GUIDELINE

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Erectile dysfunction and coronary artery disease prediction: evidence-based guidance and consensus

Editor's Choice

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SUMMARY

- A significant proportion of men with erectile dysfunction (ED) exhibit early signs of coronary artery disease (CAD), and this group may develop more severe CAD than men without ED (Level 1, Grade A).
- The time interval among the onset of ED symptoms and the occurrence of CAD symptoms and cardiovascular events is estimated at 2–3 years and 3–5 years respectively; this interval allows for risk factor reduction (Level 2, Grade B).
- ED is associated with increased all-cause mortality primarily due to increased cardiovascular mortality (Level 1, Grade A).
- All men with ED should undergo a thorough medical assessment, including testosterone, fasting lipids, fasting glucose and blood pressure measurement. Following assessment, patients should be stratified according to the risk of future cardiovascular events. Those at high risk of cardiovascular disease should be evaluated by stress testing with selective use of computed tomography (CT) or coronary angiography (Level 1, Grade A).
- Improvement in cardiovascular risk factors such as weight loss and increased physical activity has been reported to improve erectile function (Level 1, Grade A).
- In men with ED, hypertension, diabetes and hyperlipidaemia should be treated aggressively, bearing in mind the potential side effects (Level 1, Grade A).
- Management of ED is secondary to stabilising cardiovascular function, and controlling cardiovascular symptoms and exercise tolerance should be established prior to initiation of ED therapy (Level 1, Grade A).
- Clinical evidence supports the use of phosphodiesterase 5 (PDE5) inhibitors as first-line therapy in men with CAD and comorbid ED and those with diabetes and ED (Level 1, Grade A).
- Total testosterone and selectively free testosterone levels should be measured in all men with ED in accordance with contemporary guidelines and particularly in those who fail to respond to PDE5 inhibitors or have a chronic illness associated with low testosterone (Level 1, Grade A).
- Testosterone replacement therapy may lead to symptomatic improvement (improved wellbeing) and enhance the effectiveness of PDE5 inhibitors (Level 1, Grade A).
- Review of cardiovascular status and response to ED therapy should be performed at regular intervals (Level 1, Grade A).

Review Criteria

We performed an extensive search for articles concerning ED and CAD using multiple sources including PubMed, organizational websites and the expertise of the consensus members. All articles were assessed for levels of evidence and graded accordingly.

Message for the Clinic

ED and CAD frequently coexist. ED may be a marker (warning sign) for occult CAD with a window of opportunity for CAD risk reduction of 2–5 years. All men with CAD should be asked about ED as treatment options are safe and effective for the majority. ED is associated with increased all-cause mortality primarily due to increased cardiovascular mortality. Recognizing this link between ED and CAD may improve lives and also save lives.

Introduction

Erectile dysfunction (ED) is defined as the persistent inability to achieve and then maintain an erection to permit satisfactory sexual intercourse (1). The severity of ED is classified as mild to severe, according to the International Index of Erectile Function (2). Organic ED (i.e. that with an underlying physical aetiology) and coronary artery disease (CAD) are closely linked, as they are both consequences of endothelial dysfunction, leading to restrictions in blood flow (3,4). Similar risk factors have been identified for both conditions, including obesity, diabetes, smoking, hypertension and dyslipidaemia (5–8).

The aim of this study is to explore the hypothesis that ED is a predictor for CAD and review the

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assessment and management of cardiovascular risk in ED patients and ED in cardiac patients, according to the clinical evidence available.

What is the evidence to support ED as a predictor of CAD?

- A significant proportion of men with ED exhibit early signs of CAD.
- Men with pre-existing ED may develop more severe CAD than those without ED.
- The interval between the onset of ED symptoms and the occurrence of CAD symptoms is estimated at 2–3 years and a cardiovascular event at 3–5 years.
- There is a common endothelial pathology underlying both ED and CAD.
- Erectile dysfunction is associated with increased all-cause mortality primarily through its association with CAD mortality.

Clinical trial data suggest that the presence of ED in otherwise healthy men and in those with type 2 diabetes may be associated with early (subclinical) signs of CAD that may not be detectable during stress testing (9–13). These include significantly reduced coronary flow velocity reserve, endothelium-dependent and -independent vasodilation and coronary artery calcification (3,14–17). Furthermore, penile vascular disease in men with ED is associated with significant changes in established cardiovascular risk factors such as fasting lipids, fasting glucose, body mass index (BMI), C-reactive protein (CRP) and homocysteine (3,18–21).

Men with ED generally exhibit more severe CAD and left ventricular dysfunction than those without ED (22–24), and the severity of ED may also be correlated with the severity of CAD (23,25). Reduced peak penile systolic velocity (PPSV; i.e. blood flow) is also correlated with the risk of CAD as well as the degree and distribution of atherosclerotic lesions (16,26,27). It should be noted, however, that penile Doppler testing cannot be reliably used to identify at-risk men because of its average sensitivity and specificity, low positive predictive value and high negative predictive value (28).

In around two-thirds of men, the onset of CAD is preceded by ED (9). A number of studies have estimated the interval between the onset of ED symptoms and the occurrence of CAD symptoms as 2–3 years and a cardiovascular event [myocardial infarction (MI) or stroke] as 3–5 years (23,29,30), although longer time frames have been reported (31). In younger men (aged 40–69 years), ED may be a predictor of future CAD and cardiac events, whereas in men aged ≥ 70 years, the prognostic importance of ED is unclear (31,32). Using Framingham risk scores, the relative risk of developing CAD within 10 years in men with moderate-severe ED has been estimated as 4.9% in those aged 30–39 years, increasing to 21.1% in those aged 60–69 years (33). This compares with 4.3% and 16.6% in men without ED for the same age groups, i.e. an increase in relative risk of 1.14 and 1.27 respectively. The risk of experiencing a cardiovascular event within a 10-year timeframe is increased by 1.3–1.6 times in men with ED vs. men without ED (34,35). This compares with a factor of 1.4 for a family history of MI and 1.1 for a 20 mg/dl (0.52 mmol/l) increase in serum cholesterol concentration (34). ED is associated with increased all-cause mortality primarily through its association with CAD mortality (36).

It has been hypothesised that the phenomenon of ED symptoms preceding CAD symptoms is attributable to the differences in the size of the arteries supplying the penis and myocardium (37). Although atherosclerosis is a systemic disease, and all vessels should theoretically be affected to the same extent, this hypothesis suggests that larger arteries may not demonstrate an appreciable reduction in blood flow (manifesting as CAD symptoms) until a plaque has reached a much greater size than in smaller arteries such as those supplying the penis. It may underpin the findings that men with ED seldom report overt symptoms of CAD, whereas those with CAD will often report pre-existing ED symptoms. Furthermore, the presence of ED is associated with more severe CAD as silent atherosclerosis that may have been developing for a number of years prior to symptom onset. However, this is not always the case as many patients have severe CAD (presenting as acute coronary syndromes) in the absence of ED (9).

When and how should the patient with ED be assessed for CAD?

- All men with ED should undergo a thorough medical assessment.
- Following assessment, patients should be stratified according to their risk of future cardiovascular events.
- Those men at increased CAD risk should be evaluated by stress testing that may include investigations such as exercise electrocardiography (ECG), thallium stress testing, echocardiographic stress testing or chemical stress testing.
- However, exercise ECG demonstrates low sensitivity in men with ED, and a second imaging test may be necessary.
- In selected high-risk patients where stress testing appears normal, coronary computed tomography (CT) angiography should be considered.

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Erectile dysfunction may be a marker of early CAD, i.e. prior to plaque rupture (38). Men with ED should therefore undergo a thorough medical assessment, including blood pressure, fasting lipids and glucose measurement to facilitate risk stratification (low, intermediate or high risk of cardiovascular events) and identify opportunities for early medical intervention. Following this initial evaluation where doubt exists, stress testing is indicated to further define the individual patient's cardiovascular risk during moderate exercise, e.g. sex or walking 1 mile in 20 min (39).

- Low risk: > 4 min of treadmill exercise according to the Bruce protocol, normal blood pressure response, no symptoms, no ECG changes, no development of reversible perfusion defects on thallium imaging, no transient echo wall motion abnormalities on exercise or chemical stress testing.
- Intermediate/high risk: symptoms, ECG changes or abnormal blood pressure response apparent before 4 min of treadmill exercise completed. This is particularly helpful to the non-cardiologist caring for the ED population.

During treadmill exercise testing, men with ED may demonstrate a reduced exercise duration vs. men without ED (22,24). Furthermore, the incidence of CAD identified during treadmill exercise ECG is increased with increasing severity of ED, as measured by mean PPSV (26,27). However, in some men with ED who have subclinical non-flow-limiting CAD, a stress ECG may appear normal (12). In such individuals, other evaluations should be considered (38), such as stress echocardiography, which can more accurately detect obstructive but not non-obstructive CAD and locate the diseased vessels (40). Non-invasive, non-contrast enhanced CT, which may be used to detect coronary calcification and calculate the coronary artery calcium score (CACS) (41,42) and minimally invasive CT coronary angiography, which can allow quantification of stenoses and exclude significant CAD in individuals with a low or intermediate CACS (41) should be considered in selected patients to determine the need for an aggressive risk reduction treatment strategy.

Can cardiovascular events be prevented by intervention following the onset of ED?

- The documented interval between the onset of ED and symptomatic CAD allows for timely risk factor intervention.
- Weight loss and increased physical activity may improve erectile function.
- Medical treatment of hypertension, diabetes and hyperlipidaemia, and wherever necessary smoking cessation, should be initiated as appropriate.

Modification of lifestyle factors in men with ED is the first step in preventing future cardiovascular events. In obese men (BMI ≥ 30 kg/m^2) with ED, reduced calorie intake and increased physical activity can significantly reduce weight, decrease the concentrations of inflammatory markers (e.g. CRP) and improve erectile function (43–45). Similar results have been observed in men with the metabolic syndrome and comorbid ED (46). In men undertaking or maintaining an active lifestyle, the incidence of ED is significantly lower than in those men with a sedentary lifestyle (47). Unfortunately, there is limited evidence that once ED has occurred it can be reversed by initiation of an active lifestyle, although for overall health benefit this is recommended.

Established cardiovascular risk factors such as hypertension, diabetes and hyperlipidaemia should be managed with appropriate medical therapy (48). However, treatment should be tailored to the individual patient, as certain drugs used in the treatment of cardiovascular disease may be associated with the development of ED or exacerbation of existing ED. These include beta-blockers, thiazide diuretics, calcium channel blockers, statins, fibrates and ACE inhibitors (6,49–56) (Table 1). However, unless ED developed within 4 weeks of initiating drug therapy, there is little evidence to support switching the suspect drug to alleviate the symptoms of ED (57). Furthermore, ED may be a result of the underlying cardiovascular pathology rather than the drugs used for its treatment (58).

Conversely, in men with ED and hypertension, angiotensin II receptor blockers may improve sexual function and may be the drug of first choice in sexually active men, especially as the potential for adverse effects is low (59–61). In a number of studies involving men with ED and comorbid hypercholesterolaemia, treatment with a statin has been reported to significantly reduce low-density lipoprotein (LDL)-cholesterol concentrations and also to improve erectile function (62,63). Among men with type 2 diabetes, ED and silent CAD, treatment with statins and phosphodiesterase 5 (PDE5) inhibitors have been reported to be associated with a significant reduction in major adverse cardiac events (64). We recommend the treatment to a target LDL-cholesterol of 2 mmol/l (80 mg/dl) or less.

Table 1 Association between selected cardiac medications and ED

Drug class	Clinical trial findings
Alpha-blockers	No increased risk of ED in hypertensive men (49)
	Increased risk of ED in men with diabetes (50)
Beta-blockers	No increased risk of ED in hypertensive men (6,49)
	No significant association with ED in patients at high risk for cardiovascular disease (52)
	Increased risk of ED in men with hypertension taking non-selective beta-blockers (53)
	No increased risk of ED in men with hypertension taking selective beta-blockers (53)
	No increased risk of ED in men with diabetes (50)
	Nebivolol not associated with ED, possible benefit (57)
Thiazide diuretics	Non-significant association with increased incidence of ED in hypertensive patients (6)
	No significant association with ED in patients at high risk for cardiovascular disease (52)
	Significantly increased risk of ED in men with hypertension (53)
	Reduced risk of ED in men with diabetes (50)
Calcium channel blockers	No significant association with ED in patients at high risk for cardiovascular disease (52)
	Significantly increased risk of ED in men with hypertension (53)
	No increased risk of ED in men with diabetes (50)
	No increased risk of ED in hypertensive men (49)
ACE inhibitors	No significant association with ED in patients at high risk for cardiovascular disease (52)
	No increased risk of ED in men with hypertension (49,53)
	Increased risk of ED in men with diabetes (50)
Angiotensin receptor blockers (ARBs)	Not associated with ED (59,60)
	May improve ED (59,60)
Statins	No increased risk of ED in men with CAD (53)
	Increased risk of ED (55,56)
Fibrates	Increased risk of ED (54,56)

What are the key considerations in managing ED in the CAD patient?

- Management of ED is secondary to stabilising cardiovascular function and controlling cardiovascular symptoms.
- Treatment for ED should not impact negatively upon the cardiovascular status.
- Exercise tolerance should be established prior to initiation of ED therapy.
- Clinical evidence supports the use of PDE5 inhibitors as first-line therapy in men with CAD and comorbid ED.

A patient's exercise tolerance should be evaluated prior to initiation of any ED treatment, as the increased exertion associated with sexual activity may increase the risk of cardiovascular events (58). In men with a low exercise tolerance, a graduated exercise programme should be recommended and exercise tolerance re-evaluated after a predefined period of time. The extent and type of cardiovascular disease present should also form the basis of risk assessment (Table 2)(48).

Patients categorised as low-risk require no special cardiac testing or evaluation prior to the initiation of treatment for ED and resumption of sexual activity, and they can be managed within primary care (48). The high-risk category consists of patients whose cardiac conditions are sufficiently severe and/or unstable that sexual activity may pose a significant risk of ischaemic events. These individual patients should be referred for specialised cardiac assessment and treatment. Sexual activity should be deferred until their cardiovascular status has been stabilised by treatment or a decision has been made by a cardiologist that sexual activity may be safely resumed. Those patients considered as having an intermediate risk require further evaluation so that they can be definitively classified as low or high risk (Figure 1) (48).

The efficacy and safety of PDE5 inhibitors in improving erectile function in patients with clinical cardiovascular disease or cardiovascular risk factors have been established in numerous randomised controlled clinical trials. As tadalafil and vardenafil were more recently licensed than sildenafil, there are, by default, fewer published clinical trials specific to tadalafil and vardenafil in the cardiac populations.

In men with mild-moderate chronic heart failure or stable CAD, sildenafil has been shown to improve erectile function and enhance intercourse, while being associated with few adverse cardiovascular effects and no adverse effects on exercise parameters (65–69). Similarly, in men taking multiple antihypertensive agents, sildenafil and vardenafil improve erec-

Table 2 Risk categorisation for sexual activity [adapted from Ref. (48)]

Risk classification	Risk factors
Low	Asymptomatic, < 3 cardiovascular risk factors
	Controlled hypertension
	Mild, stable angina pectoris
	Postrevascularisation (no significant residual ischaemia)
	MI > 6 weeks previously
	Mild valvular disease
	Left ventricular dysfunction (New York Heart Association class I)
	Pericarditis
	Mitral valve prolapse
	Atrial fibrillation with controlled ventricular response
Intermediate	Asymptomatic, ≥ 3 cardiovascular risk factors (excluding gender)
	Moderate, stable angina pectoris
	Recent MI (≥ 2 weeks, < 6 weeks)
	Left ventricular dysfunction (NYHA class II)
	Non-cardiac sequelae of atherosclerotic disease (peripheral vascular disease, history of stroke or transient ischaemic attack)
High	Unstable or refractory angina pectoris
	Uncontrolled hypertension
	Congestive heart failure (NYHA class III or IV)
	Recent MI (< 2 weeks)
	High-risk arrhythmia
	Obstructive hypertrophic cardiomyopathy
	Moderate–severe valvular disease, especially aortic stenosis

MI, myocardial infarction; NYHA, New York Heart Association.

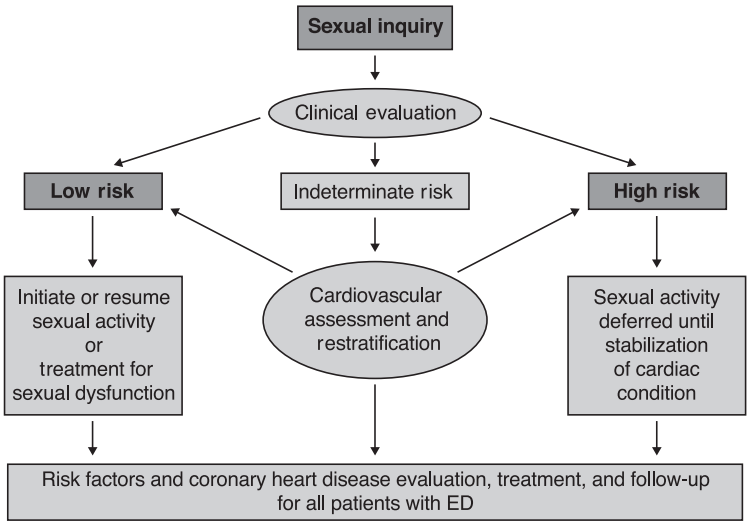

Figure 1 Princeton II evaluation algorithm for men with erectile dysfunction (ED) (48)

tile function and are well tolerated (70,71). Tadalafil achieves improvements in men with ED and hypertension treated with or without thiazide diuretics, and vardenafil is effective in men with ED and comorbid hypertension and/or dyslipidaemia (72–74). In clinical trials evaluating PDE5 inhibitors, slight decreases in mean blood pressure have been observed, but this is generally transient and asymptomatic. Furthermore, postmarketing surveillance studies have demonstrated that sildenafil and tadalafil are not associated with an increased risk of cardiovascular events (75–77). The short half-lives of sildenafil and vardenafil could be an advantage for patients with more severe cardiovascular disease,

allowing early use of supportive treatment if an adverse clinical event occurs (78,79).

Phosphodiesterase 5 inhibitors are known to potentiate the effects of nitrates, leading to potentially clinically significant reductions in blood pressure, and are therefore contraindicated in patients taking these agents (58). Two strategies may be adopted for the management of ED in such patients: using a different type of therapy for ED, or switching the patient to an alternative anti-ischaemic therapy and using a PDE5 inhibitor for the treatment of ED. Switching the anti-ischaemic therapy is an option because nitrates are a symptomatic treatment and are no more effective than placebo in reducing the risk of cardiovascular events in these patients (80). If the second approach is chosen, an interval of at least 1 week should be allowed between the discontinuation of nitrate therapy and initiation of PDE5 treatment. When oral agents are not effective for the treatment of ED, intracavernous injection therapy, transurethral alprostadil, a vacuum pump and surgical implantation of a penile prosthesis are alternatives requiring specialised referral and advice (81).

When should testosterone concentrations be measured?

- A low testosterone concentration is associated with increased risk of cardiovascular events and the presence of numerous established cardiovascular risk factors.
- A low testosterone may inhibit the effectiveness of PDE5 inhibitors.
- There is currently no evidence that testosterone replacement therapy increases cardiovascular risk.

The testosterone deficiency syndrome (TDS) is an established cause of ED (82), and there is increasing evidence that it is also associated with all-cause mortality and in particular, cardiovascular death (83–87). As TDS is also associated with type 2 diabetes, metabolic syndrome, visceral fat accumulation, abnormalities of coagulation, inflammatory cytokines and dyslipidaemia, it is clearly integral to other cardiovascular risk factors (86–88).

One of the problems in detecting TDS is the lack of awareness of its existence among the general medical community, including cardiologists. In addition, the signs and symptoms may (rather unhelpfully) not be specific to TDS. However, with the accumulating evidence of an association among TDS and cardiovascular comorbidities and an increased risk of mortality when compared with men with normal testosterone levels, there is a compelling need to screen men at risk of low testosterone levels (86). Testosterone (and selectively free testosterone) levels should be measured in all men with ED in accordance with contemporary guidance, particularly in those who fail to respond to PDE5 inhibitors or who have a chronic illness associated with low testosterone (e.g. heart failure, diabetes)(59,60). Although the American College of Physicians states there is no evidence for routine hormonal testing, we believe that testing will further help us to clinically elaborate risk, given the association among low testosterone, metabolic syndrome and type 2 diabetes, and facilitate optimal therapy (89).

While there is no clinical evidence that testosterone replacement therapy reduces cardiovascular risk or all-cause mortality (randomised trials are needed), there are clinical data to support a symptomatic benefit in hypogonadal men with angina or heart failure (90,91). Importantly, there is no evidence to suggest that testosterone replacement therapy increases cardiovascular risk.

Practically, what are the key steps in the follow up of the patient with ED and CAD?

- Review of cardiovascular status and response to ED therapy should be performed at regular intervals.

Initial follow up of cardiac patients starting ED therapy should include an assessment of the impact of the increased exertion associated with sexual activity on their cardiovascular status, evaluation of ED treatment response and satisfaction with treatment (58). Once the patient is stable on ED therapy, regular follow up consultations should monitor their cardiovascular status and continuing efficacy of ED therapy. The patient should be made aware that a number of trials with one or a number of agents may be necessary before finding the correct one for them. If possible, the patient's partner should be involved in all consultations to provide feedback regarding the success of ED treatment.

Should patients with diabetes be treated differently?

- Men with diabetes should be assessed and managed for their lifestyle and comorbidities in a similar way to men without diabetes.
- PDE5 inhibitors are first-line treatment for ED in men with comorbid diabetes.
- If PDE5 inhibitor therapy is unsuccessful, patients should be referred for specialist assessment and management.

Erectile dysfunction is a marker for silent CAD in men with type 2 diabetes (13,92). The issue of ED in men with diabetes should therefore be discussed by healthcare professionals at least annually, and men with diabetes who develop ED should be encouraged to report their symptoms as soon as possible (NICE Guidelines 2008). If ED is diagnosed, a PDE5 inhibitor is the recommended first-line treatment in these patients (in the absence of contraindications) (93). This decision is supported by evidence from numerous clinical trials evaluating sildenafil, tadalafil and vardenafil in men with ED and diabetes, which have demonstrated that they significantly improve erectile function and increase the likelihood of successful intercourse attempts in men with diabetes (94–98). Importantly, the efficacy of sildenafil, tadalafil and vardenafil is not altered by the degree of glycaemic control or by the presence of diabetes-related complications (99–102). Although the incidence of cardiovascular adverse effects in diabetic men receiving sildenafil in clinical studies is slightly higher than in those receiving placebo (94,96), this is because of the increased risk of events in diabetics rather than sildenafil and does not represent a contraindication to sildenafil therapy. Sildenafil is more effective, if cardiovascular risk factors are well controlled (103).

Is ED associated with increased mortality?

- ED is significantly associated with increased all-cause mortality
- ED is primarily associated with increased cardiovascular mortality

The prospective population-based study of 1709 men in the Massachusetts Male Aging Study (MMAS) report on a follow-up of 15 years (36). The main outcome measures were all-cause mortality, cardiovascular disease (CVD), malignant neoplasms and other causes. Of 403 men who died, 371 had complete data. After adjusting for age, body mass index, alcohol intake, hypertension and diabetes, men with ED had a 26% higher risk for all-cause mortality and a 43% higher risk of death due to CVD compared with men without ED. In this study ED predicted mortality primarily due to CVD as strongly as established cardiovascular risk factors.

In 1549 men with cardiovascular disease ED was evaluated as a predictor of mortality and cardiovascular outcomes in the ONTARGET/TRANSEND trial (104). ED was evaluated at baseline, at 2-year follow-up and at the penultimate visit before the end of the study. After adjusting for possible confounders, ED was significantly predictive of all-cause death and the composite of cardiovascular death, myocardial infarction, stroke and heart failure in men with CVD. The identification of men with ED and CVD therefore offers the opportunity for aggressive risk reduction treatment to further reduce cardiovascular events and potentially lengthen life.

How can strategies for professional and public awareness of the link between ED and cardiovascular disease be improved?

The evidence supporting the relationship between ED and cardiovascular disease has continued to increase over recent years, and yet healthcare professional and public recognition around the association between the two conditions remains very limited. Specialists in the management of ED support the evidence that patients with cardiovascular disease are at risk of experiencing ED, because, importantly, ED is a critical predictor of cardiovascular disease. As authors of this publication, we hope that the evidence and consensus detailed here will encourage greater international interest and research in the subject. We encourage onward and widespread communication of our messages through all relevant public and patient associations. Recognising the relationship between ED and CAD will improve lives and save lives (105).

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