

Erectile dysfunction heralds onset of cardiovascular disease

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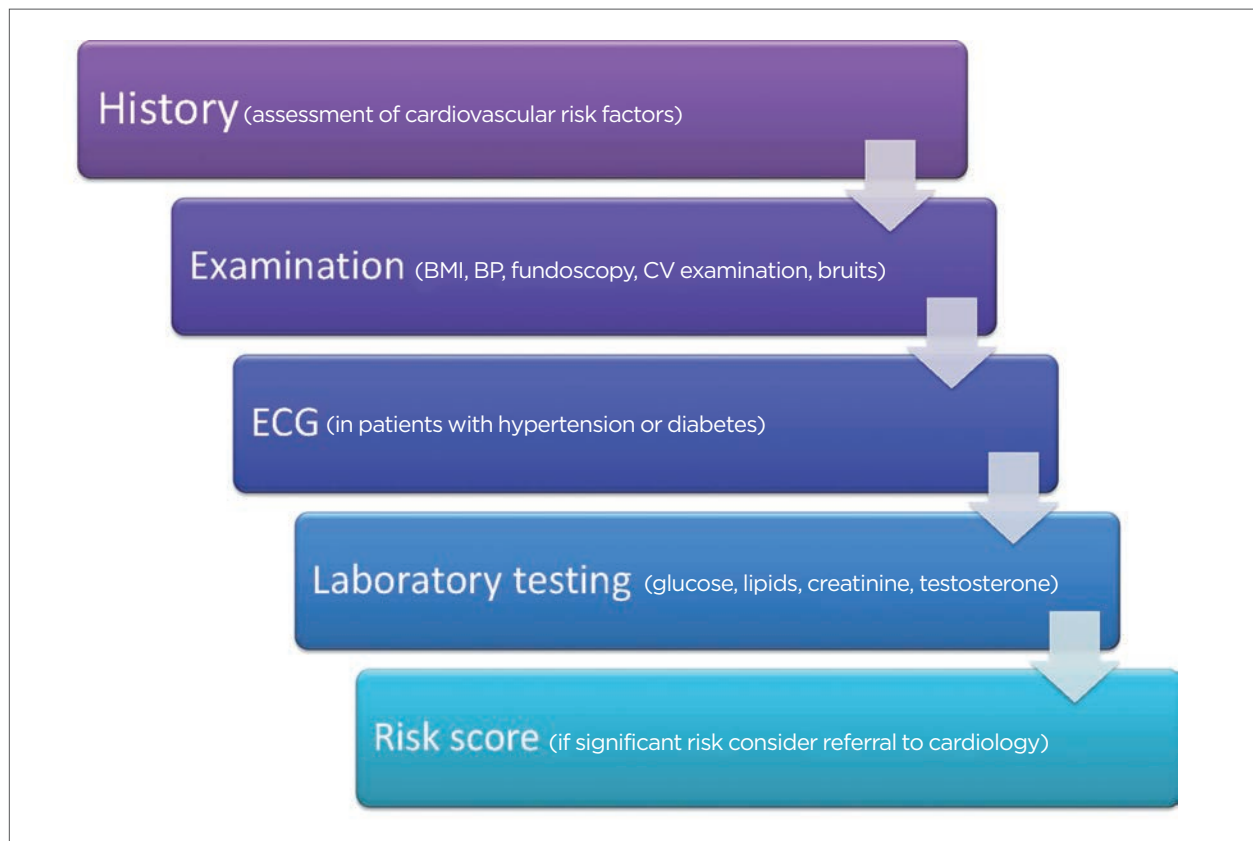
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FIGURE 1

Flow diagram for cardiovascular risk assessment and management of men with erectile dysfunction in primary care



What is the link between erectile dysfunction and CVD?



ERECTILE DYSFUNCTION (ED) RELATES TO THE INABILITY TO ACHIEVE OR SUSTAIN AN ERECTION FOR

the duration of sexual intercourse. Around 150 million men are estimated to have ED and this figure is predicted to increase to 320 million by 2025.¹

ED is usually graded using the International Index of Erectile Dysfunction (IIEF-5)² which has a high sensitivity (98%) and specificity (88%).³ ED was once assumed to be a psychological condition but has now been shown to share risk factors with cardiovascular disease including age, diabetes mellitus, smoking, hypertension and hypercholesterolaemia, suggesting an underlying vascular pathology.⁴

How should cardiovascular risk be assessed?

Evidence reveals that there is a potential link between ED and subsequent development of coronary artery disease.⁵⁻¹³ ED itself may also increase cardiovascular risk.^{14,15} Cardiovascular disease is a leading cause of mortality and morbidity worldwide. Current efforts are focused

‘The severity of erectile dysfunction has been linked with the severity of coronary artery disease’

Which patients should be referred?

on primary prevention and early detection of coronary artery disease. Therefore, patients presenting with ED may provide an early opportunity to identify at-risk individuals.

This article explores the evidence for the link between ED and cardiovascular disease, proposed mechanisms and recommendations for the assessment of patients who present with ED in primary care.

EVIDENCE FROM TRIALS

Many studies have explored the association between ED and cardiovascular risk. These include sub-studies of large trials such as the Prostate Cancer Prevention Trial.⁵ Of the 9,457 men with ED at entry

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those who developed ED during follow-up had a significant risk of subsequent cardiovascular events compared with subjects without ED. Other trials have reported similar findings.^{6,7} These findings have been corroborated by meta-analyses of cohort studies,⁸ as well as systematic reviews.⁹ The relative risk of developing coronary artery disease within ten years, in patients with moderate to severe ED, has been calculated as 14% in men aged 30-39 years and may be as high as 27% in those aged 60-69.¹⁰

‘Erectile dysfunction may also be an independent predictor of cardiovascular risk and mortality’

The association appears greater when younger men presenting with ED are considered. In a retrospective study comparing atherosclerotic events in a group of patients with ED versus an equivalent general male population with normal erectile function, the former group had a significantly higher rate of cardiovascular events, particularly those presenting at a young age.¹¹ In another case control study of patients referred for coronary angiography,¹² the severity of coronary artery disease was higher in patients with ED who were under 60.

Furthermore, in studies looking specifically at a younger cohort (20-60 years), 86% of the subjects who underwent coronary angiography were found to have co-existent ED.¹³ This highlights the importance of risk factor management and its consideration even at a young age.

The severity of ED has also been linked with the severity of coronary artery disease. A recent study⁶ compared SYNTAX scores in men undergoing coronary angiography with ILEF-5 scores. The SYNTAX score was developed for the SYNTAX trial and is an angiographic scoring system which separates patients into low, intermediate and high risk when undergoing percutaneous coronary intervention.

Men with moderate to severe ED had a significantly higher SYNTAX score compared with men with normal erectile function. The correlation between severity of coronary artery disease and ED has been duplicated in

other studies using alternate measures of severity of coronary artery disease.¹⁶

ED AS AN INDEPENDENT PREDICTOR OF CV RISK

Although ED and cardiovascular disease share many risk factors there is evidence that ED may also be an independent predictor of cardiovascular risk and mortality. A meta-analysis of 12 prospective cohort studies including 36,744 subjects¹⁴ concluded that ED significantly increased the risk of cardiovascular disease, stroke and all cause mortality. This was corroborated in a subsequent meta-analysis of 14 longitudinal studies including 92,757 subjects, detecting the ability of ED to predict events.¹⁵

The effect on increased risk of mortality is largely due to the effect of ED on cardiovascular mortality and its hazard ratios are comparable with those obtained for conventional cardiovascular risk factors.

MECHANISMS

In order to achieve and maintain an erection, there is active relaxation of the cavernosal arteries and passive restriction of venous outflow. This is mediated by the nitric oxide cyclic guanosine monophosphate (cGMP) pathway. Nitric oxide also has anti-atherogenic effects. Endothelial dysfunction is partly thought to be caused by impairment of the nitric oxide pathway and can occur throughout the arterial tree. Evidence in support of ED mediated by endothelial dysfunction comes from studies of patients with obstructive coronary artery disease undergoing endothelial function testing.¹⁷ In these patients levels of inhibitors of nitric oxide synthetase, which catalyses the production of nitric oxide, was noted to be higher in patients with severe ED.

A study comparing men with ED and vascular risk factors and men with ED and no vascular risk factors¹⁸ showed that biochemical markers of endothelial dysfunction were raised in those with ED and this was independent of vascular risk factors.

The presence therefore of endothelial dysfunction as assessed by the surrogate of ED may be a silent marker of the same disease process in the coronary tree. In fact, endothelial dysfunction itself has been associated with an increased risk of future cardiovascular events.^{19,20} Atherosclerosis is thought to be driven by inflammation secondary to endothelial damage of the intimal layer of an artery and therefore the same

process giving rise to coronary artery disease is thought to occur in the cavernosal arteries.

The artery size hypothesis has been proposed to explain the link between the two, whereby a larger vessel is able to tolerate a higher plaque burden but a smaller artery cannot²¹ and may explain why ED occurs before manifestation of coronary artery disease.

CARDIOVASCULAR RISK ASSESSMENT

There is likely to be a delay between presentation with ED and clinical presentation with coronary artery disease. In one study, ED was found to present 39 months prior to coronary symptoms.^{6,7} This provides the clinician with an opportunity to modify risk. Recommendations from the Mayo Clinic²² and a recently published review²³ regarding initial review of patients with ED include a full history, with assessment of cardiovascular risk factors (hypertension, prediabetes, diabetes, hypercholesterolaemia, smoking status and family history of premature cardiovascular disease), dietary and lifestyle assessment.

‘The artery size hypothesis may explain why erectile dysfunction occurs before manifestation of coronary artery disease’

A thorough clinical examination assessing BMI, measurement of blood pressure, examination of fundi, cardiovascular examination, auscultation for carotid bruits and vascular examination should also be performed, see figure 1, p21. An ECG is recommended in patients with hypertension or diabetes. Laboratory testing should include fasting glucose, lipid profile, creatinine and testosterone.

Risk stratification should also be performed using a conventional cardiovascular risk score. Those with a significant QRISK score or JBS3 risk score should be referred to a cardiologist. The consensus opinion^{22,24} is that intermediate- or high-risk patients should undergo exercise stress testing or CT coronary angiography

key points

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Erectile dysfunction (ED) was once assumed to be a psychological condition but has now been shown to share risk factors with cardiovascular disease including age, diabetes mellitus, smoking, hypertension and hypercholesterolaemia, suggesting an underlying vascular pathology. Evidence reveals that there is a potential link between ED and subsequent development of coronary artery disease. ED itself may also increase cardiovascular risk.

The relative risk of developing coronary artery disease within ten years, in patients with moderate to severe ED, has been calculated as 14% in men aged 30-39 years and may be as high as 27% in those aged 60-69. The association appears greater when younger men presenting with ED are considered. The severity of ED has also been linked with the severity of coronary artery disease.

The proposed pathological mechanisms are based on a theory of endothelial dysfunction which eventually leads to atherosclerosis. This occurs first in more vulnerable narrow diameter vessels such as the cavernosal arteries. The artery size hypothesis may explain why ED occurs before manifestation of coronary artery disease.

There is likely to be a delay between presentation with ED and clinical presentation with coronary artery disease. In one study, ED was found to present 39 months prior to coronary symptoms. This provides GPs with a valuable window of opportunity for risk assessment, subsequent primary prevention and early referral to a cardiologist.

Initial review of patients with ED includes a full history, with assessment of cardiovascular risk factors, dietary and lifestyle assessment. A thorough clinical examination assessing BMI, measurement of blood pressure, examination of fundi, cardiovascular examination, auscultation for carotid bruits and vascular examination should also be performed. An ECG is recommended in patients with hypertension or diabetes. Laboratory testing should include fasting glucose, lipid profile, creatinine and testosterone. Risk stratification should also be performed using a conventional cardiovascular risk score. Those with a significant QRISK score or JBS3 risk score should be referred to a cardiologist.

In patients with identified cardiovascular risk factors aggressive primary prevention should be carried out including weight loss, exercise prescription, dietary modification to address hypercholesterolaemia and glucose handling, tight control of blood pressure, and smoking cessation advice.

(CTCA). Although exercise testing may be low yield in risk stratifying patients CTCA has shown more promise.²⁵ Cardiology referral and tailored investigations may be a good compromise in equivocal cases. Nevertheless, in patients with identified cardiovascular risk factors aggressive primary prevention should be carried out including weight loss, exercise prescription, dietary modification to address hypercholesterolaemia and glucose handling, tight control of blood pressure, and smoking cessation advice.

'As erectile dysfunction often predates the development of coronary artery disease this provides GPs with a window for risk assessment'

CONCLUSION

The link between ED and coronary artery disease is well supported in the literature. Studies have shown that severity of ED predicts severity of coronary artery disease.

The proposed pathological mechanisms are based on a theory of endothelial dysfunction which eventually leads to atherosclerosis. This occurs first in more vulnerable narrow diameter vessels such as the cavernosal arteries.

Furthermore, ED itself may be an independent risk factor for cardiovascular disease as well as cardiovascular related mortality. As ED often predates the development of coronary artery disease this provides GPs with a valuable window of opportunity for risk assessment, subsequent primary prevention and early referral to a cardiologist.

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