REVIEW ARTICLE

IJCP THE INTERNATIONAL JOURNAL OF CLINICAL PRACTICE

The assessment of vascular risk in men with erectile dysfunction: the role of the cardiologist and general physician

G. Jackson,[1] A. Nehra,[2] M. Miner,[3] K. L. Billups,[4,5] A. L. Burnett,[6] J. Buvat,[7] C. C. Carson,[8] G. Cunningham,[9] I. Goldstein,[10] A. T. Guay,[11] G. Hackett,[12] R. A. Kloner,[13] J. B. Kostis,[14] P. Montorsi,[15] M. Ramsey,[16] R. Rosen,[17] R. Sadovsky,[18] A. D. Seftel,[19] R. Shabsigh,[20] C. Vlachopoulos,[21] F. C. W. Wu[22]

SUMMARY

Erectile dysfunction (ED) and cardiovascular disease (CVD) share risk factors and frequently coexist, with endothelial dysfunction believed to be the pathophysiologic link. ED is common, affecting more than 70% of men with known CVD. In addition, clinical studies have demonstrated that ED in men with no known CVD often precedes a CVD event by 2–5 years. ED severity has been correlated with increasing plaque burden in patients with coronary artery disease. ED is an independent marker of increased CVD risk including all-cause and especially CVD mortality, particularly in men aged 30–60 years. Thus, ED identifies a window of opportunity for CVD risk mitigation. We recommend that a thorough history, physical exam (including visceral adiposity), assessment of ED severity and duration and evaluation including fasting plasma glucose, lipids, resting electrocardiogram, family history, lifestyle factors, serum creatinine (estimated glomerular filtration rate) and albumin: creatinine ratio, and determination of the presence or absence of the metabolic syndrome be performed to characterise cardiovascular risk in all men with ED. Assessment of testosterone levels should also be considered and biomarkers may help to further quantify risk, even though their roles in development of CVD have not been firmly established. Finally, we recommend that a question about ED be included in assessment of CVD risk in all men and be added to CVD risk assessment guidelines.

Review criteria

We performed a PubMed search for articles pertinent to relationships between erectile dysfunction (ED) and cardiovascular disease (CVD), peripheral arterial disease, stroke, cardiovascular mortality, or all-cause mortality. The evidence-based consensus presented incorporates these articles, published guidelines and the expertise of the multi-specialty author group.

Message for the clinic

Erectile dysfunction is an independent marker of increased CVD risk, particularly in younger and middle-aged men. A cardiologist or other clinician with relevant expertise plays an important role in evaluating this risk in men with ED, who may have subclinical CVD. Increased recognition of the potential for CVD in men with ED, followed by appropriate preventive or corrective action, can improve and may save lives.

Introduction

Penile engorgement is a dilatory vascular response to sexual stimulation/arousal that requires sufficient arterial blood inflow. Erectile dysfunction (ED) is the persistent inability to achieve and then maintain an erection to permit satisfactory sexual intercourse. Epidemiologic studies suggest that moderate to severe ED affects 5–20% of men worldwide (1). ED shares common risk factors with cardiovascular disease (CVD), especially coronary artery disease (CAD), including age (2), lack of exercise, obesity, smoking, hypercholesterolemia, metabolic syndrome (1), diabetes (3), and hypertension (3). ED and CVD frequently coexist, and a large body of evidence supports ED as a predominantly vascular disease that begins with endothelial dysfunction (4). Low testosterone is often associated with both ED and CVD (5–8), but the relationship between testosterone and CVD is complex and continues to be investigated in ongoing studies.

The authors of this present review are a group of physicians and scientists who share an interest in sexual and cardiovascular medicine. This article discusses the evidence supporting ED as both consequence and harbinger of CVD and specifically discusses the role of the cardiologist in the characterization and management of cardiovascular risk, particularly among younger men. The role of testosterone in erectile function and cardiovascular health, as well as the utility of testosterone replacement therapy (TRT) is also considered.

Endothelial/vascular dysfunction: the ED/CVD common denominator

The endothelium is a single layer of cells that lines the lumen of the blood vessels. It serves as an interface

[1]Department of Cardiology, Guy's and St Thomas' Hospitals London, London, UK
[2]Department of Urology, Mayo Clinic, Rochester, MN, USA
[3]Family Medicine and Urology, Warren Alpert School of Medicine, Brown University, Providence, RI, USA
[4]Department of Urology, University of Minnesota, Minneapolis, MN, USA
[5]The James Buchanan Brady Urologiocal Institute, The Johns Hopkins Hospital, Baltimore, MD, USA
[6]Department of Urology, Cellular and Molecular Medicine, The James Buchanan Brady Urological Institute, The Johns Hopkins Hospital, Baltimore, MD, USA
[7]Centre d'Etude et de Traitement de la Pathologie de l'Appareil Reproducteur et de la Psychosomatique, Lille, France
[8]Department of Urology, University of North Carolina, Chapel Hill, NC, USA
[9]Departments of Medicine and Molecular & Cellular Biology, Baylor College of Medicine and St. Luke's Episcopal Hospital, Houston, TX, USA
[10]Department of Sexual Medicine, Alvarado Hospital, San Diego, CA, USA
[11]Center for Sexual Function/ Endocrinology, Lahey Clinic Medical Center, Peabody, MA and Department of Medicine, Tufts University School of Medicine, Boston, MA, USA
[12]Departments of Sexual Medicine, Good Hope Hospital, Birmingham, UK
[13]Research Heart Institute, Good Samaritan Hospital, Los Angeles, CA, USA and Keck School of Medicine at the University of Southern

California, Los Angeles, CA, USA
[14]Cardiovascular Institute, UMDNJ-Robert Wood Johnson Medical School, New Brunswick, NJ, USA
[15]2nd Department of Invasive Cardiology, Department of Cardiovascular Sciences, University of Milan Centro Cardiologico Monzino, IRCCS, Milan, Italy
[16]Complete Healthcare Communications, Inc., Chadds Ford, PA, USA
[17]New England Research Institutes, Inc., Watertown, MA, USA
[18]Family Medicine, SUNY Downstate Medical Center, Brooklyn, NY, USA
[19]Division of Urology, UMDNJ-Robert Wood Johnson Medical School and Cooper University Hospital, Camden, NJ, USA
[20]Division of Urology, Maimonides Medical Center, Brooklyn, NY, USA and Department of Urology, Cornell University, New York, NY, USA
[21]1st Department of Cardiology, Athens Medical School, Athens, Greece
[22]Department of Medicine and Endocrinology, Andrology Research Unit, Developmental & Regenerative Biomedicine Research Group, The University of Manchester, Manchester Academic Health Science Centre, Manchester Royal Infirmary, Manchester, UK

Correspondence to:
Graham Jackson, MD,
Guy's and St Thomas' Hospitals London
Ste 301 London Bridge Hospital, 27 Tooley Street, London, SE1 2PR, UK
Tel.: +44 2074075887
Fax: +44 2073577408
Email: gjcardiol@talk21.com

Disclosures
Full disclosures are found in Appendix A1.

between blood components and vascular tissues and regulates vascular tone, coagulation, and inflammation (9). The endothelium, which responds to shear stress, produces and responds to multiple signalling molecules, most notably nitric oxide (NO). Endothelial NO possesses antiatherogenic, antithrombotic, and anti-inflammatory properties and promotes vasodilation of the vascular smooth muscle (4,10). Cardiovascular risk factors including dyslipidemia, hypertension, and diabetes are associated with endothelial dysfunction, which is characterised by impaired vasodilation, reduced production of NO, and increased permeability to plasma constituents including low-density lipoproteins. These events cause vasoconstriction, platelet aggregation, and leucocyte adhesion (4,11). Impaired endothelial function is an independent predictor of cardiovascular events (12–14).

Erectile dysfunction may be classified as predominantly psychogenic, organic, or mixed. Most organic ED is vascular in nature, and endothelial dysfunction is believed to be the aetiologic link between CVD and vasculogenic ED (15). Because decreased penile vascular flow may reflect underlying endothelial dysfunction (16), penile blood flow has been suggested as an additional diagnostic test to identify ED patients at risk for CVD (17). Decreased penile blood flow appears to be sensitive enough to correlate with silent coronary ischaemia before overt manifestations of CAD (18). Furthermore, reductions in penile blood flow in both the flaccid state or during stimulation with vasodilators have been associated with an increased risk of a major cardiovascular event (19). Although the literature strongly supports an association between ED and endothelial dysfunction, mechanistic studies have not been performed. Hence, the possibility that these conditions result from a common disease, rather than a cause-and-effect relationship, cannot be ruled out.

A number of studies have demonstrated that endothelial dysfunction leading to ED is rarely limited to the penile vessels. Kaiser et al. reported that patients with ED but without overt systemic vascular disease had impairments in peripheral endothelium-dependent and -independent vasodilation in the absence of traditional cardiovascular risk factors (20). There was also a significant relationship between the number of circulating endothelial microparticles and the severity of ED in diabetic men (21). In men with type 2 diabetes and ED, reductions in blood pressure and platelet aggregation in response to intravenous L-arginine were attenuated compared with those without ED (22). Endothelial cell activation is an important early manifestation of the atherosclerotic process. Bocchio et al. (23) studied endothelin-1, intercellular adhesion molecules, soluble cell adhesion molecules and P-selectin in men with and without ED. They found that these products were increased in the blood of men with ED, even before penile blood flow was reduced. Vlachopoulos et al. (24) reported that presence and severity of ED was associated with markers and mediators of subclinical inflammation [e.g. high-sensitivity C-reactive protein (hsCRP), cytokines] and endothelial-prothrombotic activation (e.g. von Willebrand Factor plasminogen activator inhibitor-1, fibrinogen) in men with and without CAD. Additional emerging independent markers of vasculogenic ED presence and severity include endothelial cell-derived factors that participate in the regulation of corporal muscle tone (e.g. endothelin-1, angiotensin II, C natriuretic peptide, asymmetric dimethyl-arginine) or indicate increased endothelial cell damage or repair (e.g. endothelin-1, monocyte oxidative activity, endothelial microparticles, endothelial progenitor cells) (25). Despite ample published support for endothelial dysfunction as a pathophysiologic link between CVD and vasculogenic ED, the lack of a simple, cost-effective, sensitive, and specific method of assessment limits the utility of endothelial function as a predictor of cardiovascular events.

ED as a predictor of vascular disease, cardiovascular mortality, and all-cause mortality

Men with known CVD (26), hypertension (27) or type II diabetes (3,28) have an ED prevalence of approximately 70%. It follows that clinical enquiries about sexual function should be part of the overall evaluation of cardiac patients and be integral to evidence-based guidelines.

Although large-scale, population-based studies evaluating the incidence of asymptomatic CVD in patients with ED have not been performed, studies in men with clinically evident CVD have confirmed that ED is an independent marker of increased CVD risk (29–34) and commonly precedes clinical CAD (26,35–38), peripheral arterial disease (PAD) (39) and stroke (36). The artery-size hypothesis (40) may help explain why patients with CAD frequently report ED before CAD detection. Because the lumen of the penile arteries (1–2 mm) is considerably smaller than that of the coronary (3–4 mm), carotid (5–7 mm), and femoral (6–8 mm) arteries, endothelial dysfunction or plaque burden that significantly impairs circulation in the penile arteries may be associated with subclinical plaque disease of the larger vessels. Thus, atherosclerosis sufficient to trigger ED may not be sufficient to cause

Table 1 Artery size and atherothrombosis. A significant restriction to flow in the penile arteries may be subclinical in larger vessels (40)

Artery	Diameter (mm)	Clinical event
Penile	1–2	ED
Coronary	3–4	Ischaemic heart disease
Carotid	5–7	TIA/stroke
Femoral	6–8	Claudication

ED, erectile dysfunction; TIA, transient ischaemic attack.

Table 2 Relative risks for men with ED vs. no ED (44)

	Relative risk	95% Confidence interval	p-Value
Overall CVD	1.48	1.25–1.74	< 0.001
CAD	1.46	1.31–1.63	< 0.001
Stroke	1.35	1.19–1.54	< 0.001
All-cause mortality	1.19	1.05–1.34	0.005

CAD, coronary artery disease; CVD, cardiovascular disease; ED, erectile dysfunction.

ischaemic symptoms in other vascular beds (Table 1). This concept has particular prognostic importance in light of evidence that many myocardial infarctions (MIs) result from rupture of non-obstructive, lipid-rich atherosclerotic plaques (41).

Several studies suggest that ED has a predictive value for cardiovascular events that is comparable to or better than traditional risk factors. For example, in a population-based study of 1709 men aged 40–70 years, multivariate-adjusted analysis showed that moderate or complete ED was associated with hazard ratios (HRs) of 1.26 (95% CI, 1.01–1.57) for all-cause mortality and 1.43 (95% CI, 1.00–2.05) for CVD mortality (42). Similarly, hypertension was associated with HRs of 1.43 (95% CI, 1.15–1.78) and 1.43 (95% CI, 1.00–2.05), respectively. In multivariate-adjusted analyses of data obtained from men enrolled in the Prostate Cancer Prevention Trial, incident ED was associated with an HR for cardiovascular events [1.27 (95% CI, 1.05–1.55)] that was similar to those for smoking and family history of MI (43). Among 1549 men with known CVD who participated in the ONTARGET/TRANSCEND trial, ED was significantly predictive of all-cause death and a composite of cardiovascular death, MI, stroke, and hospitalisation for heart failure after adjustment for confounding characteristics (29). A meta-analysis of 12 prospective studies involving 36,744 men (Table 2) confirmed a statistically increased overall risk for CVD, CAD risk, stroke risk and increase in all-cause mortality in men with ED and no cardiac symptoms (44). In this study and a study of men with known CVD (33), ED was found to be an independent marker for cardiovascular events and all-cause mortality additional to conventional risk factors.

Results of three different studies suggest that the predictive strength of ED for CVD events is stronger in younger than in older men. Data from the Olmstead County Study demonstrated that ED in men 40–49 years of age was far more predictive of CAD than ED in older men (Table 3) (45). Younger age (20–29 and 30–39 years age groups) at first manifestation of ED also increased predictive value for cardiovascular events sevenfold in a retrospective study by Chew et al. (46). Most recently, a case–control study involving 242 men (mean age, 58 years) referred for elective coronary angiography showed that men < 60 years with CAD were significantly more likely to have ED than those without CAD. CAD was not associated with increased likelihood of ED in men ≥ 60 years (47). These data support ED as a powerful marker of cardiovascular risk in men in their 3rd, 4th, 5th and 6th decades, with markedly weakened prognostic potential in older men.

Although the aforementioned studies provide ample support for ED as a predictor of CVD events in younger and middle-aged men, only one study has assessed the potential of ED to improve CVD prediction beyond traditional risk factors. In a population-based study of men 40–70 years of age, addition of ED status to the Framingham Risk Score (FRS) in a multivariate statistical model resulted in reclassification of 5 of 78 (6.4%) low-risk patients to intermediate risk (31). However, the net reclassification improvement (3.1%) for ED was not statistically significant. Addition of ED to other risk calculations or templates has not been performed.

Temporal relationship between onset of ED symptoms and clinical CVD

Several reports have shown that ED symptoms are likely to precede cardiovascular events, particularly CAD. Montorsi et al. found that 49% of 300 consecutive men with acute chest pain (admitted to coronary care) and angiographically confirmed CAD (i.e. acute coronary syndromes) had ED, with 67% of those men reporting having experienced ED symptoms before CAD symptoms (48). This observation supports the artery-size hypothesis of subclinical but vulnerable coronary plaque being predicted by ED prior to rupture. The mean time interval

Table 3 Age-stratified associations between erectile dysfunction and incident coronary artery disease (45)

			Unadjusted		Comorbidity Adjusted*	
Age (year)	No. of CAD Events	Total Person-Years	HR (95% CI)	p-Value	HR (95% CI)	p-Value
40–49	21	2655	2.7 (0.9–8.1)	0.08	2.1 (0.7–6.4)	0.19
50–59	33	2882	1.3 (0.5–3.1)	0.62	1.1 (0.5–2.8)	0.79
60–69	57	1834	1.5 (0.9–2.6)	0.15	1.4 (0.8–2.4)	0.22
≥ 70	43	904	0.7 (0.3–1.2)	0.19	0.6 (0.3–1.2)	0.17

*Adjusted for diabetes, hypertension, history of smoking, or body mass index ≥ 30. CAD, coronary artery disease; CI, confidence interval; HR, hazard ratio. Reproduced with permission from reference (45).

between the onset of ED and the acute event was 38.8 months. Among chronic coronary syndrome patients with ED who enrolled in the COBRA (COmparison of Balloon vs. Rotational Angioplasty) trial, onset of sexual dysfunction occurred before CAD onset in 93%, with a mean time interval of 24 months (35). Among 192 cardiovascular high-risk patients in the Evaluation of Role of Sexual Dysfunction in the Saarland (EROSS) Program, left ventricular dysfunction was an independent risk factor for ED independent of heart failure symptoms. Moreover, symptoms of ED appeared an average of 3 years before the cardiovascular event (49). Finally, in a UK general practice study of men with CVD who attended cardiovascular rehabilitation programmes, 66% had ED, with a mean patient-reported ED duration of 5 years (50). Taken together, these data suggest that ED is an early marker of generalised ischaemic CVD and that a 2- to 5-year window of opportunity exists for mitigation of cardiovascular events in these men.

Cardiovascular risk assessment in men with ED

If one accepts that ED precedes CVD, then determination of cardiovascular risk, especially in the younger patient with ED is vital, as is identification of opportunities for early preventive intervention. A large number of cardiovascular events derive from this group but at present ED is neither routinely asked about nor formally incorporated in any CVD risk reduction strategy. The FRS (51) is helpful for estimating the likelihood of subclinical atherosclerosis as is the European Society of Cardiology (ESC) HEART SCORE (www.heartscore.org) and QRISK (52). We recommend that a question about ED be included in all CVD risk assessment performed in men and be added to all CVD risk assessment guidelines. The 2012 ESC guidelines on CVD prevention in clinical practice recommend that all men with ED undergo medical assessment, including risk stratification and risk management (53). We recommend that a thorough history, physical exam (including measures of visceral adiposity), assessment of ED severity and duration, and evaluation of fasting plasma glucose, lipids, resting electrocardiogram, family history, lifestyle factors, serum creatinine (estimated glomerular filtration rate) and albumin:creatinine ratio, and presence or absence of the metabolic syndrome be used to further characterise cardiovascular risk in all men with ED.

Evidence also supports ED severity as an important component of cardiovascular risk assessment. Greenstein et al. first reported a significant correlation between erectile function and the number of coronary vessels involved in ischaemic heart disease (54). Patients with single-vessel disease had more frequent and firmer erections with fewer difficulties in achieving an erection than men with multivessel disease. Solomon et al. later reported ED [International Index of Erectile Function (IIEF) score < 21] in 65% of 132 men undergoing coronary angiography, with greater atherosclerotic burden among those with lower IIEF scores (26). Finally, multivessel disease (vs. single-vessel disease) was an independent predictor of ED (IIEF < 26) in the COBRA trial, and severe ED (IIEF < 10) was significantly more frequent in patients with multivessel disease than in those with single-vessel disease (35).

Finally, in agreement with the British and International Societies of Sexual Medicine, the authors recommend that testosterone levels be measured in patients with a diagnosis of organic ED and for whom PDE5 inhibitors have failed. Testosterone is a key central and peripheral modulator of erectile function in animal studies (55–58), and hypogonadism is common in men with ED (59,60). Furthermore, a number of epidemiologic studies have linked low testosterone with increased all-cause and cardiovascular mortality (Table 4) (61). In a meta-analysis

Table 4 Low testosterone and increased mortality (recent publications in which $n > 500$)

Recent studies	HR (95% CI)	Nature	Men, n	Follow up (years)	Mortality
Shores et al. (84)	1.88 (1.34–2.63)	Retrospective	858	8	All-cause
Laughlin et al. (85)	1.38 (1.02–1.85)	Prospective	794	20	CVD
Khaw et al. (86)	2.29 (1.60–3.26)	Prospective	2314 of 11,606	10	All-cause and CVD
Haring et al. (87)	2.32 (1.38–3.89)	Prospective	1954	7.2	All-cause
	2.56 (1.15–6.52)				CVD
Malkin et al. (88)	2.27 (1.45–3.60)	Prospective	930	6.9	All-cause in men with coronary disease
Tivesten et al. (89)	1.65 (1.29–2.12)	Prospective	3014	4.5	All-cause
Menke et al. (90)	1.43 (1.09-1.87)	Prospective	1114	9	All-cause
Vikan et al. (91)	1.24 (1.01-1.54)	Prospective	1568	11.2	All-cause
Corona et al. (92)	7.1 (1.8-28.6)	Prospective	1687	4.3	CVD

CVD, cardiovascular disease; HR, hazard ratio.

limited to longitudinal (cohort) studies in middle-aged men, Ruige et al. (7) found no association between endogenous total testosterone (TT) levels and risk for CVD in middle-aged men. A more recent paper by Corona et al. (6) reported significant associations between both low TT and high estradiol levels and CVD in a meta-analysis of 49 cross-sectional studies. Conversely, a meta-analysis of 10 longitudinal studies performed by the same authors showed that TT was significantly lower among patients with incident overall and cardiovascular mortality in comparison with controls, but there was no difference in baseline TT and estradiol levels between cases and controls for incident CVD (6). Both groups acknowledged that low testosterone may be a marker of poor general health rather than CVD risk. Indeed, androgen deficiency has been associated with insulin resistance, type 2 diabetes mellitus (T2DM), metabolic syndrome and increased deposition of visceral fat (62–65), and 6 months of transdermal TRT significantly improved insulin resistance in a large, placebo-controlled study of hypogonadal men with T2DM (TIMES2) (66,67). At present, there is no concrete evidence that testosterone repletion can lower CVD risk. However, in a recent observational cohort study of men with low testosterone levels, testosterone treatment was associated with decreased mortality compared with no testosterone treatment (68). TRT may also improve quality of life (69) and erectile function (70), but requires careful monitoring. The authors' recommendations for cardiovascular risk assessment in men with ED and no known CVD are summarised in Figure 1.

The cardiologist's role

As ED is predominantly a vascular disease and associated with an increase in cardiovascular events, all-cause mortality and CVD mortality, the role of the cardiologist is fundamental to what is an actual or potential cardiovascular condition. In short, cardiologists have to recognise ED is within their remit, must be routinely asked about, and CVD risk evaluated and treated. How this risk is evaluated will depend on the practice of the cardiologist, local procedures and funding, but it is essential that a local policy for evaluation is established. Non-invasive evaluation, including physiological stress testing for ischaemia, circulating biomarkers and anatomical clarification [i.e. coronary computed tomography angiography (CCTA) for diagnosis of vulnerable yet subclinical plaque], may be appropriate in these patients. Despite its inability to detect non–flow-limiting lesions, exercise stress testing (EST; with or without imaging) can further characterise the cardiovascular risk in patients with ED and may be particularly helpful for identifying silent CAD in patients with diabetes. Gazzaruso et al. (71) found that, among men with T2DM, ED was significantly more prevalent in those with silent CAD (33.8%) identified by EST than those without CAD (4.7%). Chemical stress tests (dipyridamole, adenosine with nuclear imaging) may be performed in patients who cannot complete an EST (e.g. due to arthritis). If baseline electrocardiogram makes EST unavailable or non-interpretable, echocardiographic stress testing or Myoview™ (nuclear) stress testing (GE Healthcare, Arlington Heights, IL) may be used. Tests that may be used in men with ED to identify those with existing atherosclerotic vascular disease (e.g. CAD) or those at high risk are listed in Table 5. The most appropriate order of testing, and the prognostic superiority of one test over another in men with ED have not been established. However, in a comparison of risk markers for improvement in cardiovascular risk prediction, CCTA provided superior discrimination and risk

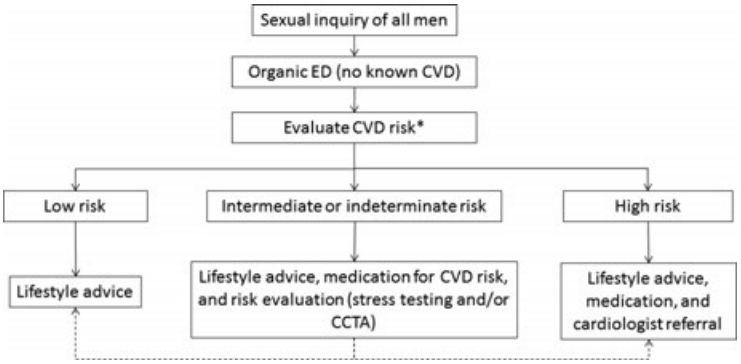

Figure 1 Cardiovascular risk assessment in men with erectile dysfunction and no known cardiovascular disease. *Based on the Framingham Risk Score, HEART SCORE, or QRISK. A thorough history, physical exam (including measures of visceral adiposity), assessment of ED severity and duration, and evaluation including fasting plasma glucose, resting electrocardiogram, serum creatinine (estimated glomerular filtration rate) and albumin:creatinine ratio, and presence or absence of the metabolic syndrome may be used to further characterise cardiovascular risk. Additional markers of increased risk will depend on local practice and availability [CACS, CIMT, ABI, PWV, hsCRP, HbA1c, LpPLA2, urinary albumin excretion, endothelial function (i.e. EndoPAT)]. Men with diabetes, and those in whom PDE5 inhibitors have been unsuccessful, should be considered high risk. ABI, ankle-brachial index; CACS, coronary artery calcium scoring; CAD, coronary artery disease; CCTA, coronary computed tomography angiography; CIMT, carotid intima-media thickness; CVD, cardiovascular disease; ED, erectile dysfunction; HbA1c, haemoglobin A1c; hsCRP, high-sensitivity C-reactive protein; LpPLA2, lipoprotein-associated phospholipase; PDE5, phosphodiesterase type 5; PWV, pulse wave velocity

classification compared with other risk markers (72,73). As ED is an independent marker of increased risk in those men identified using conventional risk markers (intermediate risk, i.e. 5% to < 20%, and high risk, > 20% estimated risk over 10 years) but who have no cardiac symptoms, the risk could be most accurately refined using CCTA. In addition, men aged 30–60 years with ED and no cardiac symptoms are at substantially increased 10-year risk and therefore should be considered for CCTA (74). Invasive coronary angiography should then be considered when non-invasive evaluation suggests significantly increased CVD risk.

Table 5 Tests that may be used in men with ED to identify those with, or at risk for, cardiovascular disease

Test	Studies supporting use in characterization of cardiovascular risk	Studies supporting use in characterization of cardiovascular risk in men with ED
Coronary computed tomography angiography and coronary artery calcium scoring	(93,94)	(95)
Carotid intima-media thickness	(96)	(97)
Ankle-brachial index	(98)	(39)
Pulse wave velocity	(99)	(97)
C-reactive protein	(100,101)	(102)

ED, erectile dysfunction.

Cardiovascular risk reduction in men with ED

Because ED often precedes cardiovascular events, timely intervention to control risk factors in the man presenting with ED symptoms is paramount. Lifestyle modification (i.e. reduced caloric intake, increased physical activity, and smoking cessation) is a rational first step towards prevention of cardiovascular events, and may improve erectile function in men with ED (75). Esposito et al. (75) have shown that lifestyle changes and weight reduction can result in clinically significant improvements in erectile function, CRP and measures of endothelial function. Established risk factors, including smoking, obesity, metabolic syndrome, hypertension, dyslipidemia and diabetes are highly prevalent among men with ED and should be identified and addressed. In a study using a nationally representative sample of 272,325 men with ED, region-adjusted prevalence rates were 41.2% for hypertension, 41.8% for hyperlipidemia, and 19.7% for diabetes mellitus (76). Conversely, among 104 male patients being treated at a hypertension centre in New York, 68% had some degree of ED based on the IIEF (27). Similarly, Giuliano et al. found that 71% of 2377 men with diabetes (but no hypertension) had ED based on the IIEF-5 (3).

Finally, a practice-based study of 215 men with ED and 100 matched controls showed that, after exclusion of confounding factors, low HDL-C and high total cholesterol/HDL-C ratio were significant predictors of ED (77). Correction of blood pressure, lipid, and glycemic abnormalities reduces risk for cardiovascular events and should be a priority in men with ED. Furthermore, treatment with angiotensin receptor blockers (78–80) and statins (81,82) have been shown to improve erectile function in men with hypertension and dyslipidemia, respectively. A recent meta-analysis and systematic review of the effects of lifestyle changes on erectile function strengthened the evidence that lifestyle modification and pharmacotherapy for CVD risk factors improved sexual function in men with ED (83). Addressing lifestyle modification therefore benefits sexual function as well as CVD risk.

Conclusions

Erectile dysfunction should be considered a vascular disease until proven otherwise. Because data show that the occurrence of ED symptoms often precedes a cardiovascular event by 2–5 years, it provides a unique window of opportunity for risk mitigation. Thorough risk assessment of men presenting with ED and no cardiac symptoms is imperative. Traditional risk factors, such as smoking, hypertension, and hypercholesterolemia should always be assessed. Furthermore, we recommend that a question on ED be included in all cardiovascular risk assessment and be incorporated into risk assessment guidelines. 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. A cardiologist or other clinician with relevant expertise plays a particularly important role in evaluating the CVD risk in men with ED who may have subclinical CVD. Increased recognition of the potential for CVD in men with ED, followed by appropriate preventive action, can improve and may save lives.

Acknowledgements

Melinda Ramsey is an employee of Complete Healthcare Communications, Inc. who were paid consultants to Pfizer in connection with the development of this article.

All authors contributed to the drafting and critical revision of the article, and all approved the submitted version.

References

1 Hatzimouratidis K, Amar E, Eardley I, et al. Guidelines on male sexual dysfunction: erectile dysfunction and premature ejaculation. *Eur Urol* 2010; **57**: 804–14.
2 Feldman HA, Goldstein I, Hatzichristou DG, et al. Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. *J Urol* 1994; **151**: 54–61.
3 Giuliano FA, Leriche A, Jaudinot EO, de Gendre AS. Prevalence of erectile dysfunction among 7689 patients with diabetes or hypertension, or both. *Urology* 2004; **64**: 1196–201.
4 Jackson G. Prevention of cardiovascular disease by the early identification of erectile dysfunction. *Int J Impot Res* 2008; **20**: S9–14.
5 Wu FC, von Eckardstein A. Androgens and coronary artery disease. *Endocr Rev* 2003; **24**: 183–217.
6 Corona G, Rastrelli G, Monami M, et al. Hypogonadism as a risk factor for cardiovascular mortality in men: a meta-analytic study. *Eur J Endocrinol* 2011; **165**: 687–701.
7 Ruige JB, Mahmoud AM, De Bacquer D, Kaufman JM. Endogenous testosterone and cardiovascular disease in healthy men: a meta-analysis. *Heart* 2011; **97**: 870–5.
8 Buvat J, Maggi M, Gooren L, et al. Endocrine aspects of male sexual dysfunctions. *J Sex Med* 2010; **7**: 1627–56.
9 Kharbanda RK, Deanfield JE. Functions of the healthy endothelium. *Coron Artery Dis* 2001; **12**: 485–91.
10 Ganz P, Vita JA. Testing endothelial vasomotor function: nitric oxide, a multipotent molecule. *Circulation* 2003; **108**: 2049–53.
11 Kirby M, Jackson G, Simonsen U. Endothelial dysfunction links erectile dysfunction to heart disease. *Int J Clin Pract* 2005; **59**: 225–9.
12 Rubinshtein R, Kuvin JT, Soffler M, et al. Assessment of endothelial function by non-invasive peripheral arterial tonometry predicts late cardiovascular adverse events. *Eur Heart J* 2010; **31**: 1142–8.
13 Kitta Y, Obata JE, Nakamura T, et al. Persistent impairment of endothelial vasomotor function has a negative impact on outcome in patients with coronary artery disease. *J Am Coll Cardiol* 2009; **53**: 323–30.
14 Yeboah J, Crouse JR, Hsu FC, et al. Brachial flow-mediated dilation predicts incident cardiovascular events in older adults: the Cardiovascular Health Study. *Circulation* 2007; **115**: 2390–7.
15 Bivalacqua TJ, Usta MF, Champion HC, et al. Endothelial dysfunction in erectile dysfunction: role of the endothelium in erectile physiology and disease. *J Androl* 2003; **24**: S17–37.
16 Francavilla S, Bocchio M, Pelliccione F, et al. Vascular aetiology of erectile dysfunction. *Int J Androl* 2005; **28**(Suppl. 2): 35–9.
17 Montorsi P, Ravagnani PM, Galli S, et al. Association between erectile dysfunction and coronary artery disease: matching the right target with the right test in the right patient. *Eur Urol* 2006; **50**: 721–31.
18 Corona G, Fagioli G, Mannucci E, et al. Penile doppler ultrasound in patients with erectile dysfunction (ED): role of peak systolic velocity measured in the flaccid state in predicting arteriogenic ED and silent coronary artery disease. *J Sex Med* 2008; **5**: 2623–34.
19 Corona G, Monami M, Boddi V, et al. Male sexuality and cardiovascular risk. A cohort study in patients with erectile dysfunction. *J Sex Med* 2010; **7**: 1918–27.
20 Kaiser DR, Billups K, Mason C, et al. Impaired brachial artery endothelium-dependent and -independent vasodilation in men with erectile dysfunction and no other clinical cardiovascular disease. *J Am Coll Cardiol* 2004; **43**: 179–84.
21 Esposito K, Ciotola M, Giugliano F, et al. Endothelial microparticles correlate with erectile dysfunction in diabetic men. *Int J Impot Res* 2007; **19**: 161–6.
22 De Angelis L, Marfella MA, Siniscalchi M, et al. Erectile and endothelial dysfunction in type II diabetes: a possible link. *Diabetologia* 2001; **44**: 1155–60.
23 Bocchio M, Desideri G, Scarpelli P, et al. Endothelial cell activation in men with erectile dysfunction without cardiovascular risk factors and overt vascular damage. *J Urol* 2004; **171**: 1601–4.
24 Vlachopoulos C, Aznaouridis K, Ioakeimidis N, et al. Unfavourable endothelial and inflammatory state in erectile dysfunction patients with or without coronary artery disease. *Eur Heart J* 2006; **27**: 2640–8.
25 Vlachopoulos C, Ioakeimidis N, Terentes-Printzios D, Stefanadis C. The triad: erectile dysfunction–endothelial dysfunction–cardiovascular disease. *Curr Pharm Des* 2008; **14**: 3700–14.

26 Solomon H, Man JW, Wierzbicki AS, Jackson G. Relation of erectile dysfunction to angiographic coronary artery disease. *Am J Cardiol* 2003; **91**: 230–1.

27 Burchardt M, Burchardt T, Baer L, et al. Hypertension is associated with severe erectile dysfunction. *J Urol* 2000; **164**: 1188–91.

28 Garcia-Malpartida K, Marmol R, Jover A, et al. Relationship between erectile dysfunction and silent myocardial ischemia in type 2 diabetic patients with no known macrovascular complications. *J Sex Med* 2011; **8**: 2606–16.

29 Bohm M, Baumhakel M, Teo K, et al. Erectile dysfunction predicts cardiovascular events in high-risk patients receiving telmisartan, ramipril, or both: The ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial/Telmisartan Randomized AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease (ONTARGET/TRANSCEND) Trials. *Circulation* 2010; **121**: 1439–46.

30 Schouten BW, Bohnen AM, Bosch JL, et al. Erectile dysfunction prospectively associated with cardiovascular disease in the Dutch general population: results from the Krimpen Study. *Int J Impot Res* 2008; **20**: 92–9.

31 Araujo AB, Hall SA, Ganz P, et al. Does erectile dysfunction contribute to cardiovascular disease risk prediction beyond the Framingham risk score? *J Am Coll Cardiol* 2010; **55**: 350–6.

32 Batty GD, Li Q, Czernichow S, et al. Erectile dysfunction and later cardiovascular disease in men with type 2 diabetes: prospective cohort study based on the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified-Release Controlled Evaluation) trial. *J Am Coll Cardiol* 2010; **56**: 1908–13.

33 Blumentals WA, Gomez-Caminero A, Joo S, Vannappagari V. Should erectile dysfunction be considered as a marker for acute myocardial infarction? Results from a retrospective cohort study. *Int J Impot Res* 2004; **16**: 350–3.

34 Gazzaruso C, Solerte SB, Pujia A, et al. Erectile dysfunction as a predictor of cardiovascular events and death in diabetic patients with angiographically proven asymptomatic coronary artery disease: a potential protective role for statins and 5-phosphodiesterase inhibitors. *J Am Coll Cardiol* 2008; **51**: 2040–4.

35 Montorsi P, Ravagnani PM, Galli S, et al. Association between erectile dysfunction and coronary artery disease. Role of coronary clinical presentation and extent of coronary vessels involvement: the COBRA trial. *Eur Heart J* 2006; **27**: 2632–9.

36 Ponholzer A, Temml C, Obermayr R, et al. Is erectile dysfunction an indicator for increased risk of coronary heart disease and stroke? *Eur Urol* 2005; **48**: 512–8; discussion 7–8.

37 Salem S, Abdi S, Mehrsai A, et al. Erectile dysfunction severity as a risk predictor for coronary artery disease. *J Sex Med* 2009; **6**: 3425–32.

38 Vlachopoulos C, Rokkas K, Ioakeimidis N, et al. Prevalence of asymptomatic coronary artery disease in men with vasculogenic erectile dysfunction: a prospective angiographic study. *Eur Urol* 2005; **48**: 996–1002; discussion 3.

39 Polonsky TS, Taillon LA, Sheth H, et al. The association between erectile dysfunction and peripheral arterial disease as determined by screening ankle-brachial index testing. *Atherosclerosis* 2009; **207**: 440–4.

40 Montorsi P, Ravagnani PM, Galli S, et al. The artery size hypothesis: a macrovascular link between erectile dysfunction and coronary artery disease. *Am J Cardiol* 2005; **96**: 19M–23M.

41 Fischer A, Gutstein DE, Fayad ZA, Fuster V. Predicting plaque rupture: enhancing diagnosis and clinical decision-making in coronary artery disease. *Vasc Med* 2000; **5**: 163–72.

42 Araujo AB, Travison TG, Ganz P, et al. Erectile dysfunction and mortality. *J Sex Med* 2009; **6**: 2445–54.

43 Thompson IM, Tangen CM, Goodman PJ, et al. Erectile dysfunction and subsequent cardiovascular disease. *JAMA* 2005; **294**: 2996–3002.

44 Dong JY, Zhang YH, Qin LQ. Erectile dysfunction and risk of cardiovascular disease meta-analysis of prospective cohort studies. *J Am Coll Cardiol* 2011; **58**: 1378–85.

45 Inman BA, Sauver JL, Jacobson DJ, et al. A population-based, longitudinal study of erectile dysfunction and future coronary artery disease. *Mayo Clin Proc* 2009; **84**: 108–13.

46 Chew KK, Finn J, Stuckey B, et al. Erectile dysfunction as a predictor for subsequent atherosclerotic cardiovascular events: findings from a linked-data study. *J Sex Med* 2010; **7**: 192–202.

47 Riedner CE, Rhoden EL, Fuchs SC, et al. Erectile dysfunction and coronary artery disease: an association of higher risk in younger men. *J Sex Med* 2011; **8**: 1445–53.

48 Montorsi F, Briganti A, Salonia A, et al. Erectile dysfunction prevalence, time of onset and association with risk factors in 300 consecutive patients with acute chest pain and angiographically documented coronary artery disease. *Eur Urol* 2003; **44**: 360–4; discussion 4–5.

49 Baumhakel M, Bohm M. Erectile dysfunction correlates with left ventricular function and precedes cardiovascular events in cardiovascular high-risk patients. *Int J Clin Pract* 2007; **61**: 361–6.

50 Hodges LD, Kirby M, Solanki J, et al. The temporal relationship between erectile dysfunction and cardiovascular disease. *Int J Clin Pract* 2007; **61**: 2019–25.

51 Third Report of the National Cholesterol Education Program (NCEP). Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002; **106**: 3143–421.

52 Collins GS, Altman DG. An independent external validation and evaluation of QRISK cardiovascular risk prediction: a prospective open cohort study. *BMJ* 2009; **339**: b2584.

53 Perk J, De Backer G, Gohlke H, et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J* 2012; **33**: 1635–701.

54 Greenstein A, Chen J, Miller H, et al. Does severity of ischemic coronary disease correlate with erectile function? *Int J Impot Res* 1997; **9**: 123–6.

55 Goglia L, Tosi V, Sanchez AM, et al. Endothelial regulation of eNOS, PAI-1 and t-PA by testosterone and dihydrotestosterone in vitro and in vivo. *Mol Hum Reprod* 2010; **16**: 761–9.

56 Traish AM, Park K, Dhir V, et al. Effects of castration and androgen replacement on erectile function in a rabbit model. *Endocrinology* 1999; **140**: 1861–8.

57 Morelli A, Filippi S, Mancina R, et al. Androgens regulate phosphodiesterase type 5 expression and functional activity in corpora cavernosa. *Endocrinology* 2004; **145**: 2253–63.

58 Zhang XH, Morelli A, Luconi M, et al. Testosterone regulates PDE5 expression and in vivo responsiveness to tadalafil in rat corpus cavernosum. *Eur Urol* 2005; **47**: 409–16; discussion 16.

59 Guay AT, Velasquez E, Perez JB. Characterization of patients in a medical endocrine-based center for male sexual dysfunction. *Endocr Pract* 1999; **5**: 314–21.

60 Buvat J, Bou Jaoude G. Significance of hypogonadism in erectile dysfunction. *World J Urol* 2006; **24**: 657–67.

61 Araujo AB, Dixon JM, Suarez EA, et al. Clinical review: endogenous testosterone and mortality in men: a systematic review and meta-analysis. *J Clin Endocrinol Metab* 2011; **96**: 3007–19.

62 Grossmann M, Thomas MC, Panagiotopoulos S, et al. Low testosterone levels are common and associated with insulin resistance in men with diabetes. *J Clin Endocrinol Metab* 2008; **93**: 1834–40.

63 Laaksonen DE, Niskanen L, Punnonen K, et al. Sex hormones, inflammation and the metabolic syndrome: a population-based study. *Eur J Endocrinol* 2003; **149**: 601–8.

64 Osuna JA, Gomez-Perez R, Arata-Bellabarba G, Villaroel V. Relationship between BMI, total testosterone, sex hormone-binding-globulin, leptin, insulin and insulin resistance in obese men. *Arch Androl* 2006; **52**: 355–61.

65 Kapoor D, Aldred H, Clark S, et al. Clinical and biochemical assessment of hypogonadism in men with type 2 diabetes: correlations with bioavailable testosterone and visceral adiposity. *Diabetes Care* 2007; **30**: 911–7.

66 Jones TH, Arver S, Behre HM, et al. Testosterone replacement in hypogonadal men with type 2 diabetes and/or metabolic syndrome (the TIMES2 study). *Diabetes Care* 2011; **34**: 828–37.

67 Grossmann M. Low testosterone in men with type 2 diabetes: significance and treatment. *J Clin Endocrinol Metab* 2011; **96**: 2341–53.

68 Shores MM, Smith NL, Forsberg CW, et al. Testosterone treatment and mortality in men with low testosterone levels. *J Clin Endocrinol Metab* 2012; **97**: 2050–58.

69 Hackett G. Long acting testosterone undecanoate improved ageing male symptom scores but not depression versus placebo in a hypogonadal population with type 2 diabetes. 14th European Society of Sexual Medicine Congress, Milan, Italy, 2011.

70 Buvat J, Montorsi F, Maggi M, et al. Hypogonadal men nonresponders to the PDE5 inhibitor tadalafil benefit from normalization of testosterone levels with a 1% hydroalcoholic testosterone gel in the treatment of erectile dysfunction (TADTEST study). *J Sex Med* 2011; **8**: 284–93.

71 Gazzaruso C, Giordanetti S, De Amici E, et al. Relationship between erectile dysfunction and silent myocardial ischemia in apparently uncomplicated type 2 diabetic patients. *Circulation* 2004; **110**: 22–6.
72 Yeboah J, McClelland RL, Polonsky TS, et al. Comparison of novel risk markers for improvement in cardiovascular risk assessment in intermediate-risk individuals. *JAMA* 2012; **308**: 788–95.
73 Gaziano JM, Wilson PW. Cardiovascular risk assessment in the 21st century. *JAMA* 2012; **308**: 816–7.
74 Vlachopoulos CV, Terentes-Printzios DG, Ioakeimidis NK, et al. Prediction of cardiovascular events and all-cause mortality with erectile dysfunction: a systematic review and meta-analysis of cohort studies. *Circ Cardiovasc Qual Outcomes* 2013; **6**: 99–109.
75 Esposito K, Giugliano F, Di Palo C, et al. Effect of lifestyle changes on erectile dysfunction in obese men: a randomized controlled trial. *JAMA* 2004; **291**: 2978–84.
76 Seftel AD, Sun P, Swindle R. The prevalence of hypertension, hyperlipidemia, diabetes mellitus and depression in men with erectile dysfunction. *J Urol* 2004; **171**: 2341–5.
77 Roumeguere T, Wespes E, Carpentier Y, et al. Erectile dysfunction is associated with a high prevalence of hyperlipidemia and coronary heart disease risk. *Eur Urol* 2003; **44**: 355–9.
78 Dusing R. Effect of the angiotensin II antagonist valsartan on sexual function in hypertensive men. *Blood Press Suppl* 2003; **2**: 29–34.
79 Fogari R, Zoppi A, Poletti L, et al. Sexual activity in hypertensive men treated with valsartan or carvedilol: a crossover study. *Am J Hypertens* 2001; **14**: 27–31.
80 Baumhakel M, Schlimmer N, Bohm M. Effect of irbesartan on erectile function in patients with hypertension and metabolic syndrome. *Int J Impot Res* 2008; **20**: 493–500.
81 Gokkaya SC, Ozden C, Levent Ozdal O. et al. Effect of correcting serum cholesterol levels on erectile function in patients with vasculogenic erectile dysfunction. *Scand J Urol Nephrol* 2008; **42**: 437–40.
82 Saltzman EA, Guay AT, Jacobson J. Improvement in erectile function in men with organic erectile dysfunction by correction of elevated cholesterol levels: a clinical observation. *J Urol* 2004; **172**: 255–8.
83 Gupta BP, Murad MH, Clifton MM, et al. The effect of lifestyle modification and cardiovascular risk factor reduction on erectile dysfunction: a systematic review and meta-analysis. *Arch Intern Med* 2011; **171**: 1797–803.
84 Shores MM, Matsumoto AM, Sloan KL, Kivlahan DR. Low serum testosterone and mortality in male veterans. *Arch Intern Med* 2006; **166**: 1660–5.
85 Laughlin GA, Barrett-Connor E, Bergstrom J. Low serum testosterone and mortality in older men. *J Clin Endocrinol Metab* 2008; **93**: 68–75.
86 Khaw KT, Dowsett M, Folkerd E, et al. Endogenous testosterone and mortality due to all causes, cardiovascular disease, and cancer in men: European prospective investigation into cancer in Norfolk (EPIC-Norfolk) Prospective Population Study. *Circulation* 2007; **116**: 2694–701.
87 Haring R, Volzke H, Steveling A, et al. Low serum testosterone levels are associated with increased risk of mortality in a population-based cohort of men aged 20–79. *Eur Heart J* 2010; **31**: 1494–501.
88 Malkin CJ, Pugh PJ, Morris PD, et al. Low serum testosterone and increased mortality in men with coronary heart disease. *Heart* 2010; **96**: 1821–5.
89 Tivesten A, Vandenput L, Labrie F, et al. Low serum testosterone and estradiol predict mortality in elderly men. *J Clin Endocrinol Metab* 2009; **94**: 2482–8.
90 Menke A, Guallar E, Rohrmann S, et al. Sex steroid hormone concentrations and risk of death in US men. *Am J Epidemiol* 2010; **171**: 583–92.
91 Vikan T, Schirmer H, Njolstad I, Svartberg J. Endogenous sex hormones and the prospective association with cardiovascular disease and mortality in men: the Tromso Study. *Eur J Endocrinol* 2009; **161**: 435–42.
92 Corona G, Monami M, Boddi V, et al. Low testosterone is associated with an increased risk of MACE lethality in subjects with erectile dysfunction. *J Sex Med* 2010; **7**: 1557–64.
93 Detrano R, Guerci AD, Carr JJ, et al. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. *N Engl J Med* 2008; **358**: 1336–45.
94 Johnson KM, Dowe DA. The detection of any coronary calcium outperforms Framingham risk score as a first step in screening for coronary atherosclerosis. *AJR Am J Roentgenol* 2010; **194**: 1235–43.
95 Jackson G, Padley S. Erectile dysfunction and silent coronary artery disease: abnormal computed tomography coronary angiogram in the presence of normal exercise ECGs. *Int J Clin Pract* 2008; **62**: 973–6.
96 Nambi V, Chambless L, Folsom AR, et al. Carotid intima-media thickness and presence or absence of plaque improves prediction of coronary heart disease risk: the ARIC (Atherosclerosis Risk In Communities) study. *J Am Coll Cardiol* 2010; **55**: 1600–7.
97 Vlachopoulos C, Aznaouridis K, Ioakeimidis N, et al. Arterial function and intima-media thickness in hypertensive patients with erectile dysfunction. *J Hypertens* 2008; **26**: 1829–36.
98 Fowkes FG, Murray GD, Butcher I, et al. Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis. *JAMA* 2008; **300**: 197–208.
99 Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. *J Am Coll Cardiol* 2010; **55**: 1318–27.
100 Ridker PM, Glynn RJ, Hennekens CH. C-reactive protein adds to the predictive value of total and HDL cholesterol in determining risk of first myocardial infarction. *Circulation* 1998; **97**: 2007–11.
101 Ridker PM, Rifai N, Rose L, et al. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. *N Engl J Med* 2002; **347**: 1557–65.
102 Chang ST, Chu CM, Hsu JT, et al. Independent determinants of coronary artery disease in erectile dysfunction patients. *J Sex Med* 2010; **7**: 1478–87.

Paper received September 2012, accepted April 2013

Appendix A1

Author	Employment	Consultant	Speaker	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Nehra (nothing to disclose)							
Jackson			Pfizer, Lilly, Bayer				
Miner		Lilly, Abbott, Auxilium, BI, Endo			GSK, Auxilium		
Billups		Endo Pharmaceuticals, Abbott Laboratories					
Burnett		Endo Pharma, Abbott, Timm Medical, VIVUS, Auxilium Inc, Shionogi Pharma				Grant support: Pfizer; Clinical Trials: VIVUS, Auxilium	
Buvat		Lilly Nextmed					
Carson		GSK, Lilly, Pfizer, Auxilium	GSK, Lilly, Pfizer, Auxilium				
Cunningham		Abbott, Endo Pharma, GSK, Repros Therapeutics	Abbott, Endo Pharma, Merck				
Ganz		Pfizer, Gilead, Roche					
Goldstein		Coloplast, Medtronic Vascular, Slate, Vivus	Abbott, Auxilium, Coloplast, Eli Lilly, Endo, Medtronic Vascular, Slate		Auxilium, BioSante, Medtronic Vascular, Slate, Target Health		Pfizer, Bayer
Guay		Auxilium, Abbott, Endo Pharmaceuticals, Repros Therapeutics					
Hackett			Bayer, Lilly		Bayer, Lilly		
Kloner			Pfizer				
Kostis		Merck/Schering, Palatin Technologies, Inc.	Forest, Merck, Sanofi-Aventis			Research support: Medtronic, Novartis	
Montorsi (nothing to disclose)							
Ramsey (nothing to disclose)							
Rosen		Lilly, BI, Palatin, Auxilium					
Sadovsky		Pfizer, BI, Lilly					
Seftel		Auxilium, Endo, Actient, Abbott, Lilly, Pfizer					
Shabsigh (nothing to disclose)							
Vlachopoulos		Lilly				Research support: Pfizer	
Wu		Lilly	Galapagos		Bayer		