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Carvedilol and Hydrochlorothiazide in Hypertensives with Metabolic Disorder: Not Always Bad News – An Austrian Survey

S. Perl, S. Sock, K. Stoschitzky, J. Plank, E. Kvas, R. Zweiker

Abstract: *Introduction:* According to recent guidelines, betablockers (BB) are not first-choice anti-hypertensives for diabetic and dyslipidemic patients, though third-generation BB like carvedilol might have more beneficial metabolic effects than older compounds. We aimed at investigating metabolic parameters in hypertensive patients on the combination of carvedilol with a thiazide-type diuretic.

Methods: In 427 centers, 2163 hypertensives (52 % men) were recruited in this observational investigation [mean \pm SD]: age 64 ± 11 y, BMI 29 ± 4 kg/m², waist circumference: 97 ± 13 cm (women), 105 ± 11 cm (men). Visits were scheduled every three months. Blood pressure (BP), lipid parameters, waist circumference and HbA_{1c} were measured and cardiovascular risk was calculated according to the New Zealand Risk Score (MACCE within 5 years).

Results: At entry, systolic blood pressure was 163 ± 16 mmHg, diastolic BP 94 ± 9 mmHg, heart rate 73 ± 11 bpm, total cholesterol 229 ± 44 , LDL cholesterol 137 ± 39 , HDL cholesterol 52 ± 17 , triglycerides 196 ± 96 mg/dl and HbA_{1c} 7.1 ± 1.1 %.

After a mean follow-up of 12 months, therapy had reduced systolic BP by 27 ± 16 mmHg ($p < 0.01$) and diastolic BP by 14 ± 9 mmHg ($p < 0.01$). Metabolic parameters showed significant improvements as follows: total cholesterol -25 ± 35 mg/dl, LDL cholesterol -17 ± 30 mg/dl, HDL cholesterol $+3 \pm 10$ mg/dl, triglycerides -31 ± 75 mg/dl and HbA_{1c} -0.5 ± 0.8 (all $p < 0.01$). The cal-

culated cardiovascular risk was significantly reduced from 4.7 ± 1.5 to 4.0 ± 1.1 % (-13 %).

Conclusion: This trial shows experience in carvedilol/HCT therapy in a large number of patients and reflects real-world conditions. It shows that third-generation BB with alpha-blocking properties should not raise metabolic concerns even in combination with low-dose diuretics. Treatment choices for dyslipidemic and/or diabetic hypertensives should take into account differences between older and newer BB.

Kurzfassung: Carvedilol und Hydrochlorothiazid bei Hypertonikern mit Stoffwechsell-

Betrachtungsweise? Einleitung: Nach den derzeit gültigen Richtlinien für die Behandlung der Hypertonie gelten Betablocker nicht mehr als Therapie der ersten Wahl, vor allem, wenn die Hypertonie mit Diabetes mellitus und/oder Dyslipidämie vergesellschaftet ist. Betablocker der dritten Generation wie Carvedilol weisen jedoch positive metabolische Effekte auf. Diese Untersuchung wurde durchgeführt, um die Effekte von Carvedilol in Kombination mit einem Thiazid-Diuretikum (TD) in einem großen Kollektiv österreichischer Hypertoniker mit Diabetes mellitus II und/oder Dyslipidämie zu untersuchen.

Methoden: In 427 Zentren wurden 2163 hypertensive Patienten (52 % Männer) in eine Praxisstudie rekrutiert [mean \pm SD]: Alter 64 ± 11 Jahre, BMI 29 ± 4 kg/m², Bauchumfang: 97 ± 13 cm

(Frauen), 105 ± 11 cm (Männer). Visiten wurden alle 3 Monate durchgeführt. Blutdruck (BD), Lipidparameter, Bauchumfang und HbA_{1c} wurden gemessen und das kardiovaskuläre Risiko mittels New Zealand Risk Score ermittelt (MACCE-Rate innerhalb von 5 Jahren).

Ergebnisse: Zu Studienbeginn zeigten sich folgende Basiswerte: Blutdruck $163 \pm 16/94 \pm 9$ mmHg, Herzfrequenz 73 ± 11 bpm, Gesamtcholesterin 229 ± 44 , LDL-Cholesterin 137 ± 39 , HDL-Cholesterin 52 ± 17 , Triglyzeride 196 ± 96 mg/dl und HbA_{1c} $7,1 \pm 1,1$ %. Nach einer Behandlungsdauer von 12 Monaten zeigte sich eine Reduktion des systolischen BD um 27 ± 16 ($p < 0,01$) und des diastolischen BD um 14 ± 9 mmHg ($p < 0,01$). Die metabolischen Parameter verbesserten sich ebenfalls signifikant: Cholesterin -25 ± 35 mg/dl, LDL -17 ± 30 mg/dl, HDL $+3 \pm 10$ mg/dl, Triglyzeride -31 ± 75 mg/dl und HbA_{1c} $-0,5 \pm 0,8$ (alle $p < 0,01$). Auch das errechnete kardiovaskuläre Risiko reduzierte sich signifikant von $4,7 \pm 1,5$ auf $4,0 \pm 1,1$ % (-13 %).

Schlussfolgerung: Diese Praxisstudie mit Beobachtungscharakter belegt die Auswirkungen der Therapie mit Carvedilol in einem großen Patientenkollektiv mit Stoffwechsellstörungen. Die Ergebnisse belegen, dass eine Therapie mit Carvedilol, einem Betablocker der dritten Generation mit vasodilatierenden Eigenschaften die metabolische Situation nicht ungünstig beeinflusst, selbst wenn sie mit niedrigen Dosen eines Diuretikums kombiniert wird. **J Hyperton 2009; 13 (2): 22–6.**

■ Introduction

According to the recently published European guidelines [1], betablockers (BB) are no longer considered as first-line therapy for hypertensives without compelling indications, e. g. unstable angina, post-myocardial infarction or heart failure, especially in the presence of type-2 diabetes mellitus (DM) and/or dyslipidemia. In the 2006 letter of recommendation of the BHS/NICE [2], BB are actually only fourth-line therapy for uncomplicated hypertensives. Both recommendations were mainly based on trials comparing the first-generation BB atenolol (which was used in up to 75 % of trials according to a recent meta-analysis [3]) to various other antihypertensive drug classes. These older BB may worsen insulin resist-

ance and call for increased doses or numbers of antidiabetic agents [4, 5], besides being implicated in an increased incidence of new-onset diabetes [6]. Furthermore, besides having dyslipidemic effects, thiazide diuretics (TD) might also worsen the glycemic status of diabetics, especially at high doses and when combined with BB [7].

Third-generation BB such as carvedilol might have more beneficial effects even in difficult metabolic circumstances. Carvedilol, a vasodilating non-cardioselective betablocker, is a compound that seems to allow the clinician to use a cardioprotective agent without the problematic hemodynamic and metabolic actions of traditional betablocker therapy. In contrast to conventional betablockers, carvedilol maintains cardiac output, has a less pronounced effect on heart rate, and reduces blood pressure (BP) by decreasing vascular resistance [8]. Several studies have shown that in hypertensive diabetics, carvedilol was better able than atenolol [9, 10] or metoprolol [11] to improve glucose and lipid metabolism parameters and

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Table 1: Baseline and follow-up characteristics

	Baseline	FU 1	FU 2	FU 3	FU 4
BP _{systolic}	163 ± 16	145 ± 14	140 ± 12	138 ± 11	136 ± 11*
BP _{diastolic}	94 ± 9	86 ± 8	83 ± 7	81 ± 7	80 ± 6*
Total cholesterol (mg/dl)	229 ± 44	215 ± 38	208 ± 35	207 ± 34	204 ± 33*
HDL cholesterol (mg/dl)	52 ± 17	52 ± 15	53 ± 16	53 ± 15	54 ± 15*
LDL cholesterol (mg/dl)	137 ± 39	129 ± 35	123 ± 32	123 ± 32	120 ± 31*
Triglycerides (mg/dl)	196 ± 96	184 ± 81	172 ± 70	172 ± 74	170 ± 68*
HbA _{1c} (mg%)	7.1 ± 1.1	7.0 ± 1.0	6.9 ± 0.9	6.8 ± 0.9	6.7 ± 0.9*

BP = blood pressure (mmHg); HDL = high-density lipoprotein (mg/dl); LDL = low-density lipoprotein (mg/dl); FU = follow-up at 3, 6, 9 and 12 months (FU 1–4); * $p < 0.001$ from baseline to FU 4

reduce lipid peroxidation. In addition, metoprolol also caused a significant weight gain compared to carvedilol [11]. The mechanism behind these advantages might be explained by the combined inhibition of adrenergic alpha- and beta-receptors.

The objective of the present survey was to investigate the effects of carvedilol in a fixed combination with 12.5 mg TD on blood pressure, and lipid and glucose metabolism in a large sample of outpatients with arterial hypertension as well as DM and/or hyperlipidemia.

Methods

Study Population

For this study, we recruited 2163 patients with newly diagnosed hypertension or hypertension not sufficiently controlled by antihypertensive therapy. Diagnosis and control of hypertension were defined by standardized office blood pressure readings $> 140/90$ mmHg on two different occasions. Metabolic inclusion criteria were the presence of non-insulin-dependent diabetes mellitus (glucose ≥ 126 mg/dl or treatment for DM) and/or hyperlipidemia (at least one of the following: triglycerides > 150 mg/dl, total cholesterol > 200 mg/dl or lipid-lowering therapy). All probands had to be aged over 18 years.

Exclusion criteria were: current therapy with BB and/or TD, known hypersensitivity towards carvedilol or hydrochlorothiazide, sick sinus syndrome, atrioventricular block, bradycardia with ventricular frequency < 50 bpm, hypotension < 85 mmHg, bronchial asthma, chronic obstructive pulmonary disease, pulmonary hypertension, liver failure, severe renal dysfunction, hypokalemia, hyponatremia, therapy with MAO inhibitors, verapamil or diltiazem, pregnancy or unwillingness to participate in the survey.

Study Protocol

The study was designed as a prospective non-interventional survey in offices of general practitioners and specialists in internal medicine as well as outpatient departments of hospitals. All patients included received a 25-mg carvedilol and 12.5-mg hydrochlorothiazide combination once daily for 12 months. Ongoing antihypertensive, antidiabetic, and anti-lipidemic therapy was continued.

Visits were scheduled at 3-month intervals. According to standard medical practice, blood pressure, body weight, waist

circumference, HbA_{1c}, lipid status and urine microalbumin excretion were measured at every visit.

The absolute cardiovascular risk was calculated according to the New Zealand Risk Score [12] that classifies risk for a cardiovascular event within 5 years as mild ($< 10\%$), moderate (10–15%), high (15–20%) and very high ($> 20\%$). Cardiovascular events are defined as new angina pectoris, myocardial infarction, coronary heart disease, stroke, and transient ischemic attack.

As this was an observational study of a large population sample, there was no control group.

Statistics

All valid measurements collected were used in the statistical analysis. Database management and all statistical analyses were performed with SPSS 15.0. Results were presented as mean values and standard deviations. The Wilcoxon matched pairs test was used to compare different time points. $P < 0.01$ was considered statistically significant.

Results

The study included 2163 patients (52% male) from 427 centres. Mean age was 64 ± 11 years, mean body weight 84.9 ± 15.1 kg, BMI 29 ± 4 kg/m². Baseline characteristics were comparable in men and women, except waist circumference (97 ± 13 cm in women and 105 ± 11 cm in men).

In the whole sample, 27% of patients had newly diagnosed hypertension; 73% were uncontrolled with their ongoing antihypertensive therapy. All patients had dyslipidemia, in 1265 DM was also present. At entry, urine microalbumin excretion was present in 56% of patients. The baseline and follow-up data for blood pressure and laboratory measurements are shown in Table 1.

After one year of additional therapy with carvedilol in combination with hydrochlorothiazide, the following results were achieved: systolic BP was reduced by 27 ± 16 mmHg ($p < 0.01$) and diastolic BP by 14 ± 9 mmHg ($p < 0.01$). The reduction of both systolic and diastolic BP was more pronounced within the first three months (Fig. 1a). Pulse pressure was lowered from 69 ± 15 mmHg at baseline to 55 ± 10 mmHg (13 ± 14 mmHg; $p < 0.01$) (Fig. 1b).

Therapy response was defined by either a systolic BP reduction of 20 mmHg or diastolic BP reduction of 10 mmHg or

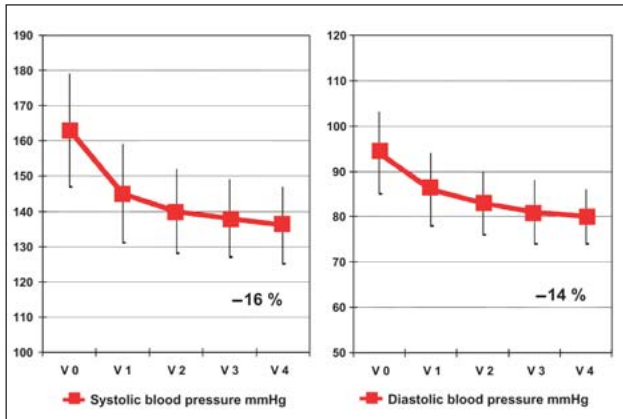


Figure 1a: Systolic and diastolic blood pressure (mmHg) reduction; baseline visit (V₀) to visit after 1 year (V₄).

achievement of normal BP levels. The responder rate for the carvedilol-hydrochlorothiazide combination therapy was 94.4 % in women and 93.5 % in men. At the end of follow-up, BP levels had normalized (< 140/90 mmHg) in 78 % of women and in 77 % of men.

Waist circumference was reduced by 2.5 ± 4.0 cm in women and 3.6 ± 5.5 cm in men (p < 0.01 for either) and body weight decreased from 85 ± 15 kg to 83 ± 14 kg (p < 0.01).

Metabolic parameters showed significant improvements as follows: total cholesterol -25 ± 35 mg/dl, LDL -17 ± 30 mg/dl, HDL +3 ± 10 mg/dl, triglycerides -31 ± 75 mg/dl and H_{bA1c} -0.5 ± 0.8 (all p < 0.01). The time course of reduction of H_{bA1c} levels in the diabetic cohort is shown in Figure 2. The total cholesterol/HDL cholesterol quotient, which strongly

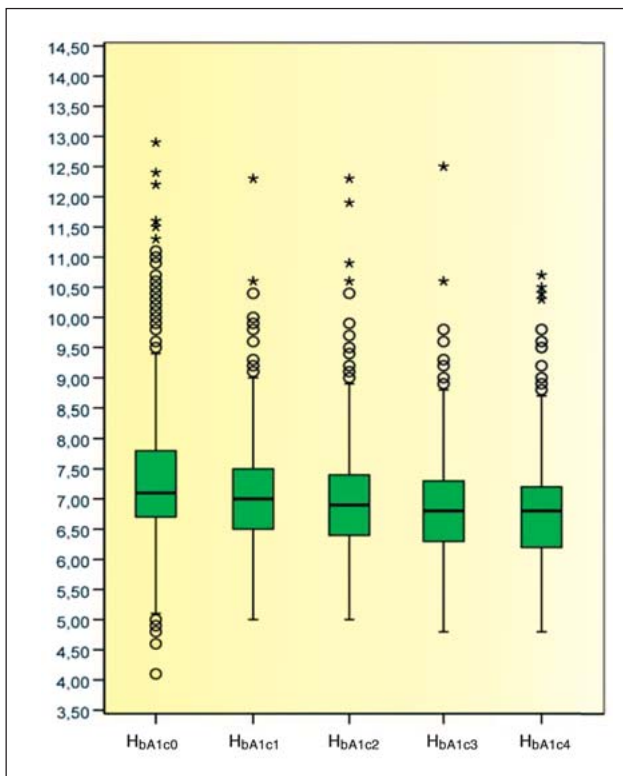


Figure 2: H_{bA1c} levels (mg %); baseline visit (V₀) to visit after 1 year (V₄).

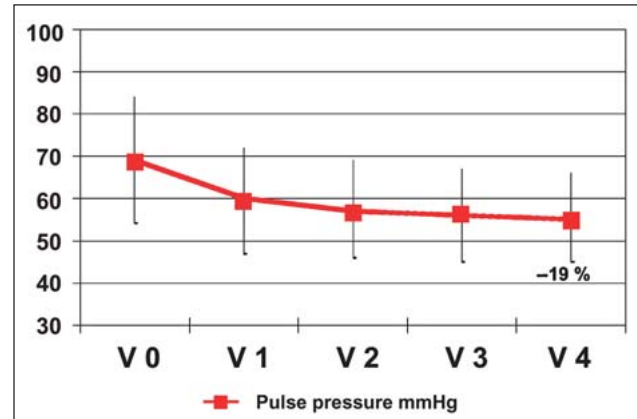


Figure 1b: Pulse pressure (mmHg) reduction; baseline visit (V₀) to visit after 1 year (V₄).

correlates with cardiovascular risk, was reduced significantly from 4.7 ± 1.5 to 4.0 ± 1.1 (-13 %).

Total cardiovascular risk, calculated by the New Zealand Cardiovascular Risk Score, was changed as follows: at baseline, 34 % of women and 48 % of men had a calculated 5-year risk ≥ 20 %. After one year of therapy, only 7 % of women and 16 % of men remained at high risk.

Discussion

Our study demonstrated that the combination of carvedilol plus hydrochlorothiazide in addition to standard medical care significantly reduces systolic and diastolic blood pressures. Our data did not show an aggravation of metabolic parameters, which can often be seen as a result of betablocker therapy. Moreover, a reduction of the calculated 5-year cardiovascular risk could be achieved in these patients.

These findings agree with data from the CORIPULS study [13], which also showed a significant reduction in systolic and diastolic BP, as well as in pulse pressure, and a neutral metabolic effect over an observation period of 2 months. We extended the observation to 12 months to see whether these short-term effects could be maintained or even improved during a longer observation period. Our data resulted in a BP reduction comparable to the CORIPULS study, confirming the highest reduction within the first 3 months. Pulse pressure also served as a strong predictor for cardiovascular risk [14] and was significantly reduced in this observational trial.

For the treatment of hypertension, several drug classes with different glucometabolic effects are recommended. Large outcome trials indicate that the level of glycemic control predicts cardiovascular events [15]. Several studies resulted in a higher incidence of metabolic disorders and sometimes the induction of type-2 diabetes mellitus due to the chronic administration of higher dosages of thiazide diuretics or the prescription of beta-blocking agents [16–18]. These studies were mainly done with first-generation BB [3]. The diabetogenic effect shown in these trials might be due to the following: reduction of blood flow to the skeletal muscle tissue induced by diminished blood volume and cardiac output or blockade of the β₂-adrenergic receptor, respectively [19]. Some authors

suggest that this increases the distance that insulin has to traverse to procure the entrance of glucose into the cell at the membrane level. Conversely, they suggest that the lack of diabetogenic effect of ACE inhibitors, calcium antagonists, and angiotensin receptor antagonists could be due to the fact that these drugs cause vasodilatation and may increase skeletal muscle blood flow [20]. Until now, these effects have mainly been shown in ACE inhibitors and angiotensin-receptor antagonists [7, 21, 22]. Due to its alpha-receptor-blocking capabilities, carvedilol also has a pronounced vasodilating effect, which might explain the antidiabetic effect. A small number of trials proved metabolic neutrality or even a metabolic benefit after therapy with the third-generation BB carvedilol in hypertensive patients [23–25]. Recently published data demonstrated a better metabolic profile for carvedilol than for bisoprolol in patients with chronic heart failure [24]. Another trial proved reduction in total cholesterol and triglycerides when carvedilol was administered after acute myocardial infarction [26]. Our trial mainly included high-risk hypertensive patients, who suffered from diabetes mellitus, hyperlipidemia or both. In these high-risk patients, we could not only prove a neutral metabolic effect but also a significant improvement of metabolic parameters. In contrast to former studies [27], we did not find that betablockade led to weight increase. We therefore suggest that third-genera-

tion betablockers with alpha-blocking properties such as carvedilol are able to improve rather than worsen control of metabolically compromised patients.

We were also able to calculate the individual cardiovascular risk for each patient before and after therapy using the New Zealand risk score. The risk charts used are based on data from the Framingham cohort and discriminate risk groups of 5–20 % for a fatal or non-fatal cardiovascular event within 5 years [12]. This approach is in line with current recommendations of the ESH/ESC guidelines committee for tailoring therapy in hypertensive patients. Approximately half of our patient cohort had an estimated 5-year-risk for a cardiovascular event > 20 % (65 % of men, 52 % of women). This absolute risk was significantly reduced after one year of therapy in 23 % of men and 12 % of women (Fig. 3).

As this score is not only influenced by blood pressure but also by metabolic parameters and the presence of diabetes, total risk reduction can only be gained by both reducing blood pressure and improving metabolic control.

While the large number of patients represents real-world medicine, the main limitation of our survey is the lack of a controlled design. The effects shown in our cohort therefore might be explained in part by better surveillance of participating patients by their doctors and by adjustments

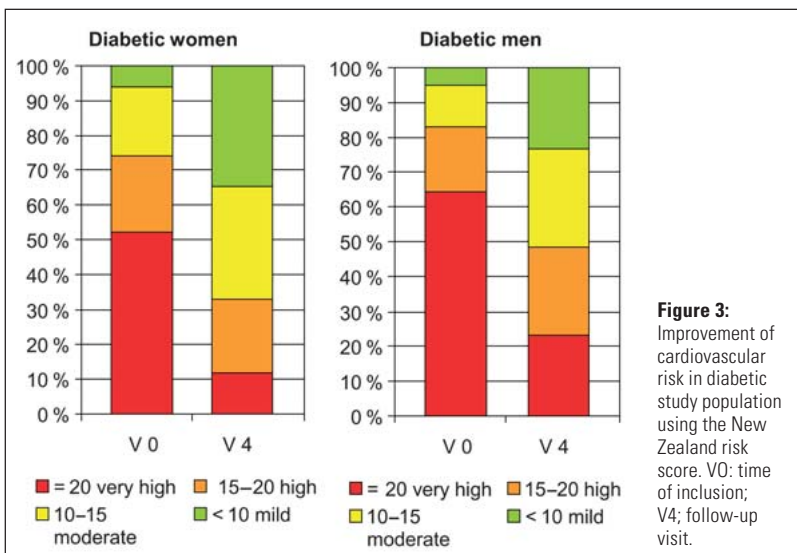


Figure 3: Improvement of cardiovascular risk in diabetic study population using the New Zealand risk score. V0: time of inclusion; V4: follow-up visit.

of concomitant medications. Nevertheless, the data presented could serve as an important argument for a sophisticated approach to beta-blocking agents as a class. Carvedilol in combination with a low-dose diuretic effectively controlled hypertension and showed beneficial rather than detrimental effects on metabolic control, even in dyslipidemic and/or diabetic patients.

■ Practical Aspects

Betablockers are no longer regarded as first-choice therapy in the treatment of uncomplicated hypertension. However, they cannot be dismissed from the optimum treatment of many cardiovascular diseases. It seems important to distinguish between betablockers of past generations and new generations with vasodilating properties. Our data show that the third-generation betablocker carvedilol does not worsen the metabolic status of patients even if it is combined with low doses of a thiazide diuretic. These considerations should have impact on the choice of therapy.

Acknowledgement

The survey was sponsored by Roche Austria. The study was designed and conducted by the authors. The study sponsor received the data only after the study had been completed. All data were received, checked and analyzed independently by the authors. All statistical analyses for this paper were done by Hermesoft® (E. Kvas). The corresponding author had full access to all data in the study and had final responsibility to submit this manuscript for publication.

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