

Original Research Article

Erectile dysfunction: prevalence, risk factors and involvement of antihypertensive drugs intervention

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Abstract

Purpose: To explore the literature regarding prevalence, risk factors and the involvement of antihypertensive drugs in erectile dysfunction (ED).

Methods: Original research articles, reviews, editorials and case reports published in English language on the prevalence of sexual/erectile dysfunction in hypertensive men taking antihypertensive drugs and risk factors were identified through a search of four bibliographic databases, namely, PubMed, EMBASE, CINAHL and EBSCO Health.

Results: Recent analyses suggest that hypertensive men of almost all age groups suffer from ED but it is more prevalent in elderly male patients. The involvement of β -blockers was found to be controversial. Nevertheless, some evidence had been found regarding the use of propranolol in high doses.

Conclusion: The present review indicates the need for research to unravel the role of β -blockers in the manifestation of ED in hypertensive males, whom there are no contributory factors such as sedentary lifestyle, aging, stress and anxiety, etc.

Keywords: Hypertension, Antihypertensive drugs, β -Blockers, Propranolol, Erectile dysfunction, Life style, Risk factors

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INTRODUCTION

Hypertension (blood pressure > 140/90 mm Hg) is managed by a number drugs of different pharmacological groups. The treatment often requires the use of multiple drugs in combination. However, antihypertensive drugs such as diuretics, potassium sparing diuretics and β -blockers are believed in to be involved in erectile dysfunction (ED) [1,2]. ED refers to diminished libido, erectile failure (inability of achieving and/or maintaining sufficient penile erection for

intercourse) and different types of ejaculatory problems [3]. This disorder has a negative impact on lowering blood pressure [4-6]. The fear of ED and its manifestation leads to emotional disturbances and noncompliance to the therapy, thus affecting patient's health [7, 8]. Therefore, the present article focused in exploring the facts regarding the prevalence, risk factors and involvement of antihypertensive drugs. The literature review indicated several reports about a significant prevalence of the dysfunction in normal population.

The present review of literature was carried out to respond to the question, 'are there any clear, demonstrable and meaningful relationship between the use of antihypertensive drugs and manifestation of ED'? By doing so, we wish to examine and assemble the available evidence regarding the role of antihypertensive drugs, particularly β -blockers in manifestation of ED. Additionally, by uncovering the underlying causes of ED and exploring the mechanisms by which antihypertensive drugs manifest this disorder, we may provide information to healthcare providers for selecting drugs, having safer profile and appropriate dose. This article may certainly leave a beneficial impact on clinical and pharmaceutical care practices involved in effective management of hypertensive patients who are high risk for ED.

EXPERIMENTAL

Search strategy

A literature search was conducted on PubMed, EMBASE, CINAHL, ProQuest and EBSCO Health databases to find all potentially relevant publications. The key words used for search include: "antihypertensive agents", "sexual dysfunction", "erectile dysfunction", " β -blockers" and "risk factors". The reference lists of primary original articles and review articles were also reviewed so that further relevant studies could be taken into account.

Study selection

Research articles, reviews, editorials, and case reports published in English language regarding the use of antihypertensive drugs, particularly β -blockers, and the manifestation of ED were included, and the data was then published as opinions, commentaries and conference abstracts were excluded due to the insufficiency of information.

Data extraction

One investigator reviewed the papers to evaluate potential relevance. The data were drawn from the included studies to identify the results of investigations indicating the relationship between antihypertensive therapy, particularly β -blockers, and ED. Additionally, descriptive features and data analysis methods were identified that could indicate the strength of evidence. The risk factors, comorbidities and ED mechanism of antihypertensive drugs were also extracted.

RESULTS

Prevalence of erectile dysfunction (ED)

The normal population was also found to be suffering from ED. A study indicated that twenty six person per one thousand were found to suffer from ED [9]. Another study indicated that more than half of the men's population (52 %), aged 40 - 70 years, were suffering from some degree of ED [10]. An interview-based study conducted by psychologist involving 98 sexually active men, aged 20 - 35, shows that 8.25 % of the respondents reported ED during intercourse and 18.50 % during masturbation [11]. In addition, a study conducted on matrimonially stable couples, men age (37.42 ± 11.15 years) and women age (35.04 ± 10.07 years), indicated that 7 % men failed in achieving an erection and 9 % could not maintain erection [12].

Risk factors

ED was found in almost all age groups but the incidences were higher in elderly men. A study indicated the prevalence of 2 %, 6.7 % and 24 % in respondents aged ≤ 40 , 55 and 70 years [13]. A similar relationship was revealed in another study, in which the prevalence was 1 - 10 % in younger males (< 40 years), 2 - 9 % in middle age (40 - 50 years), 20 - 40 % in older people (60 - 69 years) and 50 - 100 % in elderly people (> 70 years) [14].

A German population-based study indicated that 19.2 % ED surged was related to age (2.3 - 53.4 %) and comorbidities like hypertension and diabetes [15]. A Turkish population-based study indicated 69.2 % age-adjusted overall incidence of ED with varying degree of severity (33.2 % mild, 27.5 % moderate and 8.5 % severe) [16]. This study further indicated that age, lower education, unemployment, hypertension, diabetes and depression were the contributing factors for ED [16]. An age-adjusted prevalence of ED in Brazil, Italy, Malaysia and Japan was reported to be 15 %, 17 %, 22 % and 34 %, respectively [17]. These populations also indicated aging, heavy smoking, cardiac diseases and diabetes were the other risk factors [17]. A Tampere Ageing Male Urological Study indicated the relationship of the dysfunction with age (mean score increase from 0.82 (50 years) to 1.85 (75 years), hypertension ($r = 5.1$), cardiac diseases ($r = 6.5$), diabetes ($r = 17.5$) and smoking ($r = 4.6$) [18]. An Italian study indicated prevalence (19.9 %) and other factors as: higher

age (4.6 % in male < 25 years, 37.65 in male > 74 years), diabetes (Odds ratio (OR) 1.2, 95 % CI 1.1 - 1.4), hypertension (OR 1.3, 95 % CI 1.1 - 1.4) and cardiopathy (OR 1.5, 95 % CI 1.3 - 1.8) [19]. A study involving 2869 men in Vienna indicated 32.2 % prevalence of ED and high risk contributors; diabetes (OR 3.0, 95 % CI 1.53 - 5.87), hypertension (OR 2.05, 95 % CI 1.61 - 2.6), hyperlipidemia, stress and sedentary lifestyle [20].

The first large study to explore the prevalence of sexual dysfunction in hypertensive subjects "Treatment of Mild Hypertension Study" indicated that this disease was considerably low in females (4.9 %) compared to males (14.4 %) [21]. However, in this study, mild-hypertensive patients and patients of 45 - 69 years were included, whereas severe-hypertensive, diabetic and elderly patients (> 70 years) were excluded, and only one question was used to assess the disease [21]. A study carried out on 2130 hypertensive Spanish men indicated 45.8 % prevalence, whereas it was 18.5 % in the general population [22]. Similarly, a study involving 634

Greek men indicated that 35.2 % hypertensive subjects and 14.1 % normal subjects suffered from ED [23]. The manifestation of ED was said to be more common in hypertensive population compared to that of the normotensives [21-24]. A number of studies showed that ED shared many risk factors of the cardiovascular diseases such as atherosclerosis [25], hypertension, hyperlipidemia, diabetes mellitus [26], smoking [27], obesity and inactive lifestyle [28]. The prevalence of ED in the presence of different comorbidities is summarized in Table 1.

Etiology of ED in hypertensive patients and probable mechanism

The etiologies of ED in hypertensive patients are almost similar to that of the general population. There are several social, psychological, physiological and drug-related effects that can enhance the incidence of the disease. However, based on the literature review, etiologies of the dysfunction and probable mechanisms by which antihypertensive drugs manifest ED are shown in Table 2.

Table 1: Erectile dysfunction (ED) and some risk factors

ED prevalence	Risk factor	No. of reports [ref]
33-89 %	Aging (>40 years)	8 [29-36]
27-68 %	Hypertension	3 [37-39]
42-75 %	Coronary artery disease	6 [40-45]
75 %	Heart failure	1 [46]
20-65 %	Diabetes mellitus	5 [47-51]
High prevalence*	Hyperlipidemia	3 [52-54]
High prevalence*	Smoking	4 [55-58]
25-90 %	Depression and anxiety	1 [59]
High prevalence*	Medication	3 [60-62]

*Exact percentage was not reported

Table 2: Etiology of erectile dysfunction (ED) and mechanisms of dysfunction

Etiology	Mechanism
Arterial insufficiency	Decreased blood flow toward corpus cavernosum [4]
Endothelial dysfunction	The insufficient vasodilatory response of penile vessels and trabecular smooth muscle relaxation because of reduction in nitric oxide availability (NO) derived by endothelium [63]
Depression and anxiety	Decreased sex drive and impairment of NO release [63]
β -blockers	Ambiguous mechanism; lower the level of testosterone resulting in the decrease in sexual drive and function, and depress Leydig cell's activity involving β_2 receptors (although, their role in ED is not clear, they mediate vasodilation in response to increases in adrenaline during erection. Therefore, non-selective β -blockers increase the possibility of ED [64-66]. Propranolol due to its higher lipophilicity enters into the central nervous system and inhibits sympathetic stimulation, thus decreasing erection [67].
Diuretics 1- Aldosterone antagonist 2- Thiazide diuretics	Anti-androgen effect: compete with dihydrotestosterone and testosterone for androgen receptor binding sites and weak inhibition of testosterone biosynthesis [63]. Unknown role [63].

Antihypertensive drugs and ED

The summary of the literature reported regarding the involvement of antihypertensive drugs particularly β -blockers in ED, study design, sample size, drugs used and the major findings is given as follows:

The literature has numerous reports regarding the relation between ED and β -blockers. A multicenter, randomized, placebo-controlled trial, recruiting 697 hypertensive patients (21 - 65 years), taking atenolol and chlorthalidone indicated that ED was severe in 11 % participants [68]. A prospective, randomized, double blind study, conducted on 192 men suffering from coronary heart disease, indicated that sex life of the subjects was not affected by using metoprolol, because ED scores remained the same in the drug and placebo groups. Around 60 % of the study population had no complaints regarding erection and reaching orgasm [69].

The effect of carvedilol and valsartan (angiotensin-receptor blockers) on sexual activity and plasma testosterone was compared in a randomized, double blind, crossover study, recruiting 160 hypertensive men (40 - 49 years), indicated ED in 15 patients taking carvedilol (13.5 %), and 1 patient each taking valsartan and placebo [70]. In another double blind, parallel arm study, conducted on 110 hypertensive men (age 40 - 49 years), using valsartan and atenolol to evaluate their role on sexual activity and testosterone levels indicated that atenolol significantly reduced sexual activity (from 6.0 episodes of sexual intercourse/month to 4.2 episodes/month vs placebo, $p < 0.01$), whereas valsartan significantly improved sexual function compared to atenolol ($p < 0.05$), but the effect was not significant compared to placebo ($p = 0.058$) [71]. Silvestri *et al* [72] carried out a two phase study - first phase parallel study and second double blind, placebo-controlled, single crossover study on 96 men (40 % with angina and 60 % hypertension), aged (52 ± 7 years), who were well-informed about sexual side effects of atenolol and it had been indicated that ED incidences were only 3.1 % in a group not knowing the drug, 15.6 % in a group knowing the drug and 31.2 % in a group aware of the side effects of the drug.

A placebo-controlled study involving 134 hypertensive males using Propranolol and Chlorothiazide revealed 11 % cases of impotence and 7 % failed ejaculation in

propranolol group, 14 % impotence and 5 % failed ejaculation cases in placebo group and 10 % impotence and 6 % failed ejaculation cases in untreated hypertension group [73]. A multicenter, randomized, double blind, clinical trial on 626 mild to moderate hypertensive men using drugs such as captopril, methyldopa, propranolol and hydrochlorothiazide indicated that the participants taking captopril raised less complaints of ED than those taking propranolol [74]. Two case reports in the year 1976 indicated that ED in hypertensive patients was caused by the use of propranolol [75,76]. Warren *et al* [77] reported 5 % incidence of sexual dysfunction in a prospective follow-up study on 63 patients (49 men and 11 women) suffering from angina pectoris and being treated with Propranolol. In another independent study, the same authors reported that 5 % incidence of ED was due to the use of propranolol [78]. A randomized, double blind, crossover study which recruited 40 hypertensive male patients showed that 18 % cases of impotence and 27 % diminished libido were in a group consuming propranolol at a dose of 320 mg/day [79].

Two further reports were found which indicate that propranolol-induced ED is dose-related. The first study [80] conducted on 46 patients with no prior ED indicated 15 % cases of complete erectile failure (getting mean daily dose of 143 mg/day) and 28 % cases of decrease in quality of erection (receiving mean daily dose of 124 mg/day) and in the second study [79] participants receiving a dose of 180 - 320 mg/day suffered from complete erectile failure or decreased potency, while 57 % of those treated with 120 - 160 mg/day reported other complaints similar to that of the first study. Interestingly, patients taking a mean daily dose of 83 mg/day of propranolol did not report any incidence of ED [80].

Moreover, in the study of Holliefield *et al* [79] not even a single person out of 40 subjects, consuming propranolol 160 mg/day, complained of ED; only 2 persons out of 11 (18 %) reported complete erectile failure/impotence (taking a dose of ≥ 320 mg) and 3 out of 11 (27 %) reported a decreased sexual desire. Only one study addressed the effect of propranolol upon ejaculation and this study revealed 7 % incidence of failed ejaculation in hypertensive subjects [73]. On the other hand, 6 % of the general population, 10 % untreated group and 5 % taking placebo, reported the same problem. Hence, there was very little support regarding the effects of propranolol on ejaculation.

DISCUSSION

The results of this literature survey were stunning in a number of aspects. Firstly, the reported literature did not support the involvement of β -blockers in the manifestation of ED. Secondly, we did not find even a single study conducted on retrospective data regarding β -blockers-induced ED. Almost all of the studies were prospective. Its probable cause may be the unavailability of sufficient data in the patient's record needed to draw conclusions about the involvement of β -blockers in the manifestation of ED. Furthermore, hypertensive patients taking β -blockers may suffer from ED because of psychological factors (depression, stress, anxiety, loss of relation and known side effects of drugs), co-morbidities, adjuvant medication, heavy smoking, obesity and sedentary lifestyle. On the other hand, in this literature survey, we found concrete evidence regarding the involvement of propranolol in the manifestation of ED.

However, we did not find any clear mechanism which suggested that propranolol caused the disease. The involvement of atenolol and carvedilol in manifestation of ED was controversial, since only one study indicated that carvedilol had a negative impact on sexual function [70]. Two studies [68,71] revealed that ED was caused by atenolol; in the first [68] the difference between the two groups, receiving atenolol and usual diet and those receiving placebo and usual diet was not statistically significant ($p > 0.05$). Contrary to the findings of second study [71], Silvestri *et al* [72] reported that the incidence of ED was very high in those subjects who were well-informed regarding sexual side effects of atenolol than those unaware of the given antihypertensive agent (31.2 vs 3.1 %).

These findings indicate that awareness of the patients regarding the side effects of the drug played a contributory role in the manifestation of this disorder [72]. In addition, anxiety, stress and fear were also reported to be involved in causing sexual dysfunctions [81]. Numerous studies suggest that anxiety is common amongst sufferers of sexual dysfunctions, with varying levels and nature of anxiety and anxiety reduction procedures improve some aspects of sexual dysfunctions [80]. It is suggested that the knowledge of side effects produce anxiety that may affect sex life or erectile function [72]. Therefore, further investigations are required in order to understand and clarify the role of β -adrenergic receptor antagonists in causing erectile dysfunction.

CONCLUSION

Erectile dysfunction (ED) is a widespread problem among the hypertensive male population and it adversely affects both patient's quality of life and adherence to treatment regimen. The reported data do not support the conventionally held belief that β -blockers induce ED. However, it was evident that the involvement of propranolol, if used in higher doses, could cause ED and induce ejaculatory disturbances. The etiology of ED in hypertensive males is multifactorial and may be caused by vascular disease, decreased heart capacity, medications and/or other factors such as heavy smoking, psychological issues, obesity and physical inactivity.

REFERENCES

1. *Drugs that cause sexual dysfunction. Med Lett Drugs Ther.* 1980; 22(25): 108-110.
2. *Drugs and male sexual dysfunction. Br Med J.* 1979; 2(6195): 883-884.
3. Lue TF. *Erectile dysfunction. N Engl J Med.* 2000; 342(24): 1802-1813.
4. Virag R, Bouilly P, Frydman D. *Is impotence an arterial disorder? A study of arterial risk factors in 440 impotent men. Lancet.* 1985; 1(8422): 181-184
5. Slag MF, Morley JE, Elson MK, Trencle DL, Nelson CJ, Nelson AE, Kinlaw WB, Beyer HS, Nuttall FQ, Shafer RB *et al.* *Impotence in medical clinic out patients. JAMA.* 1983; 249(13): 1736-1740.
6. Sannerstedt R. *Negative consequences of reduction of blood pressure influence on sexual function. Acta Med Scand.* 1979; 628: 93-94.
7. Nies AS. *Adverse reactions and interactions limiting the use of antihypertensive drugs. Am J Med.* 1975; 58(4): 495-503.
8. Hoffmann WF. *The behavioral side effects of the anti-hypertensive agents. Am Fam Physician.* 1981; 23(2): 213-216.
9. Johannes CB, Araujo AB, Feldman HA, Derby CA, Kleinman KP, McKinlay JB. *Incidence of erectile dysfunction in men 40 to 69 years old: longitudinal results from the Massachusetts male aging study. J Urol.* 2000; 163(2): 460-463.
10. Petrie M, Murray JM. *Changes in notions about heart failure. Lancet.* 2001; 358(9280): 432-434.
11. Reading AE, Wiest WM. *Analysis of self-reported sexual behavior in a sample of normal males. Arch Sex Behav.* 1984; 13(1): 69-83.
12. Frank E, Anderson C, Rubenstein D. *Frequency of sexual dysfunction in normal couples. N Engl J Med.* 1978; 299(3): 111-115.
13. Kinsey AC, Pomeroy WB, Martin CF. *Sexual behavior in the human male. Philadelphia: Saunders.* 1948; pp.804.

14. Shamloul R, Ghanem H. Erectile dysfunction. *Lancet*. 2013; 381(9861): 153-165.
15. Braun M, Wassmer G, Klotz T, Reifenrath B, Mathers M, Engelmann U. Epidemiology of erectile dysfunction: results of the "Cologne Male Survey". *Int J Impot Res*. 2000; 12(6): 305-311.
16. Akkus E, Kadioglu A, Esen A, et al. Prevalence and correlates of erectile dysfunction in Turkey: a population-based study. *Eur Urol*. 2002; 41(3): 298-304.
17. Nicolosi A, Moreira ED Jr, Shirai M, Bin Mohd Tambi MI, Glasser DB. Epidemiology of erectile dysfunction in four countries: cross-national study of the prevalence and correlates of erectile dysfunction. *Urology*. 2003; 61(1): 201-206.
18. Shiri R, Koskimäki J, Häkkinen J, et al. Effects of age, comorbidity and lifestyle factors on erectile function: Tampere ageing male urological study (TAMUS). *Eur Urol*. 2004; 45(5): 628-33.
19. Mirone V, Ricci E, Gentile V, Basile-Fasolo C, Parazzini F. Determinants of erectile dysfunction risk in a large series of Italian men attending andrology clinics. *Eur Urol*. 2004; 45(1): 87-91.
20. Ponzolzer A, Temml C, Mock K, Marszalek M, Obermayr R, Madersbacher S. Prevalence and risk factors for erectile dysfunction in 2869 men using a validated questionnaire. *Eur Urol*. 2005; 47(1): 80-6.
21. Jr 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): 8-14.
22. Martin-Morales A, Sanchez-Cruz JJ, Saenz de TI, Rodriguez-Vela L, Jimenez-Cruz JF, Burgos-Rodriguez R. Prevalence and independent risk factors for erectile dysfunction in Spain: results of the *Epidemiologia de la Disfuncion Erectil Masculina Study*. *J Urol*. 2001; 166(2): 569-75.
23. Doumas M, Tsakiris A, Douma S, et al. Factors affecting the increased prevalence of erectile dysfunction in hypertensive compared to normotensive individuals. *J Androl*. 2005; 27(3): 469-77.
24. Aranda P, Ruilope LM, Calvo C, Luque M, Coca A, Gil de Miguel A. Erectile dysfunction in essential arterial hypertension and effects of sildenafil: results of a Spanish national study. *Am J Hypertens*. 2004; 17(2): 139-145.
25. Kaiser FE, Viosca SP, Morley JE, Mooradian AD, Davis SS, Korenman SG. Impotence and aging: clinical and hormonal factors. *J Am Geriatr Soc*. 1988; 36(6): 511-519.
26. Seftel AD, Sun P, Swindle R. The prevalence of hypertension, hyperlipidemia, diabetes mellitus and depression in men with erectile dysfunction. *J Urol*. 2004; 171(1): 2341-2345.
27. Shabsigh R, Fishman IJ, Schum C, Dunn JK. Cigarette smoking and other vascular risk factors in vasculogenic impotence. *Urology*. 1991; 38(3): 227-232.
28. Derby CA, Mohr BA, Goldstein I, Feldman HA, Johannes CB, McKinlay JB. Modifiable risk factors and erectile dysfunction: can lifestyle changes modify risk? *Urology*. 2000; 56(2): 302-306.
29. Feldman HA, Goldstein I, Hatzichristou DG, Krane RJ, McKinlay JB. Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. *J Urol*. 1994; 151(1): 54.
30. Chew KK, Earle CM, Stuckey BG, Jamrozik K, Keogh EJ. Erectile dysfunction in general medicine practice: prevalence and clinical correlates. *Int J Impot Res*. 2000; 12(1): 41-45.
31. Moreira Jr. ED, Bestane WJ, Bartolo EB, Fittipaldi JA. Prevalence and determination of erectile dysfunction in Santos, southeastern Brazil. *Sao Paulo Med J*. 2002; 120(2): 49-54.
32. Morillo LE, Díaz J, Estevez E, et al. Prevalence of erectile dysfunction in Columbia, Ecuador, and Venezuela: a population-based study (DENSA). *Int J Impot Res*. 2002; 14(2): S10-S18.
33. Shiri R, Koskimäki J, Hakama M, et al. Prevalence and severity of erectile dysfunction in 50-75-years old Finnish men. *J Urol*. 2003; 170(1): 2342-2344.
34. Bacon CG, Mittleman MA, Kawachi I, Giovannucci E, Glasser DB, Rimm EB. Sexual function in men older than 50 years of age: results from the health professionals Follow-up study. *Ann Intern Med*. 2003; 139(3): 161-168.
35. Safarinejad MR. Prevalence and risk factors for erectile dysfunction in a population-based study in Iran. *Int J Impot Res*. 2003; 15(4): 246-252.
36. Bai Q, Xu QQ, Jiang H, Zhang WL, Wang XH, Zhu JC. Prevalence and risk factors of erectile dysfunction in three cities of China: a community based study. *Asian J Androl*. 2004; 6(4): 343-348.
37. Jensen J, Lendorf A, Stimpel H, Frost J, Ibsen H, Rosenkilde P. The prevalence and etiology of impotence in 101 male hypertensive outpatients. *Am J Hypertens*. 1999; 12(3): 271-275.
38. Burchardt M, Burchardt T, Baer L, et al. Hypertension is associated with severe erectile dysfunction. *J Urol*. 2000; 164(4): 1188-1191.
39. Cuellar de LAJ, Ruiz GV, Campos GJC, Perez HS, Brotons MF. Prevalence of erectile dysfunction in patients with hypertension. *Med Clin (Barcelona)*. 2002; 119(14): 521-526.
40. Wabrek AJ, Burchell C. Male sexual dysfunction associated with coronary artery disease. *Arch Sexual Behav*. 1980; 9(1): 69-75.
41. Dhabuwala CB, Kumar A, Pierce JM. Myocardial infarction and its influence on male sexual dysfunction. *Arch Sexual Behav*. 1986; 15(6): 499-504.
42. Diokno AC, Brown MB, Herzog R. Sexual function in elderly. *Arch Intern Med*. 1990; 150(1): 197-200.
43. Montorsi F, Briganti A, Salonia A, et al. Erectile dysfunction prevalence, time of onset and association with risk factors in 300 consecutive patients with acute

- chest pain and angiographically documented coronary artery disease. *Eur Urol*. 2003; 44(3): 360–365.
44. Kloner RA, Mullin SH, Shook T, et al. Erectile dysfunction in the cardiac patient: how common and how should we treat? *J Urol*. 2003; 170(2): S46–S50.
 45. Solomon H, Man JW, Wierzbicki AS, Jackson G. Relation of erectile dysfunction to angiographic coronary artery disease. *Am J Cardiol*. 2003; 91(2): 230–231.
 46. Jaarsma T, Dracup K, Walden J, Stevenson LW. Sexual function in patients with advanced heart failure. *Heart Lung*. 1996; 25(4): 262–270.
 47. McCulloch DK, Campbell IW, Wu FC, Prescott RJ, Clarke BF. The prevalence of diabetic impotence. *Diabetologia*. 1980; 18(4): 279–283.
 48. Klein R, Klein BE, Lee KE, Moss SE, Cruickshanks KJ. Prevalence of self-reported erectile dysfunction in people with long-term IDDM. *Diabetes Care*. 1996; 19(2): 135–141.
 49. Alonso SE, Sánchez MD, Benito FR, Fernández GM, Palancar de la Torre JL, Tejero CI, et al. Impotence in diabetic patients: detection of prevalence and social health implications. *Aten Primaria*. 1997; 20(8): 435–439.
 50. Siu SC, Lo SK, Wong KW, Ip KM, Wong YS. Prevalence of and risk factors for erectile dysfunction in Hong Kong diabetic patients. *Diabet Med*. 2001; 18(9): 732–738.
 51. Yamasaki H, Ogawa K, Sasaki H, et al. Prevalence and risk factors of erectile dysfunction in Japanese men with type 2 diabetes. *Diabetes Res Clin Pract*. 2004; 66(1): S173–S177.
 52. Wei M, Macera CA, Davis DR, Hornung CA, Nankin HR, Blair SN. Total cholesterol and high density lipoprotein cholesterol as important predictors of erectile dysfunction. *Am J Epidemiol*. 1994; 140(10): 930–937.
 53. Saltzman EA, Guay AT, Jacobson J. Improvement in erectile function in men with organic erectile dysfunction by correction of elevated cholesterol levels: a clinical observation. *J Urol*. 2004; 172(1): 255–258.
 54. Nikoobakht M, Nasseh H, Pourkasmaee M. The relationship between lipid profile and erectile dysfunction. *Int J Impot Res*. 2005; 17(6): 523–6.
 55. Mannino DM, Klevens RM, Flanders WD. Cigarette smoking: an independent risk factor for impotence? *Am J Epidemiol*. 1994; 140(11): 1003–1008.
 56. McVary KT, Carrier S, Wessells H. Smoking and erectile dysfunction: evidence based analysis. *J Urol*. 2001; 166(5): 1624–32.
 57. Mirone V, Imbimbo C, Bortolotti A, et al. Cigarette smoking as a risk factor for erectile dysfunction: results from an Italian epidemiological study. *Eur Urol*. 2002; 41(3): 294–297.
 58. Gades NM, Nehra A, Jacobson DJ, et al. Association between smoking and erectile dysfunction: a population based study. *Am J Epidemiol*. 2005; 161(4): 346–351.
 59. Araujo AB, Durante R, Feldman HA, Goldstein I, McKinlay JB. The relationship between depressive symptoms and male erectile dysfunction: cross-sectional results from the Massachusetts Male Aging study. *Psychosom Med*. 1998; 60(4): 458–465.
 60. Keene LC, Davies PH. Drug-related erectile dysfunction. *Adv Drug React Toxicol Rev*. 1999; 18(1): 5–24.
 61. Brock GB, Lue TF. Drug-induced male sexual dysfunction. An update. *Drug Saf*. 1993; 8(6): 414–26.
 62. Derby CA, Barbour MM, Hume AL, McKinlay JB. Drug therapy and prevalence of erectile dysfunction in the Massachusetts Male Aging Study cohort. *Pharmacotherapy*. 2001; 21(6): 676–683.
 63. Rastogi S, Rodriguez JJ, Kapur V, Schwarz ER. Why do patients with heart failure suffer from erectile dysfunction? A critical review and suggestions on how to approach this problem. *Int J Impot Res*. 2005; 17(1): S25–S36.
 64. Andersson KE, Wagner G. Physiology of penile erection. *Physiol Rev*. 1995; 75(1): 191–236.
 65. Becker AJ, Ückert S, Stief CG, Truss MC, Machtens S, Scheller F, Knapp WH, Hartmann U, Jonas U. Plasma levels of cavernous and systemic norepinephrine and epinephrine in men during different phases of penile erection. *J Urol*. 2002; 164(2): 573–577.
 66. Simonsen U. Interactions between drugs of erectile dysfunction and drugs of cardiovascular disease. *Int J Impot Res*. 2002; 14(3): 178–188.
 67. Bathen J. Propranolol erectile dysfunction relieved. *Ann Intern Med*. 1978; 88(5): 716–717.
 68. Wassertheil-Smoller S, Blafox MD, Oberman A, et al. Effect of anti-hypertensives on sexual function and quality of life: the TAMI study. *Ann Intern Med*. 1991; 114(8): 613–620.
 69. Franzen D, Metha A, Seifert N, Braun M, Höpp HW. Effects of β -blockers on sexual performance in men with coronary heart disease; A prospective randomized and double blinded study. *Int J Impot Res*. 2001; 13(6): 348–351.
 70. Fogari R, Zoppi A, Poletti L, Marasi G, Mugellini A, Corradi L. Sexual activity in hypertensive men treated with valsartan or carvedilol: a crossover study. *Am J Hypertens*. 2001; 14(1): 27–31.
 71. Fogari R, Preti P, Derosa G, et al. Effects of antihypertensive treatment with valsartan on sexual activity and plasma testosterone in hypertensive men. *Eur J Clin Pharmacol*. 2002; 58(3): 177–180.
 72. Silvestri A, Galetta P, Cerquetani E, et al. Report of erectile dysfunction after therapy with β -blockers is related to patient knowledge of the side effects and is reversed by placebo. *Eur Heart J*. 2003; 24(21): 1928–1932.
 73. Bauer GE, Baker J, Hunyor SN, Marshall P. Side effects of antihypertensive treatment: a placebo-controlled study. *Clin Sci Mol Med*. 1978; 4: 341–4.
 74. Croog SH, Levine S, Testa MA, Sudilovsky A. The effects on antihypertensive therapy on quality of life. *N Engl J Med*. 1986; 314(26): 1657–1664.
 75. Knarr JW. Impotence from propranolol? *Ann Intern Med*. 1976; 85(2): 259.

76. Miller RA. *Propranolol and impotence. Ann Inter Med.* 1972; 85(5): 682.
77. Warren SG, Brewer DL, Orgain ES. *Long-term propranolol therapy for angina pectoris. Am J Cardiol.* 1976; 37(3): 420-426.
78. Warren SC, Warren SG. *Propranolol and sexual impotence. Ann Inter Med.* 1977; 86(1): 112.
79. Burnett WG, Chanine RA. *Sexual dysfunction as a complication of propranolol therapy in men. Cardiovasc Med.* 1979; 4: 811-815.
80. Hollifield JW, Sherman K, Zwagg RV, Shand DG. *Proposed mechanisms of propranolol's antihypertensive effect in essential hypertension. N Engl J Med.* 1976; 295(2): 68-73.
81. Norton JR, Jehu D. *The role of anxiety in sexual dysfunction: a review. Arch Sex Behav.* 1984; 13(2): 165-183.