

ERECTILE DYSFUNCTION AS A CARDIOVASCULAR RISK MARKER

Dr Colin Teo, Dr Lau Weida

ABSTRACT

Erectile dysfunction is a common problem affecting up to 30 percent of men above 40 years old. Cardiovascular risk factors are closely associated with the development of vasculogenic erectile dysfunction. This explains the keen interest in identifying erectile dysfunction as a cardiovascular risk marker. A review of the literature reveals that erectile dysfunction has been shown to precede the development of coronary artery disease, and a number of hypotheses has been generated to support this association. Hence, it appears paramount that a complete assessment of erectile dysfunction would invariably involve assessment of cardiovascular risk factors and cardiac risk stratification. The Princeton III Consensus recommendation provides a straightforward guide for this purpose. The cardiologist should be involved early in the management of all patients with high cardiovascular risk, and some patients in the intermediate risk group.

Keywords:

Erectile Dysfunction; Cardiovascular Risk Factors; Coronary Artery Disease; Testosterone Deficiency Syndrome; Framingham Risk Score;

SFP2017; 43(1): 26-29

INTRODUCTION

Erection is a complex phenomenon which involves a delicate and coordinated equilibrium among the neurological, vascular, and tissue compartments. It includes arterial dilation, trabecular smooth muscle relaxation, and activation of the corporeal veno-occlusive mechanism. Erectile dysfunction (ED) is defined as the persistent inability to attain and maintain an erection sufficient to permit satisfactory sexual performance.¹

The normal erection requires the autonomic nervous system activation of the parasympathetic system and inhibition of sympathetic activity. Nitric oxide (NO) released from the endothelium is the principal neurotransmitter mediating penile erection. Nitric oxide increases the production of cGMP, which in turn leads to relaxation of cavernous smooth muscle, and increased blood flow to the corpora cavernosa. The congested corpora cavernosa leads to compression of efferent veins, decreasing venous drainage. The significant increase of intracavernous pressure results in erections.

COLIN TEO

Senior Consultant and Head of Department
Department of Urology
Khoo Teck Puat Hospital, Alexandra Health

LAU WEIDA

Associate Consultant
Department of Urology
Khoo Teck Puat Hospital, Alexandra Health

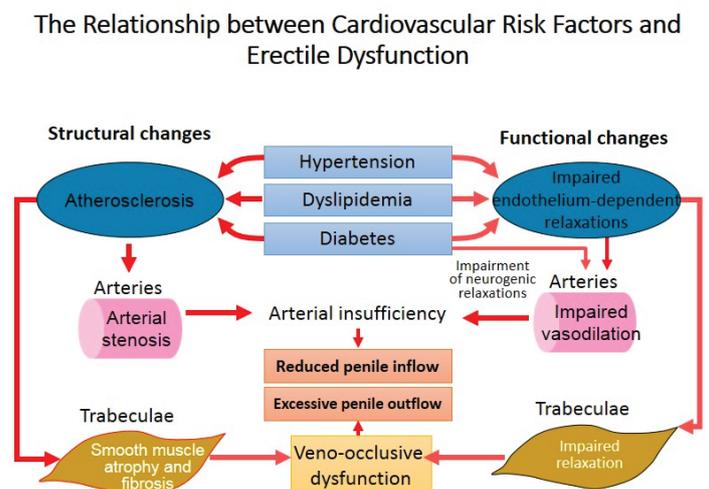
Erectile dysfunction is a common problem with a high prevalence and incidence worldwide. The prevalence worldwide is 16 percent in men aged 20 to 75 years old. The prevalence increases in older age; up to 35–40 percent in men older than 40 years old.² In Singapore, a population-based study involving 729 men more than 30 years old was conducted. Using the International Index of Erectile Dysfunction (IIEF) as a screening tool, up to 51 percent of men had some degree of erectile dysfunction, out of whom 23.2 percent had mild ED, 8.8 percent moderate, and 19.3 percent had severe ED.³

The International Society of Impotence Research classifies erectile dysfunction as being either organic or psychogenic. Organic causes of erectile dysfunction are further differentiated to vasculogenic (arteriogenic, cavernosal, or mixed), neurogenic, anatomic, and hormonal. Vasculogenic causes and their related conditions such as obesity, diabetes mellitus, dyslipidaemia, metabolic syndrome, lack of exercise, and smoking are important risk factors for ED.

PATHOPHYSIOLOGY OF ED AND THE RELATIONSHIP BETWEEN ED AND CAD

Men with ED commonly have underlying vasculogenic conditions which are risk factors for cardiovascular disease. Cardiovascular consequences of underlying conditions include endothelial dysfunction, impaired vasodilation, and development of atherosclerotic lesions. Arterial insufficiency and veno-occlusive dysfunction as a result of underlying conditions leads to reduced blood flow into the penis and excessive outflow, this in turn leads to ED.⁴ (See Figure 1.)

Figure 1: The Relationship between Cardiovascular Risk Factors and Erectile Dysfunction



Adapted from Saenz de Tejada I et al. In: Erectile dysfunction. Eds. A Jardin et al. 2000; 65-102.

In 2000, a subgroup analysis from the prospective random-sample cohort Massachusetts Male Aging Study (MMAS) involving 513 men with no erectile dysfunction, diabetes, or heart disease at baseline, showed prospective evidence that ED shares similar atherogenic risk factors with coronary artery disease (CAD), including active and passive smoking, overweight, hypertension, and diet.⁵

One frequently quoted pathophysiologic mechanism used to explain the association between ED and CAD is the **artery-size hypothesis**. This hypothesis proposed a common pathophysiologic mechanism linking ED and CAD. Given the systematic nature of atherosclerosis, it could be hypothesised that all vascular beds might be affected to the same extent, but the onset of symptoms might be related to the artery size. The size of penile arteries is smaller (1–2mm) compared with that of coronary arteries (3–4mm), and the same level of endothelial dysfunction and atherosclerosis may lead to a more significant reduction of blood flow in erectile tissues compared with that in coronary arteries. Based on this hypothesis, ED affecting penile arteries should usually precede CAD and its symptoms, including angina and myocardial infarction.⁶

This hypothesis has been supported by a study published by JAMA in 2005. In this study, men aged 55 years old or older who were randomised to the placebo group (n=9457) in the Prostate Cancer Prevention Trial (PCPT) were evaluated 3-monthly for cardiovascular disease, ED and cardiovascular disease. Of these men, 8053 had no cardiovascular disease at study entry. After adjustment for important covariates including age, body mass index, blood pressure, serum lipids, diabetes, family history of myocardial infarction, race, smoking history, physical activity, and quality of life, incident ED was associated with a hazard ratio of 1.25 (95% CI:1.02-1.53, 0=0.04) for subsequent cardiovascular events during study follow-up. For men with either incident or prevalent ED, the hazard ratio was 1.45 (95% CI: 1.25-1.69; p<0.001). Noting that these ratios were in the range of risk associated with smoking or family history of myocardial infarction, the authors concluded that ED is a harbinger of cardiovascular clinical events in men.⁷

Another possible association between ED and CAD is the role of inflammation. Low-grade subclinical inflammation affects endothelial function and leads to a prothrombotic status. Studies have reported that ED onset and severity are associated with an increased expression of inflammatory markers. Vlachopoulos et al found that ED was related to an increased circulating level of these inflammatory markers in individuals with or without CAD, but no differences were reported when comparing the circulating levels of pro-inflammatory markers between men with ED alone and those with CAD alone. Thus it was inferred that ED and CAD are equivalent in terms of inflammatory and pro-thrombotic activation, and that ED might confer such an incremental burden on top of CAD.⁸

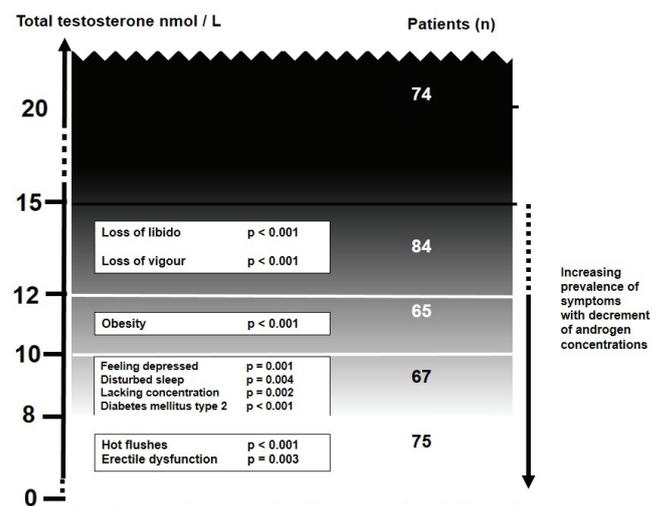
TESTOSTERONE DEFICIENCY SYNDROME LEADING TO CARDIOVASCULAR RISK FACTORS AND ED

Testosterone deficiency syndrome (TDS) is also known as late-onset hypogonadism and andropause. TDS refers to the age-related decline in testosterone levels in ageing men, resulting in various clinical symptoms. As men age, the testes decline in function and testosterone secreted by them decreases. It has been reported that circulating testosterone concentration decreases by 0.4–2.0 percent yearly. This is due to a reduction in the function and size of the Leydig cells of the testes, as well as reduced amplitude of gonadotrophin secretion. In the USA, the crude prevalence of TDS in males aged at least 45 years old is estimated to be 38.7 percent, while in Asian countries, the reported prevalence of hypogonadism (defined as total testosterone <11 nmol/l) was 18.2–19.1 percent.⁹

TDS is increasingly recognised as a risk factor for the metabolic syndrome and its constituents including obesity, hypertension, dyslipidemia, and diabetes mellitus. Other than its association with chronic cardiovascular risk factors, low testosterone levels are also known to be an independent risk factor for mortality. In a study on male veterans, mortality in men with normal testosterone levels was 20.1 percent vs 24.6 percent in men with equivocal testosterone levels and 34.9 percent in men with low testosterone levels. After adjusting for age, medical morbidity, and other clinical covariates, low testosterone continued to be associated with increased mortality (hazard ratio, 1.88; 95% CI, 1.34-2.63, p<0.01), while equivocal testosterone levels were not significantly different from normal testosterone levels.¹⁰

At the same time, an adequate amount of testosterone is essential for the cascading mechanisms driving the penile erection response, including the production of nitric oxide synthase, release of nitric oxide, and augmentation of the synthesis of cGMP leading to arteriolar dilatation and relaxation of the corporeal smooth muscle. Hence it is highly likely that erectile dysfunction may be one of the presenting symptoms of testosterone deficiency.¹¹ [See Figure 2.]

Figure 2: Metabolic Risk Factors and Erectile Dysfunction Associated with Testosterone Deficiency



Adapted from Zitzmann et al. Association of specific symptoms and metabolic risks with serum testosterone in older men. J Clin Endocrinol Metab 2006; 91(11):4335-43

THE EFFECTS OF TESTOSTERONE REPLACEMENT THERAPY AND CARDIOVASCULAR MORTALITY RISKS

There is a significant body of evidence showing that testosterone replacement therapy (TRT) can favourably modify cardiovascular risk factors, including a decrease in insulin resistance, waist circumference, and fat mass. Some studies have also shown that men with metabolic syndrome experience reversal of the features of the syndrome after testosterone replacement.¹²

Two recent publications have raised concern that TRT increases cardiovascular risk. These studies were retrospective observational analyses and have been criticised, based on detailed epidemiologic and statistical analyses. They have been reviewed by the US Food and Drug Administration (FDA) who concluded that, “each of the studies had major limitations, precluding the ability to draw definitive conclusions”.^{13,14} On the other hand, a meta-analysis in 2014 that included 75 randomised, placebo-controlled trials of testosterone treatment and evaluated the incidence of major adverse cardiovascular events, did not find any association between testosterone therapy and actual cardiovascular events.¹⁵

The above controversies led the US FDA to issue a statement in 2015 to state that healthcare professionals should prescribe testosterone therapy only for men with low testosterone levels caused by certain medical conditions and confirmed by laboratory tests; and that healthcare professionals should make patients aware of the possible increased cardiovascular risk when deciding whether to start or continue a patient on testosterone therapy.¹⁶ In the meantime, the majority of international guidelines, including the European Association of Urology (EAU) guidelines on male hypogonadism, as well as the American Association of Clinical Endocrinologists (AACE) guidelines recommend that symptomatic men who have unequivocally low total and/or free testosterone levels confirmed on 2 separate occasions on samples drawn before 10 am, be considered for TRT after fully counselling the patient about the expected benefits and side-effects of the treatment. Patients should be assessed for cardiovascular risk factors before commencing TRT, and secondary prevention in men with pre-existing cardiovascular disease must be optimised.^{17,18}

CARDIOVASCULAR SCREENING AS PART OF ED MANAGEMENT

The Third Princeton Consensus Conference discussed the role of cardiovascular disease screening in ED patients according to cardiovascular risks. For organic ED patients with no previous cardiovascular disease, the panel recommends they be considered at increased risk for cardiovascular disease. The evaluation should include (1) patient history, including age, traditional cardiovascular risk factors, and lifestyle; (2) physical examination, noting blood pressure, waist circumference, BMI, fundal arterial changes, cardiac auscultation, carotid bruits, and palpation of femoral and pedal pulses; (3) ED severity score and

duration; (4) resting electrocardiogram; (5) fasting plasma glucose level; (6) serum creatinine level and albumin-to-creatinine ratio; (7) total testosterone level; and (8) plasma lipid levels. The panel recommends the Framingham Risk Score (FRS) as a starting point for estimating the likelihood of future cardiac events in men with ED.¹⁹ This algorithm was first developed based on data obtained from the Framingham Heart Study to estimate the 10-year risk of developing CAD. The FRS is gender specific, and the variables include age, total cholesterol, cigarette smoking, HDL cholesterol, and systolic blood pressure.²⁰ Having reviewed the above comprehensive list, the physician is advised to individualise the tests to the patient.

After the initial evaluation, exercise ability should be considered to estimate cardiovascular risk associated with sexual activity. Sexual activity is equivalent to walking 1 mile on the flat in 20 min or briskly climbing 2 flights of stairs in 10 sec. Further evaluation using the exercise stress test is required for intermediate-risk patients. These patients are then re-stratified to low- or high-risk based on the results of stress testing.¹⁹

Patients with known cardiovascular disease should be categorised to low, intermediate, and high risk. (See Table 1.) The low-risk group consists of individuals for whom sexual activity does not represent a significant cardiovascular risk. The high-risk group consists of patients with cardiac conditions severe enough to lead to a significant risk related to sexual activity. They should be referred to a cardiologist for further evaluation and receive intensive risk-factors treatment. Similar to patients with intermediate exercise ability, the intermediate cardiovascular risk group should undergo an exercise-stress test to re-stratify to low- or high-risk groups.²¹ In all, the physician, urologist and cardiologist should collaborate closely to diagnose cardiovascular risk factors in patients presenting with ED, implement risk-factor lifestyle modification, and identify patients who would benefit from further cardiology assessment.

Table 1: Cardiac Risk Stratification (based on 2nd Princeton Consensus)

Low-risk category	Intermediate-risk category	High-risk category
Asymptomatic, < 3 risk factors for CAD (excluding sex)	≥3 risk factors for CAD (excluding sex)	High risk arrhythmias
Mild, stable angina (evaluated and/or being treated)	Moderate, stable angina	Unstable or refractory angina
Uncomplicated previous MI	Recent MI (>2, < 6 weeks)	Recent MI < 2 weeks
LVD/CHF (NYHA class I)	LVD/CHF (NYHA class II)	LVD/CHF (NYHA Class III/IV)
Post-successful coronary revascularisation	Non-cardiac sequelae of atherosclerotic disease (eg. Stroke, peripheral vascular disease)	Hypertrophic obstructive and other cardiomyopathies
Controlled hypertension		Uncontrolled hypertension
Mild valvular disease		Moderate-to-severe valvular disease

CONCLUSION

Erectile Dysfunction and CAD should be considered 2 different presentations of the same systemic disorder. The associations between the 2 conditions include cardiovascular risk factors, chronic inflammation and testosterone deficiency, leading to

atherosclerosis and endothelial dysfunction. There is adequate evidence to show that ED precedes CAD, and its presentation should prompt further assessment of cardiovascular risk factors and CAD. There are existing algorithms to guide the evaluation of patients with ED for cardiovascular disease.

REFERENCES

- Hatzimouratidis K, Giuliano F, Moncada I, Munner A, Salonia A, Verze P. EAU guidelines on erectile dysfunction, premature ejaculation, penile curvature and priapism. In: EAU Guidelines 2016 edition; March 2016.
- Rosen RC, Fisher WA, Eardley I, Niederberger C, Nadel A, Sand M, et al. The multinational Men's attitudes to life events and sexuality (MALES) study: I Prevalence of erectile dysfunction and related health concerns in the general population. *Curr Med Res Opin*. 2004;20:607–17.
- Tan JK, Hong CY, Png DJ, Liew LC, Wong ML. Erectile Dysfunction in Singapore: prevalence and its associated factors — a population-based study. *Singapore Med J*. 2003;44:20–6.
- Saenz de Tajeda I, Gonzalez-Cadavid N, et al. "Anatomy, physiology and pathophysiology of erectile dysfunction". In: Jardin A, Wagner G, Khoury S, Giuliano F, Padma-Nathan H, Rosen R, eds. *Erectile Dysfunction*. Plymouth: Health Publication Ltd; 2000. p. 65–102.
- Feldman HA, Johannes CB, Derby CA, Kleinman KP, Mohr BA, Araujo AB, et al. Erectile dysfunction and coronary risk factors: prospective results from the Massachusetts male aging study. *Prev Med*. 2000;30:328–38.
- Gandaglia G, Briganti A, Jackson G, Kloner RA, Montorsi F, Montorsi P et al. A systematic review of the association between erectile dysfunction and cardiovascular disease. *Eur Urol*. 2014;65:968–78.
- Thompson IM, Tangen CM, Goodman PJ, Probstfield JL, Moinpour CM, Coltman CA. Erectile dysfunction and subsequent cardiovascular disease. *JAMA*. 2005;294:2996–3002.
- Vlachopoulos C, Aznaouridis K, Ioakeimidis N, Stefanadis C. Unfavourable endothelial and inflammatory state in erectile dysfunction patients with or without coronary artery disease. *Eur Heart J*. 2006;27:2640–8.
- Society for Men's Health. Testosterone Deficiency Syndrome Guidelines. Singapore: Society for Men's Health; 2013.
- Shores MM, Matsumoto AM, Sloan KL, Kivlahan DR. Low serum testosterone and mortality in male veterans. *Arch Intern Med*. 2006;166:1660–5.
- Zitzmann M, Faber S, Nieschlag E. Association of specific symptoms and metabolic risks with serum testosterone in older men. *J Clin Endocrinol Metab*. 2006;91:4335–43.
- Yassin DJ, Doros G, Hammerer PG, Yassin AA. Long-term testosterone treatment in elderly men with hypogonadism and erectile dysfunction reduces obesity parameters and improves metabolic syndrome and health-related quality of life. *J Sex Med*. 2014;11:1567–76.
- Vigen R, O'Donnell CI, Baron AE, Grunwald GK, Maddox TM, Bradley SM, et al. Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. *JAMA*. 2013;310:1829–36.
- Finkle WD, Greenland S, Ridgeway GK, Adams JL, Frasco MA, Cook MB, et al. Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men. *PLoS One*. 2014;9:e85805.
- Corona G, Maseroli E, Rastrelli G, Isidori AM, Sforza A, Mannucci E, et al. Cardiovascular risk associated with testosterone-boosting medications: a systematic review and meta-analysis. *Expert Opin Drug Saf*. 2014;13:1327–51.
- US FDA report March 3, 2015. [Internet] Available from <http://www.fda.gov/drugs/drugsafety/ucm436259.htm>
- Dohle GR, Arver S, Bettocchi C, Jones TH, Kliesch, Punab M. EAU guidelines on male hypogonadism. In: EAU Guidelines 2016 edition. March 2016.
- Goodman N, Guay A, Dandona P, Dhindsa S, Faiman C, Cunningham GR, et al. American Association of Clinical Endocrinologists and American College of Endocrinology position statement on the association of testosterone and cardiovascular risk. *Endocr Pract*. 2015;21:1066–73.
- Nehra A, Jackson G, Miner M, Billups KL, Burnett AL, Buvat J, et al. The Princeton III Consensus recommendations for the management of erectile dysfunction and cardiovascular disease. *Mayo Clin Proc*. 2012;87:766–78.
- Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation*. 1998;97:1837–47.
- Kostis JB, Jackson G, Rosen R, Barrett-Connor E, Billups K, Burnett AL, et al. Sexual dysfunction and cardiac risk (the Second Princeton Consensus Conference). *Am J Cardiol*. 2005;96:313–21.

LEARNING POINTS

- **Current evidence has established ED as a cardiovascular risk marker.**
- **A patient with ED and cardiovascular risk factors should be screened for testosterone deficiency as a common aetiology.**
- **Patients with ED should be appropriately screened for cardiovascular risk factors and cardiovascular diseases according to established recommendations.**
- **Cardiovascular risk stratification aids in the involvement of cardiologists in the management of patients with intermediate or high cardiovascular risks.**