Update of the position paper on arterial hypertension and erectile dysfunction

Margus Viigimaa[a,b], Charalambos Vlachopoulos[c], Michael Doumas[d], Jacek Wolf[e], Konstantinos Imprialos[d], Dimitios Terentes-Printzios[c], Nikolaos Ioakeimidis[c], Andres Kotsar[f], Urmo Kiitam[a,b], Konstantinos Stavropoulos[d], Krzysztof Narkiewicz[e], Athanasios Manolis[g], Bojan. Jelakovic[h], Dragan Lovic[i], Reinhold Kreutz[j], Konstantinos Tsioufis[c], Giuseppe Mancia[k], for the European Society of Hypertension Working Group on Sexual Dysfunction

Sexual health is an integral part of overall health, and an active and healthy sexual life is an essential aspect of a good life quality. Cardiovascular disease and sexual health share common risk factors (arterial hypertension, diabetes mellitus, dyslipidemia, obesity, and smoking) and common mediating mechanisms (endothelial dysfunction, subclinical inflammation, and atherosclerosis). This generated a shift of thinking about the pathophysiology and subsequently the management of sexual dysfunction. The introduction of phosphodiesterase type 5 inhibitors revolutionized the management of sexual dysfunction in men. This article will focus on erectile dysfunction and its association with arterial hypertension. This update of the position paper was created by the Working Group on Sexual Dysfunction and Arterial Hypertension of the European Society of Hypertension. This working group has been very active during the last years in promoting the familiarization of hypertension specialists and related physicians with erectile dysfunction, through numerous lectures in national and international meetings, a position paper, newsletters, guidelines, and a book specifically addressing erectile dysfunction in hypertensive patients. It was noted that erectile dysfunction precedes the development of coronary artery disease. The artery size hypothesis has been proposed as a potential explanation for this observation. This hypothesis seeks to explain the differing manifestation of the same vascular condition, based on the size of the vessels. Clinical presentations of the atherosclerotic and/or endothelium disease in the penile arteries might precede the corresponding manifestations from larger arteries. Treated hypertensive patients are more likely to have sexual dysfunction compared with untreated ones, suggesting a detrimental role of antihypertensive treatment on erectile function. The occurrence of erectile dysfunction seems to be related to undesirable effects of antihypertensive drugs on the penile tissue. Available information points toward divergent effects of antihypertensive drugs on erectile function, with diuretics and beta-blockers possessing the worst profile and angiotensin receptor blockers and nebivolol the best profile.

Keywords: adherence to antihypertensive treatment, arterial hypertension, erectile dysfunction, management of sexual dysfunction, subclinical cardiovascular disease

Abbreviations: ARBs, angiotensin receptor blockers; CAD, coronary artery disease; IIEF, International Index of Erectile Function; METs, metabolic equivalents of exercise; NO, nitric oxide; OSAS, obstructive sleep apnea syndrome; PDE-5, phosphodiesterase type 5; TRT, testosterone replacement therapy

INTRODUCTION

Arterial hypertension represents an enormous public health problem as it affects more than one billion adult individuals worldwide [1]. Increased blood pressure levels result in significant vascular damage, and thus, hypertension is associated with increased rates of cardiac, cerebrovascular, and renal disease [2]. The advent of antihypertensive therapy and the subsequent lowering of blood pressure offered tremendous benefits in alleviating the deleterious effects of hypertension, by reducing drastically the rates of heart failure, stroke, myocardial infarction (MI), and chronic kidney disease [3,4].

Erectile dysfunction is currently considered a significant health issue that exerts a major impact on the life quality of affected patients and their sexual partners [5]. The introduction of phosphodiesterase-5 (PDE-5) inhibitors revolutionized the management of erectile dysfunction, offering an effective, well tolerated, and simple oral therapy. During

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[a]Centre of Cardiology, North Estonia Medical Centre, [b]Institute of Health Technologies, Tallinn University of Technology, Tallinn, Estonia, [c]1st Cardiology Department, National and Kapodestrian University of Athens, [d]2nd Propedeutic Department of Internal Medicine, Aristotle University, Thessaloniki, Greece, [e]Department of Hypertension and Diabetology, Medical University of Gdansk, Gdansk, Poland, [f]Tartu University Hospital, Tartu, Estonia, [g]Cardiology Department, Asklepeion Hospital, Athens, Greece, [h]Department of Nephrology, Hypertension, Dialysis and Transplantation, University of Zagreb, Croatia, [i]Clinic for Internal Disease Intermedica, Nis, Serbia, [j]Institut für Klinische Pharmakologie und Toxikologie, Charité - Universitätsmedizin Berlin, Germany and [k]University of Milano Bicocca, Milano, Italy

Correspondence to Margus Viigimaa, MD, PhD, Centre of Cardiology, North Estonia Medical Centre, Tallinn, Estonia, Institute of Health Technologies, Tallinn University of Technology, Tallinn, Estonia. E-mail: Margus.Viigimaa@regionaalhaigla.ee

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the last two decades, significant advances in the pathophysiology of erectile dysfunction revealed that erectile dysfunction is of vascular origin in the majority of cases, and thus its prevalence is higher in patients with overt cardiovascular disease or cardiovascular risk factors [6].

The close association between arterial hypertension and erectile dysfunction was timely recognized by the European Society of Hypertension (ESH), which included lectures, debates, and seminars on sexuality related problems in hypertensive patients in each annual meeting for over a decade. In addition, a Working Group on Sexual Dysfunction and Arterial Hypertension was formed within the ESH, which has been very active during the last years in promoting the familiarization of hypertension specialists and related physicians with erectile dysfunction, through numerous lectures in National and International meetings. Moreover, a chapter about erectile dysfunction was incorporated in the ESH guidelines from 2007 and thereafter [2,7–9], while two newsletters [10,11], a position paper [12], and a book specifically addressing erectile dysfunction in hypertensive patients [13] were published during this decade.

The aim of this manuscript is to update the position paper about erectile dysfunction and hypertension, incorporating the information that accumulated during the 8-year interval from the previous one, and also expanding in some new areas, as our knowledge and understanding of this field evolves.

PREVALENCE AND IMPORTANCE OF ARTERIAL HYPERTENSION

The global prevalence of hypertension was estimated to be approximately 1.1 billion in 2015 and is expecting to reach 1.5 billion in 2020 [1,14]. In adults, the prevalence of the disease is approximately 35–40% and is expected to increase by approximately 15% in 2025 [14]. The prevalence of hypertension is significantly increasing with age, reaching up to 60% in patients older than 60 years. The high prevalence of hypertension seems to be consistent around the world and similar between low-income, medium-income, and high-income countries [15].

Hypertension was found to be responsible for 10 million deaths over 200 million disability-adjusted life years [16]. Furthermore, it was the leading contributor to premature death worldwide. Importantly, SBP levels greater than 140 mmHg were responsible for approximately 70% of the mortality and morbidity burden. Accumulating evidence suggests an independent association between elevated blood pressure levels and cardiovascular events, such as hemorrhagic and ischemic stroke, MI, heart failure, and peripheral artery disease [17]. Increased blood pressure levels are also independently associated with increased risk for the development of chronic kidney disease [17]. Moreover, the relation between hypertension and morbidity and mortality risks has been shown in all ages and races [18–20].

PREVALENCE OF ERECTILE DYSFUNCTION

Accumulating data suggests that erectile dysfunction is highly prevalent in the general population. Although prevalence rates as high as 74% have been reported [21–31], data from large epidemiological studies around the world, the Cross-National Study, the MALES study, the Health Professionals Study, and the MATeS study, point towards an average prevalence of erectile dysfunction in the general population of around 15–20% [28,32–35,36]. Of note, sexual dysfunction seems to be more frequent in women than in men in the general population [37].

The prevalence of erectile dysfunction is even higher in the setting of arterial hypertension. The association between both diseases has been evaluated in several studies. The TOMHS study was the first large trial to report the prevalence of erectile dysfunction in patients with hypertension. It was noted that 14.4 and 4.8% of men and women, respectively, reported sexual dysfunction. It has to be noted, however, that patients with diabetes, severe hypertension, and aged over 70 years were excluded from the study, while the assessment of sexual function was performed with only one question and not with validated measures [38]. Since then, several studies have indicated that hypertension is related with even a seven-fold increased risk for erectile dysfunction [22–31, 39,40–42]; overall, erectile dysfunction seems to be almost twice as prevalent in patients with hypertension compared with individuals with normal blood pressure [43,44]. Some qualitative characteristics need to be noticed: erectile dysfunction is more severe in individuals with than without hypertension [45], and the prevalence of erectile dysfunction increases with the co-existence of other cardiovascular risk factors; the greater the number of clustering comorbidities, the higher the prevalence of erectile dysfunction [21]. Further credence comes from a sub-study of the ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) and Telmisartan Randomized AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease (TRANSCEND) trials, which included high-risk patients and reported that 52 and 58% of the study populations, respectively, had erectile dysfunction of various degrees at baseline [46]. Data from the SPRINT study indicate that the same applies for women with hypertension as well, with a 52.5% reported prevalence of sexual dysfunction in female study participants with arterial hypertension [47]. Erectile dysfunction is highly prevalent in patients with overt cardiovascular disease as well. Approximately half of patients with coronary artery disease (acute or chronic) and the vast majority of patients with heart failure suffer from erectile dysfunction [48].

IMPORTANCE OF ERECTILE DYSFUNCTION

A growing body of evidence indicates that erectile dysfunction greatly impairs the quality of life of affected individuals. erectile dysfunction clearly impairs the sexual quality of life, and patients with erectile dysfunction often feel anxious regarding the initiation of a sexual intercourse, fearing sexual intimacy and foreplay, and bother about their sexual life as a whole, lack confidence about their sexual performance, and thus have decreased satisfaction with their sexual life [49–51]. Erectile dysfunction exerts a major psychological impact on affected patients, compromising their self-esteem, their self-confidence, and their mood [52]. Of sentinel importance is the psychological sequela of

erectile dysfunction, with a significant impairment of patients' psychological well being, deconstructing the masculinity stereotype, impairing the self-esteem and the self-confidence of affected individuals, generating anxiety and triggering depressive symptoms.

Of major clinical importance is another aspect: the role of erectile dysfunction as a prognostic marker for the development of cardiovascular disease, which has been at the epicenter of the erectile dysfunction research field [53]. Prospective observational studies with long follow-up periods demonstrated that prevalent or incident erectile dysfunction is associated with significantly increased risk of cardiovascular events [54–57]. Supporting these findings, a meta-analysis of 35 744 participants found erectile dysfunction to be associated with increased risks for cardiovascular disease (48%), coronary artery disease (CAD) (46%), cerebrovascular disease (35%), and all-cause mortality (19%). A larger meta-analysis of more than 92 000 patients showed similar results. Erectile dysfunction was related with increased risks for cardiovascular events, MI, cerebrovascular events, and all-cause death by 44, 62, 39, and 25%, respectively [58,59].

DIAGNOSIS OF ERECTILE DYSFUNCTION

Medical and sexual history is crucial for the diagnosis of erectile dysfunction. In all patients diagnosed with erectile dysfunction, a thorough medical history should be assessed. This should include potential cardiovascular symptoms, other risk factors and comorbidities (diabetes, hypertension, obesity, dyslipidemia, etc.), family history of premature atherothrombotic cardiovascular disease, lifestyle factors, and administered medications. Important information might emerge from the sexual history of the patients. The presence of acute onset, intermittent course, normal erections in the morning, and history of psychosexual problems points towards psychogenic erectile dysfunction. On the contrary, organic erectile dysfunction is characterized by gradual onset, constant symptoms, and an inconsistent profile of morning erections. Furthermore, individuals with cardiovascular disease or risk factors, advanced age, or metabolic abnormalities are more likely to suffer from predominantly organic erectile dysfunction [53,60–65].

Specifically designed questionnaires are an essential part for the assessment of sexual history. The International Index of Erectile Function (IIEF) is a validated 15-item, self-evaluation questionnaire that is widely used for assessing erectile function, orgasmic function, desire, satisfaction, and overall sexual satisfaction. Alternatively, a five-item questionnaire (IIEF-5) is available for a quicker assessment of sexual activity. Six of the fifteen questions of the IIEF-15 are used for the evaluation of erectile function with a minimum score of 1 and a maximum of 5 for each question. A score of less than 25 is indicative of erectile dysfunction. In the shortened version of the five-item questionnaire, a score of 21 or less, point towards the presence of erectile dysfunction [66,67]. It should be highlighted that the IIEF-15 and especially the IIEF-5 could be used not only by andrologists and urologists but also by a wide array of other specialists, including cardiologists, internists, nephrologists, diabetologists, general practitioners, and others.

A careful clinical examination of the heart and peripheral circulation is also mandatory. Laboratory exams, such as fasting plasma glucose, urinary protein, and estimation of glomerular filtration rate, would allow for a more accurate estimation of the cardiovascular risk of the patients. In all patients, the calculation of a cardiovascular risk score (SCORE or Framingham) is necessary to evaluate the level of cardiovascular risk. Given the relation of testosterone and cardiovascular risk, the measurement of testosterone levels is recommended in all patients with organic erectile dysfunction, especially in cases where PDE-5 inhibitor therapy failed to produce sexual function improvements. In the case of asymptomatic patients free of cardiovascular disease, the determination of several cardiovascular biomarkers might offer important information for cardiovascular risk assessment. Central intima–media thickness, aortic stiffness, ankle–brachial index, albuminuria, and coronary artery calcium were associated with erectile dysfunction and shown to predict cardiovascular events. Several of them (aortic stiffness, albuminuria) were shown to have an increased predictive value for cardiovascular events in the setting of erectile dysfunction (Table 1) [53,60–65]. Finally, a penile Doppler would provide important information to identify vasculogenic erectile dysfunction [53,60–65].

TABLE 1. Prognostic biomarkers of cardiovascular disease in patients with erectile dysfunction

Biomarkers	Association with vasculogenic ED	Overall CV predictive value	Association with CV prevalence in ED	CV predictive value in ED	Response to treatment	Availability	Cost
Testosterone	+++	++	+	+	+	++++	+
hsCRP	++	+++	+	–	+	++++	+
Troponin	+	++	-	–	–	+++	+
Natriuretic peptides	++	++	+	–	–	+++	+
Fibrinogen, IL-6	+++	++	+	–	+	++	++
Carotid IMT	+++	++	+	–	+	++	++
Aortic stiffness	+++	+++	+	+	++	++	++
ABI	++	+++	+	–	–	+++	+
CCTA	++	+++	+	–	–	+	+++
CAC	++	++	+	–	–	+	+++
Endothelial dysfunction	+++	+	+	–	++	++	++
Albuminuria (micro- or macro-)	+	+++	+	+	–	++++	+
Penile color Doppler	++++	–	+	++	++	+	+++
PET of penile arteries	+++	–	–	–	–	+	++++

Association with erectile dysfunction, availability, response to treatment, prognostic value and cost of biomarkers (scored from 0 to 4+). Modified with permission from Vlachopoulos *et al.*, 2010. ABI, ankle–brachial index; CAC, coronary artery calcium; CCTA, coronary computed tomography angiography; CVD, cardiovascular disease; ED, erectile dysfunction; IL-6, interleukin-6; IMT, intima–media thickness.

MANAGEMENT OF ERECTILE DYSFUNCTION

Sexual counseling and lifestyle modification represent the cornerstone for the management of vasculogenic erectile dysfunction. However, long-term lifestyle modification is achieved in a minority of patients. Thus, the majority of patients require pharmacologic therapy for the management of vasculogenic erectile dysfunction [53,60–65]. The obvious choice is to add a PDE-5 inhibitor; however, switching administered antihypertensive therapy represents an attractive alternative that might prove beneficial [53,60–65].

Sexual counseling: such a crucial step; if we do not ask, patients may not tell us

Sexual counseling is of utmost importance to ameliorate the sexual life, and thus the quality of life of patients with erectile dysfunction and cardiovascular disease and/or risk factors.

Sexual counseling might be a long-term or short-term process and is provided either immediately after an acute event or as a part of prolonged counseling [68,69]. The process should cover several topics, such as the safety of engagement in sexual intercourse, when is the proper and safest time (after an acute cardiovascular event) for sexual re-initiation, how intense the intercourse should be, the impact of concomitant drugs or diseases on sexual function, and the efficacy and safety of PDE-5 inhibitors use [70].

Lifestyle modification

Lifestyle modification was found to significantly reduce the risk for erectile dysfunction and should accompany any pharmacological or psychological management of such patients [71].

Tobacco use should be evaluated in all patients with erectile dysfunction and recommendation for smoking cessation should be made. Smoking exposure is significantly associated with the severity of sexual function in erectile dysfunction men [72], whereas an improvement in erectile dysfunction severity is observed in a quarter of patients after smoking termination; no improvements are found in patients reinitiating smoking. Of note, ameliorating effects of smoking cessation are noted within 24–36 h after smoking termination in heavy smokers [73].

Obesity is also a risk factor for erectile dysfunction, with studies suggesting an increased prevalence of erectile dysfunction among obese patients compared with men of normal body weight [74]. However, it has been noted that underweight patients are also at higher risk for erectile dysfunction compared with individual with normal body weight. The relation of erectile dysfunction with increased body weight is multifactorial. Obese patients commonly suffer from type 2 diabetes, hypertension, and metabolic syndrome, conditions closely associated with vascular damage, and thus erectile dysfunction [75]. Of major importance, benefits in erectile function are observed with weight loss [76]. In morbidly obese men, gastric bass surgery and the following weight loss were associated with significant amelioration of sexual function [77,78]. Therefore, weight reduction is recommended in all patients with erectile dysfunction and increased BMI.

The cardioprotective effect of Mediterranean diet has been demonstrated in several studies and meta-analyses; therefore, benefits in the setting of erectile dysfunction might be expected [79]. Several nutritional supplements, such as folic acid, calcium, vitamin C and E, omega-3 fatty acids, as well as specific foods (chocolate, green tea, blueberries, pomegranate) might be of benefit, based on small studies [80,81]. Erectile dysfunction is significantly higher in patients with excessive alcohol consumption. Data from the Massachusetts Male Aging Study showed that excessive consumption increased the risk for impotence to develop from 17 to 29% [82].

Several studies have shown that exercise offers significant benefits in erectile dysfunction. In healthy individuals with erectile dysfunction, erectile function, sexual desire, intercourse satisfaction, and overall satisfaction were higher in patients who were exercising compared with sedentary individuals [83,84]. In the setting of cardiovascular risk factors or disease, physical activity was associated with significant reductions in the risk for erectile dysfunction, even up to 50% [85–90]. Data from interventional studies have also shown that implementation of exercise in patients with cardiovascular risk factors without overt cardiovascular disease resulted in reduction in erectile dysfunction reporting by up to 70% [91–94]. In addition, combination of exercise and PDE-5 inhibitors was related with greater erectile dysfunction-related benefits compared with either intervention alone [95–97].

Adherence to antihypertensive therapy

Improved adherence to antihypertensive therapy and improved blood pressure control rates are expected to be a major goal of hypertension research in the years to come. Poor medication adherence is undoubtedly multifactorial and complex. The most important factors driving discontinuation of or poor adherence to therapy are drug side effects (either real or perceived) followed by inadequate blood pressure control [98,99]. Erectile dysfunction seems to be a major contributing factor. Antihypertensive drug-associated erectile dysfunction may compromise medication adherence and the willingness to persist on lifelong treatment [100,101]. Indeed, erectile dysfunction associated with antihypertensive medications is commonly reported by patients as a reason to poor adherence to therapy [100,102]. A focus group study of patients with hypertension and their sexual partners revealed that a commonly discussed strategy to handle the detrimental effects of antihypertensive drugs on erectile function was to withdraw antihypertensive therapy or follow selective nonadherence before a sexual intercourse [103]. PDE-5 inhibitors seem to promote adherence to antihypertensive therapy, enhance blood pressure control rates, and might thus provide the opportunity to reduce cardiovascular risk in patients with hypertension and erectile dysfunction [104].

Antihypertensive treatment

Drug effects

Treated patients with hypertension are more likely to have sexual dysfunction compared with untreated ones, suggesting a detrimental role of antihypertensive treatment on erectile function [43,105–109]. The occurrence of erectile dysfunction seems to be related to undesirable effects of antihypertensive drugs on the penile tissue. It remains to be clarified whether the lower blood pressure levels impair the blood supply towards the penile vasculature, thus resulting to erectile dysfunction. It should be highlighted that treated patients with hypertension usually suffer from more severe forms of the disease and target-organ damage of greater extent. Subsequently, the high prevalence of erectile dysfunction comes with no surprise [110].

The one-million dollar question for the practicing physician is whether all antihypertensive drugs exert detrimental effects on erectile function or differences exist between the various drug categories. Accumulating evidence strongly indicates divergent effects of the various antihypertensive drugs on erectile function, pointing towards not only between-class differences but also within-class differences. Available data come from experimental, observational, and clinical studies. Collectively, available information points toward divergent effects of antihypertensive drugs on erectile function, with diuretics and beta-blockers possessing the worst profile and angiotensin receptor blockers (ARBs) and nebivolol the best profile (Table 2). Therefore, a more detailed description about the effects of ARBs and nebivolol on erectile function is provided.

Angiotensin receptor blockers

ARBs seem to present neutral properties on sexual function, whereas some studies suggest an even ameliorating role on sexual activity. The effect of ARBs on erectile function was assessed in several clinical studies. A study comparing valsartan with carvedilol showed that treatment with valsartan improved sexual function compared with baseline.

TABLE 2. The effect of different antihypertensive drug classes on erectile function

Antihypertensive drug	Effect on erectile function
ACE inhibitors	⁻/↑
ARBs	–/↑
Alpha blockers	–/↑
Beta blockers	
Nonselective	↓↓
ß1-selective (except nebivolol)	↓/-
Nebivolol	↑
Calcium channel blockers	–
Centrally acting drugs	↓↓
Diuretics	
Loop	↓/–
Potassium-sparing	
MRA	↓
Non-MRA	–
Thiazide or thiazide-like (except indapamide)	↓
Indapamide	–/↑

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist.

Carvedilol on the other hand was related with worsening of sexual activity [111]. Similar results were noted in a study comparing valsartan with atenolol. Although the beta-blocker decreased the number of sexual intercourses and testosterone levels, valsartan resulted in significant increases of sexual activity [112]. Further credence comes from a comparison study of losartan with nebivolol, the only beta-blocker that seems not to share the detrimental effects of beta-blockers on sexual function. Losartan had a neutral impact on sexual activity whereas no differences on terms of sexual activity were noted between the two actively treated groups [113]. Furthermore, co-administration of losartan with tadalafil significantly ameliorated sexual function in patients with diabetes and erectile dysfunction compared with monotherapy with either drug. Of note, patients with mild-to-moderate erectile dysfunction responded better to losartan treatment compared with patients with severe erectile dysfunction [114].

Combination treatment with felodipine and losartan was found to improve sexual desire scores in untreated men with hypertension compared with treatment with felodipine and metoprolol [115]. The same combinations of drugs were examined in women with hypertension. Sexual function was significantly improved, testosterone levels were reduced, and estradiol increased in the felodipine–irbesartan group [116]. In patients with hypertension and with or without sexual dysfunction, losartan was related with significant improvements in sexual satisfaction, frequency of sexual activity, and erectile function in patients with erectile dysfunction at baseline. On the contrary, in patients without sexual dysfunction, losartan had no effect on sexual activity. Furthermore, improvements in quality of life were reported from the majority (73.7%) of the treated patients with erectile dysfunction [117]. Lastly, treatment with irbesartan alone or in combination with hydrochlorothiazide was also related with significant reductions of erectile dysfunction prevalence and increases in intercourse satisfaction in patients with hypertension and metabolic syndrome [118].

Important data comes from a sub-analysis of the ONTARGET/ TRANSCEND trials. In high-risk patients, treatment with telmisartan and/or ramipril was not related with benefits on erectile function or prevention of new-onset erectile dysfunction. However, it has to be stated that both drugs were added on preexisting antihypertensive therapy that potentially could affect sexual activity. More specifically, calcium channel blockers, diuretics and beta-blockers were used by 39.2, 23.7, and 57.7% of patients, respectively. Therefore, RAS inhibitors seem to have a neutral effect on erectile function in high-risk patients on multiple antihypertensive treatment, including drugs that have a detrimental effect on sexual function (diuretics and beta-blockers) [46].

Nebivolol

Nebivolol is a third-generation beta-blocker with vasodilatory properties secondary to enhancement of nitric oxide bioavailability [119]. Experimental data demonstrate that nebivolol results in increases of endothelial nitric oxide synthase activation and phosphorylation, and endothelium-dependent relaxation of the corpora cavernosa. On the contrary, such benefits were not demonstrated with other

beta-blockers (metoprolol, atenolol) or calcium channel blockers (amlodipine) in the penile tissue. Similar results with that of nebivolol were noted with RAS blockers (benazepril and losartan) [119–125].

Several studies confirm the superiority of nebivolol over other beta-blockers on erectile function. An observational study of approximately 1000 middle-aged and older high-risk patients with hypertension reported that atenolol and bisoprolol were more frequently used by patients with erectile dysfunction whereas nebivolol was associated with the lowest prevalence of erectile dysfunction (odds ratio: 0.53). Of note, patients on nebivolol had higher scores in every aspect of IIEF questionnaire (indicating better erectile function) compared with patients on any other beta blocker. On the contrary, carvedilol and metoprolol were associated with the highest percentage of moderate or severe erectile dysfunction [126]. Another cross-sectional survey performed by the same team noted that among 1242 patients with erectile dysfunction and high-risk hypertension, erectile dysfunction was independently and inversely associated with nebivolol treatment (odds ratio: 0.22) in the two younger quartiles [127].

The beneficial impact of nebivolol on erectile function has been demonstrated in several randomized clinical studies. The MR NOED study compared nebivolol with metoprolol in patients with mild hypertension. Metoprolol was associated with detrimental effects on erectile function. On the contrary, nebivolol did not share the detrimental effects of metoprolol, and erectile function remained unaltered. In addition, other subscores (orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction) were significantly improved with nebivolol whereas remained unaltered with metoprolol [128]. In another study of middle-aged men with hypertension, the impact of nebivolol on sexual activity was compared with the effects of atenolol with and without chlorthalidone. The number of sexual intercourses per month was significantly decreased with atenolol and was further aggravated with the addition of the diuretic. Nebivolol on the other hand did not affect the number of sexual intercourses after 3 months of treatment [129]. A recent study of patients undergoing coronary artery bypass grafting evaluated the effect of nebivolol and metoprolol on erectile function. It was found that metoprolol was associated with significant reductions in IIEF scores whereas nebivolol use was not related with significant differences from baseline [130].

Overall, the aforementioned data indicate that nebivolol does not share the detrimental effects of other beta-blockers on erectile function and should be the preferred beta-blocker in patients who value their sexual life. Indeed, the recent ESH guidelines for the management of arterial hypertension state: 'It has no adverse effect on the risk of new-onset diabetes and a more favourable side effect profile than classical beta-blockers, including less adverse effects on sexual function' [2].

Switching antihypertensive treatment

In real life, erectile dysfunction in treated patients with hypertension is usually managed by the addition of PDE-5 inhibitors. However, handling a drug-associated side effect with the addition of another drug instead of trying to switch the culprit drug (when possible) seems at least unorthodox.

Given the divergent effects of the various antihypertensive drug categories on erectile function, the most important question for the practicing physician is whether switching from one category to another might prove of clinical benefit regarding erectile dysfunction. Several studies provide significant relevant information.

Data from large studies have confirmed the beneficial role of switching prior therapy to ARBs on erectile dysfunction. In a study of more than 2000 patients with hypertension, the number of intercourses per week was increased in the valsartan ($n = 1899$) and valsartan-hydrochlorothiazide ($n = 276$) groups, whereas it declined in controls ($n = 27$). Of major significance, switching previous antihypertensive therapy to valsartan was found to improve sexual activity [131]. In another study, approximately 3500 treatment-naive or under treatment with other blood pressure-lowering drugs patients received monotherapy with valsartan. A significant reduction of erectile dysfunction prevalence and improvements in orgasmic function and sexual desire and satisfaction were observed with valsartan compared with baseline [132]. Last, in a small study of 44 patients with hypertension, switching prior treatment with beta-blockers to nebivolol for 3 months resulted in significant improvements in erectile function scores. Importantly, in more than half of the patients experiencing improvements, erectile function was normalized [133].

However, it has to be stated that these results come from studies that are of open-design, did not include control group at all or the control group was not of sufficient size to estimate potential differences with the actively treated group.

Obstructive sleep apnea and treatment of both hypertension and erectile dysfunction

The prevalence of erectile dysfunction is high among patients with obstructive sleep apnea syndrome (OSAS) with a prevalence of more than 50%. In addition, OSAS was found to be an independent risk factor for the presence of erectile dysfunction [134]. However, it is not well established if this relation exists for all OSAS severity stages or only in the moderate and severe stages of the disease, for which a strong association with erectile dysfunction exists [135–140]. Treatment with continuous positive airway pressure (CPAP) is the gold standard option for the management of OSAS. In the setting of erectile dysfunction, various studies support a potential benefit in erectile function with CPAP treatment. In study of approximately 100 OSAS patients, CPAP treatment improved erectile function in patients with moderate and severe erectile dysfunction after 6–12 months of treatment [141]. In general, the beneficial effects of CPAP on erectile dysfunction seem to be apparent after a few days of treatment and maintained with long-term therapy [142–146]. The response rates with CPAP are ranging from 6 to 75% of the patients, with adherence to CPAP, compliance to treatment, and age being the main predictors of erectile dysfunction response to CPAP treatment [142–146]. Several studies examined the impact of CPAP on erectile dysfunction compared with PDE-5 inhibitors use. Both interventions were related with benefits in various

domains of sexual function, with PDE-5 inhibitors being superior to CPAP treatment. Combination of both, however, resulted in greater benefits compared with each intervention alone [147–151].

PDE-5 inhibitors

PDE-5 isoenzyme is distributed in an abundance of body tissues, including the corpora cavernosa of the penis. Inhibition of the enzyme leads to increases of the intracellular cGMP, prolonging the duration of its action, resulting in increased nitric oxide bioavailability, vascular smooth muscle relaxation, increased blood flow in the corpora cavernosa, and penile erection [152,153]. Currently, four PDE-5 inhibitors are approved worldwide (sildenafil, vardenafil, tadalafil, avanafil) and two agents are approved in some countries (udenafil, mirodenafil). The within-class differences in pharmacodynamic and pharmacokinetic properties, allow an individualized treatment approach based on the needs and preferences of the patient. Sildenafil citrate was the first member of this class to be approved for the treatment of erectile dysfunction with an onset of action of approximately 20 min, a half-life of 4 h, and a duration of action as long as 12 h [154–156]. Vardenafil presents similar onset and duration of action as sildenafil, whereas tadalafil is the member of the class with the longest duration of action (half-life of 17.5 h and duration of action up to 36 h) [156–159]. Avanafil on the other hand, presents the shortest onset of action and remains active for more than 6 h, presenting a favourable safety profile [160].

The efficacy of PDE-5 inhibitors in patients with hypertension has been examined in several clinical studies. Sildenafil was very efficacious in both uncontrolled and controlled randomized studies in patients with hypertension [161–164]. Vardenafil increased the scores related to vaginal insertion and maintenance of erection in 83 and 67% of patients with hypertension and erectile dysfunction compared with the 58 and 35% in the placebo group, respectively [165]. Furthermore, a post hoc analysis of sildenafil studies evaluated the effect of the drug in patients on blood pressure-lowering regimens. In approximately 1200 patients on antihypertensive medication and sildenafil or placebo, PDE-5 inhibition was related with significant improvements in erectile function. The results were similar with those of the patients not receiving antihypertensive drugs [166]. Lastly, PDE-5 inhibitors seem to be effective even when administrated with diuretics, which are known to have a detrimental role on erectile function. Among 2500 erectile dysfunction patients with hypertension from 14 randomized studies, 163 received both tadalafil and thiazide diuretics. Tadalafil was found to improve all sexual efficacy outcomes, irrespective of concomitant diuretic administration [167].

Patients with hypertension are commonly suffering from overt cardiovascular disease or other cardiovascular risk factors [168]. In patients with several cardiovascular risk factors (hypertension, dyslipidemia, diabetes mellitus, obesity, metabolic syndrome), PDE-5 inhibitors demonstrated a 60–70% response rate. These findings suggest that cardiovascular risk factors do not significantly attenuate the beneficial effect of the drugs on sexual activity [169–182]. Furthermore, sildenafil resulted in improvements of erectile function in patients with coronary artery disease [183–185] and stable heart failure [186], whereas vardenafil was also related with such benefits in patients with history of cardiovascular disease in real-life settings [187].

Most of the abovementioned studies indicated that the majority of adverse events are mild (facial flushing, headache, palpitation, rhinitis, dizziness, dyspepsia, nausea), and generally the drugs are well tolerated in individuals with hypertension. Furthermore, it seems that the incidence of the adverse events is not related with either the number of concomitant antihypertensive drugs or the class of regimen used. Thus, PDE-5 inhibitors can be safely administrated in patients with treated hypertension [169–182]. In terms of cardiovascular safety, concerns have been raised when initial reports related sildenafil use with MI [188]. Since then, several studies have demonstrated no association between the use of sildenafil and the risk for CAD or MI [189–194]. In general, serious adverse events seem to be similar among sildenafil-treated patients and placebo-users, as demonstrated by analysis of pooled data from studies of the drug [195]. Lastly, accumulating data support that vardenafil, tadalafil, and avanafil share the same safety profile with sildenafil in terms of serious adverse and cardiovascular events [196–198].

Several studies have investigated the interaction of PDE-5 inhibitors with nitrates. The co-administration of PDE-5 inhibitors and nitrates is strictly contra-indicated because of the risk of severe symptomatic hypotension; in acute situations, nitrates should not be administered until 24 h (for sildenafil, vardenafil, and avanafil) or 48 h (for tadalafil) have passed after PDE-5 inhibitor intake [199–204].

Although alpha-blockers are not considered as a first-line option for the management of patients with hypertension, uroselective alpha-blockers are widely used for the treatment of benign prostate hypertrophy. The co-administration of PDE-5 inhibitors with alpha-blockers is not contra-indicated, given that some precautions are taken. Uroselective alpha-blockers should be preferred. When initiating therapy with either drug, prior treatment should be stable for at least 1 month, and initial dosing should be half the usual, with careful up-titration. Lastly, a 6-h interval between administration of the two drugs is recommended [205–210].

Testosterone replacement therapy

Testosterone is a major component of the physiological processes of erectile function. Sexual desire, arousal, and behavior are triggered by testosterone. Studies in patients with erectile dysfunction showed that individuals with decreasing levels of sexual desire have progressively lower concentrations of the hormone [211–213]. Testosterone is also involved in the regulation of corporeal expression and activity of both endothelial and neuronal NOS and enhances NO production.

Several studies have shown a close relation between low testosterone levels and cardiovascular disease. Important data comes from a meta-analysis of 70 studies of more than 5000 and more than 7100 patients with and without cardiovascular disease, respectively. It was found that patients with cardiovascular disease had significantly lower testosterone levels compared with patients free of cardiovascular

disease [214]. Supporting evidence comes from another meta-analysis of 12 studies and more than 17 000 men. After 7.9 years, men with lower testosterone levels were found to have increased cardiovascular and all-cause mortality. In addition, a reduction in testosterone levels of 2.18 SD, was associated with a 35 and 25% increase in the risks for all-cause and cardiovascular mortality, respectively [215].

The abovementioned data point toward potential cardiovascular benefits with testosterone replacement therapy (TRT) in patients with low hormone levels. Older meta-analytic data have shown that in general, TRT seems well tolerated in terms of cardiovascular morbidity and mortality [216–218]. However, some studies during the last decade reported increased rates of cardiovascular events with TRT, casting doubts about the cardiovascular safety of this therapeutic approach [219–221]. It has to be noted that these studies have been heavily criticized, based either on small study sample and short follow-up period or concerns about the statistical methodology used [222,223]. On the other hand, some other studies revealed significant cardiovascular benefits with TRT therapy [224–226,227–230], supporting the cardiovascular safety of TRT.

In conclusion, large prospective studies examining the impact of TRT on cardiovascular morbidity and mortality in relevance with posttreatment and pretreatment testosterone levels, and different drug doses are needed to unveil the real relation of TRT and cardiovascular outcomes.

Inquiry for asymptomatic CAD

Erectile dysfunction preceded the onset of CAD by 3 years in more than 70% of patients with angiographically proven CAD [231]. In a smaller study of patients with sexual dysfunction without symptoms of CAD, approximately one-fifth and one quarter of them had silent CAD and were positive in treadmill or stress echocardiography tests, respectively [232].

The artery size hypothesis has been proposed as a potential explanation for the observed relation between erectile dysfunction and CAD. Artery size varies according to location; penile arteries are smaller (1–2 mm), compared with the coronary (3–4 mm), carotid (5–6 mm), and femoral arteries (6–8 mm). Given the smaller size of the penile vasculature, the same atherosclerotic plaque burden and endothelial dysfunction of the arterial tree have a greater impact on the blood flow of such arteries, compared with larger ones. Subsequently, clinical presentations of the atherosclerotic and/or endothelial disease in the penile arteries might precede the corresponding manifestations from larger arteries [233].

The questions with the greatest clinical significance are 'who' and 'when' to screen for the presence of CAD. First, the cause of erectile dysfunction should be determined. Psychogenic erectile dysfunction should be identified and treated properly. On the contrary, diagnosis of vasculogenic erectile dysfunction should encourage a more intensive approach for the cardiovascular management of these patients. In patients with erectile dysfunction, an assessment of their cardiovascular risk with the use of the SCORE of Framingham risk scores seems mandatory. Patients at high risk should be referred to a cardiologist and undergo a stress test to identify any subclinical CAD. In patients at low or intermediate risk, the determination of cardiovascular biomarkers would allow the identification of patients with increased cardiovascular burden (Fig. 1) [53,60–65]. Among various biomarkers, indices of arterial stiffness, testosterone levels, and microalbuminuria were shown to have a significant predictive role of cardiovascular disease in patients with erectile dysfunction. Alternative options, but with less predictive potency, include the coronary artery calcium score and carotid intima–media thickness. In patients with increased biomarkers and/or hypogonadism, a stress test would be a rational option, followed by cardiologist evaluation [65]. In general, erectile dysfunction seems to precede overt CAD by 2–5 years [53,60–65]. Therefore, diagnosis of erectile dysfunction offers an important 'time window' to determine cardiovascular biomarkers, timely recognize subclinical CAD, and intensify the management of cardiovascular risk factors [53,60–65].

GAPS IN KNOWLEDGE

Erectile dysfunction remains an under-appreciated issue in patients with arterial hypertension, and thus the jury is still out on a variety of aspects about erectile dysfunction in patients with hypertension. It seems of utmost importance to summarize the most significant gaps in knowledge, in order to boost relevant clinical research, and subsequently improve the management of patients with hypertension. There is no doubt that several other aspects need to be also clarified, but an extensive list might deviate the focus from the most significant and clinical meaningful topics.

The exact prevalence of erectile dysfunction in patients with hypertension, potential geographic, social, and cultural variations, the association of erectile dysfunction with demographic factors, comorbidities, and the various forms of target organ damage in patients with hypertension need to be further investigated. We, therefore, propose a large European epidemiological study covering the aforementioned topics, with ESH excellence centers being the core and local centers acting as satellites to capture accurate real life data.

The impact of erectile dysfunction on life quality of the individual patient with hypertension and the impact of psychological factors (anxiety, depression) on the association between erectile dysfunction and arterial hypertension are not adequately clarified. Relevant information requires the cooperation of hypertension specialists with psychiatrists and psychologists, and might be proven of great benefit for the better understanding of erectile dysfunction in patients with hypertension and subsequently for the most appropriate management of these patients.

Our knowledge about the impact of various categories of antihypertensive drugs on erectile function is currently based either in small appropriately designed clinical studies comparing only two agents or sub-analyses of large studies with inherent limitations (subgroup analysis, secondary outcomes, inappropriate methodology regarding erectile dysfunction in older studies). We, therefore, propose that a large, prospective, multicenter, randomized European study is needed to evaluate the effect of first choice drugs (ARBs, angiotensin-converting enzyme inhibitors, calcium channel blockers, diuretics, and beta blockers) along with

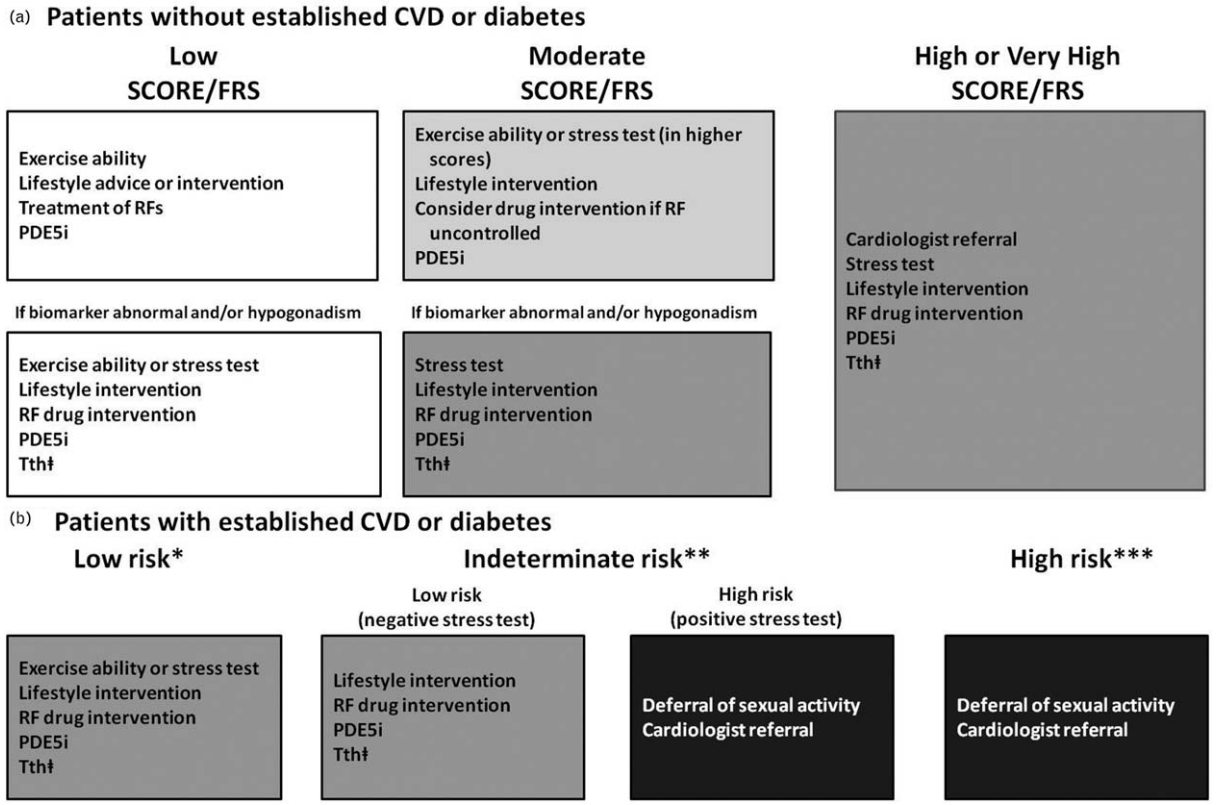

FIGURE 1 Management of erectile dysfunction patient with and without cardiovascular disease. Modified with permission from Vlachopoulos *et al.* [53]. * Low-risk patients include those with complete revascularization (e.g. via coronary artery bypass grafting, stenting, or angioplasty), patients with asymptomatic controlled hypertension, those with mild valvular disease, and patients with left ventricular dysfunction/heart failure (NYHA classes I and II) who achieved five metabolic equivalents of the task (METS) without ischemia on recent exercise testing. **Indeterminate risk patients include diabetic patients, those with mild or moderate stable angina pectoris, past myocardial infarction (2–8 weeks) without intervention awaiting exercise electrocardiography, congestive heart failure (NYHA class III), and noncardiac sequelae of atherosclerotic disease (e.g. peripheral artery disease and a history of stroke or transient ischemic attack); this patient with erectile dysfunction may require assessment for additional vascular disease using carotid intima–media thickness or ankle–brachial index and subsequent reclassification to low or high risk. ***High-risk patients include those with unstable or refractory angina pectoris, uncontrolled hypertension, congestive heart failure (NYHA class IV), recent myocardial infarction without intervention (2 weeks), high-risk arrhythmia (exercise-induced ventricular tachycardia, implanted internal cardioverter defibrillator with frequent shocks, and poorly controlled atrial fibrillation), obstructive hypertrophic cardiomyopathy with severe symptoms, and moderate-to-severe valve disease, particularly aortic stenosis. ‡Where appropriate CVD, cardiovascular disease; FRS, Framingham risk score; NYHA, New York Heart Association; PDE5i, phosphodiesterase type 5 inhibitors; RF, risk factor; Tth, testosterone therapy.

alpha blockers on erectile function. The proposed study could be of short duration (3 months are an adequate time period) and should have erectile dysfunction as primary endpoint, in order to uncover the effects of monotherapy, potential between-class and within-class differences (e.g. nebivolol versus other beta blockers), and shed light on the beta blocker debate, that is, whether the detrimental effects of beta blockers on erectile function are real or perceived as suggested by two studies [234–236].

Combination therapy is required in about two-thirds of patients with hypertension, and is currently recommended as the initial therapeutic strategy in the majority of patients with arterial hypertension in the 2018 European guidelines [2]. However, information about the impact of combination therapy on erectile function is scarce and fragmented [237]. To overcome this severe limitation, either separate clinical studies are needed to evaluate the impact of the most common combinations or the abovementioned large study can be of longer duration (12 months) and evaluate the impact of combination therapy in addition to monotherapy.

Furthermore, it is important to assess the way erectile dysfunction is managed throughout Europe and observe the efficacy of its management, that is, switching of treatment versus initiation of PDE-5 inhibitors versus alternative treatments (i.e. testosterone).

Importantly, the effect of erectile dysfunction diagnosis or management as a mean of medication adherence and optimal regulation of blood pressure could strengthen and expand the clinical role of recognition of erectile dysfunction by several different specialties.

Finally, the implementation rates of these suggestions in real life are largely unknown. erectile dysfunction in patients with hypertension seems to remain under-appreciated, under-recognized, and under-treated. Whether the intense efforts of the Working Group and the numerous lectures in International and National meetings have improved the recognition of erectile dysfunction in patients with arterial hypertension remains unclarified and needs to be measured in order to form future strategic plans and priorities.

CONCLUSION

Assessment of sexual function should be part of routine history taking by all physicians treating patients with arterial

hypertension, not only as a part of a holistic approach of the patient but in the effort to pursue significant and tangible benefits. The essential first step for the treating physician is to initiate the discussion about sexual function and function to engage in an open dialogue with the patient and the sexual partner. In this, the patient (couple) shall be informed about the magnitude of the problem and ensured that effective and safe treatment is available. Finally, a realistic plan in co-operation with the couple in terms of shared-decision making should be developed.

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Conflicts of interest

There are no conflicts of interest.

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