

Significance of initial blood pressure and comorbidity for the efficacy of a fixed combination of an angiotensin receptor blocker and hydrochlorothiazide in clinical practice

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Background: Two-thirds of all patients with arterial hypertension need drug combinations to achieve blood pressure (BP) goals. Fixed combinations have high efficacy and result in high patient compliance. 300 mg irbesartan plus 25 mg hydrochlorothiazide (HCTZ) has been investigated only in clinical trials but not in daily practice.

Methods: A multicenter, noninterventional, noncontrolled observational study with 8123 patients seen by 1604 physicians in daily practice. BP reduction (office measurements), co-morbid disease and tolerability were documented over a 6-month observational period.

Results: At mean baseline BP of $161 \pm 15/94 \pm 10$ mmHg, administering of fixed combination resulted in a substantial BP reduction averaging $28 \pm 15/14 \pm 10$ mmHg ($P < 0.001$). Decrease of systolic BP ran parallel with increasing systolic baseline BP (Spearman's Rho -0.731 ; $P < 0.0001$; diastolic BP vs diastolic baseline BP Rho 0.740 ; $P < 0.0001$), independent from patient characteristics (age, obesity, diabetes or nephropathy) but enhanced with short history of hypertension ($P < 0.0001$ vs long history), prior beta blockers ($P = 0.001$ vs prior angiotensin receptor blockers [ARBs]), prior calcium channel blockers ($P = 0.046$ vs prior ARBs) and no prior medication ($P = 0.012$ vs prior ARBs). High compliance ($>98\%$) and low incidence of adverse events (0.66%) were documented.

Conclusions: The fixed combination of 300 mg irbesartan with 25 mg HCTZ was efficacious and tolerable in an unselected patient population in primary care.

Keywords: hypertension, combination therapy, obesity, irbesartan, noninterventional study, diuretics

Introduction

Arterial hypertension is one of the commonest direct or indirect causes of increased cardiovascular morbidity and mortality worldwide. Its prevalence, for example, in the UK is 42%, in Spain it is 47% and in Germany it is 55%, while the rate in the US and in Canada is 28% and 27% respectively.¹ Despite this strikingly high prevalence, the control rate of treated patients worldwide is low. Even in the US, only half of all treated patients achieve the target values (53.1%), and in Germany the figure is only 33.6%.² An average reduction in systolic blood pressure of 2 mmHg would in fact be associated with a 7% reduction in the stroke rate and a 10% reduction in ischemic heart diseases.³

Since many patients are not adequately controlled with monotherapy, nowadays the majority of patients are treated with a combination of 2 or more antihypertensive drugs.

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In Germany around one-third of patients receive monotherapy, one-third a combination of 2 substances and one-third a combination of 3 and more drugs (IMS Datamonitor 2003). The relevant guidelines^{4,5} recommend that combination therapy should be initiated early. The guidelines of the ESH/ESC 2007⁵ provide for the use of combination therapy if monotherapy is unsuccessful after the antihypertensive agent has been changed and in high dosages, or if patients with high cardiovascular risk present with blood pressure values which are 20/10 mmHg above the target values. Nowadays the general recommendation for combination therapy is the combination of blockers of the renin-angiotensin system with thiazide diuretics or calcium antagonists.^{4,5} The advantage of a fixed dose combination is increased compliance, which ensures effective and lasting control of blood pressure.

Irbesartan has proved effective in reducing blood pressure in a number of clinical studies.⁶⁻⁸ With the fixed combination of 300 mg irbesartan and 25 mg hydrochlorothiazide (HCTZ), a high-dose combination has been available for some time now which achieves an even greater reduction in blood pressure.⁹ In addition, the RAPIHD study showed that the primary use of this combination in patients with severe hypertension is also effective and well tolerated.¹⁰

However, the results from randomized, controlled studies cannot be applied without further evaluation in everyday practice, because of their specific patient selection, close monitoring and generally short duration. The aim of the noninterventional study on hand was therefore to investigate the efficacy of the high-dose combination therapy under practice conditions in a non-selected patient population, and to document possible rare, so far undetected side effects of this fixed combination.

Patients and methods

The noninterventional, noncontrolled study was conducted with the aid of practice-based doctors throughout Germany (*i-Control*). These were a random sample of specialists in general medicine, internal medicine, cardiology and of practitioners from all the regions defined by the Institute of Medical Statistics (IMS). The study was registered in accordance with § 67 (6) German Drugs Law (AMG) at the Federal Institute of Drugs and Medical Devices (BfArM) and at the National Association of Statutory Health Insurance Physicians (KBV).

Issue investigated

The investigation was conducted in order to document the efficacy and tolerability of the fixed combination of irbesartan 300 mg/HCTZ 25 mg (CoaprovelTM 300 mg/25 mg;

sanofi-aventis Deutschland GmbH, Berlin) in patients with arterial hypertension who had previously received pharmacotherapy and whose blood pressure was so far not controlled by other antihypertensives.

Patients

Patients were documented who at the time of the investigation were at least 18 years old, showed primary arterial hypertension with blood pressure values $\geq 140/90$ mmHg (diabetics $\geq 130/80$ mmHg) and in whom previous pharmacotherapy of the hypertension had not resulted in the target blood pressure being achieved. In addition, the doctors had a free selection of patients within the scope of drug licensing (indications and contraindications), that is, no other inclusion and exclusion criteria were defined. They were also able to adjust the dosage of the concomitant medication throughout the duration of the study as desired.

Documented variables

At the enrolment visit, demographic data (age and gender) and also anamnestic data relating to cardiovascular risk factors were collected. In addition the weight, height, abdominal measurement (waist circumference), hip measurement, diseases related to the hypertension, previous antihypertensive therapy and concomitant medication, as well as a number of laboratory values for classification into certain risk groups were documented. At the optional check-up after 3 months, changes in blood pressure and medication as well as the occurrence of adverse events were documented. At the end of the observation after 6 months, a number of demographic data were again measured in the practice and blood pressure readings, medication and changes in the laboratory values were documented. In particular, the individual target blood pressure value for the documented patient was requested at the start of the investigation and it was verified that it had been achieved during the further course of the investigation.

Execution

The physicians were asked to document patients who were being treated with a combination of irbesartan 300 mg/HCTZ 25 mg because of inadequately controlled primary arterial hypertension. The documentation forms were recorded by the Clinical Research Organization (CRO) *factum – Gesellschaft für Statistik, wissenschaftliche Information und Kommunikation mbH*, Offenbach. The data in all documentation forms were examined for their plausibility. The documentation forms did not undergo comparison with the source documents for monitoring. The patients were recorded in pseudonymized

form, ie, only the age and gender of the patient were entered in the documentation, and all data collected during the observation were treated confidentially. Data were electronically stored in accordance with data protection provisions. The fees for documentation activities were paid in accordance with the official scale of physicians' fees (Gebührenordnung für Ärzte, GOÄ).

Adverse drug reactions

Adverse drug reactions (ADRs) were explicitly asked about and recorded in detail (nature, date, duration, result, and causal relationship with the therapy). All physicians were asked to report serious adverse events to the pharmaceutical manufacturer immediately, which notified the BfArM in accordance with legal requirements.

Statistics

The statistical analysis was descriptively conducted, exploratively assessed, and then produced in tabular and graphic form. For categorical data absolute and relative frequencies and for steady variables average and standard deviation were calculated. The confidence intervals were calculated with the aid of the statistics program BIAS Version 8.4.6, publ. epsilon for theta of a binomial distribution; all other calculations were performed with the aid of the statistics program SPSS for Windows (Release 15.0). The statistical testing procedures conducted were the Mann–Whitney U test or the Kruskal–Wallis test for group differences in terms of changes in blood pressure. The Spearman's Rho was used for rank correlations (relationship of initial blood pressure to reduction in blood pressure). In order to be able to record rare ADRs, the number of cases was set at 8000 patients: this allows ADRs up to an incidence of 0.1% to be recorded with a probability of almost 100% and ADRs with an incidence of 0.01% with a probability of 55.1%.

Results

A total of 8123 patients were included in the observation between November 2006 and January 2008 in 1604 centers (median: 5 patients per center).

The patients had an average age of 63.4 ± 11.3 years. 50.8% of them were male, and the patients had an average BMI of 29.4 ± 4.9 kg/m². The initial blood pressure was $160.5 \pm 15.3/93.9 \pm 9.6$ mmHg with an average duration of hypertension of 8.4 years (Table 1). No concomitant diseases were present in 14.1% of the patients. The most common concomitant diseases were lipid metabolic disorders (53.7%), diabetes mellitus (38.8%) and metabolic syndrome (19.1%).

Medication

During the observation phase all patients received 300 mg irbesartan/25 mg HCT. In addition, some patients received further concomitant medication, comprising after 6 months 37.2% beta blockers, 25.3% calcium antagonists, 12.8% diuretics and 8.4% angiotensin-converting enzyme (ACE) inhibitors. Concomitant medication with alpha blockers or aldosterone antagonists was rare (Table 2). When making the decision in favor of a combination, the doctors most commonly switched from an ACE inhibitor medication (54.7%), diuretics (50.3%) and beta blockers (49.0%).

Antihypertensive effect according to baseline blood pressure

After a follow-up observation of 6 months the systolic blood pressure was reduced on average by 27.9 ± 15.2 mmHg and the diastolic by 14.0 ± 10.2 mmHg compared with the initial blood pressure (in each case $P \leq 0.001$ compared with initial value). Based on a target value of $<140/90$ mmHg, 68.6% of the patients were normalized (systolic normalization 71.9%, diastolic 88.3%).

Figure 1A presents the reduction in systolic blood pressure achieved as a function of the initial systolic blood

Table 1 Patient characteristics at the start of therapy

Patient population	Evaluable data (n)	Values
Total number of patients	8123	
Men (%)	8037	50.8
Age (years; mean \pm SD)	7970	63.4 ± 11.3
Body weight (kg; mean \pm SD)	8083	85.8 ± 16.0
BMI (kg/m ² ; mean \pm SD)	8079	29.4 ± 4.9
Smokers (%)	7589	22.8
Blood pressure practice measurement		
Systolic (mmHg; mean \pm SD)	8096	160.5 ± 15.3
Diastolic (mmHg; mean \pm SD)	8094	93.9 ± 9.6
Duration of hypertension (years; average \pm SD)	7952	8.4 ± 6.5
Concomitant diseases^a		
Diabetes mellitus (%)	8102	38.8
Peripheral arterial disease (%)	8102	6.3
Diabetic nephropathy (%)	8102	4.8
s/p myocardial infarction (%)	8102	6.9
Lipid metabolic disorder (%)	8102	53.7
Cardiac insufficiency (%)	8102	8.2
s/p stroke (%)	8102	4.4
No concomitant diseases (%)	8102	14.1

^aPhysician defined, no specific testing.

Abbreviations: SD, standard deviation; BMI, body mass index; s/p, status post.

Table 2 Therapy of arterial hypertension before and during observation

	Before the study		After start of study		After 3 months		After 6 months	
	n	%	n	%	n	%	n	%
ACE inhibitors	4435	54.7	664	8.2	649	8.0	682	8.4
Beta blockers	3976	49.0	2946	36.3	2945	36.3	3015	37.2
Diuretics	4081	50.3	1068	13.2	996	12.3	1042	12.8
Calcium antagonists	2569	31.7	1878	23.2	1931	23.8	2052	25.3
AT ₁ blockers	2159	26.6	— ^a	— ^a	— ^a	— ^a	— ^a	— ^a
Alpha blockers	378	4.7	292	3.6	285	3.5	308	3.8
Aldosterone antagonists	144	1.8	114	1.4	112	1.4	127	1.6
Irbesartan 300 mg/HCTZ 25 mg	— ^a	— ^a	8110	100.0	7855	96.9	7869	97.0
Other	651	8.0	544	6.71	536	6.6	597	7.4
No medication	104	1.3	0	0.0	0	0.0	9	0.1
1 active substance group	1779	21.9	0	0.0	25	0.3	51	0.6
2 active substance group	2745	33.8	3812	47.0	3642	44.9	3634	44.8
3 active substance group	2082	25.7	2679	33.0	2611	32.2	2,622	32.3
>3 active substance groups	1310	16.2	1619	20.0	1629	20.1	1697	20.9
Not specified	90	1.1	0	0.0	203	2.5	97	1.2

^aIrbesartan/HCTZ was not asked about at the start and other AT₁ blockers were not asked about during the course of the study.

Abbreviations: ACE, angiotensin-converting enzyme; HCTZ, hydrochlorothiazide.

pressure (Rho -0.731 ; $P < 0.0001$). Figure 1B presents the reduction in diastolic blood pressure achieved as a function of the diastolic initial blood pressure (Rho -0.740 ; $P < 0.0001$). Figures 2A and B shows the proportion of patients with normalized blood pressure as a function of the systolic/diastolic initial blood pressure. Here, too, a direct dependence of the frequency of normalization on the systolic initial blood pressure is shown: the higher the initial blood pressure, the lower was the normalization of both parameters of systolic and diastolic blood pressure.

Antihypertensive efficacy according to patient characteristics

Depending upon classification of the patient population based on the parameters of age, BMI, diabetes, duration of hypertension, nephropathy and previous therapy, the values for the reduction in systolic blood pressure ranged from -26.8 to -30.2 mmHg. The reduction in blood pressure did not depend on patient characteristics such as age, obesity, diabetes and nephropathy. In contrast, the reduction in blood pressure in the case of short duration of the disease was increased vs long duration ($P < 0.0001$). Likewise blood pressure reduction in case of prior treatment with beta blockers ($P = 0.001$), calcium antagonists ($P = 0.046$) and no prior therapy ($P = 0.012$) was increased compared with angiotensin receptor blockers (Figure 3).

Compliance

Most (96.5%) of the patients took the medication for the whole duration of the observational period (2.1% not specified). Of the 110 patients (1.36%) who terminated the therapy prematurely (22 because of adverse events), 44.6% were male and 17.3% were smokers. The average age of drop-outs was 64.7 ± 12.5 years, and the average BMI was 29.8 ± 4.8 kg/m². Of the drop-outs, 88.2% had concomitant diseases, with lipid metabolic disorders at 47.3% and diabetes mellitus and obesity (BMI > 30 kg/m²) each at 41.82% being most commonly represented.

Tolerability of the therapy

Adverse events occurred during the observation in a total of 54 patients (0.66%). These were classified as ADRs in 35 patients (0.43%) (Table 3). The adverse event was rated as serious in a total of 12 patients (5 with ADRs).

ADRs are listed in Table 4. The serious ADRs included: transient ischemic attacks with signs of paralysis, ischemic optic neuropathy with visual impairment or blindness in the left eye, death of a patient as a result of carcinoma (the doctors considered a connection with the medication to be unlikely for the patients named above), myocardial infarction (unrelated or unlikely related), and also hypotension and vertigo (doctors' opinion: possible).

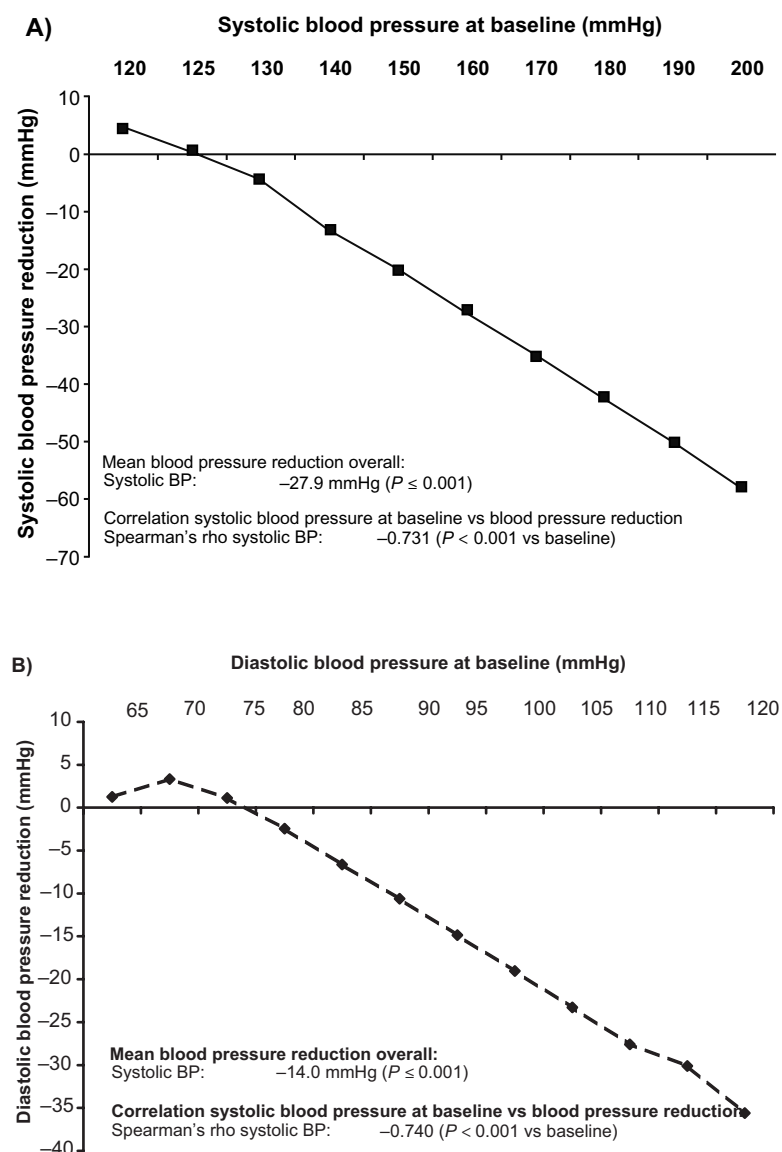


Figure 1 Reduction in blood pressure (BP) after 6 months as a function of the systolic **A)** and diastolic **B)** initial blood pressure value.

Discussion

The patients documented in this noninterventional observational study were predominantly hypertensive patients with increased cardiovascular risk, whose blood pressure was so far not controlled, or only inadequately controlled, by monotherapy or low-dose combination therapy. Current guidelines recommend initial high-dose combination therapy for such patients.^{4,5} Observation of the use of irbesartan 300 mg/HCTZ 25 mg over a period of 6 months produced the following important findings in this context: 1) The use of the fixed combination resulted in a clear further reduction in blood pressure (27.9/14.0 mmHg, $P < 0.001$). 2) An almost linear increase in efficacy can be expected depending on the systolic initial blood pressure.

The higher the initial blood pressure, the greater the decrease in blood pressure. This might be significant especially for older patients with predominantly increased systolic blood pressure. 3) The efficacy is quantitatively not dependent on the presence of a range of concomitant diseases. 4) High compliance of >98% because of a low incidence of adverse events (0.66%) facilitates long-term adequate control of blood pressure.

Efficacy of irbesartan 300 mg/HCTZ 25 mg in everyday practice

In 1999 Kochar et al⁹ tested the antihypertensive efficacy of the combination of irbesartan and HCTZ in various dosages for 8 weeks in a matrix study. At an average initial

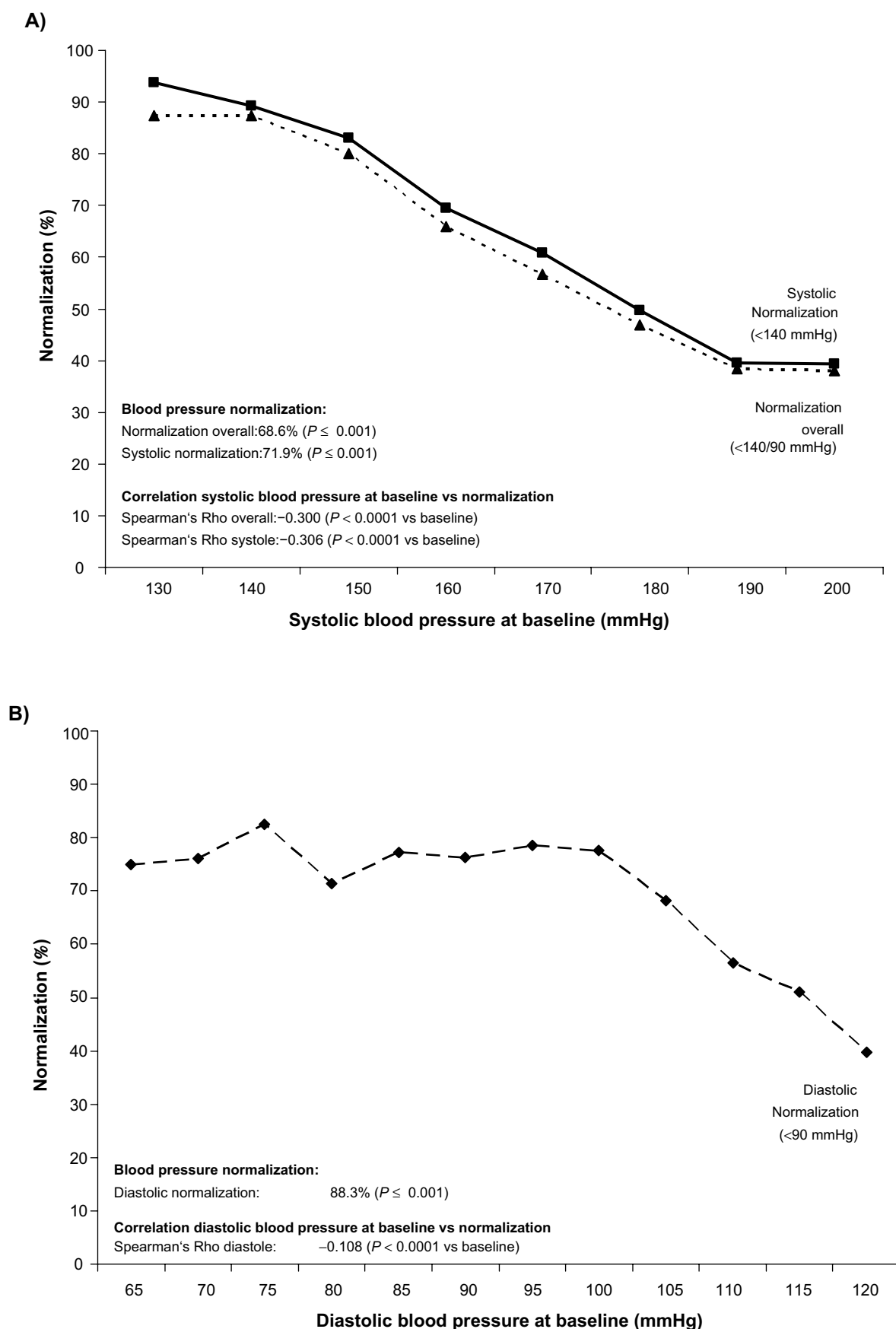


Figure 2 Normalization of blood pressure (BP) after 6 months in total and as a function of the systolic **A)** and diastolic **B)** initial blood pressure value.

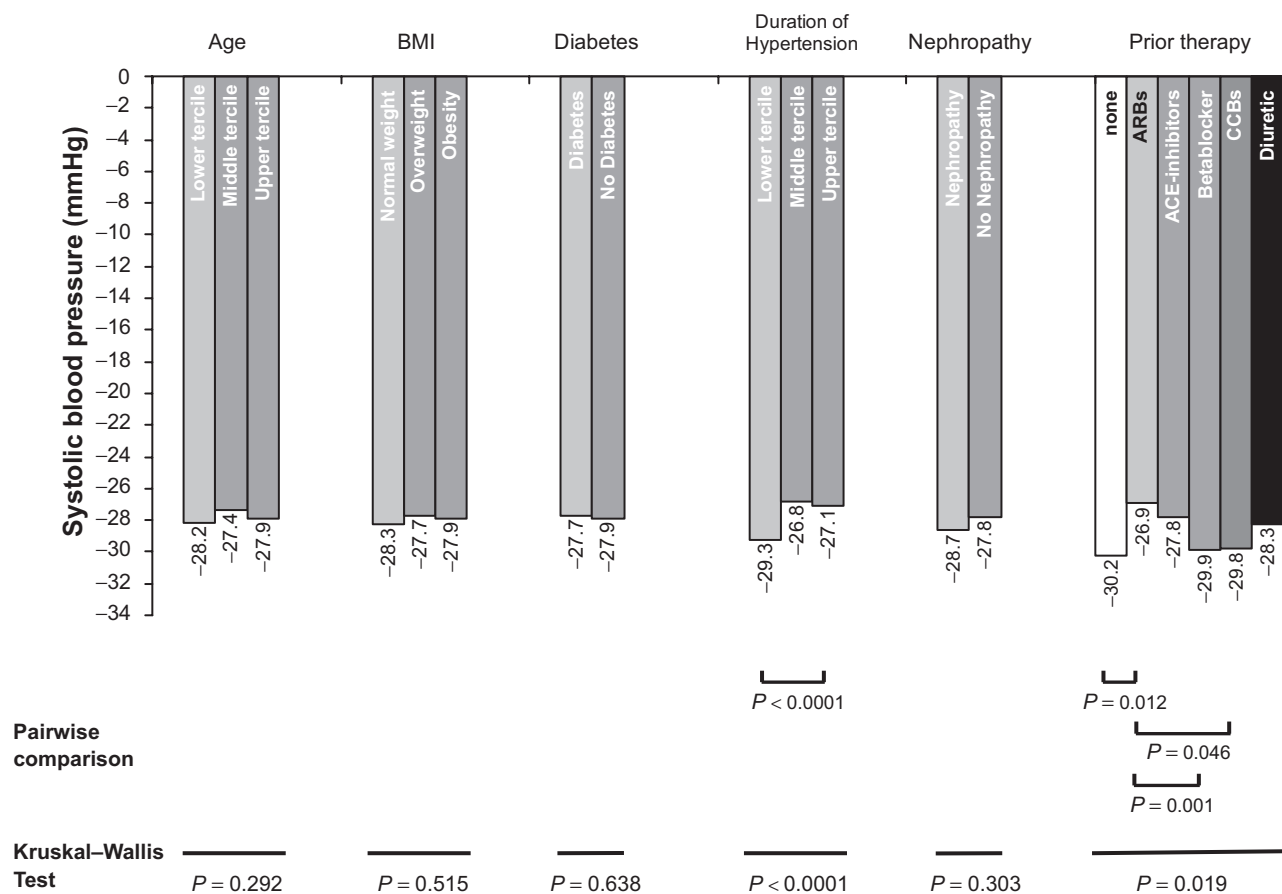


Figure 3 Reduction in systolic blood pressure (BP) (mmHg) as a function of defined patient characteristics/previous medication. Use of the Kruskal-Wallis Test for differences within groups. Significant *P*-values for pairwise comparisons are indicated; other comparisons are not significant. Age: Lower tertile (LT) up to 58 years, middle tertile (MT) > 58 to 69 years, upper tertile (UT) > 69 years; body mass index (BMI): LT up to 25 kg/m², MT > 25 to 30 kg/m², UT > 30 kg/m²; duration of hypertension: LT up to 5 years, MT > 5 to 10 years, UT > 10 years.

Abbreviations: ACE, angiotensin-converting enzyme; CCBs, calcium channel blockers.

Table 3 Number of patients with adverse events (AE) without causal relationship or adverse drug reactions (ADR) in the observation period

Total population (n = 8123) (multiple answers possible)	n	%
Patients without AE	8,056	99.18
Patients with AE	54	0.66
Serious	12	0.15
Not serious	43	0.53
Therapy discontinued because of AE	22	0.27
Patients with ADR	35	0.43
Serious	5	0.06
Not serious	30	0.37
No verification possible	13	0.16

Notes: Binominal confidence interval calculated according to BIAS Version 8.4.6.

blood pressure of $151 \pm 14.7/100 \pm 4.2$ mmHg, an average reduction in blood pressure of $23.1 \pm 15.0/14.4 \pm 8.0$ was achieved in this study with irbesartan 300 mg/HCTZ 25 mg. In a further study of Neutel, patients with severe hypertension (initial blood pressure 171.5/77.4 mmHg) were treated for 7 weeks with the irbesartan/HCTZ high-dose combination.¹⁰ A reduction in blood pressure of 31.7/24.5 mmHg was achieved. The results of the noninterventional study supplement these data and findings with data from everyday clinical practice. The reduction in systolic blood pressure extrapolated from the clinical studies for this initial blood pressure is 27.4; in fact an average reduction in blood pressure of 27.9 mmHg was achieved. Because of the lack of a wash-out phase, the lack of guidance for the changeover and the lack of concomitant medication, in theory a lower reduction in blood pressure would be expected, but this was not confirmed in the study.

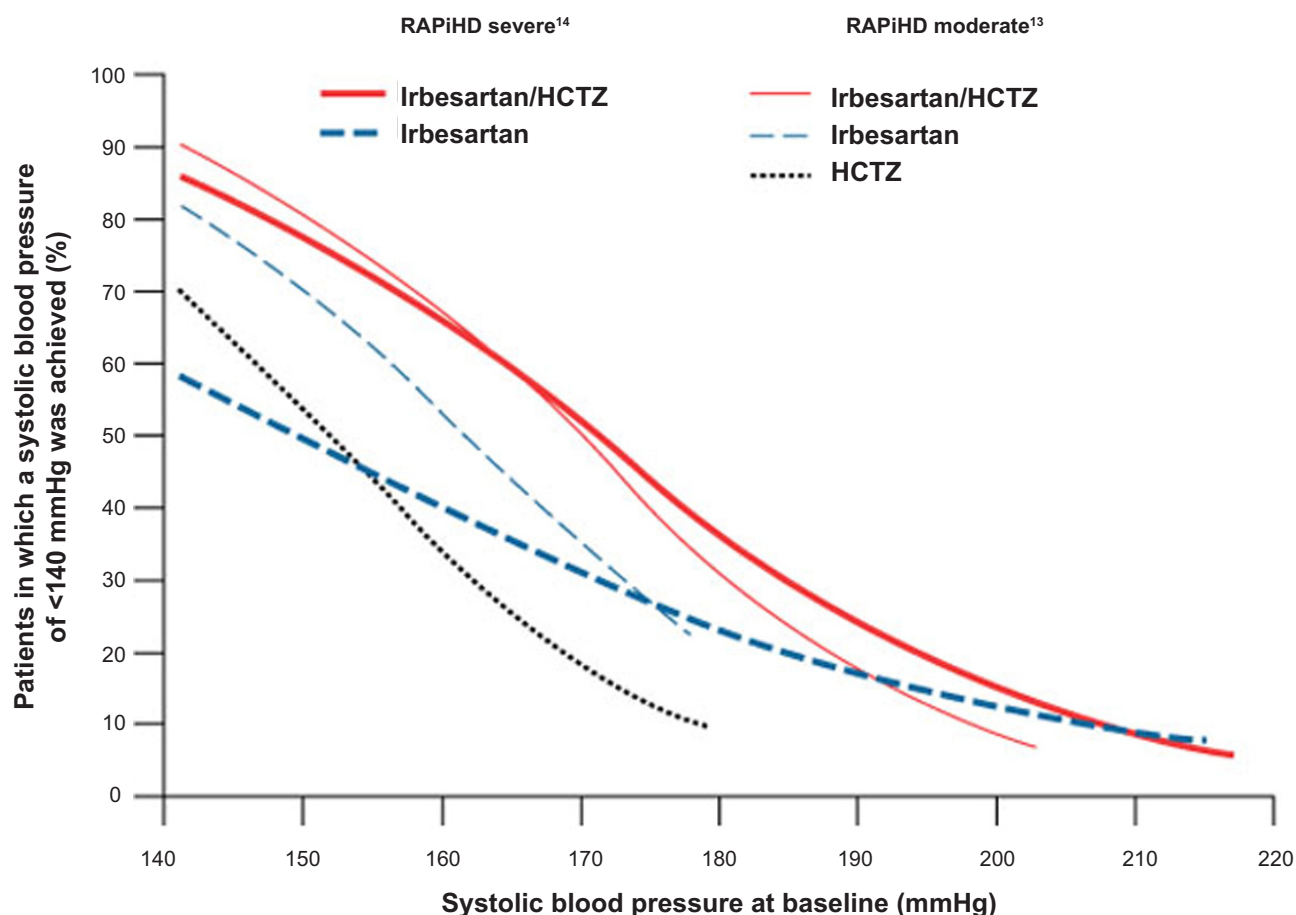


Figure 4 Systolic normalization (<140 mmHg) according to systolic initial blood pressure value in the studies RAPIHD severe¹⁰ and RAPIHD moderate²⁴ (after Franklin)¹⁸. RAPIHD severe was a 7-week trial in patients with severe hypertension (seated DBP [SeDBP] ≥ 110 mmHg). Eligible patients entered a 7-day single-blind placebo lead-in period. Patients with SeDBP ≥ 110 mmHg at 2 consecutive visits during the lead-in period were randomized in a 2:1 ratio to irbesartan/HCTZ 150/12.5 mg fixed-dose combination therapy force-titrated to 300/25 mg after week 1 or irbesartan 150 mg monotherapy force-titrated to 300 mg after week 1. RAPIHD moderate was a 12-week trial in patients with moderate hypertension (seated SBP [SeSBP] 160–180 mmHg or SeDBP 100–110 mmHg). Eligible patients entered a 21-day single-blind placebo wash-out period before randomization in a 3:1:1 ratio to irbesartan/HCTZ 150/12.5 mg fixed-dose combination therapy force-titrated to 300/25 mg after week 2, irbesartan 150 mg monotherapy force-titrated to 300 mg after week 2, or HCTZ 12.5 mg monotherapy force-titrated to 25 mg after week 2.

Abbreviation: HCTZ, hydrochlorothiazide.

To date there are no direct comparisons available of the relative efficacy of irbesartan 300 mg/HCTZ 25 mg with fixed combinations of other sartans with 25 mg HCTZ. However the relative efficacy from the comparison of substances in monotherapy^{7,8,11} is generally maintained for the corresponding combinations with HCTZ.^{12,13} These studies showed a greater reduction in blood pressure from 150 mg irbesartan compared with 50 mg losartan^{7,11,13} both with and without HCTZ. In a study with losartan 100 mg/HCTZ 25 mg, a reduction in blood pressure of 24.0/11.8 mmHg was achieved at an initial blood pressure of 160.8/94.4 mmHg.¹⁴ These data are largely comparable with the data on hand (reduction in blood pressure 27.9/14.0 at an initial blood pressure of 160.5/93.9 mmHg), even if they are nominally higher. Other data relating to the efficacy

of high-dose fixed combinations in everyday practice are not yet available.

Predictor of reduction in blood pressure

The antihypertensive efficacy of substances is quite decisively dependent on the blood pressure values at the start of the study.¹⁵ A range of studies has shown that the higher the initial value, the higher the achievable reduction in blood pressure^{16,17} or the more common is the normalization of blood pressure after the start of therapy^{16–19} (see also Figure 4). This might be related to a regression to the mean phenomenon in single patients but certainly not in the majority of patients in this study of more than 8123 patients. Thus the average reduction in blood pressure in the study of Schühlen et al was 26.8/13.5 mmHg, and in patients with severe hypertension

Table 4 Adverse drug reactions (ADR) coded according to MedDRA® Version 10.0

Total population (n = 8123)	n	%
MedDRA® primary System		
Organ Classes (SOC)		
Patients with ADR	35	0.43
Cardiac disorders	2	0.02
Eye disorders	1	0.01
Gastrointestinal disorders	5	0.06
General disorders and administration site conditions	5	0.06
Investigations	1	0.01
Metabolism and nutrition disorders	2	0.02
Musculoskeletal and connective tissue disorders	1	0.01
Nervous system disorders	15	0.18
Renal and urinary disorders	1	0.01
Respiratory, thoracic and mediastinal disorders	4	0.05
Skin and subcutaneous tissue disorders	4	0.05
Vascular disorders	6	0.07
Patients without ADR	8075	99.41
Verification not possible	13	0.16
Total	8123	100.0

(41.7/20.5 mmHg). In particular, an analysis of the prediction of the reduction in blood pressure in the INCLUSIVE study showed that an increase of 1 mmHg in the systolic initial blood pressure can predict an additional reduction of 0.9 ± 0.1 mmHg in the systolic blood pressure.²⁰ The study presented here also shows a linear relationship between the systolic/diastolic blood pressure at the start of the study and the achievable reduction in blood pressure (Figure 1). On the other hand, the incidence of hypotension in the study on hand is rare, even in higher dosages. Clear effects on blood pressure are not expected in normotensive patients. Out of over 8123 patients, only 13 terminated the therapy because of vertigo or hypotension.

The analysis of the study on hand continued to show no dependency of the reduction in blood pressure on age, diabetes, weight and nephropathy. These results therefore confirm previous analyses of the efficacy of irbesartan/HCTZ in various patient populations.^{10,21–23} In contrast, the predictor analysis of the INCLUSIVE study reported that higher reductions in blood pressure were to be expected in patients with higher initial blood pressure values (see above), type 2 diabetes (+5.0 mmHg), with statin intake (+2.1 mmHg) and for women (+3 mmHg).²⁰

Compliance and tolerability

Irbesartan is well tolerated both in monotherapy and also in combination with HCTZ. In a pooled analysis¹⁸ of the two

RAPiHD studies (moderate and severe),^{10,24} 37.0% adverse events occurred, which were ascribed to the medication in 12.5% of the patients (0.9% serious). These figures were only slightly raised compared with irbesartan monotherapy. In the healthcare study on hand, <1% adverse events were reported; 0.43% were linked to the medication (0.06% serious).

Conclusions

The fixed combination of 300 mg irbesartan and 25 mg HCTZ is effective and well tolerated. The effect increases depending on the initial blood pressure, but is largely independent of various patient characteristics. This study thus confirms the data from previous clinical studies for a nonselected patient group in everyday practice.

Acknowledgments

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Disclosures

The study was conducted by sanofi-aventis Deutschland GmbH. RES declares to have received research support and lecture honoraria from AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Novartis, sanofi-aventis, and Takeda. PB declares to have received research support and lecture honoraria from sanofi-aventis, Daiichi Sankyo, Takeda. MS is an employee of sanofi-aventis.

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