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Treatment of Erectile Dysfunction in Patients with Cardiovascular Disease

Guide to Drug Selection

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Contents

Abstract

Erectile dysfunction (ED) is common in cardiac patients and shares the same risk factors – smoking, hypertension, hyperlipidaemia and diabetes mellitus. Sexual activity is not unduly stressful to the heart and, providing patients are properly assessed using established guidelines, sexual intercourse can be enjoyed without increased risk. The treatment of ED in patients with cardiovascular disease has been transformed by the introduction of the oral phosphodiesterase type 5 inhibitors, the first of which was sildenafil. Success in restoring erectile

function is possible in up to 80% of patients (depending on the aetiology) with minimal adverse effects. A synergistic hypotensive effect with nitrates, and almost certainly nicorandil, is the only major contraindication. ED in asymptomatic patients may be a marker of silent vascular disease or increased vascular risk factors and should alert the physician to the need for cardiac risk screening. ED is common in patients with cardiovascular disease and should be routinely enquired about. ED is a distressing condition for the man and his partner, and severely impairs quality of life. Patients with cardiovascular disease and patients with diabetes represent the largest group of patients with ED, the majority of whom benefit from the drug therapies currently available. Addressing ED in patients with cardiovascular disease can lead to a substantial improvement in quality of life and success is not difficult to achieve.

Erectile dysfunction (ED) is the persistent inability to achieve and maintain an erection sufficient to permit sexual intercourse.[1] In the general population ED affects, to a varying severity, up to 52% of men aged 40–70 years.[2] In 1995, it was estimated that ED affected over 152 million men worldwide. As ED increases in incidence with age (a man aged 70 years is three times more likely to have ED than a man aged 40 years) and as we are an aging population, it is estimated that by the year 2025 over 300 million men worldwide will have some degree of ED.[3]

ED is a very distressing condition that not only negatively impacts on the man's sexual ability but also quality of life overall, both for the man and his partner. ED leads to depression, anxiety and loss of self-esteem and can contribute significantly to 20% of relationship breakdowns.[4] Men are reluctant to seek help for fear of not being taken seriously or out of embarrassment[5] (figure 1) and become isolated within their relationship, which may lose all aspects of intimate contact. The tragedy is that treatment is readily available and highly effective, yet not utilised by many. Nearly 90% of men who have successful treatment for their ED report significant improvement of overall and emotional well-being. Therefore, driving men alone or as a couple to seek help is a major educational challenge which needs to be met by medical, social and political initiatives.

The aetiology of ED was until recently felt to be predominantly psychogenic, but with our increasing knowledge of the physiology of penile erection and pathophysiology of ED, it is now recognised to be mainly an organic condition with vascular disease responsible for 70% of cases.[6] For most men the aetiology may be multifactorial, especially in the elderly (75% of men aged over 80 years have ED), with endocrine, cellular, neural and iatrogenic causes exacerbating vascular ED or being independently causative. Organic ED will have psychological consequences that must be recognised and addressed as part of the overall management.

This article provides an overview of the drug treatment options for patients with cardiovascular disease and ED, and discusses the wider issues of ED acting as a marker for occult vascular disease, especially coronary artery disease (CAD).

1. Physiology of Penile Erection

A penile erection occurs in response to stimuli which may be visual, erotic, olfactory, auditory or

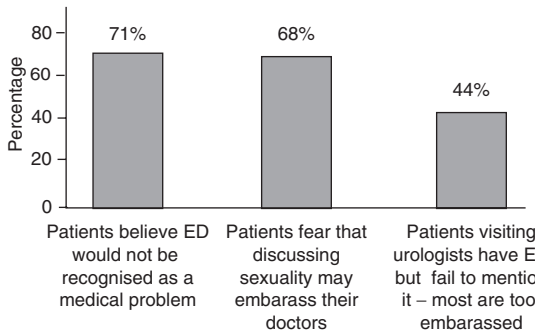


Fig. 1. Patients are reluctant to talk to their doctors about erectile dysfunction (ED) – why?[5]

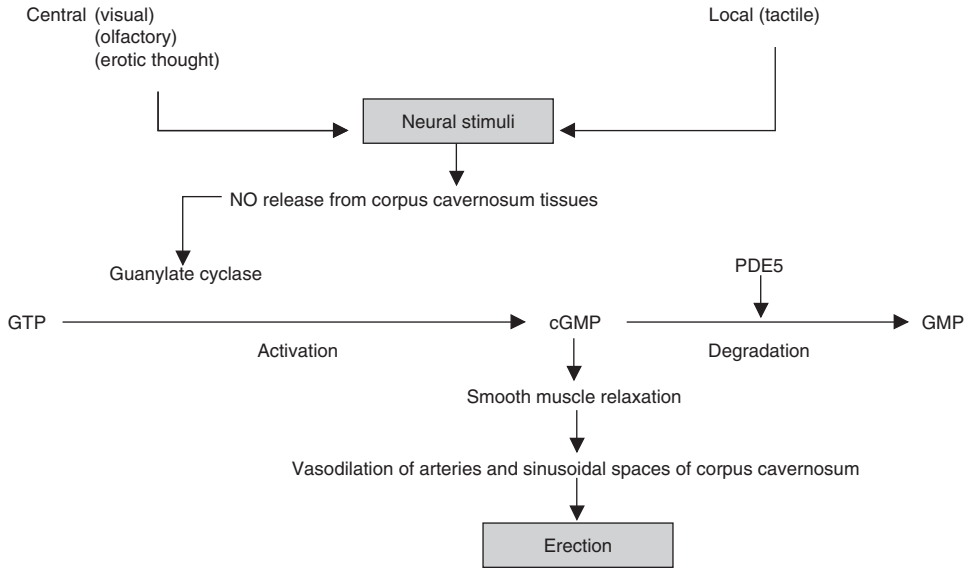


Fig. 2. Mechanism of penile erection (reproduced from Giuliano,[7] with permission from The European Society of Cardiology). **cGMP** = cyclic guanosine monophosphate; **GTP** = guanosine 5′-triphosphate; **NO** = nitric oxide; **PDE5** = phosphodiesterase 5.

tactile.[6] It is a neurovascular event which may be modulated by hormonal and psychological factors. On sexual stimulation there is increased parasympathetic activity and decreased sympathetic activity. The parasympathetic nerves release neurotransmitters, of which the most important is nitric oxide (NO) which is also released by the vascular endothelium (figure 2).[7] NO activates a soluble guanylate cyclase which raises the intracellular concentration of cyclic guanosine monophosphate (cGMP). cGMP then activates a specific protein kinase which leads to the inhibition of calcium channels and the opening of potassium channels. The end result is relaxation of the smooth muscle in the penile arteries and the spongy tissue of the corpora cavernosa. A several-fold increase in blood flow to the penis occurs and as the penis becomes erect with intracavernosal pressures of up to 100mm Hg venous outflow is occluded and the erection is sustained. cGMP is regulated by phosphodiesterase (PDE)5 which enzymatically degrades and inactivates this cyclic nucleotide. Penile rigidity is lost and flaccidity returns. When we consider the cascade of events, there are several areas where disturbances in the neurovascular sequence might lead to ED, but most attention has focused on PDE5 and its inhibition.

2. Vasculogenic Erectile Dysfunction (ED)

Vascular diseases are the most common cause of ED with endothelial dysfunction being the common denominator.[8] While atherosclerosis is the most common vascular disease linked to ED, its risk factors are also associated with the development of ED (figure 3) and these include cigarette smoking, hypertension, hyperlipidaemia and diabetes mellitus. Before attributing the ED to a purely vascular cause, a detailed assessment of the patient's history may identify other factors that are contributory or, occasionally, the main reason for the development of ED.

2.1 Psychogenic ED

Psychological issues affect all men with ED because of the importance of sexual activity to the male psyche, and lead to general anxiety, depression and performance-related anxiety. The presence of normal nocturnal erections indicates the neurovascular mechanisms are intact and points to a predom-

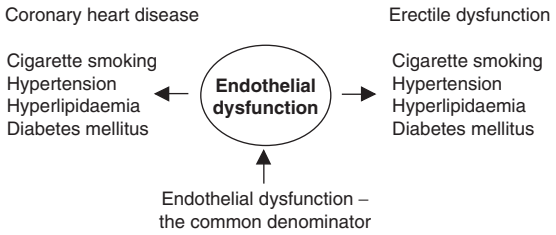


Fig. 3. Risk factors for erectile dysfunction (ED) and coronary heart disease.[8]

inantly psychogenic cause for ED. Psychosexual counselling is advised for these patients

2.2 Neurological ED

Both central and peripheral nervous diseases can lead to ED. Aside from obvious traumas such as spinal cord injury or specific diseases such as multiple sclerosis, Parkinson's disease and cerebrovascular disease can complicate both the assessment and management of vasculogenic ED.

2.3 Endocrine-Induced ED

Testosterone is important for both male sex drive and penile erection. A reduction in libido may be a consequence of testicular male hypogonadism – nocturnal erections may diminish and there may be less penile rigidity or difficulty in sustaining an erection. Serum testosterone measurements should be undertaken when loss of libido is a significant complaint and this can occur in men with predominantly vasculogenic ED as the age groups at presentation are similar.

2.4 Iatrogenic ED

A large number of drugs, whether prescribed or recreational, can affect sexual function. These drugs include:

- cardiovascular drugs: thiazide diuretics, β-adrenoceptor antagonists, calcium channel antagonists, centrally acting agents (e.g. methyldopa, clonidine, reserpine, ganglion blockers), digoxin, lipid-lowering agents, ACE inhibitors, recreational drugs, such as alcohol (ethanol), marijuana, amphetamines, cocaine, anabolic steroids, heroin (diamorphine);
- psychotropic drugs: major tranquillisers, anxiolytics and hypnotics, tricyclic antidepressants, selective serotonin reuptake inhibitors;
- endocrine drugs: antiandrogens, estrogens, gonadotropin-releasing hormone analogues, testosterone; and
- others: cimetidine, ranitidine, metoclopramide, carbamazepine.

The negative impact may be on erections, ejaculation or sex drive. There is little evidence that changing cardiovascular drug therapy will restore erectile function, suggesting it is the underlying disease process that is more important. However, if there is a strong temporal relationship between the commencement of treatment and the onset of ED (2–4 weeks) it is logical to change therapy if it is safe to do so. Antihypertensive agents, especially thiazide diuretics, are the most frequently incriminated and a switch to angiotensin II receptor antagonists or α-adrenoceptor antagonists should be considered.[9] Where drugs are prognostically important, such as β-adrenoceptor antagonists post-myocardial infarction, the decision to discontinue therapy should be approached with caution and only undertaken after considering overall risks.

Radical pelvic surgery may damage the parasympathetic nerves that run close to the prostate. Radiotherapy for bladder, prostate or rectal cancer can lead to ED secondary to vasculogenic damage, perhaps superimposed on surgical nerve damage.

3. ED and Cardiovascular Disease

3.1 Prevalence

The Massachusetts Male Aging Study[2] was a random sample, cross-sectional, observational study of 1709 healthy men aged 40–70 years to assess the impact of aging on a wide range of health-related issues.[2] Fifty-two percent of respondents reported some degree of ED (17% mild, 25% moderate, 10% complete) with the prevalence increasing with age. Cardiovascular disease was significantly associated with ED. The incidence was doubled in patients with hypertension, tripled in diabetic patients and in those with established coronary disease it was qua-

drupled. Cigarette smoking increased the prevalence 2-fold for all of these conditions and a positive relationship was found for reduced high-density lipoprotein-cholesterol and ED.

The association between hyperlipidaemia and ED has been studied in apparently healthy men who complained of ED.[10] Over 60% had hyperlipidaemia and 90% of these had evidence of penile arterial disease using Doppler ultrasound studies. Diabetes is commonly associated with ED with a prevalence of 50% (range 27–70% depending on age and disease severity). The onset of ED usually occurs within the first 10 years of diagnosis of diabetes.[11]

Men aged over 50 years with established CAD have an ED incidence of 40% and in those post-myocardial infarction or -vascular surgery the incidence ranges from 39% to 64%, depending on diagnostic criteria.[12]

3.2 The Endothelial Link

Endothelial dysfunction is defined as an abnormal endothelial response leading to a reduction in the bioavailability of NO and impaired vasodilatation. This results in an inability of the smooth muscle cells to relax throughout the vasculature. The reduced bioavailability of NO leads to the development of atherosclerosis, increased platelet aggregation, vessel wall inflammation and smooth muscle cell proliferation. Endothelial dysfunction is, therefore, common to cardiovascular disease and ED, establishing an intimate link between the two pathologies which explains to a significant degree the prevalence of ED in the conditions associated with endothelial dysfunction (e.g. diabetes) and the toxic risk factors such as cigarette smoking.[3]

4. ED as a Marker of Vascular Disease

As ED and vascular disease share the same risk factors, the possibility arises that ED in otherwise asymptomatic men may be a marker of silent vascular disease, especially CAD.[13] This has now been established to be the case and represents an important new means of identifying those at risk of vascular disease.

Pritzker[14] studied 50 asymptomatic men (other than ED) aged 40–60 years who had cardiovascular risk factors (multiple in 80%). Exercise ECG was abnormal in 28 men and subsequent coronary angiography in 20 men identified severe CAD in six, moderate two vessel disease in seven and significant single vessel CAD in a further seven men. In a study of 132 men attending day case angiography, 65% had some degree of ED and, importantly, over 50% had experienced ED before their CAD diagnosis had been made.[15] ED also correlates with the severity of CAD with single vessel disease patients having less difficulty in obtaining an erection.[16]

Any asymptomatic man who presents with ED that does not have an obvious cause (e.g. trauma) should be screened for vascular disease and have blood glucose, lipids and blood pressure (BP) measurements. Ideally, all such patients should undergo elective exercise ECG to facilitate risk stratification.[17]

5. ED and the Patient with Cardiovascular Disease

5.1 The Cardiovascular Response to Sexual Activity

Several studies have been performed using ambulatory ECG and BP monitoring comparing the heart rate, ECG and BP response to sexual activity with other normal daily activities.[18] The energy requirement during sexual intercourse is not excessive for couples in a longstanding relationship. The average peak heart rate is 110–130 beats per minute and the peak systolic BP 150–180mm Hg, resulting in a rate pressure product of 16 000–22 000. Expressed as a multiple of the metabolic equivalent (MET) of energy expenditure expanded in the resting state (MET = 1), sexual intercourse is associated with a work load of 2–3 METs before orgasm and 3–4 METs during orgasm.[18] Younger couples, who are not usually the individuals we advise, may be more vigourous in their activity expending 5–6 METs. The average duration of sexual intercourse is 5–15 minutes. Therefore, sexual intercourse is not an extreme or sustained cardiovascular stress for

patients in a longstanding relationship who are comfortable with each other. Casual sexual intercourse, which must be separated from extramarital sexual intercourse with a longstanding 'other partner', may involve a greater cardiac workload because of lack of familiarity and age mismatch (usually older men with a younger woman) with different activities and expectations.[18]

By using our knowledge of MET equivalents in the clinical setting we can advise on sexual safety by comparing sexual intercourse to other activities. Some of the daily activities and MET equivalents are as follows:

- sexual intercourse with established partner: normal (lower range) = 2–3 METs;
- sexual intercourse with established partner: vigourous activity (upper range) = 5–6 METs;
- lifting and carrying objects (9–20kg) = 4–5 METs;
- walking 1 mile in 20 minutes on the level = 3–4 METs;
- playing golf = 4–5 METs;
- gardening (digging) = 3–5 METs;
- do-it-yourself, wallpapering, etc. = 4–5 METs;
- light housework, e.g. ironing, polishing = 2–4 METs;
- heavy housework, e.g. making beds, scrubbing floors = 3–6 METs.

The analogy of walking 1.5km (1 mile) in 20 minutes on the flat or climbing up and down at least two flights of stairs is the most useful.

5.2 Exercise Testing

Using METs, sexual intercourse is equivalent to 3–4 minutes of the standard Bruce treadmill protocol. Where doubts exist about the safety of sexual intercourse, an exercise test can help guide decision-making. If a man can manage at least 4 minutes on the treadmill without significant symptoms, ECG evidence of ischaemia, a fall in systolic BP or dangerous arrhythmias, it will be safe to advise on sexual activity.[19] Drory et al.[20,21] studied 88 men with CAD (off therapy) using ambulatory ECGs and bicycle exercise tests. On ambulatory ECGs one-third of the men had ischaemia during sexual intercourse and all of them had ischaemia on the bicycle exercise ECG. All patients without ischaemia on the exercise test (n = 34) also had no ECG changes during sexual intercourse. All ischaemic episodes during sexual intercourse were associated with an increasing heart rate identifying a potentially important therapeutic role for heart rate lowering drugs (β-adrenoceptor antagonists, verapamil, diltiazem).

If a patient is unable to perform an exercise test because of mobility problems a pharmacological stress test should be utilised.

A man who cannot achieve 3–4 METs should be further evaluated by angiography if appropriate.[19]

Advice on METs in the clinical setting and relating this advice to sexual intercourse should also include the 'real world' advice of avoiding stress, a heavy meal or excess alcohol consumption prior to sexual intercourse. It is always important to individualise advice rather than rely only on general statistical advice.

5.3 Guidelines for the Management of ED

Recognising the need for advice on management of ED two consensus panels (UK and American) have produced similar guidelines dividing cardiovascular risk into three practical categories with management recommendations.[19,22] The UK consensus guidelines have recently been updated (figure 4).[19] It is recommended that all men with ED should undergo a full medical assessment. Baseline physical activity needs to be established and cardiovascular risk graded low, intermediate or high. Most patients with low or intermediate cardiac risk can have their ED managed in the outpatient or primary care setting.

6. Measurements of ED

As ED is a very personal problem, questionnaires have been developed for self-administration in the natural home (private) setting. The most commonly used questionnaires are the International Index of Erectile Function (IIEF), Sexual Encounter Profile and Global Assessment Questionnaire (table I).[23] Using the IIEF scoring system with the questions relating to the previous 4 weeks, ED is classed as

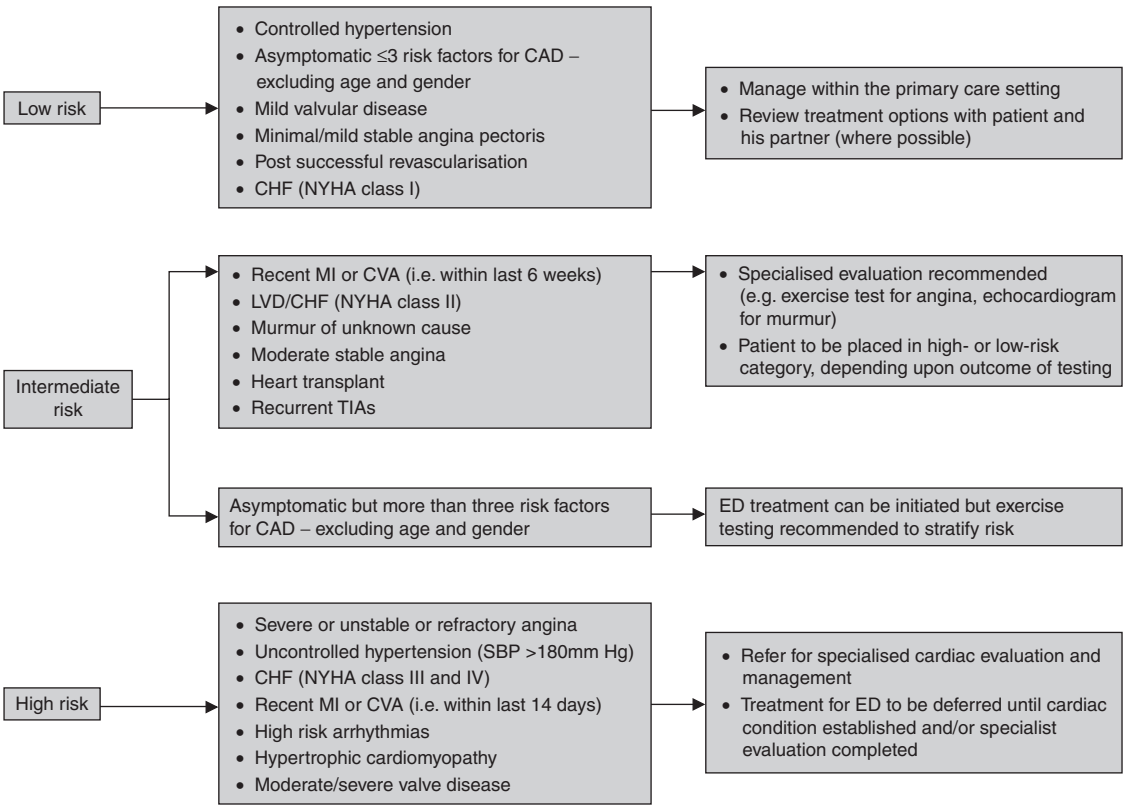


Fig. 4. Algorithm for the management of erectile dysfunction (ED) according to graded cardiovascular risk. **CAD** = coronary artery disease; **CHF** = congestive heart failure; **CVA** = cerebrovascular accident; **LVD** = left ventricular dysfunction; **MI** = myocardial infarction; **SBP** = systolic blood pressure; **TIA** = transient ischaemic attack.

severe (scores 1–10), moderate (11–16), mild (17–25) and normal (≥26). Therapeutic success can be monitored by repeating questionnaires at regular intervals and, of course, failure to respond will become evident also.

7. Treating ED in the Patient with Cardiovascular Disease

There is no evidence that treating ED in patients with cardiovascular disease increases cardiac risk; however, this is with the proviso that the patient is properly assessed and the couple or individual (self stimulation may be the only form of sexual activity) are appropriately counselled.[19] There is more to sexual activity than an erect penis and, as a consequence of the male's ED, over time couples may have lost the touching, caring aspects of an intimate relationship so that detailed advice and support (short- and long-term) is an essential part of overall management. Oral drug therapy is the most widely used because of its acceptability and effectiveness, but all therapies have a place in management. The philosophy is not to accept failure and to always be positive during what, for many men and their partners, is an uncertain time. The treatment of ED and the awareness of its frequency and importance follows from the introduction of the oral PDE5 inhibitor sildenafil.[7]

7.1 Phosphodiesterase (PDE)5 Inhibitors

To say that sildenafil has transformed the management of ED would be a substantial understatement. Its mechanism of action by blocking degradation of cGMP by PDE5 promotes blood flow into the

Table I. Erectile function assessment instruments – questions relevant to erectile dysfunction

International Index of Erectile Function[23] – erectile function domains		**Score range[a]**
1.	Over the past 4 weeks, how often were you able to get an erection during sexual activity?	0–5
2.	Over the past 4 weeks, when you had erections with sexual stimulation, how often were your erections hard enough for penetration?	0–5
3.	Over the past 4 weeks, when you attempted sexual intercourse, how often were you able to penetrate (enter) your partner?	0–5
4.	Over the past 4 weeks, during sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?	0–5
5.	Over the past 4 weeks, during sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?	0–5
15.	Over the past 4 weeks, how do you rate your confidence that you can keep your erection?	1–5
Total range		1–30[a]
Sexual Encounter Profile		**Response**
2.	Were you able to insert your penis into your partner's vagina?	Yes/no
3.	Did your erection last long enough to have successful intercourse?	Yes/no
Global Assessment Questionnaire		**Response**
1.	Has the treatment you have been taking improved your erections?	Yes/no

a The higher the score, the better the erectile function.

penis (figure 2) and the restoration of erectile function. Vardenafil and tadalafil have recently been added to this family of drugs.[24,25] Because their mechanism of action is the same, there is no reason to assume there will be any significant differences in ED effectiveness, but their PDE selectively and half-life may be of clinical importance. Potency is not clinically relevant because it is a way of expressing *in vitro* concentrations of a drug; in short, give dose equivalents and the clinical endpoint will be the same.

Haemodynamically, PDE5 inhibitors have mild nitrate-like actions (sildenafil was originally intended to be a drug for stable angina).[26] As PDE5 is present in smooth muscle cells throughout the vasculature and the NO/cGMP pathway is involved in the regulation of BP, PDE5 inhibitors have a modest hypotensive action. In healthy men a single dose of sildenafil 100mg transiently lowered BP by an average of 10/7mm Hg with a return to baseline at 6 hours post dose. There was no effect on heart rate.[26]

As NO is an important neurotransmitter throughout the vasculature and is involved in the regulation of vascular smooth muscle relaxation, a synergistic and clinically important interaction with oral or sublingual nitrates can occur. A profound fall in BP can result. The mechanism involves the combination of nitrates increasing cGMP formation by activating guanylate cyclase and PDE5 inhibition decreasing cGMP breakdown by inhibiting PDE5. The concomitant administration of PDE5 inhibitors and nitrates is a contraindication to their use and this recommendation also extends to other NO donors such as nicorandil. Clinical guidelines regarding timing of nitrate use post PDE5 inhibitor or use of PDE5 inhibitor after cessation of oral or sublingual nitrates are not specified, but recent studies have proved helpful. In a study involving healthy volunteers receiving sildenafil, which has a short half-life (see section 7.1.1), at a dosage of 100mg did not react with sublingual nitrates 6 hours post use.[27] Tadalafil, with its long half-life, did not react with nitrates at 48 hours post use. No data are available for vardenafil, but as its half-life is similar to sildenafil a similar result is to be expected. Oral nitrates are not prognostically important drugs and they can therefore be discontinued and, if needed, alternative agents substituted. After oral nitrate cessation, and provided there has been no clinical deterioration, PDE5 inhibitors can be used safely. It is recommended that the time interval prior to PDE5

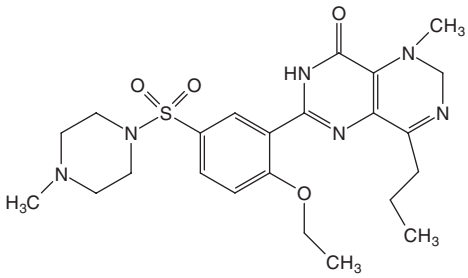
inhibitor use is five half-lives that equals 5 days for the most popular once-daily oral nitrate agents.

When comparing the three PDE5 inhibitors (figure 5), there are differences in PDE selectivity and half-life. PDE inhibitors are functionally heterogeneous enzymes that belong to at least 11 families (table II) and comprise at least 45 distinct proteins encoded by at least 21 genes.[7] Of the reactions studied to date (besides PDE5), the role of PDE6 in visual transduction is the most relevant in clinical practice as PDE3 is not influenced (potentially an adverse reaction on cardiac myocytes). Tadalafil is 780-fold more selective for PDE5 than for PDE6, whereas sildenafil is 6.8-fold and vardenafil 2.9-fold more selective for PDE5 than PDE6. Transient visual disturbances, usually a blue haze, are less likely with tadalafil.[7] However, tadalafil is less selective for PDE11, but this appears not to be of clinical significance.

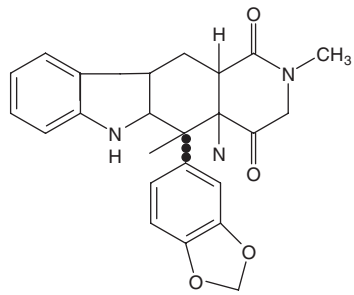
Tadalafil has a half-life of 17.5 hours with a period of responsiveness of 36 hours or longer, whereas sildenafil and vardenafil have a duration of action of 3–5 hours. Onset of action following sexual stimulation is approximately 30 minutes with maximal effect achieved at 1 hour with sildenafil and vardenafil and 2 hours for tadalafil. Tadalafil absorption is not influenced by food, whereas sildenafil and vardenafil are more effective 2 hours after a meal.[24,25]

7.1.1 Sildenafil

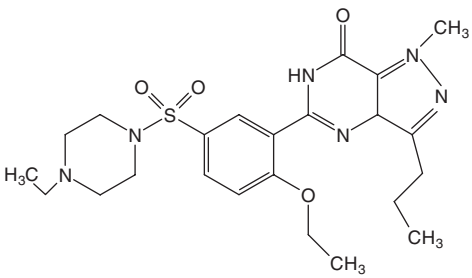
Sildenafil is the first oral treatment for ED and the most extensively evaluated.[28] Overall success rates in patients with cardiovascular disease of 80% or greater have been recorded with no evidence of tolerance. Patients with diabetes with or without additional risk factors, with their more complex and extensive pathophysiology, have an average success rate of 60%. In randomised trials to date, open-label or outpatient monitoring studies the use of sildenafil is not associated with any excess risk of myocardial infarction, stroke or mortality. In patients with stable angina pectoris there is no evidence of an ischaemic



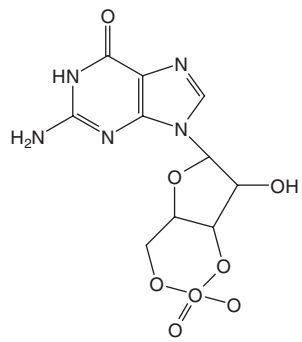
Sildenafil



Tadalafil



Vardenafil



cGMP

Fig. 5. Molecular structure of the phosphodiesterase 5 inhibitors and cyclic guanosine monophosphate (cGMP).

Table II. Relative selectivity of phosphodiesterase (PDE) 5 inhibitors (reproduced from Giuliano,[7] with permission from The European Society of Cardiology)

Family	Tadalafil	Sildenafil	Vardenafil
PDE1a	20 000	290	630
PDE1b	21 000	1100	5000
PDE1c	11 000	110	460
PDE2a	49 000	19 000	72 000
PDE3a	38 000	12 000	7700
PDE3b	18 000	17 000	15 000
PDE4a	30 000	6000	46 000
PDE4b	22 000	5800	33 000
PDE4c	23 000	5200	34 000
PDE4d	13 000	3600	16 000
PDE6	780	6.8	2.9
PDE7a	47 000	22 000	200 000
PDE8a	30 000	19 000	310 000
PDE9a	19 000	540	3600
PDE10a	9000	3100	12 000
PDE11a	14	1500	640

effect due to coronary steal, and in one large, double-blind, placebo-controlled, exercise study sildenafil 100mg increased exercise time and diminished ischaemia (figure 6).[29] A study of the haemodynamic effects in men with severe CAD identified no adverse cardiovascular effects and a potentially beneficial effect on coronary blood flow reserve.[30] Studies in patients with and without diabetes have demonstrated improved endothelial function acutely and after long-term oral dose administration, which may have implications beyond the treatment of ED.[26] Sildenafil has also been shown to attenuate the activation of platelet IIb/IIIa receptor activity.[31] Hypertensive patients on mono- or multiple therapy have experienced no increase in adverse events with the exception of doxazosin, a nonselective α-adrenoceptor antagonist. Occasional postural effects have occurred when sildenafil was taken within 4 hours of doxazosin 4mg; an advisory to avoid this time interval is now in place. Sildenafil has also been proven effective in heart failure patients who were deemed suitable for ED therapy (figure 7).[32] The incidence of ED in heart failure patients is 80%, making this finding of major clinical importance. On average, the sildenafil dose is 50mg with 25mg advised initially in those over 80 years of age because of delayed excretion. Sildenafil 100mg is invariably needed in patients with diabetes. There are several clinical points that need emphasising.

- The first dose may not be effective and it may take seven to eight attempts before sexual intercourse is possible. A longer duration and severity of ED influences the time to effectiveness. The patient must be informed of this possibility or emotional distress can follow the first failure.
- Sexual stimulation is essential.
- An empty stomach and avoiding alcohol or cigarette smoking facilitates the effect.
- The time to peak effect is 1 hour with a duration of up to 6 hours.
- Sildenafil 100mg has no additional adverse cardiac effects above the 50mg dose and should be routinely prescribed if the 50mg dose after four attempts is not effective.

Sildenafil's short half-life makes it the drug of choice in patients with the more severe cardiovascular disease, allowing early use of support therapy if an adverse clinical event occurs. Its quick onset of action and predictable duration suits many patients, but some couples do complain of a lack of spontaneity – most often the partner.

7.1.2 Tadalafil

Tadalafil has also been extensively evaluated in patients with cardiovascular disease and has a similar safety and efficacy profile to sildenafil.[24] Studies have shown no adverse effects on cardiac contraction, ventricular repolarisation or ischaemic

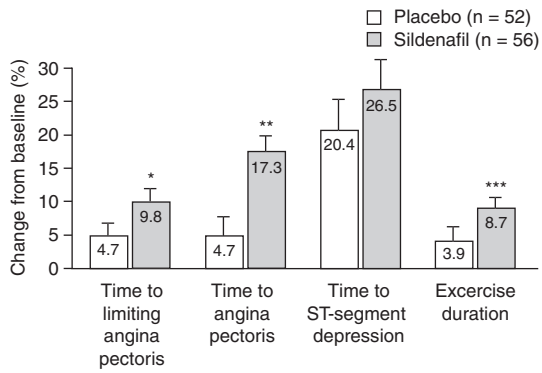


Fig. 6. Effect of sildenafil on exercise time and ischaemia in stable angina pectoris patients.[29] * p = 0.04; ** p = 0.0039; *** p = 0.495.

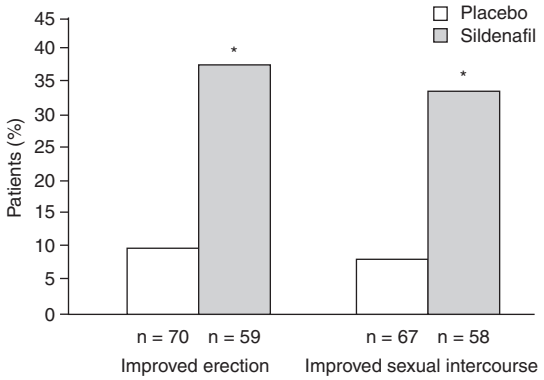


Fig. 7. Successful treatment of erectile dysfunction in heart failure patients deemed suitable for therapy. * $p < 0.0001$.[32]

threshold. A similar hypotensive effect has been recorded with a dose of doxazosin 8mg so caution is needed. As hypotension does not occur in the supine position and as tadalafil has a long half-life it is suggested tadalafil is taken in the morning and doxazosin in the evening. There is no interaction of tadalafil with the selective α-adrenoceptor antagonist tamsulosin, which can, therefore, be prescribed as an alternative to doxazosin for benign prostate hypertrophy.[33] Specific recommendations for tadalafil 10mg and 20mg are similar to sildenafil apart from the following.

- Food does not affect its onset of activity; however, I would caution against sexual activity within 2 hours of a heavy meal as it would occur at the time of increased cardiac work to digest the food.
- Its peak effect is 1–2 hours.
- Its effective duration has been recorded beyond 36 hours.
- Sublingual nitrates cannot be used for 48 hours post tadalafil dose.[34]

Because of its long half-life, tadalafil may not be the first choice for the patients with more complex cardiovascular disease. However, as 80% of patients with cardiovascular disease stratify into low risk it is an alternative for the majority.[19] When spontaneity is an issue, tadalafil is a logical alternative to sildenafil.

7.1.3 Vardenafil

Since vardenafil has a very similar chemical structure to sildenafil (figure 5), it is not surprising that it has a similar clinical profile. One study has reported no impairment of exercise ability in stable CAD patients receiving vardenafil 10mg.[35] Similar clinical efficiency for all three agents has been observed in patients with diabetes.[11] While vardenafil is an alternative to sildenafil it appears to offer little, if any, therapeutic difference and currently lacks the extensive data supporting the effectiveness and safety of sildenafil and tadalafil. However, there is no reason to assume it is less safe. Open-label patient preference studies are open to so much bias that the claims need to be placed firmly in the context of each individualised study rather than be generalised.[36]

7.1.4 Adverse Effects

As PDE5 inhibitors have the same vasodilating properties, adverse effects are similar. Headaches and flushing are the most frequent adverse effects, are usually well tolerated. Dyspepsia and rhinitis occasionally occur. Discontinuation rates due to adverse events are ≤1%. Tadalafil is associated with more back pain, which may be due to venous congestion, and this affects 5–6% of patients.[24,25,28]

7.2 Apomorphine

Apomorphine is a dopamine D_1/D_2 receptor agonist acting specifically in the paraventricular and supraoptic nuclei of the hypothalamus.[37] The subsequent triggering of neural outflow stimulates the spinal cord and parasympathetic outflow increases, leading to smooth muscle relaxation. It is administered sublingually in a rapid-acting 2mg or 3mg dosage. Its peak effect occurs in 15–20 minutes, allowing a rapid response if sexual activity begins. Its overall efficacy is less than the PDE5 inhibitors and is confined to the milder cases of ED. In nondiabetic patients, the percentage of attempts resulting in an erection firm enough for sexual intercourse using apomorphine 2mg or 3mg was 47% versus 34.8% with placebo ($p < 0.001$). Safety has been established in patients with hypertension, CAD, hyperlipidaemia and diabetes.[36] No signif-

icant cardiovascular drug interaction has been recorded and concomitant nitrate use is not a contraindication.[36] Apomorphine has an emetic adverse effect, i.e. nausea (5% of patients), which is dose related and tends to diminish with repeated drug exposure. Other adverse effects include headache, dizziness, somnolence and, rarely, syncope.[36]

The response to apomorphine in clinical practice has been disappointing in comparison with the PDE5 inhibitors, almost certainly because of the ED aetiology being peripheral at the endothelial level rather than central. However, in milder cases it provides an alternative choice that may suit some couples.

7.3 Other Oral Agents

Yohimbine, an α-receptor antagonist, is widely available. It acts centrally and peripherally.[38] Properly designed trials in patients with ED have not been performed and its efficacy has not been established. In the era of evidence-based medicine it cannot be recommended for the treatment of ED.

Phentolamine has been studied in buccal formation but is not approved for the treatment of ED and concerns about the potential cardiovascular adverse effects will be a significant problem.[39]

Arginine is the source of NO and usually is present in abundance. Arginine deficiency, which may occur in hyperlipidaemia, renal patients and some diabetic patients, might respond to supplementation but no data exist to support this concept.

7.4 Other Therapies

When oral agents are not effective, intracavernous injection therapy, transurethral alprostadil, vacuum pumps or surgical intervention are alternatives requiring specialised referral and advice.[40] There is no evidence that cardiovascular risk is increased using these strategies. It is important not to 'give up' if the simple oral drug strategies are not fully effective.

8. PDE Inhibitors and the Future

The mechanism of action of PDE inhibitors has prompted their evaluation in the treatment of vascular disease, especially where peripheral vascular resistance is increased. Reports of clinical benefit in pulmonary hypertension, hypertension, cardiac failure and Raynaud's disease have attracted great interest, suggesting a clinical role beyond the treatment of ED.[27] In many ways these developments reinforce the safety of this class of drugs in patients with cardiovascular disease and if the benefit on endothelial dysfunction is confirmed a possible preventative action on vascular disease progression, for example in patients with diabetes, is a consideration worthy of further study.

9. Conclusion

ED is common in patients with cardiovascular disease and should be routinely enquired about. The cardiac risk of sexual activity in patients with cardiovascular disease is minimal in properly assessed patients. The restoration of a sexual relationship is a possibility for the majority of patients with cardiovascular disease and ED using oral PDE5 inhibitors, which have an excellent safety profile (avoiding nitrate use). Follow-up of patients is essential to ensure proper use of therapy, provide support and offer alternative approaches if needed. ED is a marker for cardiovascular disease as well as its consequence; therefore, its identification (in the asymptomatic male) provides the opportunity to address other cardiovascular risk factors and detect silent but significant vascular pathology.

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