Antihypertensive treatment in patients with class 3 obesity

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Abstract:

Background: Even though patients with class 3 obesity (body mass index ≥ 40 kg/m^2) are prone to arterial hypertension and respond less to antihypertensive drugs, they are not considered in hypertension treatment guidelines and data from prospective clinical trials are lacking.

Methods: In a *post hoc* analysis of a clinical trial, we compared patients with class 3 obesity with patients with class 1/2 obesity.

Results and Conclusions: Blood pressure control in class 3 obesity was less likely to be achieved with hydrochlorothiazide monotherapy. While addition of amlodipine, irbesartan, or aliskiren to hydrochlorothiazide improved the blood pressure response, amlodipine was less effective and induced peripheral edema in 19% of patients with class 3 obesity.

Keywords: obesity, hypertension, renin, aliskiren, irbesartan, placebo, morbid obesity

Introduction

The prevalence of class 3 obesity [body mass index (BMI) ≥40 kg/m^2] in the USA increased fourfold between 1986 and 2000 [Sturm, 2003]. The 2007-2008 National Health and Nutrition Examination Survey showed that 4% of men and 7% of women had class 3 obesity [Flegal *et al.* 2010]. Class 3 obesity is associated with increased mortality compared with class 1/2 obesity, largely caused by increases in hypertension, diabetes, and hyperlipidemia [McTigue *et al.* 2006]. Blood pressure control is particularly difficult to achieve in patients with class 3 obesity because the need for multiple antihypertensive drugs increases with rising body mass index [Bramlage *et al.* 2004]. Yet, clinical trials on antihypertensive treatment in patients with class 3 obesity have not been conducted. We previously reported data from a 12-week, randomized, double-blind trial in 489 patients with obesity and arterial hypertension who were non-responders to hydrochlorothiazide (HCT) [Jordan *et al.* 2007]. We now report the results of a *post hoc* analysis of blood pressure control at week 12 in the subgroup of patients with class 3 obesity compared with patients with class 1/2 obesity.

Methods

We included men and women aged at least 18 years with hypertension and BMI of 30 kg/m^2 or higher. Patients with diastolic blood pressure of 110 mmHg or higher or systolic blood pressure of 180 mmHg or higher were excluded, as were patients with secondary hypertension, diabetes mellitus, history of severe cardiovascular or cerebrovascular disease, or other severe diseases. Patients provided written informed consent, and the study protocol was approved by local ethical committee review boards. Following screening, antihypertensive medications were discontinued for 2–4 weeks. Then, a single-blind run-in period with HCT 25 mg once daily for 4 weeks was begun. Patients whose blood pressure was controlled with HCT were discontinued from the study. Non-responders to single-blind HCT were randomized to double-blind, once-daily treatment with aliskiren 150 mg, irbesartan 150 mg, amlodipine 5 mg, or placebo in addition to HCT 25 mg. After 4 weeks, aliskiren, irbesartan, and amlodipine doses were doubled and treatment continued for an additional 8 weeks. Changes from baseline in blood pressure at week 12 were analyzed separately for the subgroups of patients (intent-to-treat population) with class 1/2 obesity or class 3 obesity at baseline using a two-way analysis of covariance model. Blood pressure control rates were analyzed for each subgroup using a logistic regression model. All statistical tests were performed at a two-sided significance level of 0.05, and 95% confidence intervals were

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provided for differences between treatment groups.

Results

The baseline characteristics of patients with class 1/2 and patients with class 3 obesity are given in Table 1. The class 3 obesity subgroup was younger overall, and comprised a higher proportion of women and patients with metabolic syndrome compared with the class 1/2 obesity subgroup. Blood pressure was not different between both obesity groups.

At week 12, 34.7% of patients with class 1/2 obesity and 16.7% of patients with class 3 obesity on placebo/HCT had their blood pressure controlled to up to 140/90 mm Hg (Figure 1). In class 3 obesity, aliskiren/HCT treatment achieved blood pressure control in an additional 52% of patients compared with placebo/HCT (p = 0.004), 18.8% compared with irbesartan/HCT [p = nonsignificant (NS)], and 25.0% compared with amlodipine/HCT (p = 0.036). In class 3 obesity, aliskiren/HCT combination treatment lowered blood pressure by 14.7/13.8 mm Hg, equating to an additional reduction of 7.6/7.8 mm Hg compared with continuing HCT 25 mg alone (p = 0.086 for systolic and p = 0.013 for diastolic blood pressure, compared with placebo/HCT). Irbesartan/HCT and amlodipine/HCT lowered BP by 17.3/10.6 and 11.6/10.8 mmHg respectively (both p = NS *versus* aliskiren/HCT).

Selected adverse events (AEs) and safety laboratory data are given in Table 2. Treatment with amlodipine/HCT was associated with the highest incidence of AEs in both BMI subgroups due to a higher rate of peripheral edema with amlodipine. The only serious AE suspected to be related to study treatment was a case of peripheral edema in a patient in the class 1/2 obesity subgroup receiving amlodipine/HCT. There were no deaths during the study. Mean potassium levels tended to increase with aliskiren/HCT and irbesartan/HCT, as did the incidence of potassium elevations to greater than 5.5 mmol/liter (5/103 and 3/109 patients in the class 1/2 obesity subgroup). Two patients with class 1/2 obesity exhibited serum potassium greater than 6.0 mmol/liter with aliskiren/HCT. Serum potassium reductions to less than 3.5 mmol/liter were most common with amlodipine/HCT (12/109 patients *versus* 5/103, 3/109, and 5/107 patients with aliskiren/HCT, irbesartan/HCT, and HCT, respectively). Two cases of serum creatinine elevation to higher than 177 μmol/liter were seen in patients with class 1/2 obesity on HCT alone. The only notable laboratory abnormalities in the class 3 obesity subgroup were two cases of potassium less than 3.5 mmol/liter (one each with aliskiren/HCT and amlodipine/HCT).

Discussion

Patients with class 3 obesity represent a hard-to-treat group prone to hypertension and associated cardiovascular complications. Treatment guidelines advocate weight loss in this patient group as a means to lower blood pressure. A recent scientific statement by the European Society of Hypertension Working Group on Obesity reviewed the evidence for blood pressure influences of weight loss [Straznicky *et al.* 2010]. Even with profound weight loss induced by bariatric surgery, long-term blood pressure control is not achieved in many patients [Sjostrom *et al.* 2000]. Most patients with hypertension and class 3 obesity ultimately require antihypertensive therapy.

In the majority of patients with class 3 obesity in this study, low-dose HCT monotherapy did not control blood pressure, thus extending and confirming previous observations. In a German survey conducted in the primary care setting, patients with obesity and hypertension were on more antihypertensive medications while blood pressure was less well controlled compared with normal weight patients with hypertension [Bramlage *et al.* 2004]. In 7357 high-risk vascular outpatients a BMI of at least 30 kg/m^2 decreased the likelihood of having blood pressure controlled [Bhan *et al.* 2010]. Similarly, patients with a BMI of at least 30 kg/m^2 in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) required more antihypertensive medications but were nevertheless less likely to attain target blood pressure [Cushman *et al.* 2002].

Renin–angiotensin system inhibitors may be particularly useful in a combination regimen in patients with severe obesity in terms of efficacy and they are well tolerated. From a pathophysiological point of view, renin–angiotensin system inhibition is a sensible treatment approach. Studies applying the norepinephrine spillover technique showed excessive renal sympathetic activation in obesity-associated arterial hypertension [Rumantir *et al.* 1999]. Renal sympathetic activation may

Table 1. Patient baseline and demographic characteristics.

Parameter	Class 1/2 obesity (BMI 30 to <40 kg/m²) (*n* = 435)				Class 3 obesity (BMI ≥ 40 kg/m²) (*n*=54)				Totals	
	Aliskiren/ HCT (*n* = 106)	Irbesartan/ HCT (*n* = 109)	Amlodipine/ HCT (*n* = 110)	HCT alone (*n* = 110)	Aliskiren/ HCT (*n* = 16)	Irbesartan/ HCT (*n* = 10)	Amlodipine/ HCT (*n* = 16)	HCT alone (*n* = 12)	Class 1/2 obesity (*n* = 435)	Class 3 obesity (*n* = 54)
Age, years	54.2 ± 11.7	53.3 ± 10.9	55.9 ± 12.0	56.0 ± 12.0	45.2 ± 10.5	50.0 ± 12.5	50.2 ± 10.3	47.3 ± 12.8	54.9 ± 11.7	48.0 ± 11.3
Men, n (%)	55 (52)	46 (42)	46 (42)	49 (45)	5 (31)	2 (20)	7 (44)	3 (25)	196 (45)	17 (32)
Weight, kg	94.2 ± 13.3	93.6 ± 12.2	92.8 ± 12.8	93.1 ± 12.6	128.5 ± 16.5	122.3 ± 17.0	123.2 ± 18.0	117.3 ± 10.0	93.4 ± 12.7	123.3 ± 16.0
BMI, kg/m²	33.2 ± 2.7	33.2 ± 2.6	33.3 ± 2.6	33.0 ± 2.7	45.5 ± 5.1	46.6 ± 4.8	42.9 ± 2.6	43.3 ± 3.0	33.2 ± 2.6	44.4 ± 4.2
Waist circumference, cm	109 ± 10	107 ± 12	109 ± 11	108 ± 11	127 ± 12	129 ± 16	125 ± 12	124 ± 13	108 ± 11	126 ± 13
Duration of hypertension, years	8.8 ± 8.4	8.3 ± 8.0	9.9 ± 9.0	8.5 ± 8.1	6.3 ± 5.3	7.3 ± 3.2	6.0 ± 5.0	10.5 ± 11.5	8.9 ± 8.4	7.3 ± 6.9
Metabolic syndrome*, n (%)	75 (71)	76 (70)	68 (62)	67 (61)	14 (88)	9 (90)	14 (88)	8 (67)	286 (66)	45 (83)
Current smoker, n (%)	15 (14)	19 (17)	28 (26)	24 (22)	3 (19)	1 (10)	2 (13)	0	86 (20)	6 (11)
msDBP, mmHg	96.7 ± 5.0	96.5 ± 4.1	96.7 ± 5.0	97.2 ± 4.6	97.4 ± 4.4	98.0 ± 7.2	96.1 ± 5.4	97.3 ± 4.7	96.8 ± 4.7	97.1 ± 5.2
msSBP, mmHg	149.4 ± 11.9	149.1 ± 13.4	150.4 ± 11.5	149.1 ± 10.9	149.3 ± 10.1	148.4 ± 13.6	145.6 ± 10.8	152.7 ± 14.7	149.5 ± 11.9	148.8 ± 12.0

Baseline msDBP and msSBP were evaluated at baseline of the double-blind treatment period after the single-blind HCT run-in period. Data are expressed as mean ± standard deviation unless otherwise stated.
*Metabolic syndrome was defined as any three of the following, according to National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) diagnostic criteria: waist circumference >102 cm for men or >88 cm for women; triglycerides ≥150 mg/dl (≥1.69 mmol/liter); high-density lipoprotein cholesterol <40 mg/dl (<1.04 mmol/liter) for men or <50 mg/dl (<1.29 mmol/liter) for women; BP ≥130/85 mmHg; fasting glucose ≥110 mg/dl (≥6.1 mmol/liter).
BMI, body mass index; msDBP, mean sitting diastolic blood pressure; msSBP, mean sitting systolic blood pressure.

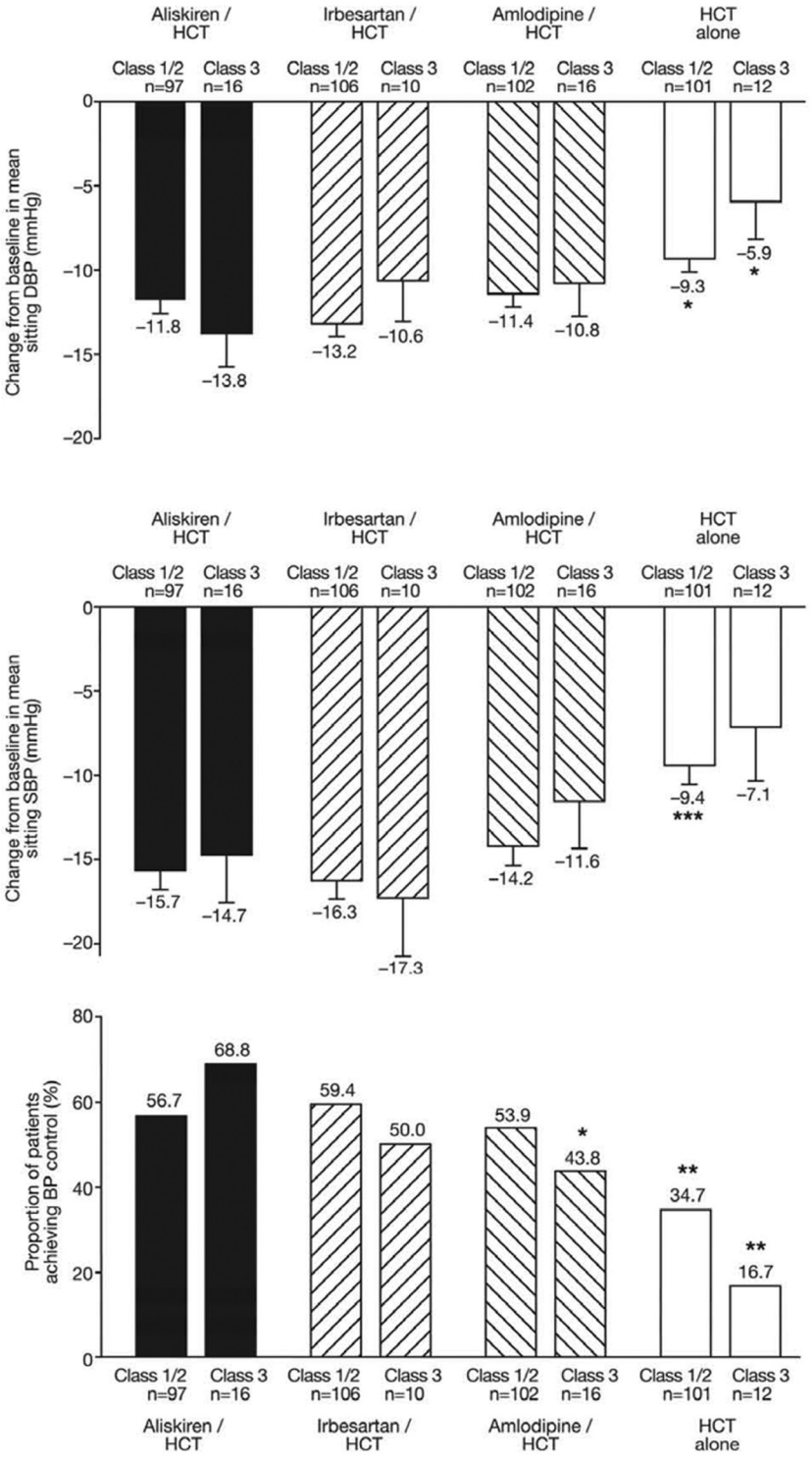

Figure 1. Changes from baseline in mean sitting diastolic blood pressure (DBP, upper panel) and mean sitting systolic blood pressure (SBP, middle panel) at week 12 endpoint in patients according to body mass index (BMI) subgroup [intent-to-treat (ITT) population]. Blood pressure data are presented as the least-squares mean ± standard error of the mean (SEM). *$p < 0.05$, ***$p < 0.0001$ *versus* aliskiren/hydrochlorothiazide (HCT) in pairwise comparisons. The lower panel shows the percentage of patients with blood pressure control (<140/90 mmHg). *$p < 0.05$, **$p < 0.01$ *versus* aliskiren/HCT in a logistic regression model with treatment and region as factors and centered baseline as covariate.

Table 2. Safety and tolerability.

Adverse event	Aliskiren/ HCT	Irbesartan/ HCT	Amlodipine/ HCT	HCT	Total
Class 1/2 obesity (BMI 30 to <40 kg/m²)	n = 106	n = 109	n = 110	n = 110	n = 435
Any AE	41 (38.7)	40 (36.7)	49 (44.5)	42 (38.2)	172 (39.5)
Nasopharyngitis	8 (7.5)	5 (4.6)	6 (5.5)	3 (2.7)	22 (5.1)
Headache	5 (4.7)	2 (1.8)	6 (5.5)	4 (3.6)	17 (3.9)
Back pain	1 (0.9)	2 (1.8)	5 (4.5)	5 (4.5)	13 (3.0)
Peripheral edema	0	0	11 (10.0)	2 (1.8)	13 (3.0)
Dizziness	3 (2.8)	3 (2.8)	1 (0.9)	2 (1.8)	9 (2.1)
Discontinuations due to AEs	1 (0.9)	4 (3.7)	5 (4.5)	4 (3.6)	14 (3.2)
SAEs	1 (0.9)	3 (2.8)	4 (3.6)	4 (3.6)	12 (2.8)
*Laboratory values (mean ± SD)**					
Potassium, mmol/liter					
Baseline	4.22 ± 0.45	4.15 ± 0.40	4.20 ± 0.38	4.24 ± 0.43	
Week 12	4.33 ± 0.60	4.30 ± 0.41	4.14 ± 0.51	4.16 ± 0.42	
Change	0.11 ± 0.59	0.15 ± 0.44	−0.06 ± 0.50	−0.08 ± 0.49	
Creatinine, µmol/liter					
Baseline	81.8 ± 16.1	78.3 ± 16.0	78.2 ± 14.2	81.9 ± 19.7	
Week 12	82.0 ± 17.0	81.1 ± 19.6	79.2 ± 15.9	83.0 ± 22.9	
Change	0.2 ± 11.7	2.8 ± 11.2	1.1 ± 10.4	1.1 ± 14.7	
Class 3 obesity (BMI ≥40 kg/m²)	n = 16	n = 10	n = 16	n = 12	n = 54
Any AE	7 (43.8)	3 (30.0)	8 (50.0)	5 (41.7)	23 (42.6)
Nasopharyngitis	2 (12.5)	1 (10.0)	1 (6.3)	2 (16.7)	6 (11.1)
Peripheral edema	1 (6.3)	1 (10.0)	3 (18.8)	0	5 (9.3)
Gastroenteritis	1 (6.3)	2 (20.0)	0	1 (8.3)	4 (7.4)
Headache	0	1 (10.0)	3 (18.8)	0	4 (7.4)
Dry mouth	0	0	2 (12.5)	0	2 (3.7)
Discontinuations due to AEs	1 (6.3)	0	1 (6.3)	0	2 (3.7)
SAEs	1 (6.3)	0	0	0	1 (1.9)
Laboratory values (mean ± SD)[$]					
Potassium, mmol/liter					
Baseline	4.08 ± 0.40	3.95 ± 0.31	4.13 ± 0.27	4.11 ± 0.41	
Week 12	4.29 ± 0.47	4.17 ± 0.34	4.10 ± 0.28	4.31 ± 0.16	
Change	0.21 ± 0.39	0.22 ± 0.48	−0.03 ± 0.38	0.20 ± 0.45	
Creatinine, µmol/liter					
Baseline	69.9 ± 11.0	67.1 ± 10.1	72.3 ± 9.7	70.4 ± 21.3	
Week 12	65.9 ± 10.3	68.3 ± 9.8	68.5 ± 11.7	73.4 ± 21.3	
Change	−4.0 ± 10.7	1.2 ± 6.6	−3.7 ± 8.7	3.0 ± 6.4	

Values are presented as the number (%) of patients unless otherwise stated.
*Values at baseline and week 12 not available for all patients; *n* = 100–102 (aliskiren/HCT), *n* = 104–107 (irbesartan/HCT), *n* = 104–106 (amlodipine/HCT) and *n* = 102–104 (HCT alone).
[$]Values at baseline and week 12 not available for all patients; *n* = 15 (amlodipine/HCT) and *n* = 11 (HCT alone).
AE, adverse event; BMI, body mass index; HCT, hydrochlorothiazide; SAE, serious adverse event.

contribute to renin–angiotensin system activation in patients with obesity and hypertension [Engeli and Sharma, 2001]. Consequently, sodium retention, volume expansion, and increases in cardiac output may ensue [Messerli *et al.* 1981; Stelfox *et al.* 2006; Strazzullo *et al.* 2001]. Renin–angiotensin system inhibitors do not promote diabetes mellitus. One potential advantage of aliskiren is that it achieves relatively high concentrations in the adipose tissue of patients with obesity and hypertension [Boschmann *et al.* 2012]. Moreover, relevant aliskiren tissue concentrations can still be

measured 8 weeks after treatment discontinuation [Boschmann *et al.* 2012].

Our analysis supports previous observations suggesting that obesity modulates the efficacy of dihydropyridine calcium channel blockade [Schmieder *et al.* 1993]. Moreover, in a relatively large proportion of patients with class 3 obesity, the clinical utility of dihydropyridine calcium channel blockers is limited by occurrence of peripheral edema.

Although further studies are required to confirm our *post hoc* analysis on a small subpopulation of patients with class 3 obesity and hypertension, direct renin inhibition with aliskiren is another therapeutic option for the hard-to-treat group of patients with severe obesity.

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Conflict of interest statement

SWB, SL, DLK, and MFP are Novartis employees. JJ served as a consultant and lecturer for Novartis.

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