SEXUAL MEDICINE REVIEWS

Erectile Dysfunction and Subclinical Cardiovascular Disease

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ABSTRACT

Background: An association between erectile dysfunction (ED) and cardiovascular (CV) disease (CVD) has long been recognized, and studies suggest that ED is an independent marker of CVD risk. More significantly, ED is a marker for both obstructive and non-obstructive coronary artery disease (CAD) and may reveal the presence of subclinical CAD in otherwise asymptomatic men.

Aim: To discuss the role of ED as an early marker of subclinical CVD; describe an approach to quantifying that burden; and propose an algorithm for the evaluation and management of CV risk in men 40–60 years of age with vasculogenic ED, those presumed to have the highest risk for a CV event.

Methods: A comprehensive review of original literature and expert consensus documents was conducted and incorporated into clinical recommendations for ED management in the context of CV risk.

Outcomes: Assessment and management of ED may help identify and reduce the risk of future CV events. Initial evaluation should distinguish between vasculogenic ED and ED of other etiologies.

Results: For men with predominantly vasculogenic ED, we recommend that initial CV risk stratification be based on the 2013 American College of Cardiology/American Heart Association atherosclerotic CV disease risk score. Management of men with ED who are at low risk for CVD should focus on risk factor control; men at high risk, including those with CV symptoms, should be referred to a cardiologist. Intermediate-risk men should undergo non-invasive evaluation for subclinical atherosclerosis. Evidence supports use of a prognostic markers, particularly coronary calcium score, to further understand CV risk in men with ED.

Conclusions: Clinicians must assess the presence or absence of ED in every man >40 years of age, especially those men who are asymptomatic for signs and symptoms of CAD. We support CV risk stratification and CVD risk factor reduction in all men with vasculogenic ED. **Miner M, Parish SJ, Billups KL, et al. Erectile Dysfunction and Subclinical Cardiovascular Disease. Sex Med Rev 2018;XX:XXX–XXX.**

Key Words: Erectile Dysfunction; Cardiovascular Risk Stratification; Vasculogenic; American College of Cardiology/American Heart Association Score for Men; Coronary Calcium Score

INTRODUCTION

Cardiovascular (CV) disease (CVD) is the leading cause of death among men in the United States.[1] Erectile dysfunction (ED) is a common problem in men that increases with age and may drive them to seek medical attention in the absence of other CV symptoms.[2] The link between ED and CVD is well established, and the relationship has been characterized by shared risk factors and the potential that ED may predict CVD events.[3–7] However, an emerging paradigm indicates that predominantly vascular ED is an independent marker of CVD risk and may reveal the presence of subclinical vascular disease in a man who otherwise has no expression of coronary artery disease

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(CAD).[8] Therefore the presence of ED may provide an opportunity for CVD risk mitigation in men with unrecognized CVD and clinically silent CAD plaque burden.[6] The purpose of this review is to discuss the role of ED as an early marker of subclinical CVD burden, discuss a means to quantify that burden, and propose an algorithm for the evaluation and treatment of CV risk in men 40−60 years of age with vasculogenic ED, those men presumed at highest risk for a CV event.

The relationship between ED and clinical CVD was originally 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 2-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 identified ED as a substantial independent risk factor for CVD[7]; and the QRISK (a CVD risk algorithm developed in the United Kingdom National Health Service and updated annually) group published one of the first risk scores to incorporate ED as an independent risk factor into their updated 10-year CV risk model, calculating a 25% increased risk for average middle-aged men.[8]

The temporal relationship between ED and subclinical CVD progression is less clear. Is ED a precursor to CVD, or does underlying CVD first manifest as ED? Available data come from cross-sectional studies correlating symptoms of ED and overt CVD or highly limited prospective cohort studies correlating ED incidence or severity with incident CV events.[3−5,9−11] A few studies have revealed a 2- to 3-year time interval between onset of ED symptoms and CVD symptoms.[5] More recent studies have examined the interrelationships among subclinical CVD (ie, early atherosclerosis), ED, and overt CVD (myocardial infarction or cerebrovascular accident).[12,13]

Half of men with sudden CVD events have no previous symptoms of CAD, and between 70% and 89% of sudden cardiac events occur in men.[14−19] ED may be the single warning of this risk of sudden CVD events.[19,20] ED severity has been correlated with atherosclerotic coronary disease burden, and the presence of ED has been independently associated with CVD events.[20,21]

THE TEMPORAL RELATIONSHIP OF ED, SUBCLINICAL CVD, AND CLINICAL CVD

Vlachopoulos et al[2] published a systematic review and meta−analysis demonstrating that ED patients at intermediate CVD risk had a higher relative risk (RR) of CVD events compared with those at low or high CVD risk; for intermediate risk: RR 1.51 (95% CI 1.35−1.70) vs high risk: RR 1.30 (95% CI 1.20−1.42); $P = .048$; and low risk: RR 0.93 (95% CI 0.72−1.19); $P = .001$. Consistent with previous studies, they also showed an inverse relationship between prevalence and CV impact of age of onset on ED.[2,10,11] RR of CVD events was higher among younger ED patients, with log of RR decreasing linearly as age in years increased ($P < .001$).[2,10,11] Three additional meta-analyses expand the relationship among ED, CVD risk, and all-cause mortality. Dong et al[22] examined 12 prospective studies involving more than 36,000 participants, finding that the combined RR for men with ED were 1.48 (95% CI 1.25−1.74) for CVD, 1.46 (95% CI 1.31−1.63) for coronary heart disease, 1.35 (95% CI 1.19−1.54) for stroke, and 1.19 (95% CI 1.05−1.34) for all-cause mortality. Guo et al[23] found a similar pooled adjusted RR of 1.47 (95% CI 1.29−1.66) for CVD events in over 45,000 participants. And lastly, Yamada et al[24] examined the risk in diabetic men vs non-diabetic men with ED in cohort and observational studies. In the observational studies they noted the odds ratio of diabetic men with ED vs without ED for CVD events as 3.39 (95% CI 2.58−4.44), 3.43 (95% CI 2.46−4.77) for coronary heart disease, and 2.63 (95% CI 1.41−4.91) for peripheral vascular disease.

This relationship between ED and CVD risk could indicate the potential usefulness of ED as a predictor in patients within the intermediate CVD risk score group, which commonly consists of middle-aged men, a population that will benefit from further testing according to American College of Cardiology (ACC)/American Heart Association (AHA) 2013 preventive guideline.[25]

There is increasing interest in describing the burden of subclinical CVD in patients with ED.[12] The coronary artery calcium (CAC) score 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 CV risk.[26,27] To date, limited studies have examined CAC scores in patients with ED, yet they reveal that men with ED have higher CAC scores compared with healthy subjects.[28] Consistent with this finding, Jackson[29] showed that among 65 ED patients aged 38−73 years with no cardiac symptoms, 81% of patients had calcified plaque. Finally, Yaman and colleagues[30] 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, implying a positive correlation between ED severity and CAC.[30]

The Multi-Ethnic Study of Atherosclerosis was the first to reveal that subclinical CVD is a predictor of ED.[12] This pivotal finding provided evidence that a CAC score can serve as a disease score and surrogate for an accelerated atherosclerosis process in arteries including penile arteries and vascular ED.[13] This was also the first study to explore temporality in the relationship between ED and subclinical CVD. Development of ED was found 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, *highlighting the potential*

role of atherosclerosis testing—particularly CAC scoring and carotid plaque—in predicting ED and overt CVD.[12] 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 and indications for the evaluation of subclinical CVD within at-risk patients before and once they develop ED[12,31,32] (Figure 1).

Few studies have examined the effect of CV risk factor modification on both ED and CVD, but much of the recent development of knowledge takes place in the men's health domain. Among the shared risk factors, modification of tobacco use, hyperlipidemia, dietary change, weight loss, and exercise in targeted patients has revealed symptomatic improvement in ED.[33–38] A randomized single-blind study of 110 obese men aged 35–55 years, without diabetes, hypertension, or hyperlipidemia, who had an IIEF of 21 or less, assessed the effect of weight loss and increased physical activity on erectile and endothelial function; results showed that after 2 years, body mass index decreased more in the intervention group as did serum concentrations of interleukin 6, and C-reactive protein.[38] The mean IIEF score (SD) in the intervention group improved from 13.9–17 with 17 men in the intervention group normalizing their sexual function.[38] This study suggests that patients who are at high risk need aggressive risk factor modification, which then could improve present ED and delay or prevent the future onset of ED and perhaps overt CAD.

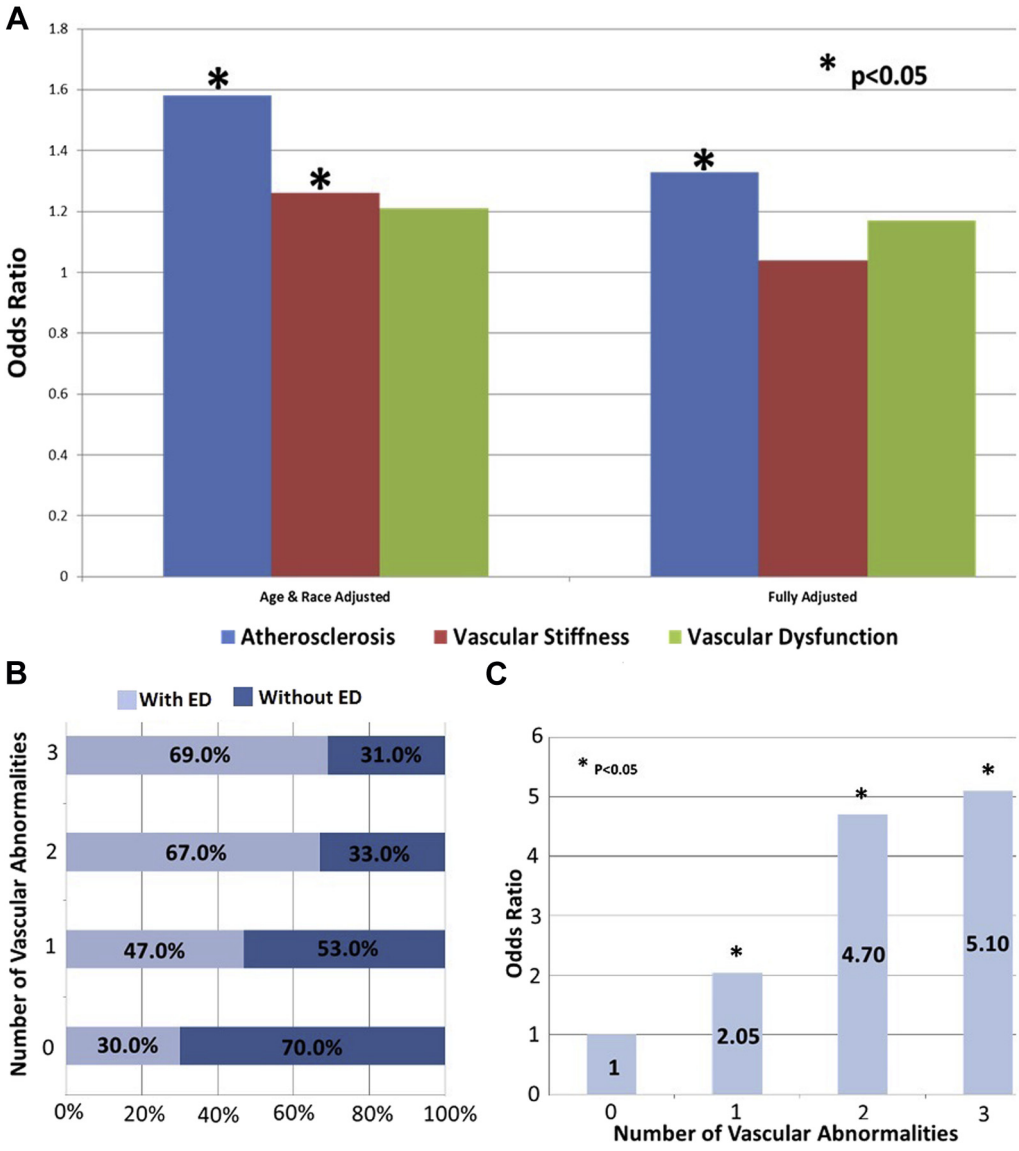

Figure 1. Relationship between erectile dysfunction (ED) and subclinical vascular disease in Multi-Ethnic Study of Atherosclerosis. **A**, Odds ratios for ED, by subclinical disease domain. Adjusted for: age, race, smoking, family history, log triglycerides, low- and high-density lipoprotein cholesterol, beta-blockers, Center for Epidemiologic Studies Depression Scale, education, body mass index, waist circumference, tricyclic antidepressant 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. Adapted.[12]

EVALUATION AND MANAGEMENT OF CV RISK IN MEN WITH ED UTILIZING THE ACC/AHA RISK CALCULATOR: A FOCUS ON IDENTIFICATION OF SUBCLINICAL CAD

Given the relationship between subclinical CVD, ED, and clinical CVD, we recommend that men with predominantly perceived vascular ED should undergo CV risk assessment. Primary vasculogenic ED is characterized by gradual onset and a steady weakening of erectile rigidity and shorter duration of the erection.[7] These changes are evident under most or all circumstances, including the morning erection, nocturnal erection, or sexually stimulated erection.[7] Yet it must always be recognized that even within primary vasculogenic ED, a significant psychological component must be addressed, often with the use of sensate focus therapy.[39,40]

In parallel, a sexual history assessment should be integrated into all CV risk assessments and may be of increased importance in populations with a lower burden of risk (younger men) or predilection for more silent coronary disease (diabetic men) as determined by the presence or absence of comorbidities or age.[41] Thereby, all men should be questioned about their sexual history and functioning as part of the initial assessment of CV risk. Symptomatic men (those with exertional chest pain or shortness of breath) with ED are presumed to have CAD and are therefore at high risk for CVD events and should be referred to cardiology for more advanced testing and potential need for intervention.[41,42]

We recommend evaluation of fasting plasma glucose, serum creatinine, estimated glomerular filtration rate (men with impaired renal function are at greater risk of vasculogenic ED),[43] albumin:creatinine ratio, serum lipids, and assessment of cardiometabolic syndrome, components that may be used to further characterize CV risk.[36,37]

We also recommend measurement of total testosterone levels, particularly for patients who have failed a trial of phosphodiesterase type 5 inhibitors.[41,42] Though the relationship between endogenous testosterone levels and CV morbidity and mortality has not been completely clarified, in a prior meta-analysis, Araujo et al[44] found that low testosterone at enrollment represented a risk factor for overall morbidity and a trend toward increased risk for CV mortality. Based on established guidelines, we recommend considering testosterone therapy for men with total testosterone <10.4 nmol/L (300 ng/dL) who are symptomatic (decreased libido, decreased spontaneous erections, low energy, increased fatigue, or loss of muscle mass and strength).[45] Although there is no worldwide consensus for the biochemical testosterone threshold proposed for the definition of testosterone deficiency, the majority of the andrology societies recognize that testosterone therapy should be offered to symptomatic individuals when the circulating total testosterone level is <8 nmol/L (231 ng/dL).[46,47] There is also general agreement that a total testosterone level >12 nmol/L (346 ng/dL) does not require testosterone repletion.[47] Sexual dysfunction represents the most important determinant for medical evaluation of testosterone deficiency and is related to the most specific symptoms associated with testosterone deficiency.[48,49] Indeed, data from the European Male Aging Study, a population-based survey on more than 3,400 subjects across 8 European centers, recognized that a triad of sexual symptoms (low libido, reduced spontaneous, and sex-related erections) is the only syndrome associated specifically with testosterone deficiency.[50] Similar results have been recently confirmed in a large sample of subjects seeking medical care for sexual dysfunction.[51]

We believe that the 2013 ACC/AHA risk assessment guidelines are an appropriate starting point for CAD risk stratification in younger, middle-aged men with ED or in diabetic men with ED.[42,52] Due to the reliance on a small number of traditional risk factors and the strong reliance of age in the risk estimates, we propose more advanced testing for all men aged 40–60 years with vasculogenic ED, as these patients normally do not score as high risk with the new ACC/AHA risk estimator and likely have significant unaccounted-for risk.[12,27]

The ACC/AHA risk calculator incorporates age, sex, total and high-density lipoprotein cholesterol, smoking, systolic blood pressure, use of antihypertensive medications, and history of diabetes.[25,27] It is vital to note that all CV risk scores have certain limitations and are unable to capture the duration and intensity of exposure to a risk factor.[7] Scores also lack certain risk factors such as family history, serum creatinine, and testosterone levels that could be taken into account in men with ED.[7]

We recommend evaluation for sleep apnea and other chronic sleep disorders in patients diagnosed with ED and especially those men with obesity or testosterone deficiency.[52–55]

After the initial assessment outlined above, the physician will be able to recommend a number of lifestyle changes (ie, diet, exercise, smoking cessation, improved sleep habits) that will contribute to reduction in both CV risk and ED.[52–55] Additionally, the screening may help identify specific CV risk factors that require treatment (ie, diabetes, hypertension, hyperlipidemia, obstructive sleep apnea).[36,37,53–56]

Men who appear to be at high risk for CV events based on atherosclerotic CVD (ASCVD) score >10% may be referred to a cardiologist[41,52] (Figure 2). We suggest that those men not referred and all other men with vasculogenic ED and no overt CVD symptoms undergo further non-invasive evaluation using CAC scoring as the primary diagnostic test to detect subclinical atherosclerosis for the purpose of advanced risk stratification.[41,52,57,58] The 2013 ACC/AHA guidelines recommend CAC for risk stratification (class IIB recommendation) in those in whom risk remains uncertain; citing CAC is the single strongest tool for risk stratification.[25] The 2017 guidelines from the Society of Cardiovascular Computed Tomography recommend CAC scoring for those with ASCVD risk of 5–20%, and also in those with <5% risk with a strong family history of CAD or other strong

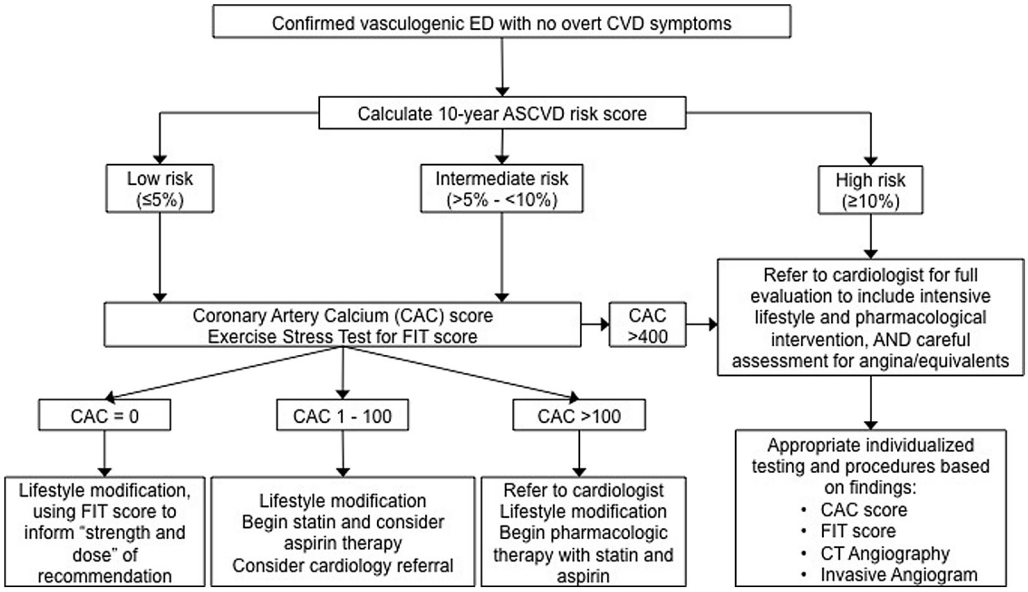

Figure 2. Evaluation and management of cardiovascular (CV) risk in men with vasculogenic erectile dysfunction (ED) but no known CV disease (CVD) recommended for the primary care clinician, cardiologist, and urologist. Symptomatic men are presumed to have CVD and are therefore at high risk for CV events. A thorough history; physical exam (including measures of visceral adiposity); assessment of ED severity and duration; and evaluation of fasting plasma glucose, resting electrocardiogram, serum creatinine (estimated glomerular filtration rate) and albumin:creatinine ratio, and presence or absence of the metabolic syndrome and obstructive sleep apnea may be used to further characterize CV risk. Adapted.[52] ASCVD = atherosclerotic CVD; CAC = coronary artery calcium; CT = computed tomography.

emerging risk factors.[59] And lastly, although the European guidelines on CVD prevention in clinical practice recognize a moderate level of evidence (grade B) for the use of CAC in CVD risk stratification, these guidelines do not specifically comment on the emerging relationship between ED and CVD risk.[60]

Exercise stress testing with calculation of the FIT treadmill score may also have appropriate roles in the evaluation of men with vasculogenic ED.[61] While exercise stress testing does not identify non-flow-limiting lesions, it has been suggested that exercise stress testing may be useful in identifying silent CAD in men with ED and diabetes and many flow-limiting lesions.[58,61] Most importantly, exercise stress testing can help assess an individual's exercise capacity, which is perhaps the strongest predictor of overall mortality after accounting for age.[61]

Given the limitations of other markers for CVD risk assessment and in light of the growing body of evidence supporting the use of CAC as a diagnostic and prognostic tool, we support the use of CAC scoring as the first diagnostic test for further risk assessment in all intermediate-risk men 40−60 years old with confirmed vasculogenic ED without overt CVD symptoms.[57−59]

Imaging of CAC with the latest multi-detector scans takes only a few seconds, and the cost of the test is currently less than $150 in many metropolitan areas in the United States.[58,59]

This expanded use of CAC in both research and clinical 1settings has raised concerns regarding radiation exposure and health care costs. However, with modern technology, the radiation dose associated with CAC is as low as 0.5−1.5 mSv (similar to a bilateral mammogram).[59] With regards to cost, we hope that future analyses will present improved outcomes at lower overall health care costs if CV events are prevented. Indeed, a recent study showed that screening for CVD in men presenting with ED would result in a 20% decrease in CV events (1.1 million CV events) saving $21.3 billion over 20 years.[63] In another cost-effective analysis, Hong et al[64] and others found when using CAC for implementation of statin therapy per the 2013 ACC/AHA guidelines, CAC resulted in increased costs (+$81) and near-equal quality-adjusted life years (+0.01) for an incremental cost-effectiveness ratio of $8,100/quality-adjusted life years compared with a treat-all strategy. In an example of treating 10,000 patients all with statin therapy, the treat-all strategy would theoretically avert 21 ASCVD events, but would add 47,294 person-years of statins. With CAC costs <$150, and higher cost and/or disutility associated with statin therapy, CAC strategy was favored to guide the use of statin therapy in the intermediate-risk group.[64]

This approach treats atherosclerosis as a continuum that can be impacted by many traditional and non-traditional risk factors that result in inflammation, subclinical atherosclerosis, and finally clinically apparent CVD.[65] In fitting with this theory, the presence of subclinical atherosclerosis has been shown to predict future CVD complications and death.[66,67] The growth of technology over the past 2 decades has allowed for direct measurement of subclinical atherosclerosis and therefore further stratification of an individual's risk for a CVD event.[59] We propose the use of CAC score to guide initiation of pharmacotherapy in low-risk and intermediate-risk patients and to guide intensity of therapy in high-risk patients[42,52,57,62,67,68] (Figure 2).

CVD RISK MITIGATION STRATEGIES IN PATIENTS WITH ED

The foremost intervention after a patient has been diagnosed with vasculogenic ED is lifestyle modification in accordance with CV healthy habits.[35–38,67] Guidelines do not recommend the systematic use of statins in patients with ED, based on conflicting results from studies on the local effects of statins on ED.[33,34] We propose that further treatment decisions should be guided by the calculation of the 10-year ASCVD risk score using the 2013 ACC/AHA risk calculator. From this score, patients can be stratified into low risk (ASCVD <5%), intermediate risk (5–10%), and high risk (>10%).[62,68,69] Here, 5–10% is used as an intermediate-risk group to account for the known problem of overestimation with the new risk estimator.[69]

We propose the use of CAC score to guide initiation of pharmacotherapy for intermediate-risk patients and to guide intensity of therapy in high-risk patients. For patients with CAC score 1–100, we advocate for at least an intermediate-dose statin; and for patients with CAC score >100, we advocate for aspirin plus consideration for high-intensity statin therapy.[42,52] For patients initially screened to intermediate risk who have a CAC score >400, we recommend similar evaluation to other high-risk patients (ASCVD >10%).[42,52] In addition to CAC evaluation, we also recommend consideration of exercise stress testing with FIT score for intermediate- and high-risk patients if not referred previously to cardiology. The results of the FIT score can be used as a motivating factor to improve CV health that may also improve ED symptoms.[42,52,61] We suggest that an updated and modified algorithm for CVD risk assessment could play an important role in identification, treatment, and prevention of CVD in younger men (ages 40–60 years) with vasculogenic ED.

CONCLUSION

ED is a common problem in aging men and may serve as a useful clinical hook that will get them into the clinician's office. Given the emerging evidence that ED is an independent risk factor for CVD, men who present to physician offices with ED symptoms provide an opportunity for CV risk mitigation that would otherwise go unrecognized. Vasculogenic ED should be seen as a warning sign of silent or future CVD. The presence of vascular ED can be easily determined with careful questioning of the patient, including an astute query about a man's sexual function. Strategies that aid in evaluation and treatment of ED may also be helpful in managing and improving CV health. In men who are determined to have predominantly vasculogenic ED, CV risk should be evaluated using traditional risk factors included in the 2013 ACC/AHA ASCVD risk estimator, and we also recommend non-invasive evaluation with CAC scoring and potential FIT treadmill scoring. High-risk or symptomatic patients should be referred to a cardiologist for careful assessment that may include further imaging. All men with vasculogenic ED should have significant CV risk factor mitigation.

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