Chapter 19
Approach to Erectile Dysfunction in Patients with Hypertension and Coronary Artery Disease

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Introductory Text

Undoubtedly, arterial hypertension is a major public health problem, which affects >25 % of the general population. Hypertensive patients are not only under major cardiovascular risk, but experience a lower health quality. Erectile dysfunction (ED) is considered to be one of the most important quality-of-life complications of hypertension and coronary artery disease (CAD) [1]. Given the fact that high blood pressure affects all the vessels of the body, it is not surprising that several structural and functional alterations in the penile vasculature are induced by hypertension [2–5].

This chapter aims to summarize the epidemiology and pathophysiology of ED in patients with hypertension and CAD, to discuss the management of ED in untreated and treated hypertensive patients as well as in patients with CAD, to present ED as an early indicator of asymptomatic CAD, and finally to highlight the role of sexual counseling in CAD patients.

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Epidemiology of Erectile Dysfunction in Hypertension and in Coronary Artery Disease

The elements about the risk for ED when hypertension occurs come either from small clinical studies or large studies that include subgroups of hypertensive men. Specifically, Derby et al. [6] used a single question for self assessed ED in the population-based sample of Massachusetts Male Aging Study (MMAS) and they found that hypertensive patients aged 40–70 years had an 80 % greater risk for ED. Braun et al. [7] performed the Cologne Male Survey aiming to evaluate the epidemiology of male sexuality in Germany. The group of hypertensives aged 30–80 years had a 58 % increased risk for ED. A similar proportion was reported by Martin Morales et al. [8] who estimated the prevalence for ED in Spain in a cross-sectional study, using the International Index of Erectile Function (IIEF) questionnaire. Marumo et al. [9] used the same questionnaire (IIEF) and found a 48 % prevalence of sexual dysfunction in the hypertensive men included in the study. A cross-national study [10] of the prevalence of ED in community-based populations in Brazil, Italy, Japan and Malaysia showed that among a random sample of 540 hypertensive men aged 40–70 years the odds ratio for ED was 1.45 (95 % confidence intervals 1.15–1.84). Mirone et al. [11] examined the determinants of ED in men who asked for a free of charge urologic or andrologic consultation. They suggested a 30 % increased risk of ED in men with hypertension (odds ratio 1.30, 95 % confidence intervals 1.10–1.40). Ponholzer et al. [12] used the IIEF-5, too. They assessed the prevalence and risk factors for ED in 2869 men aged 20–80 years in the area of Vienna. They examined hypertension as a risk factor for ED and estimated an odds ratio of 2.05 (95 % confidence intervals 1.61–2.60). One year later, Saigal et al. [13] analyzed data from the 2001–2002 National Health and Nutrition Examination Study in order to evaluate the prevalence of ED in a population of 3,506 men, 20 years and older. They found that ED affected almost 20 % of participants and hypertension was one of the modifiable risk factors which were independently associated with ED (odds ratio 1.56). The Male Attitudes Regarding Sexual Health (MARS) study [14] was a cross-sectional, nationally representative probability survey, which included 1,955 men, $\geq$ 40 years old. Lauren et al. aimed to estimate by race/ethnicity in the United States, the prevalence of ED and the impact of socio-demographic, health, relationship, psychological and lifestyle variables. The probability for ED increased with hypertension about 60 %. Selvin et al. [15] carried out a cross-sectional analysis of data from adult male participants in the 2001–2002 National Health and Nutrition Examination Survey (NHANES) and they aimed to assess the prevalence of ED in the US adult male population. The prevalence of ED among men with hypertension was 44.1 %.

Several studies have, over the years, demonstrated that the prevalence of sexual dysfunction is almost twice as frequent and of higher severity in hypertensive individuals than in the normotensive population [16]. Furthermore, it has been reported, by Doumas et al., that hypertensive subjects have up to a seven fold higher incidence of sexual dysfunction than normotensive individuals, with a relative risk that

ranges from 1.3 to 6.9 [2]. Bulpitt et al. observed a prevalence of 7 % of erectile dysfunction among normotensive men, versus 17 % and 25 % in men with untreated and treated hypertension, respectively [17].

In a sample of 594 men aged 30–75 years from primary health-care clinics (298 normotensive and 296 hypertensive participants), ED was reported by 24 % of normotensive subjects and 66 % of hypertensive patients [18]. Moreover, Cordero et al. demonstrated that the prevalence of ED increased linearly with age [19].

Erectile dysfunction and coronary artery disease (CAD) share several common risk factors. Aging, genetic susceptibility, hypertension, dyslipidemia, obesity, metabolic syndrome, hypertriglyceridemia, and diabetes mellitus contribute to the development of both CAD and ED [20–22].

Montorsi et al. showed that almost half of the 300 patients with CAD (49 %) had a history of ED [23]. Interestingly, ED symptoms appeared before CAD in 70 % of the patients by an average of approximately 3 years. Furthermore, Thompson et al. demonstrated that men with ED had 1.5 fold higher risk for cardiovascular events compared to them without ED [24].

In addition, a recent meta-analysis [25], which included about 90,000 patients, proved that after a follow-up period of about 6 years, patients with sexual disorders, compared with individuals without, had an increased risk for cardiovascular events by 44 %, for myocardial infarction 62 % and for all-cause mortality 25 %. A prior meta-analysis of 12 prospective cohort studies, involving 36,744 participants, suggested that ED increases the risk of coronary heart disease by 46 % and all-cause mortality by 19 % [26].

Pathophysiology of Erectile Dysfunction

There is a variety of factors that contribute to the normal erectile function. They are physiological, neurological, hormonal, vascular and cavernosal factors. Any abnormality or malfunction of these factors may provoke sexual dysfunction.

Neurogenic ED is defined as the inability to initiate and maintain a penile erection due to neurologic dysfunction. The causes of neurogenic ED can be central or peripheral neuropathies or a traumatic loss of neural function. The most common neurological disorders include stroke, spinal cord injury, multiple sclerosis, Parkinson's disease and radical pelvic surgeries [27].

High blood pressure impairs blood vessels. Male erectile is a vascular phenomenon. So the association between hypertension and ED is strong. Particularly, hypertension induces structural and functional abnormalities of the penile arteries. Atherosclerosis is the most principal structural abnormality which causes flow-limiting stenosis [28–30].

Montorsi et al. proposed the artery-size hypothesis. According to this and given the systemic nature of atherosclerosis, all vascular beds should be impaired. Penile arteries are smaller in diameter (1–2 mm) than coronary arteries (3–4 mm). Thus, larger coronary arteries better tolerate the same amount of plaque compared to the

smaller penile arteries. According to this hypothesis ED occurs before coronary artery disease becomes symptomatic [31]. Other structural abnormalities occurring due to hypertension are the smooth muscle hypertrophy of the wall of the cavernous arteries and the increase in type III collagen fibers in the extracellular matrix [4]. The main functional abnormalities induced by high blood pressure are the defective nitric oxide-induced vasodilatory mechanism, due to decreased nitric oxide bioavailability [5] and the activation of the renin-angiotensin system, since angiotensin II causes vascular hypertrophy. Furthermore, angiotensin II acts on angiotensin type 1 receptors and causes the contraction of the corporeal smooth muscle [32].

There exists an important association of ED and hormonal alterations. Testosterone deficiency, hypogonadism or hyperprolactinemia have been shown to be associated with a higher risk of CAD and cardiac mortality [5, 33]. This relation is explained by the fact that low androgen levels might have proinflammatory and proapoptotic effects on endothelial tissue [34, 35]. Furthermore, androgens maintain the smooth muscle homeostasis, since they act on arterial tissues and vascular remodeling.

Diabetes mellitus (DM) type 2 is among the most common risk factors for ED. It may cause ED through a variety of alterations on psychology, endothelial cell function, central nervous system and peripheral nerve function. Except the neuronal and endothelial problems regarding the penis in diabetics, low testosterone is another factor, which exacerbates the sexual function [36]. The risk of ED is three fold higher among diabetic men (28 % vs 9.6 %). Moreover, ED in diabetics occurs at an earlier age (15 % at 30 years and 55 % at 60 years) [37].

Smoking is another parameter which contributes to the onset of ED through several mechanisms, such as hemodynamic alterations via nicotine, toxic agents which affect the vascular endothelium, hypercoagulability and increased platelet accumulation. It may impair penile erection by the deterioration of endothelium-dependent smooth muscle relaxation. Moreover, abnormal penile vascular findings and therefore ED are being significantly increased as risk factors, such as smoking, accumulate [38]. Interestingly, Jaffe et al. [39] showed that smoking may provoke ED by reducing high-density lipoprotein (HDL) and enhancing fibrinogen concentrations. It has been shown that the prevalence of erectile dysfunction was 40–70 % higher among smokers, compared to nonsmokers [40]. Also, smoking increases the age-adjusted risk of ED.

In addition, chronic renal failure and uremia have been associated with a high prevalence of ED (20–50 %) [41]. Psychological factors, hormonal alterations and atheromatous disease may be responsible for this association [42]. Uremia results in impaired nerve and endothelial-mediated relaxation of the smooth muscle of the corpus cavernosum [43].

Finally, specific antihypertensive drug categories, such as central acting drugs, beta-blockers and diuretics, impair the sexual function [16]. It has been demonstrated that the number of sexual intercourses per month was significantly lower with beta-blockers (both the first generation beta-blockers, such as atenolol, and the newer, such as carvedilol) than with placebo [44–46]. On the other hand, Croog et al [47] demonstrated that adding propranolol or methyldopa in mono therapy with a

thiazide worsened the sexual symptoms, while this effect did not appear when patients were treated with captopril plus a diuretic. A large UK trial (MRC) divided hypertensives into four treatment groups: bendrofluazide, propranolol, or a placebo for either of these drugs. Twice as many participants taking bendrofluazide for treatment of mild hypertension reported ED compared to those taking propranolol or placebo [48]. In the Treatment of Mild Hypertension Study (TOMHS), the prevalence of sexual dysfunction in men taking low dose of chlorthalidone for 2 years was higher compared to placebo (17.1 % versus 8.1 %; p = 0.025) [49].

Finally, many psychotropic drugs cause sexual dysfunction. The most important of them are antidepressants, such as the selective serotonin repute inhibitors and venlafaxine, and antipsychotics, such as risperidone and olanzapine [50].

Management of Erectile Dysfunction in Untreated Hypertensives

The primary step in the approach of hypertensive patients with erectile dysfunction who are not receiving antihypertensive treatment is the exclusion of other comorbidities or drugs. Indeed psychiatric, neurological, urologic and endocrine diseases should be excluded in order to establish the vasculogenic origin of the sexual dysfunction.

The next option a physician has approaching an untreated hypertensive is the lifestyle modification. As it has been mentioned above, the principal abnormality that occurs in ED is the endothelial dysfunction and thus risk factors like obesity, decreased physical activity, smoking, hypertension, diabetes mellitus and dyslipidemia have been linked with sexual dysfunction [1–5]. Derby et al. showed that moderate physical activity decreases the risk of ED up to 30 % compared to sedentary lifestyle [51]. Moreover, Chung et al. demonstrated that obesity increases the risk of ED up to 30 % and on the other hand physical activity was associated with a 30 % lower risk [52].

The next or parallel step when approaching a hypertensive patient with ED is to find the proper antihypertensive treatment, when it is indicated. Accumulating data indicate that antihypertensive drugs affect erectile function [53]. Beta blockers (like propranolol) and diuretics impair sexual function [53, 54]. However, nebivolol, which is a newer representative of its class, is considered to improve erectile function through increased nitric oxide bioavailability [55, 56].

On the other part, calcium antagonists and angiotensin converting enzyme inhibitors seem to have no effect on sexual function [57–59]. Nevertheless, angiotensin receptor blockers (ARBs) seem to ameliorate sexual function, since they block the vasoconstrictive action of angiotensin II, thus preventing termination of erection [44, 45].

In conclusion, ARBs, nebivolol, ACE-inhibitors and calcium antagonists are indicated for the treatment of untreated hypertensives with ED. ARBs and nebivolol are definitely the best choice towards this direction. On the other hand, diuretics and beta-blockers should be avoided, if possible.

Management of Erectile Dysfunction in Treated Hypertensives

What options do we have when encountering patients with ED who are already on antihypertensive treatment? In this case there is an important question: Is hypertension per se, antihypertensive medication or both, the factors causing erectile dysfunction?.

Doumas et al. demonstrated that the prevalence of sexual dysfunction in treated hypertensives is double than the prevalence in untreated patients (40.4 % versus 19.8 %) [16]. These findings indicate that antihypertensive therapy might be implicated in sexual dysfunction. Nevertheless, hypertensive patients, who are on antihypertensive medications, may have more severe hypertension, significant target organ damage or more comorbidities than untreated patients and perhaps these factors are responsible for sexual dysfunction.

It is true that medically induced erectile dysfunction is one of the major reasons for poor adherence and treatment discontinuation. This fact may have harmful effects on patients' cardiovascular profile [60, 61] and this is why we have to come up successfully against sexual dysfunction in patients who are already under antihypertensive therapy.

First of all, approaching this patient we should exclude other comorbidities, drugs and psychogenic factors that might contribute to sexual problems. Lifestyle modification such as weight loss, physical activity, should be recommended by the physicians [62].

If these steps fail to relieve erectile dysfunction, a change of antihypertensive drugs should be considered. Beta-blockers and diuretics should be the first categories to be changed, unless they are strictly indicated for the specific patient, due to other comorbidities. Beta-blockers have been associated with poor sexual desire and with erectile dysfunction [63–65]. Older drugs, such as central acting agents, diuretics and beta-blockers are associated with worse sexual function than newer drugs, such as angiotensin receptor blockers, angiotensin converting enzyme (ACE) inhibitors and calcium antagonists. Some small clinical trials [32, 66, 67] showed that not only the first-generation beta-blockers, such as atenolol, but also the newer, like carvedilol, have a negative effect on sexual function. On the other hand, angiotensin receptor blockers represent the mainstay of therapy [68], since they not only do not exert a detrimental role on sexual function, but they seem to have a beneficial role compared to placebo. The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) and Telmisartan Randomized Assessment Study in Cardiovascular Disease (TRANSCEND) studies attempted to assess erectile function by using a validated questionnaire [69]. In the ONTARGET study, erectile function was not affected by the angiotensin-converting enzyme inhibitor ramipril, the angiotensin receptor blocker telmisartan, and their combination. In the TRANSCEND study there were no different effects in sexual function with telmisartan or placebo. The Nitric Oxide, Erectile Dysfunction and Beta-Blocker Treatment (MR-NOED) trial found that nebivolol improved sexual activity and avoided erectile dysfunction in male

hypertensive patients on long-term beta-adrenoceptor antagonist therapy [70]. The influence of calcium channel antagonists on erectile function has not been assessed by any clinical trial, but they are considered to have no particular effect on sexual function [71].

To sum up, nebivolol and angiotensin II receptor antagonists are considered to have a beneficial effect on erectile function [72]. However, treating physicians should count in other comorbidities that may require the use of specific antihypertensive drugs, despite of its deleterious effects on sexual function, such as beta-blockers in heart failure patients. Nonetheless, even if sexual dysfunction carries on after modifying to one of the indicated drug categories, administration of phosphodiesterase type 5 (PDE-5) inhibitors is recommended for the treatment of sexual dysfunction.

Erectile Dysfunction as an Early Diagnostic Indicator of Asymptomatic Coronary Artery Disease

As has been mentioned above, erectile dysfunction and coronary artery disease share several common risk factors and they often coexist. The second Princeton Guidelines suggested that ED and CVD are both results of endothelial dysfunction and also ED should be considered as a cardiovascular risk marker [73].

This role of ED as an "early diagnostic window" for asymptomatic CAD can be explained by the "artery size hypothesis". Both ED and CAD arise out of endothelial dysfunction and atherosclerosis. However, smaller arteries, such as penile arteries, are the first to be affected, prior to the larger ones, like coronary arteries, since the same size of plaque has a greater effect on blood flow through the penile arteries than through the coronary vessels.

Given the fact that an acute coronary syndrome often occurs as a result of the rupture of a subclinical plaque, ED may also be a warning sign of an acute coronary event [25]. It is interesting that ED occurs approximately 3 years before symptomatic CAD [74]. Several studies showed a temporal relationship between ED and CAD and they estimated that ED is presented about 2–5 years before a cardiovascular event. Hodges et al. [75] examined 207 patients with CVD attending cardiovascular rehabilitation programs and 165 age-matched controls from general practice in the UK. These patients completed four questionnaires. Fifty-six percent of the patients with CVD had symptoms of ED at the time of the study and they started about 5 ± 5.3 years ago. On the contrary, of the individuals in the control group 37 % had ED symptoms for about 6.6 ± 6.8 years. In the COBRA (AssoCiation Between eRectile dysfunction and coronary Artery disease) trial [76], 93 % of patients with a chronic coronary syndrome had ED symptoms for about 24 (range 12–36) months before the onset of angina. Furthermore, the time intervals for patients with one-, two-, and three- vessel disease were 12 (9.5–24), 24 (16.5–36) and 33 (21–47) months, respectively. Conclusively, there was a significant relationship between the

number of vessels involved and the time intervals between ED and CAD onset ($p=0.016$).

The possibility of underlying coronary stenosis on a patient with vasculogenic ED has been estimated about 50 % and the possibility of asymptomatic CAD about 10 % [23, 77]. The large Prostate Cancer Prevention Trial proved that ED at entry or that developed later, during follow-up, predict any cardiac event with a hazard ratio of 1.45 ($p<0.001$, 95 % confidence interval: 1.25–1.69). Moreover, the cardiovascular risk associated with ED was at least as great as the risk associated with smoking, hypercholesteloremia, and family history of myocardial infarction [24]. A meta-analysis, including 36,744 participants, estimated that men with ED, compared with the reference group, had a risk of 48 % for cardiovascular disease, 46 % for coronary heart disease, 35 % for stroke and 19 % for all cause mortality, after adjustment for traditional cardiovascular risk factors [26].

Three studies, two meta-analyses and one systematic review, attempted to investigate the link between ED and the prediction of CVD [25, 26, 78, 79]. A population-based, longitudinal study included 1400 men aged 40–75 years, with no known CAD and with a follow-up of 10 years [79]. Men aged 40–49 years old with ED at baseline had a 50-fold greater cardiovascular risk than men who had normal erections (48.52 versus 0.94) and five-fold in the group 50–59 years. Chew et al. demonstrated that ED is not only significantly associated with, but also predictive of subsequent atherosclerotic CV events, in particular when ED occurs at a younger age [80]. Furthermore, a coronary angiographic study showed that men <60 years old with ED presented a higher risk of CAD (2.3 times) and more severe disease [81]. A meta-analysis of prospective cohort studies, including 36,744 men suggested that ED significantly increases the risk of CVD, CAD, stroke and all cause mortality and the increase was independent of conventional cardiovascular risk factors. Moreover, similar findings were reported by Vlachopoulos et al., who examined 14 studies in which were involved 92,757 men. Interestingly, the relative risk was higher at younger ages and intermediate-risk groups.

Since erectile dysfunction is linked with cardiovascular parameters, it could constitute a trustworthy tool for detecting asymptomatic cardiovascular disease. Therefore, sexual function should be incorporated into CVD risk assessment for all men and both cardiologists and general physicians should intervene with advice for lifestyle modification, weight loss, healthy diet and exercise.

Management of Erectile Dysfunction in Coronary Artery Disease Patients

Cardiovascular risk is defined as the risk of morbid events over a 3- to 5- year interval from the onset of ED [23, 75]. As it has been mentioned above, ED should be used as a trustworthy tool to evaluate CVD risk reduction. Several studies showed that ED is significantly associated with increased cardiovascular events. Araujo

et al. estimated that ED was associated with hazard ratios (HRs) of 1.43 (95 % confidence intervals 1.00–2.05) for CVD mortality and they suggested that this HR is equivalent to HRs of some traditional CVD risk factors (such as age, smoking, hypertension, diabetes, dyslipidemia) [82]. Moreover, ED is predictive of asymptomatic CAD. The time interval among the onset of ED symptoms and the appearance of CAD symptoms is estimated at 2–5 years [23, 29, 75]. Furthermore, ED appears to be of more prognostic significance for CAD in younger men, aged 40–49 [79]. Also, Chew et al. showed that atherosclerotic cardiovascular events are seven times more likely in men <40 years old with ED [79]. Thus, ED may be reliable and useful in evaluating cardiovascular risk in younger patients. Also, as it has been reported above, a recent meta-analysis of 36,744 men, demonstrated that the more severe the ED is, the greater the cardiovascular risks are [26].

The Framingham Risk Score (FRS) is a powerful tool which estimates the 10 year cardiac event risk in patients and it is suggested by the 2010 ACCF/AHA guideline [83] for assessment of cardiovascular risk in asymptomatic adults. Nevertheless, it is doubtful whether the FRS estimates risk in younger patients suitably, in particular those with ED.

Although the Princeton III consensus recommendations for the management of erectile dysfunction and cardiovascular disease proposes the FRS as a method to assess subclinical atherosclerosis in men with ED, more CVD risk factors should be investigated in men with ED aged 30–60 years [84].

Lifestyle modification is recommended in order to improve the patients' cardiovascular health. Particularly, smoking cessation seems to reduce mortality in CAD by 36 % [85]. Physical activity is considered to reduce the occurrence of diabetes mellitus II and CAD by 30–50 % in physical active versus sedentary individuals [86–89]. Also, weight loss, healthy diet and moderate alcohol consumption can reduce CAD mortality by 36 % [90].

As regards the parameters in the context of laboratory testing, DM doubles the risk for CVD [91]. eGFR < 60 ml/min and ratio of urinary albumin to creatinine >10 mg/g are associated with increased cardiovascular mortality [92, 93].

Testosterone measurement has become debatable in men without symptoms of low testosterone. Guay et al. found that 36 % of the patients in a medical endocrine-based center for male sexual dysfunction had hypogonadism [94]. This medical condition is a potential cause of ED [95, 96] and testosterone replacement therapy (TRT) is very effective [96].

A meta-analysis of 19 studies showed no association between endogenous total testosterone (TT) level and CVD risk in middle-aged men [97]. Another meta-analysis of 49 cross-sectional studies proved that lower TT levels and higher estradiol levels correlate with increased CVD risk [98]. On the other hand, the previous meta-analysis [97] showed that low TT levels predict increased risk for CVD in elderly men. It was also discussed that low TT may constitute a marker of poor health. Indeed, several studies demonstrated that androgen deficiency is associated with insulin resistance, DM II and metabolic syndrome [99–102]. In this direction, a meta-analysis of five randomized controlled trials showed that TRT was associated with a

significant reduction of fasting plasma glucose, homeostatic model assessment index, triglycerides and waist circumference and an increase in HDL levels [103].

Testosterone levels should be measured in all men diagnosed with organic ED [84], especially for those who had no beneficial effects undergoing a PDE5 inhibitor therapy [83]. Consequently, males with TT levels <230 ng/dL seem to benefit from TRT. Men with TT levels between 231 and 346 ng/dL, with symptoms like decreased libido or ED and without contraindications should undergo TRT for 4–6 months, after extensive analysis of the potential risks and complications. The TRT should be continued more than 6 months only if there is a clinical profit [84].

High sensitivity C reactive protein (hsCRP) is an independent predictor of coronary events [83]. A meta-analysis of 54 long-term prospective studies and approximately 160,000 people without a history of vascular disease showed that high CRP concentration was associated with increased risk of CAD (37 %), ischemic stroke (27 %), vascular mortality (55 %) and nonvascular mortality (54 %).

Additionally, serum uric acid measurement is recommended, since high levels have been associated with increased cardiovascular risk [104]. Lipoprotein-associated phospholipase A2 levels seems to be independent predictors of CVD in healthy individuals after adjustment for hsCRP and traditional risk factors [105]. Moreover, glycated hemoglobin has been associated with risks of cardiovascular disease and it has been proved that the addition of glycated hemoglobin to prediction models of CAD improved CAD prediction in non diabetics without previous history of CAD [106].

Exercise stress testing is considered to be useful to evaluate CAD risk in patients with ED and DM II, since in patients with DM II, the rates of men with asymptomatic CAD and ED were seven times greater than the rates of participants with ED and without CAD (33.8 % versus 4.7 %) [107]. CIMT, CACS and ABI have been proposed by the 2010 ACCF/AHA guidelines state in the context of assessment of intermediate-risk patients [83]. Finally, endothelial dysfunction seems to be associated with higher cardiac death, myocardial infarction, revascularization and cardiac hospitalization in symptomatic outpatients during a 7 years follow-up [108].

As discussed previously, ED and CVD share several risk factors, and ED is an independent predictor of CVD. Therefore, the assessment of sexual function should be included into the initial evaluation of cardiovascular risk for all men [109, 110]. A meta-analysis of ten studies proved that episodic physical and sexual activity was associated with a high risk of acute cardiac events among individuals with high levels of habitual physical activity [111]. Thus, the physicians should estimate the cardiovascular risk associated with sexual activity in patients.

The PDE5 inhibitors (such as sildenafil, tadalafil, vardenafil, and avanafil) are used to treat ED. Analyses of placebo-controlled and postmarketing surveillance data have shown no new significant cardiovascular events [112, 113]. Additionally, several studies have demonstrated that PDE5 inhibitors have a possible role in the management of hypertension [114–116] and endothelial dysfunction [117–119] in patients at risk for CVD. Also, TRT should be performed for men with low or intermediate TT levels. Other approaches, like exercise, weight loss [120, 121], and partner and relationship factors [122–124], should be incorporated, too.

Furthermore, possible effects on erectile function of agents used to manage cardiovascular risk factors should be considered. The b-blocker nebivolol is less likely to cause ED than other b-blockers, since it has direct vasodilating properties [55, 125]. Angiotensin receptor blockers are considered to cause ED less likely than diuretics [66, 126]. Statins have been suggested to improve erectile function in men with and without PDE5 inhibitors [127–129].

Closing, it is clear that a careful and comprehensive approach to cardiovascular risk reduction will meliorate the overall health, and especially vascular health, including sexual function.

Sexual Counseling

Erectile dysfunction is a condition which affects and contributes significantly to the impaired life quality of both patients and their sexual partners. However, it is also under-reported, under-recognized and under-treated. Therefore, sexual counseling is a complex process on which the health-care professional should identify and manage patients with sexual dysfunction and also, determine, control and encounter factors limiting sexual activity [130, 131].

Some of the most common and considerable topics which should be discussed are the following: is sexual activity safe for a patient with CVD and when (after an acute event)?, which sexual position is suggested?, is sexual activity impaired by other drugs and comorbidities?, are PDE5 inhibitors safe?.

Although the advantages of regular exercise have been proved by several studies and it is considered that it reduces the risk for cardiovascular morbidity and mortality [132–138], some studies suggest that acute rigorous exercise may provoke an acute cardiac event [139–141]. Acute cardiac events occurring during or shortly after sexual intercourse are the so-called sexually-induced or coital acute cardiac events. However, coital angina is not very frequent and it represents less than 5 % of angina events [142].

A recent systematic review and meta-analysis assessed the effect of episodic physical and sexual activity on acute cardiac events. Episodic sexual activity was associated with an increased risk of acute myocardial infarction (relative risk = 2.70; 95 % CI: 1.48–4.91). However, the absolute rate of acute cardiac events is limited, since sexual activity is infrequent and its' effect is transient. The absolute rate of myocardial infarction is 2–3 per 10,000 person-years for every 1 h of additional sexual activity per week. Furthermore, the association between sexual activity and acute cardiac events depends on habitual physical activity. For every additional time per week an individual is involved in physical activity, the relative risk for myocardial infarction is reduced by 45 % [111].

Therefore, an individual who manages more than 3–5 METs during treadmill exercise test without developing symptoms like angina or dyspnea, ischemia at electrocardiogram, hypotension or arrhythmia, may engage in sexual intercourse without significant risk [143].

Unfortunately, there is a lack of evidence-based recommendations about the appropriate time after an acute event a patient should be exposed to sexual activity. Certainly, advice should be disease specific. After an acute MI, the interval of 1 week seems safe, provided that the patient did not have any serious complications (e.g., angina) during hospitalization, and mild-to-moderate physical activity does not trigger angina or dyspnea.

The intensity of sexual activity, which is a form of exercise, depends on the type and the duration of sexual activity. Boolean et al. demonstrated that non-coital sexual activities (non-coital stimulation of husband by wife and self-stimulation by husband) were associated with lower energy expenditures than coital activities [144]. It has also been shown that sexual activity provides modest physical stress, comparable with stage II of the Bruce treadmill protocol for men and Stage I for women. Moreover, the duration of treadmill exercise predicts the duration of sexual activity. Particularly, an increase of 2.3 min in sexual activity duration has been observed per each minute of treadmill duration [145].

Sexual problems are very common in patients with heart failure [146]. These patients often experience shortness of breath and fatigue [147]. Patients with advanced heart failure (classes III and IV according to New York Heart Association) should postpone sexual intercourse until their condition is improved.

When dyspnea or angina comes up with sexual activity, alternative types of sexual activity, convenient positioning and relaxation before and after activities may be very helpful. Sexual positions are considered to affect the energy expenditure during sexual activity. Bohlen et al., also, found that the man on top positioning requires more energy expenditure than the man on bottom positioning [144]. It is very helpful to recommend convenient and comfortable positions in patients with CVD.

A very significant factor which impairs sexual function is the concomitant medication a patient takes. In particular, patients with cardiovascular disease use drugs which may affect erectile function, such as diuretics and b-blockers [55, 148], as it has been reported previously. Therefore, the physician has to take into account both the beneficial and the negative effects and to replace drugs by others that have neutral effect or even actuate a reverse of erectile dysfunction.

PDE-5 inhibitors are vasorelaxing agents that block the activity of PDE-5 isoenzyme, which is localized throughout the smooth muscle cells of the vasculature. Thus, they increase the cyclic guanosine monophosphate (cGMP), exerting vasodilating properties. Given the fact that PDE-5 inhibitors are associated with few side effects, they can be safely administered in both hypertensive patients taking multiple antihypertensive regimes and patients with cardiovascular risk factors or cardiovascular disease [149, 150]. However, co-administration with organic nitrates is considered to be contraindicated, due to possible episodes of symptomatic hypotension [151]. Furthermore, precaution should be taken when PDE-5 inhibitors are combined with a-blockers, since there is a high risk of orthostatic hypotension effect. Thus, lower starting doses should be recommended in patients receiving a-blockers [53], and of course, close patient monitoring.

References

1. Manolis A, Doumas M. Sexual dysfunction: the 'prima ballerina' of hypertension-related quality-of-life complications. J Hypertens. 2008;26:2074–84.
2. Manolis AJ, Doumas M, Viigimaa M, Narkiewitz K. Hypertension and sexual dysfunction. European Society of Hypertension Scientific Newsletter: Update on Hypertension Management. Eur Soc Hyp. 2011;32:1–2.
3. Manolis A, Doumas M. Hypertension and sexual dysfunction. Arch Med Sci. 2009;5:S337–50.
4. Doumas M, Douma S. Sexual dysfunction in essential hypertension: myth or reality? J Clin Hypertens. 2006;8:269–74.
5. Viigimaa M, Doumas M, Vlachopoulos C, et al.; European Society of Hypertension Working Group on Sexual Dysfunction. Hypertension and sexual dysfunction: time to act. J Hypertens. 2011;29:403–7.
6. Derby CA, Araujo AB, Johannes CB, et al. Measurement of erectile dysfunction in population-based studies: the use of a single question self-assessment in the Massachusetts Male Aging. Int J Impot Res. 2000;12:197–204.
7. Braun M, Wassmer G, Klotz T, et al. Epidemiology of erectile dysfunction: results of the "Cologne Male Survey.". Int J Impot Res. 2000;12:305–11.
8. Martin-Morales A, Sanchez-Cruz JJ, Saenz de Tejada I, et al. Prevalence and independent risk factors for erectile dysfunction in Spain: results of the Epidemiologia de la Disfunction Erectil Masculina Study. J Urol. 2001;166:569–75.
9. Marumo K, Nakashima J, Murai M. Age-related prevalence of erectile dysfunction to Japan: assessment by the International Index of Erectile Function. Int J Urol. 2000;8:53–9.
10. Nicolosi A, Moreira Jr ED, Shirai M, et al. Epidemiology of erectile dysfunction in four countries: cross-national study of the prevalence and correlates of erectile dysfunction. Urology. 2003;61:201–6.
11. Mirone V, Ricci E, Gentile V, et al. Determinants of erectile dysfunction risk in a large series of Italian men attending andrology clinics. Eur Urol. 2004;45:87–91.
12. Ponholzer A, Temml C, Mock K, et al. Prevalence and risk factors for erectile dysfunction in 2869 men using a validated questionnaire. Eur Urol. 2005;47:80–6.
13. Saigal CS, Wessels H, Pace J, et al.; Urologic Diseases in America Project. Predictors and prevalence of erectile dysfunction in a racially diverse population. Arch Intern Med. 2006;166:207–12.
14. Laumann EO, West S, Glasser D, et al. Prevalence and correlates of erectile dysfunction by race and ethnicity among men aged 40 or older in the United States: from the male attitudes regarding sexual health survey. J Sex Med. 2007;4:57–65.
15. Selvin E, Burnett AL, Platz EA. Prevalence and risk factors for erectile dysfunction in the US. Am J Med. 2007;120:151–7.
16. Doumas M, Tsakiris A, Douma S, et al. Factors affecting the increased prevalence of erectile dysfunction in Greek hypertensive compared with normotensive subjects. J Androl. 2006;27(3):469–77.
17. Bulpitt CJ, Dollery CT, Carne S. Changes in symptoms in hypertensive patients after referral to hospital clinic. Br Heart J. 1976;38:121–8.
18. Bener A, Al-Ansari A, Al-Hamaq AO, et al. Prevalence of erectile dysfunction among hypertensive and nonhypertensive Qatari men. Medicina. 2007;43:870–8.
19. Cordero A, Bertomeu-Martinez V, Mazon P, Facila L, et al. Erectile dysfunction in high-risk hypertensive patients treated with beta-blockade agents. Cardiovasc Ther. 2010;28:15–22.
20. Fung MM, Bettencourt R, Barrett-Connor E. Heart disease risk factors predict erectile dysfunction 25 years later: the Rancho Bernardo study. J Am Coll Cardiol. 2004;43(8):1405–11.
21. Alberti L, Torlasco C, Lauretta L, et al. Erectile dysfunction in heart failure patients: a critical reappraisal. Andrology. 2013;1(2):177–91.
22. Ianni M, Callegari S, Rizzo A, et al. Pro-inflammatory genetic profile and familiarity of acute myocardial infarction. Immun Ageing. 2012;9(1):14.

23. Montorsi F, Briganti A, Salonia A, et al. Erectile dysfunction prevalence, time of onset and association with risk factors in 300 consecutive patients with acute chest pain and angiographically documented coronary artery disease. Eur Urol. 2003;44(3):360–4; discussion 4–5. Epub 2003/08/23.
24. Thompson IM, Tangen CM, Goodman PJ, et al. Erectile dysfunction and subsequent cardiovascular disease. JAMA. 2005;294(23):2996–3002.
25. Vlachopoulos CV, Terentes-Printzios DG, Ioakeimidis NK, et al. Prediction of cardiovascular events and all-cause mortality with erectile dysfunction: a systematic review and meta-analysis of cohort studies. Circ Cardiovasc Qual Outcomes. 2013;6(1):99–109.
26. Dong JY, Zhang YH, Qin LQ. Erectile dysfunction and risk of cardiovascular disease: meta-analysis of prospective cohort studies. J Am Coll Cardiol. 2011;58(13):1378–85.
27. Siddiqui MA, Peng B, Shanmugam N, et al. Erectile dysfunction in young surgically treated patients with lumbar spine disease: a prospective follow-up study. Spine (Phila Pa 1976). 2012;37:797–801.
28. Solomon H, Man JW, Jackson G. Erectile dysfunction and the cardiovascular patient: endothelial dysfunction is the common denominator. Heart. 2003;89(3):251–3. Epub 2003/02/20.
29. Montorsi P, Ravagnani PM, Galli S, et al. Association between erectile dysfunction and coronary artery disease: matching the right target with the right test in the right patient. Eur Urol. 2006;50(4):721–31. Epub 2006/08/12.
30. Montorsi P, Ravagnani PM, Galli S, et al. Common grounds for erectile dysfunction and coronary artery disease. Curr Opin Urol. 2004;14(6):361–5. Epub 2005/01/01.
31. Burchardt M, Burchardt T, Baer L, et al. Hypertension is associated with severe erectile dysfunction. J Urol. 2000;164:1188–91.
32. Becker AJ, Uckert S, Stief CG, et al. Possible role of bradykinin and angiotensin II in the regulation of penile erection and detumescence. Urology. 2001;57:193–8.
33. Hale TM, Okabe H, Bushfield TL. Recovery of erectile function after brief aggressive antihypertensive therapy. J Urol. 2002;168:348–54.
34. Mirone V, Imbimbo C, Fusco F, et al. Androgens and morphologic remodeling at penile and cardiovascular levels: a common piece in complicated puzzles? Eur Urol. 2009;56(2):309–16. Epub 2009/01/17.
35. Vlachopoulos C, Aznaouridis K, Ioakeimidis N, et al. Unfavorable endothelial and inflammatory state in erectile dysfunction patients with or without coronary artery disease. Eur Heart J. 2006;27(22):2640–8. Epub 2006/10/24.
36. Morelli A, Corona G, Filippi S, et al. Which patients with sexual dysfunction are suitable for testosterone replacement therapy. J Endocrinol Invest. 2007;30(10):880–8.
37. Koldny RC, Kahn CB, Goldstein HH. Sexual function in diabetic men. Diabetes. 1973;23:306–9.
38. Shabsigh R, Mulvany MJ. The myogenic response: established facts and attractive hypotheses. Clin Sci (Lond). 1999;96:313–26.
39. Jaffe A, Chen Y, Kisch ES, et al. Erectile dysfunction in hypertensive subjects: assessment of potential determinants. Hypertension. 1996;28:859–62.
40. Salonia A. Blackwell Publishing Ltd. Int J Androl. 2003;26:129–36.
41. Papadopoulou E, Varouktsi A, Lazaridis A, et al. Erectile dysfunction in chronic kidney disease: from pathophysiology to management. World J Nephrol. 2015;4:379–87.
42. Rosas SE, Joffe M, Franklin E, et al. Prevalence and determinants of erectile dysfunction in haemodialysis patients. Kidney Int. 2001;59:2259–66.
43. Saenz de Tejada I, Goldstein I, Azadzoi K, et al. Impaired neurogenic and endothelium-mediated relaxation of penile smooth muscle from diabetic men with impotence. N Engl J Med. 1989;320:1025–30.
44. Fogari R, Zoppi A, Poletti L, et al. Sexual activity in hypertensive men treated with valsartan or carvedilol: a crossover study. Am J Hypertens. 2001;14:27–31.
45. Fogari R, PretI P, Derosa G, et al. Effect of antihypertensive treatment with valsartan or atenolol on sexual activity and plasma testosterone in hypertensive men. Eur J Clin Pharmacol. 2002;58:177–80.

46. Douma S, Doumas M, Petidis K, et al. Beta blockers and sexual dysfunction: bad guys – good guys. In: Momoka E, Narami M, editors. Beta blockers: new research. New York: Nova Science Publishers Inc; 2008. p. 1–13.
47. Croog SH, Levine S, Sudilovsky A, et al. Sexual symptoms in hypertensive patients. A clinical trial of antihypertensive medications. Arch Intern Med. 1988;148:788–94.
48. Medical Research Council Working Party on Mild to Moderate Hypertension. Adverse reactions to bendrofluazide and propranolol for the treatment of mild hypertension. Lancet. 1981;2:539–43.
49. Grimm Jr RH, Grandits GA, Prineas RJ, et al. Long term effects on sexual function of five antihypertensive drugs and nutritional hygienic treatment in hypertensive men and women: treatment of mild hypertension study (TOMHS). Hypertension. 1997;29:8–14.
50. Seretti A, Chiesa A. A meta-analysis of sexual dysfunction in psychiatric patients taking antipsychotics. Int Clin Psychopharmacol. 2011;26:130–40.
51. Derby CA, Mohr BA, Goldstein I, et al. Modifiable risk factors and erectile dysfunction: can lifestyle changes modify risk? Urology. 2000;56:302–6.
52. Chung WS, Sohn JH, Park YY. Is obesity an underlying factor in erectile dysfunction? Eur Urol. 1999;36(1):68–70.
53. Manolis A, Douma M. Antihypertensive treatment and sexual dysfunction. Curr Hypertens Rep. 2012;14:285–92.
54. Douma S, Doumas M, Tsakiris A, Zamboulis C. Male and female sexual dysfunction: is hypertension an innocent bystander or a major contributor? Rev Bras Hypertens. 2007;14:139–47.
55. Doumas M, Tsakiris A, Douma S, et al. Beneficial effects of switching from beta-blockers to nebivolol on the erectile function of hypertensive patients. Asian J Androl. 2006;8:177–82.
56. Brixius K, Middeke M, Lichtental A, et al. Nitric oxide, erectile dysfunction and beta-blocker treatment (MR NOED study): benefit of nebivolol versus metoprolol in hypertensive men. Clin Exp Pharmacol Physiol. 2007;34:327–31.
57. Viigimaa M, Vlachopoulos C, Lazaridis A, Doumas M. Management of erectile dysfunction in hypertension: tips and tricks. World J Cardiol. 2014;6:908–15.
58. Viigimaa M, Lazaridis A, Doumas M. Management of sexual dysfunction in hypertensive patients. Cardiol Clin Practice. 2012;4:53–60.
59. Doumas M, Viigimaa M, Papademetriou V. Combined antihypertensive therapy and sexual dysfunction: terra incognita. Cardiology. 2013;125:232–4.
60. Svensson S, Kjellgren KI, Ahler J. Reasons for adherence with antihypertensive medication. Int J Cardiol. 2000;76:157–63.
61. Lowentritt BH, Sklar GN. The effect of erectile dysfunction on patient medication compliance. J Urol. 2004;171:231–5.
62. Esposito K, Giugliano D. Lifestyle/dietary recommendations for erectile dysfunction and female sexual dysfunction. Urol Clin North Am. 2011;38(3):293–301.
63. Doumas M, Anyfanti P, Triantafyllou A. Management of erectile dysfunction: do not forget hypertension. Arch Intern Med. 2012;192(7):597–8.
64. Baumhakel M, Schlimmer N, Kratz M, et al. Cardiovascular risk, drugs and erectile function – a systematic analysis. Int J Clin Pract. 2011;65:289–98.
65. Silvestri A, Galetta P, Cerquetani E, et al. Report of erectile dysfunction after therapy with beta-blockers is related to patient knowledge of side-effects and is reversed by placebo. Eur Heart J. 2003;24:1928–32.
66. Llisterri JL, Lozano Vidal JV, Aznar Vicente J, et al. Sexual dysfunction in hypertensive patients treated with losartan. Am J Med Sci. 2001;321(5):336–41.
67. Dusing R. Effect of the angiotensin II antagonist valsartan on sexual function in hypertensive men. Blood Press Suppl. 2003;2:29–34.
68. Doumas M, Douma S. The effect of antihypertensive drugs on erectile function: a proposed management algorithm. J Clin Hypertens (Greenwich). 2006;8(5):359–64.
69. Jackson G, Benjamin N, Jackson N, et al. Effects of sildenafil citrate on human hemodynamics. Am J Cardiol. 1999;83(5A):13C–20.

70. Montague DK, Jarow JP, Broderick GA, et al.; Erectile Dysfunction Guideline Update Panel. The management dysfunction: an AUA update. J Urol. 2005;174:230–9.
71. Lauman EO, Paik A, Rosen RC. Sexual dysfunction in the United States: prevalence and predictors. JAMA. 1999;281(6):537–44.
72. Mancia G, Fagard R, Narckiewicz K, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J. 2013;34(28):2159–219.
73. Jackson G, Rosen RC, Kloner RA, et al. The second Princeton consensus on sexual dysfunction and cardiac risk: new guidelines for sexual medicine. J Sex Med. 2006;3:28–36.
74. Vlachopoulos C, Rokkas K, Ioakeimidis N, et al. Inflammation, metabolic syndrome, erectile dysfunction, and coronary artery disease: common links. Eur Urol. 2007;52(6):1590–600.
75. Hodges LD, Kirby M, Solanky J, et al. The temporal relationship between erectile dysfunction and cardiovascular disease. Int J Clin Pract. 2007;61:2019–25.
76. Montorsi P, Ravagnani PM, Galli S, et al. Association between erectile dysfunction and coronary artery disease. Role of coronary clinical presentation and extent of coronary vessels involvement: the COBRA trial. Eur Heart J. 2006;27:2632–9.
77. Vlachopoulos C, Rokkas K, Ioakeimidis N, et al. Prevalence of asymptomatic coronary artery disease in men with vasculogenic erectile dysfunction: a prospective angiographic study. Eur Urol. 2005;48(6):996–1002.
78. Gandaglia G, Briganti A, Jacjson G, et al. A systematic review of the association between erectile dysfunction and cardiovascular disease. Eur Urol. 2014;65:968–78.
79. Inman BA, Sauver JL, Jacobson DJ, et al. A population-based, longitudinal study of erectile dysfunction and future coronary artery disease. Mayo Clin Proc. 2009;84:108–13.
80. Chew KK, Finn J, Stuckey B, et al. Erectile dysfunction as a predictor for subsequent atherosclerotic cardiovascular events: findings from a linked-data study. J Sex Med. 2010;7:192–202.
81. Riedner CE, Rhoden EL, Fuchs SC, et al. Erectile dysfunction and coronary artery disease: an association of higher risk in younger men. J Sex Med. 2011;8:1445–53.
82. Araujo AB, Travison TG, Ganz P, et al. Erectile dysfunction and mortality. J Sex Med. 2009;6(9):2445–54.
83. Greenland P, Alpert JS, Beller GA, et al. 2010 ACCF/AHA guideline foe assessment of cardiovascular risk in asymptomatic adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation. 2010;122(25):e584–636.
84. Nehra A, Jackson G, Miner M, et al. The Princeton III consensus recommendations for the management of erectile dysfunction and cardiovascular disease. Mayo Clin Proc. 2012;87(8):766–78.
85. Critchley JA, Capewell S. Mortality risk reduction associated with smoking cessation in patients with coronary heart disease: a systematic review. JAMA. 2003;290(1):86–97.
86. Thompson PD, Buchner D, Pina IL, et al. Exercise and physical activity in the prevention and treatment of atherosclerotic cardiovascular disease: a statement from the Council of Clinical Cardiology (Subcommittee on Exercise, Rehabilitation, and Prevention) and the Council on Nutrition, Physical Activity, and Metabolism (Subcommittee on Physical Activity). Circulation. 2003;107(24):3109–16.
87. Netz Y, Wu MJ, Becker BJ, et al. Physical activity and psychological well-being in advanced age: a meta-analysis of intervention studies. Psychol Aging. 2005;20(2):272–84.
88. Bassuk SS, Manson JE. Epidemiological evidence for the role of physical activity in reducing risk of type 2 diabetes and cardiovascular disease. J Appl Physiol. 2005;99(3):1193–204.
89. Mozaffarian D, Wilson PW, Kannel WB. Beyond established and novel risk factors: lifestyle risk factors for cardiovascular disease. Circulation. 2008;117(23):3031–8.
90. Cloutier M, Adamson E. The Mediterranean diet – newly revised and updated. HarperCollins Publishers, New York, New York, USA; 2004.
91. Sarwar N, Gao P, Seshasai SR, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet. 2010;375(9733):2215–22.

92. van der Velde M, Matsushita K, Coresh J, et al. Lower estimated glomerular filtration rate and higher albuminuria are associated with all-cause and cardiovascular mortality: a collaborative meta-analysis of high-risk population cohorts. Kidney Int. 2011;79(12):1341–52.
93. Matsushita K, van der Velde M, Astor BC, et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. Lancet. 2010;375(9731):2073–81.
94. Guay AT, Velasquez E, Perez JB. Characterization of patients in a medical endocrine-based center for male sexual dysfunction. Endocr Pract. 1999;5(6):314–21.
95. Blute M, Hakimian P, Kashanian J, et al. Erectile dysfunction and testosterone deficiency. Front Horm Res. 2009;37:108–22.
96. Buvat J, Montorsi F, Maggi M, et al. Hypogonadal men non-responders to the PDE-5 inhibitor tadalafil benefit from normalization of testosterone levels with a 1 % hydroalcoholic testosterone gel in the treatment of erectile dysfunction (TADTEST study). J Sex Med. 2011;8(1):284–93.
97. Ruige JB, Mahmoud AM, De Bacquer D, et al. Endogenous testosterone and cardiovascular disease in healthy men: a meta-analysis. Heart. 2011;97(11):870–5.
98. Corona G, Monami M, Boddi V, et al. Low testosterone is associated with an increased risk of MACE lethality in subjects with erectile dysfunction. J Sex Med. 2010;7(4):1557–64.
99. Grossmann M, Thomas MC, Panagiotopoulos S, et al. Low testosterone levels are common and associated with insulin resistance in male with diabetes. J Clin Endocrinol Metab. 2008;93(5):1834–40.
100. Laaksonen DE, Niskanen N, Punnonen K, et al. Sex hormones, inflammation and the metabolic syndrome: a population-based study. Eur J Endocrinol. 2003;149(6):601–8.
101. Osuna JA, Gomez-Perez R, Arata-Bellabarba G, et al. Relationship between BMI, total testosterone, sex hormone – binding-globulin, leptin, insulin and insulin resistance in obese men. Arch Androl. 2006;52(5):355–61.
102. Kapoor D, Aldred H, Clark S, et al. Clinical and biochemical assessment of hypogonadism in men with type 2 diabetes: correlations with bioavailable testosterone and visceral adiposity. Diabetes Care. 2007;30(4):911–7.
103. Corona G, Monami M, Rastrelli G, et al. Testosterone and metabolic syndrome: a meta-analysis study. J Sex Med. 2011;8(1):272–83.
104. Krishnan E, Sokolove J. Uric acid in heart disease: a new C-reactive protein? Curr Opin Rheumatol. 2011;23(2):174–7.
105. Koenig W, Khuseyinova N, Lowel H, et al. Lipoprotein-associated phospholipase A2 adds to risk prediction of incident coronary events by C-reactive protein in apparently healthy middle-aged men from the general population: results from the 14-year follow-up of a large cohort from southern Germany. Circulation. 2004;110(14):1903–8.
106. Selvin E, Steffes MW, Zhu H, et al. Glycated hemoglobin, diabetes and cardiovascular risk in diabetic adults. N Engl J Med. 2010;362(9):800–11.
107. Gazzaruso C, Giordanetti S, De Amici E, et al. Relationship between erectile dysfunction and silent myocardial ischemia in apparently uncomplicated type 2 diabetic patients. Circulation. 2004;110(1):22–6.
108. Rubinshtein R, Kuvin JT, Soffler M, et al. Assessment of endothelial function by non-invasive peripheral arterial tonometry predicts late cardiovascular adverse events. Eur Heart J. 2010;31(9):1142–8.
109. DeBusk R, Drory E, Goldstein E, et al. Management of sexual dysfunction in patients with cardiovascular disease: recommendations of The Princeton Consensus Panel. Am J Cardiol. 2000;86(2):175–81.
110. Kostis JB, Jackson G, Rosen R, et al. Sexual dysfunction and cardiac risk (the Second Princeton Consensus Conference). Am J Cardiol. 2005;96(2):313–21.
111. Dahabreh IJ, Paulus JK. Association of episodic physical and sexual activity with triggering of acute cardiac events: systematic review and meta-analysis. JAMA. 2011;305(12):1225–33.
112. Giuliano F, Jackson J, Montorsi F, et al. Safety of sildenafil citrate: review of 67 double-blind placebo-controlled trials and the postmarketing safety database. Int J Clin Pract. 2010;64(2):240–55.

113. Kloner RA, Jackson G, Hutter AM, et al. Cardiovascular safety update of tadalafil: retrospective analysis of data from placebo-controlled and open-label clinical trials of tadalafil with as needed, three times-per-week or once-a-day dosing. Am J Cardiol. 2006;97(12):1778–84.
114. Doumas M, Lazaridis A, Katsiki N, Athyros V. PDE-5 inhibitors: clinical points. Curr Drug Targets. 2015;16(5):420–6.
115. Scranton RE, Lawler E, Botteman M, et al. Effect of treating erectile dysfunction on management of systolic hypertension. Am J Cardiol. 2007;100(3):459–63.
116. Oliver JJ, Melville VP, Webb DJ. Effect of regular phosphodiesterase type 5 inhibition in hypertension. Hypertension. 2006;48(4):622–7.
117. Kimura M, Higashi Y, Hara K, et al. PDE5 inhibitor sildenafil citrate augments endothelium-dependent vasodilation in smokers. Hypertension. 2003;41(5):1106–10.
118. Gillies HC, Robin D, Jackson G. Coronary and systemic hemodynamic effects of sildenafil citrate: from basic science to clinical studies in patients with cardiovascular disease. Int J Cardiol. 2002;86(2–3):131–41.
119. Katz SD, Balidemaj K, Homma S, et al. Acute type 5-phosphodiesterase inhibition with sildenafil enhances flow mediated vasodilation in patients with chronic heart failure. J Am Coll Cardiol. 2000;36(3):845–51.
120. Esposito K, Giugliano F, Di Palo C, et al. Effect of lifestyle changes on erectile dysfunction in obese men: a randomized controlled trial. JAMA. 2004;291(24):2978–84.
121. Wing RR, Rosen RC, Fava JL, et al. Effects of weight loss intervention on erectile function in older men with type 2 diabetes in the Look AHEAD trial. J Sex Med. 2010;7(1):156–65.
122. Fisher WA, Eardley I, McCabe M, et al. Erectile dysfunction (ED) is a shared sexual concern of couples II: association of female partner characteristics with male partner ED treatment seeking and phosphodiesterase type 5 inhibitor utilization. J Sex Med. 2009;6(11):3111–24.
123. Riley A. The role of the partner in erectile dysfunction and its treatment. Int J Impot Res. 2002;14 suppl 1:S105–9.
124. Riley A. When treating erectile dysfunction, do not forget the partner. Int J Clin Pract. 2008;62(1):6–8.
125. Boydak B, Naltbangil S, Fici F, et al. A randomized comparison of the effects of nebivolol and atenolol with and without chlorothalidone on the sexual function of hypertensive men. Clin Drug Investig. 2005;25(6):409–16.
126. Baumhakel M, Schlimmer N, Bohm M, DO-IT Investigators. Effect of irbesartan on erectile function in patients with hypertension and metabolic syndrome. Int J Impot Res. 2008;20(5):493–500.
127. Bank AJ, Kelly AS, Kaiser DR. The effects of quinapril and atorvastatin on the responsiveness to sildenafil in men with erectile dysfunction. Vasc Med. 2006;11(4):251–7.
128. Saltzman EA, Guay AT, Jacobson J. Improvement in erectile function in men with organic erectile dysfunction by correction of elevated cholesterol levels: a clinical observation. J Urol. 2004;172(1):255–8.
129. Dadkhah F, Safarinejad MR, Asgari MA, et al. Atorvastatin improves the response to sildenafil in hypercholesterolemic men with erectile dysfunction not initially responsive to sildenafil. Int J Impot Res. 2010;22(1):51–60.
130. Nikolai MPJ, Both S, Liem SS, et al. Discussing sexual function in the cardiology practice. Clin Res Cardiol. 2013;102:329–36.
131. O'Donovan K. Addressing the taboos: resuming sexual activity after myocardial infarction. Br J Card Nurs. 2007;2:165–75.
132. Kokkinos P, Myers J, Kokkinos JP, et al. Exercise capacity and mortality in black and white men. Circulation. 2008;117:614–22.
133. Kokkinos P, Manolis A, Pittaras A, et al. Exercise capacity and mortality in hypertensive men with and without additional risk factors. Hypertension. 2009;53:494–9.
134. Blair SN, Kampert JB, Kohl III HW, et al. Influences of cardiorespiratory fitness and other precursors on cardiovascular disease and all-cause mortality in men and women. JAMA. 1996;276:205–10.

135. Kokkinos P, Myers J, Doumas M, et al. Exercise capacity and all-cause mortality in prehypertensive men. Am J Hypertens. 2009;22:735–41.
136. Kokkinos P, Doumas M, Myers J, et al. A graded association of exercise capacity and all-cause mortality in males with high-normal blood pressure. Blood Press. 2009;18:261–7.
137. Kokkinos P, Myers J, Faselis C, et al. Exercise capacity and mortality in older men: a 20-year follow-up study. Circulation. 2010;122:790–7.
138. Faselis C, Doumas M, Kokkinos JP, et al. Exercise capacity and progression from prehypertension to hypertension. Hypertension. 2012;60:333–8.
139. Gunby P. Snow falls; ischemic heart deaths rise. JAMA. 1979;241:1987.
140. Glass RI, Zack Jr MM. Increase in deaths from ischemic heart disease after blizzards. Lancet. 1979;8114:485–7.
141. Trichopoulos D, Katsouyanni K, Zavitsanos X, et al. Psychological stress and fatal heart attack: the Athens (1981) earthquake natural experiment. Lancet. 1983;8322:441–4.
142. DeBusk RF. Sexual activity in patients with angina. JAMA. 2003;290:3129–32.
143. Drory Y. Sexual activity and cardiovascular risk. Eur Heart J Suppl. 2002;4:H13–8.
144. Bohlen JG, Held JP, Sanderson MO, et al. Heart-rate, rate-pressure product, and oxygen uptake during four sexual activities. Arch Intern Med. 1984;144:1745–8.
145. Palmeri ST, Kostis JB, Casazza L, et al. Heart rate and blood pressure response in adult men and women during exercise and sexual activity. Am J Cardiol. 2007;100(12):1795–801.
146. Hoekstra T, Jaarsma T, Sanderman R, et al. Perceived sexual difficulties and associated factors in patients with heart failure. Am Heart J. 2012;163:246–51.
147. Hoekstra T, Lesman-Leegte E, Luttik ML, et al. Sexual problems in elderly male and female patients with heart failure. Heart. 2012;98:1647–52.
148. Dusing R. Effect of the angiotensin II antagonist valsartan on sexual function in hypertensive men. Blood Press. 2003;12:S29–34.
149. Pickering TG, Shpherd AM, Puddey I, et al. Sildenafil citrate for erectile dysfunction in men receiving multiple antihypertensive agents: a randomized controlled trial. Am J Hypertens. 2004;17:1135–42.
150. Kloner RA, Sadovsky R, Johnson EG, et al. Efficacy of tadalafil in the treatment of erectile dysfunction in hypertensive men on concomitant thiazide diuretic therapy. Int J Impot Res. 2005;17:450–4.
151. Webb DJ, Muirhead GJ, Wulff M, et al. Sildenafil citrate potentiates the hypotensive effects of nitric oxide donor drugs in male patients with stable angina. J Am Coll Cardiol. 2000;36:25–31.