Erectile Dysfunction: A Harbinger of Cardiovascular Disease Risk

2

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Abstract

Cardiovascular diseases (CVDs) are a significant source of morbidity and mortality despite improvements in treatment. The recognition of CV risk and the early identification of CVD are crucial to facilitate early intervention and preventative strategies. This chapter presents a critical review of the literature on the role of erectile dysfunction (ED) as an early marker for CVD risk. ED and CVD share a number of risk factors, while ED itself may be considered an important risk factor for CVD, particularly in younger men with arteriogenic ED. Epidemiological data support an association between ED and CVD, with reports suggesting that ED often occurs years prior to the onset of CVD. This reflects the shared pathophysiological mechanisms of ED and CVD and the earlier emergence of symptoms in small-diameter arteries, such as those in penile tissue, secondary to atherosclerosis and endothelial dysfunction. The importance of these observations is considered with respect to the clinical implications of studies exploring the predictive value of ED for future CVD risk. The chapter concludes with clinical insights into the role of ED in CVD risk assessment and the integration of ED assessment in routine CVD health screenings.

Keywords

Cardiovascular · Risk · Erectile dysfunction · Pathophysiology · Screening

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2.1 Introduction: Connections Between Erectile Dysfunction and Cardiovascular Health

Cardiovascular (CV) health is recognised as an important determinant of a number of health outcomes at the population level [1]. Apart from the morbidity caused by CV diseases (CVD) and the loss of enjoyment of physical activities, it is estimated that CVD mortality accounts for one-third of all deaths globally, equivalent to more than 17.9 million deaths per year [2]. Furthermore, poor CV health is consistently predictive of the risk of cancer, poor quality of life (QoL) and higher healthcare costs [1]. The past few decades have seen dramatic advances in therapeutic interventions for CVD, which have led to improvements in survival in patients with established CVD over time, although these improvements appear to have largely plateaued [3]. Despite improvements in survival, CVD remains an important source of mortality and morbidity once established [4]. Subsequently, there has been an important focus on the need for the early identification of those at risk of CVD in order to facilitate early interventions as well as preventative strategies that can support positive CV health for the index patient and their family members who are at heightened risk [5].

The previous chapter highlighted the importance of erectile dysfunction (ED) as a source of morbidity among men while also emphasising the importance of ED as a marker of fitness from an evolutionary perspective. The presence of ED in men is linked to the loss of the baculum (penile bone present in some mammals) and the increased susceptibility of erectile mechanisms to stressors and disease [6]. Specifically, ED may serve as a marker for poor CV fitness/health during sexual selection, which illustrates the interrelated nature of ED and CVD in men [7]. On this basis, the presence of ED may be indicative of poor CV health and the risk of future CVD in men.

Evidence supporting a link between ED and CVD relates to epidemiological data and pathophysiological observations. Despite growing data depicting an increasing trend in young men presenting with ED in the real-life setting [8, 9], both ED and CVD are more likely to occur with increasing age and are often comorbid conditions, with an increased risk of ED in men with CVD and a higher prevalence of CVD in men with ED than without. The first real-life study in this setting found that ED is present in 49% of men with existing CVD [10], while it has been shown that CVD is 45% more likely to occur in men with versus without ED [11].

Epidemiological studies have highlighted that both ED and CVD have numerous shared risk factors [12]. Risk factors for CVD are well established and include a range of modifiable lifestyle and environmental, as well as non-modifiable, risk factors [13]. Risk factors specific to ED have been identified and overlap with many of these, such as smoking, obesity, diabetes, arterial hypertension and dyslipidaemia (Table 2.1). Meta-analyses support an association between ED and both hypertension (odds ratio (OR) 1.54–1.74) and diabetes (OR 2.08–3.62)—two common CV risk factors [14]. Similarly, dyslipidaemia has been associated with the risk of ED [15], and current smoking behaviour is associated with a 51% increased risk of ED [16]. A similar risk has been observed even for e-cigarette smoking and ED [17, 18].

Table 2.1 Risk factors for erectile dysfunction and cardiovascular disease

Shared risk factors for erectile dysfunction and cardiovascular disease
Hypertension
Diabetes
Dyslipidaemia
Cigarette smoking
Obesity
Low levels of physical activity (sedentary lifestyle)
Metabolic syndrome

Adapted from reference [23]

In a meta-analysis of eight observational studies (including 12,067 men), there was a 2.6-fold increase of ED in patients with metabolic syndrome (MetS), with all components of MetS, other than high-density lipoprotein levels, correlated with an increased risk of ED [19]. It was also shown that men with type 1 or 2 diabetes mellitus have a 3.62-fold increased risk of ED as compared with healthy controls in a meta-analysis of 145 studies (including 88,577 men) [20]. These shared risk factors for ED and CVD are also linked to shared pathophysiological events in these conditions, most notably the contribution of risk factors for vascular endothelial dysfunction as a driver of disease [21]. Indeed, reductions in endothelium-dependent smooth muscle relaxation, endothelial nitric oxide synthase (eNOS) activity and NO availability, as well as oxidative stress and vascular hypertrophy, have all been associated with common CV risk factors [22].

The potential for ED to be linked to CV health is an important observation in published literature, reflecting the evolutionary role of ED as a marker for CV fitness. Importantly, the presence of ED may be considered not only a complication of CV risk factors but also an early sign of future CVD [12]. This is a key consideration as the emergence of ED prior to the onset of other CD manifestations may have value in clinical practice. Montorsi et al. [10] have reported that a nearly 3-year lead time can manifest between the onset of ED and CV events, which importantly would allow, if recognised, a window for risk modification and hopefully mitigate the likelihood of a CV event. The remainder of this chapter will explore this relationship from the perspective of epidemiology, shared pathophysiology and consideration of the predictive value of ED for CV risk assessment.

2.2 Epidemiological Studies Linking ED to CV Risk

Numerous epidemiological studies have supported a link between ED and CVD, as well as ED and the risk of CVD (Table 2.2). These studies included data from the general population, as well as cohorts of patients with diabetes or other conditions where CVD and ED are common. Importantly, these data suggest not only that ED and CVD are associated conditions but also that ED is linked to the risk of CVD.

An analysis of 300 consecutive patients with acute chest pain and angiographically confirmed coronary artery disease (CAD) found a 49% prevalence of ED in this population, with no significant difference in angiographic characteristics or clinical

Table 2.2 Summary of prospective studies evaluating the link between erectile dysfunction and cardiovascular risk or cardiovascular events

Author and date	Population	Follow-up	Outcomes	HR (95% CI)
Thompson et al. [24]	Men aged >55 years in the placebo group of the prostate cancer prevention trial (n = 9457)	7 years	First CV event	1.45 (1.25–1.69)[a]
Schouten et al. [34]	Men aged 50–75 years without a known history of CVD (n = 1248)	6.33 years	CV events (acute MI, sudden death or stroke)	2.6 (1.3–5.2)[a]
Gazzaruso et al.[35]	Men with T2DM and silent CAD (n = 291)	47.2 months	Deaths due to CAD, CHF or sudden death; nonfatal MI, unstable angina, need for repeat revascularisation, stroke or TIA, and symptomatic PAD	2.1 (1.6–2.6)[a]
Inman et al.[36]	Men aged 40–79 years in the Olmsted County study of urinary symptoms and health status among men	10 years	Angiographically diagnosed CAD, MI, sudden cardiac death	1.8 (1.2–2.6)[a]
Banks et al.[26]	Men aged ≥45 years (n = 95,037)	1.9 years (hospitalisation) and 2.2 years (mortality)	CV events or deaths with or without a known history of CVD	CV events without CVD history: 1.35 (1.19–1.53)[a] CV events with a known CVD history: 2.37 (1.87–3.01)[a]

Adapted from Gandaglia et al. [31]
Abbreviations: *CAD* coronary artery disease, *CHF* congestive heart failure, *CV* cardiovascular, *CVD* cardiovascular disease, *HR* hazard ratio, *MI* myocardial infarction, *PAD* peripheral artery disease, *T2DM* type 2 diabetes mellitus, *TIA* transient ischaemic attack
[a] Statistically significant ($P < 0.05$)

characteristics between those with and without ED [10]. However, in those with ED, it was reported that 67% of patients experienced ED symptoms prior to any CAD symptoms. The mean period of time between ED and CAD symptom onset was 38.8 months (range 1–168 months). The study also found that in patients with ED and type 1 diabetes mellitus, the development of sexual dysfunction preceded the onset of CAD in all patients. These findings suggest that not only is ED strongly associated with CAD but that symptoms of ED also tend to precede those of CAD, often years

prior to the onset of other CV manifestations. The lack of differences between those with and without ED highlights the vulnerability of penile arteries to disease, leading to the onset of ED before the development of other imaging or clinical markers [10]. The small size of the cavernosal arteries relative to the coronary vessels and the high demand for rapid and dramatic vasodilation of the cavernosal vascular bed allows for the recognition by the host of suboptimal responses within the penile circulation, typically years prior to coronary symptoms [42].

Other studies also suggest that ED and CVD are not only associated but that ED is an independent marker of future CV events. For instance, a longitudinal assessment of 9500 men in the United States Prostate Cancer Prevention Trial found that men with incident ED had higher risks of CV events [24]. The onset of CAD in a sample of 285 men with ED and CAD at baseline suggested that ED preceded the onset of CAD by approximately 2–3 years [25]. Other research also suggested that ED is predictive of subsequent CV events and CV mortality, even when controlling for other risk factors [26, 27]. Data from prospective studies examining the link between ED and CVD are summarised in Table 2.2.

The link between ED and future CV events has also been explored in a number of meta-analyses. For instance, a meta-analysis of seven cohort studies (including 45,558 men) found that ED was associated with 1.41 times higher risk of CVD, 1.23 times higher risk of all-cause mortality and 1.43 times higher risk of myocardial infarction compared to men without ED [28]. A meta-analysis of 16 published studies (including 92,757 men) found that ED increases the risk of future CV events by 44%, with a 62% increased risk for myocardial infarction and 39% increased risk for cerebrovascular events, while increasing the risk of all-cause mortality by 25% over a mean period of 6.1 years of follow-up [29]. In addition, a recent large retrospective cohort study of 430,261 men found that ED was associated with a higher rate of major adverse CV events (MACE) (8.94%) as compared with men without ED (4.58%) [30]. Therefore, a large body of data supports a link between ED and CVD while also highlighting that ED is often a precursor to CVD, increasing the risk of CVD compared with men without ED.

Overall, analyses have suggested that ED can precede the onset of CVD by approximately 2–5 years [31]. This is an important observation because the presence of ED at an earlier stage than other manifestations of CVD may be indicative of the presence of subclinical disease and/or CV risk factors that could have an impact on future health [8]. Indeed, a meta-analysis of studies evaluating the link between ED and subclinical CVD found that ED was consistently associated with endothelial dysfunction (measured by flow-mediated dilation) and carotid intima-media thickness [32]. Furthermore, ED has been linked with an increase in high-sensitivity troponin levels, a biomarker for future CV risk, as well as future CV mortality [33]. Therefore, ED appears to be linked to a high risk of CV events in the future. The critical clinical takeaway message is that, particularly for a younger man (<50 years) with arteriogenic ED, it should be considered a risk factor for CVD until proven otherwise [45].

In summary, the evidence to date strongly supports an association between ED and CVD in men. Importantly, ED is frequently seen in men without overt CVD or

with subclinical disease and has been associated with an increased risk of future CV events and mortality. These findings collectively suggest that ED may be an important early marker of CVD, highlighting the importance of CV risk factors in causing ED and CVD. The following section considers the pathophysiological mechanisms connecting ED and CVD in order to explore this association further and to support a role for ED as an early marker of CVD.

2.3 Shared Pathophysiological Mechanisms Between ED and CVD

The pathophysiology of ED is complex but is strongly linked to arterial flow in the corpora cavernosa [23]. Specifically, vasculogenic erectile function is facilitated through a combination of arterial dilation, sinusoid relaxation and venous compression in the penis [23]. Risk factors for ED and CVD may affect blood vessels, resulting in endothelial dysfunction, thickening of the tunica media and flow-limiting stenosis [8, 37], reflecting both functional and structural changes.

Endothelial dysfunction is a term that indicates an altered responsiveness of the endothelium to vasoactive stimuli and has been termed the 'common denominator' for ED and CVD [38]. Functional changes in arteries subsequent to CV risk factors lead to endothelial dysfunction, reductions in endothelium-mediated relaxations and reduced vasodilation of blood vessels [37]. Specific changes in endothelial function observed in people with ED include a reduction in endothelial nitric oxide synthase (eNOS) availability, reduced responsiveness to NO-mediated vasodilation and increased responsiveness to vasoconstrictive factors [21]. Other functional changes in the endothelium have been noted and include an increase in the expression of adhesion molecules, the release of pro-inflammatory factors, altered expression of growth factors and cytokines and the production of reactive oxygen species, all of which are detrimental to vasodilation in normal erectile function [21].

Structural changes are important mediators of CVD and ED and include arterial wall thickening and stenotic changes in arteries, whereby inflammatory reactions and atherosclerotic plaques reduced the effective lumen size for arterial blood flow [39]. Numerous CV risk factors are linked to atherosclerotic changes and arterial stiffness, including dyslipidaemia and smoking [40]. Over time, structural changes combined with functional changes in penile arteries reduce the potential for effective vasodilation, with reduced blood flow to the penile tissues and ED as a consequence [21]. A summary of the shared pathophysiological mechanisms seen in ED and CVD is presented in Fig. 2.1.

ED and CVD can be considered different manifestations of the same spectrum of disease [41] based on the degree to which risk factors overlap and endothelial dysfunction contributes to pathogenesis. The potential for ED to serve as a precursor of CV events or an early marker of CV risk may be explained by a number of mechanisms. One major conjecture is the artery size hypothesis [42]. Importantly, manifestations of CVD often present first in blood vessels with the smallest diameters, reflecting a vulnerability of these vessels to critical atherosclerosis and

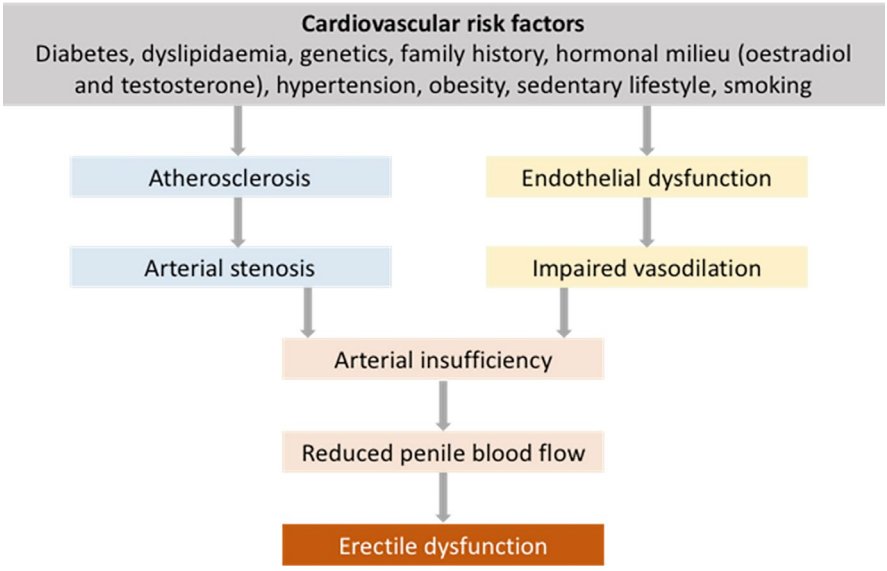

Fig. 2.1 Overview of the pathophysiological links between cardiovascular disease and erectile dysfunction. This figure illustrates the role of cardiovascular risk factors in increasing the risk of structural arterial changes (atherosclerosis and arterial stenosis) and functional arterial changes (endothelial dysfunction and impaired vasodilation), resulting in arterial insufficiency, reduced penile blood flow and the symptoms of erectile dysfunction. (Adapted from reference [46])

other mechanisms [42]. While the coronary arteries are a good example of smaller vessel disease leading to CVD manifestations, such as myocardial infarction, smaller blood vessels in the corpora cavernosa may be more susceptible to endothelial damage [31]. Penile arteries are typically 1–2 mm in diameter, as compared with coronary arteries, which are 3–4 mm, and carotid arteries, which are 5–7 mm in diameter [36]. Accordingly, a lower burden of atherosclerosis is needed to result in the occlusion of the artery lumen in smaller vessels, making penile vessels susceptible to disease.

Another hypothesis suggests that older patients, who are at higher risk of both ED and CVD, exhibit arterial stiffness, which increases systolic and decreases diastolic blood pressure [39]. The stiffness of large arteries accompanied by systolic hypertension can cause pressure waves in smaller-diameter arteries, including penile arteries, increasing the risk of atherosclerosis in these vessels [5, 43]. Other mechanisms include changes in eNOS production, resulting in endothelial dysfunction and atherosclerosis, and the potential for chronic hypoxaemia stimuli to increase vasomotor tone, stimulate vascular growth factor production and increase vasoconstriction of arterioles [5]. Indeed, obstructive sleep apnoea is a condition characterised by the potential for hypoxaemia and is associated with CV risk factors and ED [44].

Therefore, symptoms of ED may be an early indicator of ongoing endothelial damage in other vasculature (e.g. coronary arteries), preceding symptoms of wider

CVD [45]. The implications of the role of ED as an early marker of CVD are considered in the following section, with a focus on the predictive value of ED when assessing CV risk in men.

2.4 The Predictive Value of ED in Assessing CV Risk

The assessment of CV risk is an important part of preventative medicine [47]. The Framingham studies provided an important development in identifying risk factors for CVD and highlighted how they may be considered collectively for an individual patient in the prediction of MACE [48, 49]. Consideration of the 'global' CV risk of a patient, rather than the presence of single risk factors, led to the implementation of risk models, calculators and scores. These approaches tend to consider the most common CV risk factors identified in epidemiological studies, including age, sex assigned at birth, hypertension, dyslipidaemia, diabetes mellitus and smoking, with some variation depending on the specific model or risk calculator employed [47]. Prospective studies have provided support for these strategies in estimating absolute or relative risk of MACE and in guiding risk stratification of patients as low, intermediate or high risk, which provides a basis for targeted lifestyle recommendation and pharmacological therapy [50–53].

Despite the widespread use of these tools and their value in risk stratification, they are associated with some important limitations. Firstly, these tools tend to have validity only when used in populations with the same features as the cohort in which they were validated, often reducing their accuracy for use in younger or older cohorts and in ethnic minority groups [5, 54]. Secondly, the tools often do not take into account the lifetime risk of CV events but provide risk over a typical period of 10 years, with age being weighted as one of the most important determinants of risk [5]. Consequently, younger patients (e.g. men aged $\leq$40 years) are often not classified as having a high risk of MACE, even in the presence of multiple risk factors. Another limitation is the use of a limited number of CV risk factors within these tools, which may improve the feasibility of implementation in practice but can reduce the sensitivity of risk estimation in a proportion of patients [55].

A proportion of patients classified as low or intermediate risk for MACE using these tools still experience a significant number of events. This likely reflects, at least in part, the effect of risk factors that are not included in common risk models and calculators [5]. The inclusion of other risk factors has been proposed as a means of reducing the 'residual risk' of CV events, particularly in specific patient populations (e.g. younger patients, those without traditional risk factors and those with risk levels at the threshold of treatment) [56]. For instance, the Joint British Societies 3 Board risk calculator includes risk factors that may be excluded from other calculators (e.g. body mass index, family history of CVD) and reduces the influence of age and gender on risk, which can be estimated across the lifetime of the individual [57]. While wider validation of this calculator is needed across populations, there is a growing emphasis on improving CV risk estimation by refining tools, including exploring the integration of additional risk factors and biomarkers into these tools.

Overall, there is a clear need for CV risk estimation to overcome the limitations of adopting a small number of risk factors that may underestimate risk in many populations while emphasising the need for an early marker of risk [41]. The role of ED in this context has been recognised as potentially valuable in refining risk estimation and adding to existing tools, based on its emergence as a unique early feature within the spectrum of CVD pathophysiology.

The importance of ED as a predictor of CV events has been explored in some studies, emphasising the value of ED as an early marker for CVD. As noted in Table 2.2, data indicate that the risk of CV events in patients with ED is increased as compared with men without ED. Therefore, the potential to screen for CVD and CV risk factors in men presenting with ED could have value in practice and has been explored in a number of studies. One modelling study found that screening for CVD in men with ED is cost-effective for the secondary prevention of CVD [58]. Furthermore, the screening of men with ED, regardless of severity, was associated with a substantial reduction in CVD events over 10 years and was shown to be cost-effective over this time period in a modelling study conducted in the Swiss population [59].

The inclusion of ED within routine CV screening tools or risk assessments also requires consideration. The QRISK3 calculator has incorporated ED diagnosis or treatment in men as a variable for CV risk estimation, reflecting the potential importance of this feature in enhancing risk estimation [60]. However, the inclusion of ED in this score is binary and does not consider the severity of ED, which may be a potential limitation in risk stratification [26, 60]. Indeed, the severity of ED has been linked to CV risk and outcomes in a meta-analysis of 25 studies (154,794 patients), where it was found that severe ED was associated with a higher risk of CVD and all-cause mortality compared to mild or moderate ED [61]. Evidence suggests that available risk scores may reliably identify patients with arteriogenic ED, making this a simple marker to evaluate in practice [45]. Therefore, the severity of ED may be an important aspect to include in clinical risk scoring for CVD.

When ED associated with vascular causes is identified in a patient, ED may be considered a potential risk factor for CVD. The presence of ED in this context should prompt a careful assessment of additional CV risk factors and initiation of preventative strategies against MACE. It is recommended that a formal CV risk score be applied in these patients, supplemented with a detailed clinical history, physical examination, assessment of the severity and duration of ED, fasting plasma glucose assessment, electrocardiography, measurement of serum creatinine and albumin:creatinine ratio, assessment of plasma lipid profile and evaluation of MetS [5]. Total testosterone levels should also be assessed as a potential cause of ED, which may prompt testosterone therapy [5]. Referral to a cardiologist should be considered in men with ED and a high CV risk, while additional testing may be indicated in those with intermediate CV risk.

The Princeton III Consensus (Expert Panel) guidelines, published in 2012, advocated for exercise stress testing, the assessment of carotid intima-media thickness and the non-invasive assessment of endothelial function to guide CV risk assessment in patients with ED [47]. Recently, the Princeton IV Consensus (Expert Panel)

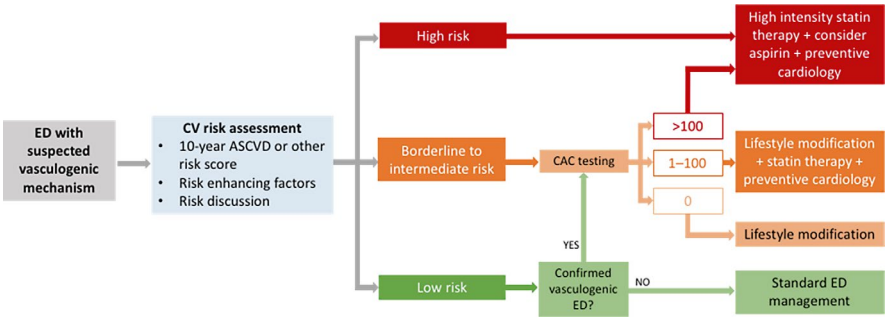

Fig. 2.2 Illustration of how erectile dysfunction may prompt cardiovascular risk assessment. A patient with suspected vasculogenic erectile dysfunction (ED) should undergo a cardiovascular (CV) risk assessment incorporating a 10-year atherosclerotic cardiovascular disease (AVSCD) risk scoring (or the use of a similar score). (Kloner et al. [31]; Arnett et al. [63])

guidelines [62] updated these recommendations, emphasising the importance of considering men with ED as at high risk of CVD until proven otherwise. In this Expert Panel Consensus, it is recommended that CV risk scoring should be performed using the 2019 American College of Cardiology (ACC)/American Heart Association (AHA) atherosclerotic CVD (ASCVD) risk score for all men with predominantly vasculogenic ED [63]. This score relies on traditional risk factors for CVD, and therefore, augmentation is recommended in younger men (aged 40–60 years) with vasculogenic ED and borderline/intermediate risk (5–20%), as this group may have their risk underestimated [64]. Coronary artery calcium measurement has subsequently been introduced as a routine evaluation that can enhance CV risk assessment in this cohort and may have value in improving risk estimation [62, 65]. Following these assessments, CAC scores may be used to guide the need for lifestyle interventions, statin therapy, aspirin use and other interventions, along with referral to cardiologists in those with high risk of CV events [62].

There remains some uncertainty over the optimal sequence of tests and the superiority of one test over another in CV risk prognostication. In addition, other risk scores may also be preferred for populations outside of the United States, where the ASCVD was validated [66]. A pragmatic strategy aligned with available guidance is presented in Fig. 2.2 for supporting CV risk assessment in men presenting with ED.

2.5 Conclusions: The Role of ED Assessment in Routine CV Health Screenings

CVD is a common cause of morbidity and mortality in men, particularly among older age groups. A constellation of risk factors has been clearly linked to CVD and future CV risk, including lifestyle risk factors. However, at present, there is no perfect single marker that is predictive of future CV risk. The importance of preventative strategies in mitigating the risk of future CVD events, including myocardial

infarction and stroke, highlights the need for improvements in risk prediction. In particular, there is a need to establish early markers for CVD to maximise opportunities for prevention.

This chapter reviews the existing medical literature and supportive evidence for the inclusion of ED assessment as part of routine CV health screenings, with ED serving as a valuable marker for future CV risk in men. ED is a condition that strongly reflects risk factors for CVD and is predictive of CVD, presenting years prior to the onset of most common CVD manifestations. In ageing men, ED should be considered a potentially valuable marker of future CV risk and should be routinely included in CV health screenings. In patients with CV symptoms or pre-existing CV conditions, sexual function screening should be performed, including an evaluation of erectile function. This may include the use of validated questionnaires to assess ED, such as the brief version of the International Index of Erectile Function-5 (IIEF-5) [29]. The assessment of ED should prompt a wider evaluation of lifestyle risk factors and comorbidities that may contribute to poor outcomes, providing an opportunity for targeted lifestyle advice and interventions [62]. This may also include an evaluation of non-traditional risk factors for CVD, such as metabolic or hormonal profiles, ED severity, penile artery flow characteristics and psychological factors [5].

The diagnosis of ED should be followed by detailed sexual health assessment, counselling, shared decision-making and appropriate interventions, such as phosphodiesterase type 5 inhibitor (PDE5i) therapy [66]. The benefits of PDE5i therapy have been observed in improving ED symptoms and subsequent sexual activity levels and also in providing cardioprotective effects [67, 68]. These observations are largely based on retrospective studies and may be influenced by confounding factors, such as increased levels of sexual activity rather than the pharmacological effects of PDE5is, accounting for improvement in CV risk [62]. However, evidence suggesting the dose-dependent effects of PDE5i therapy on adverse CV outcomes, as well as the absence of CV risk reduction from other pharmacotherapies that improve sexual activity (e.g. alprostadil), is suggestive of direct CV benefits from PDE5is [62, 69]. Therefore, the early identification of vasculogenic ED and the recognition that its onset can be considered an early signal of CVD, leading to risk reduction therapy and appropriate management with PDE5is, may have positive effects on future CV risk, which should be explored further in prospective studies.

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