

ORIGINAL ARTICLE

Effect of irbesartan on erectile function in patients with hypertension and metabolic syndrome

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Pathogenesis of erectile dysfunction (ED) is related to endothelial dysfunction and therefore associated with cardiovascular risk factors. Patients with a combination of risk factors, as in metabolic syndrome, are thus likely to have an increased risk of developing endothelial and ED. The angiotensin receptor antagonist irbesartan has been shown to improve endothelial function in cardiovascular high-risk patients, which suggests a beneficial effect of treatment with irbesartan on ED. The aim of the present study was to determine the influence of irbesartan on ED in patients with a metabolic syndrome. A total of 1069 consecutive hypertensive patients with a metabolic syndrome from the Documentation of hypertension and metabolic syndrome in patients with Irbesartan Treatment survey were included. Patients were treated with irbesartan or the combination of irbesartan/hydrochlorothiazide for 6 months. ED was assessed using the international index of erectile function. The Cologne Evaluation Questionnaire of Erectile Dysfunction served as a control. Erectile function increased significantly ($P < 0.0001$) after 6 months of treatment with irbesartan, irrespective of dosage and independent of additional treatment with hydrochlorothiazide. Prevalence of ED declined to 63.7% from 78.5% at baseline, along with a significant increase in orgasmic function ($P < 0.001$) and intercourse satisfaction ($P < 0.001$). Treatment with irbesartan alone, as well as in combination with hydrochlorothiazide is associated with an improvement of sexual desire, frequency of sexual contacts and erectile function in hypertensive patients with the metabolic syndrome. These results suggest a beneficial role of angiotensin receptor antagonists in the treatment of metabolic syndrome, and ED.

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Introduction

Erectile dysfunction (ED) is defined as the inability to attain or maintain penile erections sufficient for satisfactory sexual performance.¹ The synthesis of nitric oxide by the endothelium of the penile arteries, the corpus cavernosum and the non-adrenergic/noncholinergic nerves is crucial to the attainment of penile erection. Thus, endothelial dysfunction, as the initial step of atherosclerosis is closely associated with impaired erectile function.

Consistently, there is a strong association of cardiovascular risk factors such as hypertension, hypercholesterolemia, diabetes, smoking and obesity with the extent of ED. Apart from a correlation of the incidence of ED and age, the Massachusetts Male Aging Study, as well as the Cologne Male Survey demonstrated an increase of ED in patients with cardiovascular risk factors or diseases.^{2,3} Therefore, especially patients with a combination of risk factors as in the metabolic syndrome are supposed to have an increased risk of developing ED.⁴

Angiotensin II stimulates the production of free radicals within the endothelial monolayer with subsequent increase of oxidative stress and development of endothelial dysfunction.^{5,6} Moreover, local angiotensin II, synthesized in cavernosal tissue exerts direct effects on erectile function, as indicated by the termination of spontaneous erection by intracavernosal injection of angiotensin II.⁷ Thus, inhibition of the renin–angiotensin system (RAS)

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may improve erectile function by inhibition of specific effects of angiotensin II in the corpus cavernosum, reduction of blood pressure and amelioration of endothelial function in the corpus cavernosum and the penile arteries.⁸ Several angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor antagonists have been shown to increase frequency of sexual encounters and to improve erectile function in cardiovascular risk patients.^{9–12} In addition, the angiotensin receptor antagonist irbesartan ameliorates endothelial function, blood pressure, inflammatory markers and insulin resistance in patients with the metabolic syndrome and is thus likely to have beneficial effects on erectile function.^{13–15} The objective of this open and prospective study (DO-IT, Documentation of hypertension and metabolic syndrome in patients with Irbesartan Treatment) was to evaluate the prevalence of ED in hypertensive patients with the metabolic syndrome and its changes in response to treatment with the angiotensin receptor antagonist irbesartan or the combination of irbesartan/hydrochlorothiazide (HCTZ).

Materials and methods

Study population

A total of 1069 consecutive male patients from the DO-IT survey with hypertension and metabolic syndrome were enrolled in the ED substudy. The study was conducted in Germany from September 2004 to January 2006. A total of 649 general practitioners admitted consecutive patients in accordance to the inclusion criteria of the DO-IT survey. Elevated blood pressure ($>130/85$ mm Hg) or current treatment with antihypertensive drugs and at least two additional criteria: waist circumference >102 cm, triglycerides >150 mg per 100 ml, high-density lipoprotein (HDL) <40 mg per 100 ml and fasting glucose level >110 mg per 100 ml. Patients were either treated with irbesartan (150 or 300 mg) or the combination of irbesartan/HCTZ (150/12.5 or 300/12.5 mg), respectively, for 6 months according to the decision of the attending physician. Follow-up was performed after 3 and 6 months. Additional analysis of subgroups with regard to treatment regime (irbesartan vs irbesartan/HCTZ) and inclusion characteristics (patients with and without antihypertensive treatment prior to the study) was carried out. The study was performed in accordance with the Declaration of Helsinki.

Evaluation of erectile function

Erectile function, as well as orgasmic function, sexual desire and intercourse satisfaction were assessed using the IIEF (international index of erectile function).¹⁶ Severity of ED was determined

by using the IIEF domain for erectile function. The KEED score (Cologne Evaluation Questionnaire of Erectile Dysfunction), previously validated in the “Cologne Male Survey” which comprises socio-demographic characteristics, medical history, prior surgery as well as questions regarding sexual desire and activity and general satisfaction, served as a control.²

Statistical analysis

All data are expressed as mean \pm s.d. Statistical significance was assumed at a P -level <0.05 . Means between two categories were compared by using the two-sided Student's t -test. Relation of variables was determined by Pearson's correlation. The Bowker test and the McNemar test were employed for the analysis of symmetry; change of intergroup differences was analyzed by using the Fisher's exact test. Statistical analysis was performed with SAS 9.1.

Results

Baseline characteristics

A total of 1069 male hypertensive patients with the metabolic syndrome (average baseline blood pressure 158/94 mm Hg) at a mean age of 59.3 ± 9.5 years (19–84 years) were included in the substudy on ED. Baseline characteristics and treatment at the time of enrollment are shown in Table 1. Antihypertensive treatment was changed in 38.5% of patients, 11.1% of the patients had already been treated with irbesartan or irbesartan/HCTZ before enrollment, whereas about half of the patients (50.2%) obtained antihypertensive treatment for the first time. Systolic and diastolic blood pressure significantly decreased after treatment for 6 months (systolic -24 ± 15 mm Hg, $P < 0.0001$; diastolic -14 ± 9 mm Hg, $P < 0.0001$). Patients treated with irbesartan/HCTZ showed a significantly greater reduction in systolic blood pressure (-25 ± 14 mm Hg) compared to those treated with irbesartan alone (-22 ± 15 mm Hg, intergroup difference $P < 0.001$), whereas change of diastolic blood pressure did not differ significantly ($P = 0.08$). The reduction of systolic (-26 ± 14 mm Hg) as well as diastolic blood pressure (-16 ± 9 mm Hg) in patients without prior antihypertensive treatment exceeded the lowering of blood pressure achieved in patients who already received antihypertensive treatment at baseline (systolic -23 ± 15 mm Hg, $P = 0.004$; diastolic -13 ± 9 mm Hg, $P < 0.001$).

At baseline 779 patients (80.6%) reported a desire for regular sexual activity. At follow-up after 6 months, this number had increased significantly to 848 patients (87.8%, $P < 0.0001$). One-third (27.6%) of the patients treated with irbesartan or irbesartan/HCTZ for 6 months, showed a significant increase in

Table 1 Baseline characteristics of patients

	Total	Irbesartan (n = 388)	Irbesartan/HCTZ (n = 673)	P-value	Antihypertensive treatment (n = 725)	No antihypertensive treatment (n = 344)	P-value
Age (years)	59.3 ± 9.5	58.0 ± 9.4	60.0 ± 9.6	0.001	60.7 ± 9.6	56.4 ± 8.8	<0.001
SBP (mm Hg)	158 ± 14	157 ± 14	159 ± 14	0.008	158 ± 15	159 ± 14	0.356
DBP (mm Hg)	94 ± 9	94 ± 9	95 ± 9	0.022	94 ± 9	96 ± 8	<0.001
Duration of hypertension (years)	5.0 ± 4.5	4.6 ± 4.2	5.3 ± 4.7	0.016	6.0 ± 4.6	3.0 ± 3.5	<0.001
Smoking/former smoking	711 (66.6%)	243 (63.0%)	476 (71.0%)	0.008	509 (70.7%)	215 (62.9%)	0.011
Diabetes	701 (65.6%)	242 (62.4%)	455 (67.6)	0.093	514 (70.9%)	187 (54.4%)	<0.001
CAD	305 (28.5%)	80 (20.6%)	225 (33.4)	<0.001	261 (36.0%)	44 (12.8%)	<0.001
MI	110 (10.3%)	34 (8.8%)	76 (11.3%)	0.210	98 (13.4%)	12 (3.5%)	<0.001
Heart failure	86 (8.0%)	28 (7.2%)	57 (8.5%)	0.557	80 (11.0%)	6 (1.7%)	<0.001
Stroke/TIA	40 (3.7%)	10 (2.6%)	30 (4.5%)	0.134	36 (5.0%)	4 (1.2%)	0.002
Hyperlipidemia	24 (2.2%)	8 (2.1%)	15 (2.2%)	1.000	16 (2.2%)	8 (2.3%)	1.000
Nephropathy	95 (8.9%)	32 (8.4%)	63 (9.4%)	0.578	86 (11.9%)	9 (2.6%)	<0.001
BPH	181 (16.9%)	62 (16.0%)	118 (17.5%)	0.553	149 (20.6%)	32 (9.3%)	<0.001
Hepatic steatosis	462 (43.2%)	177 (45.6%)	283 (42.1%)	0.274	341 (47.0%)	121 (35.2%)	0.001
Platelet inhibitor	333 (31.2%)	116 (29.9%)	215 (32.0%)	0.493	290 (40.0%)	43 (12.5%)	<0.001
β-Blocker	337 (31.5%)	123 (31.7%)	214 (31.8%)	1.000	337 (46.5%)	0 (0.0%)	
ACE inhibitor	103 (9.6%)	35 (9.0%)	67 (10.0%)	0.666	103 (14.2%)	0 (0.0%)	
Diuretic	173 (16.2%)	83 (21.4%)	88 (13.1%)	0.001	173 (23.9%)	0 (0.0%)	
CCB	198 (18.5%)	62 (16.0%)	134 (19.9%)	0.119	198 (27.3%)	0 (0.0%)	
α-Blocker	46 (4.3%)	13 (3.4%)	33 (4.9%)	0.274	46 (6.3%)	0 (0.0%)	
Statin	537 (50.2%)	163 (42.0%)	372 (55.3%)	<0.001	404 (55.7%)	133 (38.7%)	<0.001
Oral antidiabetics	495 (46.3%)	169 (43.6%)	323 (48.0%)	0.180	356 (49.1%)	139 (40.4%)	0.009
Insulin	119 (11.1%)	41 (10.6%)	78 (11.6%)	0.686	102 (14.1%)	17 (4.9%)	<0.001

Abbreviations: BPH, benign prostate hyperplasia; CAD, coronary artery disease; CCB, calcium channel blocker; DBP, diastolic blood pressure; MI, prior myocardial infarction; SBP, systolic blood pressure; TIA, transient ischemic attack.
The table demonstrates baseline characteristics and current treatment at baseline of all patients (total) and the subgroups: treatment with irbesartan or irbesartan/HCTZ; patients with and without prior antihypertensive treatment.

Table 2 Association of cardiovascular risk factors and comorbidities with erectile function in univariate analysis

Variable	P-value	Correlation
Age	<0.0001	-0.4566
BMI	<0.0001	-0.1359
HbA1c	0.0159	-0.0785
SBP	0.0250	-0.0692
DBP	0.0242	-0.0696
Duration of hypertension	<0.0001	-0.1977
Heart rate	0.0019	-0.0964
Waist circumference	<0.0001	-0.1230
Smoking	0.0045	-0.0877
Diabetes	0.0003	-0.1120
CAD	<0.0001	-0.2452
Heart failure	<0.0001	-0.1438
Prior myocardial infarction	0.0052	-0.0860
Benign prostate hyperplasia	<0.0001	-0.1627

Abbreviation: BMI, body mass index; CAD, coronary artery disease; DBP, diastolic blood pressure; SBP, systolic blood pressure.

Correlation was performed with the IIEF erectile dysfunction domain, a decrease of the score indicates a decrease of erectile function.

the frequency of sexual encounters ($P < 0.0001$). The extent of increase in frequency of sexual encounters did not differ significantly among the subgroups analyzed (irbesartan 30.6%, irbesartan/HCTZ 26.1%, $P = 0.16$; prior antihypertensive treatment 27.0%, no prior antihypertensive treatment 34.0%, $P = 0.52$).

The IIEF questionnaire, which was completed by 1024 patients revealed a prevalence of ED of 78.5% and a mean ED score of 16.9 ± 9.2 among the study population at baseline. The IIEF and the KEED score correlated strongly concerning the assessment of ED (-0.8597 , $P < 0.0001$).

Predictors of erectile dysfunction

In univariate analysis, cardiovascular risk factors and distinct comorbidities at baseline correlated with a reduced sum score in the ED domain of the IIEF, which represents a decrease in erectile function (Table 2). Systolic ($P = 0.025$) and diastolic blood pressure ($P = 0.024$), as well as the duration of hypertension ($P < 0.0001$) correlated significantly with the ED domain of the IIEF. Serum concentrations of HDL ($P = 0.733$), triglycerides ($P = 0.172$) or low-density lipoprotein ($P = 0.092$) did not exert any significant influence on erectile function.

Current use of calcium channel blockers ($P = 0.0008$), diuretics ($P < 0.0001$), antidiabetics ($P < 0.0001$) and statins ($P = 0.003$) was shown to impair erectile function significantly, whereas β -blockers ($P = 0.229$), ACE inhibitors ($P = 0.099$) and α -blockers ($P = 0.105$) had no significant effect on erectile function in univariate analysis.

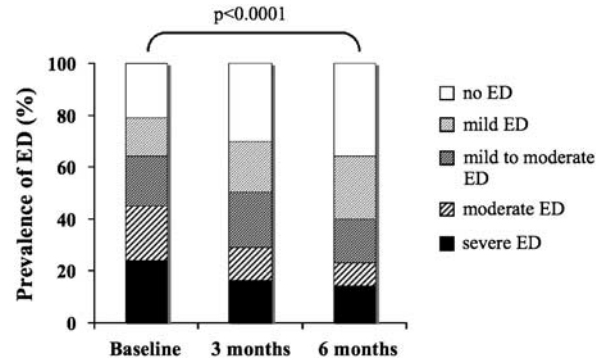


Figure 1 Influence of 6 months treatment with irbesartan or irbesartan/hydrochlorothiazide on prevalence and severity of erectile dysfunction. IIEF, international index of erectile function, an increase of the IIEF-score indicates improvement of erectile function.

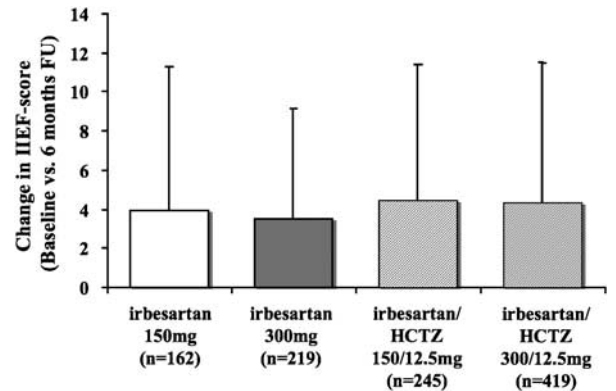


Figure 2 Change of IIEF score dependent on treatment with either irbesartan or the combination of irbesartan/hydrochlorothiazide. IIEF, international index of erectile function, an increase of the IIEF score indicates improvement of erectile function. HCTZ, hydrochlorothiazide. Intergroup difference not significant.

Influence of treatment on erectile dysfunction

Prevalence and severity of ED decreased significantly after treatment for 6 months ($P < 0.0001$; Figure 1). This result was independent of dosage of irbesartan and was not significantly altered by addition of HCTZ: IIEF score: $+3.9 \pm 7.4$ (irbesartan 150 mg), $+3.5 \pm 5.7$ (irbesartan 300 mg), $+4.4 \pm 7.0$ (irbesartan 150 mg/HCTZ 12.5 mg) and $+4.3 \pm 7.2$ (irbesartan 300 mg/HCTZ 12.5 mg; intergroup difference n.s.; Figure 2). The extent of increase in the IIEF score was similar in patients with ($+4.0 \pm 6.8$) and without ($+4.2 \pm 7.0$) prior hypertensive treatment ($P = 0.639$). Consistently, overall prevalence of ED in the study population decreased from 78.5% at baseline to 63.7% at follow-up after 6 months ($P < 0.0001$). Prevalence of ED at follow-up equally decreased in patients with (from 71.8 to 56.5% at follow-up) and without previous antihypertensive treatment (from 81.8 to 67.1% at follow-up, intergroup difference $P = 0.144$). The amount of reduction in ED observed in patients receiving irbesartan (from 74.5 to 58.3% at follow-up) compared to those

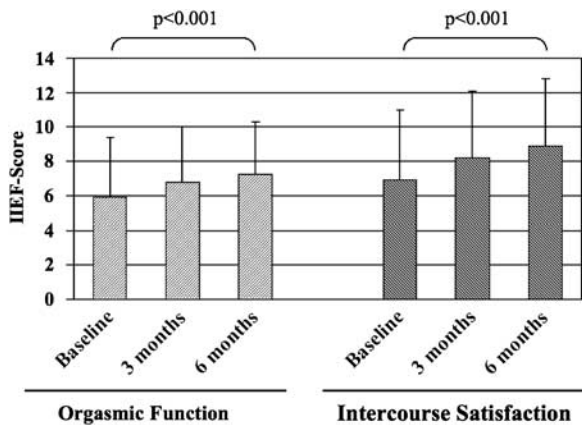


Figure 3 Change in orgasmic function and intercourse satisfaction during 6 months treatment with irbesartan or irbesartan/hydrochlorothiazide ($n=1024$). IIEF, international index of erectile function, increase of the score indicates improvement of function.

receiving irbesartan/HCTZ (from 80.9 to 66.6% at follow-up, intergroup difference, $P=0.188$) did not differ significantly. The appraisal of ED with the KEED score (969 questionnaires completed) was consistent with the results of the IIEF, in revealing a significant decrease in prevalence of ED after treatment with irbesartan or irbesartan/HCTZ (from 58.3% at baseline to 38.5% at 6 months follow-up ($P<0.0001$)).

Orgasmic function and intercourse satisfaction ameliorated significantly after 6 months treatment with irbesartan or irbesartan/HCTZ (Figure 3).

Discussion

ED is a major problem in the elderly and is considered to be an early symptom of generalized atherosclerosis.⁴ In the general population, prevalence of ED amounts to approximately 20–30%, with a steep age-related increase.² Moreover, due to the association of cardiovascular risk factors and cardiovascular diseases with ED, prevalence of ED rises up to 50–75% in cardiovascular high-risk patients, depending on the method of evaluation used.^{3,17,18}

Patients suffering from the metabolic syndrome, including risk factors like hypertension, insulin resistance, obesity and dyslipidemia are considered to be predisposed to develop cardiovascular diseases, which contributes to the incremental role of the metabolic syndrome in health economics, especially in the industrialized Western countries.¹⁹ The present study demonstrates a high prevalence of ED in hypertensive patients with the metabolic syndrome, who represent a cardiovascular high-risk population.²⁰ Regarding the crucial role of nitric oxide in the physiology of erectile function, impairment of the endothelial monolayer in the penile

arteries and the corpus cavernosum may account for these results.

Cardiovascular risk factors and erectile dysfunction
Age, body mass index, waist circumference, hypertension, duration of hypertension, diabetes, smoking, coronary heart disease, heart failure, myocardial infarction and benign prostate hyperplasia were associated with a decrease in the ED score of the IIEF in univariate analysis, that is, with an impairment of erectile function. This observation emphasizes the association of cardiovascular risk factors with ED in hypertensive patients with the metabolic syndrome.^{3,21}

Treatment of hypertension and diabetes is alleged to contribute to an impairment of erectile function.^{3,22,23} The present data indicate an association of a decrease in erectile function with current use of diuretics, calcium-channel blockers, antidiabetics and statins. These results are consistent with prior findings, which demonstrated a decrease in erectile function in patients treated with the calcium channel blocker nifedipine and the diuretic chlorthalidone, but not in patients who received β -receptor blockers.^{20,23–26} The adverse influence of treatment with statins on erectile function is somewhat surprising, taking into account the pleiotropic effects of statins, as for instance the improvement of endothelial function due to an upregulation of the endothelial nitric oxide synthase.^{27,28} Recently the hydroxymethylglutaryl (HMG) coenzyme A reductase inhibitor rosuvastatin has been shown to exert beneficial effects on erectile function in diabetic mice.²⁹ Moreover, in patients with ED who received sildenafil, atorvastatin tended to improve erectile function.³⁰ Thus, impairment of erectile function by treatment with statins is unlikely. On the contrary, provided that endothelial function is improved by treatment with statins, this effect would have to be regarded as beneficial to erectile function. Conflicting results of our study might be explained by distinct comorbidities, present in patients treated with statins. Treatment with statins was significantly more frequent in patients with prior antihypertensive treatment as well as in patients treated with the combination of irbesartan/HCTZ. Patients in these subgroups tended to have pronounced comorbidities, such as hypertension, diabetes and so on, and divergent determining factors, such as age.

Influence of irbesartan on erectile function

Inhibition of the renin-angiotensin system has recently been demonstrated to increase the frequency of sexual encounters.^{11,12} Furthermore, selective blockade of the angiotensin receptor with valsartan or losartan improved erectile function and

sexual desire in hypertensive male patients.^{9,10} In addition, the angiotensin receptor antagonist irbesartan has been shown to decrease blood pressure, insulin resistance and endothelial dysfunction significantly in patients suffering from the metabolic syndrome.^{13,31} These results are concurrent with the present findings, which demonstrate a significant decrease of systolic and diastolic blood pressure through treatment with irbesartan or irbesartan/HCTZ, as well as an association of these treatment regimes with an increase in sexual desire and in the frequency of sexual encounters. Hence, the erectile function score increased throughout the treatment period of 6 months with the angiotensin receptor antagonist, indicating an improvement of erectile function. Consistently, prevalence of ED declined by about 15% in all subgroups. Positive effects of treatment on erectile function are likely to be causally associated with a reduction in blood pressure. This suggestion is supported by the results of those patients without prior antihypertensive treatment. Improvement of erectile function was pronounced in this subgroup, supposedly because the reduction in systolic and diastolic blood pressure was significantly higher in this group in comparison with patients who already received antihypertensive treatment before enrollment.

Diuretics are considered to impair erectile function.²³ Surprisingly, the improvement in erectile function as well as the change of prevalence of ED was comparable in patients irrespective of the addition of the diuretic HCTZ to the treatment regime. On the one hand, beneficial effects of irbesartan are likely to exceed the supposed adverse effect of diuretics on erectile function. Moreover, blood pressure reduction was significantly higher in patients treated with the combination. Thus, the negative effect of the diuretic on erectile function might have been biased by an improvement in blood pressure reduction in these patients. On the other hand, a previous study which highlighted an impairment of erectile function by treatment with diuretics detected this effect in the first 12 months of treatment only, whereas after treatment for 24 months, erectile function was found not to be impaired anymore.²³ Thus, in the course of treatment, blood pressure reduction is likely to overcome the questionable negative effect of diuretics. Indeed, this suggestion is in conflict with the present results in univariate analysis of cardiovascular drugs affecting erectile function. Nevertheless, it is consistent with the study mentioned above. A follow-up period of 6 months is apparently too short for balancing the effects of diuretics in terms of ED.

Irbesartan has been shown to reduce vascular inflammation and consecutively improve endothelial function independent of blood pressure reduction.¹³ Consistently, recent findings demonstrated that rather the combination of increased endothelial function, decreased insulin resistance and reduced

oxidative stress is likely to account for these results in patients with the metabolic syndrome.^{13,19,31} The present study reveals an association of multiple cardiovascular risk factors, especially blood pressure, body mass index, waist circumference, diabetes and HbA1c with ED in univariate analysis. These parameters in particular are known to be ameliorated by treatment with angiotensin receptor antagonists.^{13,31} Thus, beneficial effects of angiotensin receptor blockade on vascular endothelial function are likely to affect the endothelium of the penile arteries and the corpora cavernosa just as well, with consecutive improvement of erectile function, independent of blood pressure. This, however, cannot be concluded from the present results and remains to be investigated.

Methodology and limitations

The IIEF is an established, internationally validated questionnaire of ED.^{16,32} Moreover, the KEED score, previously validated in the general population around Cologne, Germany, in the course of the Cologne Male Survey, was used as a control.^{2,25} Results from both questionnaires correlated significantly in the present study population of patients with the metabolic syndrome. Thus, results are suggested to be valid and likely to be independent from incorrect response to the questionnaires. Nevertheless, a remaining bias by test experience of patients cannot be excluded, taking into account the absence of a placebo group. However, the IIEF-ED score has previously been used in numerous trials and a recent placebo-controlled trial did not reveal any change of the score in the placebo group after 12 weeks.³²

The results of the study are limited to the open label design without a placebo control group. Patients included in this study might have had a benefit from closer monitoring and improved therapeutic management with a potential consecutive increase in erectile function. In addition, high prevalence of ED at baseline implicates an improvement of treated patients. A relevant influence of these possible confounders cannot be excluded, yet, it is not considered to be highly significant with regard to pronounced changes in prevalence of ED.

In conclusion, treatment with the angiotensin receptor antagonist irbesartan or the combination of irbesartan and HCTZ is associated with an improvement in sexual desire, frequency of sexual contacts and erectile function in hypertensive patients with the metabolic syndrome. These effects are, at least in part, likely to be dependent on a reduction in blood pressure. The notion that mechanisms beyond blood pressure reduction play a role in the beneficial effects of irbesartan on erectile function is plausible with regard to the advantageous effects of irbesartan on endothelial

function, but cannot be concluded from the present study. Whether treatment with ACE inhibitors, angiotensin receptor antagonists or the combination thereof has different effects on endothelial and erectile function will be evaluated in the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial/Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (ONTARGET/TRANSCEND) substudy of ED.²⁰

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Conflicts of interest

M Baumhäkel and M Böhm received grants for lectures, clinical trials and animal studies from BMS, Germany, not related to the present study.

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