Self Reported Sexual Dysfunction in Men and Women Treated With Bisoprolol, Hydrochlorothiazide, Enalapril, Amlodipine, Placebo, or Bisoprolol/Hydrochlorothiazide

L. Michael Prisant, MD;[1] Matthew R. Weir, MD;[2] William H. Frishman, MD;[3] Joel M. Neutel, MD;[4] Michael E. Davidov, MD;[5] Andrew J. Lewin, MD[6]

Quality of life may be impaired by antihypertensive therapy. Perceived sexual dysfunction by antihypertensive drugs diminishes quality of life and results in noncompliance with antihypertensive therapy. To assess the impact of various classes of antihypertensive therapy vs. combination therapy, self reported adverse reactions were catalogued by gender using COSTART (Coding Symbols for Thesaurus of Adverse Reaction Terms) of impotence or libido decrease in six randomized, blinded, prospective trials in which subjects received placebo, 5 mg qd–20 mg bid enalapril, 2.5–10 mg qd amlodipine, 6.25–25 mg qd hydrocholorothiazide (HCTZ), bisoprolol 5 mg qd, or a combination of 2.5–10 mg qd bisoprolol/6.25 mg HCTZ. The average duration of drug exposure was 6–14 weeks (range of 1 day to 23 weeks). Comparison among groups was performed using Fisher's exact test. There was no statistical difference between treatment with respect to impotence (p=0.688), decrease in libido (p=0.970), or overall sexual dysfunction (p=0.705) for 1251 men. Of the 661 women studied, decrease in libido was reported in only two subjects. It is concluded that short term exposure to antihypertensive drugs is associated with self reported impotence at no greater prevalence than it is with placebo in men. The combination of bisoprolol/6.25 mg HCTZ is not more likely to be associated with sexual dysfunction than placebo, HCTZ, bisoprolol, enalapril, or amlodipine. Also sexual dysfunction is reported less frequently in women than men. (J Clin Hypertens. 1999;1:22–26)

From the Hypertension Unit, Section of Cardiology, Medical College of Georgia, Augusta, GA;[1] Division of Nephrology and Clinical Research Unit, University of Maryland Medical Center, Baltimore, MD;[2] Department of Medicine, New York Medical College, Valhalla, NY;[3] Department of Medicine, University of California, Irvine, CA and the Orange County Heart Institute and Research Center, Orange, CA;[4] Hypertension Research Center, Falls Church, VA;[5] and the National Research Institute, Los Angeles, CA;[6] Address for correspondence/reprint requests: L. Michael Prisant, MD, Professor of Medicine, Medical College of Georgia, BBR-6515A, Hypertension Unit, Section of Cardiology, Augusta, GA 30912–3105
Manuscript received April 26, 1999; accepted June 14, 1999

Sexual dysfunction occurs with the vascular disease associated with aging, hypertension, diabetes mellitus, and heart disease and with associated medications.[1] Quality of life may be impaired by antihypertensive drug therapy.[2] Sexual dysfunction due to antihypertensive drugs may diminish quality of life and result in noncompliance with antihypertensive therapy and failure to achieve blood pressure control.[3] Various first line antihypertensive drugs (most notably diuretics and ß-blockers) are associated with sexual dysfunction. HCTZ, chlorthalidone, and bendrofluazide

have been reported to cause sexual dysfunction, while indapamide may be less likely to result in impotence.[4–7] In contrast, the Veterans Affairs Cooperative Study Group on single drug therapy for hypertension in men did not observe an increase in the frequency of impotence from baseline with HCTZ.[8] Randomized trials do not support the clinical observation that ß-blockers cause sexual dysfunction for groups of patients.[4,5,8]

The antihypertensive effectiveness of the combination of bisoprolol, a ß-blocker, with an ultra low dose of 6.25 mg HCTZ has been documented in comparison to placebo and monotherapy with HCTZ, bisoprolol, amlodipine, or enalapril.[9–13] Changes in metabolic parameters associated with this fixed dose combination have been clinically insignificant and adverse events are similar to placebo.[9–11,13] But physicians continue to be concerned that a combination of a ß-blocker and a diuretic may cause sexual dysfunction.

This analysis was performed to compare the impact of various classes of antihypertensive drug therapy (HCTZ, enalapril, bisoprolol, and amlodipine), a fixed dose combination therapy (6.25 mg HCTZ/bisoprolol) and placebo on the short term rate of sexual dysfunction. Our hypothesis was that diuretic assigned subjects would be most likely to have sexual dysfunction. Furthermore, it was predicted that the combination of a diuretic and ß-blocker would be more likely than monotherapy to have volunteered complaints of sexual dysfunction.

METHODS

To assess the impact of various classes of antihypertensive monotherapy vs. combination therapy, spontaneously self reported adverse reactions were catalogued by gender using COSTART of impotence or decrease in libido in six randomized, blinded, prospective trials in which subjects received: 1) placebo; 2) bisoprolol 2.5–10 mg with 6.25 mg HCTZ once daily; 3) enalapril 5 mg once daily up to 20 mg twice daily; 4) amlodipine 2.5–10 mg once daily; 5) HCTZ 6.25–25 mg once daily; and 6) bisoprolol 5–20 mg once daily. The average duration of drug exposure per treatment was 6–14 weeks (range of 1 day to 23 weeks). These studies have been previously published.[9–14] All randomized patients were included in this analysis.

Study 1 was a 20 center, randomized, double blind, placebo controlled, parallel group study to evaluate the antihypertensive effects of bisoprolol 5, 10, and 20 mg vs. placebo in subjects with essential hypertension.[14] After a 4–6 week single blind, placebo run in period, subjects were treated with bisoprolol or placebo for 4 weeks.

Study 3 was a 24 center, randomized, placebo controlled, double blind, 3x4 factorial trial to evaluate bisoprolol 2.5, 10, or 40 mg once daily alone or in combination with 6.25 or 25 mg HCTZ.[9] After a 4–6 week single blind placebo phase, 512 mild to moderate hypertensive subjects were treated with placebo or active therapy for 12 weeks.

Study 29 was a multicenter, randomized, placebo controlled, parallel group study in stages 1–2 hypertensive patients.[10] It consisted of a 4–6 week single blind, placebo run in period, followed by a 4 week double blind treatment period. Patients received either placebo (n=75), 5 mg bisoprolol (n=151), 5 mg bisoprolol/6.25 mg HCTZ (n=150), or 25 mg HCTZ (n=133).

Study 41 was a single blind, 24 hour ambulatory blood pressure monitoring study including 36 stage 1–3 hypertensive patients.[11] After a placebo run in phase, all patients received 5 mg bisoprolol/6.25 mg HCTZ once daily.

Study 43 was a 17 week, multicenter, randomized, double blind, 3 arm parallel group, dose escalation trial comparing bisoprolol/HCTZ, amlodipine, and enalapril in the treatment of patients (n=218) with stage 1 and 2 hypertension.[12] After a 4–5 week single blinded placebo period, a 4 week double blind dose titration period began. Medication could be increased one dose level at a time in 2 week intervals until the sitting diastolic blood pressure (DBP) was ≤90 mm Hg. Patients whose sitting DBP was ≤90 mm Hg remained on the same dose. The doses for titration were 2.5/6.25, 5/6.25, and 10/6.25 mg qd for patients on bisoprolol/HCTZ; 2.5, 5, and 10 mg qd for patients on amlodipine; and 5, 10, and 20 mg qd for enalapril.

Study 48 was a 23 week, multicenter, randomized, double blind, 4 arm parallel group dose escalation trial comparing bisoprolol/HCTZ, amlodipine, enalapril, and placebo in the treatment of patients (n=323) with stage 1 and 2 hypertension.[13] After a 4–5 week single blind placebo washout period, a 6 week double blind dose titration period followed. The medication could be increased one dose level at a time in 2 week intervals after randomization until the seated DBP was ≤90 mm Hg. Patients whose seated DBP was ≤90 mm Hg remained on the same dose. The doses for titration were 2.5/6.25, 5/6.25, and 10/6.25 mg qd for patients on bisoprolol/HCTZ; 2.5, 5, and 10 mg qd for patients on amlodipine; and 5 mg qd, 10 mg qd, 10 mg bid, and 20 mg bid for enalapril. A 12 week, two stage dose maintenance phase followed titration. During the first

TABLE I. RATE OF SELF REPORTED SEXUAL DYSFUNCTION AMONG MEN IN RANDOMIZED TRIALS						
	PLACEBO	BISOPROLOL/HCTZ	ENALAPRIL	AMLODIPINE	HCTZ	BISOPROLOL
N	190	333	102	103	134	389
Age	54.0 year	52.8 year	55.8 year	54.3 year	54.0 year	52.6 year
Impotence n (%)	2 (1.1)	6 (1.8)	2 (2.0)	3 (2.9)	2 (1.5)	4(1.0)
Libido ↓ n (%)	2 (1.1)	4 (1.2)	1 (1.0)	2 (1.9)	1 (0.7)	4 (1.0)
Overall n (%)	4 (2.1)	10 (3.0)	3 (2.9)	4 (3.9)	2 (1.5)	7 (1.8)
*Includes all formulations, strengths, and brands combined for each of the drugs.						

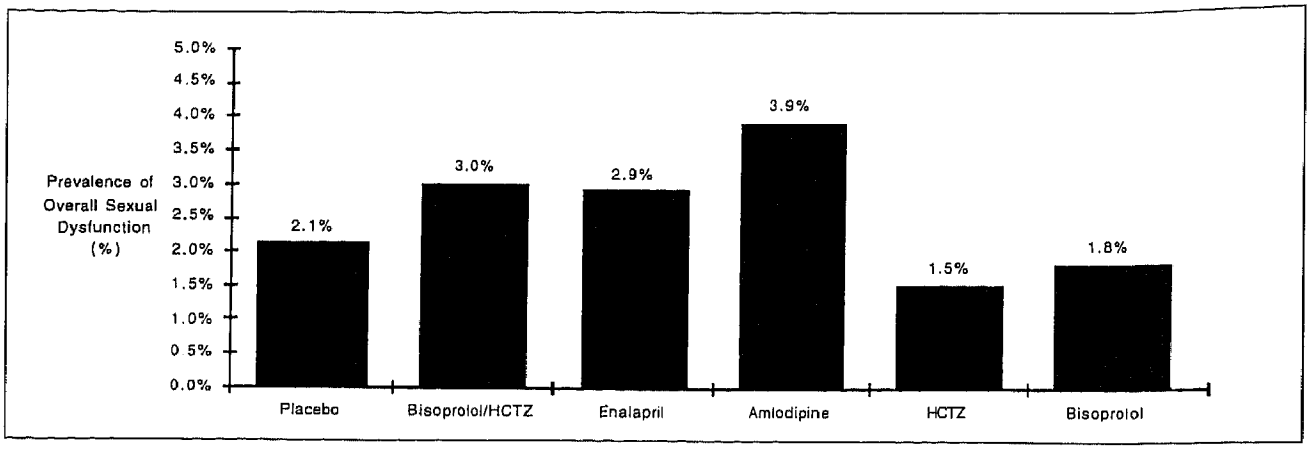

Figure. Overall rate of self reported sexual dysfunction among men.

stage of the maintenance phase, patients remained on the same dose of their last titration dose for 6 weeks. At 6 weeks, patients with seated DBP >95 mm Hg were dropped from the study. The remaining patients were treated for an additional 6 week dose maintenance phase until the study was completed.

STATISTICS

Comparison among groups were performed using Fishers' exact test.

RESULTS

The group size, mean age, and number of adverse events for 1251 men are displayed in Table I. Main results are depicted in the figure. There was no statistical difference between treatment for impotence (p=0.69), libido decrease (p=0.97), or overall sexual dysfunction (p=0.71). The group size, mean age, and number of adverse events for 661 women are displayed in Table II. Since there were only two events, no statistical analysis was performed.

DISCUSSION

Overall Rate of Sexual Dysfunction

This analysis has provided data on self reported sexual dysfunction in a cohort of 1912 hypertensive subjects exposed to placebo, monotherapy, or combination drug therapy for 6–14 weeks (range of 1 day to 23 weeks). Short term exposure to antihypertensive drugs or placebo is associated with a 1.7% (32 of 1912) overall rate of sexual dys-

TABLE II. RATE OF SEXUAL DYSFUNCTION AMONG WOMEN IN RANDOMIZED TRIALS						
	PLACEBO	BISOPROLOL/HCTZ	ENALAPRIL	AMLODIPINE	HCTZ	BISOPROLOL
N	102	206	53	51	76	173
Age	55.6 year	54.8 year	56.2 year	51.6 year	57.8 year	56.7 year
Libido ↓ n (%)	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	1 (0.6)
Overall n (%)	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	1 (0.6)

function. The rate of self reported sexual dysfunction among women is 0.3% (2 of 661) compared to 2.4% (30 of 1251) in men, which accounted for 65.4% of the study population.

In the Treatment Of Mild Hypertension Study (TOMHS), attending physicians asked female study participants if they had difficulty having an orgasm or a change in the frequency of sexual activity.[15] Men were asked about difficulty obtaining and maintaining an erection or a change in the frequency of sexual activity. Nurse interviewers asked similar questions at 3 month intervals over 4 years. The rate of decreased sexual activity reported to the nurse interviewers was lower than the rate to the physician interviewer in both women and men suggesting a pattern of underreporting.[15]

Unlike the TOMHS, our population did not have questions formally asked at each visit. Questions about adverse reactions were elicited in a nonleading fashion, and symptoms were spontaneously volunteered and subsequently coded using the FDA COSTART criteria. It is reasonable to assume, therefore, that the adverse effect was bothersome enough to be vocalized and, thus, was impairing quality of life. If all patients were asked about sexual dysfunction, it is possible that the rate would have been higher and would have included subjects for which this adverse reaction was not bothersome.[16] If all patients were asked about sexual dysfunction, still some patients would not have disclosed a problem. The study design accounts for the low rates of perceived sexual dysfunction. The Medical Research Council Working party used a standard questionnaire which requested information about impotence.[17] At 12 weeks, the prevalence of impotence was 8.9% for placebo, 13.8% for propranolol, and 16.2% for bendrofluazide ($p<0.05$ vs. placebo) among 1130 men studied. Sexual dysfunction data was not reported for the 958 women.

Rate of Sexual Dysfunction in Women

The physiology of sexual response in women and men are similar; therefore, adverse drug reactions causing sexual dysfunction should be similar in men and women.[18] The rate of self reported sexual dysfunction in women in this study is 0.3% (2 of 661) compared to 2.4% (30 or 1251) in men ($p=0.0003$, women vs. men). A rate of 4.9% in 344 women and 14.4% of 577 men at baseline for any sexual problem was reported in the TOMHS.[15] After 12 months of treatment with either acebutolol, amlodipine, chlorthalidone, doxazosin, enalapril, or placebo, approximately 3% of women and 10% of men reported a problem with sexual activity.[5]

A survey of the Oxford Hypertension Clinic found 50% of 208 men experiencing erectile difficulty and 22% of 178 women experiencing difficulty in sexual arousal ($p\leq0.0001$ for men vs. women).[19] The influence of drug therapy, which included ß-blockers, diuretics, methyldopa, and vasodilators, on sexual dysfunction was significantly greater in men, but not women. The British Department of Health and Social Security Hypertension Care Computing Project did not observe a relationship of sexual dysfunction with antihypertensive drug therapy among 1080 women (ages 40–69) respondents to a questionnaire.[20] For the 1285 men questioned, there was a relationship of sexual dysfunction to hydralazine, but not to ß-blockers, diuretics, or their combination. There were no untreated patients for comparison in this report.

Our study is consistent with other studies showing a low rate of sexual dysfunction among women taking antihypertensive drugs. However, our study does not resolve the question: "is sexual dysfunction in hypertensive women uncommon or understudied?"[21] It may be that men are more likely to volunteer information about sexual problems compared with women. Whether women should be directly questioned about libido, lubrication, and orgasmic function by female investigators to elicit an appropriate assessment requires further study. Even with an anonymous questionnaire, hypertensive males report a greater frequency of drug induced sexual problems than hypertensive females (43% vs. 17%, $p<0.01$).[22]

Rate of Sexual Dysfunction Among Drugs and Placebo

Our data shows an overall low rate of reported sexual dysfunction with no difference among the treatment groups. The combination of bisoprolol/6.25 mg HCTZ is not more likely to be associated with sexual dysfunction than HCTZ, bisoprolol, enalapril, amlodipine, or placebo. In a small study, bisoprolol monotherapy did not worsen sexual functioning in men with newly diagnosed hypertension, and in men on antihypertensive medication, bisoprolol improved certain sexuality parameters.[23] Many other studies have examined sexual functioning, but the TOMHS systematically collected data over 4 years of follow up. At 12 months, the rate of obtaining an erection increased from 10% to 12% in the chlorthalidone group, but decreased from 6% to 1.3% in the doxazosin group.[5] However, a decreased frequency of sex occurred in 22% of the enalapril group, 19.5% of the amlodipine group, 19.5% of the chlorthalidone group, 17.7% of acebutolol

group, 11.6% of the doxazosin group, and 11.3% of the placebo group. At 24 months, the incidence of erectile dysfunction was 17.1% among chlorthalidone treated patients compared with 8.1% among placebo treated patients (p=0.025).[15] In addition, compared to chlorthalidone, the incidence of 5.6% among doxazosin treated subjects was significantly less. By 48 months, there was no difference among the treatment groups. Finally, there was no difference in the incidence of a reported decrease in sex frequency through 24–48 months during follow up by treatment group for either men or women. Based on these data, one would predict that HCTZ would be associated with more sexual dysfunction at least in the short term. However, it is possible that the ultra low dose of HCTZ is less likely to cause this problem.

Based on previous studies, multiple drugs in combination are associated with more sexual dysfunction.[24,25] It is unclear whether the erectile dysfunction is due to the presence of more vascular disease or the drugs used. One study observed a worsening of function of a 25 mg HCTZ bid in combination with methyldopa or propanolol, but not with captopril.[24]

CONCLUSIONS

Short term exposure to antihypertensives drugs or placebo is associated with a low rate of self reported impotence and decreased libido in men. Sexual dysfunction is reported less frequently in women than men. The combination of bisoprolol/6.25 mg HCTZ is not more likely to be associated with sexual dysfunction than HCTZ, bisoprolol, enalapril, amlodipine as monotherapy, or placebo.

REFERENCES

1 Feldman HA, Goldstein I, Hatzichristou DG, et al. Impotence and its medical and psychosocial correlates: Results of the Massachusetts Male Aging Study. *J Urol.* 1994;151(1):54–61.

2 Weir MR, Prisant LM, Papademetriou V, et al. Antihypertensive therapy and quality of life. Influence of blood pressure reduction, adverse events, and prior antihypertensive therapy. *Am J Hypertens.* 1996;9(9):854–859.

3 Prisant LM, Carr AA, Bottini PB, et al. Sexual dysfunction with antihypertensive drugs. *Arch Intern Med.* 1994;154(7):730–736.

4 Medical Research Council Working Party. MRC trial of treatment of mild hypertension: Principal results. *BMJ.* 1985;291:97–104.

5 The Treatment of Mild Hypertension Research Group. The Treatment of Mild Hypertension Study. A randomized, placebo-controlled trial of a nutritional hygienic regimen along with various drug monotherapies. *Arch Intern Med.* 1991;151:1413–1423.

6 Chang SW, Fine R, Siegel D, et al. The impact of diuretic therapy on reported sexual function. *Arch Intern Med.* 1991;151:2402–2408.

7 Leonetti G, Rappelli A, Salvetti A, et al. Long-term effects of indapamide: Final results of a two-year Italian multicenter study in systemic hypertension. *Am J Cardiol.* 1990;65:67H–71H.

8 Materson BJ, Reda DJ, Cushman WC, et al. 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;328:914–921.

9 Frishman WH, Bryzinski BS, Coulson LR, et al. A multifactorial trial design to assess combination therapy in hypertension. Treatment with bisoprolol and hydrochlorothiazide. *Arch Intern Med.* 1994; 154(13):1461–1468.

10 Frishman WH, Burris JF, Mroczek WJ, et al. First-line therapy option with low-dose bisoprolol fumarate and low-dose hydrochlorothiazide in patients with stage I and stage II systemic hypertension. *J Clin Pharmacol.* 1995;35(2):182–188.

11 Lewin AJ, Lueg MC, Targum S, et al. A clinical trial evaluating the 24-hour effects of bisoprolol/hydrochlorothiazide 5 mg/6.25 mg combination in patients with mild to moderate hypertension. *Clin Cardiol.* 1993;16(10):732–736.

12 Prisant LM, Weir MR, Papademetriou V, et al. Low-dose drug combination therapy: An alternative first-line approach to hypertension treatment. *Am Heart J.* 1995;130(2):359–366.

13 Neutel JM. Rolf CN, Valentine SN, et al. Low-dose combination therapy as first line treatment of mild-to-moderate hypertension: The efficacy and safety of bisoprolol/HCTZ versus amlodipine, enalapril, and placebo. *Cardiovasc Rev Rep.* 1996;17(11):33–45.

14 Davidov ME, Singh SP, Vlachakis ND, et al. Bisoprolol, a once-a-day beta-blocking agent for patients with mild to moderate hypertension. *Clin Cardiol.* 1994;17(5):263–268.

15 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.

16 Kong BW, Clive J, Kong SH. Quality of life as a vital clinical sign. *J Hum Hypertens.* 1990;4(2):121–123.

17 Report of Medical Research Council Working Party on Mild to Moderate Hypertension. Adverse reactions to bendrofluazide and propranolol for the treatment of mild hypertension. *Lancet.* 1981;2:539–543.

18 Duncan L, Bateman DN. Sexual function in women. Do antihypertensive drugs have an impact? *Drug Safety.* 1993;8(3):225–234.

19 Riley AJ, Steiner JA, Cooper R, et al. The prevalence of sexual dysfunction in male and female hypertensive patients. *Sexual and Marital Therapy.* 1987:2:131–138.

20 Bulpitt CJ, Beevers DG, Butler A, et al. The effects of anti-hypertensive drugs on sexual function in men and women: A report from the DHSS Hypertension Care Computing Project (DHCCP). *J Hum Hypertens.* 1989;3:53–56.

21 Lewis C. Duncan LE, Ballance DI, et al. Is sexual dysfunction in hypertensive women uncommon or understudied? *Am J Hypertens.* 1998;11(6):733–735.

22 Watts RJ. Sexual functioning, health beliefs and compliance with high blood pressure medications. *Nurs Res.* 1982;31:278–283.

23 Broekman CPM, Haensel SM, van de Ven LLM, et al. Bisoprolol and hypertension: Effects on sexual functioning in men. *J Sex Marital Ther.* 1992;18(4):325–331.

24 Croog SH, Levine S, Sudilovsky A, et al. Sexual symptoms in hypertensive patients. A ethical trial of antihypertensive medications. *Arch Intern Med.* 1988,148:788–794.

25 Hogan MJ, Wallin JD, Baer RM. Antihypertensive therapy and male sexual dysfunction *Psychosomatics.* 1980;21:234–237.