American Journal of Men's Health
2017, Vol. 11(3) 552–563

DOI: 10.1177/1557988316630305
journals.sagepub.com/home/JMH
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The Association of Erectile Dysfunction and Cardiovascular Disease: A Systematic Critical Review

Omer A. Raheem, MD[1], Jeannie J. Su, MD[2], Joel R. Wilson, MD[3], and Tung-Chin Hsieh, MD[1]

Abstract

Despite strong association between erectile dysfunction (ED) and cardiovascular disease (CVD), there is a paucity of clear clinical guidelines detailing when and how to evaluate for ED in patients with known CVD, or vice versa. This systematic review discuss the role of cardiologists and urologists in the characterization of risk and management of CVD in the setting of ED, as well as contrasting the current evaluation of CVD and ED from the standpoint of published consensus statements. A comprehensive literature review utilizing MEDLINE®, the Cochrane Library® Central Search, and the Web of Science was performed to identify all published peer-reviewed articles in the English language describing ED and CVD across various disciplines. There is strong consensus that men with ED should be considered at high risk of CVD. Available risk assessment tools should be used to stratify the coronary risk score in each patient. The 2012 Princeton III Consensus Conference expanded on existing cardiovascular recommendations, proposing an approach to the evaluation and management of cardiovascular risk in men with ED and no known CVD. This systematic review highlights the similarities and differences of the existing clinical guidelines and recommendations regarding assessment and management of ED and CVD, as well as the pathophysiological linkage between ED and CVD, which may permit physicians, including urologists, to perform opportunistic screening and initiate secondary prophylaxis with regard to cardiovascular risk factors, particularly in young, nondiabetic men with ED.

Keywords

erectile dysfunction, cardiovascular disease

Introduction

Erectile dysfunction (ED) is a common problem affecting 15% of men in the age range of 40 to 50 years, 45% of men in their 60s, and 70% of men older than 70 years (Selvin, Burnett, & Platz, 2007). In addition to being a distressing condition itself, ED is thought to be a harbinger of cardiovascular disease (CVD) and mortality. ED and CVD share many common risk factors, including age, hypertension, diabetes, insulin resistance, smoking, increased body mass index (BMI), cholesterol, and lower high-density lipoprotein (HDL; Austoni et al., 2005; Chen et al., 2013; Chew, Bremner, Jamrozik, Earle, & Stuckey, 2008; Corona et al., 2010 Corona, Monami, Boddi, Balzi, et al., 2010,; Mirone et al., 2002; Salem, Mehrsai, Heydari, & Pourmand, 2014; Solomon, Man, Wierzbicki, & Jackson, 2003; Turek, Hastings, Sun, King, & Keenan, 2013). There is a growing body of evidence that ED is a sentinel marker of subclinical CVD and likely precedes symptomatic coronary artery disease (CAD). Studies have reported an increased prevalence of ED in patients with CAD compared with men without CAD (Gazzaruso et al., 2004) as well as an increased risk of CVD in men with ED compared with men without ED (Ponholzer, Temml, Obermayr, Wehrberger, & Madersbacher, 2005). In a retrospective study of 62 men admitted to the hospital for first myocardial infarction (MI), 51.6% of patients were reported to have preexisting ED (Puchalski, Szymanski, Kowalik, Filipiak, & Opolski, 2013). ED has been demonstrated to occur on average 3 to 5 years prior to the cardiovascular event (Baumhakel & Bohm, 2007; Hodges, Kirby, Solanki, O'Donnell, & Brodie, 2007). Given the high prevalence of ED, however, it may not be

[1]University of California, San Diego, Department of Urology, San Diego, CA, USA
[2]Yale School of Medicine, Department of Urology, New Haven, CT, USA
[3]University of California, San Diego, Department of Medicine, Division of Cardiovascular Medicine, San Diego, CA, USA

Corresponding Author:
Tung-Chin Hsieh, MD Department of Urology, UC San Diego Health, 200 West Arbor Drive #8897, San Diego, CA 92103-8897, USA.
Email: tmikehsieh@ucsd.edu

practical to perform a systematic cardiologic screening on every patient with ED. It is thus important to identify who is at increased risk of developing CVD.

There are several hypotheses on the pathophysiology of ED as a sentinel marker of vascular dysfunction. The artery size hypothesis stipulates that ED is an earlier symptom of systemic atherosclerosis (Montorsi et al., 2005). Assuming that atherosclerosis progresses in all major vascular beds at a relatively similar pace, Montorsi et al. (2005) argue that symptoms will manifest earlier in the smaller arterial branches such as the penile artery rather than in the larger vessels of the heart and limbs, which are able to better tolerate the same degree of atherosclerosis or obstruction. In accordance with this hypothesis, Rogers et al. (2010) reported that the degree of stenosis in the internal pudendal arteries was similar to that found in the coronary artery (52% to 65%) and that the average internal pudendal artery vessel diameter was just slightly smaller than the average coronary artery diameter. Another proposed mechanism centers on the development of ED as a result of endothelial cell and smooth muscle dysfunction prior to occlusive disease (Ryu et al., 2013). Vlachopoulos et al. (2006) identified elevated levels of inflammatory and endothelial-prothrombotic markers/mediators in ED patients with and without CAD, inferring that the increased levels of these markers underscore the involvement of endothelial dysfunction in the pathogenesis of ED and the link between ED and CVD. Other potential mechanisms of ED dysfunction are the autonomic imbalance represented as heart rate variability and chronotropic incompetence and dynamic postexercise autonomic dysfunction as independent predictors for adverse CVD outcomes in men with ED (Ioakeimidis et al., 2015; J. Y. Lee, Joo, et al., 2011).

The implications of ED on CAD risk are treated disparately by urologic and cardiovascular societies. In 2012, the Princeton III Consensus Conference, a multispecialty collaborative expert panel, expanded on these recommendations, proposing an approach to the evaluation and management of cardiovascular risk in men with ED and no known CVD (Nehra et al., 2012). The panel "considered all men with ED who are older than 30 years to be at increased CVD risk" and recommended "a thorough noninvasive and, when indicated, invasive evaluation of CVD status" (Nehra et al., 2012). The European Guidelines on CVD prevention in clinical practice state that ED is a marker of CAD but do not outline specific steps to consider once ED is diagnosed (Perk et al., 2012). The joint American College of Cardiology/American Heart Association (ACC/AHA) guideline statement from 2010 regarding the assessment of risk in asymptomatic adults makes no mention of ED in the diagnostic assessment of CAD (Greenland et al., 2010). The joint 2013 ACC/AHA guideline on the assessment of cardiovascular risk mentions ED with the following disclaimer: "The following variables were given consideration as risk predictors but their contribution awaits further consideration at a later time: BMI, waist circumference, lipoprotein (a), left bundle branch block, sleep apnea, ED, systemic lupus erythomatosus, rheumatoid arthritis and physical activity" (Goff et al., 2014). Kalka et al. (2013) evaluated patients with CVD and ED and identified that erection quality was significantly correlated with exercise tolerance, and exercise training had a positive effect on both exercise tolerance and erection quality.

Accurate cardiovascular risk assessment is essential to determining who will benefit from the most aggressive primary prevention strategies. This systematic review aims to discuss the role of the clinicians, cardiologists, and urologists in the characterization and management of cardiovascular risk in the setting of ED.

Research Design and Method

A detailed, comprehensive literature review was performed to identify all published peer-reviewed articles in the English language describing ED and CVD across various disciplines. The search was conducted using the MEDLINE® database, the Cochrane Library® Central Search, and the Web of Science. Initial search terms were ED and CVD. Search results were screened for appropriate studies with particular emphasis placed on clinical and experimental studies as well as review articles. Articles referenced were screened to maximize review and inclusion of pertinent data. While English-language text was not a specific search parameter, only English-language publications were considered. All relevant studies collected were carefully examined to extract relevant data pertaining to ED and CVD for the period between 2000 and 2015.

Results

Evidence Synthesis

Risk Stratification. Both the 2013 joint ACC/AHA guidelines on the assessment of cardiovascular risk and the 2012 Princeton III Consensus recommend the utilization of global risk calculators to estimate risk of atherosclerotic disease (Goff et al., 2014; Jackson et al., 2013). The 2013 joint ACC/AHA introduced a new pooled cohort atherosclerotic CVD risk estimator tool, which considers age, gender, race, HDL, total cholesterol, diabetes, hypertension treatment, smoking status, and systolic blood pressure (Goff et al., 2014). Most calculators, including the pooled cohort risk equations, and the older Framingham Risk Score (FRS), European System Coronary Risk Evaluation,

Prospective Cardiovascular Munster, and Reynolds risk score, estimate the 10-year risk of heart disease or stroke.

Using global risk calculators, patients can be stratified into low (<5% or 10%), intermediate (5% or 10% to 20%), and high (>20%) risk of developing CVD. None of these tools, however, are ideal. For example, the pooled cohort risk equations do not consider other factors like family history and kidney function. Since 2002, the National Cholesterol Education Program Adult Treatment Panel III has considered diabetes as a CAD equivalent.

Despite the increasing evidence linking ED to CVD, none of these calculators include the presence or severity of ED. Ponholzer et al. (2005) calculated the 10-year risk of developing CVD using the FRS in men with varying degrees of ED identified that men with moderate versus severe ED had a 65% ($p < .001$) and 43% ($p = .041$) increased relative risk for developing coronary heart disease or stroke, respectively. One possible point of divergence is whether the presence of ED confers risk independent of these risk factors. One large prospective trial of 1,709 men indicated that while ED is associated with increased incidence of CAD, it did not predict outcomes better than FRS alone (Araujo et al., 2010).

Comparison of the Published Guidelines

Similarities

Electrocardiogram (EKG). The joint ACC/AHA 2010 guideline states that a resting EKG is reasonable tests. EKG may also be considered in asymptomatic adults with and without hypertension or diabetes (Greenland et al., 2010).

Stress testing. Cardiac stress testing is advocated for assessing symptomatic patients with increased risk of CAD. However, it only detects lesions with moderate to severe stenosis (>50% to 70%), whereas risk of plaque rupture (acute coronary syndrome) is relatively independent of stenosis severity. Pooled sensitivity and specificity estimates extracted from large meta-analyses have suggested that exercise stress testing without imaging has a sensitivity and specificity of 73% to 90% and 50% to 74%, respectively, for detecting obstructive coronary atherosclerosis in symptomatic patients (Shamloul et al., 2004). This improves to between 81% and 85% to 95% with either echocardiography imaging or nuclear imaging (Chang et al., 2010 Chang, Chu, Hsu, Chung, et al., 2010; Chiurlia et al., 2005; Shamloul et al., 2004). Patients with stress EKG indicative of ischemia have lower mean cavernous artery peak systolic velocity (PSV) compared with those without ischemic heart disease (PSV = 19.58 ± 3.65 cm/s vs. 36.21 ± 16.3 cm/s; $p = .003$; Shamloul et al., 2004). A PSV of less than 35 cm/second had a sensitivity of 50%, specificity of 100%, positive predictive value of 100%, and negative predictive value of 59.3% in predicting ischemic heart disease with an abnormal EKG (Shamloul et al., 2004).

Biomarkers. Serum biomarkers including high-sensitivity C-reactive protein (hs-CRP), glycosylated hemoglobin test (HgA1c), urinary albumin excretion, and lipoprotein-associated phospholipase A2 level are helpful in assessing vascular risk in asymptomatic patients. Specifically, hs-CRP (Billups et al., 2003; Chang et al., 2010 Chang, Chu, Hsu, Hsiao, et al., 2010; Chiurlia et al., 2005; Nehra et al., 2012; Puchalski et al., 2013; Vlachopoulos et al., 2008; Yao et al., 2012). HgA1c (Weinberg, Eisenberg, Patel, Chertow, & Leppert, 2013), microalbuminuria (Busari, Opadijo, Olarewaju, & Oladosu, 2013), and lipoprotein-associated phospholipase A2 (Otunctemur et al., 2014) have been positively correlated with ED. Similarly, these biomarkers have been reported to be strongly correlated with CAD, hs-CRP (Albert, Glynn, & Ridker, 2003; Kaptoge et al., 2010; Koenig et al., 2003), HgA1c (Selvin et al., 2010; Silbernagel et al., 2011), microalbuminuria (Gazzaruso et al., 2004; Madison et al., 2006, Perkovic et al., 2008), and lipoprotein-associated phospholipase A2 (Jenny et al., 2010).

Carotid intimal media thickness (CIMT). CIMT is a marker of generalized early atherosclerosis, including CAD, and is associated with risk factors for atherosclerotic disease. Increases in CIMT are directly related to an increased risk of MI and stroke in adults older than 65 years of age (O'Leary et al., 1999). Studies have demonstrated that patients with ED have higher CIMT (Goksu et al., 2014; Vlachopoulos et al., 2008). Vlachopoulos et al. (2008) reported that CIMT is independently associated with age ($p = .015$) and ED ($p = .024$). Bocchio et al. (2005) identified that, among men with ED and no clinically evident atherosclerosis, CIMT > 1.0 mm increased the risk of severe ED (odds ratio [*OR*] = 2.6; 95% [confidence interval] CI [1.1, 5.9]) even after controlling for smoking and medications associated with ED. Sexual Health Inventory for Men (SHIM) score has been inversely correlated with CIMT regardless of the presence of metabolic syndrome (Unal et al., 2014). Patients with ED are more likely to have peripheral atherosclerosis (CIMT or femoral IMT ≥ 0.9 mm; 66.4% vs. 36.5%; $p < .001$) with a significantly higher prevalence of carotid plaques (CIMT > 1.3 mm; 25.2% vs. 9.6%; $p < .05$) and an even higher prevalence of femoral plaques (40.3% vs. 11.5%; $p < .001$; Foresta et al., 2008); interestingly, femoral plaques were more prevalent in patients with ED than carotid plaques (40.3% vs. 25.2%; $p < .001$).

Coronary artery calcium score (CACS). Coronary artery calcification can be noninvasively quantified using non-

contrast computerized tomography or electron beam scan. Presence of coronary calcification correlates strongly with presence of additional noncalcified atheroma, and is therefore a surrogate marker for overall coronary atherosclerotic burden. In the Multi-Ethnic Study of Atherosclerosis, the addition of CACS to prediction models based on traditional cardiovascular risk factors led to a significant improvement in risk stratification (Polonsky et al., 2010). Yaman et al. (2008) identified a significant negative correlation between SHIM score and CACS score as determined by multiple detector computed tomography (MDCT; $r = -.497$; $p < .0001$). Chiurlia et al. (2005) reported that patients with ED were at an increased risk of having a volume of coronary calcification in the highest quartile compared with controls without ED (*OR* = 3.68; 95% CI [1.62, 8.34]; $p = .002$) and that coronary artery calcification occurred at a younger age in ED patients than in controls.

Ankle-brachial index (ABI). The ratio of the ankle-systolic to brachial-systolic blood pressure is a simple noninvasive test used to measure lower extremity arterial obstruction and serves as a screening tool for peripheral artery disease. In Polonsky et al. (2009) men with ED had a higher prevalence of having an ABI ≤ 0.9 than those without (32% vs. 16%, $p < .001$), regardless of tobacco use, age, or presence of CAD. Several studies have demonstrated that an ABI ≤ 0.9 is associated with an increased risk of all-cause and cardiovascular mortality even after adjusting for baseline CVD and cardiovascular risk factors (Feringa et al., 2006; Newman, Sutton-Tyrrell, Vogt, & Kuller, 1993). Feringa et al. (2006) reported that after adjusting for clinical risk factors, lower resting ABI values (hazard ratio [HR] per 0.10 lower ABI = 1.08; 95% CI [1.06, 1.10]), lower postexercise ABI values (HR per 0.10 lower ABI = 1.09; 95% CI [1.08, 1.11]), and higher reductions of ABI values over baseline readings (HR per 10% lower ABI = 1.12; 95% CI [1.09, 1.14]) were associated with a higher incidence of mortality).

Differences

Sexual history. The 2012 Princeton III Consensus recommends that a sexual history be performed in all men to assess the presence of ED. Similarly, in 2005, the Minority Health Institute developed an algorithm using ED as a clinical tool to identify men at increased risk of CVD in which they stipulated that all men 25 years and older should be asked about ED regardless of sexual dysfunction complaints (Billups, Bank, Padma-Nathan, Katz, & Williams, 2005). The 2013 joint ACC/AHA guideline on the assessment of cardiovascular risk offers no specific advice regarding more evidence that different arteries develop atherosclerosis at different rates for patients with ED (Goff et al., 2014).

Patients with ED are at higher risk of developing CVD (*OR* = 1.85; 95% CI [1.34, 2.56]; $p < .001$) including hypertension (*OR* = 1.47; 95% CI [1.05, 2.07]; $p = .021$), ischemic heart disease (*OR* = 1.80; 95% CI [1.10, 2.94]; $p = .010$), peripheral artery disease (*OR* = 2.37; 95% CI [0.89, 6.30]; $p = .084$), and stroke (*OR* = 3.30; 95% CI [1.22, 8.88]; $p = .027$; Chew et al., 2008). ED is an efficient predictor of silent CAD in diabetic men (Gazzaruso et al., 2004). Patients with ED have been demonstrated to possess decreased coronary flow reserve (*OR* = 15.4; $p = .02$), which is an early sign of CAD (Borgquist, Gudmundsson, Winter, Nilsson, & Willenheimer, 2006). PSV < 35 has been demonstrated to have a 50% sensitivity and 100% specificity for detecting ischemic heart disease in one small cohort ($N = 40$) of men older than 40 years (Shamloul et al., 2004).

Presence of ED has been demonstrated to be an independent predictor and risk factor for cardiovascular events, cardiovascular-related morality, and all-cause mortality (Araujo et al., 2009; Banks et al., 2013; Chew et al., 2008; Corona et al., 2010 Corona, Monami, Boddi, Cameron-Smith, Fisher, et al., 2010). Several studies identified that incident ED is associated with subsequent cardiovascular events (Dong, Zhang, & Qin, 2011; Guo et al., 2010; Salem et al., 2009; Schouten et al., 2008; Thompson et al., 2005), and patients with lower penile blood flow on Doppler have been identified to have increased risk of major adverse cardiac events (HR = 1.75%; 95% CI [1.10, 2.78]; $p < .05$; Corona et al., 2010 Corona, Monami, Boddi, Cameron-Smith, Lotti, et al., 2010). In a study by Araujo et al. (2009), ED was associated with an increased risk of CVD mortality (HR = 1.43; 95% CI [1.00, 2.05]) and all-cause mortality (HR = 1.26; 95% CI [1.01, 1.57]). A meta-analysis of seven cohort studies with a total of 45,558 subjects reported an increased risk of developing a CVD event (risk ratio [RR] = 1.41; 95% CI [1.22, 1.64]; $p < .001$), all-cause mortality (RR = 1.23; 95% CI [1.02, 1.48]; $p = .034$), and MI (RR = 1.43; 95% CI [1.10, 1.85]; $p = .007$; Guo et al., 2010). Similarly, another meta-analysis by Dong et al. (2011) of 12 prospective cohort studies involving 36,744 subjects demonstrated that men with ED have an increased RR of CVD (RR = 1.48; 95% CI [1.25, 1.74]) including CHD (HR = 1.46; 95% CI [1.31, 1.63]), stroke (HR = 1.35; 95% CI [1.19, 1.54]), and all-cause mortality (HR = 1.19; 95% CI [1.05, 1.34]).

Several studies have reported that the predictive value of ED and CAD is especially apparent in younger men (Inman et al., 2009; Riedner et al., 2011). Inman et al. (2009) identified that the CAD incidence rates (per 1,000 person-years) were increased in men with ED compared with those without ED (age: 40s, 48.52 vs. 0.94; 50s, 27.15 vs. 5.09; 60s, 23.97 vs. 1.72; 70s, 29.63 vs. 23.30); although ED had relatively little impact on the development of

cardiac events in men older than 70 years, it resulted in a nearly 50-fold increase men in their 40s. In addition to presence of ED correlating to presence of CAD, the severity of ED is positively correlated with the severity of CAD (Akilli, Gok, Soylu, & Kayrak, 2007; Bhatia et al., 2013; Kumar et al., 2013; Umul et al., 2014). Imaging studies have identified a positive correlation between angiographic CAD and internal pudendal arterial disease (Rogers et al., 2010). Patients with one-vessel disease have firmer, more frequent erections obtained with less difficulty compared with men with multivessel disease (Greenstein et al., 1997). These findings were confirmed by Canat, Cicek, Atis, Gurbuz, and Caskurlu (2013) who reported that ED was more prevalent in men with multivessel disease and that the severity of ED correlated with the number of occluded vessels (mean International Index of Erectile Function: 24.2 ± 4.3, 20.4 ± 4.9, 20.5 ± 4.2 for single-, two-, three-vessel disease, respectively). Solomon et al. (2003) identified an inverse correlation between Gensini score (to assess the severity of CAD) and International Index of Erectile Function–5 score (r = .17; p = .05). Despite this correlation, patients with mild ED have been demonstrated to possess the same risk factor profile as the general ED population (J. C. Lee, Benard, Carrier, Talwar, & Defoy, 2011).

Abdominal obesity. Central adiposity has been associated with numerous cardiac complications such as coronary heart disease, heart failure, and sudden death. Abdominal obesity increased risk of acute MI (Yusuf et al., 2004). Waist to hip ratio has been demonstrated to be an independent determinant of CAD in ED patients (Chang et al., 2010 Chang, Chu, Hsu, Chung, et al., 2010). After controlling for potential confounders, men with high waist circumference or an obese BMI were at approximately 50% increased odds of having ED compared with men with a low waist circumference (*OR* = 1.51; 95% CI [1.19, 1.92]) or a normal BMI (*OR* = 1.46; 95% CI [1.13, 1.89]) for obese BMI (Janiszewski, Janssen, & Ross, 2009).

Kidney function. The 2012 Princeton III Consensus recommends the collection of serum creatinine (Cr) level (estimated glomerular filtration rate) and albumin to Cr ratio. Chronic kidney disease is a risk factor for the development of CVD (Zhang, Brenner, Koenig, & Rothenbacher, 2010). A study of middle-aged men followed for an average of 14.75 years reported that an elevated serum Cr (>116 micromol/L) increased the risk of stroke (RR = 1.6; 95% CI [1.1, 2.1]) in both normotensive and hypertensive men; men with serum Cr levels above the 97.5th percentile had significant increases in all-cause mortality and overall cardiovascular mortality (Wannamethee, Shaper, & Perry, 1997). In addition to baseline renal function being a strong independent risk factor for adverse cardiac events, worsening renal function in the post-MI period has been demonstrated to increase risk of cardiovascular death (Jose et al., 2006). ED is also highly prevalent in men on hemodialysis and associated with lower Cr levels (Costa, Reis, Pereira, Ponciano, & Oliveira, 2014; Messina et al., 2007). ED has been associated with elevated urinary albumin–Cr ratio (*OR* = 2.2; 95% CI [1.05, 5.01]; p = .037) in type 2 diabetic men (Yu et al., 2010). In addition to elevated Cr and microalbuminuria, the European Society of Cardiology guidelines highlights that anemia can be an additional independent factor for CVD with reduced overall survival (Perk et al., 2012).

Testosterone level. The 2012 Princeton III Consensus recommends that testosterone levels be measured in all men with ED, especially when phosphodiesterase 5 therapy has failed. The American College of Physicians recommends that testosterone levels should be collected in men who are clinically symptomatic (e.g., fatigue, depression, lack of libido, weight gain), which is supported by both the British Society for Sexual Medicine and the International Society for Sexual Medicine. It is worth mentioning that Testosterone Supplemental Therapy (TST) for "hypogonadism" defined by the presence of symptoms and low testosterone level is still off-label use per the Food and Drug Administration. Recent studies have demonstrated an inconsistent relationship between testosterone levels and CVD as well as increased mortality with low serum testosterone (Cao et al., 2010; Malkin et al., 2010; Park, Shim, Lee, Lee, & Lee, 2012). A study by Corona et al. (2010 Corona, Monami, Boddi, Cameron-Smith, Lotti, et al., 2010) reported that after adjustment for age and Chronic Diseases Score, low testosterone (total testosterone [TT] < 8 nmol/L) was significantly associated with cardiovascular death (HR = 7.1; 95% CI [1.8, 28.6]), p < .001) in patients with ED (Corona et al., 2010 Corona, Monami, Boddi, Balzi, et al., 2010). W. C. Lee et al. (2014) identified a significant negative correlation between the TT level and the FRS in men with sexual dysfunction after analysis via multiple linear regression (p = .048). Recently, a study of 802 asymptomatic, intermediate cardiovascular risk patients reported that lower serum testosterone levels were strongly associated with severe (*OR* = 0.78; 95% CI [0.62, 0.86]; p < .001) and moderate ED (*OR* = 0.85; 95% CI [0.72, 0.97]; p < .001; Novo et al., 2015). Other studies have also indicated an increased risk of heart attack, death, and stroke in patients on TST. On March 3, 2015, the Food and Drug Administration recently issued black box warning directives to TST manufacturers because of an increased risk of MI and stroke. Until this risk is further described, TST should be reserved for patients who have hypogonadism and not low testosterone due to

aging. Indeed, patients whom are prescribed TST for clinical and/or biochemical hypogonadism (TT < 300 ng/dL) should be screened for underlying prostate cancer, with digital rectal examination and prostate-specific antigen, breast cancer as well as cardiovascular risks.

Serum uric acid levels. Uric acid is a marker of endothelial dysfunction and associated with CVD (Krishnan & Sokolove, 2011). A meta-analysis of 11 studies identified that an elevated serum uric acid level increased risk of both all-cause mortality (RR = 1.24; 95% CI [1.09, 1.42]) and cardiovascular mortality (RR = 1.37; 95% CI [1.19, 1.57]; Zhao, Huang, Song, & Song, 2013). Interestingly, however, after stratification for gender, all-cause mortality was increased in men but not in women and vice versa for cardiovascular mortality (Zhao et al., 2013). Another prospective study reported that uric acid predicts stroke and all-cause mortality even after adjustment for covariates including blood pressure, *glomerular filtration rate*, and albumin to Cr ratio (Storhaug et al., 2013). However, although plasma uric acid was associated with CVD in subjects with normal glucose metabolism (*OR* = 1.66, 95% CI [1.06, 1.58]), it was not associated with CVD in subjects with impaired glucose metabolism (*OR* = 0.81, 95% CI [0.55, 0.19]; $p = .165$; Wijnands et al., 2014). Uric acid levels have been associated with ED on univariate but not multivariate analysis (Solak et al., 2014). In hypertensive patients, uric acid is an independent determinant of ED (*OR* = 1.76; 95% CI [1.28, 2.41]; $p = .04$). A 1 mg/dL increase in serum uric acid level has been associated with an approximately twofold increase in risk of ED (*OR* = 2.07; 95% CI [1.63, 2.64]; Salem et al., 2014). In one study, a uric acid level of >5.2 mg/dL had 76.2% sensitivity, 43.7% specificity, 62.9% positive, and 59.4% negative predictive value for determining ED (Aribas et al., 2014).

Coronary computed tomography angiography. Multidetector computed tomography–coronary angiography (MDCT-CA) is an anatomical imaging study that has made it possible to more accurately identify calcified and noncalcified coronary lesions. Several trials have identified that MDCT has a sensitivity of 85% to 99%, specificity of 64% to 90%, a positive predictive value of 64% to 91%, and a negative predictive value of 83% to 99% (Budoff et al., 2008; Meijboom et al., 2008; Miller et al., 2008) in detecting coronary lesions compared with invasive coronary angiography. Its high negative predictive value has increased the test's value to rule out CAD in patients with low to intermediate risk of disease and as a second-line test to verify the findings in equivocal functional tests. Studies have demonstrated that MDCT-CA can better detect subclinical coronary artery plaques in men with ED and no evidence of CAD than exercise EKG (Jackson, 2013; Jackson & Padley, 2008). In Umul et al. (2014), of 14 patients with moderate ED, 21.4% and 28.5% had low and moderate CAD risk, respectively, and of the 16 patients with severe ED, 25%, 31.2%, and 25% had moderate, moderately high, and high CAD risk, respectively, as determined by MDCT-CA.

Pulse wave velocity (PWV). This is a measure of vascular stiffness and vascular damage. It is calculated by measuring the distance and transit time between two recording sites. The carotid-femoral PWV has been established as an index of aortic stiffness. A meta-analysis of 17 longitudinal studies by Vlachopoulos, Aznaouridis, and Stefanadis (2010) reported an increase in the pooled relative risk of total cardiovascular events (RR = 2.26; 95% CI [1.89, 2.70]), cardiovascular mortality (RR = 2.06; 95% CI [1.68, 2.42]), and all-cause mortality (RR = 1.90; 95% CI [1.61, 2.24]) for high versus low aortic PWV subjects; a 1 m/s increase in aortic PWV resulted in an age-, sex-, and risk factor–adjusted risk increase of 14%, 15%, and 15% in total cardiovascular events, cardiovascular mortality, and all-cause mortality, respectively. Vlachopoulos et al. (2008) identified that carotid-femoral PWV was significantly elevated in men with ED (8.89 ± 1.38 vs. 8.11 ± 1.10 m/s, $p = .007$) and that ED, along with age and mean BP, was an independent predictor of PWV ($p = .018$). Chang et al. (2010 Chang, Chu, Hsu, Chung, et al., 2010) looked the potential of PWV and several other measures of arterial stiffness as markers to identify cardiovascular risk factors in ED patients; they identified that PWV was positively correlated with age, diabetes duration, hypertension duration, smoking, systolic and diastolic blood pressure, and waist circumference, and negatively correlated with HDL.

Brachial artery flow–mediated dilatation (FMD). FMD of the brachial artery occurs due to endothelial nitric oxide release and is an estimate of endothelial function. Several studies have demonstrated that brachial artery FMD is an independent predictor of cardiovascular events (Green, Jones, Thijssen, Cable, & Atkinson, 2011). Brachial artery FMD has been demonstrated to be impaired in patients with ED versus controls (Bhatia et al., 2013; Chiurlia et al., 2005; Kaiser et al., 2004; Lojanapiwat, Weerusawin, & Kuanprasert, 2009; Vlachopoulos et al., 2008 Yavuzgil et al., 2005). Vlachopoulos et al. (2008) reported on multivariate analysis, after adjusting for confounders, brachial artery FMD (per 1% increase; *OR* = 0.73; 95% CI [0.52, 0.98]; $p = .05$) and fibrinogen (per 1 mg/dL increase; *OR* = 1.109; 95% CI [1.009, 1.029]; $p < .001$) remained independent predictors of presence of ED. Yavuzgil et al. (2005) identified that SHIM scores were weakly correlated with FMD ($r = .25$, $p = .028$) in patients with ED. The predictive value of FMD and

inverse relation between FMD and ED severity were duplicated in Bhatia et al. (2013). A receiver-operating characteristic analysis by Yao et al. (2012) demonstrated that FMD has a high ability to predict ED in young males with low FRS (area under curve = 0.921, $p < .001$). Yao et al. (2012) also identified that a FMD < 10.25% has an 82.8% sensitivity and 100% specificity for the diagnosis of ED. These findings suggest that endothelial dysfunction is the underlying pathophysiology of ED.

Discussion

Although both ED and CVD share pathophysiological mechanisms and often coincide, there is limited agreement about whether ED should trigger further cardiovascular testing or improves the prediction of CVD beyond traditional risk factors. Indeed, utilization of ED as a novel marker of CAD is under intense investigation. ED appears to be a marker of severity of CVD. In a study by Araujo et al. (2009), ED was associated with an increased risk of CVD mortality (HR = 1.43; 95% CI [1.00, 2.05]) and all-cause mortality (HR = 1.26; 95% CI [1.01, 1.57]). In a large meta-analysis of 12 prospective cohort studies constituting a total of 36,744 subjects, Dong et al. (2011) demonstrated that men with ED have an increased RR of CVD (RR = 1.48; 95% CI [1.25, 1.74]) including CHD (HR = 1.46; 95% CI [1.31, 1.63]), stroke (HR = 1.35; 95% CI [1.19, 1.54]), and all-cause mortality (HR = 1.19; 95% CI [1.05, 1.34]). It is less well established whether ED predicts a higher likelihood of future CHD. For example, one retrospective case control study by Hodges et al. (2007), 55% of men had ED prior to presenting with acute coronary syndromes, compared with 43% of age-matched controls. The overall high prevalence of ED in controls leads to low specificity for predicting coronary events. A second retrospective study by Baumhakel and Bohm (2007) suggested ED preceded onset of left ventricular systolic dysfunction by 3.04 ± 7.2 years, a finding limited by low numbers of respondents ($N = 13$). While the findings of this study suggested that left ventricular systolic dysfunction worsened ED, the putative mechanistic connection between the two, endothelial dysfunction, was significantly weakened by the fact that nonischemic forms of ventricular dysfunction were not excluded. Thus, there are only limited retrospective data to suggest that ED can serve as an effective precedent marker for clinical CAD. In a well-designed long-term prospective trial of 1,709 with no prior CAD or diabetes, Araujo et al. (2009) examined whether ED predicts CVD beyond traditional risk factors such as FRS. Araujo et al.'s (2009) study reported ED was associated with CVD incidence controlling for age (HR = 1.42; 95% CI [1.05, 1.90]), age and traditional CVD risk factors (HR = 1.41; 95% CI [1.05, 1.90]), as well as age and FRS (HR = 1.40; 95% CI [1.04, 1.88]). Despite these significant findings, it was concluded that ED did not improve risk assessment above traditional methods (FRS), which clearly questioned the validity of utilizing ED as novel marker for predicting CAD (Araujo et al., 2010). Available risk assessment tools should be used to stratify (low, intermediate, and high) the coronary risk score in each patient. Many ED patients carry an intermediate risk of CAD. Those patients should undergo additional noninvasive tests to "enrich" prevalence of CAD and further stratify risk with the ultimate goal of identifying patients with subclinical CVD. Information from emerging noninvasive tests, such as ultrasound imaging of CIMT, hs-CRP, and MDCT-CA, could be integrated as biomarkers to assess the risk of CAD, but more information is necessary before widespread clinical application is readily accepted. Notwithstanding, the risk of CAD in the overall ED patient population is yet poorly quantified, although it seems to be higher than the general population without ED.

Traditionally, the associated risk factors, such as smoking, hypertension, and hyperlipidemia, should always be assessed in the setting of cardiovascular risk and disease. Furthermore, the 2012 Princeton III Consensus Conference expanded on the existing cardiovascular recommendations, proposing an approach to the evaluation and management of cardiovascular risk in men with ED and no known CVD. The expert panel "considered all men with ED who are older than 30 years to be at increased CVD risk" and recommended "a thorough noninvasive and, when indicated, invasive evaluation of CVD status." This recommendation indeed emphasizes that a question on ED should be included in all cardiovascular risk assessment and be incorporated into risk assessment guidelines. Adding to this, the assessment of testosterone levels and measures of abdominal visceral adiposity should be considered, even though their roles in development of CVD have not been firmly established. In a recent cost-effective analysis, Pastuszak et al. (2015) reported that screening for CVD in men presenting with ED can be a cost-effective intervention for secondary prevention of both CVD and, over the longer term, ED. Together, the reduction in acute CVD and ED treatment cost would save US$28.5 billion over 20 years.

Despite the controversial role of ED in cardiovascular risk prediction and assessment, there may be a critical benefit in evaluating and managing cardiovascular risk in young men with moderate to severe ED and no known history of diabetes, CVD, or CAD as recommended by the 2012 Princeton III Consensus Conference (Nehra et al., 2012). The urologist's role is particularly critical in screening those high-risk patients (younger, moderate to severe ED, nondiabetics, no prior cardiovascular risks) and referring them to cardiology for

further evaluation and assessment. The cardiologist is fundamental in determining and managing cardiovascular risk and disease. As ED is a disease of the endothelium and the vascular system and associated with an increase in cardiovascular risk, cardiologists must recognize the significance of ED and its potential sequelae, which has been highlighted in the 2012 Princeton III Consensus, recommending that a local policy for evaluation be established, which may include noninvasive evaluation including stress tests, biomarkers, and anatomical clarification. Likewise, primary care physicians (PCP) and general practitioner (GP) have an important role in ED and CVD. A continuing medical education program for PCP and GP awareness consisting of four review articles, six research articles, and a live half-day seminar conducted by a GP, urologist, and cardiologist on the cardiovascular implications of ED markedly improved physician knowledge, attitudes, and self-confidence in the diagnosis and treatment of ED (Mas et al., 2011). Such seminars are highly encouraged to increase awareness and knowledge of ED and CVD among these health providers. Although the Princeton consensus did include an expert panelist in urology, the exact role of the urologist remains to be clearly established in the setting of ED and CVD. This can be partly explained by the fact that either patients with cardiovascular risk and disease often seek an opinion from a PCP, GP, or cardiologist, or that urologists are not routinely assessing for clinical or subclinical CVD when encountering ED patients. Study limitation must be acknowledged that although English-language text was not a specific search parameter, only English-language publications were considered.

Conclusion

Several population-based studies have described a link between ED and CVD with similar pathophysiological sequelae of atherosclerosis and endothelial dysfunction. The link between ED and CVD may permit physicians, including urologists, to perform opportunistic screening and initiate secondary prophylaxis with regard to cardiovascular risk factors in men with ED. Notably, there is some degree of variation between cardiologists and other clinicians as far as initial assessment and subsequent treatment. The urologist's involvement in these consensuses, recommendations, and guidelines are highly encouraged, aiming to improve patient quality care and overall health.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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