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## Management of erectile dysfunction in hypertension: Tips and tricks

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**Core tip:** The prevalence of erectile dysfunction is approximately 2-fold higher in hypertensive patients compared to normotensive individuals. However, erectile dysfunction remains under-reported, under-recognized, and under-treated in hypertensive patients. Lifestyle modification should be the mainstay of treating erectile dysfunction in patients with untreated hypertension. Switching antihypertensive therapy should be considered in treated hypertensive patients, unless administered drugs are absolutely indicated for the individual patient. Otherwise, phosphodiesterase-5 inhibitors should be used, since they are both effective and safe in hypertensive patients. Finally, erectile dysfunction offers the opportunity to recognize asymptomatic cardiovascular disease with obvious benefits for cardiovascular event prevention.

### Abstract

Arterial hypertension is a major risk factor for cardiovascular disease and affects approximately one third of the adult population worldwide. The vascular origin of erectile dysfunction is now widely accepted in the vast majority of cases. Erectile dysfunction is frequently encountered in patients with arterial hypertension and greatly affects their quality of life of hypertensive patients and their sexual partners. Therefore, the management of erectile dysfunction in hypertensive patients is of paramount importance. Unfortunately, erectile dysfunction remains under-reported, under-recognized, and under-treated in hypertensive patients, mainly due to the lack of familiarity with this clinical entity by treating physicians. This review aims to discuss the more frequent problems in the management of hypertensive patients with erectile dysfunction and propose ways to overcome these problems in everyday clinical practice.

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### INTRODUCTION

Undoubtedly, heart disease is and will continue to be one of the major health problems of modern society. Approximately one death every forty seconds occurs due to cardiovascular (CV) disease in the United States alone and arterial hypertension is one of the greatest culprits for it<sup>[1]</sup>. Considering the fact that around 25% of the global

population suffer from arterial hypertension, predicted to reach 1.5 billion people in the foreseeable future, it is easily deduced that a respectful part of the general population is under major and constant CV risk<sup>[2,3]</sup>.

In addition, those patients experience a lower health quality and exhibit lower scores in the widely acceptable quality of life parameters. Sexual dysfunction, an acknowledged condition frequently co-existing with hypertension, contributes significantly to the impaired health quality of both hypertensive patients and their sexual partners<sup>[4,5]</sup>.

An equally valuable observation though, is the fact that sexual dysfunction could indeed indicate asymptomatic CV disease. A solid amount of evidence accumulated over the last years has pointed out towards that trend moving, hesitatingly though, sexual dysfunction in the surface of scientific interest. As such, commonly under-reported, under-recognized and under-treated, sexual dysfunction could indeed play its role in cardiovascular risk assessment and stratification.

Despite physician's inexperience and patient's reluctance to disclose sexual dysfunction problems, attempts to estimate the magnitude of this clinical condition have predicted that over 150 million men worldwide experience some degree of erectile dysfunction. Several studies have demonstrated a wide range regarding the prevalence of erectile dysfunction, which is even higher in patients with essential hypertension where the relative risk is approximately two times higher than in normotensive individuals<sup>[6-11]</sup>. The etiology can be found in the structural and functional abnormalities of the penile arteries induced by high blood pressure. Smooth muscle hypertrophy, stenotic lesions due to atherosclerosis and impaired blood flow are among the prominent structural alterations whereas endothelial dysfunction and the defective nitric oxide-induced vasodilatory mechanism belong to the main functional abnormalities induced by increased blood pressure<sup>[12,13]</sup>. As a matter of fact, sexual dysfunction is encountered more frequently that it is indeed believed underlining the need for a more proper and concrete assessment.

This review aims to discuss the more frequent problems in the management of hypertensive patients with erectile dysfunction and propose ways to overcome these problems in everyday clinical practice.

## UNTREATED HYPERTENSIVE PATIENTS

Vasculogenic sexual dysfunction is the main cause of sexual dysfunction in untreated hypertensive patients. However, due to the complex etiologic and pathophysiologic nature of sexual dysfunction, exclusion of concomitant diseases and drugs should be the initial step when approaching a hypertensive patient with this clinical condition that is not receiving any antihypertensive medication. Consequently, a significant amount of neurological, psychiatric, urologic and endocrine disorders should be ruled out before vasculogenic sexual dysfunction is diagnosed.

When the diagnosis of vasculogenic sexual dysfunction

has been carefully reached, physicians will have to come up with an effective treatment. Appropriate lifestyle measures and adoption of a healthier attitude could represent an initial, efficient and cost-effective treatment option<sup>[14]</sup>. This is due to the fact that traditional CV risk factors such as hypertension, physical inactivity-obesity, smoking and dyslipidemia have been consistently linked with endothelial and consequently sexual dysfunction<sup>[15]</sup>. In this context, it has been demonstrated that moderate physical activity can reduce up to 30% the risk of erectile dysfunction contrary to sedentary life, which exerts a deleterious effect<sup>[16]</sup>. Interestingly, the beneficial effect of physical exercise on sexual dysfunction seems to be independent of its favorable impact on the general cardiovascular profile<sup>[17]</sup>. In terms of caloric reduction, Mediterranean diet exerts a positive effect on sexual function parameters of patients with metabolic syndrome<sup>[18]</sup>. Moreover, combined physical exercise and caloric restriction can result in weight reduction which in succession can reduce up to 30% the risk of obesity-associated erectile dysfunction<sup>[19]</sup>.

Whereas lifestyle modification is a reasonable initial step when approaching a hypertensive patient with sexual dysfunction, finding the appropriate antihypertensive treatment is usually the next "complicated" move to care for. Several observational and clinical studies have consistently associated antihypertensive medication with sexual dysfunction<sup>[20]</sup>. Whether one class of antihypertensive agents is associated exclusively or more with erectile dysfunction compared to another, however, is a difficult puzzle to solve as there are many other factors (comorbid conditions, concomitant medications, personal characteristics) to be taken into account at the same time. In addition, erectile dysfunction has never been studied as the primary end-point before and as a result a definite causative relationship between antihypertensive medication and sexual dysfunction has never been proven.

Despite the existing controversies, available data so far imply the old generation b-blockers (*e.g.*, propranolol) as the major culprits for sexual dysfunction with the newer ones (carvedilol, celiprolol) to exert a less pronounced negative effect<sup>[21-24]</sup>. A luminous exception to the rule, nebivolol, is a newer agent of its class which significantly ameliorates erectile dysfunction through increased nitric oxide generation, an effect consistently demonstrated in recent studies<sup>[25,26]</sup>. Diuretics, even on adjunct therapy, constitute another antihypertensive agent negatively associated with sexual function<sup>[27-29]</sup>. On the other hand, calcium antagonists and angiotensin converting enzyme inhibitors seem to demonstrate a neutral effect<sup>[30-32]</sup>. Interestingly, angiotensin receptor blockers (ARBs) by blocking the vasoconstrictive action of angiotensin II seem to positively affect erectile function and are thus regarded as a first-line treatment in hypertensive patients with erectile dysfunction<sup>[22,25,33-35]</sup>.

## TREATED HYPERTENSIVE PATIENTS

Whereas management of sexual dysfunction in previ-

ously untreated hypertensive patients can be a challenging procedure, confronting the same clinical condition in individuals under antihypertensive regime can be even more demanding. In such cases there will always be a question hovering over physicians head. Is hypertension *per se*, antihypertensive medication or both, the causative factors provoking sexual dysfunction<sup>[15]</sup>?

Duration and severity of hypertension are undoubtedly associated with erectile dysfunction. As a result, patients with long-standing (> 5-6 years) and severe hypertension are expected to suffer more frequently from sexual dysfunction, which indeed appears in a more severe form<sup>[36,37]</sup>.

When antihypertensive medication comes to the fore, certain issues need to be carefully addressed. This is due to the fact that medically induced erectile dysfunction is one of the major reasons for non-adherence and treatment discontinuation, a reality that could have deleterious consequences on patient's cardiovascular profile and health quality in the long term<sup>[38,39]</sup>.

Like the case of untreated hypertensive patients, evaluation of sexual dysfunction in hypertensive patients under antihypertensive regime, should primarily exclude other concomitant diseases and pharmaceutical agents. Consecutively, a competent physician with advanced communicational skills should try to "discover" medically induced erectile dysfunction since a vast majority of patients being under complex antihypertensive regimes usually attribute the undesirable effect to normal aging thus not relating it to their current medication. Moreover, even physicians seldom report the cases of sexual dysfunction associated with certain medications. When medically induced sexual dysfunction is finally disclosed and a shift in medication is deemed necessary, b-blockers along with diuretics should generally be the first categories to be changed, unless they are deemed absolutely indicated for the individual patient. Ideally, an ARB could constitute the mainstay of therapy in these cases. If sexual dysfunction still persists, then more effective remedies should be elected paving the way for the introduction of phosphodiesterase-5 inhibitors (PDE-5).

### **PDE-5 inhibitors**

Since their introduction in the therapeutic field, more than a decade ago, PDE-5 inhibitors have revolutionized the treatment of sexual dysfunction. By blocking the activity of PDE-5 isoenzyme, localized throughout the smooth muscle cells of the vasculature (genital vessels included), PDE-5 inhibitors increase the levels of cyclic guanosine monophosphate thus exerting vasodilating properties and facilitating penile erection<sup>[40-42]</sup>. Due to these properties, sildenafil was the first drug of its class to receive wide acceptance. Its short half-life, food interactions and the associated visual disturbances however, paved the way for the development of newer PDE-5 inhibitors. As such vardenafil with its more rapid onset of action, and tadalafil with its longer half-life and the lack of food interactions or side effects, have offered signifi-

cant alternatives to sildenafil<sup>[43-50]</sup>.

Due to their vasorelaxing effect, administration of PDE-5 inhibitors in hypertensive individuals was initially confronted with great suspicion. A wealth of clinical data however has proven that PDE-5 inhibitors are associated with few side effects and provoke a small and insignificant reduction in blood pressure with minimal heart rate alterations in both normotensive and hypertensive patients as well. As a matter of fact, they can be safely and effectively administered to hypertensive individuals even when they are already taking multiple antihypertensive agents<sup>[51-56]</sup>. The sole exception to the rule is co-administration with organic nitrates, which is an absolute contraindication due to profound and possibly hazardous hypotension effect<sup>[57,58]</sup>. Moreover, precaution should be taken when PDE-5 inhibitors are combined with a-blockers where, due to possible orthostatic hypotension effect, lower starting doses should be implemented in the therapeutic regime<sup>[59-62]</sup>.

Apart from their beneficial effect in erectile dysfunction and their safe profile in antihypertensive medication, PDE-5 inhibitors have even more advantages to demonstrate. Several lines of evidence has proven that patients receiving PDE-5 inhibitors are more likely to initiate an antihypertensive regime and more willing to add a new agent to their existing treatment, a fact that raises significantly patient's adherence and as a matter of fact control of high blood pressure and quality of life<sup>[63,64]</sup>. Moreover, a handful of clinical data has demonstrated the considerable vasodilating and anti-proliferative properties of PDE-5 inhibitors in the pulmonary vasculature, establishing them as a first-line treatment in patients with pulmonary arterial hypertension<sup>[65,66]</sup>. The same properties have been considered as potentially responsible for improving microcirculation in patients with secondary Raynaud phenomenon and ameliorating cardiopulmonary exercise performance in patients with heart failure<sup>[67,68]</sup>. In addition, the therapeutic implementation of PDE-5 inhibitors has expanded in the field of benign prostate hyperplasia-lower urinary tract symptoms (BPH-LUTS). The common pathophysiologic substrate between erectile dysfunction and BPH-LUTS has rendered PDE-5 inhibitors an effective treatment which significantly improves measures of both conditions while at the same time exhibits high efficacy and safety. The beneficial effect is much more pronounced when taking into consideration the fact that a-blockers, the mainstay of therapy for benign prostate hyperplasia frequently provoke sexual side effects, erectile dysfunction included<sup>[69]</sup>.

### **Management beyond PDE-5 inhibitors**

Despite remarkable therapeutic efforts, it is evident that a relative proportion of patients with erectile dysfunction will fail to respond to oral pharmacotherapy including PDE-5 inhibitors. The management of non-responders calls for second and third-line treatment implementation.

Surgical implantation of a penile prosthesis, either the inflatable (2- and 3-piece) or the malleable device, is a

feasible technique that offers a third-line treatment and a more permanent solution to the problem of erectile dysfunction. Interestingly, prosthesis implantation receives a significantly high satisfaction rate as evidenced by the proportionate scores in sexual satisfaction scales. Mechanical failure and infection are the two major disadvantages of those prosthetic implants however, their great efficacy, safety and satisfaction rate in general render them an attractive solution when conservative treatment fails<sup>[70-74]</sup>.

## CARDIOVASCULAR RISK PREDICTION

One of the most interesting aspects considering the properties of sexual dysfunction is that, during the last decades, it transformed from being a reliable quality of life index into a significant CV risk predictor.

Towards this direction, several sufficiently powered studies have demonstrated a higher incidence of erectile dysfunction in patients with coronary artery disease, either asymptomatic or overt. At the same time, patients with erectile dysfunction are more prone to have established coronary artery stenosis of more than 50% and consequently evident CV disease<sup>[75]</sup>. This is in conformity with the “artery size hypothesis” according to which smaller arteries (*e.g.*, penile arteries) are the first to undergo a vascular lesion prior to the larger ones (*e.g.*, coronary arteries). Moreover, in such patients erectile dysfunction is connected to the number of occluded vessels and more interestingly occurs over three years before coronary artery disease becomes apparent<sup>[76-80]</sup>.

Several other facts support the close relationship between sexual dysfunction and CV disease. Endothelial dysfunction mediated by decreased nitric-oxide bioavailability as well as atherosclerotic lesions constitute a common pathophysiologic substrate affecting both CV disease and erectile dysfunction, a disease considered to be primarily of vascular origin<sup>[76,80-82]</sup>. Several traditional CV risk factors (diabetes mellitus, hypertension, dyslipidemia, and smoking) are frequently found in individuals with erectile dysfunction, conferring a detrimental cardiovascular burden to them. More interestingly, the increased cardiovascular risk observed in those patients is independent of the aforementioned CV risk factors<sup>[81-88]</sup>.

A recent systematic review and meta-analysis of relevant studies in this field confirmed that erectile dysfunction is associated with increased risk of CV events and all-cause mortality<sup>[89]</sup>. The pooled relative risks were 1.44 (95%CI: 1.27-1.63) for total CV events, 1.19 (95%CI: 0.97-1.46) for CV mortality, 1.62 (95%CI: 1.34-1.96) for myocardial infarction, 1.39 (95%CI: 1.23-1.57) for cerebrovascular events, and 1.25 (95%CI: 1.12-1.39) for all-cause mortality, for men with *vs* without erectile dysfunction. Of note, the relative risk was higher in intermediate-compared with high- or low-CV-risk populations and with younger age, with obvious clinical implications. Interestingly, the relative risks were higher when erectile dysfunction was diagnosed with the use of a questionnaire compared with a single question (RR =

1.61; 95%CI: 1.38-1.86 *vs* RR = 1.27; 95%CI: 1.18-1.37, respectively; *P* = 0.006).

Since erectile dysfunction presents such an intimate relationship with CV parameters, it is easily deduced that it could constitute a powerful tool for detecting asymptomatic CV disease. Consequently, recognition of sexual dysfunction in a hypertensive individual should prompt further diagnostic procedures and therapeutic interventions in order to disclose its silent cardiovascular risk and improve patient’s quality of life and life expectancy.

## SEXUAL ACTIVITY IN PATIENTS WITH CV DISEASE

Considering the fact that CV disease presents with higher incidence in patients with erectile dysfunction while at the same time sexual activity by itself poses potential CV risks, the appropriate management of those complex conditions is of utmost importance. Accordingly, the working group of the third Princeton Consensus Conference developed practical guidelines and a simplified algorithm in order to manage sexual dysfunction and sexual activity implementation issues in patients with different levels of CV risk, including hypertensive patients<sup>[90]</sup>.

In particular, patients are classified into three categories (low, intermediate, high) depending on their CV risk profile. Individuals with controlled hypertension belong to the low-risk group where sexual dysfunction can be safely managed with the approved medical therapies regardless of the number or class (with the exception of  $\beta$ -blockers and diuretics) of agents of the patient’s antihypertensive regime. Moreover, patients of this group can safely initiate or reinstitute sexual activity without any need for additional cardiovascular evaluation.

On the contrary, patients with uncontrolled hypertension (poorly controlled, untreated, accelerated or malignant) belong to the high risk group where both treatment of sexual dysfunction and sexual activity resumption must be deferred until a thorough and specialized evaluation and stabilization has primarily been made.

Erectile dysfunction usually precedes cardiovascular events by 3 to 5 years. Therefore, sexual function should be incorporated into cardiovascular disease risk assessment for all men. Recently, algorithms for the management of patients with erectile dysfunction according to the risk for sexual activity and future cardiovascular events were proposed<sup>[91]</sup>. A comprehensive approach to cardiovascular risk reduction (comprising of both lifestyle changes and pharmacological treatment) will result in significant benefits on overall vascular health, including sexual function. Proper sexual counselling will exert beneficial effects on the quality of life of hypertensive patients with erectile dysfunction and will improve adherence to antihypertensive drug therapy<sup>[91]</sup>.

## CONCLUSION

The prevalence of erectile dysfunction is approximately

2-fold higher in hypertensive patients compared to normotensive individuals. However, erectile dysfunction remains under-reported, under-recognized, and under-treated in hypertensive patients. Hypertension *per se* and antihypertensive drug therapy may contribute to the development of erectile dysfunction in patients with arterial hypertension. The management of erectile dysfunction in hypertensive patients is tricky and should take into account the different effects of antihypertensive drug categories on erectile function. Lifestyle modification should be the mainstay of treating erectile dysfunction in patients with untreated hypertension. Switching antihypertensive therapy should be considered in treated hypertensive patients, unless administered drugs are absolutely indicated for the individual patient. Otherwise, PDE-5 inhibitors should be used, since they are both effective and safe in hypertensive patients. Finally, erectile dysfunction offers the opportunity to recognize asymptomatic cardiovascular disease and better characterize the relevant risk with obvious benefits for cardiovascular disease prevention.

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