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PERSPECTIVE

Should patients with erectile dysfunction be evaluated for cardiovascular disease?

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The landmark Massachusetts Male Ageing Study shed new light on the prevalence of erectile dysfunction (ED) and drew attention to ED as a disease of ageing. Over the years, ED has been linked to the development of cardiovascular disease (CVD) in some patients. There is clear evidence that ED and CVD share and have a similar risk factor profile. CVD is one of the most recognizable causes of mortality and early detection coupled with prevention of mortality from CVD has been the prime interest of many researchers. Consequently, there has been a multidisciplinary curiosity regarding the proposal to use ED as a marker for future CVD. In fact, there have been several proposals to use ED as a screening tool for future CVD. We performed a comprehensive search of two main databases—PubMed and Cochrane Library using a combination of keywords such as acute myocardial infarction, coronary artery disease (CAD) and ED. Journal articles from January 2000 to June 2011 were reviewed. We included all articles discussing the relationship between ED and CVD in the English language. All the relevant randomized controlled trials, cohort and retrospective studies, and review articles were included in our overall analysis in an attempt to answer the question whether all patients with ED should be clinically evaluated for CVD. The results showed a link between ED and the development of future CVD in some patients, but ED was not shown to be an independent risk predictor that is any better than the traditional Framingham risk factors. Screening for CVD may, however, be rewarding in younger patients with severe ED and in patients with concurrent CVD risk factors.
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INTRODUCTION

Erectile dysfunction (ED), the persistent inability to achieve or maintain a penile erection sufficient for satisfactory sexual performance,[1] is a clinical condition encountered frequently in the practice of Urology. According to the most recent estimates, ED affects about 150 million men worldwide and more than 50% of men aged 40–70 years in the United States.[2] Traditionally, ED has always been described as an affliction of the old and patients presenting to a urological practice often did not feel the need to report any symptoms, even when prompted. The Massachusetts Male Ageing Study (MMAS) as the first cross-sectional, community-based, random-sample, multidisciplinary epidemiological survey on ED in men in the United States[3] shed more light on the scope of ED. In addition to studies like this, the introduction of oral phosphodiesterase type 5 inhibitors changed the dialog about ED and meant recognizing ED as a treatable disease.[4] Furthermore, new incidence studies began to report ED in younger men than has usually been observed. For example, a cross-sectional analysis of the data from the 2001–2002 National Health and Nutrition Examination Survey which included 2126 adult male participants reported an overall prevalence of ED in men aged $\geqslant$20 years of 18.4% (95% confidence interval (CI): 16.2–20.7).[4] Studies that followed suit began to note the commonalities in the risk factor profile for cardiovascular disease (CVD) and ED. Many postulated that ED sharing so many risk factors in common with CVD could be considered a harbinger for future CVD.[5] Feldman and his colleagues in 2000 examined data from the MMAS looking at ED and coronary risk factors and reported a positive correlation between age and traditional risk factors.[3] In fact, Bohm *et al.*[6] (2010) showed that in high-risk CVD patients—defined by the administration of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker to decrease cardiovascular events—ED predicted cardiovascular morbidity and mortality. As a result, a general interest spanning several disciplines in the medical community was cast on the link between ED and CVD. As a recognized leading cause of death, many proposed that cardiovascular events leading to death could be prevented by preemptively treating patients who present with ED. This review took a systematic look at the last decade from January 2000 to June 2011 to determine whether patients with known ED should be clinically evaluated for CVD.

METHODS

We performed a comprehensive search of two main databases—PubMed and Cochrane Library using a combination of keywords such as acute myocardial infarction, coronary artery disease (CAD) and erectile dysfunction (ED). Journal articles from January 2000 to June 2011 were reviewed. We included all articles discussing the relationship between ED and CVD in the English language. All relevant randomized controlled trials, cohort and retrospective studies, and

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review articles were included in our overall analysis in an attempt to answer the question whether all patients with ED should be clinically evaluated for CVD.

RESULTS

Most of the studies examined were retrospective reviews, some too small to draw any meaningful conclusions. Some of these studies, however, established reasonable statistical association between ED and CVD. This association was found to be feeble in some studies when compared against the association between CVD and other traditional risk factors. Several studies cautioned that in spite of any association that might exist between ED and CVD, ED was not better at predicting future CVD more than the traditional risks factors. While some studies drew the conclusion that ED should be considered an independent risk predictor of cardiovascular events, the validity of these conclusions was not supported in larger well-conducted studies. Two well-executed large prospective studies[7,8] showed the association between ED and CVD, but failed to confirm ED as an independent risk predictor of future cardiovascular events. ED was associated with increased CVD incidence; however, ED was unable to predict those patients who will later on develop CVD better than the routine Framingham risk factors. Risk factors identified in most of the studies to heighten future predictability included ED severity and age. The occurrence of these risk factors in conjunction with ED increased the predictability of future CVD.

The link between ED and CVD

The link between ED and CVD has been postulated both at the pathophysiological and clinical levels. The physiology of sustaining normal erections is a neurovascular phenomenon under the influence of psychological control.[9] This means that the etiology of ED can stem from dysfunctional nerves, vascular insufficiency, hormonal causes or psychological factors. However, vasculogenic etiology (arterial and veno-occlusive combined) is the most implicated cause of ED in the general population.[9] Vasculogenic ED may result from impairment of endothelial-dependent and/or -independent smooth muscle relaxation (functional vascular ED), occlusion of the penile arteries by atherosclerosis (structural vascular ED) or a combination of these two processes.[1] Hence, the endothelium provides the pathophysiological link between ED and CVD because endothelial dysfunction has been established as an important process in the development of atherosclerotic CVD.[10] On the clinical level, many studies have successfully demonstrated that ED and CVD share common etiologies and risk factors.[11] Peripheral arterial disease caused by the gradual deposition of atherosclerotic plaques in the arterial system means limited blood supply to end organs. There is the diffused deposition of these plaques in various arterial beds, but the presentation of symptoms is determined by the degree and percentage of luminal occlusion.[12] Montorsi *et al.*[12] popularized the artery size hypothesis in 2004, claiming that even though atherosclerosis is a diffused process with multivessel involvement, there is differential clinical presentation of symptoms as a consequence of the different sizes of the arteries supplying various end organs. Consequently, a given patient with many risk factors of atherosclerosis is likely to develop ED first followed by cardiac ischemic symptoms because of the smaller size of the cavernosal arteries in comparison to the coronaries. This end organ vascular insufficiency will present clinically as ED, cerebral vascular accident and CAD when the cavernosal, carotid, coronary circulations are affected respectively.[10] In addition, Kaiser *et al.*[13] suggested in their 2004 investigation of endothelial-dependent and -independent vasodilation in men with ED that the penile vascular bed is particularly dependent on nitric oxide for vasodilation of arteries to produce inflow as well as vasodilation of trabeculae smooth muscle of the lacunar spaces to prevent venous outflow, which may both account for the increased susceptibility of the penile vascular bed to deficiencies in the nitric oxide–cyclic guanosine monophosphate vasodilator system. Deficiencies in this system are 'a likely contributor to vascular ED'.

ED and the vascular endothelium

Building on the 'artery size' paradigm, the various portions of the arterial tree are affected at different times and at different rates. According to this paradigm, 50% or more of the arterial lumen is affected before any arterial insufficiency is observed clinically.[10] The size and diameter of the penile arteries cause this part of the arterial tree to be most susceptible and sensitive to the least amount of plaque deposition.[12,14] A small plaque deposition or endothelial disturbance in the penile circulatory system is likely to present with ED symptoms, unlike in the coronary arteries where the burden of achieving 50% luminal occlusion means more plaque deposition and endothelial disturbance.[10,12–14] This usually takes several years to become clinically apparent. Hence, ED is regarded as a sentinel event for future CVD. Six studies that particularly addressed the functionality of the endothelium and/or vascular system are shown in the **Table 1**. Kaiser *et al.*[13] showed that patients with ED and without clinical CVD had a defect in their endothelial-dependent and -independent vasodilation that occurred before the development of other overt functional or structural systemic vascular disease. Kaya *et al.*[15] showed that the endothelial function was impaired in ED patients with no apparent CVD or diabetes mellitus (DM). Endothelial function was measured as a difference in the endothelial-dependent percentage change of brachial artery diameter with flow mediated dilation (FMD) (6.01 ± 2.9 *vs.* 12.3 ± 3.5) and brachial artery response to nitroglycerine (12.8 ± 4.2 *vs.* 17.8 ± 5.2) among the ED and non-ED group.[15] Uslu *et al.*[16] similarly showed that FMD of the brachial artery was significantly decreased in the ED group compared to the controls ($4.1\%\pm3.1\%$ *vs.* $9.7\%\pm3.5\%$; $P<0.001$) and the relationship between ED and FMD was significant ($r=-0.66$, $P<0.001$). Baumhakel *et al.*[17] explored the notion that endothelial dysfunction is common in patients with decreased left ventricular ejection fraction (LVEF), by examining 192 cardiovascular high-risk patients from the Evaluation of Role of Sexual Dysfunction in the Saarland program. LVEF was measured by magnetic resonance imaging, angiography and echocardiography. ED correlated with moderate-to-severe impairment in ejection fraction ($P=0.001$), and symptoms of ED presented 3.04 ± 7.2 years prior to a cardiovascular event ($P=0.005$).[17] Lojanapiwat *et al.*[18] measured the FMD to evaluate endothelial function by comparing the percentage change of brachial arterial diameter after brachial arterial occlusion among ED patients and aged matched control subjects. The percentage change of FMD was $8.7\%\pm1.0\%$ and $5.1\%\pm0.6\%$ ($P=0.007$) in ED patients and controls respectively.[18] Polonsky *et al.*[19] performed a larger and most recent study looking at the relationship of ED and peripheral arterial disease (PAD) as determined by screening ankle-brachial index. The results showed that men with ED were found to have significantly more PAD than men without ED (32% *vs.* 16%, $P<0.01$), with a stepwise increase in the prevalence of PAD with increasing ED severity.[19] Solomon *et al.*[20] convincingly showed that plaque burden in the coronary circulation was correlated to International Index of Erectile Function (IIEF) score. There was

Table 1 Relationship between erectile dysfunction (ED) and early vascular endothelial dysfunction

Author (year)	*Study design*	*No. with/no. without ED*	*Evaluation*	*Intervention*	*Results*
Kaiser *et al.* [13] (2004)	Case–control	30/27	Systemic vascular parameters penile Doppler IIEF	Carotid/brachial artery compliance/ distensibility Aortic pulse wave velocity Coronary calcification Brachial artery vasodilation	Brachial artery FMD (1.3% *vs.* 2.4%, P=0.014) Vasodilation to NTG (13.0% *vs.* 17.8%, P<0.05)
Kaya *et al.* [15] (2006)	Case–control	32/25	Penile Doppler US and IIEF	Endothelial-dependent BFMV and brachial artery response to 0.4 mg NTG	Endothelial BFMV: 6.01±2.9 *vs.* 12.3±3.5 Brachial artery response to NTG: 12.8±4.2 *vs.* 17.8±5.2
Uslu *et al.* [16] (2006)	Case–control	30/25	IIEF and penile Doppler US	Aortic strain and distensibility, endothelial-dependent brachial artery FMD	Aortic strain: 3.7%±2.7% *vs.* 9.5%±3.2% Aortic distensibility: 1.5%±1.0% *vs.* 4.7%±2.9% Brachial artery FMD: 4.1%±3.1% *vs.* 9.7%±3.5%; P<0.001
Baumhakel and Bohm [17] (2007)	Cohort	154/38	IIEF High-risk CVD	MRI or angiography to determine LVEF	Decreased LVEF (EF ⩽40%) associated with ED
Lojanapiwat and Weerusawin [18] (2009)	Case–control	41/38	IIEF-5	Brachial artery FMD	Brachial artery FMD change: 8.7%±1.0% *vs.* 5.1%±0.6%(P=0.007)
Polonsky *et al.* [19] (2009)	Prospective cohort	310/380	IIEF	ABI to screen for PAD	PAD prevalence 32% *vs.* 16%

Abbreviations: ABI, ankle brachial index; BFMV, brachial flow mediated vasodilation; CVD, cardiovascular disease; EF, erectile function; FMD, flow-mediated dilatation; IIEF, International Index of Erectile Function; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; NTG, nitroglycerine; PAD, peripheral arterial disease; US, ultrasonography.

objective ED present in 65% of the 132 men with angiographic coronary disease in this cross-sectional study. The erectile function score correlated with cardiovascular risk factors (r=0.54, P<0.001) and with the atherosclerotic disease burden (r= 0.44, P<0.001) as assessed by Gensini score, even after allowance for drug therapies associated with ED.[20]

Clearly, all of the above studies showed that the endothelial function is impaired in ED patients with no apparent CVD and ED can be the first clinical presentation of subclinical endothelial dysfunction. This led to the conclusion that in most cases, ED could be the first clinical presentation of subclinical endothelial dysfunction prior to the appearance of clinical CVD.

ED concurrent with CVD and/or other CVD risk factors

With several shared risks factors and with ED being considered an immediate result of endothelial dysfunction, some studies argued that the concomitant existence of ED and CVD in some patients should warrant clinical evaluation of these patients (**Table 2**). Feldman and colleagues[3] examined ED and coronary risk factors using data from the MMAS to complement their previous study, which detailed the incidence of ED in the full MMAS sample. In this study, they showed that coronary risk factors could predict ED in a healthy subsample of men from the MMAS free of ED or vascular disease at baseline.[3] Kloner and colleagues[21] in 2003 administered a Sexual Health Inventory for Men Questionnaire to 76 patients with chronic stable CAD in the

Table 2 Association between erectile dysfunction (ED) and other known cardiovascular disease (CVD) risk factors

Author (year)	*Study design*	*Patients (age)*	*ED (%)*	*Risk factor correlate*	*Results*
Feldman *et al.* [3] (2000)	Prospective cohort	513 (40–70)	18	Smoking BMI ⩾28 kg m^{-2}	Baseline smoking almost doubled the likelihood of moderate/severe ED
Kloner *et al.* [21] (2003)	Cohort	76 (40–82)	70	Chronic stable CAD	ED common in patient with chronic stable CAD
Roumeguere *et al.* [22] (2003)	Prospective cohort	315 (35–75)	68.3	Hyperlipidemia	70.6% prevalence of hypercholesterolemia in the ED group
Sesayama *et al.* [23] (2003)	Population	6112 (30–70)	81	CVD Diabetes	65% CVD and DM among patients with severe/ moderate ED
Mittawae *et al.* [24] (2006)	Cohort	800 (28–75)	43.2	Hypertension	Statistical correlation between duration of HTN and ED
Montorsi *et al.* [25] (2006)	Cohort	285 (53.6±8.5)	22–65	Coronary syndrome	Age, multiple vessels and chronic coronary syndrome as opposed to acute predicted ED
Selvin *et al.* [4] (2007)	Cross-sectional	2126 (⩾20)	18.4	Diabetes Hypertension	51.3% prevalence among men in the ED group with DM
Chang *et al.* [26] (2009)	Prospective cohort	141 (54±10.3)	100	Metabolic syndrome	The presence of MS and number of MS components influence the severity of ED
Lee *et al.* [27] (2011)	Randomized control trial	176 (mild ED) 14 537 (database) (18–89)	100	Hypertension, diabetes, dyslipedemias and hypercholesterolemia	The two groups were very similar in terms of risk factors

Abbreviations: CAD, coronary artery disease; DM, diabetes mellitus; HTN, heart disease and hypertension; MS, metabolic syndrome.

outpatient setting to address the question of how often we treat ED in the cardiac patients. There was a 70% ED prevalence in this group suggesting the common nature of ED among men with chronic stable CAD.[21] Roumeguère *et al.*[22] paired 215 patients with ED against 100 patients with no ED. By comparing the prevalence of hypercholesterolemia among these groups showed that HDL-C and TC/HDL-C ratio were significant predictors of ED, and found an increased 10-year coronary heart disease (CHD) risk of 56.6% in the ED group as opposed to 32.6% in the non-ED group ($P<0.05$).[22] A Japanese epidemiological study conducted by Sesayama *et al.*[23] in 2003 collected data from 6112 Japanese male patients from 447 outpatient clinics. There was 81% ED prevalence in the group. ED was noted to be predominant among men with CVD (odds ratio (OR): 2.82; 95% CI: 1.95–4.23, $P<0.0001$) and DM (OR: 2.88; 95% CI: 2.26–3.70, $P<0.0001$). DM, heart disease and hypertension displayed significant correlations with ED with ORs of 2.88, 2.82 and 1.79, respectively.[23] In a large Egyptian population study by Mittawae and colleagues[24] in 2006, the investigators found a 43.2% prevalence of ED in 800 hypertensive patients. Comorbidities and complications described as myocardial infarction, cerebral vascular accident and congestive heart failure were significantly more prominent in ED patients than in non-ED patients ($P<0.05$).[24] Montorsi *et al.*[25] in 2006 investigated the association between ED and CAD by dividing 285 patients into three aged-matched groups based on the severity of acute coronary syndrome and the number of diseased vessels. Severe ED (IIEF<10) was significantly more frequent in the two- and three-vessel disease groups when compared to the one-vessel disease group (31% *vs.* 12.5%, $P<0.01$).[25] Selvin and colleagues,[4] while investigating the risk factors for ED in the United States, performed a cross-sectional analysis of data from The National Health and nutrition examination survey which reported the crude incidence of ED in patients with CVD to be 50.0% (95% CI: 41.7–58.3), while the crude incidence of ED among men with DM was 51.3% (95% CI: 41.9–60.7) and this incidence remained high even after age adjustment.[4] Chang *et al.*[26] divided 141 ED patients in the three groups based on ED severity and investigated the prevalence of metabolic syndrome (MS) among the groups. The prevalence of MS among ED patients was 32.6%. They also reported that significantly lower IIEF scores in patients with MS than in patients without MS (7.6±6.4 *vs.* 11.6±7.4, $P=0.003$) and concluded that the presence of MS among others may influence the severity of ED.[26] Lee *et al.*[27] compared the underlying risks for diseases associated with ED in a population of men with mild ED relative to a general ED clinical trial population and reported interesting patterns. ED duration was 3.5±3.2 (<1–18) *vs.* 4.6±4.7 (<1–45) years. The prevalence of comorbidities associated with ED was reported as hypertension: 26.1% *vs.* 32.8% and DM: 13.6% *vs.* 22.1%. Even though the authors concluded that the groups were similar,[27] the large number of patients in the general ED clinical trial population diluted out the prevalence of these risks factors in that group.

The above studies are confirmatory to the large body of evidence suggesting that ED and CVD share a risk factor profile. Consequently, ED is mostly diagnosed in patients with concurrent comorbidities such as hypertension, hypercholesterolemia, diabetes, chronic coronary artery disease and CVD. The high prevalence of CVD risk factors in ED patients suggests a correlation between ED and CVD.

ED precedes and is associated with CVD

Several studies in the last decade have intricately linked ED to the development of future CVD. Although most of these studies have been retrospective in nature, there have been a few population-based, prospective studies with the same conclusions (**Table 3**). Montorsi *et al.*[28] looked at ED prevalence, time of onset and association with risk factors in 300 consecutive patients with acute chest pain and angiographically documented CAD. The prevalence of ED in these patients was 49%. In the 147 patients with concurrent ED and CAD, ED became clinically evident prior to anginal or non-invasive detection of CAD in 67% of the patients. The reported time interval between the onset of ED and CAD in these patients was 38.8 months (range: 1–168 months).[28] El-Sakka and Morsy[29] investigated a cohort of 303 men with ED. The penile vasculature was assessed using penile Doppler ultrasonography and the digital inflection regidometer. Patients were then referred to a cardiologist for routine laboratory investigation of ischemic heart disease. The results showed that a reduced peak systolic velocity of the cavernous artery is associated with ischemic heart disease (IHD) in patients with mainly arteriogenic ED.[29] Using men from the placebo group in the Prostate Cancer Prevention Trial, Thompson *et al.*[11] made a landmark revelation that ED was a harbinger of cardiovascular clinical events in some patients. These men were evaluated every 3 months for CVD and ED between 1994 and 2003. The 4247 men without ED at baseline were included in the analysis for incident

Table 3 Association between erectile dysfunction (ED) and future cardiovascular disease (CVD)

Author (year)	*Study design*	*Patients (age)*	*ED (%)*	*ED timing/results*
Montorsi *et al.* [28] (2003)	Prospective cohort	300 (33–86)	49	Angina preceded ED in >70% patients
El-Sakka and Morsy [29] (2004)	Cohort	303 (59.8±7.3)	76.2	31.4% of IHD Association between IHD and arterigenic ED Higher grade IHD correlated with decreasing PSV ($P<0.05$)
Thompson *et al.* [11] (2005)	Prospective randomized control trial	4247 (62±6)	65 at 7 years	11% CVE at 5 years in men with incident ED
Min *et al.* [30] (2006)	Prospective cohort	221 (23–88)	54.8	ED patient showed severe CHD (MPS summed stress score >8): 43.0% *vs.* 17.0%
Hodges *et al.* [31] (2007)	Case–control	207 *vs.* 165 (61±9)	66 *vs.* 37	ED may precede CVD by as much as 5 years
Stuckey *et al.* [32] (2007)	Case–control	49 *vs.* 50 (40–70)	50	Standing pulse pressure and flow debt repayment were both lower in the ED group
Ma *et al.* [33] (2008)	Cohort	2306 (54.2±12.7)	26.7	Incidence of CHD higher in ED than non-ED group
Gazzaruso *et al.* [34] (2008)	Prospective cohort	291 (54.8±7)	40.5	61.2% *vs.* 36.4% between ED and non-ED patients in experiencing major adverse cardiac event
Schouten *et al.* [35] (2008)	Population cohort	1248 (50–75)	31.5	11.7% population attributable risk fraction for ED
Chew *et al.* [36] (2010)	Retrospective cohort	2318 (20–89)	100	Men with ED had a higher incidence of atherosclerotic cardiovascular event

Abbreviations: IHD, ischemic heart disease; CHD, coronary heart disease; CVD, cardiovascular disease; CVE, cardiovascular event; MPS, myocardial perfusion single; PSV, peak systolic velocity.

ED and subsequent CVD. Incident ED was associated with subsequent CVD (hazard risk (HR): 1.25; 95% CI: 1.02–1.53, $P=0.04$).[11] In 2006, Min *et al.*[30] looked at the degree of predictability of CHD using ED in a population of men referred for stress testing. The 221 men referred for stress testing were prospectively screened for ED using validated questionnaires. The prevalence of ED was 54.8%, and patients with ED had more severe CHD with an myocardial perfusion single photon emission CT summed stress score of >8 (43.0% *vs.* 17.0%, $P<0.001$) than those without ED.[30] The temporal relationship between ED and CVD was portrayed by Hodges *et al.*[31] in 2007 in a design that included 207 patients with CVD and 165 matched controls. Participants completed several questionnaires to assess for ED and other medical history before and after a cardiac event. ED was reported in 66% of those in the CVD group with a mean duration of 5±5.3 years as opposed to 37% in the control group with a mean duration of 6.6±6.8 years ($P<0.05$). This led to the conclusion that that ED can precede CVD by as much as 5 years.[31] Stuckey *et al.*[32] in 2007 matched 49 men with ED to 50 controls and showed that standing pulse pressure was higher in the ED group (50±1 mmHg *vs.* 43±2 mmHg, $P<0.004$) and a 30 : 15 relative risk ratio which is lower in the ED group (0.97±0.01 *vs.* 1.01±0.01, $P<0.02$). These findings predicted future cardiovascular dysfunction.[32] Ma *et al.*[33] in 2008 examined a cohort of 2306 Chinese men with type II diabetes for diabetic complications over a period of 4 years. There was a 26.7% prevalence of ED at baseline. The incidence of CHD events was higher in men with ED than those without (19.7/1000 person-years, 95% CI: 14.3–25.2 *vs.* 9.5/1000 person-years, 95% CI: 7.4–11.7). They further reported that men who developed CHD events were older, had a higher frequency of ED and microvascular complications as well as longer duration of type II diabetes among others.[33] Gazzaruso *et al.*[34] in 2008 used ED to predict cardiovascular event and death in diabetic patients with angiographically proven asymptomatic CAD. The 291 ED cases with DM II and silent CAD proven *via* angiography were assessed for ED. The difference in the ED prevalence between patients that sustained a major adverse cardiac event and those who did not was 61.2% *vs.* 36.4% ($P=0.001$). Further analysis showed that ED predicted a major adverse cardiac event with a HR of 2.1 (95% CI: 1.6–2.6; $P<0.001$).[34] The Krimpen study by Schouten *et al.*[35] was a longitudinal population-based cohort study which assessed the severity of ED as a risk indicator for CVD. During the average follow-up of 6.3 years, cardiovascular end points were determined in 1248 men without CVD at baseline. There was report of approximately 31% erectile rigidity abnormality (22.8% reduced erectile rigidity and 8.7% severely reduced erectile rigidity). There were a total of 58 cardiac events over the study period and after adjusting for age and calculated Framingham risks scores, a multiple variable Cox proportional hazards model showed HRs of 1.6 (95% CI: 1.2–2.3) for reduced erectile rigidity and 2.6 (95% CI: 1.3–5.2) for severely reduced erectile rigidity in predicting a cardiac event.[35] Chew *et al.*[36] in 2010 used data linked to hospital morbidity and death registrations on a cohort of men to show the role of ED in predicting atherosclerotic CV events subsequent to the manifestation of ED. Standardized incidence rate ratios were used as the main outcomes measure. Of the 1660 men in the cohort without prior atherosclerotic CVD, men with ED had a statistically significant higher incidence of atherosclerotic cardiovascular event (standardized incidence rate ratio: 2.2; 95% CI: 1.9–2.4). Younger age at first manifestation of ED (HR: 1.07; 95% CI: 1.06–1.08) and the presence of comorbidities were all associated with higher HRs for subsequent atherosclerotic events.[36] Speel and colleagues[37] comprehensively evaluated 158 patients with penile pharmaco duplex ultrasonography to determine the penile vascular status of these patients. Using a cuff acceleration time of 100 ms to determine cavernosal arterial insufficiency, and Framingham risks function to determine the 4–12 years of coronary heart disease risk, and extrapolating the results to the Dutch male ageing population, they were able to conclude that men in the age group of 50–59 years with cavernosal arterial insufficiency showed a significantly increased risk to develop coronary heart disease.[37]

Obviously, ED is strongly associated with CVD and the temporal relationship between the ED and the presentation of subsequent CVD has been substantiated in most studies.

ED as an independent risk predictor of CVD

The Framingham risk profile framework has traditionally been used to determine the 10-year CVD risk. Even though there is an opinion that Framingham risk factors were not all inclusive, Framingham risk calculation is still the a recognizable tool in clinical practice. Although ED has been shown in many studies to be associated with CVD, the clinical utility of screening all ED patients for future CVD will be of no value if ED is not deemed an independent risk predictor of future CVD. Several studies reviewed failed to show ED as an independent risk predictor of future CVD (**Table 4**). Ponholzer *et al.*[38] in 2005 studied men participating in a health screening project and calculated the risk of CHD or stroke within 10 years depending only on the severity of ED. Of the 2495 men in the CHD risk cohort, there was a 65% increase in relative risk for the development of CHD within 10 years only in men with moderate/severe ED compared to those without ED.[38] These findings were later confirmed by Salem *et al.*[39] who looked at the severity of ED as a risk predictor for CAD: the 183 men documented CAD and 134 matched controls. They determined the prevalence of ED and the distribution of CAD risks factors among the groups. There was an 88.5% prevalence of ED in the CAD groups compared to 64.2% prevalence in the non-CAD group. They concluded that a significant association existed between ED and CAD; however, only the severity of ED could be considered an independent risk predictor.[39] In a population-based longitudinal study, Inman *et al.*[7] assessed the association between ED and the long-term risk of CAD, specifically looking at the role of age as a potential modifier of this association. They performed biennially screening for ED in a random sample of 1402 community dwelling men with regular sexual partners without baseline CAD. They found that the prevalence of ED was age-related with 2% in the 40–49 age group, 6% in the 50–59 age group and 17% in the 70–79 age group and 39% in men older than 70. By analyzing the CAD incidence densities between the groups, they concluded that ED in younger men is associated with marked increase in the risk of future cardiovascular event, whereas ED in older men is of little prognostic value.[7] Araujo *et al.*[8] in 2010 asked a specific question of whether ED contributes to CVD risk prediction beyond the Framingham risk score. To answer this question, they prospectively looked at 1057 men completely free of CVD and diabetes at study entrance in a population-based study. The average follow-up period was 11.7 years and subjects were followed for ED and CVD. ED was associated with CVD incidence after controlling for age, age and traditional CVD risk factors as well as age and Framingham risk score. They concluded that despite the association between ED and CVD, ED did not significantly improve the prediction of CVD.[8] A prospective study by Ponholzer *et al.*[40] in 2010 used IIEF in 2506 men with a negative cardiac or cerebral vascular disease history. These men were followed for an average of 6.8 years. Men without ED at baseline had 1.9% of a cardiovascular event within this time period as opposed to 2.9% in the ED group. However, in

Table 4 Erectile dysfunction (ED) as an independent risk predictor for cardiovascular disease (CVD)

Author (year)	*Patients (age)*	*Study design*	*Evaluations*	*Results*	*Comments*
Ponholzer *et al.* [38] (2005)	2495 (30–69)	Cohort	IIEF-5 10-year CHD risk estimate using the Framingham risk profile algorithm	CHD within 10 years: 13.2% *vs.* 8.0% for moderate/severe ED *vs.* no ED	Moderate/severe ED is associated with increased risk for CHD within 10 years unlike mild ED
Salem *et al.* [39] (2009)	183 with CAD and 134 without CAD (40–69)	Case–control	Logistic regression analysis to assess the effects of classic risk factors and ED severity on CAD	ED prevalence was 88.5% in the CAD group and 64.2% in non-CAD group Significant association between severe ED and CAD (OR: 2.22; 95% CI: 1.11–6.03; $P<0.05$)	ED associated with CAD, severe ED an independent risk predictor
Inman *et al.* [7] (2009)	1402 (40–79)	Prospective cohort	Brief male sexual function inventory (BMSFI) Biennial screening Incidence densities for CAD calculated	Association between ED and incident CAD declined with age; 48.52 (40–49) *vs.* 27.15 (50–59) *vs.* 23.97 (60–69) *vs.* 29.63 ($\geqslant$70)	ED associated with marked increase in the risk of future cardiovascular event in young men; no prognostic value in older men
Araujo *et al.* [8] (2010)	1057 (40–70)	Prospective population-based	23-item questionnaire on sexual activity CVD: self-report, MMAS linkage to NDI and medical records	261 new cases of CVD ED associated with CVD after controlling for age, FRS, *etc.* ED did not improve prediction for CVD	ED does not improve prediction for CVD beyond the traditional risk factors

Abbreviations: CAD, coronary artery disease; CHD, coronary heart disease; CVD, cardiovascular disease; CVE, cardiovascular event; IHD, ischemic heart disease; MMAS, Massachusetts Male Ageing Study; NDI, National Death Index.

further analysis, it was reported that in contrast to age, hypertension and diabetes, ED was not an independent risk factor for a cardiovascular event (HR: 0.92, 95% CI: 0.53–1.61, $P=0.78$).[40] Miner[41] in 2011 in a systematic review proposed an algorithm to be used to direct the assessment of cardiometabolic risks in patients with ED by classifying these patients into low-, intermediate- and high-risk groups. The key elements used in these risk stratification were Framingham/Score/the Second Princeton Consensus Conference. The author proposed that ED patients in the low-risk category could be substratified based on whether they were younger or older than 60 years.[41] In a similar fashion, the 2010 review on 'Erectile dysfunction and coronary artery disease prediction: evidence-based guidance and consensus' by Jackson *et al.*[42] also suggested in various ways that the severity of ED may be correlated to the severity of CAD, ED may be a better predictor of future CAD in younger men than older men and finally, many patients present with severe CAD in the absence of ED, even though as one might expect owing to the artery-size hypothesis and silent atherosclerotic deposition, that ED should be a prelude to severe CAD.[42]

Even though there is an overwhelming relationship in terms of shared risk factors between ED and CVD with the vascular circulation as the mediator of the two, the above studies conclude that not every patient with ED will benefit from a CVD clinical evaluation. ED is not any better at predicting the occurrence of CVD in every patient beyond those standard risk factors proposed at Framingham. However, ED can be more predictive in younger patients and in those with a severe degree of ED.

CONCLUSION

From a literature review encompassing the last decade, ED presents as part of a ubiquitous vascular process. This conclusion is buttressed by the fact that ED has several risks factors in common with other vascular disease processes. ED, however, tends to present several years before other vascular processes because of the susceptibility of penile arteries to atherosclerotic deposition and/or other vascular pathology owing to their small size when compared to arteries in other vascular beds. Most of the articles reviewed linked ED as a sentinel or harbinger event for future cardiovascular or other vascular events. In spite of the establishment of this correlation, some well-conducted studies referenced in this review[7,8] have also shown that ED is not superior at predicting future CVD than the already established Framingham risk factors. In other words, ED is not an independent risk predictor of future cardiovascular events. However, in the presence of other CVD risk factors and other patient-related factors as most studies have concluded, the predictability of ED for future CVD is better correlated. Patient age, ED severity, duration of ED and the presence of other Framingham risk factors are some of the variables that should guide clinicians when deciding which ED patients should be clinical evaluated or are at risk for future CVD.

The clinical evaluation of patients for CVD is not without cost both to the health-care system and to the patient. Patient anxiety, clinical tests and studies such as comprehensive lipid panels, cardiac panel, stress testing, echocardiography and coronary angiography and various heart scans are a few of the additional costs that will be born by the system. Unlike ED which can be screened by a simple questionnaire by way of the validated Sexual Health Inventory for Men or IIEF score, CVD lacks a parallel simple screening tool. Hence, without a cheap and easy to administer screening tool, not every patient with ED should be evaluated clinically for CVD because of the low predictability of ED for CVD. It might, however, be worthwhile referring younger patients with ED, patients with a host of other cardiovascular risk factors or those with very severe ED to a cardiologist for further evaluation. Thus, our ultimate question of whether patients with ED should be

evaluated clinically for CVD remains a multidimensional consideration by the treating urologist.

COMPETING FINANCIAL INTERESTS

The authors would declare no competing financial interests.

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