incorporate ED as an independent risk factor. Using this updated 10-year cardiovascular risk model, they calculated a 25% increased risk for average middle-aged men with ED to suffer an adverse cardiovascular event, including the presence of coronary heart disease, ischemic stroke, or transient ischemic attack [8].

However, the temporal relationship between ED and subclinical CVD progression is far less clear. Is ED a precursor to CVD, or does underlying CVD first manifest as ED? The limited data available on the interaction between these two entities has not allowed researchers to establish the most likely temporal sequence. In addition, the available data is limited by cross-sectional studies correlating symptoms of ED and overt CVD or small prospective cohort studies correlating ED incidence or severity with incident cardiovascular events [3–5,9,10]. While a few studies have revealed a 2–3 year time interval between onset of ED symptoms and CVD symptoms, our research group has been interested in the interrelationships between subclinical CVD (i.e., early atherosclerosis as assessed by various imaging techniques), ED, and overt CVD [1,5,11].

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In this paper we will not only review the recent research updates on the relationship between ED and clinical CVD, but we will also discuss the importance of the data on early subclinical detection of CVD in improving risk stratification in those patients with low or intermediate risk for ED and CVD. We close with a preventive cardiologist's perspective and role in risk assessment, evaluation and management for patients presenting with ED.

Recent studies on the relationship, interaction, and temporality of ED, subclinical CVD, and clinical CVD

The research around temporality of ED and CVD has evolved from simply reporting a high prevalence of ED among CVD patients to further exploring shared histopathologic pathways including chronic inflammation, endothelial dysfunction and atherosclerosis [12, 13]. All of these pathophysiological pathways are closely correlated and are commonly present in patients for decades before CVD becomes clinically evident [14]. Outcome studies showed that not only traditional CVD risk factors could predict ED, but also ED can serve as an independent risk factor for CVD [4, 9].

In 2013, Vlachopoulos et al. published a systematic review of 14 studies that examined the ability of ED to predict CVD events and all-cause mortality. As is common in the field, ED was diagnosed using a variety of methods in the studies included in the review – a common limitation to this line of research. The authors demonstrated that ED patients at intermediate CVD risk (1.51, 1.35–1.70) had a higher relative risk (RR) of CVD events compared with those at high (1.30, 1.20–1.42;p=0.048) or low (0.93, 0.72–1.19;p=0.001) CVD risk [2]. Consistent with previous studies, they also showed an inverse relation between age and risk of developing CVD among patients with ED [2, 10]. The RR of CVD events was higher among younger ED patients, with the RR (on the log scale) decreasing linearly as age increases ($p<0.001$). This data has important implications for using ED in younger men with intermediate CVD risk scores as a potential predictor for overt CVD. This could indicate the potential usefulness of ED as a predictor in young to middle age patients, as well as in the intermediate CVD risk score group who commonly is overlooked regarding early preventive evaluation and management. In fact, intermediate risk patients are the population that benefit most from advanced risk assessment according to the American Heart Association/American College of Cardiology (ACC/AHA) 2013 preventive guidelines [2].

In order to help better evaluate these patients, researchers have considered various ways to better detect asymptomatic patients within this intermediate CV risk group. This has renewed interest in determining the burden of subclinical disease in patients with ED [1]. In particular, there is increasing interest in the coronary artery calcium (CAC) score, which has been endorsed by recent ACC/AHA guidelines for further risk stratification of the intermediate-risk patient and shown to be the single best predictor of cardiovascular risk [15, 16]. However, limited studies to date have examined CAC scores in patients with ED.

In 2005, Chiurlia et al. compared 70 patients with vascular ED assessed by penile Doppler, with 73 healthy matched controls, showing that patients with ED have higher CAC scores compared with healthy subjects [17]. In that study, mean CAC score was found to be 143.3±230 among the ED patients and 32.4±59.2 in the controls. Consistent with this

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finding, in 2013 Jackson et al. showed that among 65 ED patients aged 38–73 years with no cardiac symptoms, the majority of the patients (81%) had calcified plaque in coronary arteries, exceeding expectations based on age ED was evaluated in this study using the Sexual Health Inventory for Men (SHIM) Score [18]. Finally, Yaman et al. categorized 60 patients with ED and 23 patients without ED according to the severity of ED measured by the international index of erectile function (IIEF) and then compared CAC scores. An increasing IIEF score indicates decreasing ED severity. A significant negative correlation between IIEF scores with CAC scores was observed (Pearson correlation, $r = -0.497$; $P < 0.0001$) implying a positive correlation between ED severity and CAC levels [19].

Most recently, a large-scale study was published that attempted to describe the temporal relationship between subclinical CVD and ED as well as further delineate and comment on the shared pathogenesis. Feldman et al. followed 1,862 men from the Multi-Ethnic Study of Atherosclerosis (MESA), all of whom were free of overt CVD and treatment for ED at baseline, for a mean of 9 years. The study authors measured the predictive value of a comprehensive set of cardiovascular tests for the future development of ED (measured nine years after baseline). ED was assessed using the single, standardized Massachusetts Male Aging Study (MMAS) question on ED symptoms. Baseline evaluation of subclinical vascular disease was performed through multiple modalities: cardiac computed tomography, carotid ultrasound, brachial artery flow-mediated dilation, cardiac MRI, and ankle-brachial indices (ABI). The authors then characterized which domain of subclinical vascular disease (tests encompassing subclinical atherosclerosis and vascular stiffness and dysfunction) best correlated with the development of ED, aiming to describe the implications of their results for determining the optimal modality for screening middle-aged men. For the vascular stiffness/dysfunction domain, aortic and carotid distensibility and brachial flow-mediated dilation were measured respectively; for the atherosclerosis domain, coronary artery calcium (CAC), carotid plaque burden, carotid artery thickness, and ABI were evaluated [1].

This study showed that men with higher levels of subclinical atherosclerosis and vascular stiffness/dysfunction at baseline had a higher prevalence of ED 9 years later. Among the tests used to identify subclinical CVD, only CAC>100 and carotid plaque≥2 (odds ratios 1.43 and 1.33 respectively) showed independently significant risk for ED beyond a comprehensive set of cardiovascular risk factors. In addition, MESA participants with abnormalities in multiple subclinical vascular disease domains had the highest prevalence of ED in follow-up. These results are illustrated in Figure 1 [1].

This was the first study to explore temporality in the relationship between ED and subclinical CVD. Development of ED in many individuals appeared to occur sometime during the progression from baseline subclinical vascular disease to clinically overt CVD. A strong association was observed between baseline subclinical disease as assessed by CAC and carotid plaque and subsequent ED, thus establishing the evidence for subclinical CVD predicting ED and highlighting the potential role of atherosclerosis testing – particularly CAC scoring and carotid plaque – in prediction of ED. At the same time, given the strengths of ED as a predictor of future coronary and cerebrovascular events, there appear to be clear clinical implications for the increased evaluation of subclinical CVD for at-risk patients before and once they develop ED [1,20,21].

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Imaging can play a critical role in improving the evaluation and management of men at risk for ED and CVD. Studies have also showed that modifying shared risk factors, including tobacco use, hyperlipidemia, and dietary change/weight loss/exercise in targeted patients is associated with symptomatic improvement in ED [22–26]. Therefore, patients with high burden of subclinical atherosclerosis detected by CAC would benefit from aggressive risk factor modification, potentially helping to delay or prevent the future onset of ED and overt CVD.

Clinical Recommendations from Expert Groups

In addition to what we have reviewed and highlighted as possible interventions to benefit the ED and CVD risk assessment in middle aged men, many expert opinions have been previously published to help guide the evaluation in this population. Past recommendations from these clinicians have favored a more proactive evaluation strategy for patients without clinical CVD presenting with ED. The Princeton Consensus III identifies these patients as having increased CVD risk until their recommended evaluation suggests otherwise [7]. In males over 30 years of age, the Consensus recommends starting the evaluation with a noninvasive assessment, which includes exercise stress testing, ankle brachial indices (ABI), or carotid intima-media thickness (cIMT) evaluation. However, the specific test ordered is ultimately guided by the evaluating primary care physician, men's health expert, or cardiologist [7]. For patients with clinical CVD, the expert consensus recommends assessment of cardiovascular risk associated with sexual activity; elective stress testing for low-risk patients, standardized stress testing for intermediate-risk patients, and cardiology referral for high-risk patients [7].

Since the release of the Princeton Consensus III statement, other reviews by Shah (2016) and Miner (2014) have advocated updated proactive strategies for CVD evaluation in patients presenting with ED to their primary care providers. In additional to selective use of lipoprotein (a) in patients with strong family history of CVD [27], recommendations have expanded the role of various imaging methods focusing predominantly on CAC scoring and exercise testing in these patients with ED [28,29]. Vascular ED was defined through medical history and clinical impression by Miner (2014) [28].

Recommendations for subclinical atherosclerosis risk assessment in patients at risk for erectile dysfunction

Given the body of evidence on the relationship between clinical CVD, subclinical CVD, and ED, we recommend that all men with vascular ED should undergo cardiovascular risk assessment. Additionally, individuals not already considered to be high risk (i.e. 10-year CVD risk >20%) in previous evaluations should also undergo cardiovascular reassessment following a diagnosis of vascular ED. In parallel, a sexual history assessment should be integrated into all cardiovascular risk assessments and may be of increased importance in populations with a lower burden of risk or predilection for more silent coronary disease [2,10,30,31].

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Erectile dysfunction expert groups recommend using traditional risk scores as the first step in cardiovascular risk stratification among men with vascular erectile dysfunction [7] (Table 1). However, these risk scores have certain limitations, such as scores are unable to capture the duration and intensity of exposure to a risk factor. Scores also lack information regarding family history and serum creatinine and testosterone level, which are risk factors that should be taken into account when assessing CVD risk in men with ED [7]. A predominant role is also assigned to chronologic age in score determination, which has the potential of risk underestimation in young adults with vascular ED. To overcome such limitations, risk assessment tools have been identified which could help stratify risk further among younger men with ED. The Princeton III Consensus emphasized the use of certain prognostic tools that are no longer favored, including carotid intima-media thickness (cIMT) and ankle-brachial index (ABI) testing; however appropriate emphasis was placed on lifestyle and physical fitness. Most importantly, stress testing may be useful for assessing cardiorespiratory fitness in men with ED before resuming sexual activity and in detecting silent coronary artery disease among men who have ED and diabetes [7,32]. Stress testing could also allow clinicians to calculate a FIT Treadmill Score, which is a novel fitness score used to quantify all-cause mortality risk [33,34]. Cardiorespiratory fitness level measured by stress testing was found to be associated with improved cardiovascular prognosis in patients with ED [35]. While more evidence is required to support the use of stress testing as a risk stratification tool in asymptomatic individuals, we support its use for many patients with ED when combined with the FIT treadmill scoring for prognostic guidance.

Perspective of the preventive cardiologist

To aid in decision making for clinicians, we present an algorithm for assessing risk among patients with vascular ED (Table 2). Based on the current available evidence and consistent with recent cardiology society guidelines, we recommend CAC scoring over other risk assessment tools including ABI and cIMT for risk stratifying patients with vascular ED who are considered intermediate risk (5%–20% 10-year CVD risk) – consistent with the recent Society of Cardiovascular Computed Tomography (SCCT) guidelines on appropriate use of CAC scoring [36]. CAC can also be used in low risk patients (<5% risk) who have a strong family history of heart disease. This recommendation echoes statements in the Princeton III consensus statement, which states that CAC can be used for further risk assessment in patients with vascular ED [7]. CAC scores, which are considered to be the most sensitive marker for early CVD, are not only higher in men with ED, but also correlate with the severity of ED [19,37,38]. Additionally, stress testing and FIT Treadmill Score can also be used to guide further management in those patients with high clinical suspicion and indeterminate results by CAC scan.

There is a lack of definitive data on the prognosis of patients with vascular ED with a CAC score of zero. However, the 10-year cardiovascular risk in the general population with CAC=0 is very low. Therefore, for patients diagnosed with vascular ED and a CAC=0, we support the predominant focus on lifestyle changes and improving unhealthy cardiovascular habits. For low or intermediate risk patients with a CAC score between 1–100, we support comprehensive lifestyle interventions as the mainstay of management, along with administration of moderate intensity statin therapy. Select young men could also be referred

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to a preventive cardiologist for discussion of pharmacologic options on an individual basis (Table 2). In the general population, individuals who have a CAC score > 100 and are asymptomatic still have high CVD event rates [39]. Therefore, for men diagnosed with vascular ED who have a CAC score > 100, we recommend high-intensity statin, aspirin therapy, and referral to a preventive cardiologist for individualized risk management therapy.

We are intrigued about the possibility of a high CAC score also foreboding the future onset of ED symptoms. Therefore, we cautiously endorse the use of CAC scoring in individuals at the highest risk of developing ED (i.e. patients with metabolic syndrome traits) for the dual purpose of predicting CVD and ED risk and intervening early. Among these patients, those with a strong family history of CVD may also have their serum lipoprotein(a) (Lp(a)) levels assessed [27].

Identification of these patients would allow for aggressive management of other CVD risk factors. Thus, for men with ED or at risk for ED, we recommend a subclinical atherosclerosis risk assessment approach that highlights CAC testing over other risk assessment tools.

Conclusion

Subclinical CVD, ED, and clinical CVD appear to lie on a continuum, with shared risk factors driving progression from subclinical CVD to ED and overt CVD. While the impact of subclinical CVD testing on cardiovascular treatment decisions and outcomes is not quantified, we believe this remains the best risk evaluation tool for ED and future CVD events [20, 23, 34]. In particular, the CAC score – which has been shown to anticipate both symptomatic ED and CVD events – remains an excellent tool for risk stratifying middle-aged men and driving lifestyle and pharmacologic treatment decisions.

The morbidity of CVD is magnified by its predilection for silence. It has been suggested that ED may be the first symptomatic presentation of CVD for many men; however, to date, the data is incomplete. Detection of subclinical vascular disease, early in the shared disease process, holds promise for producing a positive impact on both symptomatic conditions.

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• Of importance

•• Of major importance

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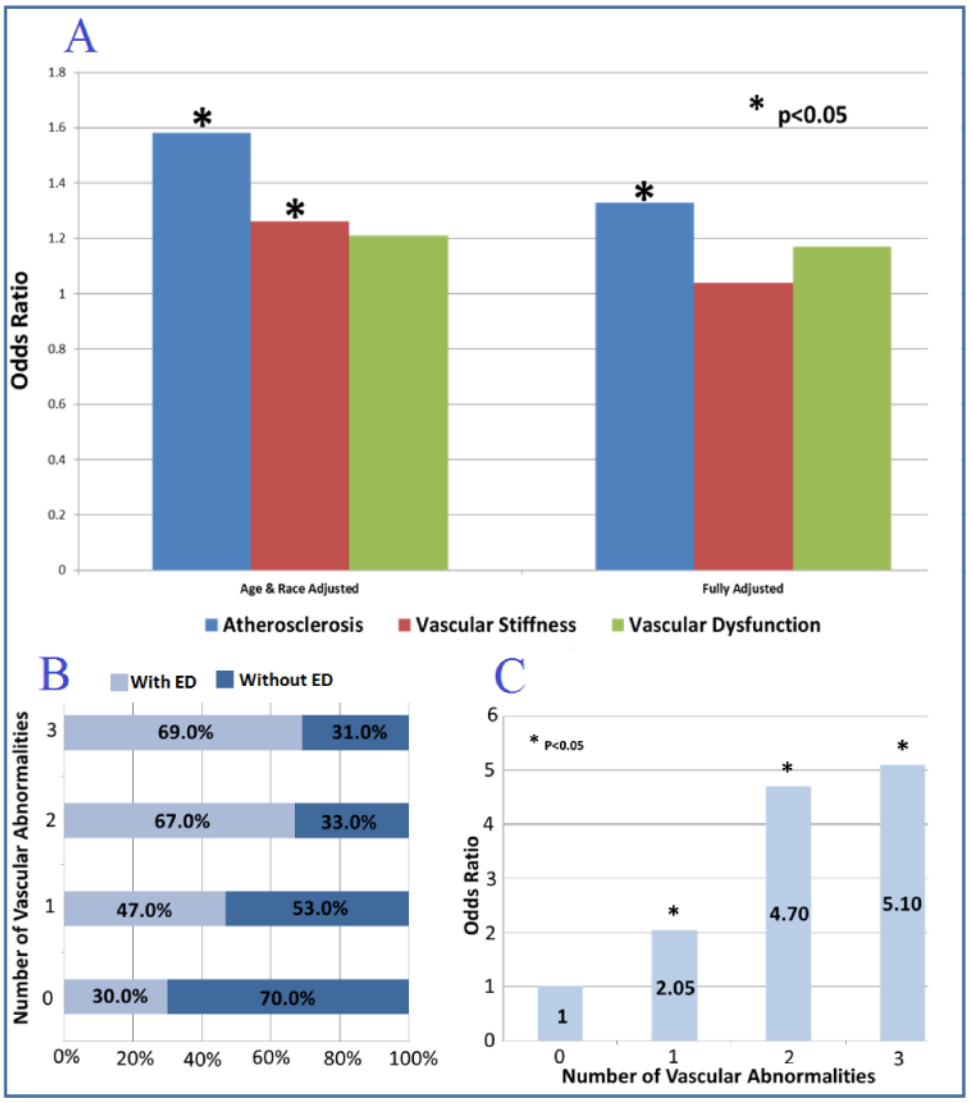

Figure 1. Relationship between ED and Subclinical Vascular Disease

Feldman et al., 2017

(A) Odds ratios for ED, by subclinical disease domain. Adjusted for: age, race, smoking, family history, log triglycerides, LDL, HDL, beta blockers, CES-D, education, BMI, waist circumference, TCA medications, non-TCA medications, anti-psychotic medication, systolic and diastolic blood pressure, hypertension medication, diabetes, hyperlipidemia, lipid-lowering therapy.

(B) Frequency of ED among patients with different number of vascular abnormalities

(C) Odds ratios for ED in patients with different number of vascular abnormalities

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Table 1

Summary of current society guidelines

	American Urologic Association, 2011	American Heart Association, 2012/2013	American College of Cardiology, 2014
Cardiovascular significance of ED as risk factor	Views ED as a CVD risk factor	Views ED as a variable CVD risk factor whose impact needs to be further evaluated	Views ED as a CVD risk factor
Management of comorbid disease and risk factors	Recommend optimal management of comorbid disease and risk factors in all patients	No change in management of comorbid disease and risk factors	Recommend optimal management of comorbid disease and risk factors in all patients
Further cardiovascular risk stratification among ED patients	Risk-stratification per Princeton III Consensus recommendations: **1** Non-invasive imaging for **all patients**, **2** Cardiology referral for **intermediate risk patients**	No recommendations	**1** Non-invasive imaging for **intermediate-risk patients** **2** Cardiology referral for **high-risk patients**
ED treatment timing	Deferral of ED treatment until cardiac condition is stabilized	No recommendations on relative timing of ED and CVD treatment	No recommendations on relative timing of ED and CVD treatment

Abbreviations: ED, erectile dysfunction; CVD, cardiovascular disease

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Table 2

Algorithm for CVD risk assessment and management in asymptomatic men with confirmed vascular ED and no known CVD

10-Year ASCVD risk	CAC score	Next steps
Low risk (<5%)	CAC = 0	Lifestyle modification, may use FIT treadmill score to inform frequency and strength of recommendation
Intermediate risk (5% – 20%)	CAC 1–100	Lifestyle intervention + consider statin and aspirin therapy + may consider referral to cardiologist
	CAC > 100	Refer to cardiologist + statin and aspirin therapy + lifestyle intervention
	CAC > 400	Refer to cardiologist for intensive pharmacological and lifestyle intervention, and assessment for angina/anginal equivalents Further management will be based on results of CAC score, stress testing, or CT Angiography as appropriate
High risk (>20%)		