International Journal of Impotence Research (2005) 17, S19–S24

0955-9930/05 $30.00
www.nature.com/ijir

Erectile dysfunction as an early sign of cardiovascular disease

KL Billups[1]*

[1]*The EpiCenter for Sexual Health & Medicine, Edina, Minnesota, USA*

A body of evidence from basic science and clinical research is emerging to provide a compelling argument for endothelial dysfunction as a central etiologic factor in the development of atherosclerosis and vascular disease (ischemic heart disease, stroke, and claudication). Erectile dysfunction (ED) is another prevalent vascular disorder that is now thought to be caused by endothelial dysfunction. In fact, a burgeoning literature is now available that suggests that ED may be an early marker for atherosclerosis and cardiovascular disease (CVD). The emerging awareness of ED as a barometer for CVD represents a unique opportunity to enhance preventive vascular health in men. The diagnosis of ED could become a powerful clinical tool to improve early detection of atherosclerosis and initiate prompt aggressive medical management of associated cardiovascular risk factors.
International Journal of Impotence Research (2005) **17,** S19–S24. doi:10.1038/sj.ijir.3901425

Keywords: erectile dysfunction; cardiovascular disease; endothelial dysfunction; prevention

Introduction

Erectile dysfunction (ED) is defined as the persistent inability to maintain or achieve a penile erection sufficient for satisfactory sexual performance. There are a number of underlying (obesity, sedentary lifestyle, atherogenic diet), traditional (age ≥ 45 y, high LDL cholesterol, low HDL cholesterol, hypertension, diabetes, smoking), and emerging (insulin resistance/metabolic syndrome) risk factors that are shared between erectile dysfunction and cardiovascular disease.[1–3] Evidence is emerging that endothelial dysfunction is an important common denominator between these two conditions.[4] In fact, a burgeoning literature is now available, which suggests that ED may indeed be an early marker for atherosclerosis, cardiovascular risk, and subclinical systemic vascular disease.[5,6] Recognizing ED as a sign of early endothelial dysfunction could have a huge impact on preventive healthcare by providing a clinical tool for physicians to identify men at an early stage prior to the development of atherosclerosis or an adverse vascular event.

This paper will review the relationship between ED and cardiovascular disease, including the role of endothelial dysfunction as a common etiologic factor for both. New evidence from clinical studies showing that ED precedes the development of cardiovascular disease will be reviewed and placed into perspective.

*Correspondence: KL Billups, MD, 7455 France Avenue South, Suite 362, Edina, MN 55435, USA.
E-mail: klbillups@earthlink.net

Erectile dysfunction and cardiovascular disease

Erectile dysfunction is a remarkably common condition.[1] Difficulty attaining or sustaining a firm erection is the earliest and most common symptom of ED. As many as 30 million men in the US are estimated to have ED.[7] The Massachusetts Male Aging Study (MMAS) surveyed 1290 primarily Caucasian men between the ages of 40 and 70 y and found that ED was present in 52% of this large community sample.[8] Data from the National Health and Social Life Survey, which included a national probability sample of 1410 men, indicate that 16% of men younger than 40 have ED. In addition, African Americans are 20% more likely than Caucasians to have ED.[9]

Though the pathophysiology of ED is multifactorial and includes arterial, neurogenic, hormonal, cavernosal, iatrogenic, and psychogenic causes,[7–9] it is now widely accepted that organic ED in a substantial majority of men is due to underlying vascular causes, especially atherosclerosis.[6,10–12] Numerous clinical epidemiology studies have demonstrated that ED is highly prevalent in men with vascular risk factors for cardiovascular disease. Diabetes,[13,14] hypertension,[15] dyslipidemia,[16] cigarette smoking, obesity, and sedentary lifestyles[2,8,17] are all associated with an increased incidence of ED. This

concept of ED being an outcome of cardiovascular disease is well accepted today.

The link between erectile dysfunction, atherosclerosis, and endothelial dysfunction

An emerging basic science and clinical database provides a strong argument for endothelial and smooth muscle dysfunction as a central etiologic factor in systemic and peripheral vascular diseases, including ED. The endothelium, which is the layer of epithelial cells that lines the structures of the cardiovascular system, is pivotal to the regulation of vasomotor tone. Endothelial cells are a primary source of nitric oxide (NO), which is a nonadrenergic-noncholinergic vasodilatory neurotransmitter involved in the regulation of vascular wall function. Endothelial dysfunction, which is associated with impaired vasodilatation, precedes the development of atherosclerotic lesions[3] and can be caused by vascular insults, such as diabetes, cigarette smoking, hyperlipidemia, and hypertension.[18] At the cellular level, endothelial dysfunction results in impaired release of NO. Oxidative stress (ie, free radical damage), which interferes with the NO pathway and also is directly toxic to the endothelium, is a causal factor in clinically evident occlusive cardiovascular disease and the vascular damage associated with preclinical disease. Free radical damage and impaired function and availability of NO also result in increased adhesion and aggregation of platelets and neutrophils and the release of vasoconstrictor substances.[4,5] Many men will note that the onset of ED, specifically difficulty being able to maintain a firm erection, occurs before they are diagnosed with cardiovascular disease (hypertension, dyslipidemia, diabetes, coronary artery disease, or peripheral vascular disease). The anatomic structure of the penis and the physiology of the getting and maintaining an erection provide clues as to why the penile vascular bed has some unique properties that facilitate early detection of systemic vascular disease.

The penis is a richly vascularized organ, and penile erections are, in large part, a vascular event. The penile anatomy consists of the two corpus cavernosa and the ventral corpus spongiosum that surrounds the urethra. The corpus cavernosa are supplied by the dorsal and cavernous arteries, with venous return occurring via the subtunical venular plexus, the deep dorsal vein, and others. Penile erection is the result of a complex and coordinated series of events involving vascular response, neuronal pathways, and psychosomatic stimulation. The NO pathway is activated upon sexual stimulation, and NO is released into penile smooth muscle from both the vascular endothelium of the penis and the autonomic, cavernous nerve terminals. Within the penile smooth muscle, NO activates guanylyl cyclase, which increases the concentration of the second messenger, cyclic guanosine monophosphate (cGMP). The elevated concentrations of cGMP result in relaxation of arterial smooth muscle in the penis and a marked rise in penile blood pressure. In addition, cGMP relaxes trabecular smooth muscle, which facilitates engorgement of the sinusoidal spaces, lengthening and enlargement of the penis, and compression of the subtunical venules (Figure 1). The net result is complete occlusion of penile venous outflow and trapping of blood within the corpus cavernosa. Nitric oxide from autonomic nerve endings in the penile tissue are believed to initiate smooth muscle relaxation and the erectile response, while NO from penile vascular and sinusoidal endothelial cells is felt to play an important role in maintain a firm erection. Detumescence or flaccidity occurs following release of norepinephrine and contraction of the intracorporeal smooth muscle.[7,19]

A functioning NO pathway is therefore a primary determinant of smooth muscle tone, arterial inflow, and restricted venous outflow in the physiology of erection. Disruption of any of these factors can lead to ED. Endothelial dysfunction, which is associated with impaired release and activity of NO, underlies the pathophysiology of vascular ED.[4,20]

The penis as a vascular organ may be very sensitive to changes in oxidative stress and systemic NO levels for several reasons. The small diameter of the cavernosal arteries and the high content of endothelium and smooth muscle on a per gram tissue basis (compared to other organs) may make the penile vascular bed a sensitive indicator of systemic vascular disease. Therefore, ED can be the result of any number of structural or functional abnormalities in the penile vascular bed. For instance, ED may result from occlusion of the cavernosal arteries by atherosclerosis (structural vascular ED), impairment of endothelial dependent and/or independent smooth muscle relaxation (functional vascular ED), or a combination of these two factors. Erectile dysfunction caused by functional vascular factors occurs early and is likely linked to oxidative stress and decreased availability of nitric oxide. These functional factors initially result in poor relaxation of penile endothelium and smooth muscle that presents clinically as ED, particularly difficulty maintaining a firm erection. This early clinical symptom of poor maintenance caused by functional endothelial cell dysfunction probably occurs before the development structural, occlusive penile arterial disease and may be one of the earliest signs of systemic cardiovascular disease. Over time, these systemic functional factors can lead to the development of chronic cardiovascular disease.[5]

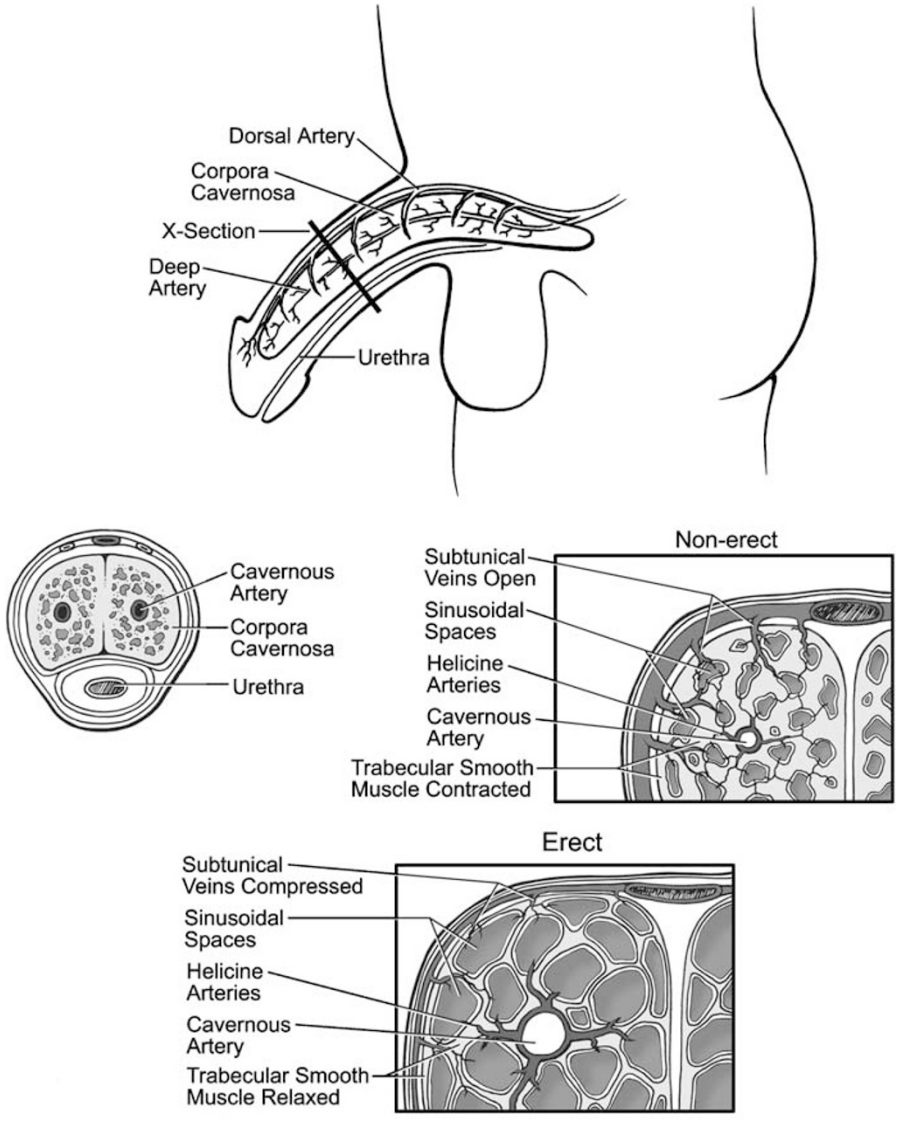

Figure 1 Anatomy of penile erection and detumescence (reproduced with permission from Kevin L Billups, MD).

Erectile dysfunction as an early marker for vascular disease

Recently conducted studies that measured early markers of cardiovascular disease and endothelial dysfunction demonstrate that damage to the penile vascular bed occurs before systemic vascular illness becomes clinically apparent.[21–23] In one study that assessed disease in vascular beds other than the penis, 30 men with Doppler-proven ED and no clinical evidence of cardiovascular disease (mean age: 46 y) did not differ from 27 healthy, age matched controls across a number of measures for peripheral vascular structure and function (ie rapid cat scan imaging for coronary calcification, aortic pulse wave velocity, and carotid intima media thickness), except those that assessed systemic endothelial function using flow mediated brachial artery vasodilatation studies. When compared with controls, men with ED exhibited significantly lower brachial artery flow-mediated, endothelium-dependent vasodilation ($P \leq 0.05$) and endothelium-independent vasodilation (ie, blunted response to 0.4 mg sublingual nitroglycerin; $P = 0.02$), which suggests the presence of a peripheral vascular abnormality in the NO pathway[21] (Figures 2 and 3).

In another study biochemical markers of endothelial cell activation were used to compare 45 men with ED and no clinical cardiovascular disease with 25 age matched normals. The men with ED had penile blood flow Doppler studies that were normal in all except two men. Biochemical and structural markers compared between the ED and normal men included carotid IMT, soluble P-selectin, ICAM-1, VCAM-1, and endothelin-1. Results revealed no

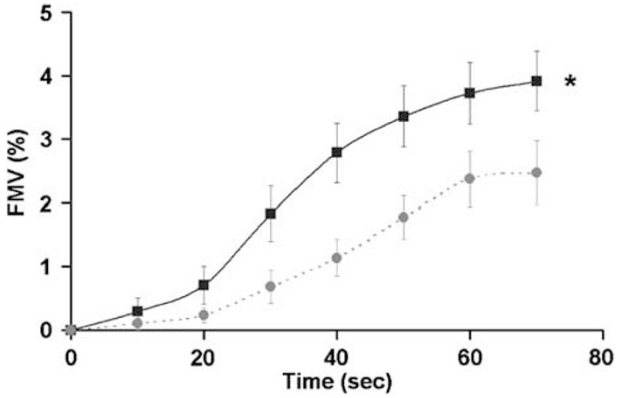

Figure 2 Brachial artery flow mediated vasodilation was significantly reduced in ED (●) *vs* NL (■) over the whole time period ($P=0.014$). The difference was also significant when comparing the percent dilation from baseline to 60 s postcuff release ($P=0.05$).

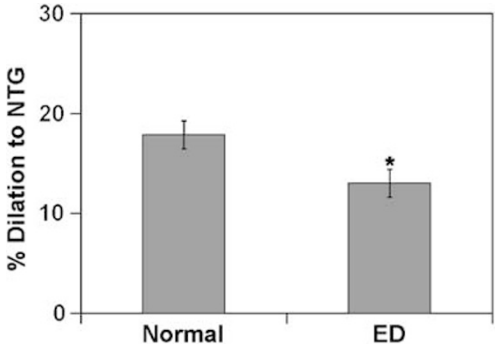

Figure 3 The vasodilator response to 0.4 mg sublingual nitroglycerin was significantly impaired in ED *vs* NL (13.0 ± 1.4 *vs* $17.8\pm1.4\%$, $P=0.02$).

difference in carotid IMT scores between the two groups but soluble P-selectin, ICAM-1, VCAM-1, and endothelin-1 levels were significantly higher in the men with ED and no cardiovascular disease.[22] Results from these two studies support the theory that symptoms of erectile difficulty precede overt structural occlusion of larger vessels, suggesting that ED is an early manifestation of systemic vascular disease.

The incidence of significant carotid arterial disease based on carotid ultrasound in men with ED has also been investigated.[23] A recent study correlated carotid intima-media thickness (carotid IMT) with CV risk factors and severity of ED in a group of 270 men. The men were divided into those who had ED with no know CV risk factors and those who had ED and multiple CV risk factors. Only one man out of 50 with ED and no CV risk factors (mean age 40 y old) had a carotid IMT study that was indicative of significant vascular disease (IMT measurement of 1.0 mm or greater). Of the 220 men with ED and multiple CV risk factors, 18% (39 of the 220 men) show a carotid IMT score indicative of significant vascular damage. Men with abnormal carotid IMT scores had more severe ED. The authors concluded that men with ED and known CV risk factors might benefit from a carotid IMT ultrasound test. The carotid IMT test has been shown to correlate with increased risk of a future adverse vascular event by detecting subclinical carotid artery disease. Those men who are found to have a carotid IMT consistent with significant vascular disease are likely good candidates for aggressive management of the associated CV risk factors to decrease the chance of a future acute vascular event.

Another recent study went a step further by providing evidence that ED may be an independent risk factor for having a future stroke. The study investigators followed 1209 men from The Massachusetts Male Aging Study (MMAS) over a 15-y period. None of these men had any history of stroke, transient ischemic attack, or known disease of the carotid arteries. The study results showed that within the group of 1209 men those who had ED were about 3 times more likely to have a stroke as compared to those men who did not have ED. Even after adjusting for age and other CV risk factors, the men with ED still had a 150% increased risk of having a stroke during the 15-y period.[24]

I believe that ED should be considered not only as an early symptom of cardiovascular disease but also as an emerging risk factor that should lower the threshold to obtain additional screening studies for coronary artery and peripheral vascular disease (ie carotid IMT ultrasound, ankle-brachial index, penile Doppler ultrasound). There may be a new role for penile Doppler ultrasound as a technique to identify men with arterial, vasculogenic ED who might benefit from early aggressive management of cardiovascular risk factors in addition to our standard ED treatments. Such a fundamental shift in thinking could profoundly affect preventive vascular medicine.

Conclusions

Erectile dysfunction is highly prevalent and for many years has been viewed as a complication of cardiovascular disease, diabetes, and hypertension. Certainly, ED and systemic vascular disease share many common risk factors. However, a robust, emerging database offers convincing evidence that ED is more than a serious quality of life issue for sexually active men, particularly those with cardiovascular disease. Penile erection is a vascular process, and the small vessels of the penis are very sensitive to occlusive changes. Endothelial dysfunction, in which damage to the lining of the arterial walls impairs the NO pathway and vasodilation, is an important pathophysiologic factor underlying both ED and cardiovascular disease. As studies in men who have ED but no overt cardiovascular disease have shown, ED may indeed be one of the first clinical manifestations of atherosclerosis,

which begins as a nonobstructive, functional process. This evidence cannot be ignored. Erectile dysfunction must now be considered an early marker of subclinical or undiagnosed cardiovascular disease. The recognition of ED as a harbinger of systemic cardiovascular disease represents a remarkable opportunity for prevention. Unfortunately, misinformation and stigma continues to prevent many men from discussing ED with their physicians and many physicians from aggressively asking men about erectile difficulty in the office setting. I firmly believe that all men 25 y of age and older should be screened for ED, regardless of their clinical presentation and level of sexual function. Patients who are discovered to have ED must be thoroughly and aggressively assessed for cardiovascular risk and occult systemic vascular disease. Clinical studies are beginning to show that treatment of risk factors for cardiovascular disease can improve erectile function. Smoking cessation results in a rapid improvement in erections[2,25] and response rates to Sildenafil therapy are higher among men with fewer vascular risk factors compared with men who have multiple risk factors.[26] A recent study has shown that aggressive intervention with diet and exercise improves ED and endothelial cell function while decreasing systemic inflammatory mediators and the severity of other traditional cardiovascular risk factors.[27] One clinical study revealed that in men with ED caused primarily by elevated LDL cholesterol levels, treatment with Atorvastatin over a 3-month-period resulted in significant improvements in penile rigidity and ED questionnaire scores.[28] Physicians should begin to consider aggressive management of cardiovascular risk factors as part of the overall evaluation and treatment process for ED.

A recent expert advisory panel review article focused on ED as an early marker of systemic atherosclerosis and introduced an algorithm for aggressive management of cardiovascular risk factors in men with ED in the primary care setting[29] (Figure 4). The advisory panel felt that the medical evaluation for ED was essentially the same as the evaluation for CVD. Four key recommendations were made in the paper. First, any man age 25 and older should be asked about ED any time they visit the physician office. Asking about ED should be a routine part of any office clinical evaluation and should be considered as part of the cardiovascular history. Second, all men with ED should have a

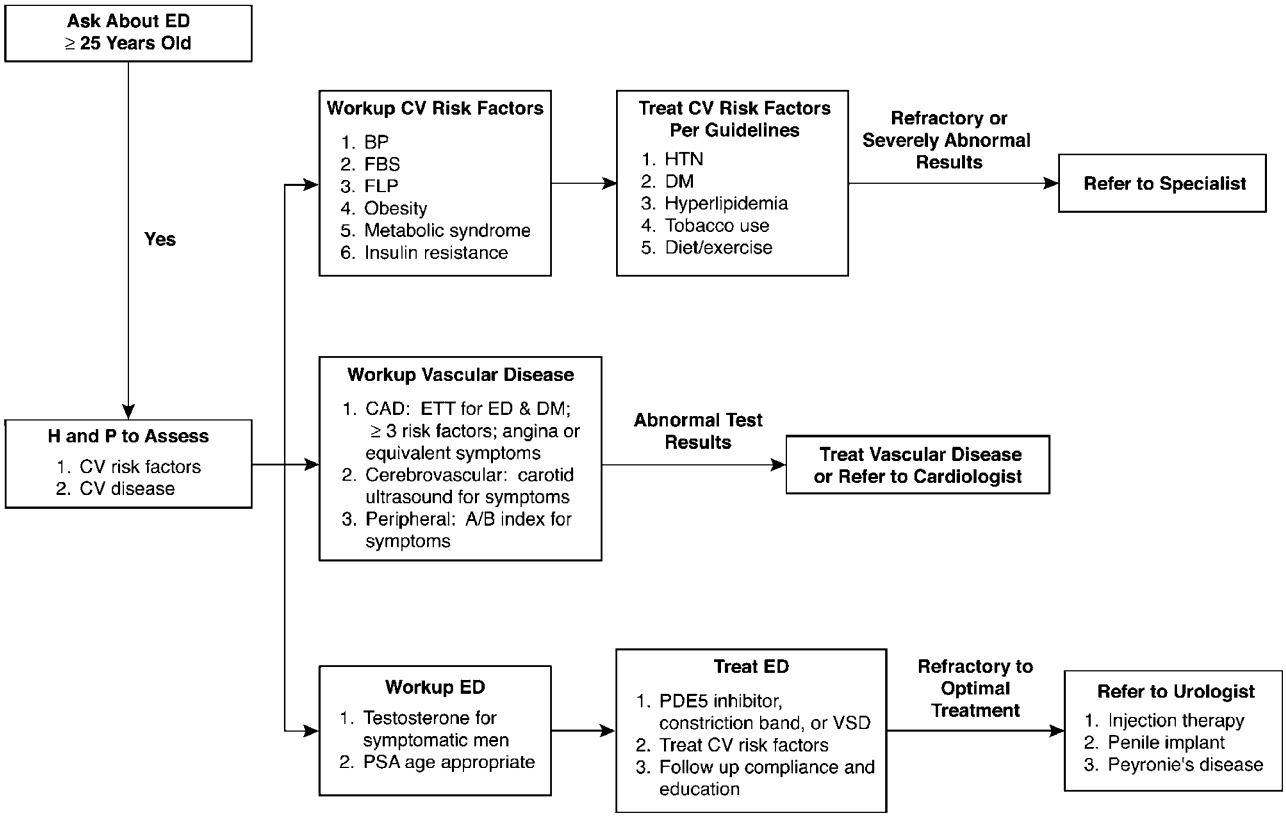

Figure 4 Cardiovascular risk assessment and management algorithm for men with erectile dysfunction seen in a Primary Care clinic setting (reproduced with permission from Kevin L Billups, MD). ED, erectile dysfunction; H and P, history and physical; CV, cardiovascular; BP, blood pressure; FBS, fasting blood sugar; FLP, fasting lipoproteins; HTN, hypertension; DM, diabetes mellitus; CAD, coronary artery disease; ETT, exercise treadmill testing; A/B index, ankle/brachial index; CVD, cardiovascular disease; PSA, prostate specific antigen; PDE5 inhibitor, phosphodiesterase-5 inhibitor; VSD, vacuum suction devices.

thorough assessment of cardiovascular risk factors. Third, it is both logical and medically prudent for physicians to assume that a patient with ED most likely has vascular disease and therefore early aggressive management of associated CV risk factors is warranted. Fourth, cardiovascular risk factors in men with ED should be aggressively managed under the current guidelines for CVD (high blood pressure, cholesterol, metabolic syndrome, and diabetes) to optimal levels. Early aggressive treatment of CV risk factors will both improve overall cardiovascular health and likely improve erectile function.

Much stills needs to be done to improve our understanding of the relationship between ED, systemic vascular disease, and endothelial dysfunction. The implications of this relationship for primary and secondary prevention of cardiovascular disease are not yet fully appreciated. The available literature makes a strong argument for the role of ED as an early marker of cardiovascular disease, and the results of these studies should not be ignored. Future evidence-based data and large-scale prospective studies of young men with ED that longitudinally monitor cardiovascular risk and emergent disease will ultimately validate current aggressive treatment decisions by clinicians and change reimbursement strategies by health care policy makers and insurers.

Education of patients and physicians is another critically underserved area. The importance of ED as a predictor of serious systemic disease must be emphasized in medical school curricula, residency training programs, and continuing medical education programs. Efforts at educating the public via television, radio, print media, and the internet are needed. The role of an individualized therapeutic alliance between the patient, his spouse or partner, and the physician should not be underestimated. Patients who understand that ED is an early waning signal for the onset of serious heart disease will be more likely to follow risk modification strategies, adhere to treatment plans, and achieve positive therapeutic outcomes. Perhaps it is time to elevate the discussion of ED to the level of a public health concern that is associated with prevention of cardiovascular disease.

References

1 NIH Consensus Development Panel on Impotence. NIH consensus conference: impotence. *JAMA* 1993; **270**: 83–90.
2 Derby CA *et al.* Modifiable risk factors and erectile dysfunction: can lifestyle changes modify risk? *Urology* 2000; **56**: 302–306.
3 Maas R, Schwedhelm E, Albsmeier J, Boger RH. The pathophysiology of erectile dysfunction related to endothelial dysfunction and mediators of vascular function. *Vasc Med* 2002; **7**: 213–225.
4 Jeremy JY *et al.* Platelets, oxidant stress and erectile dysfunction: an hypothesis. *Cardiovasc Res* 2000; **46**: 50–54.
5 Jones RWA *et al.* Oxygen free radicals and the penis. *Expert Opin Pharmacother* 2002; **3**: 889–897.
6 Solomon H, Man JW, Jackson G. Erectile dysfunction and the cardiovascular patient: endothelial dysfunction is the common denominator. *Heart* 2003a; **89**: 251–253.
7 Lue TF. Erectile dysfunction. *N Engl J Med* 2000; **342**: 1802–1813.
8 Feldman HA *et al.* Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. *J Urol* 1994; **151**: 54–61.
9 Laumann EO, Paik A, Rosen RC. Sexual dysfunction in the United States: prevalence and predictors. *JAMA* 1999; **281**: 537–544.
10 Virag R, Bouilly P, Frydman D. Is impotence an arterial disorder? A study of arterial risk factors in 440 impotent men. *Lancet* 1985; **1**: 181–184.
11 Jackson G. Erectile dysfunction and cardiovascular disease. *Int J Clin Pract* 1999; **53**: 363–368.
12 Sullivan ME, Keoghane SR, Miller MA. Vascular risk factors and erectile dysfunction. *BJU Int* 2001; **87**: 838–845.
13 Bacon CG *et al.* Association of type and duration of diabetes with erectile dysfunction in a large cohort of men. *Diabetes Care* 2002; **25**: 1458–1463.
14 Moulik PK, Hardy KJ. Hypertension, anti-hypertensive drug therapy and erectile dysfunction in diabetes. *Diabet Med* 2003; **20**: 290–293.
15 Jensen J *et al.* The prevalence and etiology of impotence in 101 male hypertensive outpatients. *Am J Hypertens* 1999; **12**: 271–275.
16 Wei M *et al.* Total cholesterol and high density lipoprotein cholesterol as important predictors of erectile dysfunction. *Am J Epidemiol* 1994; **140**: 930–937.
17 Bacon CG *et al.* Sexual function in men older than 50 y of age: results from the health professionals follow-up study. *Ann Intern Med* 2003; **139**: 161–168.
18 Kirby M, Jackson G, Betteridge J, Friedli K. Is erectile dysfunction a marker for cardiovascular disease? *Int J Clin Pract* 2001; **55**: 614–618.
19 Rehman J, Melman A. Normal anatomy and physiology, chapter 1. In: Mulcahy JJ (ed). *Male Sexual Function. A Guide to Clinical Management.* Humana Press: Totowa, NJ, 2001, pp 1–46.
20 Sullivan ME *et al.* Nitric oxide and penile erection: is erectile dysfunction another manifestation of vascular disease? *Cardiovasc Res* 1999; **43**: 658–665.
21 Kaiser DR *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**: 179–184.
22 Bocchio M *et al.* Endothelial cell activation in men with erectile dysfunction without cardiovascular risk factors and overt vascular damage. *J Urol* 2004; **171**: 1601–1604.
23 Bocchio M *et al.* Intima-media thickening of common carotid arteries is a risk factor for severe erectile dysfunction in men with vascular risk factors but no clinical evidence of atherosclerosis. *J Urol* 2005; **173**: 526–529.
24 Araujo AB, Zilber SM, O'Donnell AB, McKinlay JB. Erectile dysfunction and stroke risk in aging men: prospective results from the Massachusetts Male Aging Study. *J Urol* 2005; **173**: 291.
25 Guay AT, Perez JB, Heatley GF. Cessation of smoking rapidly decreases erectile dysfunction. *Endocr Pract* 1998; **4**: 23–26.
26 Guay AT, Perez JB, Jacobson J, Newton RA. Efficacy and safety of sildenafil citrate for treatment of erectile dysfunction in a population with associated organic risk factors. *J Androl* 2001; **22**: 793–797.
27 Esposito K *et al.* Effect of lifestyle changes on erectile dysfunction in obese men. *JAMA* 2004; **291**: 2978–2984.
28 Saltzman E, Guay A, 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**: 255–258.
29 Billups K *et al.* Erectile dysfunction is a marker for cardiovascular disease: results of the minority health institute expert advisory panel. *J Sex Med* 2005; **2**: 40–52.