Classes of antihypertensive medications and blood pressure control in relation to metabolic risk factors

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Objective **Metabolic syndrome (MetS) is associated with uncontrolled blood pressure (BP), despite use of aggressive therapy. This study was performed to assess whether the use of different classes of antihypertensive drugs might influence this association.**

Methods **We evaluated risk of uncontrolled BP (BP≥140/90 mmHg under antihypertensive treatment) at the time of the last available visit, after a mean follow-up of 5 years in 4612 hypertensive patients without prevalent cardiovascular disease (43% women, 53±11 years) from the Campania Salute Network.**

Results **At the time of the first visit, prevalence of MetS was associated with 43% increased risk of follow-up uncontrolled BP, independent of significant confounders and without a significant impact of specific classes of antihypertensive medications. At the time of the last available visit, patients with MetS had more often uncontrolled BP, despite more aggressive treatment. After adjusting for demographics, risk factors and number of antihypertensive medications, risk of uncontrolled BP was reduced with increased prescription of diuretics [DRTs; odds ratio (OR) 0.73, 95% confidence interval (CI) 0.62–0.86], renin–angiotensin system blockers [RAS-blockers (Angiotensin-converting enzyme-inhibitors or angiotensin receptor blockers); OR 0.77, 95% CI 0.66–0.91] and statins (OR 0.79, 95% 0.68–0.92, all $P<0.05$), without significant impact of the other classes of medications.**

Conclusion **Despite the use of increased number of medications, hypertensive patients with MetS are at higher risk of uncontrolled BP. Among classes of antihypertensive medications, increased prescriptions of DRTs, RAS-blockers and also statins decrease the probability of poor BP control.** *J Hypertens* **30:188–193 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Abbreviations: ACE, angiotensin-converting enzyme; ATPIII, adult treatment panel III; BP, blood pressure; GFR, glomerular filtration rate; HDL, high-density lipoprotein; MetS, metabolic syndrome; NIH, National Institute of Health; RAS-blockers, renin–angiotensin system blockers

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Introduction

Arterial hypertension is the most prevalent cardiovasular risk factor in most populations, and the leading cause for medical consultation and number of drug prescriptions [1]. It has been estimated that 26 and 28% of incident cardiovascular disease in men and women, respectively, are primarily attributable to hypertension [2]. This disappointing impact may be related to the evidence that blood pressure (BP) in hypertensive patients is still largely uncontrolled, despite the large number of prescribed medications [3,4]. Furthermore, hypertension is often part of a constellation of cardiovascular risk factors including obesity, abnormal glucose homeostasis and dyslipidemia. These features occur simultaneously more often than would be expected by chance, supporting the existence of a discrete disorder called the metabolic syndrome (MetS) [5–8].

MetS increases cardiovascular risk in the setting of hypertension, even when individual risk factors are taken into account [9–11], and reduces the probability of achieving optimal BP control, despite more aggressive treatment [12–14]. The probability of uncontrolled BP increases with the number of metabolic risk factors [12], but whether different medications prescriptions influence this association has not been clarified yet. Accordingly, this study was designed to evaluate whether the less effective BP control in the presence of clusters of risk factors associated with the phenotype of MetS is at least in part influenced by specific prescriptions of antihypertensive medications in a large number of hypertensive patients referred to a tertiary care center in Southern Italy.

Methods

As previously reported [12,15,16], we have generated an open electronic registry from a network of 23 community hospital-based hypertension clinics and 60 general practitioners, referring to the Hypertension Center of the Federico II University Hospital (Naples, Italy) in the Campania District (Campania Salute Network, http://www.campaniasalute.com/). The registry includes over

12 000 patients, who were given a smartcard including demographics and clinical information. After the first enrollment visit, all participants were followed up at the Outpatient Clinic of our Hypertension Center.

For the goal of the present study, we selected 7752 hypertensive patients without prevalent cardiovascular disease (previous myocardial infarction or angina or procedures of coronary revascularization, stroke or transitory ischemic attack, congestive heart failure) or diagnosis of secondary hypertension. From the initial event-free hypertensive population, 2911 patients were excluded because of insufficient follow-up period (i.e. last available visit performed less than 1 year from the initial visit), 27 because of chronic kidney disease more than grade 3 (by glomerular filtration rate (GFR) estimated by modification of diet in renal disease formula [17]) and 202 because missing information on BP or metabolic status.

Thus, the present analysis included 4612 hypertensive participants, free of prevalent cardiovascular disease. BP control was assessed in all participants at the time of their last available visit, after a mean follow-up of 5.0 ± 3.4 years.

The database generation of the Campania Salute Network was approved by the Federico II University Hospital Ethic Committee. Signed informed consent for using data for scientific purposes was obtained from all participants.

Measurements and definitions

SBP and DBP were measured by standard aneroid sphygmomanometer after 5 min resting in the sitting position, according to current guidelines [1,18]. We analyzed BP values obtained at the time of the first and the last available visits, respectively. Three BP measurements were obtained during each office visit, at 2-min intervals and the averages were used for analysis. Hypertension was defined as SBP of at least 140 mmHg and/or DBP of at least 90 mmHg or current antihypertensive therapy [1,19,20]. Under current antihypertensive treatment, BP less than 140/90 mmHg was considered controlled, whereas SBP of at least 140 mmHg and/or DBP of at least 90 mmHg were considered uncontrolled [1,19].

The number and type of antihypertensive medications prescribed at the time of the first and last available visit have been analyzed. Medications have been classified as follows: diuretics (DRTs), β-blockers (including β-blockers and α-β-blockers), renin–angiotensin system blockers (RAS-blockers, including angiotensin-converting enzyme (ACE)-inhibitors and angiotensin receptor blockers), calcium channel blockers (CCB) and α-blockers.

Fasting plasma glucose and lipid profile were measured by standard methods. Diabetes was defined by fasting glucose of at least 7 mmol/l (≥126 mg/dl) or by use of insulin or oral hypoglycemic therapy [20].

A modified Adult Treatment Panel III (ATP III) definition of MetS [21] was adopted, changing waist girth with BMI of at least 30 kg/m^2, the cut-point for definition of obesity, according to National Institute of Health (NIH) guidelines [22], consistent with a number of previous studies [9,11,12]. Diagnosis of MetS required at least two of the following metabolic risk factors, being the third factor present in all participants (hypertension): fasting plasma glucose of at least 6.10 mmol/l (≥110 mg/dl); plasma triglycerides of at least 1.71 mmol/l (≥150 mg/dl); high-density lipoprotein (HDL) cholesterol less than 1.04 mmol/l (<40 mg/dl)for men, or less than 1.30 mmol/l (<50 mg/dl) for women; and BMI of at least 30 kg/m^2 (as a surrogate of increased waist girth).

Statistical analysis

Data were analyzed using SPSS 12.0 software (SPSS, Chicago, Illinois, USA) and expressed as mean ± 1 SD. Differences between groups with or without follow-up uncontrolled BP were assessed by analysis of variance. χ^2-Statistics were used to determine differences in categorical variables. Logistic regression analysis was used to identify whether and what classes of medications at the time of the first visit, were associated with uncontrolled BP at the end of the follow-up, after hierarchically adjusting for sex, initial age, smoking status, SBP, heart rate, BMI, diabetes, plasma creatinine, fasting glucose, triglycerides, HDL cholesterol and total number of antihypertensive drugs (by a forward stepwise procedure with P-to-enter < 0.05 and P-to-remove ≥ 0.1). The same model was repeated substituting single metabolic variables (BMI, fasting glucose, triglycerides and HDL cholesterol) with MetS at the time of the first visit. Logistic regression was repeated after adjusting for baseline SBP and anthropometrics, metabolic variables and therapy detected at the time of the last available visit. Odds of uncontrolled BP in relation to classes of drugs used at the time of the last visit were, therefore, evaluated in patients with MetS separately. Odds ratios (ORs) and 95% confidence interval (CI) for covariates are presented. The null hypothesis was rejected at two-tailed P value less than 0.05.

Results

Among 4612 hypertensive patients without prevalent cardiovascular disease (43% women, mean age 53 ± 11years) at the time of the first visit, 28% were free of antihypertensive medications. Among treated patients, 51% exhibited initial BP more than 140 and/or 90 mmHg.

At the time of the first visit, obesity was found in 25%, abnormal fasting glucose in 18% including diabetic patients (8.6% of the total population), high triglycerides in 32% and low HDL cholesterol in 34% of the total population. Smoking habit was found in 1208 participants (26%). The number of hypertensive patients with initial MetS was 1461 (32% of study population, 41% women).

Among them, obesity was present in 55%, abnormal fasting glucose in 42% (diabetes in 20%) and high triglycerides and/or low HDL in 70%.

Proportion of smokers was similar in participants with MetS compared with those without MetS (27 versus 26%, $P = 0.43$).

At follow-up, all 4612 participants were treated with antihypertensive medications, and, among them, 1967 had uncontrolled BP, representing 43% of the total population. Uncontrolled BP was systolic and diastolic in 41%, isolated systolic in 45% and isolated diastolic in 14% of cases.

Baseline predictors of follow-up uncontrolled blood pressure

The main initial characteristics of the studied population in relation to the follow-up BP control are reported in Table 1. Compared with patients with follow-up controlled BP, those with uncontrolled BP were older, had higher initial BP, heart rate, BMI, fasting glucose, triglycerides, total cholesterol and serum creatinine levels, with lower HDL cholesterol and GFR (all $P \leq 0.03$). No significant difference was found for smoking status among participants with or without follow-up uncontrolled BP. At the time of the first visit, patients with follow-up uncontrolled BP had a significant higher prevalence of diabetes and MetS compared with those with follow-up controlled BP (all $0.03 < P < 0.0001$, Table 1).

Table 2 shows that, at the time of first visit in our outpatient clinic, higher SBP, BMI, triglycerides and number of antihypertensive medications independently increased the probability of uncontrolled BP at the time of final visit (all $P \leq 0.002$), without significant effect for other covariates, including classes of antihypertensive medications. Initial MetS was associated with 43% increased probability of uncontrolled BP (OR 1.43, 95% CI 1.25–1.63, $P < 0.0001$), independent of baseline SBP, heart rate, presence of diabetes, plasma creatinine, smoking status and number or type of initial antihypertensive medications and statins.

Table 2 Independent initial predictors of follow-up uncontrolled blood pressure

			95% CI for Exp(B)	
	P value	OR	Lower	Upper
Systolic BP (×5 mmHg)	≤0.0001	1.12	1.10	1.15
BMI (kg/m^2)	≤0.0001	1.03	1.02	1.05
Triglycerides (mmol/l)	≤0.003	1.12	1.04	1.21
Number of drugs	≤0.0001	1.20	1.13	1.27

Multivariate analysis; sex, baseline age, heart rate, presence of diabetes, plasma creatinine, fasting glucose, HDL cholesterol, smoking status and single classes of antihypertensive medications and statins did not enter the model (all $P > 0.1$). BP, blood pressure; Exp(B), exponentiation of the B coefficient; HDL, high-density lipoprotein.

Association of uncontrolled blood pressure with classes of antihypertensive drugs at the time of the last visit

At the time of the last available visit, prevalence of MetS and diabetes was 33 and 12%, respectively. Prevalence of uncontrolled BP was higher in participants with MetS compared with those without MetS (49 versus 40%, $P < 0.0001$) and in diabetic compared to nondiabetic participants (49= versus 42%, $P = 0.002$). Mean number of prescribed antihypertensive medications was significantly higher at follow-up compared with the first visit (2.1 ± 0.9 versus 1.3 ± 0.5, $P < 0.0001$).

The number of prescribed medications progressively increased from the group of patients with no metabolic risk factors to the group of patients with one, two, three or more clustered risk factors (Fig. 1, P for trend < 0.0001). In general, single-medication therapy was infrequently prescribed (31% of total studied population) and more often in hypertensive without MetS (34 versus 24% of those with MetS, $P < 0.0001$).

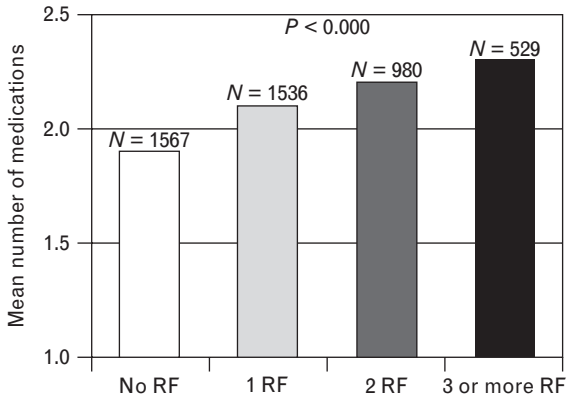
DRTs, RAS-blockers, CCBs and α-blockers were prescribed more frequently in individuals with MetS than in those without MetS, without significant differences for β-blocker prescription (Table 3). Statins were also

Table 1 Initial clinical characteristic of the hypertensive patients in relation to follow-up blood pressure control

	Follow-up controlled BP ($n = 2645$)	Follow-up uncontrolled BP ($n = 1967$)	*P*
Age (years)	53 ± 10	54 ± 11	≤0.0001
SBP (mmHg)	141 ± 16	148 ± 18	≤0.0001
DBP (mmHg)	90 ± 10	91 ± 10	≤0.0001
Heart rate (beats/min)	74 ± 11	75 ± 12	≤0.03
BMI (kg/m^2)	27 ± 4	28 ± 4	≤0.0001
Fasting glucose (mmol/l)	5.4 ± 1.1	5.6 ± 1.3	≤0.0001
Total cholesterol (mmol/l)	5.3 ± 1.0	5.4 ± 1.0	≤0.02
HDL cholesterol (mmol/l)	1.3 ± 0.3	1.2 ± 0.3	≤0.004
Triglycerides (mmol/l)	1.3 (1.0–1.8)	1.4 (1.0–1.9)	≤0.0001
Creatinine (μmol/l)	84 ± 18	86 ± 19	≤0.03
GFR (ml/min per 1.73m^2)	82 ± 18	80 ± 18	≤0.001
Smokers (%)	27	25	=0.09
Diabetes (%)	8	10	≤0.008
Metabolic syndrome (%)	28	37	≤0.0001

BP, blood pressure; GFR, glomerular filtration rate; HDL, high-density lipoprotein.

Fig. 1



Mean number of antihypertensive medications prescribed according to the number of risk factors (RF). *N*, number of hypertensive patients. *P* for trend < 0.0001.

prescribed more often in participants with MetS than in those without MetS (25 versus 22%, respectively, $P = 0.02$).

We analyzed independent correlates of uncontrolled BP at the time of the last available visit. Table 4 shows odds of uncontrolled BP in relation to classes of medications used at the time of the last available visit, adjusting for significant confounders. Initial SBP, female sex with older age, heart rate, BMI, plasma creatinine, triglycerides and higher number of antihypertensive medications at the time of the last visit were all independently associated with uncontrolled BP (all $0.02 < P < 0.0001$). Among classes of antihypertensive medications, DRTs and RAS-blockers were less likely to be prescribed when BP remained uncontrolled ($P \leq 0.002$), whereas no significant influence was observed for β-blocker, CCB or α-blocker. Prescription of statins reduced by 21% the probability of uncontrolled BP ($P = 0.003$, Table 4). Less prescription of DRTs, RAS-blockers and statins were still related to uncontrolled BP (all $P \leq 0.002$), also when analysis was adjusted for the presence of MetS, which confirmed a 35% higher risk of uncontrolled BP (OR 1.35, 95% CI 1.18–1.54, $P < 0.0001$).

Table 3 Type of antihypertensive medications prescribed at the time of the last available visit, according to presence or absence of metabolic syndrome

	No MetS ($n = 3103$)	MetS ($n = 1509$)	*P*
Diuretics (%)	48	56	≤0.0001
β-Blockers (%)	34	37	=0.08
RAS-blockers (%)	76	81	≤0.0001
Ca^{++}-channel blockers (%)	32	36	≤0.006
α-Blockers (%)	9	10	≤0.05

MetS, metabolic syndrome; RAS-blockers, renin–angiotensin system blockers (including ACE-inhibitors and angiotensin receptor blockers).

Table 4 Independent correlates of uncontrolled blood pressure in the whole population sample at the time of last available visit

			95% CI for Exp(B)	
	P value	OR	Lower	Upper
Age (year)	≤0.002	1.01	1.00	1.02
Female sex	≤0.02	1.18	1.02	1.36
Initial SBP (×5 mmHg)	≤0.0001	1.10	1.09	1.12
Heart rate (beats/min)	≤0.0001	1.02	1.01	1.03
BMI (kg/m^2)	≤0.0001	1.04	1.03	1.06
Plasma creatinine (×5 μmol/l)	≤0.001	1.03	1.01	1.04
Triglycerides (mmol/l)	≤0.0001	1.17	1.08	1.27
Number of drugs	≤0.0001	1.27	1.16	1.39
Diuretics (%)	≤0.0001	0.73	0.62	0.86
RAS-blockers (%)	≤0.002	0.77	0.66	0.91
Statins (%)	≤0.003	0.79	0.68	0.92

Multivariate analysis including data detected at the time of the last available visit (with the exception of baseline SBP); diabetes, fasting glucose, high-density lipoprotein cholesterol, smoking status, β-blockers, Ca^{++}-channel blockers, α-blockers did not enter the model (all $P > 0.1$). BP, blood pressure; CI, confidence interval; Exp(B), exponentiation of the B coefficient; OR, odds ratio; RAS-blockers, renin–angiotensin system blockers.

Evaluation of antihypertensive therapy in relation to uncontrolled BP was also carried out in the 1522 hypertensive patients with MetS (Table 5). In this subgroup, uncontrolled BP was confirmed to be independently associated with higher baseline SBP and higher number of medications at the time of the last visit ($P < 0.0001$). Prescriptions of DRTs and RAS-blockers were again associated with 28% reduced probability of uncontrolled BP in hypertensive patients with MetS, independent of other confounders (both $P < 0.03$).

Discussion

Although the effort to reduce and control BP is substantial, and a large number of medications are often prescribed, BP control in populations is still largely suboptimal [3,4,23]. We and others have previously reported that prevalence of uncontrolled BP increases with the number of metabolic risk factors, despite the use of a greater number of antihypertensive drugs [12–14], even if BP response to therapy seems not to be affected

Table 5 Independent correlates of poor blood pressure control at the time of last available visit in hypertensive patients with metabolic syndrome

			95% CI for Exp(B)	
	P value	OR	Lower	Upper
Initial SBP (×5 mmHg)	≤0.0001	1.12	1.10	1.15
Heart rate (beats/min)	≤0.0001	1.02	1.01	1.03
Number of drugs	≤0.0001	1.34	1.16	1.56
DRTs (%)	≤0.02	0.72	0.55	0.94
RAS-blockers (%)	≤0.03	0.72	0.54	0.97

Multivariate analysis including data detected at the time of the last available visit (with the exception of initial SBP); sex, age, BMI, diabetes, plasma creatinine, fasting glucose, triglycerides, smoking status, high-density lipoprotein cholesterol, β-blockers, Ca^{++}-channel blockers and α-blockers, statins did not enter into the model (All $P > 0.1$). BP, blood pressure; CI, confidence interval; DRT, diuretics; Exp(B), exponentiation of the B coefficient; OR, odds ratio; RAS-blockers; renin-angiotensin system blockers.

by presence of MetS [24]. We extended these observations by analyzing whether different therapeutic strategies could help understanding the apparent resistance to treatment associated with clusters of metabolic risk factors. We found that when MetS or single cardiovascular risk factors were taken into account at the time of initial visit in our tertiary care center, the classes of antihypertensive drugs used as initial therapy did not influence the probability of uncontrolled BP at the time of last visit. Rather, obesity and the associated clustered risk factors might offset the efficacy of initial therapy. Thus, at the time of first presentation in our Hypertension Center, type of antihypertensive therapy had scarce influence on the outcome of BP controls over time. The discontinuity and variability of medical care in these patients at the time of the onset of the study might have influenced these results.

However, after at least 1 year of strict office controls in our Hypertension Center, when management of arterial hypertension was obtained following guidelines recommendations [1,18,19], the therapeutic response of these patients appears influenced also by the choice of specific classes of antihypertensive drugs. Particularly, DRTs and RAS-blockers resulted to influence BP control also when the impact of clustered cardiovascular risk factors and other classes of antihypertensive medications was taken into account. DRTs and/or RAS-blockers reduced the odds of uncontrolled BP at the last visit, and this was evident either in the whole population sample or in the subpopulation with MetS, possibly suggesting an inadequate rate of prescription of these two classes of medications.

We do not have yet complete available data on variation of therapy during the follow-up, and we could not evaluate the impact of modification of antihypertensive therapy with addition and/or substitution of specific classes of drugs by time varying analysis, and further studies should be performed to assess this important issue. Thus, our analysis does not allow drawing cause–effect conclusions, as the association of uncontrolled BP with single classes of medications is influenced by the cross-sectional nature of the study. The more frequent prescription of all classes of medications in patients with uncontrolled BP, especially observed in those with MetS, reflects the greater, albeit often unsuccessful, effort to control BP in these patients.

The evidence that DRTs were less likely to be prescribed when BP was uncontrolled in hypertensive patients, including those with MetS, suggests that DRTs should be probably prescribed more frequently than found in this analysis to improve control of BP in populations referred to tertiary care centers. The reasons for this potential inadequacy of DRT prescription is likely in the concern, not univocal [25], that DRTs might aggravate metabolic impairment in patients with high risk of diabetes [26,27], due to the warning issued by some [18], although not all [1], guidelines. Actually, BP lowering induced by DRT has shown to significantly reduce cardiovascular events [28], even in patients with MetS, in spite of higher incidence of diabetes [29]. We previously reported in a large population, very similar in composition to the present one, that uncontrolled BP is a significant predictor of incident diabetes in the Campania Salute Network [15], independent of type of antihypertensive therapy, and we also did not find independent association between DRTs and incident diabetes, once other metabolic risk factors were taken into account. However, as diabetes is a major risk factor for microvascular and macrovascular cardiovascular complications, further studies are needed to determine whether the potential advantages of more intensive therapy with DRTs on BP control might balance possible unfavorable metabolic effects, especially in patients with MetS.

In contrast to debate on DRTs, there is currently large consensus about use of RAS-blockers in the management of hypertension, especially in patients with MetS, wherein they are considered treatment of choice, due to their benefic effect on insulin sensitivity and glycemic control [18,19,30]. Activation of the RAS has been associated with obesity and insulin resistance and has been proposed to provide a pathophysiologic link among obesity, diabetes and hypertension [30–32]. The present results confirm the positive impact of RAS-blockers on rate of BP control, mainly evident in MetS.

Even interesting and somewhat unexpected is the evidence that prescription of statins reduced the probability of uncontrolled BP in the whole population sample, but not in the subpopulation with MetS (in which prescription were much more frequent), independent of antihypertensive treatment. These results are consistent with recent studies showing slight but significant antihypertensive effect of statins, which appear to be independent of their cholesterol lowering action [33–35]. There are several mechanisms through which statins may affect BP [35], *inter alia* their favorable effects on endothelial function [36], their interaction with the RAS [37] and their ability to affect large artery compliance [38].

In conclusion, the effort to control BP in conditions of exposure to clusters of metabolic disturbances is often unsuccessful and the addition of subsequent medications does not necessarily achieve success in BP control. DRTs and RAS-blockers are possibly underused especially among hypertensive patients with MetS, wherein they might emerge as key medications to obtain targeted BP control. Moreover, statins might also play an important role in BP control.

Although purely observational, this study suggests that, in the setting of hypertension, managed in a real-life context, clustered metabolic risk factors are the most important predictors of response to therapy and more

efforts should be devoted to control this condition. Clinical trials should be implemented specifically on the phenotypes of hypertensive patients with MetS, which are confirmed to be the most resistant to standard antihypertensive therapy.

Acknowledgement

Conflicts of interest

There are no conflicts of interest.

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