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ORIGINAL RESEARCH

The Number of Pills, Rather Than the Type of Renin–Angiotensin System Inhibitor, Predicts Ambulatory Blood Pressure Control in Essential Hypertensives on Triple Therapy: A Real-Life Cross-Sectional Study

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ABSTRACT

Introduction: We evaluated the prevalence and predictors of ambulatory blood pressure (BP) control in patients taking a triple antihypertensive therapy (renin–angiotensin system inhibitor + calcium channel blocker + thiazide/thiazide-like diuretic, in either free or fixed-dose combinations) containing an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin receptor blocker (ARB).

Methods: We performed an observational cross-sectional study on 520 consecutive patients with essential hypertension taking a stable triple therapy in whom 24-h ambulatory BP was evaluated. Both number of pills and antihypertensive treatment intensity (ATI), as possible pharmacological predictors of ambulatory BP control, were taken into account.

Results: A total of 189 (36.3%) patients were taking triple therapy with ACEi and 331 (63.7%) patients were taking triple therapy with ARB. Mean age was 62.7 ± 12.2 years. Patients on triple therapy with ACEi had a significantly lower ATI and took fewer antihypertensive pills than patients on triple therapy with ARB (22.2% of patients took a single-pill triple fixed-dose combination). Patients taking triple therapy with ACEi had higher prevalence of both 24-h (54.8% vs 44.0%; $p = 0.019$) and daytime BP control (61.8% vs 49.2%; $p = 0.006$) than patients taking triple therapy with ARB, even after adjusting for age, sex, body mass index, smoking habit, type 2 diabetes mellitus, estimated glomerular filtration rate, and ATI [OR 1.5 (95% CI 1.1–2.2) and OR 1.6 (95% CI 1.1–2.4), respectively]. However, these independent associations with ambulatory BP control were lost when the number of antihypertensive pills was included in the model.

Conclusion: The higher prevalence of ambulatory BP control found in patients taking a triple therapy with ACEi was affected by the lower number of antihypertensive pills taken, which was also the key predictor of ambulatory BP control in our study. This confirms the importance of fixed-dose combinations in the management of essential hypertension.

Keywords: ABPM; Angiotensin-converting enzyme inhibitors; Angiotensin receptor blockers; Antihypertensive therapy; Blood pressure; Fixed-dose combination

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Key Summary Points

We investigated the prevalence and predictors of ambulatory blood pressure control in patients with essential hypertension taking a triple antihypertensive therapy (renin–angiotensin system inhibitor + calcium channel blocker + thiazide/thiazide-like diuretic, in either free or fixed-dose combinations)

Patients taking a triple-therapy with ACE inhibitors had a higher prevalence of both 24-h and daytime blood pressure control than patients taking a triple-therapy with angiotensin receptor blockers at univariate analysis

This association was lost after taking into account the number of antihypertensive pills taken in the multivariate analysis: the lower the number of pills, the higher the prevalence of ambulatory blood pressure control

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.14610693.

INTRODUCTION

Hypertension is a serious public health concern worldwide, representing the major cardiovascular (CV) risk factor, often coupled with dyslipidemia, smoking, and diabetes mellitus, causing atherosclerosis and cardiovascular disease [1–3]. The overall prevalence of hypertension in adults is 30–45%, with a global age-standardized prevalence of 24% and 20% in men and women, respectively, and it has increased over the last 20 years [4]. Antihypertensive drug treatment is of paramount importance to achieve blood pressure (BP) control and to reduce CV events and mortality [5, 6]. While BP control rates had improved between 2000 and 2008, they have remained substantially unchanged in more recent years [7]. The reasons for this plateau are likely complex and multifactorial including therapeutic inertia and poor therapeutic adherence, as well as poor dietary choices and declining rates of physical activity, leading to rising of incidence and prevalence of obesity [8].

The 2018 European Society of Cardiology/European Society of Hypertension (ESC/ESH) guidelines for the management of arterial hypertension [4] recommend in most cases to start the antihypertensive treatment with two drugs, preferably in a single-pill combination of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor antagonist (ARB) in association with a calcium channel blocker (CCB) or a thiazide/thiazide-like diuretic. In fact, it is estimated that at least one-third of patients with hypertension will require two drugs to achieve BP control and one-third will require three or more antihypertensive drugs [9]. Combination therapy is more likely to lead to a better BP control than monotherapy, thanks to the synergistic pharmacological actions of different drug classes, with better safety profile and tolerability compared to a high dose of a single drug [10, 11]. Moreover, single-pill combinations of fixed-dose drugs are likely to improve medication adherence and persistence, which are crucial for achieving adequate long-term BP control [12]. Hypertension guidelines [4] do not clearly recommend ACEi over ARB, among the renin–angiotensin system (RAS) inhibitors, to achieve BP control and improve CV outcomes. Several studies have compared ACEi and ARB in terms of BP control and CV mortality in patients with hypertension with conflicting results and without showing a clear superiority of one drug class over the other [13, 14].

The aim of our study was to evaluate both the prevalence and predictors of ambulatory BP control in patients with hypertension taking a triple antihypertensive therapy (RAS

inhibitor + CCB + thiazide/thiazide-like diuretic, in either free or fixed-dose combinations) containing an ACEi or an ARB in a real-life setting.

METHODS

Study Design and Population

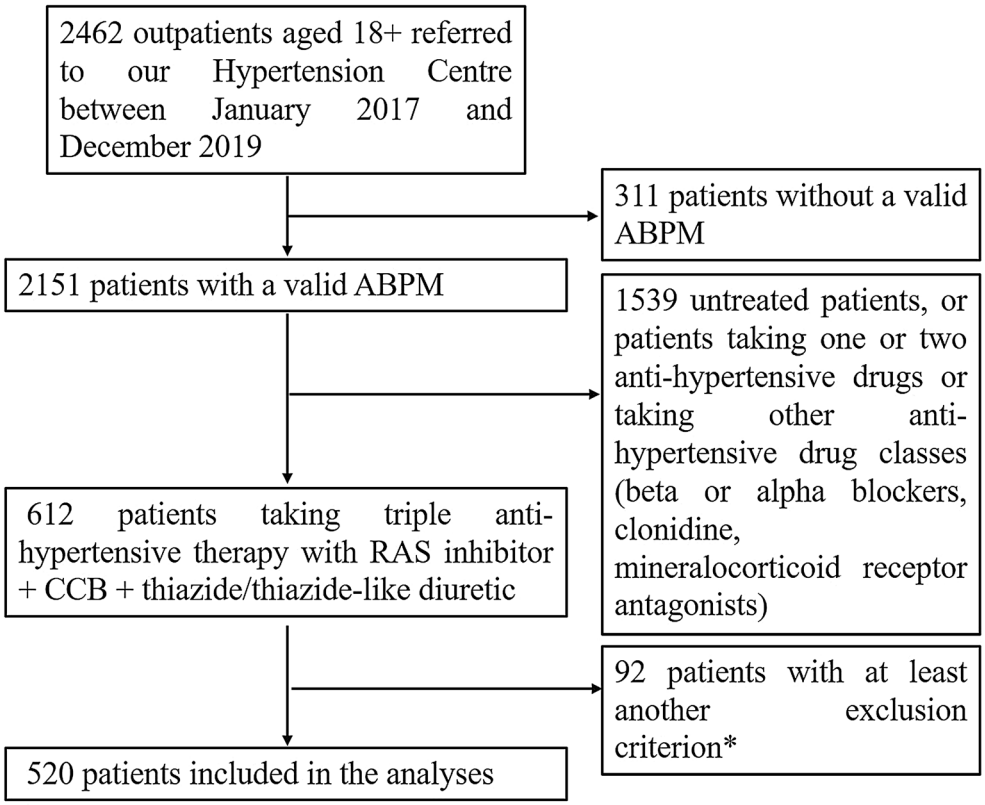
We performed an observational retrospective cross-sectional study on 520 consecutive outpatients referred to our ESH Excellence Hypertension Centre, Ancona, Italy, between January 2017 and December 2019. Most patients were referred to our Hypertension Centre by general practitioners, while only a minority by other specialists, for the proper management of high blood pressure. Therefore, our sample reflects well the community-dwelling hypertensive population. In our clinical practice, ambulatory BP monitoring (ABPM) is commonly used to evaluate BP control. We applied the following inclusion criteria: patients with essential hypertension aged at least 18 years old on a stable triple antihypertensive therapy (RAS inhibitor + CCB + thiazide/thiazide-like diuretic) and a valid 24-h ABPM. We defined "stable antihypertensive therapy" as the lack of any change in antihypertensive drug regimen within the previous 3 months, regardless of BP control. Therefore, all enrolled patients took the same number ($n = 3$) and classes of antihypertensive drugs, while the dosage and number of antihypertensive pills taken could differ from patient to patient. We applied the following exclusion criteria: permanent atrial fibrillation, major adverse CV events in the previous 3 months (transient ischemic attack/stroke, myocardial infarction, peripheral artery disease that has undergone revascularization), secondary hypertension, treatment with other antihypertensive drug classes (beta or alpha blockers, clonidine, mineralocorticoid receptor antagonists). The flow of study participants is described in Fig. 1. All participants gave their informed written consent and clinical investigations have been conducted according to the principles expressed in the Declaration of Helsinki. This study was approved by the local institutional ethics committee (Comitato Etico INRCA).

Clinical Parameters

We evaluated the following clinical parameters through consultation of medical records from routine/daily practice: patients' medical history, laboratory measurements, anthropometric measurements, ABPM parameters, and CV drug therapy. Smoking status was ascertained during recruitment and smoking habit was defined as current smoking or previous smoking of at least 100 cigarettes in a lifetime [15]. Body mass index (BMI) was defined as the body mass divided by the square of the body height and was expressed in units of kg per square meter. Fasting blood samples were collected within the same week of both the clinical visit and the placement of ABPM in all patients. The glomerular filtration rate (GFR) was estimated using the CKD-EPI creatinine equation.

Ambulatory Blood Pressure Measurements and Drug Therapy Evaluation

In our routine clinical practice, during the clinical visit, a simultaneous oscillometric automatic BP measurement is performed on both arms, and thereafter a 24-h ABPM is placed on the arm with higher readings [16], using Spacelabs 90207 and 90217 (SpaceLabs Healthcare) with appropriate cuff and bladder dimensions according to the arm circumference, in order to evaluate the BP control. Minimum quality criteria considered for a satisfactory ABPM recording were based on recommendations by Omboni et al. [17]. For each patient, 24-h BP, daytime BP (defined as the BP values from 06:00 to 22:00), nighttime BP (defined as the BP values from 22:00 to 06:00) were taken into account. The definitions of "day" and "night" periods were based on the most common answers to a questionnaire in which patients were asked about their sleeping behavior. Patients with mean 24-h BP < 130/80 mmHg, mean daytime BP < 135/85 mmHg, and mean nighttime BP < 120/70 mmHg were defined as controlled by therapy [4]. We



* permanent atrial fibrillation, major adverse CV events in the previous 3 months (transient ischemic attack/stroke, myocardial infarction, peripheral artery disease that has undergone revascularization), secondary hypertension, changes in anti-hypertensive therapy in the previous 3 months.
ABPM: ambulatory blood pressure monitoring; RAS: renin-angiotensin-system; CCB: calcium channel blocker.

Fig. 1 Flow of study participants

considered "dippers" those patients with a mean systolic BP reduction equal to or greater than 10% from day to night [4].

Given that all enrolled patients were taking three antihypertensive drugs (RAS inhibitor + CCB + thiazide/thiazide-like diuretic), we took into account both the number of antihypertensive pills taken and the antihypertensive treatment intensity (ATI) as possible pharmacological predictors of ambulatory BP control. The ATI was calculated, according to the method proposed by Law et al., to compare the different antihypertensive drugs [18, 19]. As previously reported [20], the recorded daily dose taken by patients was divided by the maximum recommended daily dose and multiplied by 100 to obtain a proportional dose (intensity) for that medication. The maximum recommended daily doses established by the Italian National Drug Agency were used for these calculations. Treatment intensity of each drug was then base-10 logarithmically transformed, assuming a log dose–response relationship of antihypertensive drugs [19]. For example, a patient taking an 80 mg daily dose of a drug for which 160 mg is the "maximum daily dose" recommended was considered to be taking 1.70 $\{\log_{10}[(80/160) \times 100]\}$ intensity units. Dual-class drugs and triple-class drugs were separated into their components and intensity was calculated separately for each compound. The sum of all the different values was recorded as ATI.

Statistical Analysis

Data were analyzed with the Statistical Package for Social Science version 13 (SPSS Inc. Chicago, Illinois, USA). A p value less than 0.05 was defined as statistically significant. Continuous variables were checked for normality. Normal continuous variables were expressed as mean ± SD. Skewed variables were expressed as median and interquartile range. Categorical variables were expressed as percentages. The χ^2 test was used to analyze the differences between categorical variables. The unpaired t test and Mann–Whitney test were used to compare quantitative variables. Logistic regression analyses were used to create adjusted models. We took into account the following covariates in the adjusted models: age, sex, BMI, smoking habit, type 2 diabetes mellitus (T2DM), estimated glomerular filtration rate (eGFR), and ATI (model 1) or number of antihypertensive pills (model 2).

RESULTS

General Characteristics

Mean age was 62.7 ± 12.2 years, with male prevalence (61.7%); 31.8% of patients were obese (BMI ≥ 30 kg/m^2) and 25.4% of patients had T2DM; 6.5% and 8.7% of patients had a history of coronary artery disease (CAD) or transient ischemic attack/stroke, respectively; 51.3% of patients were smokers and 33.8% took lipid-lowering drugs.

A total of 189 patients (36.3%) took a triple therapy with an ACEi, while the rest of the population took a triple therapy with an ARB (63.7%). The main general characteristics according to ACEi- or ARB-based triple therapy are described in Table 1. No difference in age, sex, BMI, renal function, use of concomitant medications, prevalence of smoking, and T2DM was found between the two groups. Among patients on triple therapy with ACEi, 22.2% were taking a single-pill combination with three drugs; none of the patients on triple therapy with ARB was taking a single-pill triple fixed-dose combination (no three-drug single-pill combinations with ARB are available in Italy to date). Therefore, patients in the ARB group were more likely to take free combinations and they had a slightly higher ATI compared to patients taking triple therapy with ACEi (Table 1). In particular, patients in the ARB group took higher dosages of CCB (ATI for CCB 1.85 ± 0.16 vs 1.80 ± 0.16, p = 0.001) than patients in the ACEi group. No difference emerged on the dosages of both RAS inhibitor (ATI for RAS inhibitor 1.87 ± 0.18 vs 1.85 ± 0.19, p = 0.340) and thiazide/thiazide-like diuretic (ATI for thiazide/thiazide-like diuretic 1.79 ± 0.17 vs 1.79 ± 0.21, p = 0.823). Maximum recommended daily dose of an ACEi was taken by 57.7% of patients on ACEi-based triple antihypertensive therapy, while maximum recommended daily dose of an ARB was taken by 60.7% of patients on ARB-based triple antihypertensive therapy. Perindopril was the most commonly used ACEi (41.3% within the ACEi group), while olmesartan was the most commonly used ARB (31.4% within the ARB group).

Prevalence and Predictors of Ambulatory BP Control

Ambulatory BP parameters of both ACEi and ARB groups are described in Fig. 2. Patients taking triple therapy with ACEi had a statistically significant lower 24-h and daytime systolic BP than patients taking triple therapy with ARB. Prevalence of dippers did not differ between the two groups (63.4% in the ACEi group vs 57.8% in the ARB group, p = 0.210). The overall prevalence of 24-h BP control was 47.3%. Mean ATI did not differ between controlled and uncontrolled patients (5.48 ± 0.41 vs 5.50 ± 0.34 regarding 24-h BP control, p = 0.555), while the prevalence of 24-h BP control decreased with increasing number of antihypertensive pills taken in the entire study population (Fig. 3). No difference in concomitant medications was found between controlled and uncontrolled patients (61.7% vs 60.7% p = 0.844 for 24-h BP control). Patients on ACEi-based triple therapy had better 24-h and daytime BP control (OR 1.5, 95% CI 1.1–2.2 for 24-h BP control; and OR 1.7, 95% CI 1.2–2.4 for

Table 1 Main general characteristics according to ACEi-based or ARB-based triple therapy

	All study population (n = 520)	Patients taking ACEi-based triple therapy (n = 189)	Patients taking ARB-based triple therapy (n = 331)	p*
Age (years)	62.7 ± 12.2	62.4 ± 11.8	62.8 ± 12.3	0.728
Sex (male)	61.7%	64.6%	60.1%	0.318
BMI (kg/m^2)	28.4 ± 4.4	28.2 ± 4.3	28.6 ± 4.4	0.329
Smoking habit	51.3%	50.8%	51.7%	0.849
T2DM	25.4%	29.9%	22.8%	0.073
eGFR (ml/min/1.73 m^2)	77.1 ± 22.8	77.7 ± 22.3	76.8 ± 23.1	0.660
Number of antihypertensive pills				
1	8.1%	22.2%	0.0%	
2	87.3%	77.2%	93.1%	< 0.001
3	4.6%	0.5%	6.9%	
ATI	5.49 ± 0.37	5.44 ± 0.40	5.52 ± 0.36	0.017
Use of concomitant medications	61.3%	58.5%	62.7%	0.429

*Comparison between patients taking ACEi-based triple therapy vs patients taking ARB-based triple therapy
ACEi angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *BMI* body mass index, *T2DM* type 2 diabetes mellitus, *eGFR* estimated glomerular filtration rate, *ATI* antihypertensive treatment intensity

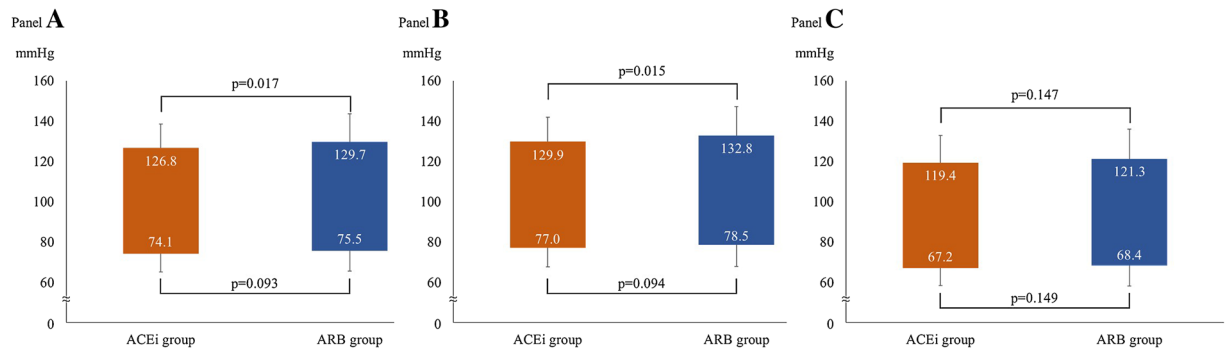


Fig. 2 Ambulatory blood pressure values and triple antihypertensive therapy with ACEi or ARB in the study population. **a** 24-h blood pressure values. **b** Daytime blood pressure values. **c** Nighttime blood pressure values

daytime BP control) than patients on ARB-based triple therapy (Fig. 4). Both associations were confirmed even after adjusting for age, sex, BMI, smoking habit, T2DM, eGFR, and ATI. However, ACEi-based triple therapy lost its independent relationship with ambulatory BP control when

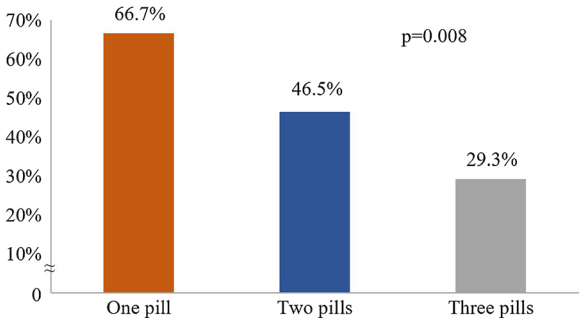


Fig. 3 Prevalence of 24-h BP control according to the number of antihypertensive pills taken in the entire study population

the number of antihypertensive pills was included in the model, instead of ATI (Table 2). Patients taking the maximum recommended daily dose of ACEi or ARB did not have a higher prevalence of 24-h BP control compared to patients not taking the maximum recommended daily dose ($p = 0.069$ and $p = 0.272$, respectively). In a subanalysis performed within the ACEi group, patients taking a single-pill triple fixed-dose combination (22.2% of the patients on ACEi) had a higher prevalence of 24-h BP control than patients taking two antihypertensive pills (77.2% of the patients on ACEi) [70.0% vs 51.0%, OR 2.2 (95% CI 1.1–4.7), $p = 0.033$]. Among patients taking ARB-based triple therapy, olmesartan was not associated with better 24-h BP control compared to other ARBs ($p = 0.370$), while, among patients taking ACEi-based triple therapy, perindopril was associated with a better 24-h BP control compared to other ACE inhibitors (64.1% vs 46.8%, $p = 0.019$). If this association was confirmed after adjustment for ATI in model 1 (OR 2.1, 95% CI 1.2–3.9, $p = 0.014$), it was lost after adjustment for the number of antihypertensive pills in model 2 ($p = 0.129$), in line with the analysis on the entire study population.

DISCUSSION

In the present study on patients with essential hypertension taking a triple antihypertensive therapy, we found that a triple therapy with an ACEi was associated with a higher prevalence of both 24-h and daytime BP control than a triple therapy with an ARB at univariate analysis. However, this association was lost after taking into account the number of antihypertensive pills taken. This parameter was independently associated with ambulatory BP control in our population, while the type of RAS inhibitor taken by patients did not affect ambulatory BP control in the adjusted model. Patients on ACEi-based triple therapy took fewer pills, thanks to the large use (22%) of a single-pill triple fixed-dose combination containing perindopril–indapamide–amlodipine, the only "triple combo" available for prescription in our country to date. Furthermore, among patients on ACEi therapy, those taking perindopril had a higher prevalence of 24-h BP control, although again this finding was due to the fewer antihypertensive pills taken. Not by chance, the single-pill ACEi-based triple fixed-dose

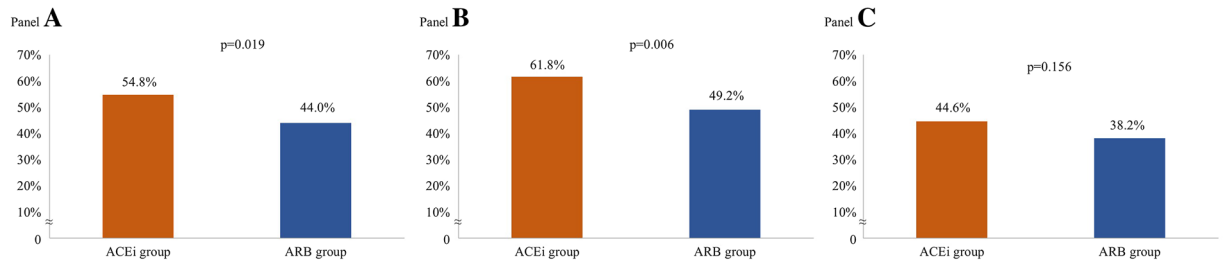


Fig. 4 Ambulatory blood pressure control and triple antihypertensive therapy with ACEi or ARB in the study population. **a** 24-h blood pressure control. **b** Daytime blood pressure control. **c** Nighttime blood pressure control

Table 2 Logistic regression models for the risk of 24-h and daytime BP control (n = 520)

Variable	24-h BP control		Daytime BP control	
	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 1 OR (95% CI)	Model 2 OR (95% CI)
Age (years)	1.0 (0.9–1.0)	1.0 (1.0–1.1)	1.0 (0.9–1.0)	1.0 (1.0–1.1)
Sex (ref. female)	0.8 (0.5–1.1)	0.8 (0.5–1.1)	0.9 (0.6–1.3)	0.9 (0.6–1.3)
BMI (kg/m^2)	1.0 (0.9–1.1)	1.0 (1.0–1.1)	1.0 (1.0–1.1)	1.0 (1.0–1.1)
Smoking habit	0.9 (0.7–1.3)	0.9 (0.7–1.4)	0.9 (0.6–1.3)	0.9 (0.6–1.3)
T2DM	1.0 (0.7–1.5)	1.0 (0.7–1.5)	0.8 (0.5–1.2)	0.8 (0.5–1.2)
eGFR (ml/min/1.73 m^2)	1.0 (0.9–1.0)	1.0 (1.0–1.1)	1.0 (0.9–1.0)	1.0 (1.0–1.1)
ACEi-based triple therapy vs ARB-based triple therapy (ref. ARB-based triple therapy)	1.5 (1.1–2.2)*	1.2 (0.8–1.9)	1.6 (1.1–2.4)*	1.4 (0.9–2.1)
ATI	1.0 (0.6–1.6)	–	0.8 (0.5–1.3)	–
Number of antihypertensive pills (ref. 1)				
1	–		–	
2		0.5 (0.2–1.0)*		0.4 (0.2–0.9)*
3		0.2 (0.1–0.7)*		0.4 (0.1–1.1)

BP blood pressure, *OR* odds ratio, *CI* confidence interval, *BMI* body mass index, *T2DM* type 2 diabetes mellitus, *eGFR* estimated glomerular filtration rate, *ATI* antihypertensive treatment intensity

*$p < 0.05$, **$p < 0.001$

Model 1 included age, sex, BMI, smoking habit, T2DM, eGFR, ATI as covariates

Model 2 included all model 1 variables except ATI, which was substituted by number of antihypertensive pills, as covariates

combination was associated with better BP control compared to the other free ACEi-based combinations.

ACEi and ARBs act on two different sites of the RAS pathway, leading to different modulation of the mediators involved in both RAS and anti-RAS arms [21]. Therefore, a different BP response after their administration could be expected, at least theoretically. However, our findings are in line with previous studies that showed no clear superiority in antihypertensive efficacy of one drug class over the other. Given the several different molecules within the same class having both different half-lives and receptor binding affinities [22, 23], it is very understandable how previous studies had found

that certain ARBs were more effective in BP lowering compared to certain ACEi [24, 25]. However, meta-analytic data showed no difference between ACEi and ARB in terms of BP reduction (− 12.9/7.7 mmHg vs − 13.3/7.8 mmHg) [26]. Likewise, both ACEi and ARB showed similar effectiveness on reduction of target organ damage, such as left ventricular hypertrophy and proteinuria, directly BP-dependent [27, 28]. Regarding major CV outcomes, such as mortality, stroke, and coronary artery disease, ACEi were likely to confer greater protection than ARB in some clinical studies [29, 30]. Several recent cohort studies showed how ACEi treatment is associated with a lower incidence of all-cause and CV death compared with ARB treatment in patients with myocardial infarction [29–31]. Meta-analyses attempted to pool the evidence from randomized controlled trials (RCTs), showing a divergent CV effect on myocardial infarction and death, likely owing to a further risk reduction by ACEi, independent of BP lowering [32, 33]. The findings from RCTs on ACEi and ARB investigating the major CV outcomes are not easily summarized and comparable for several reasons. The majority of RCTs on ACEi have been performed in historical periods when both the control of CV risk factors was less aggressive (i.e., less extensive use of lipid lowering drugs) and the targets set by guidelines were less stringent in primary and secondary prevention, thus having higher numbers of CV events affecting the magnitude of their findings and therefore not allowing a correct comparison with RCTs on ARB performed more recently [14, 34].

In our study, the number of antihypertensive pills taken by patients was found to be the key predictor of ambulatory BP control: the fewer the pills, the better the BP control. The strong link between the number of pills and the adherence to antihypertensive treatment is well known. Patients taking a fixed-dose combination therapy have from 21% to 84% higher probability of persistence to treatment than those taking a free-equivalent combination therapy [35–37]. Non-adherence to antihypertensive treatment is one of the major contributors to inadequate BP control [38, 39]. A review including 28 studies from 15 countries showed that 45.2% of patients with hypertension were non-adherent to medications and 83.7% of medication non-adherence was found in patients with uncontrolled hypertension [40]. Fixed-dose single-pill combination therapies significantly improve treatment adherence, leading to better BP control and CV outcomes [36, 37]. The relationship between fixed-dose combination therapies and BP lowering is probably mainly derived from a better adherence to therapy. Indeed, previous studies suggest no different BP reduction in patients with the same adherence to single-pill or free-dose combination therapies [36, 41]. However, if the association between treatment adherence and number of antihypertensive pills is well established, the direct comparison between single-pill combination vs free-dose combination regimens in terms of BP lowering is difficult to perform in clinical trials and the few published studies have shown conflicting results [42–44]. Likewise, the discussion on the CV outcomes is open. A recent population-based retrospective cohort study found that the risk of primary outcome (composite of death or hospitalization for acute myocardial infarction, heart failure, or stroke) was lower in patients taking single-pill fixed-dose combination treatment in the intention-to-treat analysis only, while if the analysis was limited to patients who remained adherent to medication (on treatment analysis) the significance of the association was lost, stressing the key role of treatment adherence [37]. In a recent review, Tsioufis et al. concluded that further evidence is needed to determine if the increase in adherence seen in patients taking single-pill combinations will translate into better BP control and improved CV outcomes [45]. In this context, only three studies have investigated this aspect using ABPM [46–48]. At the same time, only few studies with small samples focused on patients taking a triple antihypertensive therapy using ABPM, but they found favorable effects of a triple fixed-dose combination versus triple free combination therapies in terms of both ambulatory BP parameters and cardiac organ damage [49, 50].

Our observational study highlights how the number of antihypertensive pills, with the same intensity of treatment, is likely to be a key

determinant of BP control in the real-world clinical practice. A drug will work only if one takes it, and a single-pill combination strategy means a better adherence to prescribed therapy and a higher probability of achieving the desired target, in this case BP control.

Study Limits

The major strengths of our study are the use of ABPM that allowed a greater accuracy in the assessment of the real BP values and control [51, 52], and the accurate selection of the study population. Indeed, all patients took the three most common antihypertensive drug classes recommended by guidelines (RAS inhibitor + CCB + thiazide/thiazide-like diuretic), thus excluding possible interference from other antihypertensive drug classes. Finally, our observational study reflects real-world clinical practice. However, our study has also several limitations. First, the retrospective non-randomized design of our study does not allow the exclusion of residual confounding factors. Second, the aim of the study was beyond the evaluation of treatment adherence. The study aimed to evaluate the prevalence and predictors of ambulatory BP control in patients taking a triple therapy with an ACEi or a triple therapy with an ARB. Therefore, information regarding the adherence to prescribed antihypertensive treatment was not available in our patients, although our speculation is supported by a large and unequivocal body of literature on the strong relationship between the number of antihypertensive pills taken and the adherence to therapy. Third, the unavailability of a single-pill triple fixed-dose combination containing an ARB in our country, which did not allow the inclusion of this group in our study, may have affected our findings. Last, although the ATI has already been used in previous studies [18, 20] to compare the different drug classes, it is a derived parameter which does not take into account the different effectiveness of each antihypertensive drug class.

CONCLUSION

We found a higher prevalence of ambulatory BP control in patients taking a triple therapy with ACEi compared to patients taking a triple therapy with ARB. However, this finding was affected by the lower number of antihypertensive pills taken, which was also the key predictor of ambulatory BP control in our study. Therefore, the type of RAS inhibitor (ACEi or ARB) within the triple antihypertensive therapy did not make the difference, but the number of pills did: the lower the number of pills, the higher the prevalence of BP control. Our work emphasizes the role played by fixed-dose combination strategies that are likely to improve adherence to antihypertensive therapy and therefore BP control in patients with essential hypertension.

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manuscript. All authors read and approved the final manuscript.

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Compliance with Ethics Guidelines. All participants gave their informed written consent and clinical investigations have been conducted according to the principles expressed in the Declaration of Helsinki. This study was approved by the local institutional ethics committee (Comitato Etico INRCA).

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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