

# Erectile dysfunction as a predictor of coronary artery disease

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The authors review the evidence suggesting that erectile dysfunction may be an early warning sign of more widespread vascular disease.

Increasing evidence to suggest that erectile dysfunction (ED) may predict coronary artery disease (CAD) has led to the publication of guidance for the assessment and treatment of men with ED.<sup>1</sup> ED with an underlying physical cause and CAD both result from endothelial dysfunction, which restricts blood flow.<sup>2,3</sup> The two conditions also have similar risk factors, which include obesity, diabetes, hypertension, dyslipidaemia and smoking.<sup>4-7</sup>

Many men with ED have early signs of CAD.<sup>1</sup> In otherwise healthy men and those with type 2 diabetes, the presence of ED has been associated with early, subclinical signs of CAD, including significantly reduced coronary flow velocity reserve, endothelium-dependent and -independent vasodilation and coronary artery calcification.<sup>2,8-11</sup>

Symptoms of ED appear before those of CAD in about two-thirds of men.<sup>12</sup> This has been attributed to the arteries supplying the penis being much smaller than those supplying the myocardium.<sup>13</sup> Although atherosclerosis is a systemic disease and all arteries are likely to be affected to a similar extent, a plaque would need to reach a much greater size to cause symptoms of reduced blood flow in a larger artery than in a smaller artery. This may explain why men with ED rarely experience overt symptoms of CAD, while those with CAD often have concomitant ED (Box 1).<sup>1</sup>

## BOX 1. Hypothesis to support erectile dysfunction (ED) as a predictor of coronary artery disease (CAD)

- ED symptoms preceding CAD symptoms could be attributable to differences in the size of the arteries supplying the penis and myocardium
  - atherosclerosis is a systemic disease
  - all vessels should theoretically be affected to the same extent



- Hypothesis suggests larger arteries may not demonstrate an appreciable reduction in blood flow (manifesting as CAD symptoms) until plaque has reached a much greater size than in smaller arteries (eg supplying the penis)

Studies suggest that ED symptoms may precede CAD symptoms by around two to three years and a cardiovascular event (myocardial infarction or stroke) by around three to five years.<sup>14-16</sup>

Men with ED generally appear to have more severe CAD than those without, and ED severity may reflect CAD severity.<sup>14,17-19</sup>

Go to the Trends website ([www.trendsurology.com](http://www.trendsurology.com)) to view Mike Kirby's video on erectile dysfunction as a marker of cardiovascular disease



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In men with ED, the risk of experiencing a cardiovascular event within a 10-year timeframe is increased by 1.3–1.6 times compared to those without.<sup>20,21</sup> ED is associated with an increased risk of all-cause mortality, mainly through its association with CAD mortality.<sup>22</sup>

**ASSESSING THE PATIENT WITH ED FOR CAD**

Because ED may be a marker for early CAD,<sup>23</sup> the guidance recommends that men with ED symptoms receive a thorough medical assessment, including measurement of blood pressure, fasting lipids and glucose, to aid risk estimation and identify opportunities for early medical intervention. Patients should then be stratified as being at low, medium or high risk of cardiovascular events. Men at increased risk of CAD should be further evaluated by stress testing. If these results appear normal, coronary computed tomography angiography should be considered in selected patients, to assess the need for an aggressive risk-reduction treatment.<sup>1</sup>

**PREVENTING CARDIOVASCULAR EVENTS IN PATIENTS WITH ED**

The interval between onset of ED and symptomatic CAD provides an excellent opportunity for risk-factor reduction. Modification of lifestyle factors is the first step. In men with a body mass index of 30kg/m<sup>2</sup> or the metabolic syndrome, reducing calorie intake and increasing physical activity can significantly reduce weight, decrease inflammatory markers and improve sexual function.<sup>24–27</sup>

Patients with established cardiovascular risk factors such as hypertension, hyperlipidaemia and diabetes should be managed with appropriate pharmacotherapy,<sup>28</sup> with treatment tailored to the individual. A target low-density lipoprotein-cholesterol of 2mmol/l or less is recommended.<sup>1</sup>

**MANAGING ED IN PATIENTS WITH CAD**

Cardiovascular function and symptoms should be stabilised before initiating

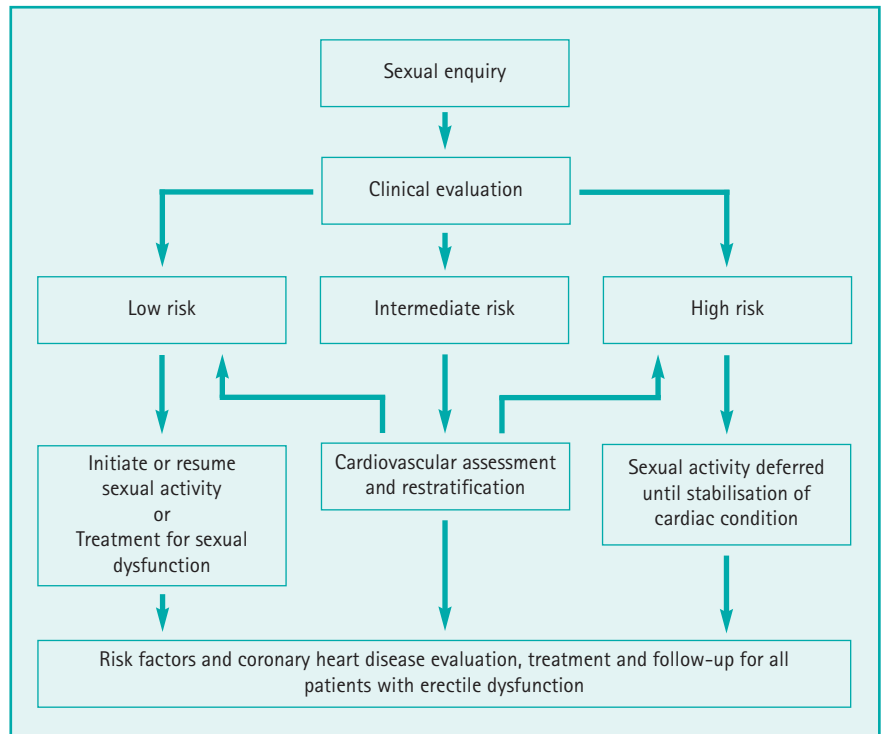


Figure 1. Princeton II evaluation algorithm for men with erectile dysfunction<sup>28</sup>

**BOX 2. Management recommendations for men at low risk of a cardiovascular event<sup>30</sup>**

**CATEGORIES OF CARDIOVASCULAR DISEASE**

- Asymptomatic, less than three major risk factors for coronary artery disease
- Controlled hypertension
- Mild, stable angina
- Post-successful coronary revascularisation
- Uncomplicated past myocardial infarction (>6–8 weeks)
- Mild valvular disease
- Left ventricular dysfunction/congestive heart failure (New York Heart Association class I)

**MANAGEMENT RECOMMENDATIONS**

- Primary care management
- Consider all first-line therapies
- Reassess at regular intervals (6–12 months)

treatment for ED.<sup>1</sup> The patient's exercise tolerance should be assessed, because the unaccustomed exertion of sexual activity may increase the risk of a cardiovascular event.<sup>29</sup> Those with low tolerance should be advised to start a graduated exercise programme, and be reassessed at a later date.<sup>1</sup>

Risk assessment is also based on the type and extent of cardiovascular disease.<sup>1</sup> The Princeton II risk categories for sexual activity can be used to classify patients as low, intermediate or high risk (Figure 1). Those at low risk require no specialised cardiac evaluation before starting

treatment for ED and resuming sexual activity, and can be safely managed in primary care. Patients at intermediate risk require further investigation in order for them to be classified as either low or high risk. In high-risk patients, sexual activity may trigger an ischaemic event and should be deferred until they have received specialised cardiac evaluation and treatment (Boxes 2–4).<sup>28,30</sup>

Clinical evidence supports the use of phosphodiesterase type 5 (PDE5) inhibitors first-line in men with ED and CAD.<sup>1</sup> Because they potentiate the effects of nitrates, PDE5 inhibitors are contraindicated in patients taking these agents.<sup>29</sup>

Consideration should be given as to whether the nitrates are an essential part of the treatment package, as they confer no prognostic benefit and therefore may be withdrawn and alternative anti-ischaemic therapy introduced, allowing PDE5 inhibitors to be prescribed.

When oral agents are inappropriate or ineffective for the treatment for ED, other options include transurethral alprostadil, intracavernosal injection therapy, a vacuum pump and penile prosthesis, all of which require specialist referral and advice.

#### PATIENTS WITH DIABETES

Men with diabetes should receive the same assessment and management of their lifestyle and comorbidities as those without the disease. PDE5 inhibitors are recommended first-line in men with ED and diabetes. If these agents are unsuccessful, patients should be referred for specialist assessment and management.<sup>1</sup>

#### TESTOSTERONE MEASUREMENT IN MEN WITH ED

Low testosterone levels are associated with the presence of a number of established cardiovascular risk factors and an increased risk of cardiovascular events.<sup>1</sup> To help define cardiovascular risk and aid optimal therapy, the guidance recommends

#### BOX 3. Management recommendations for men at intermediate risk of a cardiovascular event<sup>30</sup>

##### CATEGORIES OF CARDIOVASCULAR DISEASE

- Three major risk factors for coronary artery disease, excluding gender
- Moderate, stable angina
- Recent myocardial infarction (>2, <6 weeks)
- Left ventricular dysfunction/congestive heart failure (New York Heart Association class II)
- Non-cardiac sequelae of atherosclerotic disease (eg cerebrovascular accident, peripheral vascular disease)

##### MANAGEMENT RECOMMENDATIONS

- Specialised cardiovascular testing (eg exercise tolerance test, echocardiogram)
- Restratification into high risk or low risk based on the results of cardiovascular assessment

#### BOX 4. Management recommendations for men at high risk of a cardiovascular event<sup>30</sup>

##### CATEGORIES OF CARDIOVASCULAR DISEASE

- Unstable or refractory angina
- Uncontrolled hypertension
- Left ventricular dysfunction/congestive heart failure (New York Heart Association class III/IV)
- Recent myocardial infarction (<2 weeks), cerebrovascular accident
- High-risk arrhythmias
- Hypertrophic obstructive and other cardiomyopathies
- Moderate/severe valvular disease

##### MANAGEMENT RECOMMENDATIONS

- Priority referral for specialised cardiovascular management
- Treatment for sexual dysfunction to be deferred until cardiac condition stabilised and dependent on specialist recommendations

that testosterone levels are measured in all men with ED, and particularly those with chronic illnesses associated with low testosterone (eg diabetes and heart failure) or those who fail to respond to PDE5 inhibitors.<sup>31,32</sup>

Testosterone replacement therapy may lead to symptomatic improvement of wellbeing and enhance the effectiveness of PDE5 inhibitors. There is no evidence to suggest that testosterone replacement therapy increases cardiovascular risk.<sup>1</sup>

#### FOLLOW-UP OF THE PATIENT WITH ED AND CAD

Follow-up to review cardiovascular status and response to ED therapy should be performed at regular intervals.<sup>1</sup> Follow-up of patients starting treatment for ED should include assessment of the impact the sexual activity is having on their cardiovascular status and evaluation of their response to, and satisfaction with, the treatment.<sup>29</sup>

Once stable on ED therapy, the patient should receive regular follow-up to

monitor his cardiovascular status and efficacy of treatment. He should be informed that it may take a number of trials, with one or more treatments, before the best one is found. The patient's partner should be involved in the consultations wherever possible, to give feedback on the success of ED treatment.

### CONCLUSION

The increasing awareness of ED as a barometer for cardiovascular health represents an opportunity to improve primary prevention of vascular disease and cardiovascular events in men with and without diabetes. However, men are notoriously reticent about seeking help for sexual problems, and this was highlighted in a study investigating the relationship between ED and cardiovascular disease in 372 patients from GP practices across the UK. Results showed that in almost half of men with ED, there were missed opportunities to perform risk assessment for cardiovascular disease and provide intervention, because the men did not acknowledge or discuss the fact that they had a problem.<sup>16</sup>

Although matters may have improved since then, these findings highlight the need for doctors and nurses to be proactive in enquiring about sexual function with male patients aged 40 years and over, when they present for other reasons. It is also essential that enquiry about sexual function is on the template for routine discussion about diabetes, hypertension and secondary prevention of cardiovascular disease, and the presence of ED should be a trigger for optimisation of risk-factor control.

### Declaration of interests

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# you write

## Darunavir once-daily



In News & Notes (May/June 2011;2(3):6), the headline 'Darunavir once-daily for all' is misleading, as darunavir (Prezista) once-daily is specifically licensed for patients with HIV-1 infection who are:

- treatment naïve
- treatment experienced with no darunavir-resistant mutations.

Secondly, HIV-1 RNA copies and CD4 counts are not relevant in deciding patients' eligibility for treatment with darunavir. It is also important to emphasise that darunavir/ritonavir is licensed for use in combination with other antiretroviral drugs for treatment of HIV-1 infection.

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Editorial comment: We apologise to readers for the misleading headline and we hope that Janssen's reply opposite clarifies any confusion over the use of darunavir.



In line with European Medicines Agency labels, darunavir (Prezista) is licensed for use in HIV-positive patients as follows:

- 75mg, 150mg and 600mg tablets may be used to provide suitable dose regimens:
  - for the treatment of HIV-1 infection in antiretroviral treatment (ART)-experienced adult patients, including those who have been highly pretreated
  - for the treatment of HIV-1 infection in ART-experienced children and adolescents from the age of six years and at least 20kg body weight.

*In deciding to initiate treatment with darunavir co-administered with low-dose ritonavir, careful consideration should be given to the treatment history of the individual patient and the patterns of mutations associated with different agents. Genotypic or phenotypic testing (when available) and treatment history should guide the use of darunavir.*

- 400mg tablets may be used to provide suitable dose regimens:
  - for the treatment of HIV-1 infection in ART-naïve adults
  - for the treatment of HIV-1 infection in ART-experienced adults with no darunavir resistance-associated mutations and who have plasma HIV-1 RNA <100 000 copies/ml and CD4+ cell count ≥100 cells x 10<sup>6</sup>/l. In deciding to initiate treatment with darunavir in such ART-experienced adults, genotypic testing should guide its use.

*With regard to viral load and CD4 criteria in treatment-experienced patients, this only applies to once daily use as per the label above. The final decision to use darunavir in any patient lies with the treating clinician.*

**Dr Michael Aboud, Medical Lead, Anti-Infective, Janssen**