Antihypertensive effect of aliskiren with/without thiazide diuretic as related to BMI and metabolic syndrome in general practice

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Summary

Background: In view of the potential benefit of direct renin inhibition, this post-marketing survey was undertaken to assess blood pressure lowering and target blood pressure attainment in 905 patients with and without metabolic syndrome and with body mass indices of ≥30 kg/m² treated with aliskiren or aliskiren/hydrochlorothiazide in the primary care setting. In addition, tolerability and the prior treatment were assessed.

Methods: At an initial visit, physicians assessed blood pressure, heart rate, risk factors, signs of end organ damage and prior antihypertensive medication. Patients were prescribed aliskiren or aliskiren/hydrochlorothiazide. Efficacy and tolerability were measured by assessing blood pressure, heart rate and side effects at a further visit after two months. Blood pressure targets were defined according to the guidelines of the Swiss Society of Hypertension.

Results: Mean sitting systolic blood pressure/mean sitting diastolic blood pressure was lowered equally effectively (systolic/diastolic: p = 1.0/0.8) in patients with (–22.0 ± 15.3/–11.1 ± 8.7 mm Hg) and without metabolic syndrome (–22.0 ± 15.8/–10.9 ± 9.6 mm Hg), while target blood pressure attainment was significantly lower in patients with metabolic syndrome (35% vs 48%; p <0.001). In contrast, blood pressure was lowered to a significantly greater extent in obese subjects (body mass index ≥30 kg/m²; –23.6 ± 16.4/–12.1 ± 9.6 mm Hg) compared to patients with body mass index <30 kg/m² (–21.2 ± 15.1/–10.5 ± 9.1 mm Hg, p = 0.03/0.02) and the blood pressure control rate in this group was non-significantly higher (45.3% vs 39.4%, p = 0.09). Side effects were reported in 1.8% of all cases, none of them severe. The treatment approach of physicians before the initial visit did not differ between patients with/without metabolic syndrome.

Conclusion: Aliskiren and aliskiren/hydrochlorothiazide are effective in patients regardless of their metabolic situation. However, low blood pressure control rates suggest that more than two antihypertensive agents are needed to control blood pressure adequately in these high risk patients.

Key words: aliskiren; metabolic syndrome; obesity; blood pressure control

Introduction

The metabolic syndrome (MetS) is a clinical syndrome characterised by altered glucose metabolism (dysglycaemia), abdominal obesity and dyslipidaemia [1–3]. Because it frequently coincides (25%) with elevated blood pressure [1, 4, 5], more than 75% of obese patients are hypertensive [1]. The pathophysiology of the MetS is as yet poorly understood. However, insulin resistance is thought to play an important role as it activates the renin-angiotensin-aldosterone system (RAAS) [6, 7]. As patients with MetS are at increased cardiovascular risk [8], antihypertensive treatment needs to extend beyond mere control of the blood pressure. Intracellular formation of angiotensin II is suspected to occur in human adipocytes [9]. In this context, compounds interfering with the systemic and cellular RAAS [10] are particularly attractive in patients with MetS, since they directly address one of the pathophysiological mechanisms in associated hypertension. While current Swiss guidelines do not advise specific treatment of patients with MetS [11], ESH-ESC guidelines [12] recommend ACE-inhibitors (ACEIs) [13] and angiotensin receptor blockers (ARBs) [14] as initial

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treatment options. Although no comparative studies examining characteristics of different RAAS-inhibitors (ACEIs, ARBs or direct renin inhibitors) have yet been carried out, various trials show that aliskiren is particularly effective in patients with MetS and may lower blood pressure even more than ARB-based therapies [15]. Direct renin inhibitors (DRIs) have shown greater blood pressure reductions than irbesartan, amlodipine or placebo combination therapy with hydrochlorothiazide (HCT) [16]. In view of the potential benefit of direct renin inhibition on the extracellular and intracellular RAAS, this survey was primarily undertaken to assess whether in a primary care setting:

1. The use of aliskiren (A) and aliskiren/hydrochlorothiazide (AHCT) leads to equally effective blood pressure lowering in patients with MetS compared to patients without MetS.
2. The use of A and AHCT leads to equally effective target blood pressure attainment in patients with MetS compared to patients without MetS.

Secondarily we examined whether:

3. A and AHCT lead to similar blood pressure target attainment in patients with BMI ≥30 kg/ m^2 and BMI <30 kg/m^2.
4. Treatment approaches and substances prescribed for patients with/without MetS differ in primary care.

Methods

Swiss general practitioners were contacted by the Medical Department of Novartis Pharma Switzerland and asked to participate in a survey on the blood pressure lowering effect of A and AHCT and to include patients with either essential hypertension (>140/>90 mm Hg) and obesity, dyslipidaemia, impaired glucose tolerance or patients with normal metabolism and essential hypertension.

At an initial visit, blood pressure (measured seated according to the guidelines of the Swiss Society of Hypertension (SSH) [11]), heart rate, demographic data (age, sex, weight, height), risk factors (physical inactivity, smoking, genetic predisposition), signs of end organ damage (such as impaired renal function, stroke, heart failure, myocardial infarction, atherosclerosis, left ventricular hypertrophy, microalbuminuria (30–300 mg/24h), increased serum creatinine (♂ above 133 µmol/l, ♀ above 124 µmol/l) and prior antihypertensive medication were assessed.

Standard devices for blood pressure measurement were not provided. An extended set of data was collected (waist circumference, glucose and lipid levels) for patients with MetS (as defined in table 1). At the physician's discretion, patients were prescribed A/AHCT with or without other antihypertensive medication.

Drugs were either prescribed or given to the patients directly by the physician. No drug delivery system of the sponsor was involved.

The second visit was timed to suit the physician's routine, within two months after the initial consultation, as Swiss Ethics Committee guidelines do not allow a fixed visit time schedule in a survey in order to prevent interference with daily practice. The efficacy of the antihypertensive treatment was assessed by measuring blood pressure and heart rate. If necessary, an adjustment of the therapy (dosage and/or drugs) could be performed and documented in the questionnaire.

Side effects were recorded and forwarded to the sponsor's Drug Safety Department. In addition, serious/adverse events were reported to Swissmedic in accordance with national regulations. The efficacy and tolerability of the new antihypertensive regimen was assessed using two 4-item Likert scales (very good, good, sufficient, insufficient).

The design of this investigation (CSPH100ACH02) was approved by the Ethics Committees of Basel (Protocol no. 55/10) and Geneva (Protocol no. 10–07) to delineate this survey from a clinical study. Target blood pressures were defined according to SSH guidelines [11] (<140/90 mm Hg; <130/80 mm Hg for patients with diabetes and impaired kidney function, <150 mm Hg for patients with isolated systolic hypertension).

We performed a descriptive statistical analysis using SPSS Statistics 18 software. For the subsequent analysis, parametric methods (ANOVA and Bonferroni post-hoc-test) and non-parametric methods (Chi^2-Test and Mann-Whitney-U-Test) were used. Correlation analysis was performed using a two-sided Pearson coefficient and a significance level of $p < 0.05$.

Table 1
Definition of metabolic syndrome according to [17].

Metabolic syndrome* was defined as	Men	Both	Women
Waist circumference	>102 cm		>88 cm
Elevated triglycerides		≥1.7 mmol/l	
Low HDL	<1.0 mmol/l		<1.3 mmol/l
Elevated BP		≥130 / ≥80 mm Hg (and/or)	
Impaired fasting glucose or Diabetes mellitus		≥5.6 mmol/l	

* Metabolic syndrome has to be considered if 3 or more criteria apply.

Results

1343 patients were included within six months (February 2010 to July 2010), 526 of whom were diagnosed with MetS according to the AGLA guidelines (tab. 1) [17]. Due to missing information (baseline characteristics, blood pressure data, information about treatment modification), 62 patients were excluded, which led to a data pool of 503 patients with MetS and 778 patients without MetS. 187 patients with MetS and 189 patients without MetS received other antihypertensive medications and were therefore excluded from analysis, resulting in a total of 905 patients analyzed. There were 287 patients with BMI ≥30 kg/m² and 618 with BMI <30 kg/m².

Patient characteristics

Included patients (n = 905) had an average age of 60.3 ± 11.9 yrs (see tab. 2 for further baseline characteristics] and a blood pressure of 160.1 ± 15.9 / 94.8 ± 9.7 mm Hg. 756 (84%) patients had at least one additional risk factor. Physical inactivity (>50%) was more common in patients with MetS than in patients without MetS (72% vs 49%). In addition end organ damage was diagnosed significantly more often (p <0.001) in patients with MetS. These patients were most often described by grade II obesity (30%) and a waist circumference of 103–115 cm (56%) also occurred in this subgroup. Although 46% of patients with MetS had normal blood glucose levels, approximately 30% had type 2 diabetes. Cholesterol levels between 5.2 and 6.2 mmol/l were present in 42%. Over 50% of patients with MetS had HDL levels between 1.01 and 1.40 mmol/l.

Prior treatment

At the time of inclusion, 2.5% of patients with MetS and 2.7% without MetS had target blood pressure levels. More patients with MetS were already receiving antihypertensive therapy (52%) than patients without MetS (49%). There was no difference between the two groups with regard to the substance classes used before switching to A and AHCT (fig. 1).

Adaptation of treatment

Prior treatment was replaced by A/AHCT in 43% of patients. In 3% of cases a prior treatment with A or

Figure 1
Antihypertensive drugs used at time of inclusion.
ARB = angiotensin receptor blocker; CCB = calcium channel blocker; ACEI = angiotensin converting enzyme inhibitor; DIU = diuretic; BB = beta blocker; DRI = direct renin inhibitor.

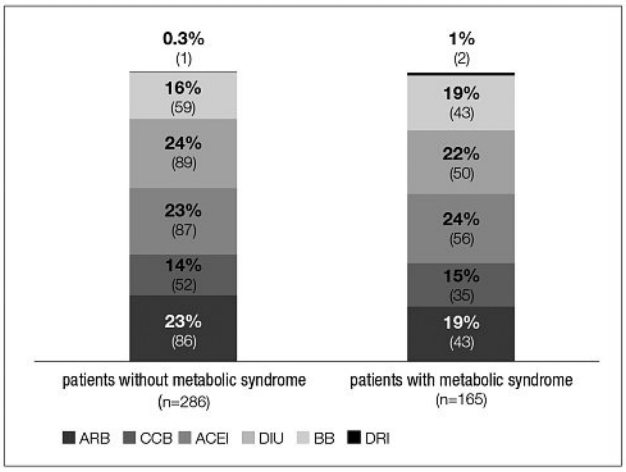


Table 2
Baseline characteristics of the patients included in the analysis.

	Patients without metabolic syndrome	Patients with metabolic syndrome[a]
Age	60.6 ± 12.2 yrs	59.6 ± 11.3 yrs
Weight	78.6 ± 13.7 kg	89.1 ± 19.4 kg[b]
Height	170.5 ± 8.5 cm	169.3 ± 9.1 cm
BMI	27.0 ± 4.2 kg/m²	31.0 ± 5.9 kg/m²
Male	353 (60%)	156 (49.4%)[c]
New hypertension	284 (48.2%)	135 (42.7%)
msSBP	159.6 ± 15.5 mm Hg	161.0 ± 16.6 mm Hg
msDBP	94.4 ± 10.0 mm Hg	95.6 ± 9.2 mm Hg
Patients with target BP	16 (2.7%)	8 (2.5%)
Heart rate	76.6 ± 9.9 bpm	78.2 ± 10.1 bpm[d]
Patients with prior antihypertensive therapy	286 (49%)	165 (52%)
1 drug	151 (26%)	78 (25%)
2 drugs	31 (5%)	26 (8%)
≥3 drugs	41 (7%)	27 (9%)
Not stated	63 (11%)	34 (11%)

[a] Metabolic syndrome has to be considered if 3 or more criteria apply; [b] Patients with metabolic syndrome vs patients without: p <0.001; [c] Patients with metabolic syndrome vs patients without: p = 0.002; [d] Patients with metabolic syndrome vs patients without: p = 0.02.

HCT was replaced by AHCT; A/AHCT was prescribed to 55% of treatment-naïve patients.

The frequency of AHCT use was similar in both groups (58% without MetS vs 60% with MetS).

Change in blood pressure and target blood pressure attainment

Regardless of treatment regimen, a systolic (SBP) and diastolic (DBP) blood pressure reduction of –22.0 ± 15.6 / –11.0 ± 9.3 mm Hg could be shown at visit 2 (baseline: 160.1 ± 15.9/94.3 ± 9.7 mm Hg) and an equally marked blood pressure reduction (p = 1.0 for SBP and p = 0.8 for DBP) was found in both patient groups. The absolute SBP/DBP lowering effect in patients with MetS was –22.0 ± 15.3 / –11.1 ± 8.7 mm Hg (fig. 2), while heart rate was reduced by –3.5 ± 8.5 bpm. Despite similar blood pressure reductions, significantly (p <0.001) fewer patients with MetS attained blood pressure targets (35%). On the other hand 48% of patients without MetS reached their targets with A/AHCT (fig. 3). Blood pressure goals were achieved more often by MetS patients treated with A 150 mg (45%) than by those treated with A 300 mg (21%, p = 0.09).

Influence of BMI on BP reduction and BP control

Comparing patients treated with A/AHCT and BMI ≥30 kg/m² vs BMI <30 kg/m², SBP/DBP decreased

Figure 2
Reduction of systolic/diastolic blood pressure and heart rate in patients with and without metabolic syndrome and patients with BMI <30 kg/m² and BMI ≥30 kg/m².

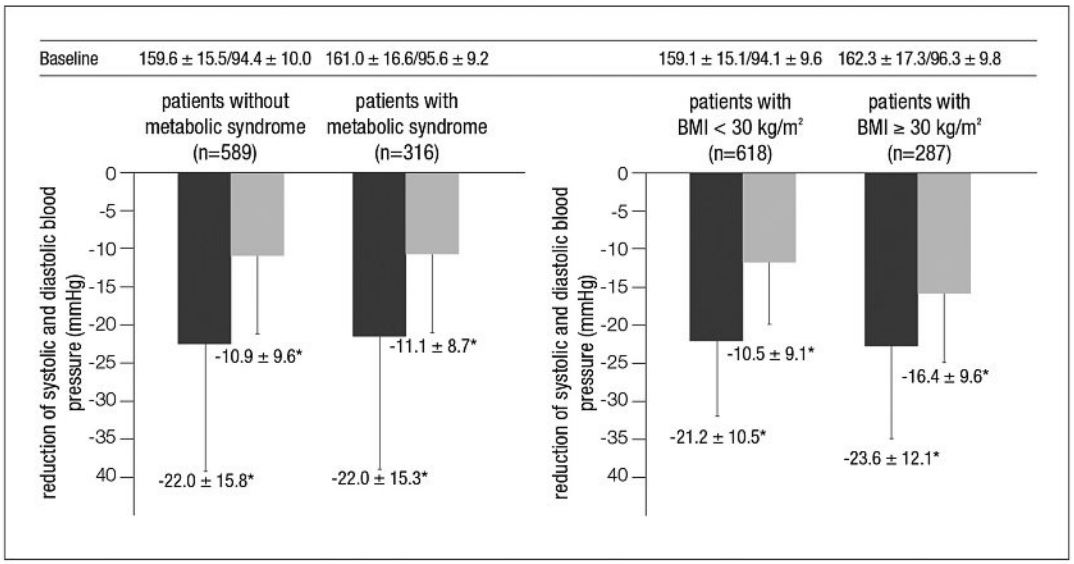
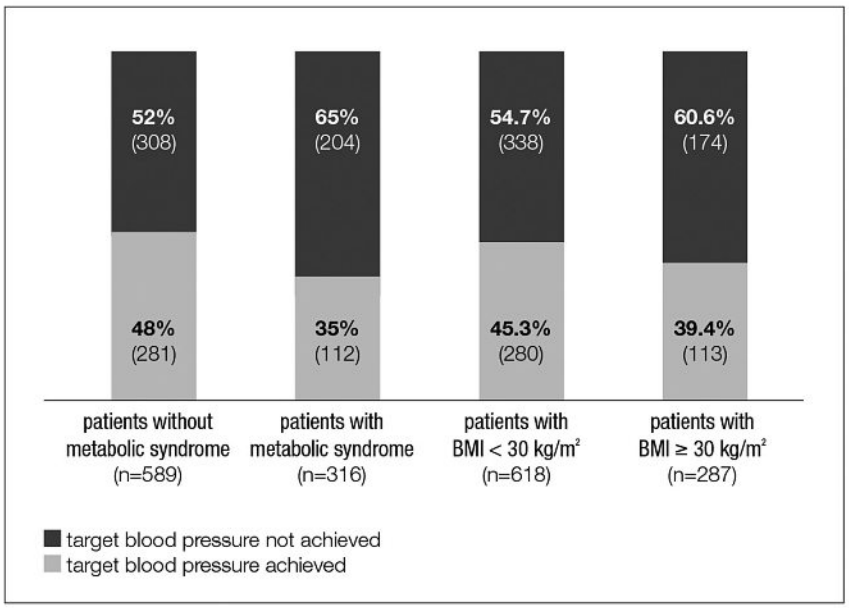


Figure 3
Patients achieving target blood pressure.



significantly in both groups (p <0.001) and more in patients with BMI ≥30 kg/m² (–23.6 ±16.4 / –12.1 ± 9.6 mm Hg vs –21.2 ± 15.1 / –10.5 ± 9.1 mm Hg; p = 0.03/0.02). Subjects with BMI ≥30 kg/m² had significantly higher baselines (162.3 ± 17.3 / 96.3 ± 9.8 mm Hg) than patients with BMI <30 kg/m² (159.1 ± 15.1 / 94.1 ± 9.6 mm Hg) (SBP/DBP: p = 0.005/0.002, [fig. 2]). The amount of BP reduction correlated positively with BMI (Pearson = 0.069 / 0.071 p = 0.04 / 0.03). Target blood pressure rate was non-significantly higher in patients with BMI >30 kg/m² (45.3% vs 39.4%, p = 0.09).

Adverse events

Side effects were reported in 1.8% of all cases included in the analysis, although none of the side effects were severe. The most commonly reported side effect was nausea (0.6%), followed by headache (0.3%), diarrhoea (0.2%) and fatigue (0.1%). There was no statistical difference between patients with or without MetS. 64% of participating physicians rated the tolerability of A/AHCT as very good. Therapy with A and AHCT was continued in 63% of patients at the end of this survey. If treatment adjustment (31%) was necessary at visit 2, the dosages of A and AHCT were modified in 79% of patients. Beta-blockers (BBs) and calcium channel blockers (CCBs) were chosen as an alternative treatment in 4% and 7% respectively.

Discussion

This survey provides evidence for the efficacy of the direct renin inhibitor aliskiren with/without HCT in patients with MetS and elevated BMI. Data show that angiotensinogen mRNA levels are elevated in the subcutaneous tissue of obese patients [18]. This leads to higher local production of angiotensin II and other angiotensin peptides in the adipose tissue [19]. The observed reduction of BP may be explained by involvement of the cellular RAAS in adipocytes [20]. This underlying concept was previously proven in a study with renin-knock-out mice (with reduction of angiotensin II) which showed a prevention of the fat-mass enlargement and reduction of blood pressure [21]. HOPE [22] and CAPPP [13] confirmed the antihypertensive effect in humans. An increase in BMI of 5 kg/m² leads to a higher mortality of up to 30% [23]. As a result, strict treatment is essential in patients with MetS. Despite the fact that ARBs and ACEIs are recommended by European guidelines [10], it is assumed that their intracellular effects are limited. As DRIs most likely inhibit the genesis of angiotensin I in the cell, various studies have shown the superiority of DRIs compared to ARBs [15] in patients with MetS. Although ALLHAT [24] has shown that modern blood pressure lowering drugs are not superior to older thiazide diuretics and health policy makers advocate the widespread use of cheaper compounds, the metabolic advantages of DRIs may justify their use despite daily treatment costs of A 300 mg: 1.53 CHF and AHCT 300/25 mg: 1.95 CHF. Various trials show that aliskiren lowers blood pressure equally effectively with or without the presence of obesity [25–27]. In addition, our results show superior BP reduction in patients with BMI ≥30 kg/m² and correlation of the blood pressure lowering effect with increasing BMI. However, patients with BMI ≥30 kg/m² had higher initial baselines and were most probably treated with higher dose formulations. On the other hand, MetS is a complex syndrome and every contributing factor increases the cardiovascular risk independently. As a result, not only adipose tissue but also impaired glucose tolerance and dyslipidaemia seem to have major influences on its pathophysiology.

The blood pressure control rate in this survey appears to be lower than that found in randomized trials. This can be explained by the following points: First of all, blood pressure goals of 130/80 mm Hg are more difficult to accomplish. In addition, physicians often fail to increase therapy when blood pressure goals are unmet, a phenomenon known as 'therapeutic inertia', and treatment for hypertension is often initiated too late. Furthermore, patients with MetS are often treated for diabetes, dyslipidaemia and other comorbidities which increase the burden of tablets and might also reduce adherence and persistence.

Unlike the ESH-ESC [10], the SSH [11] does not include treatment recommendations for patients with MetS [12]. Although the use of high-dose HCT [12] is not recommended in MetS, HCT 25 mg was used in 22.2% as combination therapy to A. Disregarding the diabetogenic effect [10] of DIUs, it can be argued that target blood pressure attainment is more important than the aggravation of pre-existing diabetes or shifts of electrolytes. Furthermore, marginal elevations of blood potassium levels with A300 mg, shown in clinical trials [16] can be counteracted by the administration of thiazides [16]. As the ESH [10] recommend RAAS-inhibitors as treatment options, the combination of a DRI with a low dose thiazide for the enhancement of antihypertensive efficacy can be assumed to be an optimal treatment approach. Surprisingly, general practitioners treated patients similarly in this survey regardless of the existence of a MetS (fig. 1). Although the number of administered substances reflects physicians' risk-awareness [8], treatment is not adequate with regard to the choice of drug classes.

Concluding remarks

Our survey shows that A or AHCT is non-inferior in reducing blood pressure in patients with MetS compared to patients without MetS and is superior in patients with a BMI ≥30 kg/m² vs patients with a BMI <30 kg/m². Our findings suggest a possible benefit of the direct renin inhibition in patients with an altered lipid metabolism such as in obesity and MetS. However, the

low rate of blood pressure target attainment leads to the conclusion that intensified treatment with more than two antihypertensive agents is needed to control blood pressure adequately. As currently no direct head-to-head comparisons of RAAS-blockers are available for patients with MetS, randomized controlled trials are needed to assess the effect of different drugs including DRIs on blood pressure in patients with obesity and MetS.

Limitations

Due to the nature of a survey, the results cannot provide hard evidence compared to a clinical study. In the absence of visit schedules and standard devices, the heterogeneity of patients was high. Furthermore, treatment adherence control as in clinical studies was not possible and an intention to treat population was not calculated previously. The data can show trends but must be set in relation to the methodology. On the other hand, the general situation of the given setting and the number of patients reflect the situation of physicians in Swiss primary care.

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