Erectile dysfunction in the cardiovascular patient

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Erectile dysfunction (ED) is common, affecting almost 40% of men over 40 years of age (with varying degrees of severity) and increases in frequency with age.1 Erectile dysfunction and cardiovascular disease (CVD) share common risk factors including age, hypercholesterolemia, hypertension, insulin resistance and diabetes, smoking, obesity, metabolic syndrome, sedentary lifestyle, and depression.2 Cardiovascular disease and ED also share a common pathophysiological basis of aetiology and progression.3 Numerous studies have established that ED (i) is frequent in men with established CVD, (ii) co-exists with occult coronary artery disease (CAD) and (iii) is an independent risk factor for future cardiovascular (CV) events both in men with established CVD and in men with no known CVD.2,4,5 In the latter group, ED precedes CAD, stroke, and peripheral arterial disease by a significant period that usually ranges from 2 to 5 years (average 3 years).2 Although the ED patient can be managed by various medical specialties, and preferably a collaborative approach is most effective, this review is oriented to the cardiologist. While this review deals exclusively with sexual health of men, female sexual health and its potential relation with CVD is also an interesting, yet underexplored, field. As in men, moderating common risk factors seems to improve female sexual health and may serve as an opportunity to decrease CVD risk, with the identification of sexual dysfunction being the starting point.6

What is erectile dysfunction?

Distinction between organic and psychogenic erectile dysfunction

Erectile dysfunction is defined as the inability to attain or maintain a penile erection sufficient for satisfactory sexual performance. Cases of ED may be classified as predominantly organic in nature, predominantly psychogenic, or mixed. Usual organic aetiologies are vasculogenic, hormonal, and neurogenic. Owing to the relationship of vasculogenic ED with CVD, it is important to distinguish men with predominantly vasculogenic ED from those with predominantly psychogenic ED or non-vasculogenic organic ED.

Table 1 offers elements for distinction between organic and psychogenic disease.7 Of note is that in cases of organic origin, a psychogenic component may co-exist. The most common organic aetiology of ED is vasculogenic (see below ‘ED and CAD: common pathophysiology’).2,3 Co-existence of vascular disease, advancing age, and the presence of CVD risk factors and metabolic disorders increase the likelihood that ED is of vasculogenic aetiology.

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Keywords

Cardiovascular disease • Erectile dysfunction • Sexual counselling

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The aetiology of predominantly psychogenic ED is multifactorial, and components may include psychiatric disorders (especially depression), interpersonal problems with the sexual partner or misconceptions about normal sexual activity. Identifying and getting treatment for those patients with psychogenic causes of ED such as depression that may also increase CVD risk is also important.

**The importance of the medical history**

While additional investigation is usually necessary, the medical and sexual history is essential and frequently the most revealing aspect of the ED assessment process. Questionnaires are an integral part of the history. The International Index of Erectile Function (IIEF), a 15-item, self-evaluation questionnaire is a validated instrument for assessing erectile function, orgasmic function, desire and satisfaction after sexual relations. An abridged version of the IIEF is a 5-item questionnaire the Sexual Health Inventory for Men (SHIM) or IIEF-5 (Table 2). Responses to the five questions range from 1 (worst) to 5 (best). Questions 2 to 4 may be graded 0 (if there is no sexual activity, or no sexual intercourse attempt) and the final score ranges from 1 to 25 points; a descending score indicates worsening of erectile function, with values \( \leq 21 \) being diagnostic of ED. Importantly, validated questionnaires correlate with the extend of CAD and improve the predictive value of ED for total cardiovascular events compared with a single-question ED diagnosis. It cannot be overemphasized that the SHIM can be effectively used not only by andrologists and urologists but by a wide array of medical specialists, such as cardiologists, diabetologists, primary care physicians, etc.

**Erectile dysfunction and cardiovascular disease: common pathophysiology**

Penile erection is largely a vascular process, and the penile endothelium and smooth muscle tissue are very sensitive to functional and structural changes. Vasculogenic ED results from an impairment of endothelial dependent or independent smooth muscle relaxation (functional vascular ED, initial stages), occlusion of the cavernosal arteries by atherosclerosis (structural vascular ED, late stages), or a combination of these. Current data support a complex interplay between endothelial dysfunction, subclinical inflammation, and androgen deficiency (Figure 1). The relationship between ED and CAD at the clinical level is supported by this common pathophysiological basis. The ‘artery size’ hypothesis explains why patients with CAD frequently report ED before CAD detection. According to this hypothesis, for a given atherosclerotic burden, the smaller penile arteries suffer obstruction earlier than the larger coronary arteries (Figure 2). The same concept holds also true in the case of non-obstructing atherosclerosis: since the smaller penile artery have a greater endothelial surface and erection requires a large degree of vasodilation to occur when compared with arteries in

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### Table 1 Differential characteristics of psychogenic vs. organic erectile dysfunction

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Predominantly psychogenic ED</th>
<th>Predominantly organic ED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Acute</td>
<td>Gradual</td>
</tr>
<tr>
<td>Circumstances</td>
<td>Situational</td>
<td>Global</td>
</tr>
<tr>
<td>Course</td>
<td>Intermittent</td>
<td>Constant</td>
</tr>
<tr>
<td>Non-coital erection</td>
<td>Rigid</td>
<td>Poor</td>
</tr>
<tr>
<td>Nocturnal/early AM erections</td>
<td>Normal</td>
<td>Inconsistent</td>
</tr>
<tr>
<td>Psychosexual problems</td>
<td>Long history</td>
<td>Secondary to ED</td>
</tr>
<tr>
<td>Partner problems</td>
<td>At onset</td>
<td>Secondary to ED</td>
</tr>
<tr>
<td>Anxiety/fear</td>
<td>Primary</td>
<td>Secondary to ED</td>
</tr>
</tbody>
</table>

Source: Persu et al.

### Table 2 The Sexual Health Inventory for Men (SHIM) or IIEF-5 over the past 6 months

<table>
<thead>
<tr>
<th>Question</th>
<th>Very low</th>
<th>Low</th>
<th>Moderate</th>
<th>High</th>
<th>Very high</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. How did you rate your confidence that you could get and keep an erection?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration?</td>
<td>No sexual activity</td>
<td>Almost never or never</td>
<td>A few times</td>
<td>Sometimes</td>
<td>Most times</td>
</tr>
<tr>
<td>3. During sexual intercourse, how often were you able to maintain your erection after you had penetrated your partner?</td>
<td>Did not attempt intercourse</td>
<td>Almost never or never</td>
<td>A few times</td>
<td>Sometimes</td>
<td>Most times</td>
</tr>
<tr>
<td>4. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?</td>
<td>Did not attempt intercourse</td>
<td>Extremely difficult</td>
<td>Very difficult</td>
<td>Difficult</td>
<td>Slightly difficult</td>
</tr>
<tr>
<td>5. When you attempted sexual intercourse, how often was it satisfactory to you?</td>
<td>Did not attempt intercourse</td>
<td>Almost never or never</td>
<td>A few times</td>
<td>Sometimes</td>
<td>Most times</td>
</tr>
</tbody>
</table>

The IIEF-5 is administered as a screening instrument for the presence and severity of ED in conjunction with the clinical assessment. The score is the sum of the responses to the five items, so that the overall score may range from 1 to 25; no ED (total score, 22–25), mild (17–21), mild to moderate (12–16), moderate (8–11), and severe ED (1–7).
Figure 1 Links between endothelial dysfunction, inflammation, testosterone deficiency, erectile dysfunction, and coronary artery disease. Modified with permission from Vlachopoulos et al.3
other organs, the same degree of endothelial dysfunction will be symptomatic in these smaller vessels but subclinical in the larger ones (i.e. coronaries). In the same context, accelerated arterial ageing (as indicated by increased arterial stiffening that also affects large arteries of ED patients) may be a common background.\textsuperscript{11,12} Erectile dysfunction is associated with an incremental inflammatory

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**Figure 2** The ‘artery size’ hypothesis. Luminal narrowing due to atherosclerotic burden will manifest clinically earlier (A) in penile arteries than in (B) coronary arteries. TIA, transient ischaemic attack. Modified with permission from Montorsi et al.\textsuperscript{10}
and endothelial-pro-thrombotic activation. Interestingly, this activation is equal to that found in CAD patients with no ED, while when these two conditions are combined the burden is additive. Androgen deficiency may be also implicated in the common pathogenetic pathways of ED and CVD; however, this warrants further substantiation.

Erectile dysfunction and cardiovascular disease: their relation in the clinical setting

Relation to cardiovascular disease, either overt or subclinical

Erectile dysfunction is frequent in patients with established CAD with prevalence rates ranging between 47 and 75% in studies. The Association Between Erectile dysfunction and coronary Artery disease (COBRA) trial tested the hypothesis that the ED rate differs in CAD patients according to the clinical presentation (acute vs. chronic coronary syndromes) and the extent of vessel involvement (one vs. two to three vessel disease). The overall ED prevalence in CAD patients was 47%, whereas in the normal coronary angiography group the ED rate was 24%. When separately considered, the ED rate was 22% in patients with acute coronary syndromes (ACS) and one-vessel disease and 55 and 65% in patients with ACS and multi-vessel disease and with chronic coronary syndrome, respectively. The study also showed that both severity (IIEF <10) and duration (>24 months) of ED were predictive of severe coronary involvement at angiography. This study offers pathophysiological and mechanistic explanations related to the clinical setting. In patients with multi-vessel disease, regardless of the clinical presentation, the advanced coronary and systemic atherosclerosis is the reason for the high rate of ED. However, in the setting of acute myocardial infarction with one-vessel disease, ED is far less frequent because the atherosclerotic burden is modest (i.e. abrupt occlusion of a single non-obstructing plaque in the absence of extensive atherosclerosis) in both the coronary and penile circulations. Conversely, and of significant clinical importance, is how often patients with ED as their first and sole clinical manifestation suffer from subclinical CAD. Previous studies reported a rate of inducible ischaemia by exercise stress testing (EST) in 22% (with a wide range of 5–56%) of ED patients reflecting differences in patient population, risk factors and criteria used for ED and CAD diagnosis. Interestingly, those patients further assessed with coronary angiography had obstructive atherosclerosis in >90% of cases. In a prospective angiographic study, we documented that 19% of ED patients suffer from clinically silent obstructive CAD.

Erectile dysfunction and risk for future cardiovascular events: the window of opportunity

Erectile dysfunction carries an independent risk for cardiovascular events. A considerable number of studies have examined the ability of ED to predict the risk of future fatal and non-fatal cardiovascular events (myocardial infarction, stroke, revascularization) and total mortality in the general population and in high CV risk patients, in diabetics and in heart failure patients. In a meta-analysis of 14 prospective cohort studies involving 92,757 men followed for a mean period of 6.1 years, ED increased significantly and independently of traditional risk factors the risk of CV events, CV mortality, myocardial infarction, cerebrovascular events, and all-cause mortality by 44, 19, 62, 39, and 25% respectively. This predictive ability also extends in men with known CVD: ED increased the risk of all-cause mortality by

Figure 3 Relation between erectile dysfunction prevalence and type of coronary syndrome (A). Time interval (months) between erectile dysfunction and coronary artery disease symptom onset in chronic coronary syndrome according to the number of vessels involved (B). ACS, acute coronary syndrome; CCS, chronic coronary syndrome, G1: ACS and 1-VD; G2: ACS and 2-3-VD; G3: CCS. VD, vessel disease; C: the control group with normal coronary angiography. With permission from Montorsi et al.
90%. Of importance, the predictive ability of ED is higher in younger ED patients despite the fact that probability of ED increases with age, most likely identifying a group of patients with early and aggressive vascular disease. Clinical implementation of ED as a biomarker relies on whether its addition on classical risk scores such as the Systematic Coronary Risk Evaluation (SCORE) or the Framingham correctly reclassifies a meaningful percentage of patients into a higher or lower risk category. To this end, data are limited. Yet, in a population-based study of men 40–70 years of age, the addition of the ED status to the Framingham risk score resulted in a reclassification of 6.4% of low-risk patients to intermediate risk. The pathophysiological basis for the predictive ability of ED has been discussed above. It should be emphasized, however, that ED should not only be viewed as a manifestation of obstructive CAD that could be identified by ischaemia revealing tests. Owing to the inflammatory and pro-thrombotic activation of the disease, it should also be regarded as an early warning sign of an imminent acute event (mainly acute myocardial infarction) due to the rupture of a subclinical plaque, and thus identification of the risk should ideally include plaque vulnerability tests. Finally, an issue that has important clinical implications is by how long the clinical manifestation of ED precedes the clinical manifestation of CAD.

According to studies, men with ED and no cardiac symptoms have an increased incidence of experiencing a cardiac event, both acute and chronic, in the ensuing 2–5 years, thus providing a ‘window of opportunity’ for risk reduction management in these patients.

Testosterone deficiency and cardiovascular disease

A component of the increased risk conferred by ED could be testosterone deficiency. Low testosterone leads to increased levels of total and LDL cholesterol, as well as to increased production of pro-inflammatory markers and mediators. Endothelial dysfunction and increased arterial wall thickness, stiffening, and calcification also ensue. On this basis it has been hypothesized that chronically lowered testosterone may increase CVD risk. Indeed, androgen deficiency has emerged as a predictor of CV events, as well as of all-cause and CV mortality, both in the general population and in patients with CV risk factors, with hypertension, with established CVD, and with ED. Viewed from the opposite angle, higher serum testosterone showed a protective role for CV events in elderly men. A 2010 meta-analysis limited to studies in middle-aged men found no association between total testosterone and cardiovascular events. Studies are listed alphabetically. Boxes represent the relative risk and lines represent the 95% confidence interval for individual studies. The diamonds and their width represent the pooled relative risks and the 95% confidence interval, respectively. CVD, cardiovascular disease; DM, diabetes mellitus; HF, heart failure; GEN, general population. Numbers in brackets are the number of references in the text—and references with S are from Supplementary material online. With permission from Vlachopoulos et al.5
(TT) levels and CVD risk. However, a more recent meta-analysis involving a larger number of studies identified significant associations between androgen deficiency and increased risk of CVD and CVD mortality. It should be stressed, however, that the nature of these studies cannot prove causality. The possibility that low testosterone may be an epiphenomenon, masking poor general health rather than modulating CVD risk per se has to be explored.

The patient is diagnosed with erectile dysfunction: how does this affect his management?

The diagnosis of ED in a patient may affect its management in two ways. The first relates to the fact that the ED patient, irrespective of whether he has or has not established CVD, is ‘reclassified’ into a higher risk category for future CV events. Management in this case is altered in the sense that more aggressive treatment of risk factors, as well as a close follow-up, is warranted. Implementation of biomarkers in this setting is desirable.

The second way relates to the risk associated with the sexual activity in a patient with either overt or occult CVD. In this case, the diagnosis of ED should prompt an initial cardiovascular assessment based on the history and clinical examination in order to define the baseline risk according to (i) the likelihood of silent CAD (especially since ED patients have a high probability to have silent CAD) or to the stage of clinically evident CAD, (ii) other cardiovascular conditions either unrelated, or related to ED (e.g. heart failure, peripheral arterial disease).

How to investigate and manage a patient with cardiovascular disease or without known cardiovascular disease

Crucial to the understanding of the relationship between ED and CVD and the management of ED patients within the context of

### Table 3. Management of a patient with CVD or without known CVD

<table>
<thead>
<tr>
<th>A. Patients without established CVD or diabetes</th>
<th>Moderate SCORE / FRS</th>
<th>Low risk*</th>
<th>Moderate SCORE / FRS</th>
<th>Low risk*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise ability</td>
<td>Lifestyle advice or intervention</td>
<td>Treatment of RFs</td>
<td>PDE5i</td>
<td>Exercise ability or stress test (in higher scores)</td>
</tr>
<tr>
<td>if biomarker abnormal and/or hypogonadism</td>
<td>if biomarker abnormal and/or hypogonadism</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B. Patients with established CVD or diabetes</th>
<th>Moderate SCORE / FRS</th>
<th>Low or Very high SCORE / FRS</th>
<th>Moderate SCORE / FRS</th>
<th>Low or Very high SCORE / FRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise ability or stress test</td>
<td>Lifestyle intervention</td>
<td>RF drug intervention</td>
<td>PDE5i</td>
<td>Tth‡</td>
</tr>
</tbody>
</table>

* Low-risk patients include those with complete revascularization (e.g. via coronary artery bypass grafting, stenting, or angioplasty), patients with asymptomatic controlled hypertension, those with mild valvular disease, and patients with left ventricular dysfunction/heart failure (NYHA classes I and II) who achieved 5 metabolic equivalents of the task METs without ischemia on recent exercise testing.

** Indeterminate risk patients include diabetics, those with mild or moderate stable angina pectoris, past myocardial infarction (2-8 wks) without intervention awaiting exercise electrocardiography, congestive heart failure (NYHA class III), and noncardiac sequelae of atherosclerotic disease (e.g. peripheral artery disease and a history of stroke or transient ischemic attack); this patient with ED may require assessment for additional vascular disease using carotid intima-media thickness or ankle-brachial index and subsequent reclassification to low or high risk.

*** High-risk patients include those with unstable or refractory angina pectoris, uncontrolled hypertension, congestive heart failure (NYHA class IV), recent myocardial infarction without intervention (<2 weeks), high-risk arrhythmia (exercise-induced ventricular tachycardia, implanted internal cardioverter defibrillator with frequent shocks, and poorly controlled atrial fibrillation), obstructive hypertrophic cardiomyopathy with severe symptoms, and moderate to severe valve disease, particularly aortic stenosis.

‡ Where appropriate

CVD: cardiovascular disease; FRS: Framingham risk score; PDE5i: phosphodiesterase type 5 inhibitors; RF: risk factor; Tth: testosterone therapy
the (potential) CVD were the consecutive Princeton Consensus Recommendations (I: 2000, II: 2005, and III: 2012). The reader is strongly encouraged to refer to the most recent, third (2012) Princeton Consensus.30 Key notions in the assessment and management of the patient with organic ED are that (i) he should be considered at increased CVD risk until recommended checks suggest otherwise, and (ii) ED identifies increased CVD risk in the presence or absence of CVD symptoms or history. 

Table 3 is a suggested algorithm for the assessment of patients and their further categorization and handling. There are parts of investigation that are common for patients both with and without CVD, while additional elements of investigation are helpful in categorizing the patient without CVD to the appropriate risk category. Determination of exercise ability and stress testing is crucial to the assessment (see also below ‘Exercise ability: the risk of sexual activity’). Patients without established CVD or diabetes should be evaluated for their risk of future events according to risk scores (SCORE or Framingham). Patients with established CVD or diabetes are by default considered at increased risk. Patients with adequate exercise ability or a negative stress test can initiate or resume sexual activity and begin treatment for ED. In patients with a positive stress test or in high-risk patients, sexual activity should be deferred until the cardiac condition has been treated and stabilized. In all cases, patient follow-up and reassessment is recommended.

Exercise ability: the risk of sexual activity

Physical and sexual activity can trigger acute cardiac events. In a recent meta-analysis, a significant association between acute cardiac events and episodic physical (relative risk 3.45 for myocardial infarction and 4.98 for sudden cardiac death) and sexual activity (relative risk 2.7 for myocardial infarction) was demonstrated.32 This association was attenuated among individuals with high levels of habitual physical activity (for every additional time per week the relative risk for myocardial infarction decreased by \( \sim 45\% \), and the relative risk for sudden cardiac death decreased by 30%). The physical demands of sexual activity have been identified as follows. Studies conducted primarily in young married men showed that sexual activity with a person’s usual partner is comparable with walking 1.5 km (or 1 mile) on the flat in 20 min or briskly climbing two flights of stairs in 10 s. Generalization, however, may not characterize all individuals (especially those who are older, are less physically fit, or have CVD) or sexual activity circumstances (e.g. extramarital, unfamiliar setting, excessive food and alcohol consumption). Therefore, completing 4 min of the standard Bruce treadmill protocol (5–6 METS) without symptoms, ST segment changes, arrhythmias, or a fall in systolic BP identifies the safety of sexual activity.30,33

Investigation for both the erectile dysfunction patient with and without overt cardiovascular disease

A thorough history (including cardiovascular symptoms, age, presence of risk factors and comorbid conditions such as obesity, hypertension, dyslipidaemia, pre-diabetes, CAD, peripheral artery disease, symptoms suggestive of sleep apnoea, family history of premature atherothrombotic CVD and lifestyle factors), assessment of ED severity (according to SHIM) and duration, and physical examination (for both heart and peripheral circulation pathology) are mandatory first-line elements of investigation. A resting electrocardiogram, measurement of fasting plasma glucose, and estimation of glomerular filtration rate are desirable tests that may be used to further characterize cardiovascular status and risk and to identify men who require additional cardiologic workup. Owing to the accumulating evidence supporting the link with CVD, the measurement of testosterone is recommended in all men with a diagnosis of organic ED, especially in those for whom phosphodiesterase type 5 (PDE5) inhibitor therapy failed.

Despite its limitations in detecting CVD without significant stenosis, EST (with or without imaging) can further define the cardiovascular risk in patients with ED and no overt CAD and may be particularly helpful for identifying silent CAD in patients with diabetes. Chemical stress tests are appropriate for patients who cannot complete an EST or in whom ECG is non-interpretable. In patients with established CVD, an interpretable EST is mandatory in the indeterminate risk category and is at the discretion of the cardiologist in the low risk category (Table 3B), since it determines exercise ability and estimates cardiovascular risk associated with sexual activity.

Additional investigation for the erectile dysfunction patient without overt cardiovascular disease

Characteristics that imply a higher risk is severe ED (SHIM 1–7) and ED duration \( \geq 3 \) years.15,30 Vascular and circulating biomarkers may help to characterize further the patient with ED.23 Of the wide array of biomarkers that have been proposed for the assessment of cardiovascular risk in asymptomatic adults,34,35 some have been studied specifically in the context of ED.31 Table 4 offers a critical evaluation of these biomarkers. Such tests should be considered as potentially helpful and thus recommended where available, but not mandatory.30 Despite its potent predictive ability recently shown,36 exposure to radiation with coronary artery calcium scoring should be carefully weighted. Although not specific for ED, it might be reasonable to evaluate biomarkers that have been proposed for the intermediate-risk patient such as uric acid, glycated haemoglobin, microalbuminuria, and lipoprotein-associated phospholipase A2.30

Lifestyle and pharmacological treatment: common considerations for erectile dysfunction and cardiovascular disease

Treatment in the patient with ED and (possible) CVD may have bidirectional benefits. Treating CVD or its risk factors may improve ED and, conversely, treatment of ED may confer an additional benefit in terms of outcome among men with established CVD.
Lifestyle modification

Lifestyle changes, common to those recommended for reduction of CVD risk, are effective in improving sexual function in men.37 These include physical exercise, improved nutrition with emphasis on the Mediterranean diet, weight control, and smoking cessation.37

Phosphodiesterase type 5 inhibitors: effects on the cardiovascular system

Treatment of ED which was previously confined to invasive procedures, cavernosal injections or to rather ineffective oral medications was revolutionized in 1999 with the introduction of the orally administered PDE5 inhibitor sildenafil. Phosphodiesterase type 5 inhibitors are the first-line therapy for ED of organic aetiology unless there is a specific contraindication to their use. This class of agents is widely used because of its effectiveness and safety.38 Interactions with cardiovascular drugs have been minimal with the exception of nitrates and other nitric oxide (NO) donors (such as nicorandil), where co-administration may result in severe vasodilation and hypotension. However, nitrates are often overused in clinical practice; therefore, the option of their discontinuation should be considered. A strong body of clinical data shows that all three agents (sildenafil, tadalafil, and vardenafl) do not increase the risk of non-fatal myocardial infarction, stroke, or cardiovascular deaths. These drugs do not exacerbate ischaemia or worsen exercise tolerance in patients with known CAD who achieve levels of exercise comparable or greater than that achieved during sexual intercourse.38,39 Phosphodiesterase type 5 is expressed throughout the human body, including the pulmonary and systemic vasculature and hypertrophied myocardium. While currently their only additional indication, beyond ED, is idiopathic pulmonary hypertension (for sildenafil and tadalafil), they show potential to be of benefit in several other conditions, such as CAD and systolic heart failure.39 Mechanisms of benefit of PDE5 inhibitors include pulmonary and systemic vasodilation, increased myocardial contractility, reduced large artery stiffness and wave reflections, improved endothelial function, and reduced apoptosis, fibrosis and hypertrophy through mechanisms involving NO, cyclic guanosine monophosphate, protein kinase G and Rho kinase.39 A very important issue is whether treatment of ED per se (and not of its risk factors and comorbidities) will have an impact on cardiovascular risk. While this applies to all therapeutic modalities of ED, it is particularly pertinent for PDE5 inhibitors, since they represent the mainstay of ED therapy. Data are limited to date. Gazzaruso et al.21 showed a trend of PDE5 inhibitors to reduce cardiovascular morbidity and mortality in diabetic patients with silent CAD and ED, while Frantzen et al.40 showed that 2 years after the introduction of sildenafil, the relative risk of the incidence of CVD among men with ED compared with healthy men significantly decreased from 1.7 to 1.1.

Regarding the follow-up of patients, after the initiation of therapy visits are recommended at 2- to 4-week intervals initially and less frequently thereafter in order to assess response to the treatment (including partner satisfaction), consider dosage titration, monitor adverse effects, and assess overall health and psychosocial functioning.

Cardiovascular drugs: do they cause ED?

While a widely held perception is that CVD drugs cause ED, data attest towards the contrary and some agents may be even beneficial.41 Only thiazide diuretics lead clearly to ED, while some older beta-blockers also do so, but the side-effect of ED was very low (~3%) when the patient was blinded for the drug administration.42

<table>
<thead>
<tr>
<th>Biomarkers</th>
<th>Association with vasculogenic ED</th>
<th>Overall CVD predictive value</th>
<th>Association with CV prevalence in ED</th>
<th>CVD predictive value in ED</th>
<th>Response to treatment</th>
<th>Availability</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>++++</td>
<td>+</td>
</tr>
<tr>
<td>High sensitivity C-reactive protein</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>++++</td>
<td>+</td>
</tr>
<tr>
<td>Fibrinogen, IL-6</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>+</td>
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<td>+</td>
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<tr>
<td>IMT</td>
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<td>+</td>
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<td>–</td>
<td>–</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Aortic stiffness</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>++</td>
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<tr>
<td>ABI</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>++</td>
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<tr>
<td>CCTA</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Endothelial Dysfunction</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Albuminuria</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>+++</td>
<td>+</td>
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<tr>
<td>Penile Doppler</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>+++</td>
<td>+</td>
</tr>
</tbody>
</table>

ABI, ankle-brachial index; CAC, coronary artery calcium; CCTA, coronary computed tomography angiography; CVD, cardiovascular disease; ED, erectile dysfunction; IL-6, interleukin-6; IMT, intima-media thickness. From Miner et al.37

Association with ED, availability, response to treatment, prognostic value and cost of biomarkers (scored from 0 to 4+).
In fact, the vasodilating nebivolol may even improve erectile function.\textsuperscript{35,43} ACE-inhibitors, angiotensin-receptor blockers, and calcium-channel blockers are reported to have neutral or even a positive effect on erectile function\textsuperscript{35,41,43} but more evidence is needed. Regarding statins, the largest body of evidence points towards a beneficial effect.\textsuperscript{44} A negative effect has been reported in high statin doses, possibly related to a potential reduction in serum testosterone levels, but this dose dependency warrants further investigation. In terms of patient management, when ED onset and therapy initiation are linked and a cause-and-effect association is presumed, a short period of drug withdrawal with monitoring for ED resolution for verification may be an option. In patients who developed ED long after the initiation of CV drug treatment, sexual dysfunction is less likely to be drug associated and PDE5 inhibition therapy may be initiated.

**Testosterone therapy and cardiovascular disease**

Testosterone therapy (TTh) should be reserved for patients who (i) are symptomatic (ED or reduced libido) of testosterone deficiency\textsuperscript{45} and (ii) they have biochemical evidence of low testosterone (TT <8 nmol/L or 2.3 ng/mL). In men with borderline TT (8–12 nmol/L or 2.3–3.5 ng/mL), a TTh trial (for 3–6 months and continuation if effective) may be envisaged. While adding a PDE5 inhibitor can be considered in men who have not improved with TTh, the usual clinical scenario is to add TTh in patients who have not responded to PDE5 inhibitors. Improvement is dependent on the testosterone levels with better results being obtained at lower levels of TT.\textsuperscript{43} Despite evidence of benefit in patients with pre-existing cardiovascular conditions (angina or heart failure), it should be emphasized that TTh is not a medication with cardiovascular indications.

Testosterone therapy in hypogonadalism modulates metabolic components associated with CV risk. The majority of prospective clinical studies indicates that treatment achieving testosterone levels within physiological limits has beneficial or neutral effects on a lipid profile other than HDL-C, beneficial or neutral effects on inflammatory mediators, and generally beneficial effects on glycaemic state.\textsuperscript{23} The lean body mass is typically increased in hypogonadal subjects, and visceral adiposity is decreased in several studies and unchanged in the remainder. Such metabolic effects have raised interest on the potential impact on cardiovascular health. Regarding symptoms in patients with pre-existing cardiovascular conditions (angina or heart failure) TTh has been either neutral or beneficial.\textsuperscript{25} Regarding CVD risk, available clinical trial data indicate that the use of testosterone in middle-aged to elderly men does not increase cardiovascular risk\textsuperscript{25} with the exception of one study in very frail (substantial limitation of mobility and a high rate of comorbidities) elderly subjects that used an off-label high, and rapid escalation, dosing regimen.\textsuperscript{46} Prospective data from large, well-designed, long-term trials of TTh are warranted.

After the initiation of TTh patients should be evaluated at 3 and 6 months, and annually thereafter to assess response to treatment and monitor adverse effects. Assessment should include physical examination with particular attention to the prostate. At these intervals testosterone levels should also be monitored, as well as PSA, haematocrit, and HDL.\textsuperscript{45}

Contraindications for TTh include (for detailed listing, please refer to Buvat et al.\textsuperscript{45}) patients with breast or prostate cancer, while patients with a palpable prostate nodule or induration, or prostate-specific antigen >4 ng/mL (or >3 ng/mL in men at high risk for prostate cancer, such as African-Americans or men with first-degree relatives with prostate cancer), should first undergo urological evaluation. Testosterone therapy is contraindicated also in patients with haematocrit >50% (TTh increases haematocrit) and uncontrolled congestive heart failure (risk of fluid retention). Risk for adverse CVD events may be increased in patients and with the mode of treatment epitomized in the study of Basaria et al.\textsuperscript{46} (see earlier).

**Special conditions: the hypertensive patient**

The links between hypertension and ED are increasingly recognized and the 2009 re-appraisal of European guidelines includes relevant statements.\textsuperscript{35,47} Erectile dysfunction is almost twice as frequent in hypertensive as in normotensive individuals and appears to be of higher severity. The relative risk of developing ED in hypertensive patients compared with normotensive individuals ranges from 1.3 to 6.9. Regarding pathophysiology, hypertension appears to cause ED per se, through a multitude of mechanisms that include prolonged exposure to elevated levels of systemic blood pressure, endothelial dysfunction, and circulation of vasoactive substance (with a pivotal role of angiotensin II) that lead to structural and functional alterations in the penile arteries. The largely unfounded (see earlier paragraph) notoriety of antihypertensive treatment for causing ED is one of the most predominant causes for non-adherence and discontinuation of antihypertensive therapy, and therefore, patients should be properly informed by physicians. Phosphodiesterase type 5 inhibitors are effective in hypertensive patients with ED and they can safely be co-administered with antihypertensive medication.\textsuperscript{39} Specifically for alpha-blockers, low starting doses of PDE5 inhibitors are preferred in patients already on alpha-blocker treatment, and likewise, low starting doses of alpha-blockers are encouraged in patients taking PDE5 inhibitors. Of clinical significance is that hypertensive men with ED are more likely to comply with their antihypertensive medication when under PDE5 inhibitors.

**Special conditions: the patient with heart failure**

A significant proportion (ranging from ~60 to 90%) of heart failure patients report ED and marked decrease in sexual interest, with ultimately one-quarter reporting cessation of sexual activity altogether.\textsuperscript{18} Erectile dysfunction contributes further to the poor quality of life and aggravates depression. Of interest, many heart failure patients place a greater importance on improving the quality of life (including sexual activity) than on improving survival. Sexual function correlates with the symptomatic status (i.e. NYHA functional class and 6-minute walk test).\textsuperscript{48} In the Evaluation of Role
of Sexual Dysfunction in the Saarland (EROSS) Program, left ventricular dysfunction was a risk factor for ED independent of heart failure symptoms. While heart failure and ED share common predisposing risk factors, heart failure by itself can cause ED or affect engagement to sexual activity. Neurohumoral activation, medication (thiazides), limited exercise capacity, and depression are responsible.30

Evaluation of functional capacity is the mainstay for the management of patients with ED.39 However, it should be kept in mind that in men with heart failure sexual activity may affect the heart differently from physical activity of similar METS due to differences in psychological anticipation and sympathetic activation.30,49 Cardiac echocardiography may offer valuable information for left ventricular performance and valvular function. For risk categories of heart failure patients and their management, please refer to Table 3 and Figure 5.

Sexual health counselling of cardiovascular disease patients

Owing to its delicate nature, discussion about the sexual life of the patient is effective not on a circumstantial visit to the doctor, but on the basis of confidence between the patient and the physician, as is usually the case with the cardiologist. Thus, the cardiologist is given a unique opportunity to identify ED and thus ‘recharacterize’ the risk of the patient. In addition, since normal sexual activity is important to most men with CVD, irrespective of age, the cardiologist can clarify issues that relate to such activity after a cardiac event or to a specific cardiac condition (e.g. heart failure). Often, such issues are hampered by misconceptions from the side of the patient. Therefore, while less than half of the patients receive information about resuming sexual activity after a cardiac event, proper counselling increases their likelihood to resume their previous level of sexual activity by 50%.50 Furthermore, the cardiologist can increase adherence to the medication by clarifying that it is uncommonly the true cause of ED. Finally, proper counselling is required to ensure safety of concomitant PDE5 inhibitors medication, the use of which has the additional advantage to increase compliance to CVD mediation, especially in hypertension. It should be noted that while patients are often reluctant to bring up the issue of sexual health, they are relieved and respond positively when their cardiologist has done so. It should also be emphasized that, frequently, sexual counselling is more effective when done together with their partner.

Conclusions

Erectile dysfunction is common in the CVD patient. It is an important component of the quality of life and it also confers an independent risk for future CV events. The usual 3-year time frame between the onset of ED symptoms and a CV event offers an opportunity for risk mitigation. Thus, sexual function should be incorporated into CVD risk assessment for all men. Algorithms for the management of patient with ED have been proposed according to the risk for sexual activity and future CV events. A comprehensive approach to cardiovascular risk reduction (comprising of both lifestyle changes and pharmacological treatment) improves overall vascular health, including sexual function. Proper sexual counselling improves the quality of life and increases adherence to medication. Testosterone assessment may be useful for both diagnosis of ED, risk stratification and further management. There are issues to be addressed, such as whether PDE5 inhibition reduces CV risk. Management of ED requires a collaborative approach and the role of the cardiologist is pivotal.

Supplementary material

Supplementary material is available at European Heart Journal online.

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References

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Acute thrombosis of bioabsorbable scaffold in a patient with acute coronary syndrome

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An 80-year-old male patient was referred to the emergency department with symptoms of unstable angina. An ECG revealed ST-segment depressions in leads V4–V6 and laboratory values showed an increased high-sensitive troponin level (0.016 ng/mL). Subsequent coronary angiography demonstrated a ruptured plaque in the left anterior descending (LAD) coronary artery (Panel A). Therefore, percutaneous coronary intervention was performed with the implantation of a bioabsorbable-vascular-scaffold (BVS, ABSORB, 3.5 × 18 mm). The implantation pressure was increased stepwise up to 12 atmospheres. The coronary blood flow was immediately restored to the TIMI III flow (Panel B). The patient was discharged to the coronary care unit (CCU) in a stable condition. Four hours later, the patient complained of acute severe chest pain with ST-segment elevations in leads V1–V6. Repeat coronary angiography documented an acute scaffold thrombosis (Panel C). After thrombectomy using a manual aspiration catheter, optical coherence tomography (OCT) was performed. Optical coherence tomography revealed marked thrombus material within the scaffold (Panels E–H; Supplementary material online, Video S1), potentially caused by incomplete strut apposition in several cross sections (Panel H, red arrows). Subsequent biolimus-eluting stent implantation (3.5 × 28 mm, 14 atmosphere) within the previously implanted BVS segment of the LAD was performed with a good final result after high-pressure balloon post-dilatation (3.5 × 12 mm, 22 atmosphere) (Panel D). The patient was transferred to the CCU and had an uneventful post-procedural course.

This is the first report of a thrombosis of a BVS in a patient with acute coronary syndrome (ACS), most likely due to incomplete scaffold expansion. As strut apposition of implanted scaffolds is not appropriately visible angiographically, it appears recommendable to perform OCT in such cases, particularly in elderly patients with calcified coronary lesions, and patients with ACS, to assess the procedural result.

Supplementary material is available at European Heart Journal online.