



# Erectile dysfunction and adherence to antihypertensive therapy: Focus on $\beta$ -blockers

Athanasios Manolis<sup>a</sup>, Michael Doumas<sup>b,\*</sup>, Claudio Ferri<sup>c</sup>, Giuseppe Mancina<sup>d</sup>

<sup>a</sup> Cardiology Department, Asklepeion Hospital, Athens, Greece

<sup>b</sup> 2nd Prop. Department of Internal Medicine, Aristotle University, 126, Vas. Olgas street, 54645 Thessaloniki, Greece

<sup>c</sup> University of L'Aquila, L'Aquila, Italy

<sup>d</sup> University of Milano-Bicocca, Italy

## ARTICLE INFO

### Keywords:

Erectile function  
Sexual function  
Erectile dysfunction  
Adherence  
 $\beta$ -blockers  
Nebivolol

## ABSTRACT

The management of arterial hypertension is very challenging in everyday clinical practice. Blood pressure control rates remain disappointingly low, despite intense efforts. Poor adherence to antihypertensive treatment is among the main causes of inadequate blood pressure control. Among the various parameters leading to poor adherence, medication adverse events seem to be the prevailing cause of treatment discontinuation. B-blockers are a class of drugs commonly used in the management of hypertension. However,  $\beta$ -blockers use has been associated with various adverse events, among which, erectile dysfunction is a prevalent one. Accumulating evidence supports the detrimental role of  $\beta$ -blockers on erectile function. Older studies have shown contradictory findings, which however may be attributed to methodological errors related with the assessment of erectile function. More recent studies, however, unveiled the negative impact of this drug category on erectile function. Nevertheless,  $\beta$ -blockers represent a class of drugs with substantial within class heterogeneity. Nebivolol presents a unique mode of action through enhanced nitric oxide bioavailability that may be associated with benefits on erectile function. Indeed, studies of nebivolol have shown improvement in erectile function, suggesting that nebivolol represents the only exception in this class of drugs in terms of erectile function.

## 1. Introduction

Arterial hypertension is a major public health issue because it affects more than 1.1 billion patients worldwide [1], and represents a very important risk factor for the development of cardiac, cerebrovascular, and chronic kidney disease as well as for dementia and premature mortality [2]. However, the awareness of the disease is limited, and only a fraction of the hypertensive patients are treated, the rate being lower in low as compared to high income countries [3]. In addition, an effective blood pressure (BP) reduction by antihypertensive treatment is rare and only a small proportion of the hypertensive population achieves BP control worldwide [4].

There is a general agreement that poor adherence to antihypertensive treatment is perhaps the most important factor preventing control of high blood pressure values [5–7]. The cardiovascular (CV) sequelae of non-adherence are of major importance, because available data consistently show that better adherence to the prescribed treatment regimen is associated with substantially lower CV risk [8], which exhibits a marked increase after treatment discontinuation [9].

While the causes of poor adherence are multiple, adverse events to the administration of antihypertensive drugs have been recognized as one of the most common reasons for drug discontinuation [5]. Erectile dysfunction (ED) is a common adverse event of several antihypertensive drug classes, including mineralocorticoid receptor antagonists, central acting drugs,  $\beta$ -blockers, and diuretics [10–14]. ED is rather common in the general population, with a prevalence ranging from 2% in young individuals (less than 40 years of age) up to 85% in patients older than 80 years [15]. In patients with risk factors, such as hypertension, diabetes mellitus, dyslipidemia, and obesity, the prevalence of ED is even higher, the same being true for patients with overt CV disease compared with those free of CV disease [15].

B-blockers are one of the major antihypertensive drug classes recommended for the management of hypertension [2]. In the 2018 European guidelines, the use of  $\beta$ -blockers is recommended for antihypertensive treatment “in combination with a diuretic or any drug from the other major classes when there is a specific indication for a  $\beta$ -blocker” [2]. Indications include angina, coronary artery disease, heart failure, and heart rate control. B-blockers are usually equivalent with

\* Corresponding author.

E-mail address: [michalisdoumas@yahoo.co.uk](mailto:michalisdoumas@yahoo.co.uk) (M. Doumas).

<https://doi.org/10.1016/j.ejim.2020.07.009>

Received 6 May 2020; Received in revised form 15 June 2020; Accepted 15 July 2020

0953-6205/ © 2020 Published by Elsevier B.V. on behalf of European Federation of Internal Medicine.

other antihypertensive classes in preventing major cardiovascular events, except for less effective prevention of stroke [2]. In the 2017 US hypertension guidelines,  $\beta$ -blockers are not recommended as first line agents unless the patient has ischaemic heart disease or heart failure [16]. Similar specific indications are mentioned in the 2018 European hypertension guidelines, which, however, include  $\beta$ -blockers among the 5 major drug classes suitable for initiation and maintenance of BP lowering treatment [2].

B-blockers are a highly heterogeneous drug class, with within-class differences in cardioselectivity, sympathomimetic activity, lipid solubility, and vasodilating capability [17]. Despite the benefits of their use for BP reduction [18],  $\beta$ -blockers administration holds the risk for several potential adverse events including bradycardia, prolongation of atrioventricular conduction time, bronchospasm, alterations of lipid and glucose metabolism, side effects related to the central nervous system, and last but not least ED [17]. The purpose of this review is to present and critically discuss the association between ED and adherence to antihypertensive therapy, with focus on  $\beta$ -blockers.

## 2. Low adherence to antihypertensive treatment. factors involved and clinical consequences

In the setting of antihypertensive treatment, low adherence is a problem of major proportions, which is indirectly emphasized by the data on BP control achieved by antihypertensive treatment in the hypertensive population. BP control has been invariably shown to be low worldwide, although with marked between-countries and continents differences. The latest figures report that in US only 25–35% of hypertensive patients achieve BP control, while in most European countries control rate is lower, and in some low income countries is minimal [3,4].

The consequences of non-adherence are highly adverse for both the patient and the healthcare system. Meta-analytic data suggest that optimal BP control is more than three times more likely in adherent compared with non-adherent individuals [19]. It has been estimated that a 10% increase in effective antihypertensive treatment by an improved adherence would prevent 14,000 deaths yearly in the United States of America [20]. Non-adherence has been associated with an increased risk of progression to hypertensive crises [21], vascular stiffening [22], left ventricular hypertrophy [23], microalbuminuria [24], myocardial infarction [7,8,25], stroke [7,8,25], heart failure [25], chronic kidney disease [26], dementia [27], hospitalizations [28] and death [29]. Daily life and work productivity [30] are also negatively affected by non-adherence along with the quality of life [31]. In terms of healthcare costs, a study carried out in 5 European countries estimated that if 70% of the patients were at least 80% adherent to their antihypertensive treatment, approximately 6500 hypertensive complications could be prevented and 36 billion euros could be saved over a decade [32].

For a long time, poor adherence has been mainly attributed to patient-related factors [5]. However, during the past few years, research efforts have highlighted the multidimensional origin of non-adherence [5]. The widely used model elaborated by the World Health Organization classifies the causes of poor adherence into 5 domains: socio-economic factors, healthcare team-related and system-related factors, condition-related factors, therapy-related factors, and patient-related factors [33]. The first domain includes age, race-ethnicity, income, unstable home, social support, health literacy, and access to health care providers [33]. The second domain centers on health care system-related factors, and more importantly, the quality of the relationship between the health care providers and the patient [33]. Lack of trust and poor communication between the patient and the treating physician are common causes of poor adherence originating from this domain [34]. Therapy-related factors include low adherence associated with multiple medications, especially when accompanied by multiple daily drug doses, and medication adverse effects [33]. On the contrary,

fewer medications, and especially fewer daily pills, are associated with better adherence and BP control [35].

Patients with limited or no side effects from drug treatment are notoriously more likely to adhere to treatment compared with patients experiencing side effects [5] which, no matter if real or perceived, are universally regarded as a major cause of poor adherence or discontinuation not only of antihypertensive treatment [36,37], but also of other CV preventive measures such as antidiabetic and lipid lowering treatments [38]. In a survey of 3394 Italian physicians following 254,192 patients, a 66% rate of discontinuation of treatment or switching to another drug was reported, a figure close to the 69% of the patients experiencing side effects. Both patients and physicians reported that inadequate BP control and drug side effects were the main reasons for switching antihypertensive treatment, while adverse effects were a main cause of poor adherence to therapy [36]. Another study of hypertensive patients in Canada found that medication side effects were the main reason for treatment discontinuation, their occurrence increasing the risk of stopping the prescribed drugs by 91% [37].

The presence of comorbidities is also an important cause of poor adherence. Multiple comorbidities, dementia, major depression, other disabilities, and alcohol abuse can adversely influence adherence [39]. Finally, several patient-related factors, such as denying the diagnosis, lack of knowledge regarding the disease-induced complications, fear for medication adverse effects, forgetfulness, and use of alternative over western medicine, may affect adherence to treatment [40,41], which can be influenced also by unexpected factors, indicating the persisting need for information on the factors responsible. This is exemplified by the data obtained in the patients of the Lombardy database in whom adherence was quantified by the availability of antihypertensive drug prescriptions over time because in Italy antihypertensive drugs are given free of charge by the National Health Service only if prescribed. Adherence was positively related to previous hospitalization for CV and renal disease. It was negatively related to hospitalization for non-CV diseases, including cancer, probably because under those circumstances patient's priorities and concern are other than CV complications. There were also unexpectedly related, however, to the density of the population where the patients lived, i.e. better in rural and worse in cities, reflecting a role of factors, perhaps of social and interpersonal nature, never considered in adherence studies [42–44].

ED is a potential adverse effect of antihypertensive treatment that majorly contributes to poor adherence to or discontinuation of treatment [45]. Withdrawal from antihypertensive therapy was reported to be a common method to handle the negative effects of antihypertensive therapy on erectile function in a study of patients with hypertension and their partners [46]. Furthermore, PDE-5 inhibitors were found to improve adherence to BP-lowering drugs. A study of non-adherent hypertensive patients showed that medication possession rates of antihypertensive and other cardiovascular drugs significantly increased after initiation of PDE-5 inhibitors therapy [47]. Among US Veterans, higher odds to initiate than terminate antihypertensive therapy were observed in patients receiving treatment for ED [48].

## 3. Erectile dysfunction

ED is defined as the persistent inability to attain and/or maintain an erection sufficient for sexual intercourse. For the diagnosis to be made, the symptoms must be present for at least 3 months, with the exception of surgical (radical prostatectomy) or trauma-induced ED, in which cases the symptoms may be present for less than 3 months. Clinical testing and partner's reports should also be used to classify the dysfunction and establish the diagnosis [49].

ED can have an organic origin, a psychogenic origin or be mixed. Organic ED emerges from vasculogenic, hormonal or neurogenic causes [14,50]. For the differential diagnosis of the ED cause, a thorough medical history, clinical examination, and the use of laboratory and imaging techniques are mandatory [14,50]. The gradual onset, constant

symptoms, and an inconsistent profile of morning erections are suggestive of organic ED. In contrast, acute onset, intermittent course, normal erections in the morning, and a history of psychosexual problems point towards psychogenic ED [14,50]. In addition, patients with metabolic abnormalities, CV disease and/or risk factors, and an advanced age are more commonly suffering from predominantly organic ED [14,50]. Testosterone levels may be helpful in differentiating hormonal from other ED causes. The use of a penile Doppler can also provide significant information for the diagnosis of vasculogenic ED [14,50]. In real life practice, the diagnosis of erectile dysfunction is usually based on specific questionnaires, which can easily and accurately detect erectile dysfunction [14].

The prevalence of ED depends on several factors such as age, presence of co-morbidities, concomitant medications, cultural, and regional beliefs. Because of the abundance of ED definitions and assessment tools for assessing the prevalence of ED over the years, the reported prevalence rates vary significantly. Patients with CV risk factors more frequently suffer from ED compared with individuals with no CV risk factors. In patients with arterial hypertension the prevalence of ED is two times higher than in normotensive individuals [12,14], and the severity of hypertension seems to be related with the severity of ED [12]. Compared with untreated hypertension, use of antihypertensive treatment is associated with significantly higher rates of ED, probably, but not exclusively, secondary to medication side effects [12]. Different drug classes differ for their relationship with ED, and combined antihypertensive treatment is associated with a worse erectile function compared with patients on monotherapy [12].

Several lines of evidence establish the impact of ED on the quality of life of the affected patients [13]. Patients with ED feel anxious about the initiation of sexual intercourse, foreplay, and intimacy, from which they tend to withdraw [51]. In addition, ED exerts a detrimental impact in their self-esteem, self-confidence and mood, thus resulting in anxiety and depressive symptoms [52]. It has also been shown that ED affects the interpersonal relationships of the affected individual, while also altering their daily activity and work performance [53]. Emotional and marital tension may also be observed in patients with sexual dysfunction [53]. On the other hand, improvements in erectile function were related with benefits in self-esteem and mood in men with ED. Importantly, use of PDE-5 inhibitors was associated with amelioration of self-confidence and esteem, sexual satisfaction, relationship status, psychological status, vitality, general health and depressive symptoms [54,55]. Of importance, ED not only affects the quality of life of the affected individual, but may also result in sexual and emotional impairment of the sexual partners [56]. In a survey of approximately 1300 women, sexual dysfunction was most commonly observed in female partners of men with ED compared with female partners of men with normal sexual function [57].

#### 4. $\beta$ -blockers

The relative degree of protection between different antihypertensive drugs is still under debate [18]; however, evidence from large scale trials shows that  $\beta$ -blockers significantly reduce hypertension-related CV outcomes when compared to placebo or other control groups with no or less intense treatment [58]. The prescription of  $\beta$ -blockers relative to other antihypertensive drug categories greatly differs by region and strongly depends on the income of the country, with low-income countries presenting higher prescription rates [4]. Likewise, the use of  $\beta$ -blockers, which is more frequent in secondary than primary prevention given their indication for post-MI and heart failure patients, differs by region according to the income of the country and other factors [59].

The use of  $\beta$ -blockers may be accompanied by several side effects, as with all antihypertensive drugs. Bradycardia and atrioventricular block, rebound hypertension and tachycardia, bronchoconstriction, alterations in lipid and glucose metabolism, increased risk for new onset diabetes mellitus, increased body weight, and nightmares represent the

most common adverse events of  $\beta$ -blockers. It has to be noticed that recent data reassure their use in patients with chronic obstructive pulmonary disease [60].

Most  $\beta$ -blocker-related problems can be attenuated by cardio-selective  $\beta$ -blockers, and this appears to be even more clearly the case for the newer generation of  $\beta$ -blockers, nebivolol and carvedilol, in particular for nebivolol which adds cardioselectivity to a vasodilatation that depends on an increased secretion of nitric oxide from the endothelial cells [61]. Because of the vasodilatation, the antihypertensive effect of vasodilator  $\beta$ -blockers is accounted by a reduction of systemic vascular resistance rather than by a reduction of cardiac output and, consequently, peripheral blood flows. Preservation of cardiac output can explain why use of these drugs is not accompanied by fatigue and restriction of exercise capacity while preservation of peripheral blood flows (in particular, skeletal muscle circulation) explains why these drugs do not increase insulin resistance and the risk of new onset diabetes.

The side effects profile of a drug bears a close relationship with discontinuation of treatment. An analysis of the Lombardy database has shown that the risk of treatment discontinuation of 445,356 newly treated patients was maximal with diuretics followed by  $\beta$ -blockers, calcium channel blockers, ACE-inhibitors, and angiotensin receptor antagonists (reflecting almost exactly the overall magnitude of their side effects) with a marked difference between the last three and the first two drug classes [42]. Similar findings have been obtained in another large cohort of newly treated patients from the same database ( $n = 433,680$ ) [43], as well as in a large meta-analysis ( $n = 935,920$ ) of studies on hypertensive patients measuring adherence by medication refill [62]. Treatment discontinuation has also been found to be high (46.7%) in 32,989 patients with heart failure initiating carvedilol, metoprolol or bisoprolol [63], with the new  $\beta$ -blocker generation performing better, however, than the old one. In a study of approximately 10,000 patients, the risk of treatment discontinuation associated with newer  $\beta$ -blockers was also significantly lower (9%) compared with atenolol, with the reduction amounting to 26% for carvedilol and 21% for nebivolol [64].

#### 5. $\beta$ -blockers and erectile dysfunction

The effects of  $\beta$ -blockers on sexual function have been addressed by experimental studies which have generated the suggestion that these drugs may have a direct detrimental effect on penile tissues. To quote some example, in one study in rats the cavernous pressure response to nerve stimulation was measured with the animals treated with clonidine, captopril or propranolol. In the clonidine and propranolol groups the cavernous pressure response was compromised, while in the captopril group only marginal alterations were observed [65]. In another experimental study in rats, the cavernous pressure response to cavernous nerve stimulation was reduced one month after propranolol treatment, which also significantly lowered cavernous cGMP concentrations compared with the untreated control group [66].

In the clinical setting, data from older clinical studies are not entirely consistent. The Medical Research Council (MRC) trial was the first large study to report impairment of sexual function with  $\beta$ -blockers. After 2 years of treatment, sexual dysfunction was reported in 22.6%, 13.2%, and 10.1% of the groups on diuretic, propranolol, and placebo, respectively [67]. The corresponding withdrawal rates were 12.6%, 6.3% and 1.3% [68]. In the Treatment of Mild Hypertension Study, the incidence of ED was higher with acebutalol than with placebo (7.9% versus 4.9%), although the difference was not statistically significant [69]. The Veterans Administration Cooperative trial reported no differences in the incidence of sexual dysfunction between patients on atenolol, hydrochlorothiazide, captopril, clonidine, diltiazem, prazosin, or placebo [70]. Another study however, found higher withdrawal rates with propranolol (13%) compared with captopril (8%) in hypertensive patients after 1 year of treatment [71]. The Trial of Antihypertensive

Interventions and Management found an incidence of ED of 11% in patients on atenolol compared with an incidence of 3% in patients receiving placebo, after 6 months of treatment [72]. Another small study assessing the impact of atenolol, trichlorothiazide, captopril, and nifedipine on sexual function, showed that the group on atenolol was the only group to report sexual-related problems [73]. It should be mentioned, however, that in these studies the ED assessment had a limited methodological accuracy. Furthermore, several investigations performed in this earlier period did not make use of designs that could minimize psychological factors and other potential confounders, an important requirement for ED studies. In 2003, Silvestri and coworkers showed that ED was extremely frequent (31.2%) in unblinded patients on  $\beta$ -blockers (atenolol 50 mg/daily) who were pre-informed of the potential ED problems associated with these drugs. The ED prevalence was about half (15.6%) in unblinded and previously uninformed patients and fell substantially (3.1%) in the group in which treatment was blinded [74].

Recent observational and clinical studies more specifically designed to assess the impact of  $\beta$ -blockers on erectile function have offered consistent and clear results. In untreated hypertensive patients administration of atenolol was accompanied by a significantly lower number of sexual intercourses versus placebo, whereas the opposite was the case with the administration of valsartan [75]. In a cross-over study, 17% of patients receiving atenolol and only 3% of those receiving lisinopril reported sexual dysfunction, the number of sexual intercourses showing a persistent decrease throughout the study with atenolol only [76]. In hypertensive patients, the incidence of sexual dysfunction was found to be four-fold greater with atenolol compared with telmisartan [77]. Combination treatment with felodipine and losartan improved the sexual desire of 218 untreated hypertensive men, an effect that was not observed when felodipine was associated with metoprolol [78]. Interestingly, despite its vasodilating properties, also carvedilol has been reported to be associated with more ED than valsartan. In one study on hypertensive patients, ED was found to be much more common (13.5% vs 0.9%) in hypertensive patients treated with carvedilol than in those treated with valsartan, an effect that was observed also in the cross-over arm of the study [79]. In another study on more than 1000 hypertensive patients at high CV risk, ED was also more frequent in patients under treatment with carvedilol; treatment with carvedilol or metoprolol was also associated with a greater prevalence of severe ED compared to patients treated with atenolol or bisoprolol [80]. The impact of ED with  $\beta$ -blocking treatment does not appear to be marginal. In 1200 high-risk hypertensives on  $\beta$ -blocker therapy more than 70% of the study participants were reported to have ED, defined as mild, moderate and severe in 38.4%, 16.8%, and 15.9% of the cases, respectively [81].

The relationship between use of  $\beta$ -blockers and an increased risk of sexual dysfunction has been also reported by a number of meta-analyses. Meta-analytic data from placebo-controlled trials have reported that in patients with arterial hypertension, coronary artery disease or heart failure,  $\beta$ -blockers were associated with a significant increase in the risk of both fatigue and sexual dysfunction (+10%) [82]. This has also been found in a meta-analysis of patients with heart failure along with an increased risk of hypotension, dizziness, and bradycardia [83]. Finally, a meta-analysis of studies assessing the impact of anti-hypertensive treatment on sexual function has shown that diuretics and  $\beta$ -blockers exert negative effects on sexual activity, while calcium channels and renin-angiotensin system blockers may have a neutral effect on erectile function [84].

## 6. Nebivolol

Nebivolol is a third-generation  $\beta$ -blocker with cardioselectivity and vasorelaxing properties. While other vasodilating  $\beta$ -blockers, such as carvedilol and labetalol, exert their vasodilatory action via blockade of  $\alpha$ -adrenergic receptors, nebivolol presents a unique vasodilating mode because it stimulates the endothelial nitric oxide synthetase, and

thus increases the nitric oxide secretion in the penile tissue [85].

Experimental data indicate a favorable effect of nebivolol on hypertension-induced structural and functional alterations in the penile tissue. A study in spontaneously hypertensive rats showed lower cavernous smooth muscle, vascular smooth muscle, and collagen III values with nebivolol, compared to amlodipine or placebo; moreover nebivolol was associated with higher endothelial nitric oxide expression in sinusoidal endothelium [86]. Another study in murine corpus cavernosum tissue found a significant increase in endothelial nitric oxide synthase activation and phosphorylation with nebivolol, compared with only a small increase with metoprolol [87]. In another mice model, nebivolol but not metoprolol improved penile endothelial function, as assessed by endothelium-dependent relaxation and reactive oxygen species production [88].

The unique effects of nebivolol on erectile function within the  $\beta$ -blocker class have been unveiled by both observational and randomized studies. In a large observational study of more than 1000 high-risk hypertensive patients treated with  $\beta$ -blockers, nebivolol was associated with a lower prevalence of ED (odds ratio: 0.27). In addition, patients on nebivolol exhibited higher IIEF scores than patients on other  $\beta$ -blockers [80]. In another observational study of 1242 hypertensive patients, ED was independently and inversely related with nebivolol administration (odds ratio: 0.22) in the two younger quartiles of study participants [81].

Data from small randomized studies point towards the same direction. A randomized study of 131 hypertensive patients revealed that the mean number of satisfactory sexual intercourses per month remained constant with nebivolol, while it decreased significantly with atenolol (with or without chlorthalidone) [89]. MR NOED was a double-blind, randomized, crossover trial comparing the effects of nebivolol and metoprolol on erectile function. It was found that the IIEF erectile function subscore was decreased by metoprolol but not nebivolol, while nebivolol (but not metoprolol) improved other secondary sexual activity scores (orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction) [90]. Another study in 119 patients with coronary artery bypass surgery found that the incidence of any grade ED was significantly lower with nebivolol than with metoprolol ( $p = 0.036$ ) [91].

Two other issues need to be noticed from the clinical point of view: the effects of switching and of combination antihypertensive therapy on erectile function. Regarding substitution of  $\beta$ -blocker therapy with nebivolol, in an open study of patients with ED while on  $\beta$ -blockers, it was found that erectile function score was improved in 69% of study participants who switched to nebivolol therapy [92]. Data on the effects of fixed combination therapy on erectile function is severely limited [93], and this aspect requires immediate attention, since fixed combination therapy is recommended by the current European guidelines [2].

The above evidence is acknowledged by both scientific societies and administrative authorities. The summary of the product characteristics produced by the European Medicinal Agency states that: "Available preclinical and clinical evidence in hypertensive patients has not shown that nebivolol has a detrimental effect on erectile function". In addition, the recent ESC/ESH guidelines for the management of arterial hypertension state for nebivolol that: "It has no adverse effect on the risk of new-onset diabetes and a more favorable side effect profile than classical  $\beta$ -blockers, including less adverse effects on sexual function" [2]. Finally, the recently published update of the ESH Working Group on sexual dysfunction highlighted the within-class differences regarding the effects of  $\beta$ -blockers on erectile function, focusing on the divergent effects of nebivolol [94]. Therefore, based on the aforementioned unique characteristics, nebivolol might be considered as a first choice agent for the management of arterial hypertension in patients who value their sexual function.



## Author contribution

Prof. Mancia and Prof. Manolis conceived the idea, Prof. Doumas and Prof. Ferri drafted the paper, and all authors critically revised the manuscript.

## Declaration of Competing Interest

Revision of the manuscript by the experts has been funded by Menarini International Operations Luxembourg S.A. [MIOL].

## Acknowledgements

Editorial assistance was provided by Edra S.p.A., Milan, Italy.

## References

- N.C.D. Risk Factor Collaboration. Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19.1 million participants. *Lancet* 2017; 389: 37–55.
- Williams B, Mancia G, Spiering W, et al. ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J* 2018;39:3021–104.
- Benjamin EJ, Muntner P, Alonso A, et al. Heart disease and stroke statistics-2019 update: a report from the American heart association. *Circulation* 2019;139:e56–528.
- Chow CK, Teo KK, Rangarajan S, et al. Prevalence, awareness, treatment, and control of hypertension in rural and urban communities in high-, middle-, and low-income countries. *JAMA* 2013;310:959–68.
- Burnier M, Egan BM. Adherence in hypertension. *Circ Res* 2019;124:1124–40.
- Krousel-Wood M, Joyce C, et al. Predictors of decline in medication adherence: results from the cohort study of medication adherence among older adults. *Hypertension* 2011;58:804–10.
- Mazzaglia G, Ambrosioni E, Alacqua M, et al. Adherence to antihypertensive medications and cardiovascular morbidity among newly diagnosed hypertensive patients. *Circulation* 2009;120:1598–605.
- Corrao G, Parodi A, Nicotra F, et al. Better compliance to antihypertensive medications reduces cardiovascular risk. *J Hypertens* 2011;29:610–8.
- Burnier M, Wuerzner G, Struijker-Boudier H, et al. Measuring, analyzing, and managing drug adherence in resistant hypertension. *Hypertension* 2013;62:218–25.
- Imprialos KP, Stavropoulos K, Doumas M, et al. Sexual Dysfunction, Cardiovascular Risk and Effects of Pharmacotherapy. *Curr Vasc Pharmacol* 2018;165:130–42.
- Manolis A, Doumas M. Antihypertensive treatment and sexual dysfunction. *Curr Hypertens Rep* 2012;14:285–92.
- 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;27:469–77.
- Manolis A, Doumas M. Sexual dysfunction: the 'prima ballerina' of hypertension-related quality-of-life complications. *J Hypertens* 2008;26:2074–84.
- Viigimaa M, Vlachopoulos C, Doumas M, editors. Erectile dysfunction in hypertension and cardiovascular disease. Switzerland: Springer International Publishing; 2015. p. 1–249.
- Doumas M., Boutari C. Erectile dysfunction: definition and size of the problem. In: ESC cardiomed (3 ed. edited by camm AJ, lüscher TF, maurer g, SerruysPW. 2018.
- Whelton PK, Carey RM, Aronow WS, et al. ACC/AHA/AAPA/ ABC/ACPM/ AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults. *Hypertension* 2018;71:e13–115.
- de Vale GT, Ceron CS, Gonzaga NA, et al. Three generations of beta-blockers: history, class differences and clinical applicability. *Curr Hypertens Rev* 2019;15:22–31.
- Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomized trials in the context of expectations from prospective epidemiological studies. *BMJ* 2009;338:b1665.
- DiMatteo MR, Giordani PJ, Lepper HS, et al. Patient adherence and medical treatment outcomes: a meta-analysis. *Med Care* 2002;40:794–811.
- Farley TA, Dalal MA, Mostashari F, et al. Deaths preventable in the U.S. by improvements in use of clinical preventive services. *Am J Prev Med* 2010;38:600–9.
- Saguner AM, Dür S, Perrig M, et al. Risk factors promoting hypertensive crises: evidence from a longitudinal study. *Am J Hypertens* 2010;23:775–80.
- Berni A, Ciani E, Cecioni I, et al. Adherence to antihypertensive therapy affects ambulatory arterial stiffness index. *Eur J Intern Med* 2011;22:93–8.
- Bruno A, Brooks DD, Abrams TA, et al. Left ventricular hypertrophy in acute stroke patients with known hypertension. *Clin Exp Hypertens* 2017;39:502–4.
- Kim YS, Kim HS, Oh HY, et al. Prevalence of microalbuminuria and associated risk factors among adult Korean hypertensive patients in a primary care setting. *Hypertens Res* 2013;36:807–23.
- Chowdhury R, Khan H, Heydon E, et al. Adherence to cardiovascular therapy: a meta-analysis of prevalence and clinical consequences. *Eur Heart J* 2013;34:2940–8.
- Roy L, White-Guay B, Dorais M, et al. Adherence to antihypertensive agents improves risk reduction of end-stage renal disease. *Kidney Int* 2013;84:570–7.
- Poon IO. Effects of antihypertensive drug treatment on the risk of dementia and cognitive impairment. *Pharmacotherapy* 2008;28:366–75.
- Pittman DG, Tao Z, Chen W, et al. Antihypertensive medication adherence and subsequent healthcare utilization and costs. *Am J Manag Care* 2010;16:568–76.
- Cherry SB, Benner JS, Hussein MA, et al. The clinical and economic burden of nonadherence with antihypertensive and lipid lowering therapy in hypertensive patients. *Value Health* 2009;12:489–97.
- Wagner S, Lau H, Frech-Tamas F, Gupta S. Impact of medication adherence on work productivity in hypertension. *Am J Pharm Benefits* 2012;4:e88–96.
- Wiklund I, Halling K, Rydén-Bergsten T, et al. Does lowering the blood pressure improve the mood? Quality-of-life results from the Hypertension Optimal Treatment (HOT) study. *Blood Press* 1997;6:357–64.
- Mennini FS, Marcellusi A, von der Schulenburg JM, et al. Cost of poor adherence to anti-hypertensive therapy in five European countries. *Eur J Health Econ* 2015;16:65–72.
- World Health Organization. Adherence to long term therapies: evidence for action; geneva: world health organization, 2003.
- Gellad WF, Grenard JL, Marcum ZA. A systematic review of barriers to medication adherence in the elderly: looking beyond cost and regimen complexity. *Am J Geriatr Pharmacother* 2011;9:11–23.
- Egan BM, Bandyopadhyay D, Shaftman SR, et al. Initial monotherapy and combination therapy and hypertension control the first year. *Hypertension* 2012;59:1124–31.
- Ambrosioni E, Leonetti G, Pessina AC, et al. Patterns of hypertension management in Italy: results of a pharmaco-epidemiological survey on antihypertensive therapy. scientific committee of the Italian pharmaco-epidemiological survey on antihypertensive therapy. *J Hypertens* 2000;18:1691–9.
- Gregoire JP, Moisan J, Guibert R, et al. Determinants of discontinuation of new courses of antihypertensive medications. *J Clin Epidemiol* 2002;55:728–35.
- Corrao G, Zambon A, Parodi A, et al. Incidence of cardiovascular events in Italian patients with early discontinuations of antihypertensive, lipid-lowering, and anti-diabetic treatments. *Am J Hypertens* 2012;25:549–55.
- Mulhem E, Lick D, Varughese J, et al. Adherence to medications after hospital discharge in the elderly. *Int J Family Med* 2013;2013:901845.
- Bokhour BG, Kressin NR. What is in a name? How biomedical language may derail patient understanding of hypertension. *Circ Cardiovasc Qual Outcomes* 2015;8:452–4.
- Morrison VL, Holmes EA, Parveen S, et al. Predictors of self-reported adherence to antihypertensive medicines: a multinational, cross-sectional survey. *Value Health* 2015;18:206–16.
- Corrao G, Zambon A, Parodi A, et al. Discontinuation of and changes in drug therapy for hypertension among newly-treated patients: a population-based study in Italy. *J Hypertens* 2008;26:819–24.
- Corrao G, Parodi A, Zambon A, et al. Reduced discontinuation of antihypertensive treatment by two-drug combination as first step. evidence from daily life practice. *J Hypertens* 2010;28:1584–90.
- Mancia G, Rea F, Corrao G, et al. Two-drug combinations as first-step anti-hypertensive treatment. *Circ Res* 2019;124:1113–23.
- Rosen RC. Sexual dysfunction as an obstacle to compliance with antihypertensive therapy. *Blood Press Suppl* 1997;1:47–51.
- Voils CI, Sandelowski M, Dahm P, et al. Selective adherence to antihypertensive medications as a patient-driven means to preserving sexual potency. *Patient Prefer Adherence* 2008;2:201–6.
- McLaughlin T, Harnett J, Burhani S, et al. Evaluation of erectile dysfunction therapy in patients previously nonadherent to long-term medications: a retrospective analysis of prescription claims. *Am J Ther* 2005;12:605–11.
- Scranton RE, Lawler E, Botteman M, Chittet al. Effect of treating erectile dysfunction on management of systolic hypertension. *Am J Cardiol* 2007;100:459–63.
- NIH Consensus Conference. Impotence. NIH Consensus Development Panel on Impotence. *JAMA* 1993;270:83–90.
- Vlachopoulos C, Jackson G, Stefanadis C, et al. Erectile dysfunction in the cardiovascular patient. *Eur Heart J* 2013;34:2034–46.
- Sánchez-Cruz JJ, Cabrera-León A, Martín-Morales A, et al. Male erectile dysfunction and health-related quality of life. *Eur Urol* 2003;44:245–53.
- Intili H, Nier D. Self-esteem and depression in men who present with erectile dysfunction. *Urol Nurs* 1998;18:185–7.
- Jenler M, Moon T, Brannan W, et al. The effect of age, ethnicity and geographical location on impotence and quality of life. *Br J Urol* 1995;75:651–5.
- Althof SE, O'Leary MP, Cappelleri JC, et al. Sildenafil citrate improves self-esteem, confidence, and relationships in men with erectile dysfunction: results from an international, multi-center, double-blind, placebo-controlled trial. *J Sex Med* 2006;3:521–9.
- Althof SE, Berner MM, Goldstein I, et al. Interrelationship of sildenafil treatment effects on the physiological and psychosocial aspects of erectile dysfunction of mixed or organic etiology. *J Sex Med* 2010;7:3170–8.
- Fisher WA, Rosen RC, Eardley I, et al. Sexual experience of female partners of men with erectile dysfunction: the female experience of men's attitudes to life events and sexuality (FEMALES) study. *J Sex Med* 2005;2:675–84.
- Fugl-Meyer KS. Erectile problems: the perspective of the female. *Scan J Urol Nephrol* 1998;32:12–8.
- Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure lowering on outcome incidence in hypertension: 4. Effects of various classes of antihypertensive drugs—overview and meta-analyses. *J Hypertens* 2015;33:195–211.
- Yusuf S, Islam S, Chow CK, et al. Use of secondary prevention drugs for

- cardiovascular disease in the community in high-income, middle-income, and low-income countries (The PURE Study): a prospective epidemiological survey. *Lancet* 2011;378:1231–43.
- [60] Corrao S, Brunori G, Lupo U, et al. Effectiveness and safety of concurrent beta-blockers and inhaled bronchodilators in COPD with cardiovascular comorbidities. *Eur Resp Rev* 2017;26. pii:160123.
- [61] Manolis A, Doumas M. Erectile function in cardiovascular disease and hypertension: the role of nebivolol. *J Hypertens Open Access* 2016;5:2.
- [62] Kronish IM, Woodward M, Sergie Z, et al. Meta-analysis: impact of drug class on adherence to antihypertensives. *Circulation* 2011;123:1611–21.
- [63] Girouard C, Grégoire JP, Poirier P, et al. Factors associated with beta-blocker initiation and discontinuation in a population-based cohort of seniors newly diagnosed with heart failure. *Patient Prefer Adherence* 2016;10:1811–21.
- [64] Choi YJ, Ah YM, Kong J. Implication of different initial beta blockers on treatment persistence: atenolol vs new-generation beta blocker, a population-based study. *Cardiovasc Ther* 2016;34:268–75.
- [65] Srilatha B, Adaikan PG, Arulkumaran S, et al. Sexual dysfunction related to anti-hypertensive agents: results from the animal model. *Int J Impot Res* 1999;11:107–13.
- [66] Zhou ZY, Yang ZH, Wang XH, et al. Increased expression of insulin-like growth factor-binding protein-3 is implicated in erectile dysfunction in two-kidney one-clip hypertensive rats after propranolol treatment. *Asian J Androl* 2011;13:851–5.
- [67] MRC Working Party on Mild to Moderate Hypertension. Adverse reactions to bendroflumazide and propranolol for the treatment of mild hypertension. report of medical research council working party on mild to moderate hypertension. *Lancet* 1981;5:39–43. 318.
- [68] Medical Research Council Working Party. MRC trial of treatment of mild hypertension: principal results. *BMJ* 1985;291:97–104.
- [69] Grimm 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(1 Pt 1):8–14.
- [70] Materson BJ, Reda DJ, Cushman WC. Single-drug therapy for hypertension in men. a comparison of six antihypertensive agents with placebo: the department of veterans affairs cooperative study group on antihypertensive agents. *N Engl J Med* 1993;328:914–21.
- [71] Croog SH, Levine S, Testa MA, et al. The effects of antihypertensive therapy on the quality of life. *N Engl J Med* 1986;314:1657–64.
- [72] Wassertheil-Smolter S, Blafox MD, Oberman A, et al. Effect of antihypertensives on sexual function and quality of life: the TAIM study. *Ann Intern Med* 1991;114:613–20.
- [73] Suzuki H, Tominaga T, Kumagai H, et al. Effects of first-line antihypertensive agents on sexual function and sex hormones. *J Hypertens* 1988;6:S649–51.
- [74] 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.
- [75] 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.
- [76] Fogari R, Zoppi A, Corradi L, et al. Sexual function in hypertensive males treated with lisinopril or atenolol: a crossover study. *Am J Hypertens* 1998;11:1244–7.
- [77] Freytag F, Schelling A, Meinicke T, et al. Comparison of 26-week efficacy and tolerability of telmisartan ad atenolol, in combination with hydrochlorothiazide as required, in the treatment of mild to moderate hypertension: a randomized, multicenter study. *Clin Ther* 2001;23:108–23.
- [78] Yang L, Yu J, Ma R, et al. The effect of combined antihypertensive treatment (felodipine with either irbesartan or metoprolol) on erectile function: a randomized controlled trial. *Cardiology* 2013;125:235–41.
- [79] 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.
- [80] Cordero A, Bertomeu-Martínez V, Mazon P, et al. Erectile dysfunction in high-risk hypertensive patients treated with beta-blockers agents. *Cardiovasc Ther* 2010;28:15–22.
- [81] Cordero A, Bertomeu-Martínez V, Mazón P, et al. Erectile dysfunction may improve by blood pressure control in patients with high-risk hypertension. *Postgrad Med* 2010;122:51–6.
- [82] Ko DT, Hebert PR, Coffey CS, et al. Beta-blocker therapy and symptoms of depression, fatigue, and sexual dysfunction. *JAMA* 2002;288:351–7.
- [83] Ko DT, Hebert PR, Coffey CS, et al. Adverse effects of beta-blocker therapy for patients with heart failure: a quantitative overview of randomized trials. *Arch Intern Med* 2004;164:1389–94.
- [84] Baumhake M, Schimmer N, Kratz M, et al. Cardiovascular risk, drugs and erectile function – a systematic analysis. *Int J Clin Pract* 2011;65:289–98.
- [85] Gao Y, Vanhoutte PM. Nebivolol: an endothelium-friendly selective b1-adrenoceptor blocker. *J Cardiovasc Pharmacol* 2012;59:16–21.
- [86] Toblli JE, Cao G, Casas G, et al. In vivo and in vitro effects of nebivolol on penile structures in hypertensive rats. *Am J Hypertens* 2006;19:1226–32.
- [87] Reidenbach C, Schwinger RH, Steinnitz D, et al. Nebivolol induces eNOS activation and NO-liberation in murine corpus cavernosum. *Life Sci* 2007;80:2421–7.
- [88] Baumhake M, Schlimmer N, Buyukafsar, Nebivolol, but not metoprolol, improves endothelial function of the corpus cavernosum in apolipoprotein E-knockout mice. *J Pharmacol Exp Ther* 2008;325:818–23.
- [89] Boydak B, Nalbantgil S, Fici F, et al. A randomized comparison of the effects of nebivolol and atenolol with and without chlorthalidone on the sexual function of hypertensive men. *Clin Drug Invest* 2005;25:409–16.
- [90] Brixius K, Middeke M, Lichtenthal 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.
- [91] Gur O, Gurkan S, Yumun G, et al. The comparison of the effects of nebivolol and metoprolol on erectile dysfunction in the cases with coronary artery bypass surgery. *Ann Thorac Cardiovasc Surg* 2017;23:91–5.
- [92] 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.
- [93] Doumas M, Viigimaa M, Papademetriou V. Combined antihypertensive therapy and sexual dysfunction: terra incognita. *Cardiology* 2013;125:232–4.
- [94] Viigimaa M., Vlachopoulos C., Doumas M., et al. European society of hypertension working group on sexual dysfunction. Update of the position paper on arterial hypertension and erectile dysfunction. *J Hypertens* 2020; 10.1097/HJH.0000000000002382.