Acta Cardiologica

ISSN: 0001-5385 (Print) 0373-7934 (Online) Journal homepage: https://www.tandfonline.com/loi/tacd20

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To cite this article: Camelia Cristina Diaconu, Maria Manea, Dragos Radu Marcu, Bogdan Socea, Arsenie Dan Spinu & Ovidiu Gabriel Bratu (2019): The erectile dysfunction as a marker of cardiovascular disease: a review, Acta Cardiologica, DOI: 10.1080/00015385.2019.1590498

To link to this article: https://doi.org/10.1080/00015385.2019.1590498

Published online: 06 Apr 2019.

ACTA CARDIOLOGICA
https://doi.org/10.1080/00015385.2019.1590498

REVIEW ARTICLE

The erectile dysfunction as a marker of cardiovascular disease: a review

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ABSTRACT

Cardiovascular disease (CVD) and erectile dysfunction (ED) are two conditions that often coexist. Both diseases are consequences of the systemic vascular disease, sharing common risk factors, like diabetes mellitus, arterial hypertension, smoking, obesity, dyslipidaemia. Furthermore, they share the same pathological basis, endothelial dysfunction. Symptoms of ED precede with three to five years the clinical manifestations of CVD. This period may be a window of opportunity for the early initiation of a prompt therapeutic action for cardiovascular risk factors. This article reviews the incidence and prevalence of CVD and ED, the common risk factors, the pathophysiological link between the two diseases, and the current diagnosis and management strategies of patients with CVD and ED, in order to prevent myocardial infarction, stroke or heart failure.

ARTICLE HISTORY
Received 17 April 2018
Revised 26 February 2019
Accepted 27 February 2019

KEYWORDS
Atherosclerosis; endothelial dysfunction; cardiovascular disease; coronary artery disease; erectile dysfunction

Introduction

Cardiovascular disease (CVD) and erectile dysfunction (ED) are two conditions that often coexist. Both diseases are consequences of the systemic vascular disease, sharing common risk factors, like diabetes mellitus, arterial hypertension, smoking, obesity and dyslipidaemia [1]. Furthermore, they share the same pathological basis, endothelial dysfunction.

According to the European Association of Urology, ED can be defined as the persistent inability to obtain and maintain an erection that is sufficient for achieving a satisfactory sexual performance [2]. This pathology has severe consequences on patients' quality of life, due to the low self esteem, depression and tendency of self-isolation that these patients tend to develop over time [3].

Erectile dysfunction can predict CVD, before the onset of symptoms of a cardiovascular event, being a marker for coronary artery disease [1]. Symptoms of ED precede with three to five years the clinical manifestations of the CVD [1]. This period may be a window of opportunity for the early initiation of a prompt therapeutic action for cardiovascular risk factors.

Epidemiological studies reported that both conditions, ED and CVD, have a high incidence and prevalence worldwide [1]. Several studies showed that ED has a prevalence up to 42% in patients with CVD [4,5]. Thompson et al. first reported the relationship between ED and CVD in 2005 [6]. In their study on 10,000 men, these authors demonstrated that the severity of ED correlates with the risk of CVD [6].

Pathophysiological links

Normal erectile function is related to a normal arterial flow. The average size of penile arteries, which ensure blood flow to the corpora cavernosa, is 1–1.5 mm, while the average size of coronary arteries is 2.7–4.3 mm [7]. These differences in the arteries size may explain why symptoms of ED occur years before symptoms of coronary artery disease. The penile arterial blood flow is impaired earlier than the coronary blood flow in male patients with systemic atherosclerosis. Vascular atherosclerotic infiltration has a negative impact on erectile function.

Patients with atherosclerosis, dyslipidaemia, diabetes mellitus, renal disease, coronary artery disease, arterial hypertension present endothelial dysfunction, which is an important pathophysiological link to vasculogenic ED [8]. Erectile dysfunction is a result of the

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altered endothelial function, being an early event in the process of atherosclerosis. The endothelium releases vasodilator and vasoconstrictor factors, which regulate the coagulation cascade. The endothelial cells produce prostaglandins, involved in the normal process of vasodilation, but also produce factors involved in vasoconstriction, like angiotensin II and endothelin. The normal erectile function is based on the vasodilation process, mediated by the nitric oxide. The nitric oxide is produced by endothelial nitric oxide synthase (eNOS), acting on the vascular lumen and on the surrounding muscle cells, with increased vasodilation mediated by cGMP. Vascular endothelium is the main structure involved in adequate tissue perfusion [8]. In normal physiological conditions, vascular endothelium has anticoagulant and antiaggregant functions due to the activity of anti-thrombin III, a heparin-like molecule. In atherosclerotic patients, with endothelial dysfunction, endothelial cells produce pro-coagulant and pro-aggregant factors, such as factor von Willebrand, fibronectin and thrombospondin. In endothelial dysfunction, the coagulation cascade is altered, leading to thrombus formation as the atherosclerotic process progresses [9,10].

Kaiser et al. performed a study on 30 patients with ED and found out that these patients had abnormal endothelial-dependent vasodilation of the brachial artery, compared with men without ED [11]. In several studies, patients with ED had high levels of high-sensitive C-reactive protein, which indicates chronic inflammation [12]. C-reactive protein induces chemokines, which alter the vascular endothelium [12]. Numerous studies revealed that atherosclerosis is associated with inflammation [13]. Badimon et al. showed a higher prevalence of endothelial dysfunction in patients with ED and inflammation, compared with patients with normal erectile function [10].

In the Olmstead County Study, men with ED, aged between 40 and 49 years, had a 50-fold higher risk of a cardiovascular event than men without ED [13]. ADVANCE (Action in Diabetes and Vascular Disease) trial revealed that ED may predict CVD in diabetic men [14]. Men diagnosed with diabetes mellitus present also endothelial dysfunction, as a consequence of the nitric oxide synthesis disorder and poor glycaemic control [15,16]. Type II diabetes patients have damaged endothelial cells because of the increased amount of reactive oxygen species (ROS). Benvenuti et al. showed that diabetes has a negative impact on erectile parameters in patients with coronary artery disease [17]. Also, Benvenuti et al. demonstrated that vascular occlusion plays a major role in ED in diabetic patients [17].

Arterial hypertension is associated with an increased sympathetic activity, which leads to impaired endothelial vasodilation [18]. High blood pressure is one of the causes of ED, through structural alterations of the vascular wall and reduced vasodilatory capacity [15]. Mulligan and Katz reported in their study that high blood pressure has a negative impact on erectile function [19].

Dyslipidaemia is another risk factor for endothelial dysfunction. Dyslipidaemic patients with angiographically normal coronary arteries have endothelial dysfunction, secondary to reduction of nitric oxide synthesis [20].

Endothelial dysfunction is present in obese patients. Obesity is associated with cytokines-like circulating intercellular adhesion molecules-1 (ICAM-1), E and P selectins, interleukin 6, which impair the endothelial function [21]. In obese patients, impairment of endothelium-dependent vasodilation has been demonstrated [22].

Smoking is associated with endothelial dysfunction, because of the toxic effect on endothelial cells, leading to structural and functional changes, with decreased activity of eNOS, activation of thrombotic factors and increased synthesis of ROS, with endothelial damage [20].

Clinical and paraclinical evaluation of patients with cardiovascular disease and erectile dysfunction

A number of studies showed that, in two-thirds of men, ED precedes the clinical onset of CVD with two or three years [1]. In men without ED, in the same age group, the relative risk for CVD is 4.3%, while in men with ED is 16.6% [1]. In the COBRA trial, a study of 700 subjects with CVD and abnormal erectile function, Montorsi et al. showed that ED was present in 42–57% of cases [23].

Erectile dysfunction is a predictor of early CVD [24]. Shamloul et al. reported that ED predicts 100% the ischaemic heart disease [25]. The study of Gazzaruso et al. revealed that men with ED had a higher incidence of major cardiovascular events compared with men with a normal erectile function [26].

In a study conducted by Montorsi et al., on 300 patients with ED, 49% had coronary artery disease documented by coronary angiography [23]. Sixty seven percent of patients reported that symptoms of ED preceded the symptoms of the coronary disease

by 34 months [23]. The COBRA trial revealed that the rate of ED in patients with coronary artery disease documented by angiography differs depending on atherosclerotic background, the severity of ED being related with severity of coronary artery disease [27]. The COBRA trial revealed that the severity of ED is related to the symptoms and extent of coronary artery disease [27].

Patients with ED may experience major cardiovascular events, such as acute myocardial infarction, unstable or stable angina, congestive heart failure, sudden cardiovascular death, stroke. Pectoral angina induced by effort is usually a result of coronary artery stenosis. In these patients, penile vessels are severely obstructed [24].

The Princeton Consensus classifies patients with ED and CVD into three categories: patients at low, intermediate or high risk [25]. Patients in the low risk group are men without symptoms at moderate exercise, less than three risk factors for CVD, and with normal sexual activity. Intermediate risk patients have mild, stable angina, signs and/or symptoms of heart failure NYHA class II and at least three risk factors for CVD. Patients in the high risk group present symptoms of unstable angina, uncontrolled values of blood pressure and symptoms of heart failure NYHA class III or IV; also, they present sexual dysfunction.

In diabetic patients with asymptomatic coronary artery disease, ED may be the only symptom, because these patients do not present typical episodes of angina. Erectile dysfunction may predict coronary artery disease in patients with type 2 diabetes mellitus. Gazzaruso et al. showed that the incidence of ED in diabetic patients with silent ischaemia is 33.8% and in diabetic patients without silent ischaemia is 4.7% [28]. Sexual dysfunction precedes the symptoms of coronary artery disease with 38.8 months in all patients with type 1 diabetes [29].

All patients with ED require an initial cardiovascular risk assessment, including personal and familial history (with focus on early cardiovascular comorbidities), physical exam, blood pressure measurement, fasting serum glucose, serum creatinine, total testosterone, complete serum lipids profile (total lipids, total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides), and resting electrocardiogram (ECG). Depending on the results of initial cardiovascular risk assessment, transthoracic echocardiography, stress echocardiography, treadmill exercise test, coronary angiography may be needed, for an early diagnosis of CVD and prompt therapeutic intervention. Subsequently, the risk of future cardiovascular events will be stratified according to the risk scales. Based on Framingham score, the relative risk of developing coronary artery disease in men with moderate or severe ED is 4.9% in the age range of 30–39 years and 21.1% for the age group 60–69 years [30].

The evaluation of the patients who suffer from ED should always include a detailed medical and sexual history, in order to establish the duration of sexual dysfunction, to identify its onset and to exclude factors or pathologies that frequently associate ED. Often, the evaluation of the patient's partner is useful for identifying a factor that can trigger a change in the patient's mental status and could be responsible for his sexual dysfunction. Psychometric questionnaires, such as the International Index for Erectile Function (IIEF) and the Sexual Health Inventory for Men (SHIM), are essential for the evaluation of erectile function, sexual desire, intercourse, orgasmic function, as well as for establishing the efficiency of the treatment [2]. A detailed physical examination can reveal anomalies of the genitourinary tract (penile deformities, prostatic disease), endocrine (signs of hypogonadism), vascular and neurological systems, that could explain the presence of ED.

Blood tests should include blood glucose, cholesterol and triglycerides, high-density lipoproteins, glycated haemoglobin (HbA1C) and hormonal tests (testosterone, prolactin and luteinising hormone). A urine exam should be performed, in order to detect albuminuria.

The evaluation may also include specific diagnostic tests, such as: nocturnal penile tumescence and rigidity test (electronic device placed on the penis over the night, which monitors the number of erections, their duration and the penile rigidity during the erections), intracavernous injection test (injection of different types of vasodilators agents into the base of the penis, that usually lead to penile tumescence within 10–15 minutes), penile duplex ultrasound, arteriography, dynamic infusion cavernosometry, cavernosography (in patients who suffer from vascular pathology associated with ED), psychological and psychiatric evaluation [2].

The ECG may reveal ischaemic changes. Transthoracic echocardiography can visualise myocardial kinetic anomalies and other anomalies specific to the ischaemic coronary disease.

The treadmill exercise test is an investigation used in patients with ED for early diagnosis of coronary heart disease. Montorsi et al. reported that exercise stress tests were positive in 56% of patients with ED and in 5% of those without [23]. Patients with ED

have a reduced capacity of exercise, with a reduced test duration, compared to patients without ED [31]. Patients diagnosed with ED will be symptomatic earlier during the test, with ECG changes, compared with men without ED. Furthermore, the more severe is ED, the higher the incidence of cases of coronary artery disease diagnosed during the test [24]. In patients with mild ED, the stress test can be normal [23]. The treadmill exercise test is recommended for assessing the patient's cardiovascular risk. In this context, the patient is classified in the low risk group if he has a stress test of over four minutes, with normal blood pressure, without symptoms or ECG changes and without anomalies of wall motion. The patient is at intermediate or high risk if he presents symptoms, changes on ECG or abnormal values of blood pressure. In patients with conditions that do not permit the exercise test, a dipyridamole stress test can be performed [25].

When the exercise stress test is positive, coronary angiography is recommended, as the gold standard for the diagnosis of coronary artery disease. ED correlates with the coronary stenosis severity and with the number of coronary vessels affected [31]. The quality of erection decreases with increased severity of coronary stenosis [32]. If ED is severe in men with stable angina, it means that a multi-vessel coronary disease is present [31]. There are also studies reporting that in patients with ED diagnosed with coronary artery disease at angiography, 67% had symptoms of ED before the onset of coronary symptoms [33].

Stress echocardiography is a method which can detect the coronary artery disease [23]. This method is used especially for patients with ED, without clinical or electrical changes on the treadmill exercise test.

Non-contrast computed tomography (CT) scan is a non-invasive method, which can be used to reveal coronary calcifications (mostly in elderly patients) and to calculate the coronary artery calcification score (CACS). This score is important because coronary artery calcification is associated with a higher probability to develop coronary artery disease. In patients with ED, coronary artery calcification was observed at a younger age than in those who do not present signs of ED [10].

AngioCT is a minimally invasive method, which can reveal coronary stenosis and can exclude severe coronary obstruction [33]. AngioCT can exclude severe coronary artery disease in patients with low or intermediate coronary artery calcium score. This method is used for patients with aggressive treatment strategy [34]. Non-contrast CT and angioCT are methods used in patients with high risk for coronary artery disease, but with a negative effort test [34]. The study of Chiurlia et al. revealed that multi-slice CT showed an increased prevalence of coronary artery calcification in patients with ED, compared with the same age patients without ED [10].

Treatment of patients with cardiovascular disease and erectile dysfunction

Erectile dysfunction is associated with increased all-cause mortality, mostly cardiovascular mortality. The Massachusetts Male Aging Study, a prospective-based study of 1709 men, revealed that men with ED had a 26% higher risk of mortality of all cause and 43% higher risk of death because of CVD [35]. Also, in ONTARGET/TRANSEND trial of 1549 men with CVD, ED was a mortality marker [27]. This trial showed that ED is a predictor of myocardial infarction, stroke and heart failure in patients with CVD [27]. Patients with ED and cardiovascular risk factors should be treated aggressively, according to the guidelines. Life-style changes and the management of risk factors are the first steps to prevent the complications of CVD in patients with ED. Lifestyle changes include increased physical activity and weight control, unsaturated fat diet, smoking cessation, reducing alcohol intake, maintaining normal values of blood pressure [31]. Men with an active lifestyle have a lower incidence of ED [25].

Cardiovascular risk factors, like diabetes, hypertension, dyslipidaemia, need a treatment strategy. Pharmacological treatment in patients with ED and CVD includes beta-blockers, diuretics, calcium channel blockers, statins, fibrates and angiotensin-converting enzyme inhibitors (ACEIs) [36], phosphodiesterase-5 inhibitors, intracavernous injections with alprostadil (prostaglandin E1), papaverine, phentolamine or the combination of these two agents, intraurethral or topical use of alprostadil.

Other therapeutic options for the management of ED are vacuum erection devices, constriction rings, low-intensity extracorporeal shock wave therapy (the existing data regarding its use and efficiency is limited), and penile prosthesis implantation. Despite the fact that penile prosthesis implantation represents the final solution for patients with pharmacological refractory ED, this alternative offers great results in terms of patients satisfaction and efficiency. Treatment should include antianginal drugs and antiplatelet agents [9].

In 1998, the first phosphodiesterase-5 inhibitor, sildenafil, was introduced. The success that this new

class of drugs had achieved at that moment in terms of efficiency, patients' overall satisfaction, ease of use and secondary reactions, has made it the first choice in the management of ED. In the years that followed its introduction on the pharmaceutical market, several new phosphodiesterase-5 inhibitors, with superior safety profiles, have been released (vardenafil, tadalafil, avanafil) [35]. Numerous studies have underlined the efficiency of phosphodiesterase-5 inhibitors in preventing the structural changes that occur over the years at the level of the small vessels, especially in diabetic patients [36]. This class of drugs has been shown to significantly reduce the oxidative stress and its end products, the inflammatory response and especially the interleukin-6 level, this pro-inflammatory cytokine being known for its implication in the endothelial dysfunction, as well as in the atherosclerosis process [37]. The daily use of phosphodiesterase-5 inhibitors in a small dosage has proved to be very efficient regarding the endothelial dysfunction improvement, these agents also providing encouraging results in reversing and even preventing the cavernousal structural changes that occur in diabetic patients. Therefore, it may be correct to assume that they are efficient also on other small vessels [35].

The use of phosphodiesterase-5 inhibitors is contraindicated in patients who have suffered a myocardial infarction or a stroke during the last 6 months, who had severe arrhythmias, arterial hypo or hypertension, unstable angina, severe heart failure. Concomitant use of phosphodiesterase-5 inhibitors and nitrate agents should be avoided, due to the risk of unpredictable variations of the blood pressure. The simultaneous use of these agents with antihypertensive drugs could slightly increase the hypotensive effect of the latter [2].

Statins reduce cholesterol and also have pleiotropic effects, improving the endothelial function [34]. Gazzaruso et al. suggest there is no difference in patients with or without ED regarding the treatment with ACEIs, angiotensin-receptor blockers, beta-blockers, calcium-channel blockers, diuretics, insulin or oral antidiabetic agents, in terms of indications and dosage [26].

In hypertensive patients with ED, angiotensin II receptor blockers (ARBs) can improve the erectile function [36]. Some of these drugs administered in patients with CVD may induce ED as a side effect. However, in most patients, ED is rather an effect of the underlying disease. The study conducted by Montorsi et al. revealed that, without treatment with beta-blockers, ED has a negative prognosis, although beta-blockers have an adverse effect on erectile function [23]. From beta-blockers, nebivolol was not associated with ED in clinical trials [38].

Gazzaruso et al. showed that diabetic patients with coronary artery disease proved at angiography are at high risk for major acute cardiac events [26]. Also, Gazzaruso et al. revealed that phosphodiesterase-5 inhibitors reduce cardiovascular morbidity and mortality in diabetic patients [26]. Using the Kaplan–Meier method, Do et al. showed that statin use is associated with a lower rate of major cardiovascular events in patients with ED [39]. Statins and phosphodiesterase-5 inhibitors, used in diabetic patients with ED and CVD, are associated with risk reduction of cardiovascular events. Studies revealed that in diabetic patients thiazide diuretics reduce the risk of ED [39].

Conclusions

Erectile dysfunction represents an early manifestation of subclinical vascular disease. Erectile dysfunction and CVD may be considered as manifestations of the same disease. Symptoms of ED appear usually three to five years before symptoms of coronary artery disease and may be a warning for the development of CVD. Therefore, male patients with cardiovascular risk factors should be routinely screened for ED. An aggressive therapeutic strategy addressing the major cardiovascular risk factors is justified in patients with ED, in order to prevent the complications of CVD and to improve the prognosis of these patients.

Disclosure statement

No potential conflict of interest was reported by the authors.

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References

[1] Jackson G, Boon N, Eardley I. Erectile dysfunction and coronary artery disease prediction: evidence-based guidance and consensus. Int J Clin Pract. 2010;64:831–832.

[2] European Society of Urology Guidelines; 2017; [cited 2018 Mar 12]. Available from: https://uroweb.org/guidelines/

[3] Lugoboni F, Zamboni L, Federico A, et al. Erectile dysfunction and quality of life in men receiving methadone or buprenorphine maintenance treatment. A

cross-sectional multicentre study. PLoS One. 2017;12: e0188994.
[4] Inman BA, St. Sauver JL, Jacobson DJ, et al. A population-based longitudinal study of erectile dysfunction and future coronary disease. Mayo Clin Proc. 2009;84: 108–113.
[5] Hackett GI. Erectile dysfunction, diabetes and cardiovascular risk. Br J Diabetes. 2016;16:52–57.
[6] Thompson IM, Tangen CM, Goodman PJ, et al. Erectile dysfunction and subsequent cardiovascular disease. JAMA. 2005;294:2996–3002.
[7] Bookstain JJ, Lang EV. Penile magnification pharmaco-arteriography: details of intrapenile arterial anatomy. Am J Roentgenol. 1987;148:883–888.
[8] Igari K, Kudo T, Toyofuku T, et al. The relationship between endothelial dysfunction and endothelial cell markers in peripheral arterial disease. PLoS One. 2016; 11:e0166840.
[9] Kaur R, Kaur M, Singh J. Endothelial dysfunction and platelet hyperactivity in type 2 diabetes mellitus: molecular insights and therapeutic strategies. Cardiovasc Diabetol. 2018;17:121.
[10] Badimon L, Vilahur G. Thrombosis formation on atherosclerotic lesions and plaque rupture. J Intern Med. 2014;276:618–632.
[11] Kaiser DR, Billups K, Mason C, et al. Impaired brachial artery endothelium-dependent and independent vasodilation in men with erectile dysfunction and no other clinical cardiovascular disease. J Am Coll Cardiol. 2004;43:179–184.
[12] Pasceri V, Willerson JT, Yeh ET. Direct proinflammatory effect of C-reactive protein on human endothelial cells. Circulation. 2000;102:2165–2168.
[13] Ross R. Atherosclerosis-an inflammatory disease. N Engl J Med. 1999;340:115–126.
[14] Salem S, Abdi S, Mehrsai A, et al. Erectile dysfunction severity as a risk predictor for coronary artery disease. J Sex Med. 2009;6:3425–3432.
[15] Miner M, Seftel AD, Nehra A, et al. Prognostic utility of erectile dysfunction for cardiovascular disease. Am Heart J. 2012;164:21–28.
[16] Bertoluci MC, Ce GV, da Silva AMV, et al. Endothelial dysfunction as a predictor of cardiovascular disease in type 1 diabetes. WJD. 2015;6:679–692.
[17] Benvenuti F, Boncinelli L, Vignoli GC. Male sexual impotence in diabetes mellitus: vasculogenic versus neurogenic factors. Neurourol Urodyn. 1993;12: 145–151.
[18] Taddei S, Bruno RM. Endothelial dysfunction in hypertension: achievements and open questions. J Hypertens. 2016;34:1492–1493.
[19] Mulligan T, Katz PG. Erectile failure in the aged: evaluation and treatment. J Am Geriatr Soc. 1988;36:54–62.
[20] Brunner H, Cockcroft JR, Deanfield J, et al. Endothelial function and dysfunction. Part II: association with cardiovascular risk factors and diseases. A statement by the Working Group on Endothelins and Endothelial factors of the European Society of Hypertension. J Hypertens. 2005;23:233–246.
[21] Park KH, Park WJ. Endothelial dysfunction: clinical implications in cardiovascular disease and therapeutic approaches. J Korean Med Sci. 2015;30:1213–1225.
[22] Weil BR, Westby CM, van Guilder GP, et al. Enhanced endothelin-1 system activity with overweight and obesity. Am J Physiol Heart Circ Physiol. 2011;301: H689–H695.
[23] Montorsi P, Ravagnani PM, Galli S, et al. Common grounds for erectile dysfunction and coronary artery disease. Curr Opin Urol. 2004;14:361–365.
[24] 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: 996–1002.
[25] Shamloul R, Ghanem HM, Salem A, et al. Correlation between penile duplex findings and stress electrocardiography in men with erectile dysfunction. Int J Impot Res. 2004;16:235–237.
[26] Gazzaruso C, Solente S, Pujia A, et al. Erectile dysfunction as a predictor of cardiovascular events and death in diabetic patients with angiographically proven asymptomatic coronary artery disease. JACC. 2008;21: 2040–2044.
[27] 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;27:2632–2639.
[28] 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: 22–26.
[29] Ponholzer A, Temml C, Obermayr R, et al. Is erectile dysfunction an indicator for increased risk of coronary heart disease and stroke. Eur Urol. 2005;48: 512–518.
[30] Min JK, Williams KA, Okwuosa TM, et al. Prediction of coronary heart disease by erectile dysfunction in men referred for nuclear stress testing. Arch Intern Med. 2006;166:201–206.
[31] Gandaglia G, Briganti A, Jackson G, et al. A systematic review of the association between erectile dysfunction and cardiovascular disease. Eur Urol. 2014;65: 968–978.
[32] Randrup E, Baum N, Allison F. Erectile dysfunction and cardiovascular disease. Postgrad Med. 2015; 127(2):1–7.
[33] Nieman K, Galema TW, Neefjes LA, et al. Comparison of the value of coronary calcium detection to computed tomographic angiography and exercise testing in patients with chest pain. Am J Cardiol. 2009;104: 1499–1504.
[34] Rodriguez JJ, Dashti R, Swarz ER. Linking erectile dysfunction and coronary artery disease. Int J Impot Res. 2005;17:12–18.
[35] Das A, Durrant D, Salloum FN, et al. PDE5 inhibitors as therapeutics for heart disease, diabetes and cancer. Pharmacol Ther. 2015;147:12–21.
[36] 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.

[37] Santi D, Granata AR, Guidi A, et al. Six months of daily treatment with vardenafil improves parameters of endothelial inflammation and of hypogonadism in male patients with type 2 diabetes and erectile dysfunction: a randomized, double-blind, prospective trial. Eur J Endocrinol. 2016;174:513–522.

[38] 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;8:177–182.

[39] Do C, Huyghe E, Lapeyre-Mestre M, et al. Statins and erectile dysfunction: results of a case/non-case study using the French Pharmacovigilance System Database. Drug Saf. 2009;32:591–597.