



Interactions between erectile dysfunction, cardiovascular disease and cardiovascular drugs

Dimitrios Terentes-Printzios[✉], Nikolaos Ioakeimidis, Konstantinos Rokkas and Charalambos Vlachopoulos

Abstract | Sexual health has a fundamental role in overall health and well-being, and a healthy and dynamic sex life can make an important contribution to a good quality of life. Sexual dysfunction, and especially erectile dysfunction (ED) in men, is highly prevalent in patients with cardiovascular disease (CVD). CVD and ED have shared risk factors and pathophysiological links, such as endothelial dysfunction, inflammation and low plasma testosterone levels. ED has been shown to be an independent and early harbinger of future CVD events, providing an important window to initiate preventive measures. Therefore, screening and diagnosing ED is essential for the primary and secondary prevention of CVD because the assessment of ED offers an easy and low-cost prognostic tool that is an alternative to other investigational cardiovascular biomarkers. Moreover, ED is a major contributing factor to the discontinuation of, or poor adherence to, cardiovascular therapy. Cardiovascular drugs have divergent effects on erectile function, with diuretics and β -blockers having the worst profiles, and renin–angiotensin–aldosterone system inhibitors and nebivolol having the best profiles. Pharmacological treatment of ED has an equivocal effect on the risk of CVD, suggesting a complex interaction between ED and drugs for CVD. In this Review, we discuss how sexual function could be incorporated into the patient history taken by physicians treating individuals with CVD, not merely as part of the diagnostic work-up but as a means to pursue tangible and essential benefits in quality of life and cardiovascular outcomes.

Historically, sexual behaviour has had an important effect on both social and political aspects of various cultures and civilizations worldwide¹. Since ancient times, sexual health has been considered to be a sign of overall health and good quality of life and has gained the attention of the medical community in order to understand and hopefully improve it. Apomorphine, the active ingredient of the lotus flower, is an effective remedy for erectile dysfunction (ED) and was used as an aphrodisiac and a possible cure for ED as long as 3,500 years ago by the Mayans and ancient Egyptians.

The importance of sexual health and especially ED has re-emerged in the clinical frontline in the past 30 years. Although talking about this problem was considered a taboo, the accidental discovery that a cardiovascular drug (sildenafil) for angina improves erectile function² led to a sudden growth in knowledge on the association between ED, cardiovascular health and relevant treatments. First, the prevalence of ED was quantified, and it was revealed to be a very common problem

affecting almost 50% of men aged >40 years (with differing degrees of severity) and an increasing prevalence with age³.

Cardiovascular disease (CVD) and ED have shared risk factors, including hypertension, diabetes mellitus, obesity and smoking, and evidence-based studies have identified pathophysiological links, including endothelial dysfunction, inflammation, ageing and low plasma testosterone levels⁴. ED has been shown to be a harbinger of CVD events, providing a possible window for prevention and treatment⁵. Screening and diagnosing ED is essential for the primary and secondary prevention of CVD because the assessment of ED offers an easy and low-cost prognostic tool as an alternative to several investigational cardiovascular biomarkers and might be a better predictor of the risk of CVD than traditional risk factors for CVD, especially in patients in the intermediate category of CVD risk^{6,7}. For this reason, the latest clinical guidelines on the prevention of CVD have introduced ED as a means of assessing the risk of CVD

Cardiovascular Diseases and Sexual Health Unit, First Department of Cardiology, Hippokraton Hospital, Medical School, National and Kapodistrian University of Athens, Athens, Greece.

[✉]e-mail: dimitristerentes@yahoo.gr

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Key points

- Erectile dysfunction (ED) is common, especially with advancing age, and shares risk factors and pathophysiological mechanisms with cardiovascular disease (CVD).
- ED is highly prevalent in men with CVD, often precedes a CVD event by 2–5 years and is a marker of general vascular disease.
- ED predicts cardiovascular events and all-cause mortality especially in men with an intermediate CVD risk score, who need further evaluation for CVD.
- Some CVD medications, such as β -blockers and diuretics, have a deleterious effect on erectile function, and physicians should be aware of these adverse effects.
- Phosphodiesterase type 5 inhibitors are not only safe for the cardiovascular system but also seem to have beneficial effects on the vasculature that could explain promising results in prognostic studies.
- Testosterone replacement therapy has shown conflicting results in terms of CVD risk and should be administered with close monitoring for possible adverse effects.

and support the need for more widespread awareness in everyday clinical practice^{6,8}. ED also seems to be a major contributing factor to the discontinuation of, and poor adherence to, cardiovascular therapy⁹. Finally, the pharmacological management of ED, in addition to the well-characterized localized beneficial effects on erectile function, also seems to have favourable systemic effects on the cardiovascular system, which have been the focus of research in the past two decades¹⁰.

In this Review, we discuss how sexual function, focusing primarily on ED in men, could be incorporated into the patient history taken by physicians treating individuals with CVD, not merely as part of the diagnostic work-up but as a means to pursue tangible and essential benefits in quality of life and cardiovascular outcomes. Exhaustive summaries of the assessment and management of ED from a urological or andrological perspective have been published previously^{11,12} and are beyond the scope of this Review, which focuses on up-to-date evidence to help cardiologists, internists and general practitioners to understand the underlying pathophysiological pathways and manage patients with ED and CVD.

ED and CVD: shared pathophysiology

Erectile function is affected by the same vascular processes that occur with ageing and the development of atherosclerosis in other vascular locations, such as the coronary and cerebral arteries⁴. In men considered to have predominantly vasculogenic ED, the difficulty in achieving an erection results from impairment of endothelial-dependent or endothelial-independent smooth muscle relaxation (functional vascular ED, initial stages), occlusion of the cavernosal arteries by atherosclerotic lesions (structural vascular ED, late stages) or a combination of these processes. Clinical and experimental data demonstrate a complex interaction between endothelial dysfunction, subclinical inflammation, ageing and androgen deficiency in the pathophysiology of ED. A relationship between ED and CVD at the clinical level is supported by these shared pathophysiological processes.

The artery size hypothesis. To describe and explain the connection between ED and CVD, as well as the occurrence of ED before the manifestation of CVD,

the artery size hypothesis was proposed¹³. Given the systemic nature of atherosclerosis, all major vascular beds should be affected to a similar extent. However, symptoms rarely become evident at different places in the vascular system at the same time. This disparity is likely to be the result of larger-diameter arteries being able to tolerate the same amount of atherosclerotic plaque better than smaller-diameter arteries. Furthermore, small changes in arteriolar diameter caused by atherosclerotic lesions in the microcirculation of the penis can result in large changes in conductance and blood inflow, as predicted by Poiseuille's law¹⁴. Therefore, in the initial stages of ED, men would rarely have concomitant coronary artery disease (CAD), because for a given atherosclerotic burden, the smaller penile arteries are obstructed before the larger coronary arteries. For this reason, ED has been colourfully described as a form of 'penile angina'¹⁵. However, by the time that the atherosclerotic burden substantially affects the coronary circulation, the penile artery will be even more damaged, accounting for the coexistence of sexual and cardiac anginal symptoms. Therefore, ED and CAD should be considered to be two different clinical manifestations of the same vascular process; ED would be predicted to precede the clinical manifestation of CAD in men, and many men with CAD would be predicted also to have ED.

The same concept holds true in the case of non-obstructive atherosclerosis. Given that the smaller penile artery has a larger endothelial surface than arteries in other organs and erection requires a high degree of vasodilatation, the same degree of endothelial dysfunction would be symptomatic in these smaller-diameter arteries but subclinical in the larger-diameter arteries, such as the coronary arteries. In the same context, accelerated vascular ageing, as measured by vascular ageing biomarkers, can underlie the adverse outcomes in ED, as indicated by the observation that increased aortic stiffness¹⁶ and pulse pressure¹⁷ (a crude index of aortic stiffness) are independent predictors of major adverse cardiovascular events in men with ED¹⁸.

Inflammatory and prothrombotic activation are mechanisms of vascular ageing and are additional steps that occur in the development of both ED and CVD. Inflammation not only leads to atherosclerosis but is also an important underlying mechanism of vascular dysfunction (in both the endothelium and the smooth muscle cells) and ageing that subsequently causes ED and CVD^{19–22}. The association between endothelial dysfunction and inflammation is bidirectional. Indeed, the dysfunctional endothelium promotes inflammation within the vessel wall through increased production of cytokines and expression of cellular adhesion molecules, and thereby creates the environment for the initiation and progression of atherosclerotic lesions in both the coronary and penile vasculature. In men with vasculogenic ED, the plasma levels of inflammatory and endothelial prothrombotic factors are higher than in men with normal erectile function¹⁹. Of note, the amount of endothelial and prothrombotic activation in men with ED is similar to that in men with CAD who do not have ED, and the burden is additive in the presence of both ED and CAD¹⁹. Low-grade inflammation might

Vasculogenic ED

ED diagnosed using penile Doppler ultrasonography when the peak systolic velocity is <35 cm/s and/or when the end-diastolic velocity is >5 cm/s.

Vascular ageing biomarkers

Biomarkers that originate from changes in the function or structure of blood vessels with age, such as aortic stiffness, carotid intima-media thickness, coronary artery calcification and endothelial function.

be responsible for the increased risk of cardiac events among men with ED even in the absence of obstructive coronary lesions²³. In these men, the artery size hypothesis cannot completely explain the increased risk of CAD, and chronic inflammation might be a shared link between ED and cardiac events. The increased pro-inflammatory and prothrombotic systemic state in men with ED might predispose them to the rupture of unstable (but not necessarily obstructive) coronary atherosclerotic plaques and the occurrence of acute coronary events.

Endothelial dysfunction has a prominent role in the pathogenesis and pathophysiology of ED. Consistent evidence shows that alterations in the crucial balance between vasoconstrictors (such as endothelin 1 and angiotensin II) and vasodilators (such as nitric oxide, prostaglandin E₂ and C-type natriuretic peptide) in the dysfunctional endothelium of penile arteries are common features of ED⁴. Preclinical and clinical investigations have shown that the signalling pathways related to the angiotensin system are important regulators of erectile function²⁴. Overproduction of angiotensin II shifts the vasomotor balance towards constriction and induces vascular remodelling, contributing to the development of ED²⁵.

Androgen deficiency is often present in men with ED²⁶. Current evidence supports a major role for testosterone in the homeostasis of the vascular tissues of the penile and cardiovascular systems²⁶. Testosterone also has a major role in the control of sexual function, acting both centrally and peripherally, and low plasma testosterone levels contribute to a range of pathophysiological processes affecting overall health and quality of life. Decreased endogenous testosterone levels have been independently associated with a higher risk of major adverse cardiovascular events and mortality in men with CVD and in men with ED^{27,28}. Specifically, a meta-analysis was conducted with data from 37 observational studies, including 43,041 individuals with a mean age of 64 years and a mean follow-up of >6 years²⁸. The meta-analysis showed for the first time that baseline plasma testosterone levels predicted cardiovascular and all-cause mortality as well as CVD morbidity²⁸. Interestingly, the capacity to predict CVD mortality was inversely related to age²⁸, supporting the hypothesis that plasma testosterone levels are involved in early vascular ageing and dysfunction processes that connect ED and CVD.

Taking into account regional factors that affect the milieu of the penis, the complex vasculature supplying the penis is known to be more susceptible to injury than other vascular beds^{29,30}. Endothelial dysfunction and pathological remodelling of the pre-penile vasculature occur with age, and are characterized by medial thickening, an impaired vasodilatation capacity and a substantially reduced penile blood flow capacity⁴. The importance of the pre-penile vasculature in the pathophysiology of ED is highlighted by the observation that endovascular intervention at this site, especially at the internal pudendal artery, leads to a modest but important improvement in erectile function in men, even those with severe and multifactorial ED^{30,31}.

ED and CVD often coexist

ED and CVD share identical principal cardiovascular risk factors and pathophysiological pathways⁴. Furthermore, in ED, several unconventional risk factors, such as depression, reduced frequency of sexual intercourse and perceived reduction in love from a partner, have been associated with worse CVD prognosis³². In many men, ED can be the first manifestation of a clinical disease spectrum that will progress to include CAD and peripheral artery disease at a later stage. In this context, the prevalence of ED is very high (>70%) among men with CVD, including CAD, cerebrovascular disease or peripheral artery disease^{33–35}. Furthermore, the prevalence of ED increases with the duration and severity of CVD^{35,36}.

The prevalence of ED is up to 75% in men with chronic stable CAD²³. In a study in 300 consecutive men presenting with acute chest pain who had angiographically documented CAD, ED was present in 49% of the study participants and 50% of them had a severe form of ED³⁶. Furthermore, two-thirds of participants reported some degree of ED before coronary symptoms and, importantly, ED preceded CAD by an average of 3 years³⁶. This time window offers a valuable opportunity for physicians to intervene and prevent future CVD events (FIG. 1). Another study examined the prevalence of ED according to the form of clinical presentation (acute versus chronic) and the severity of CAD (single-vessel versus multivessel disease), as assessed by coronary angiography, in 285 patients and a control group of 95 individuals with angiographically normal coronary arteries³⁷. The study showed an almost threefold higher prevalence of ED in men with chronic or multivessel CAD (65% and 55%, respectively) than in men with single-vessel CAD and controls (22% and 24%, respectively)³⁷. In men with chronic CAD, ED preceded CAD by 1–3 years, depending on the number of diseased vessels (by 1 year for single-vessel disease, by 2 years for two-vessel disease and by 3 years for three-vessel disease)³⁷. Further supporting this relationship is the finding that categorizing ED according to the severity of symptoms can improve the prediction of future CVD and death^{38,39}.

ED can be a marker of CAD in the absence of cardiac symptoms. Studies have shown that coronary ischaemia is inducible by exercise stress testing in 22% (range 5–56%) of men with ED, reflecting differences in the patient population, risk factors and criteria used for the diagnosis of ED and CAD²³. Interestingly, >90% of men who were further assessed by coronary angiography had obstructive atherosclerosis⁴⁰. In a landmark, prospective angiographic study, we showed that almost 20% of men presenting with ED had angiographically detectable, silent CAD⁴¹. This prevalence is substantially higher than the 4% prevalence of CAD that is found in the general population without ED symptoms⁴². The prevalence of ED was approximately 50% when angiography was performed in the setting of acute coronary syndrome⁴³. Another important study using multidetector CT revealed subclinical atherosclerotic plaques in 92% of 65 asymptomatic men with ED; these plaques might be vulnerable to rupture but are not sufficiently flow-limiting to produce a positive exercise stress test⁴⁴.

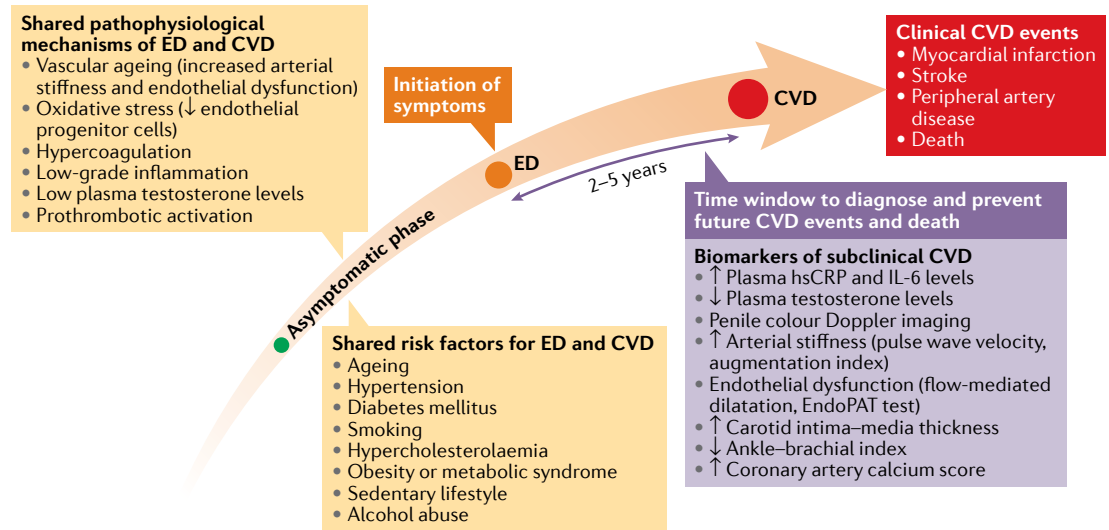


Fig. 1 | The shared pathways leading to ED and CVD. The figure shows the shared risk factors and pathophysiological mechanisms of erectile dysfunction (ED) and cardiovascular disease (CVD). A window of 2–5 years can exist between the manifestation of ED and the occurrence of CVD events, during which preventive measures can be initiated. hsCRP, high-sensitivity C-reactive protein.

In a study in 200 men with arteriogenic ED, CT confirmed obstructions of erection-related arteries in 90% of participants and increased coronary artery calcification in 40% of participants, leading to further investigation for CAD⁴⁵. This frequency of increased coronary artery calcification was identical to that found in men with ED in the large MESA study⁴⁶. These findings emphasize the need to identify those men with ED who need further investigation for silent CAD.

Among the various manifestations of CVD, a particular correlation between heart failure (HF) and ED has been highlighted^{47,48}. A high prevalence of ED in men with HF has been found in several studies. In a cohort study involving 100 men with HF, the prevalence of ED was 69%⁴⁹. Moreover, in men with HF of ischaemic aetiology, the prevalence of ED was 81%⁴⁹. Sexual health problems in HF can be attributed to a variety of demographic, clinical and treatment factors; accordingly, their investigation and management require a multidisciplinary approach⁴⁷. Data also indicate that left ventricular dysfunction is an independent risk factor for ED, unrelated to the severity of HF symptoms⁵⁰. Support for this close relationship is provided by the reduction in symptoms of ED in patients with HF after improvement in left ventricular ejection fraction with cardiac resynchronization therapy⁵¹. Diastolic dysfunction is observed in >66% of men with ED, but the association between ED and HF with preserved ejection fraction has not been thoroughly investigated^{52,53}. Finally, parameters of right ventricular dysfunction, possibly reflecting the longstanding effects of left-sided HF, also correlate with the severity of ED⁵³.

ED is a prognostic marker of CVD events

The role of ED as a predictor of CVD has been at the centre of research in the ED field since the artery size hypothesis was proposed to explain the temporal relationship between the occurrence of ED and CVD events⁵⁴ (FIG. 1). The association between ED

and CVD and the prognostic role of ED have been identified in several prospective studies and confirmed in subsequent meta-analyses (TABLE 1). The Prostate Cancer Prevention Trial⁵⁵ in 2005 was the first large longitudinal study to provide clinical confirmation of the link between ED and future CVD events and also raised further questions on the matter. Specifically, men enrolled in the placebo group of the trial with baseline ED or incidental ED that developed during the study period had a 45% increased risk of a CVD event compared with men without ED⁵⁵. However, these results were criticized because of the heterogeneity in the CVD events used as end points, the high proportion of participants who developed ED during follow-up (65% after 7 years) and the lack of validated questionnaires to establish a diagnosis of ED. Many of these shortcomings were resolved in a large (95,038 men) Australian population-based study⁵⁶. The connection between ED and CVD was further supported by the observation that the severity of ED (based on the questionnaire used for diagnosis) was positively correlated with the risk of all CVD end points, and this relationship was even stronger in men with previous CVD⁵⁶. In another study, the predictive role of the severity of ED was investigated by assessing the extent of cavernous vascular disease with the use of dynamic penile Doppler ultrasonography, which provides a more objective evaluation of vasculogenic ED severity⁵⁷. Low penile blood flow (dynamic penile peak systolic velocity <25 cm/s) independently predicted major adverse cardiac events in a general population of men and in men with hypertension; the risk of major adverse cardiac events was 2.7-fold higher in the general population and 3.5-fold higher in men with hypertension than in men with normal dynamic penile peak systolic velocity (>35 cm/s)^{58,59}.

The prognostic role of ED seems to remain important even in men at high risk of CVD events, such as those with diabetes, HF or CAD, thereby providing a useful

Table 1 | Longitudinal studies on the role of ED in predicting CVD events and mortality

Study	Population			Duration of follow-up (years)	Number (%) with ED	End points	Diagnosis of ED	Factors adjusted for	Refs
	Size (n)	Age (years)	Type						
<i>Positive association between ED and CVD</i>									
Blumentals et al. (2003, 2004)	25,650	40.1	Health-care system cohort	1	12,825 (50)	PVD, MI	ICD-9 codes	Age at ED diagnosis, smoking, obesity, and use of ACEIs, β -blockers and statins	146,147
Thompson et al. (2005)	8,063	62 \pm 6	Without CVD	7 (\pm 90 days)	3,816 (47.3)	CVD	Single question on ED graded into four groups	Age, BMI, SBP, DBP, total cholesterol, HDL cholesterol, history of diabetes mellitus, parent or sibling with a history of MI, race (white versus other), current smoker, current use of antihypertensive medication, physical activity (moderate or very active versus sedentary or light) and global self-reported health status (excellent or very good versus fair or poor)	55
Schouten et al. (2008)	1,248	60.7	Community-based study	6.33	392 (31.4)	CVD events	Single question on erectile rigidity	Age, total cholesterol, HDL cholesterol, SBP, diabetes and smoking	148
Ma et al. (2008)	2,306	54.2 \pm 12.7	With diabetes	4	616 (26.7)	CHD events	Single question	Age, diabetes duration, SBP, DBP, albuminuria, retinopathy at baseline, eGFR, use of lipid-lowering agents, use of antihypertensive medications, and use of ACEIs or ARBs	61
Gazzaruso et al. (2008)	291	54.8 \pm 7.3	With type 2 diabetes and silent CAD documented with angiography	3.9 \pm 1.8	118 (40.5)	MACE	IIEF-5 questionnaire	Age, diabetes duration, hypertension, family history of CAD, smoking, micro-albuminuria, glycated haemoglobin, BMI, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides and autonomic dysfunction	60
Inman et al. (2009)	1,402	55.4	Community-dwelling	10	158 (11.3)	CVD events	Brief Male Sexual Function Inventory	Diabetes, hypertension, BMI and history of smoking	149
Araujo et al. (2009)	1,655	55.2	Population-based study	15.2	338 (20.4)	Death from CVD, malignant neoplasms or other causes	23-item questionnaire on sexual activity	Age and BMI as continuous variables and the following as categorical variables: alcohol consumption, calories expended in physical activity, current smoking, self-assessed health, and self-reported chronic disease (heart disease, hypertension and diabetes)	150
Hebert et al. (2009)	328	55.4	With HF	8.4	293 (89.3)	All-cause death	SHIM	–	66

Table 1 (cont.) | Longitudinal studies on the role of ED in predicting CVD events and mortality

Study	Population			Duration of follow-up (years)	Number (%) with ED	End points	Diagnosis of ED	Factors adjusted for	Refs
	Size (n)	Age (years)	Type						
<i>Positive association between ED and CVD (cont.)</i>									
Araujo et al. (2010)	1,057	54	Without CVD and diabetes	11.7	178 (16.8)	CVD	23-item questionnaire on sexual activity	BMI (continuous) and the variables that are part of the Framingham Risk Score: age, HDL cholesterol and total cholesterol (all as continuous variables), as well as current smoking (yes or no) and hypertension categorized according to blood pressure readings (optimal, normal, high normal, stage I and stage II–IV)	72
Böhm et al. (2010)	1,519	64.8	At high risk of CVD	4.4 (ONTARGET) and 4.5 (TRANSCEND)	842 (55.4)	Composite of CVD death, MI, stroke, hospitalization for HF and all-cause death	IIEF-5 and the Kölner (Cologne) Evaluation of ED scores	Age, SBP, DBP, smoking, history of hypertension, diabetes, MI, stroke or TIA, PVD, alcohol consumption, use of β -blockers or calcium-channel blockers, ankle–brachial index and lower urinary tract surgery	65
Batty et al. (2010)	6,304	65.9	With type 2 diabetes	5	3,158 (50.1)	All-cause death, cardiovascular events, CHD events, cerebrovascular events	Nurses asked participants whether they had ED (yes or no)	Treatment, age, use of metformin or β -blockers, history of macrovascular or microvascular disease, requirement for assistance with daily activities, diabetes duration, cigarette smoking, alcohol intake, vigorous physical activity in previous week, glycated haemoglobin, creatinine, BMI, total cholesterol, HDL cholesterol, resting heart rate, SBP, DBP, quality of life and Mini-Mental State Examination score, age at completion of highest level of education, height, treatment allocation and ethnicity	62
Corona et al. (2010)	1,687	52.9 \pm 12.8	Patients with ED	4.3	1,687 (100)	MACE	ED severity by single question or by dynamic penile Doppler ultrasonography (PSV <25 cm/s)	Age and Chronic Diseases score	59
Chung et al. (2011)	9,006	58.5 \pm 11.4	Nationwide, population-based study	5	1,501 (16.7)	Stroke	ICD-9 codes	Monthly income, geographical location, hypertension, PVD, diabetes, CAD, atrial fibrillation and hyperlipidaemia	151
Banks et al. (2013)	95,037	60.2 \pm 10.5	General population	1.9 for hospitalization for CVD and 2.2 for death	32,186 (33.9) with moderate or severe ED	CVD events and death	Single self-assessment question on erectile function	Age, smoking, alcohol consumption, marital status, income, education, physical activity, BMI, diabetes, and current treatment for hypertension or hypercholesterolaemia	56

Table 1 (cont.) | Longitudinal studies on the role of ED in predicting CVD events and mortality

Study	Population			Duration of follow-up (years)	Number (%) with ED	End points	Diagnosis of ED	Factors adjusted for	Refs
	Size (n)	Age (years)	Type						
Positive association between ED and CVD (cont.)									
Chung et al. (2015)	1,436	75.3	Chinese individuals	11.5	179 (12.5) with severe ED (referred as completely impotent)	All-cause and CVD death (according to ICD-10)	A single question with four categories at the 4-year follow-up	Age, marital status, educational level, BMI, smoking status, alcohol use, socioeconomic status ladder, physical activity, and self-reported history of diabetes, hypertension or stroke	152
Loprinzi et al. (2015)	1,790	45.4	Population-based study	7.75	557 (31.1)	All-cause death	Single question	Age, physical activity, race/ethnicity, waist circumference, poverty-to-income ratio, serum cotinine levels and comorbidities	153
Ioakeimidis et al. (2016)	298	55 ± 9	With hypertension and symptoms of ED	4.9	52 (17) in the lowest tertile of severe arterial insufficiency	MACE	Arteriogenic ED severity by dynamic penile Doppler ultrasonography (PSV <25 cm/s)	Age, SBP and each of the other variables examined in univariate analysis in rotation, as well as plasma testosterone levels	58
Uddin et al. (2018)	1,914	69.0 ± 9.2	From the MESA study	3.8	877 (45.8)	CHD and CVD events	Self-reported ED	Age, race/ethnicity, education, smoking status, diabetes, family history of CAD, total-to-HDL cholesterol ratio, SBP, antihypertensive medication use and lipid-lowering medication use	154
No association between ED and CVD									
Frantzen et al. (2006)	1,183	35–74	Historical cohort	Up to 2	278 (23.5)	Incident CVD	ED reported by general practitioner	–	155
Ponholzer et al. (2010)	2,506	45 ± 12	Without a history of CHD or cerebrovascular disease	6.5	870 (34.7)	CVD events	IIEF-5 questionnaire	Age	67
Hotaling et al. (2012)	31,296	62	From western WA, USA	7.8	7,762 (24.8)	CVD death	Answering yes to the question, “Have you experienced impotence in the last year?”	Age, ED status, marital status, race, education, self-rating of health, antihypertensive drug use, lipid-lowering drug use, family history of CAD, current smoking status, current or former pack-years of smoking, BMI at age 45 years, past and current exercise, diagnosis of chronic kidney disease, insulin use, oral hypoglycaemic drug use, aspirin use, fruit and vegetable intake, and percentage of calories from saturated fat	68

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; CAD, coronary artery disease; CHD, coronary heart disease; CVD, cardiovascular disease; DBP, diastolic blood pressure; ED, erectile dysfunction; eGFR, estimated glomerular filtration rate; HF, heart failure; ICD, International Classification of Diseases; IIEF-5, International Index of Erectile Function-5; MACE, major adverse cardiac events; MI, myocardial infarction; PVD, peripheral vascular disease; SBP, systolic blood pressure; SHIM, Sexual Health Inventory for Men; PSV, peak systolic velocity; TIA, transient ischaemic attack.

biomarker for secondary prevention of CVD^{60–63}. Among these comorbidities, diabetes is the best-studied underlying disease in men with ED. Four studies have investigated the relationship between ED and CVD events

in men with diabetes (type 1 or type 2) and all reached the same conclusion that ED is an important predictor of CVD events in these patients^{60–62,64}. Furthermore, a substudy of the ONTARGET/TRANSCEND trials⁶⁵

confirmed the prognostic role of ED in a population of men at high risk of CVD. Finally, preliminary prospective data show at least a trend for increased mortality in men with HF and ED compared with men with HF without ED^{47,66}.

However, the emergence of some studies with neutral results led to doubts about the association between ED and CVD end points^{67,68}. These studies offer insights into the limitations and caveats of ED and its assessment as a predictor of CVD events. The first important point is that the diagnosis of ED with the use of a validated questionnaire, such as the International Index of Erectile Function (IIEF) questionnaire, seems to be advantageous in terms of substantiating the diagnosis and integrating the prognostic potential of ED compared with the use of single-question methods for diagnosing ED. Of note, the IIEF-5 questionnaire can be used not only by urologists and andrologists but also by general practitioners, internists, cardiologists, endocrinologists, nurses and others⁶⁹. A second important issue is that ED is not strongly associated with CVD risk in men with a low baseline risk of CVD⁷⁰. This finding can be explained by the observation that men with a low baseline risk of CVD tend to be younger and without overt cardiovascular risk factors and, consequently, are more likely to have psychogenic ED than vasculogenic ED. In this setting, ED is not a marker of premature vascular ageing^{20,71} and, therefore, does not have an important prognostic role for CVD events. Third, the length of follow-up in these studies is of essential importance, because at least 2–5 years is needed for the occurrence of CVD events. Shorter durations of follow-up might not detect an incremental role of ED in the prediction of CVD. Finally, a major limitation in most of the studies was the inability to demonstrate an incremental role of ED when combined with traditional risk factors and scores for CVD, such as the Framingham Risk Score. Only one of the prognostic studies investigated the predictive role of ED compared with that of the Framingham Risk Score⁷². This study, despite showing that ED is independently associated with a higher incidence of CVD, did not show a significant improvement in the prediction of CVD with the use of ED beyond that achieved with traditional risk factors⁷².

Numerous meta-analyses on the role of ED in CVD risk prediction have been performed in the past 10 years^{39,64,70,73–76}, and the three best-conducted of these^{39,70,73,77} confirmed that ED significantly increases the risk of CVD, independently of conventional risk factors for CVD⁷². In a comprehensive meta-analysis of data from approximately 100,000 participants and 14 studies with a follow-up duration of >6 years, men with ED had a 62% increased risk of myocardial infarction, a 44% increased risk of CVD events and a 25% increased risk of all-cause death compared with men without ED⁷⁰. To investigate the heterogeneity of findings between studies, we showed that the relative risk of CVD associated with ED was higher in younger men and those at intermediate risk of CVD⁷⁰. Moreover, the studies using a structured, validated questionnaire to assess ED found higher relative risks of CVD than the studies using just a single question⁷⁰. A subsequent and slightly larger

meta-analysis supported these findings on the role of ED in predicting CVD events³⁹.

Effects of CVD drugs on sexual function

Episodic sexual activity is a risk factor for acute cardiovascular events that is attenuated by habitual exercise and sexual activity^{78,79}. Conversely, having an acute cardiovascular event leads to a reduction in sexual activity and an increase in the incidence of ED, which eventually leads to a poor prognosis irrespective of cardiovascular risk factors, implying a perpetual vicious circle^{80–82}. A reduction in sexual activity and erectile function in men with CVD is very common, and is often related to the disease process, risk factors, anxiety, fear, comorbidities and treatment⁸³. The wide spectrum of patients with CVD who are affected by a reduction in sexual activity⁸³ include those with stable CAD⁸⁴, chronic HF⁸⁵ or hypertension⁹ and those undergoing cardiac interventions (such as implantation of a defibrillator⁸⁶, coronary artery bypass graft surgery⁸⁷ or heart transplantation⁸⁸). Interestingly, men with CVD who are treated are more likely to have sexual dysfunction than those who are untreated, suggesting an undesired, negative effect of treatment on erectile function⁸⁹. An early, landmark study showed a more than twofold higher prevalence of ED in men treated for hypertension than in men with untreated hypertension, mainly driven by the use of β -blockers and/or diuretics⁹⁰. This finding was confirmed in a subsequent cohort in which, even with the use of more ‘erection-friendly’ antihypertensive medications such as calcium-channel blockers, angiotensin-receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors, the prevalence of ED was higher in men treated for hypertension than in those with undiagnosed hypertension, but without substantial differences in the severity of ED⁹¹. The antihypertensive treatment might have a negative effect on penile blood flow, especially when very low levels of blood pressure are reached⁹². Even more troubling is the observation that the greater the number of cardiovascular drugs used, the larger the deleterious effect on sexual function⁸¹. The effect of cardiovascular therapy on sexual dysfunction is of great importance in men with ED associated with cardiovascular drug therapy, and appropriate management is warranted to tackle poor adherence to these drugs⁹³.

The best-studied cardiovascular drugs in terms of their effects on ED are the antihypertensive drugs because of the strong interaction between haemodynamic parameters (such as blood pressure and heart rate) and ED. The effect of antihypertensive medications on ED is a conundrum that physicians must address to achieve optimal results with this therapy and to improve the quality of life of their patients. Physicians must be aware of the possible sexual adverse effects of these medications and also have the patience and insight to motivate patients to report these adverse effects⁹⁴. Some classes of antihypertensive drug have neutral or even beneficial effects on sexual dysfunction, whereas others have been shown to have detrimental effects on sexual health⁹. Furthermore, concerns that emerged after the SPRINT trial about the possible deleterious effect of intensive blood pressure management on erectile

Arterial stiffness

Reduced capacity of an artery to expand in response to changes in blood pressure.

function were not confirmed in subsequent studies^{95,96}. Taking into account the different effects of the various classes of antihypertensive drug on erectile function, the crucial question for physicians is whether switching from one class to another or even changing between agents in the same class will be sufficient to improve erectile function.

Overall, the findings from the available studies are inconsistent and need further investigation. In general, older antihypertensive drugs (first-generation and second-generation β -blockers, diuretics and centrally-acting agents such as methyl dopa) tend to have a negative effect on erectile function, whereas newer medications have either a neutral effect (calcium-channel blockers, α -blockers and angiotensin-converting enzyme inhibitors) or beneficial effects (nebivolol and ARBs)⁹⁷ (TABLE 2). The mechanisms underlying the negative effects of diuretics on erectile function are complex and not well-defined, whereas the negative effect of β -blockers is primarily thought to be mediated by inhibition of the sympathetic nervous system, which is involved in the integration of an erection and the stimulation of testosterone release. Interestingly, a cleverly designed study showed that prejudice and knowledge about the possible adverse effects of β -blockers can produce anxiety, which ultimately might cause ED⁹⁸. In terms of effects on erectile function, the β -blocker nebivolol seems to be a more benign alternative to other, non-selective β -blockers⁹⁹, which decrease sympathetic tone in the cavernous body thereby hindering vasodilatation, reduce plasma testosterone levels through their effect on luteinizing hormone, and cause sleepiness or depression thereby decreasing libido. Specifically, nebivolol provides highly selective blockade of β_1 -adrenergic receptors and has vasodilatory properties secondary to increasing the bioavailability of nitric oxide. Furthermore, preclinical data have shown that treatment with nebivolol results in increases in endothelial nitric oxide synthase activity and endothelium-dependent relaxation of the corpora cavernosa¹⁰⁰.

With regard to the renin–angiotensin–aldosterone system, angiotensin II is involved in detumescence of the corpus cavernosum, and excessive levels of angiotensin II produce oxidative stress and local endothelial dysfunction^{24,25}. Therefore, ARBs improve endothelial function and promote vasorelaxation to improve erectile function^{24,25,101}. In terms of α -blockers, early placebo-controlled, randomized studies in patients with benign prostatic hyperplasia showed neutral or negative effects of α -blocker therapy on erectile function^{102,103}. However, in a study in which the α -blocker doxazosin was given as an antihypertensive agent, the incidence of ED was numerically but not significantly lower than in the placebo group¹⁰⁴. Nevertheless, most of these findings come from small observational studies. Most of the large studies in the literature either were conducted with underpowered control groups or were uncontrolled and their design was open-label.

The data on the effects of other cardiovascular medications on erectile function are even more scarce¹⁰⁵. Initial reports identified statin therapy as a possible cause of ED¹⁰⁶. This notion is pathophysiologically supported

by the understanding that cholesterol is the biochemical precursor for testosterone and, therefore, statins might affect plasma testosterone levels. However, later studies did not show any negative effects of statins on erectile function¹⁰⁷ and, indeed, suggested a possible beneficial effect of statins on erectile function by reversing early vascular ageing (improvement in endothelial function and arterial stiffness) that is prevalent in men with ED¹⁰⁸, either as a single therapy or in combination with phosphodiesterase type 5 (PDE5) inhibitors⁷¹.

Antiarrhythmic medications are considered to have no effects on erectile function, with the exception of β -blockers and digoxin¹⁰⁵. The two most popular but still not adequately proven theories for the deleterious effect of digoxin on erectile function are its possible inhibition of testosterone production from testicular cells and its inhibition of the corpus cavernosum, which hinders nitric oxide-induced relaxation and stimulates corporeal contraction^{109,110}. Indeed, preliminary data show that ivabradine might be a better alternative to β -blockers in terms of erectile function in men with HF¹¹¹.

The effects of antiplatelet and anticoagulant agents and nitrates on sexual function have not been properly investigated but are thought to be mostly neutral^{112,113}. Finally, scarce data exist on the effect on erectile function of the new antidiabetic medications including dipeptidyl peptidase 4 inhibitors, glucagon-like peptide 1 receptor agonists and sodium–glucose cotransporter 2 inhibitors. Initial data from small clinical studies indicate that glucagon-like peptide 1 receptor agonists might improve erectile function¹¹⁴, warranting further investigation and comparison with other classes of antidiabetic drug. Taking into account the limitations of these studies, we propose an algorithmic approach in men who present with symptoms of ED and who require treatment with cardiovascular drugs (FIG. 2).

Effects of ED treatment on CVD risk

Lifestyle modifications, avoidance of medications linked with ED, and sexual counselling are the foundations of managing ED. Indeed, dietary modifications (such as salt restriction or adherence to a Mediterranean diet¹¹⁵), regular exercise, weight loss, moderate alcohol consumption and smoking cessation have all been associated with modest but substantial improvements in erectile function^{116,117}. Similarly, optimizing the management of risk factors for CVD is another essential step in tackling both the symptoms of ED and the increased risk of CVD. However, these strategies often do not achieve the desired outcomes, necessitating the use of alternative therapies¹¹⁸ (FIG. 3). Various systemic and local treatments have been used for the management of ED. A detailed description of all the available therapies is beyond the scope of this Review. In this section, we primarily discuss the role of systemic therapies for ED that have also been linked to the risk of CVD¹¹⁹ and focus particularly on PDE5 inhibitors and testosterone-replacement therapy (TRT).

PDE5 inhibitors. The unexpected ‘adverse effect’ of an improvement in erectile function following treatment with a drug, sildenafil, being investigated for angina that made male participants in the study reluctant to return

their unused tablets is one of the most inspiring stories in modern drug development². PDE5 inhibitors have revolutionized the management of ED in men, while the absence of an equivalent therapy for women has created

a gap in the understanding and management of sexual dysfunction between men and women.

PDE5 inhibitors block the degradation of cGMP by PDE5, thereby promoting blood flow into the penis and

Table 2 | Effects of drugs for cardiovascular disease on erectile function

Study	Disease	Population		Drug	Effect on erectile function	Ref.
		Size (n)	Age (years)			
Angiotensin-converting enzyme inhibitors						
Speel et al. (2005)	Erectile dysfunction	59	60 ± 7	Quinapril versus placebo	Improvement with both	156
Angiotensin-receptor blockers						
Böhm et al. (2007)	Hypertension	1,549	66 ± 6	Telmisartan versus ramipril	No effect	35
Baumhäkel et al. (2008)	Hypertension and metabolic syndrome	1,069	59 ± 10	Irbesartan versus control	Improvement with irbesartan	101
α-Blockers						
Grimm et al. (1997)	Hypertension	557	45–69	Doxazosin versus placebo	Neutral or slightly positive effect	104
β-Blockers						
Silvestri et al. (2003)	Coronary artery disease	96	52 ± 7	Atenolol	Decrease with knowledge of potential adverse effects	98
Doumas et al. (2006)	Hypertension	44	31–65	Nebivolol versus β-blocker	Improvement with nebivolol	99
Brixius et al. (2007)	Hypertension	50	40–55	Nebivolol versus metoprolol	Decreased less with nebivolol than with metoprolol	157
Cordero et al. (2010)	Hypertension	1,007	58 ± 11	Nebivolol versus β-blocker	Decreased less with nebivolol than with β-blocker	158
Calcium-channel blockers						
Shiri et al. (2007)	Hypertension, coronary artery disease	1,665	55–75	Calcium-channel blocker versus β-blocker and diuretic	Decreased more with calcium-channel blocker than with β-blocker and diuretic	113
Omvik et al. (1993)	Hypertension	461	55	Amlodipine versus enalapril	Improvement with both	159
Yang et al. (2013)	Hypertension	218	47 ± 7	Felodipine plus irbesartan versus felodipine plus metoprolol	Better with felodipine plus irbesartan	160
Diuretics						
Chang et al. (1991)	Hypertension	176	35–70	Thiazide versus placebo	Decreased more with thiazide than with placebo	161
MRC trial (1985)	Hypertension	1,735	35–64	Thiazide versus propranolol	Decreased more with thiazide than with propranolol	162
Mineralocorticoid-receptor antagonists						
Burgess et al. (2003)	Hypertension	586	55 ± 11	Eplerenone	Decrease	163
Parthasarathy et al. (2011)	Hypertension	137	53 ± 11	Spironolactone versus eplerenone	Decreased more with spironolactone than with eplerenone	164
Statins						
Dadkhah et al. (2010)	Erectile dysfunction	131	63 ± 6	Atorvastatin versus placebo	Modest improvement	165
Joseph et al. (2018)	Intermediate cardiovascular risk	2,153	≥55	Rosuvastatin versus placebo	No effect	166
Trivedi et al. (2013)	Erectile dysfunction	173	≥40	Simvastatin versus placebo	No effect	167

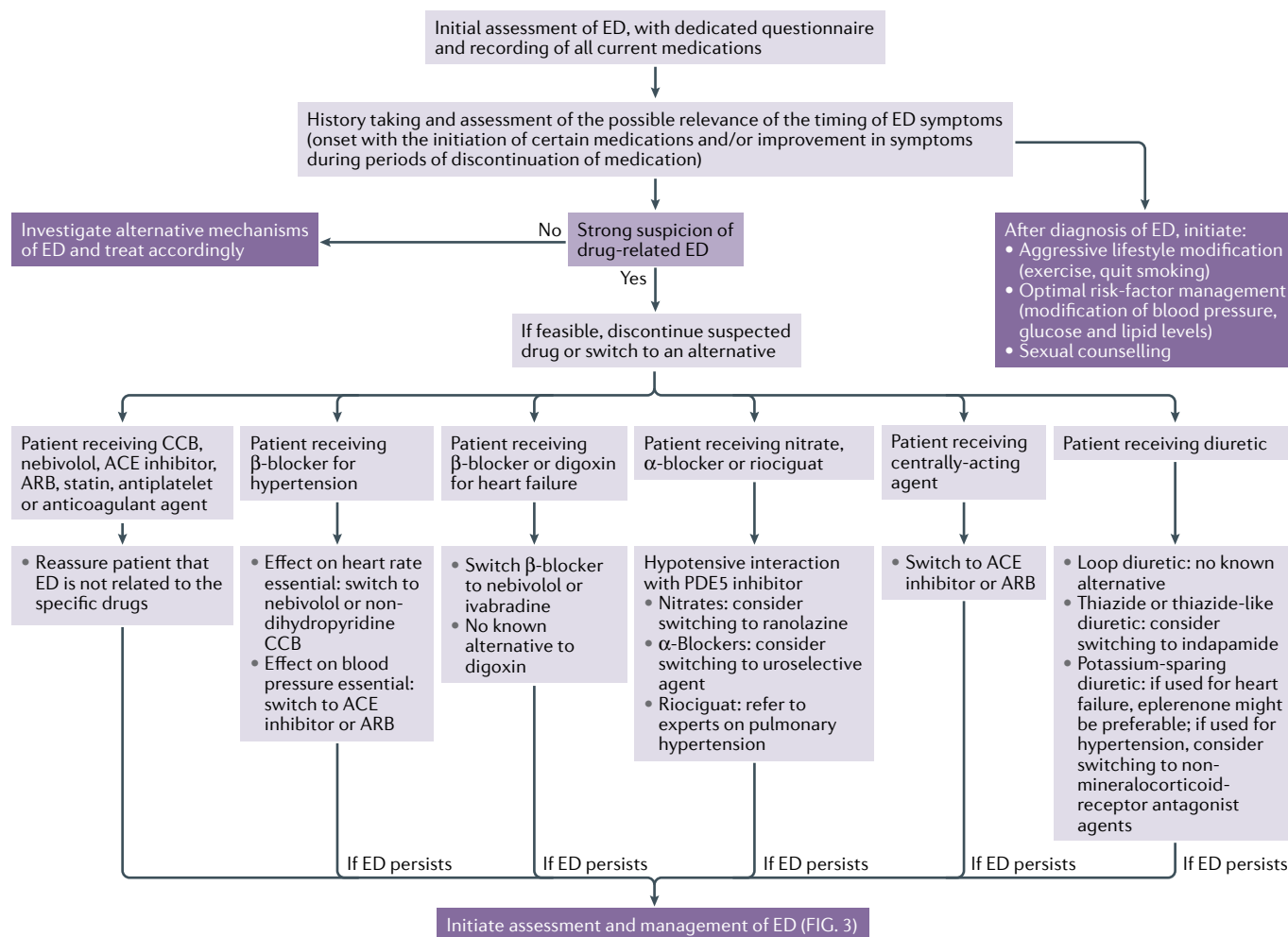


Fig. 2 | **An algorithm for managing ED associated with cardiovascular drug therapy.** The figure depicts the steps that physicians should follow in everyday clinical practice when drugs used to prevent or treat cardiovascular disease are suspected to be the cause of erectile dysfunction (ED). ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; CCB, calcium-channel blocker; PDE5, phosphodiesterase type 5.

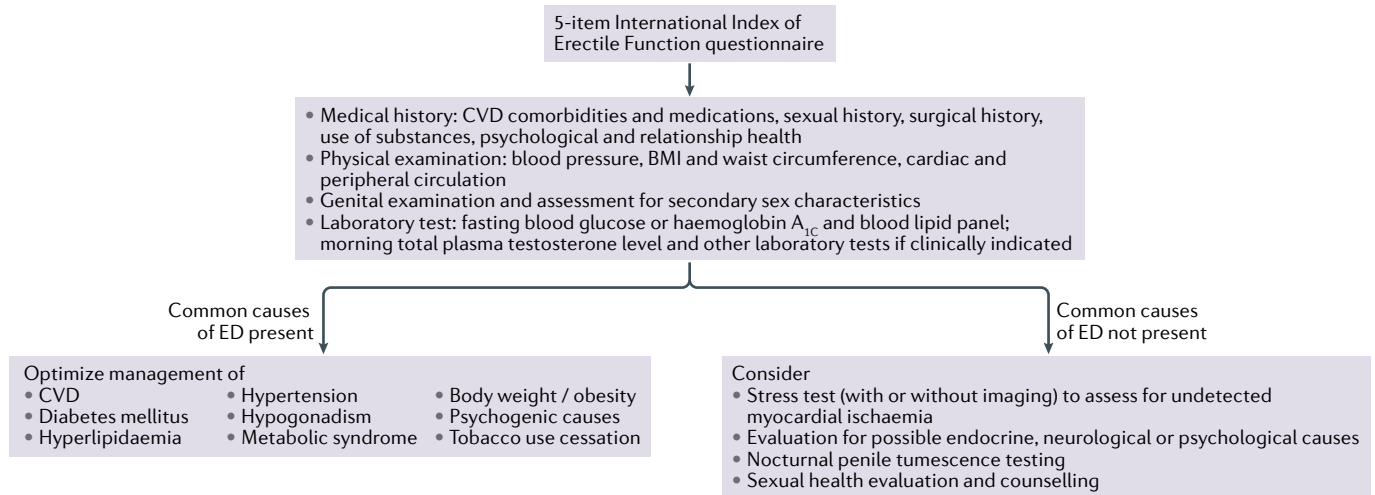
restoring erectile function. Haemodynamically, PDE5 inhibitors have mild nitrate-like actions and a modest hypotensive action because PDE5 is present in smooth muscle cells of blood vessels and the cGMP–nitric oxide pathway is involved in the regulation of blood pressure¹⁰. Non-response to PDE5 inhibitors, although uncommon, is usually multifactorial and can be the consequence of extensive endothelial damage that further reduces nitric oxide bioavailability and has increased interest in innovative, alternative treatment strategies¹²⁰.

At present, four PDE5 inhibitors (avanafil, sildenafil, tadalafil and vardenafil) are approved for medical use worldwide, and three more drugs (lodenafil, mirodenafil and udenafil) have been approved in a few countries. An individualized treatment approach in accordance with the preferences and needs of the patient is feasible owing to the unique within-class differences in pharmacokinetic and pharmacodynamic properties. In general, the extremely high efficacy of these medications (>70%, suggesting no clinically meaningful attenuation of the beneficial effect of these drugs on sexual activity by underlying risk factors for CVD) together with the

fairly infrequent occurrence of adverse effects has led to their widespread use. Nowadays, PDE5 inhibitors are even used as over-the-counter recreational drugs in younger men with mild or no symptoms. However, the report of several deaths related to cardiovascular events or the use of nitrates, which is a known contraindication to the use of PDE5 inhibitors, in the first 6 months after sildenafil was marketed for the treatment of ED raised justified concerns. Therefore, a definitive answer on their cardiovascular safety and possible sequelae was needed.

The cardiovascular safety of PDE5 inhibitors has been examined in numerous clinical studies. A meta-analysis of many of these studies was reassuring about their safety, confirming the lack of any significant signal of an increased risk of myocardial infarction or death with sildenafil compared with placebo^{121,122}. However, the interaction of PDE5 inhibitors with nitrates, α -blockers and soluble guanylate cyclase stimulators (such as riociguat, which is used in the treatment of pulmonary hypertension) should be noted. PDE5 inhibitors do not have synergistic effects on blood pressure with other antihypertensive agents,

a Evaluation of ED



b Risk assessment for sexual activity in men with ED and CVD

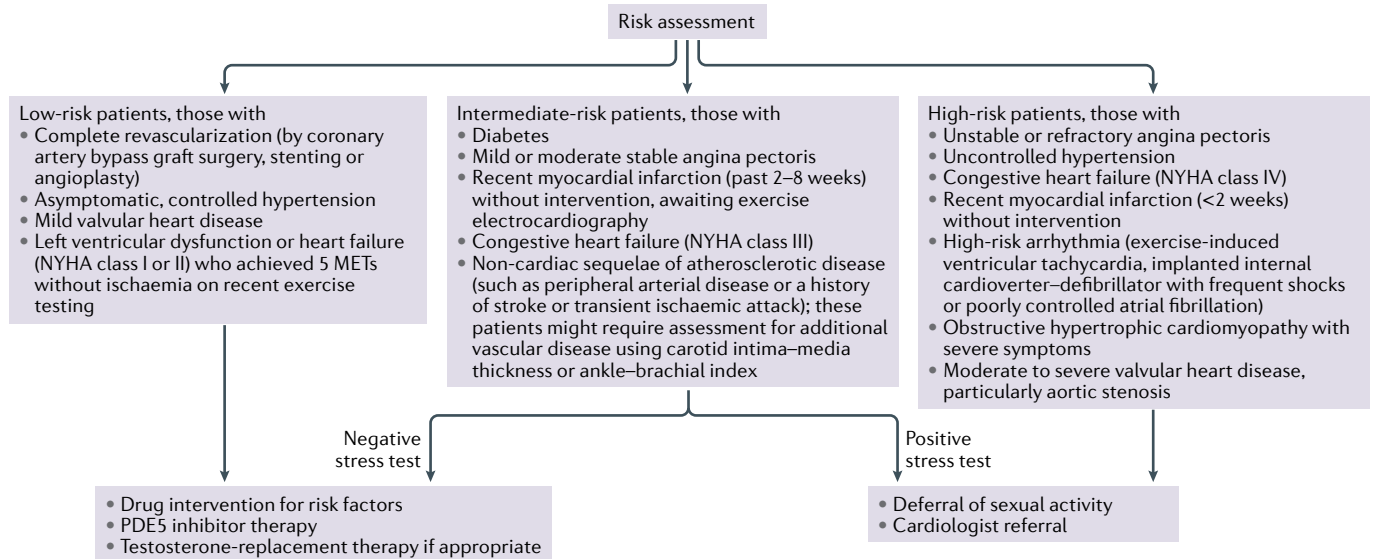


Fig. 3 | Evaluation of ED and risk assessment for sexual activity in patients with CVD. a | The figure depicts the steps in an algorithmic approach to evaluate erectile dysfunction (ED) in men with cardiovascular disease (CVD) in everyday clinical practice. The priorities are to confirm the diagnosis of ED and identify the cause. **b** | Assessment of the risk of cardiovascular events with sexual activity in men with ED and CVD, and appropriate management on the basis of underlying risk of CVD. MET, metabolic equivalent of task; PDE5, phosphodiesterase type 5.

such as β -blockers, calcium-channel blockers, diuretics, angiotensin-converting enzyme inhibitors or ARBs¹²¹. The co-administration of nitrates and PDE5 inhibitors is strictly contraindicated owing to the increased risk of symptomatic hypotension¹²³. Indeed, in emergencies such as a myocardial infarction, nitrates should not be administered until 48 h (for tadalafil) or 24 h (for avanafil, sildenafil and vardenafil) after intake of the PDE5 inhibitor. The co-administration of PDE5 inhibitors with α -blockers, used mostly for benign prostatic hyperplasia, is not contraindicated but precautions should be taken to avoid orthostatic hypotension; a 6-h interval between administration of the two drugs is recommended. Uroselective α -blockers should be favoured but patients should be monitored for possible ejaculatory dysfunction, including retrograde ejaculation and anejaculation.

Physicians should ensure when initiating therapy with either drug (a PDE5 inhibitor or an α -blocker) that previous treatment has been stable for ≥ 1 month, and initial dosing should be half the usual dose, with careful up-titration.

Post-marketing surveillance reports for PDE5 inhibitors¹²⁴, as well as several observational or randomized studies involving any of the PDE5 inhibitors either for their primary indication for ED¹²¹ or for alternative indications such as pulmonary hypertension¹²⁵ or HF¹²⁶, have not shown an increased risk of serious cardiovascular events. On the contrary, evidence for the beneficial effects of PDE5 inhibitors on the cardiovascular system is growing¹²⁷. These effects involve reduction of endothelial dysfunction¹²⁸, reversal of vascular ageing as assessed by arterial stiffness¹²⁹, reduction of

inflammatory activation and oxidative stress¹³⁰, improvement in exercise haemodynamics, reverse left ventricular remodelling (reduction of cardiac mass in patients with left ventricular hypertrophy and improvement of diastolic dysfunction despite a minimal change in afterload parameters)¹³¹, improvement in pulmonary haemodynamics and preconditioning that might protect against the adverse effects of ischaemia–reperfusion injury^{132,133}. Consequently, studies on the use of PDE5 inhibitors in various forms of CVD, such as HF, CAD, stroke and peripheral artery disease, have been performed or are ongoing, with encouraging results¹³³.

In addition, the results of large, observational studies of PDE5 inhibitors are promising but should be interpreted with caution because they are not randomized, controlled studies. Data indicate that PDE5 inhibitors can protect against future CVD events and confer a prognostic survival benefit. Specifically, a Swedish study including 43,145 patients admitted to hospital for myocardial infarction showed that men who received pharmacological treatment (PDE5 inhibitors and/or alprostadil) for ED after the myocardial infarction had a 40% lower risk of hospitalization for HF and a 33% lower mortality than those who did not receive such treatment¹³⁴. In a similar population of patients after a myocardial infarction or coronary revascularization, the same researchers showed that treatment with PDE5 inhibitors was associated with lower risks of death, myocardial infarction, HF and revascularization than treatment with alprostadil¹³⁵. Interestingly, these reductions in risk with PDE5 inhibitor treatment were dose-dependent¹³⁵. Furthermore, three medium-sized studies in men with diabetes showed that the use of PDE5 inhibitors decreased (or had a strong tendency to decrease) mortality^{60,136,137}. However, this beneficial effect of PDE5 inhibitors is not universal (depending on patient age and comorbidities)¹³⁸, and further large, randomized, controlled studies are warranted for a more definitive answer.

Testosterone-replacement therapy. Testosterone has an integral role in the physiological processes of erectile function through multiple mechanisms¹³⁹. Several observational studies have shown a strong association between low plasma testosterone levels and both CVD biomarkers and CVD events, but these studies are hampered by their inherent limitations, because they were unable to prove a causal relationship and were strongly influenced by confounders^{27,139–141}. Therefore, a possible beneficial cardiovascular effect of TRT in randomized and observational studies was greatly anticipated. Numerous studies have investigated the effects of TRT on CVD events and mortality, with conflicting results¹³⁹. The first study that generated concerns about TRT was the TOM trial¹⁴² that investigated the use of testosterone gel versus placebo gel in men with hypogonadism aged >65 years and showed a higher rate of cardiovascular events in the active treatment group. In another study, TRT was associated with an increase in non-calcified coronary plaque volume, as measured by coronary CT angiography, suggesting a potential harmful effect¹⁴³. These results contradicted the earlier neutral effects

in the rates of change in either common carotid artery intima–media thickness or coronary artery calcium that were reported in the TEAAM trial¹⁴⁴. Conversely, many studies have found substantial benefits of TRT on cardiovascular morbidity and mortality¹³⁹. All these conflicting data have been comprehensively reviewed previously¹³⁹. Of note, these studies had very different designs and comparator groups, rarely included assessment of plasma testosterone levels throughout the treatment to monitor fluctuations in levels, used different criteria for hypogonadism or their specific criteria were not reported, did not include close monitoring for potentially harmful adverse effects of treatment such as erythrocytosis, used different formulations and doses of TRT, had different adjudication of events, were primarily modest in population size, and rarely had a follow-up duration of >5 years. In summary, larger studies examining the effect of TRT on cardiovascular events, taking into consideration these limitations, are warranted to understand the true relationship between TRT and cardiovascular morbidity and mortality.

Conclusions

In summary, CVD and ED have shared risk factors and pathophysiological links, such as endothelial dysfunction and inflammation. ED also confers an independent risk of future cardiovascular events. The presence of ED can be used as a prognostic tool to improve CVD risk prediction, and the identification and treatment of ED can improve the quality of life of men with CVD and increase adherence to cardiovascular drugs associated with ED. Despite the increase in knowledge after the introduction of PDE5 inhibitors for the treatment of ED, many questions remain unanswered. The implications of a diagnosis of ED for the primary or secondary prevention of CVD should be further substantiated with appropriate randomized studies that investigate whether ED diagnosis can lead to better compliance to cardiovascular therapy, prediction of cardiovascular events incrementally to other risk factors for CVD, and prognostic benefit when managed properly. Currently, all the available data on the interaction between CVD medications and either ED or ED treatment come from small observational studies. The effects of combination antihypertensive therapy or polypills containing a statin, aspirin and antihypertensive medications on erectile function have not been properly addressed¹⁴⁵. Moreover, specific studies on strategies such as switching CVD treatment to improve erectile function have not been conducted, meaning that evidence-based algorithms cannot be created. The use of PDE5 inhibitors is safe but conclusive randomized studies on the possible beneficial or deleterious effects of treatment of ED with PDE5 inhibitors and/or TRT on cardiovascular events and mortality are also needed. Finally, raising awareness of ED among the scientific community, physicians, nurses and pharmacists is of the utmost importance because it can improve the monitoring of ED and eventually quantify the true extent of a condition that is often under-appreciated, under-reported and under-treated.

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Author contributions

All the authors researched data for the article. D.T.-P., N.I. and C.V. discussed the content of the article and wrote the manuscript. All the authors reviewed and edited the article before submission.

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