

## Why is there a need for an interdisciplinary approach to assess erectile dysfunction?

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### Abstract

Erectile dysfunction is a prevalent complaint among men. The majority of patients suffering erectile dysfunction exhibit various risk factors of vascular diseases. Erectile dysfunction used to be recognised as one of the consequences of vascular diseases in patients suffering heart attack or myocardial infarction. During the last decade, however, the role of endothelial dysfunction in the occurrence of erectile dysfunction has been signified, and it has been suggested that erectile dysfunction may not be simply a consequence of vascular diseases but an indicator of future vascular problems. Erectile dysfunction has been known as "the tip of iceberg" of a generalised vascular dysfunction, which typically happens before serious vascular problems. Considerable evidence shows a link between erectile dysfunction and vascular disorders. Several theories have been considered for the association between erectile dysfunction and vascular diseases. One of them is the "artery size" theory focusing on the differences between the diameter of the penile artery and other arteries. Another theory is based on "endothelial dysfunction", which highlights inappropriate vasoconstriction as a cause of erectile dysfunction and vascular diseases. "Age" has also been reported to have pivotal role in the development of vascular dysfunction resulting in erectile dysfunction and ultimately vascular diseases. Another theory explaining the pathophysiology of erectile

dysfunction and its relationship with vascular diseases focuses on the formation of atherosclerosis plaques. This article endeavours to review the current literature and discuss why a multidisciplinary approach is needed while assessing erectile dysfunction.

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**Key words:** Coronary artery disease; Erectile dysfunction; Myocardial infarction; Stroke vascular disease

**Core tip:** Erectile dysfunction (ED) *per se* is not a life-threatening problem but it is a harbinger of more serious vascular impairments. Indeed, a strong correlation has been documented between the severity of ED and the severity of vascular diseases, myocardial infarction and stroke. The vascular symptoms are demonstrated 2-3 years on average after exhibition of the first symptoms of erectile dysfunction. This gap provides enough time to intervene and prevent subsequent vascular problems. Notwithstanding, the predictability of subsequent vascular disease may be missed as these patients are not simultaneously evaluated by an urologist and a cardiologist.

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### INTRODUCTION

Erectile dysfunction (ED) is a prevalent complaint among men. It has been defined by the National Institute of Health Consensus Conference as "inability of the male to attain and maintain erection of the penis sufficient to permit satisfactory sexual intercourse"<sup>[1]</sup>. The prevalence of ED varies among different age groups.

**Table 1** Some of the risk factors of vascular diseases

Diabetes mellitus	Older age
Psychological problem	Male
Psychiatric impairments	Drug and alcohol use
High blood pressure	Lack of nutrients
Hypercholesterolemia	Smoking
Hypertension	Overweight and obesity
Chronic systemic diseases	Lack of physical activity
Family history	Allergy

Research has shown that the prevalence of ED among 40 and 60 year old men is 8% and 40%, respectively<sup>[2]</sup>. It has also been reported in other research that five to ten percent of men who are in their 40 s experience ED, while 40%-60% of men who are 70 years of age or more suffer this disorder<sup>[3,4]</sup>. Research has shown that patients with vascular risk factors have greater risk of ED. In one study, 90.4% of men with ischemic heart disease reported moderate to severe degrees of ED<sup>[5]</sup>. In another study, 65% of men developed vascular ED after heart transplant<sup>[6]</sup>. The rate of severe ED was also reported to be 46.8% in men suffering ischemic heart disease, 59.1% of them had 3 or more cardiovascular risk factors<sup>[7]</sup>.

A population of sixty-one million individuals in the United States suffer vascular diseases and it is still the most prevalent cause of death (40%) across the world. The risk of vascular diseases in men increases with age and becomes even worse in men suffering with ED<sup>[8]</sup>.

Erectile dysfunction was primarily recognized as one of the consequences of vascular diseases in patients suffering heart attack or myocardial infarction. During the last decade, the introduction of sildenafil citrate to the market as a treatment for ED highlighted the mechanism of male arousal and signified the role of endothelial dysfunction in the occurrence of ED. It was then suggested that ED may not be simply a consequence of vascular diseases, but it can be an indicator of future vascular problems<sup>[9]</sup>. Although it has been well recognized that there is a relationship between the risk factors of vascular diseases and the progress of ED, there are still controversies over the issue of whether ED is a consequence of vascular diseases or a risk factor and predictor for the development of future vascular diseases.

Unlike neurogenic ED and ED resulting from pelvic trauma or surgical procedures, the severity of vasculogenic ED has been reported to be closely interrelated to the severity of vascular diseases<sup>[10]</sup>. Patients suffering ED exhibit various risk factors of vascular diseases, such as hypertension and older age<sup>[11]</sup>, diabetes<sup>[12]</sup>, smoking<sup>[13]</sup>, dyslipidemia<sup>[14]</sup> and obesity<sup>[15]</sup> (Tables 1 and 2). In addition, men who experience erectile dysfunction suffer more undiagnosed ischemic heart diseases, myocardial infarction and other vascular diseases than men without ED<sup>[16]</sup>.

Considering results of many research studies that focus on the relationship between ED and vascular diseases, this article endeavours to uncover the association between ED and vascular diseases. The paper also aims

**Table 2** Some of the risk factors of erectile dysfunction

Psychological disorders	Neurological problems
Various kinds of medicines	Parkinson's
Antihypertensive	Spinal cord injury
Cardiac drugs	Alzheimer's disease
Antidepressants	Local penile diseases
Anticholinergics	Smooth muscle dysfunction
Psychotropics	Smoking
Dopamine blockers	Overweight and obesity
Chronic systemic diseases	Injuries and trauma
Renal diseases	Alcohol use
Post-organ transplant	Older age
Cancer	Allergy
Vascular disease	
Endocrine disorders	
Diabetes mellitus	
Androgen deficiency/resistance	
Vascular disorders/insufficiency	
Atherosclerosis	
Venous leakage	
Arterial insufficiency	
Veno-occlusive diseases	

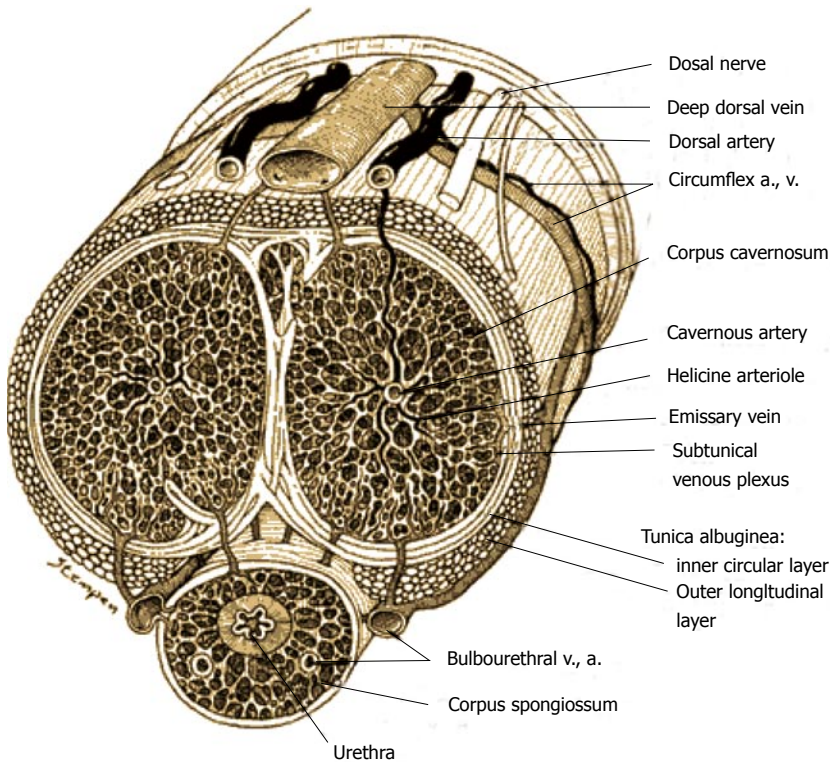
to highlight the importance of advanced medical assessment of patients suffering ED in order to prevent future vascular diseases. To this aim, the mechanism of male sexual arousal will be discussed first and factors affecting erectile function will be reviewed.

## MECHANISM OF ERECTION AND FACTORS INDUCING ERECTILE DYSFUNCTION

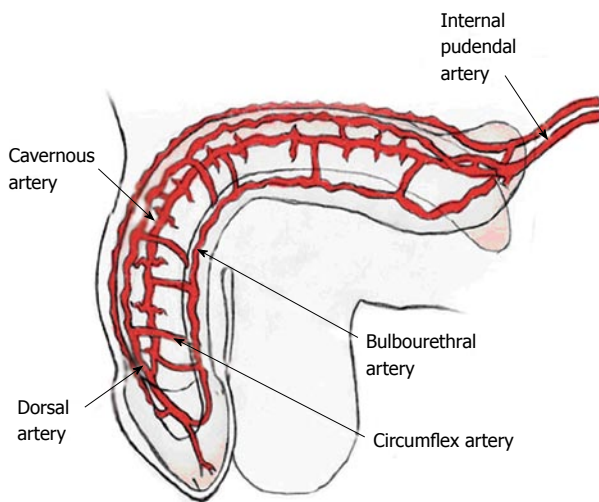
The penis is comprised of three expandable erectile bodies, including a pair of corpora cavernosa and the corpus spongiosum. The corpus cavernosum consists of sinusoidal spaces and a bundle of smooth muscles which are responsible for the sponge-like tissue of the penis. The inside of the sinusoidal space is covered with endothelial tissue. The spaces are separated by connective tissue septa. There is also a complex network of arteries and nerve terminals within the tissues (Figure 1). All of these compartments turn the penis into an erectable body<sup>[17]</sup>.

Penis blood supply is mainly provided by the paired internal pudendal artery which consecutively splits into three branches: the bulbourethral artery, dorsal artery and the cavernous artery (Figure 2). Although there are numerous small and large veins serving the glans penis, the deep dorsal vein provides the main venous drainage of the glans penis (Figure 3)<sup>[18]</sup>.

Various psychogenic and sensory stimuli influence chemical, neurological and vascular cascades and trigger penile rigidity and erection. The stimuli in addition to spinal reflex intermediate the process and result in the relaxation of both corporeal and arterial wall smooth muscles, which in turn enhances arterial inflow. On the other hand, the venous wall smooth muscles contract in order to decrease the venous outflow to a minimum level and trap the blood in the penis, leading to penile

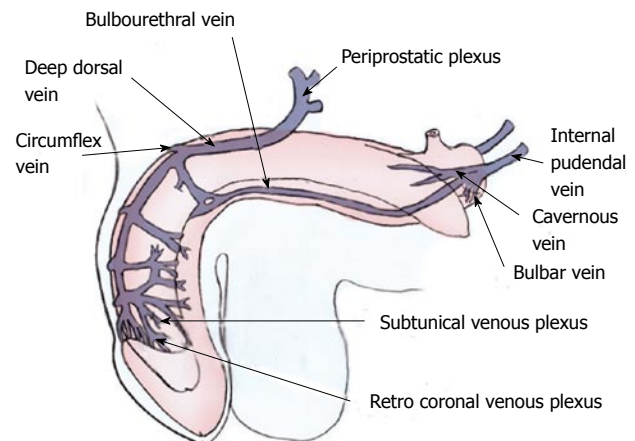


**Figure 1 Cross section of penis.** Tom Hubbard [Image]. (2012). Retrieved from <http://penis-enlargement-manual.thundersplace.org/tom-hubbard/2001-01/anatomy.html>.



**Figure 2 Arteries of penis.** Pamela I Ellsworth [Image]. (2011). Retrieved from <http://emedicine.medscape.com/article/1949325-overview#aw2aab6b3>.

erection. In fact, the penile tumescence highly depends on the balance between both contracting and relaxing factors which determine the arterial inflow and venous outflow<sup>[19]</sup>. It has been reported that 80-115 mL blood is necessary to keep a 7.5 cm penis fully rigid. At this stage, the intracorporeal pressure increases from 10-15 mmHg during flaccid state to 120 mmHg (suprasystolic pressure) during full rigidity when the penis is elevated to more than 90 degrees<sup>[20,21]</sup>. Subsequent to erection, several physical and physiological changes occur in the body, some of which are the increase of blood pressure, hyperventilation, sweating and generalized myotonia<sup>[21]</sup>. Penile tumescence can be affected by many factors creating various degrees of erectile dysfunction. A list of some of



**Figure 3 Veins of penis.** Pamela I Ellsworth [Image]. (2011). Retrieved from <http://emedicine.medscape.com/article/1949325-overview#aw2aab6b3>.

the influencing factors is presented in Table 1<sup>[21,22]</sup>.

During arousal, nitric oxide (NO) is released into the penile corpus cavernosum<sup>[23]</sup> and stimulates the formation of cyclic guanosine monophosphate. This in turn results in the relaxation of smooth muscle of both blood vessels and corpus cavernosum followed by penile tumescence<sup>[24]</sup>. The relaxing effect of NO on vascular structure is also important to the health of the vascular system. Other functions of endothelial NO that contribute to the inhibition of atherosclerosis are that it decreases oxidation of LDL, reduces platelet aggregation to the endothelium, and prevents leukocyte adhesion and infiltration into the vessel wall. Therefore, it seems that any factor influencing the formation and activity of NO may be a risk factor for vascular diseases<sup>[25]</sup>. However,

DeBusk suggests that a lack of NO causes only ED in some men. Therefore, men who suffer ED but do not have the above-mentioned risk factors may not be at greater risk of vascular diseases<sup>[26]</sup>.

## ASSOCIATION BETWEEN ERECTILE DYSFUNCTION AND VASCULAR DISEASE

Although ED is a complex problem resulting from different kinds of factors, a link between ED and vascular disorders has been identified. Research has reported that vascular disorders/insufficiency is the most prevalent cause of ED<sup>[21]</sup> and suggested that “ED is an early symptom of generalised endothelial dysfunction”<sup>[22]</sup>.

Considerable evidence shows the relationship between ED and vascular diseases. A strong correlation has been documented between the severity of ED and the severity of vascular diseases<sup>[27]</sup>. Patients who have vascular disorders, including peripheral vascular diseases, coronary diseases, cerebrovascular disorders and myocardial infarction, have a higher prevalence of ED<sup>[28]</sup>. Research has also demonstrated that more than half of the men who suffer coronary artery disease (CAD) experience ED<sup>[29]</sup>.

Erectile dysfunction has been known as “the tip of iceberg” of a generalized vascular dysfunction which typically happens before serious vascular problems<sup>[29]</sup>. The predictability of CAD in ED patients was investigated in a population-based study conducted by Inman *et al*<sup>[4]</sup>. Results from 1402 men revealed that new ED developed in 6.4% in 2 years of follow-up, in an additional 5.4% at 6 years of follow-up, and in an additional 4.9% of men at 8 years of follow-up in each screening round. In addition, after the 10 year follow-up period, 11.1% of men developed coronary artery diseases and the incidence of coronary artery diseases was strongly associated with the increase of the patient's age. It was also reported that men suffering ED had a higher incidence of coronary artery diseases during the study period. Although the study by Corona *et al*<sup>[30]</sup> lacked information on other risk factors of coronary artery diseases such as dyslipidemia and lifestyle as reported in the literature, it showed that the risk of coronary artery diseases in men with ED was 80% more than that of men without ED. This finding was in accordance with the results of other studies in which the risk of coronary artery diseases in men suffering ED was 65%<sup>[31]</sup> and 45%<sup>[32]</sup>. Similarly, it was reported in another study by Vlachopoulos *et al*<sup>[33]</sup> that 19% of men who had ED and underwent angiographic evaluation had silent coronary artery diseases.

The development of new cases of coronary heart disease in patients with ED was investigated in another study<sup>[31]</sup>. A total of 2561 men were recruited in the research and were followed up for a period of 10 years. It was reported that the risk of coronary heart disease and stroke increased with an increase of age. While the risk of development of coronary heart disease after 10

years in men who had mild ED was 2.3%-11.2%, men with moderate/severe ED had a higher risk of coronary heart disease development (65%) during a 10 year follow-up period. Furthermore, the risk of stroke was higher among men with moderate/severe ED. These findings are compatible with those of the study by Blumentals *et al*<sup>[34]</sup> in which the predictability of acute myocardial infarction (AMI) in men with ED was investigated. Their cohort study consisted of 12825 men with ED and 12825 men without ED aged from 18 to 55 years. The results showed that there were no statistically significant differences between the two groups regarding smoking, obesity, the use of ACE inhibitors and the use of beta blockers and statins ( $P > 0.05$ ).

Nevertheless, the risk of AMI among men who suffered ED was two times more than that of men without ED. The association between vascular disease and ED was also reported in an earlier study by Roumeguère *et al*<sup>[35]</sup> in which the risk of developing CAD during a ten year follow-up study was 34% higher among men with ED. Moreover, Blumentals *et al*<sup>[34]</sup> reported that the risk of AMI increased by the increase of participants' age, similar to the findings of the study by Inman *et al*<sup>[4]</sup>. A more recent study<sup>[36]</sup> supported these reports, indicating that ED is a significant marker for future stroke in men.

The link between hypertension and ED has also been documented in the research conducted by Solomon *et al*<sup>[16]</sup> in which the majority of patients who suffered ED and sought treatment for their problem had undiagnosed ischemic heart diseases and high blood pressure.

The relationship between ED and future vascular diseases was investigated in a study by Thompson *et al*<sup>[32]</sup>. In this study, 18882 men were recruited from the Prostate Cancer Prevention Trial and were allocated to either finasteride-receiving group or placebo-receiving group. Participants were then followed-up for a period of 10 years and were investigated for the development of vascular diseases. At the commencement of the study, 85% of men in the placebo arm had no vascular diseases and 53% of them did not have ED. After 5 and 6 years follow-up, 57% and after 7 years, 65% of men, respectively, developed erectile dysfunction. Compared with men who did not develop ED after 5 years, men who developed ED after 5 years were more likely to experience subsequent angina, myocardial infarction and stroke. It was also reported that this association was greater among men who had a history of hyperlipidemia or cigarette smoking. Although this study lacked information on the medications used by patients, findings of the study by Thompson *et al*<sup>[32]</sup> were similar to those of the study by Montorsi *et al*<sup>[37]</sup> in which 67% of patients who had acute chest pain and were diagnosed with CAD by the use of angiography had prior erectile dysfunction.

Diabetic patients have been reported to be at greater risk of both ED and vascular diseases<sup>[38,39]</sup>. In a cohort study by Ma *et al*<sup>[40]</sup>, 2306 diabetic men were evaluated during a 4 year follow-up period. At baseline, vascular disease was not evident in any of the participants. However, 5.3% of diabetic men (123 subjects) developed

coronary heart disease during the follow-up period. In addition, the risk of ED was significantly associated with older age and longer duration of diabetes. The findings of the study showed that the prevalence of coronary heart disease was higher among those who had both ED and diabetes than in those who were only diabetic. It was also revealed that diabetic men with ED had 1.6 times greater risk of developing coronary heart disease. Although the study by Ma *et al*<sup>[40]</sup> suffered a bias selection and lacked the use of a standard questionnaire, their findings were in accordance with the results of other studies in which diabetic men who had ED were at increased risk of developing coronary heart disease<sup>[41-43]</sup>. Similarly, results of the study by Gazzaruso *et al*<sup>[44]</sup> showed that diabetic men with ED were at 14.8% greater risk of developing coronary heart disease. Gazzaruso *et al*<sup>[44]</sup> reported that ED was the most reliable indicator and a significant risk factor for future vascular diseases, which was supported by results of a recent study by Ryu *et al*<sup>[45]</sup>.

In the study by Giuliano *et al*<sup>[42]</sup>, diabetic and hypertensive patients were evaluated in order to investigate the prevalence of ED. To this aim, a population of 7689 patients were recruited and completed the study questionnaire. Analysis of the results uncovered that 66% of patients reported subjective feeling of having ED, which was in accordance with their scores obtained from the study questionnaire indicating that 67% of hypertensive patients had ED. The prevalence of ED increased with the longer duration of hypertension. The use of beta-blockers, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers was strongly associated with the decreased risk of ED. Moreover, 71% of diabetic patients suffered ED and the risk increased with the longer duration of diabetes mellitus. It was also revealed that 78% of patients who suffered both hypertension and diabetes were diagnosed with ED. Nevertheless, there is no conclusive evidence that shows whether hypertension and diabetes mellitus *per se* induce ED or if the medications used in these patients affect their sexual functioning<sup>[42]</sup>.

## THEORIES

Vascular disease and erectile dysfunction have been reported to share common risk factors<sup>[43]</sup>. It is suggested that early treatment of risk factors of ED may diminish the incidence of future cases of vascular diseases. Moreover, patients with ED need to be tested for hidden vascular diseases and should be followed-up for future vascular impairments<sup>[46,47]</sup>.

Four theories have been developed to explicate the relationship between ED and vascular diseases. One of them is the “artery size” theory which focuses on the differences between the diameter of penile arteries (1-2 mm), coronary arteries (3-4 mm), carotid arteries (5-7 mm) and iliofemoral arteries (6-8 mm). This suggestion states that the small penile artery manifests obstruction sooner than the larger coronary and other vessels because an atherosclerotic plaque of the same size would

cause significant obstruction sooner in a smaller vessel. Therefore, it could account for the earlier appearance of ED than of CAD<sup>[48]</sup>.

Another theory highlights the existence of “endothelial dysfunction”<sup>[49]</sup>. Many men with ED exhibit endothelial cell inflammation and dysfunction. Endothelial dysfunction causes inappropriate vasoconstriction, impedes vasodilation and hinders the relaxation of smooth muscles of arterioles<sup>[50]</sup>. This theory suggests that the development of ED, CAD and atherosclerosis is based on similar endothelial dysfunction<sup>[34,51]</sup>.

The third theory suggests that “age” has a pivotal role in the development of vascular dysfunction resulting in ED and ultimately vascular disease. The elastic lamella of vessels may suffer fatigue and be susceptible to fracture due to insistent and continuous pulsations during its life span. In addition, artery stiffness is likely to occur more in elderly men. These events result in the increase of systolic blood pressure and the fall of diastolic blood pressure. The arterial rigidity and systolic hypertension negatively affect the myocardium. It also puts the strain of cardiac pulsation on smaller arteries such as pudendal and penile arteries. The high blood pressure in penile arteries ultimately causes degeneration and ischemia of penile arteries and ends in ED<sup>[52]</sup>.

Another theory explaining the pathophysiology of ED and its relationship with vascular disease emphasizes the importance of “atherosclerosis”. This condition differs from the arterial stiffness due to old age. Atherosclerosis is recognised by the formation of plaques, especially lipid plaques, in the wall of blood vessels. The large-size plaques can lead to vessel occlusion. Larger plaques may obstruct the vessel or rupture. Considering the differences in diameters of penile, coronary, carotid and iliofemoral arteries, it is suggested that the penile artery may be the first place to be obstructed by atherosclerotic plaques. The occlusion of penile arteries may have different clinical presentations, one of which can be ED<sup>[4,53]</sup>.

## CONCLUSION

Talking about sexual performance has always been a taboo during different historical eras and men suffering ED have been reluctant to discuss the issue with professionals. Although recent breakthroughs in the science of sexology and campaigns promoting sexual health have decreased the social stigma relating to ED, the true rate of this disorder is underestimated because many men refuse to refer to a physician to treat their ED. Physicians are also reluctant to talk about it and would prefer not to bring up sexual matters during visits with patients<sup>[1]</sup>. On the other hand, the majority of cases of ED who refer to physicians are treated by general practitioners (GPs) but not specialists so the existence of vascular diseases or complex medical conditions in this group of men is typically not examined<sup>[54]</sup>.

Erectile dysfunction *per se* is not a life-threatening problem but it is a harbinger of more serious vascular

impairments, such as vascular diseases, cardiac problems and cerebrovascular diseases. The Second Princeton Consensus Conference concluded that ED is an alarming signal of a hidden vascular disease. The consensus was that every man suffering different degrees of ED has to be regarded as a case of vascular disease unless proven otherwise<sup>[29,51]</sup>.

It appears that vascular disease may be possible to predict in men, specifically those with various degrees of erectile dysfunction. Research has reported that vascular symptoms are demonstrated 2-3 years on average after exhibition of the first symptoms of ED<sup>[55]</sup>. This gap provides enough time to intervene and prevent subsequent vascular problems. Notwithstanding, the existing issue is that men with ED refer to general physicians or urologists but not cardiologists so the predictability of subsequent vascular disease may be missed. To resolve this problem, a multidisciplinary approach is suggested in which the cardiologists work closely with urologists and general physicians<sup>[56]</sup>. All men with ED need a vascular assessment and must be checked for high blood pressure, hyperlipidemia and hyperglycemia. The aim is not to detect ED and treat it by the cardiologist, but to actively develop a multidisciplinary management plan, which in turn may decrease morbidity and mortality of vascular events in the future<sup>[57]</sup>.

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