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ORIGINAL ARTICLE

Hypertension Treatment with Angiotensin Receptor Blockers and Other Antihypertensive Agents: A Real-World Registry from a High-Volume Specialized Center Over TwoDecades

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Abstract

Introduction Patients with difficult to control hypertension (HTN) are often referred by general practitioners to specialized centers to estimate global cardiovascular (CV) risk profile, evaluate hypertension-mediated organ damage (HMOD), and optimize antihypertensive therapy. This referral provides a unique opportunity to analyse patients with high CV risk and HTN in a real-world setting, characterized by the rigorous adoption of uniform and state-of-the-art procedures by expert personnel.

Aim To examine (1) global CV risk profile, office and out-of-office blood pressure (BP) levels, and markers of HMOD in adult patients referred to a high-volume European Hypertension center; (2) to evaluate how these clinical parameters impact on the choice of different antihypertensive therapies.

Methods An observational, cross-sectional study was conducted in adult patients of both sexes, aged ≥ 18 years, with essential treated hypertension, who were consecutively evaluated at the Excellence Hypertension Center at Sant'Andrea Hospital in Rome, Italy. Office and out-of-office BP levels were measured, and different hypertension phenotypes were set according to European guidelines. CV risk profile was estimated according using SCORE2. Only patients with treated HTN were selected for the analysis and stratified according to antihypertensive therapies: (1) angiotensin receptor blockers (ARBs); (2) angiotensin converting enzyme (ACE) inhibitors; (3) other drugs (including diuretics, beta-blockers, calcium channel blockers, alpha-blockers, mineralocorticoid receptor antagonists).

Results From an overall database of 11,168 outpatients, a total of 5,677 patients with treated HTN were analysed (46.3% females, age 63.6 ± 13.1 years, BMI 27.4 ± 4.8 kg/m2, office BP 140.6 ± 17.5/85.5 ± 11.5 mmHg, 24-hour BP 128.7 ± 13.7/77.2 ± 9.7 mmHg, SCORE2 5.4 ± 4.3%). Among these, 52.9% were treated with ARBs, 30.2% with ACE inhibitors and 17.0% with other drugs. Patients treated with ARBs were more frequently males, and significantly older, had more frequently obesity ($P < 0.001$), dyslipidaemia ($p < 0.001$), and diabetes ($p < 0.001$) than those treated with other drug classes. They also had more frequently CV comorbidities ($P < 0.001$) and resistant HTN ($P < 0.001$). They received more BP lowering agents ($P < 0.001$), being more frequently treated with triple ($P < 0.001$), quadruple ($P < 0.001$), or more complex ($P < 0.001$) combination therapies. Comparable office and out-of-office BP control were recorded between patients treated with ARBs and those patients managed with either ACE inhibitors or other drugs.

Conclusions Among adult outpatients referred to an excellence hypertension center, the majority were treated with ARBs, alone or in combination therapies. ARB-treated patients presented more frequently CV risk factors, comorbidities, and difficult-to-treat HTN.

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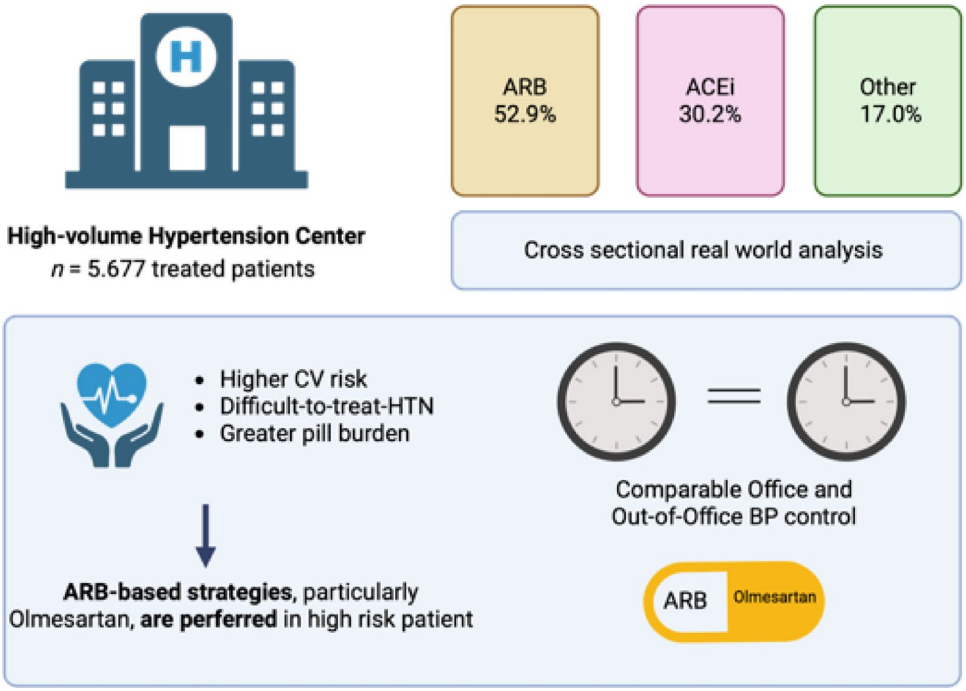
Graphical Abstract



Keywords Hypertension · Blood pressure · Angiotensin receptor blockers (ARB) · Antihypertensive drugs · Cardiovascular · Risk factors · Olmesartan

1 Introduction

Hypertension remains a major global public health challenge, largely contributing to cardiovascular (CV) morbidity and mortality worldwide. Recent estimates suggest that approximately 1.3 billion individuals have elevated blood pressure (BP), with projected increasing prevalence of the disease in both high- and low-income countries in the next decades. The burden of hypertension extends beyond CV mortality, also causing increased risk of chronic kidney and peripheral artery diseases, as well as reduction in disability-adjusted life expectancy and quality of life. Although guidelines issued by both European Society of Hypertension (ESH) [1] and European Society of Cardiology (ESC) [2] have lowered therapeutic targets and emphasised the importance of achieving early and effective BP control, aimed at reducing the burden of hypertension-related CV diseases, real-world data indicate that BP control rates remain suboptimal, even in high-income, specialised settings [3–5].

In Italy, clinical surveys and observational studies performed over the years have consistently documented high rates of uncontrolled hypertension, despite educational programs, guidelines' dissemination, and diagnostic and therapeutic advances [6–10]. These studies identified several critical aspects including relatively low awareness of the clinical consequences of the disease, persistent habit to use monotherapies or low-dose (free) combination therapies, high rates of discontinuations or self-adjustments of prescribed medications, and poor adherence by physicians to implement guidelines' recommendations in their practice as the most relevant and frequently reported causes of poor BP control [6–10].

One potential strategy to implement BP control in treated hypertension in the real-world is to integrate the predominant approach based on the evidence obtained by randomized control clinical trials and meta-analyses with evidence derived from solid real-world data originated from large population samples [11, 12]. Recent reports supported the role of real-life data for implementing the clinical management of hypertension, which may integrate our current views with observations based on larger populations, longer observations, and lower costs than those achieved by multicenter, randomized, controlled, clinical trials [11, 12].

European guidelines have emphasized the key role of specialized hypertension centers [1, 2]. They may help physicians in properly identifying hypertension phenotypes, assessing the presence of risk factors, comorbidities and markers hypertension-mediated organ damage (HMOD), which may guide therapeutic choices [13–15]. In addition, through an approach based on comprehensive assessment of

office and out-of-office BP values, they may help to adopt tailored antihypertensive strategies on the basis of the individual patients' characteristics, also in order to achieve the recommended therapeutic BP targets [1, 2]. Thus, analysing data extracted from hypertension centers' databases may offer a real-world snapshot of rigorous and uniform classification of hypertension, definition of hypertension phenotypes, estimation of CV risk profile and HMOD, evaluation of therapeutic attitudes and patient preferences for an effective clinical management of high CV risk patients or subjects with difficult-to-control or resistant hypertension.

On the basis of these considerations, the present study was performed to characterize adult outpatients with treated essential hypertension referred to a high-volume specialised hypertension center, with detailed assessment of office and out-of-office BP levels, global CV risk (via SCORE2 [16, 17]), and markers of HMOD. By stratifying patients in relation to the main antihypertensive therapeutic strategies (angiotensin receptor blockers [ARBs], angiotensin converting enzyme [ACE] inhibitors, and other drug classes), we sought to explore differences in BP control, risk profile and therapy complexity in a real-world specialized setting. The main advantages of this approach as compared to scrutinizing data from general practice are related to more homogeneous clinical approaches, standardized techniques, and expert personnel.

2 Methods

2.1 Outpatients

In this observational, cross-sectional study we included adult individuals who were consecutively evaluated for hypertension screening and global CV risk stratification, including HMOD assessment, at the Hypertension Centre, Division of Cardiology, Sant'Andrea University Hospital in Rome, Italy, from January 2004 to June 2025. Patients were referred to our unit for hypertension assessment (including home, office, and 24-hour ambulatory BP measurement), as well as for secondary hypertension screening, by local general practitioners or referring doctors. To minimize potential selection bias, all consecutive eligible patients referred to the center during the study period were included according to predefined inclusion and exclusion criteria.

To be included in the study, participants were required to fulfil the following inclusion criteria: (1) age of 18 years or more; (2) valid office and out-of-office BP measurements; (3) stable (more than 6 months) antihypertensive treatment for hypertension; (4) signature of the informed consent for study participation. The exclusion criteria included: (1) secondary hypertension; (2) severe or malignant hypertension, as defined by office systolic/diastolic BP≥190/≥120 mmHg; (3) signs and symptoms of acute HMOD; (4) recent (within the previous 6 months) history of acute CV diseases, including at least one of the following: acute coronary syndromes, transient ischemic attack, stroke, congestive heart failure, severe valvular disease, or peripheral artery disease; (5) any neurological or psychiatric disease which may at least, in part, affect the BP assessment or the signature of the informed consent; (5) active neoplastic disease or any major systemic disease; (6) patients on dual RAAS blocking agents or treated with rarely (<3%) in our clinical database. Patients presenting with very high office BP values (>190/120 mmHg) were excluded, as these levels are suggestive of hypertensive urgency or emergency, often requiring immediate treatment modifications and acute management, and therefore not representative of stable chronic antihypertensive therapy.

The study design and reporting followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [18], and the corresponding checklist was applied to ensure methodological transparency (supplementary material, online available). The study has been registered on the AIFA platform for observational studies with the number: 2283 in 2025).

The study conformed to the Declaration of Helsinki and its subsequent modifications. The confidentiality of the data of each patient included in the present study was carefully and strictly protected. Informed consent was obtained in all individuals included in the present study, which was approved by the local Ethical Committee. At our University Hospital all individuals evaluated in the outpatient clinic, are required to sign a generic consent to medical care, a specific consent for out-of-office BP monitoring and an additional consent for using individual clinical data collected in anonymous form for research purposes.

3 Office Blood Pressure Measurements

Before BP assessment, arm circumferences were measured to all patients to allow the correct choice of cuff size. On the basis of individual arm circumference, different cuff sizes (small 22–24 cm, medium 24–32 cm, large 32–38 cm and extra-large 38–55 cm) were used, in order to have proper office BP measurements, as recommended by guidelines [19, 20].

Office BP measurements were performed in the hypertension unit, excellence center for hypertension management and control recognised by ESH and the Italian Society of Hypertension (SIIA), during the morning section (from 8:00 to 12:00 AM). All BP measurements were attended and performed by ESH hypertension specialist or certified

nurses. Sequential office BP measurements were performed in a quiet room, after 5 min of rest, on the same non-dominant arm and with the participant in the sitting position, by using an automated, oscillometric device (Mobil-O-Graph PWA Monitor, I.E.M. GmbH, Stolberg, Germany).

4 Ambulatory Blood Pressure Measurements

Ambulatory Blood Pressure Monitoring (ABPM) was performed by an oscillometric device (Spacelabs 90207 On-track, Spacelabs Inc., Redmond, Washington, USA). The device was set in the Hypertension Unit after completion of the office BP measurements and the ABPM was started at about 10:00 AM, so that both these BP measurements were performed during the same visit. Automatic BP readings were obtained every 15 min during the day-time period (from 6:00 AM to 10:00 PM) and every 30 min during the night-time period (from 10:00 PM to 6:00 AM) over the 24 h [19, 20]. Each patient was instructed not to alter their usual schedule during the monitoring period, asked to avoid unusual or extreme physical activities, and to maintain the arm still during the BP measurement. Average values for the 24-hour, daytime and night-time systolic and diastolic BP levels and heart rate were extracted [19, 20]. In addition, standard deviation from average values, as well as number of BP measurements above the normal BP thresholds were collected for each period (24-hour, daytime and night-time), when available.

For all BP measurements, appropriate cuff sizes were applied, depending on arm circumference of individual patients (small 6–11 cm, small/medium 10–19 cm, medium 18–26 cm, large 22–32 cm and extra-large 33–47 cm), according to the recommendations from European guidelines [19, 20].

5 Hypertension Classification

Hypertension was diagnosed based on the presence of office systolic BP values ≥ 140 mmHg and/or diastolic BP values ≥ 90 mmHg (average of 3 repeated office measurements in the sitting position made by the same doctor with an oscillometric automatic sphygmomanometer), according to BP classifications proposed 2023 ESH guidelines [1].

Office BP levels were used to stratify treated patients into four categories. Controlled office hypertension was defined in the presence of both systolic and diastolic office BP levels below the normal thresholds of < 140/<90 mmHg. Isolated systolic hypertension (ISHT) was defined in the presence of office systolic BP ≥ 140 mmHg and diastolic BP < 90 mmHg, whereas isolated diastolic hypertension (IDHT) was set for office systolic BP < 140 mmHg and diastolic BP ≥ 90 mmHg. Systolic-diastolic hypertension (SDHT) was defined in the presence of both office systolic BP ≥ 140 mmHg and diastolic BP ≥ 90 mmHg. Controlled out-of-office hypertension was defined in the presence of both systolic and diastolic 24-hour BP levels below the normal thresholds of < 130/<80 mmHg.

5.1 Definition of Cardiovascular Risk Factors and Hypertension-Mediated Organ Damage

Overweight was defined in the presence of body mass index (BMI) ≥ 25–29 kg/m2, and obesity for BMI ≥ 30 kg/m2. Diagnosis of hypercholesterolemia was made in the presence of total cholesterol (TOT-C) levels ≥ 190 mg/dl or low density lipoprotein cholesterol (LDL-C) levels ≥ 130 mg/dl, while hypertriglyceridemia for triglyceride (TG) levels ≥ 150 mg/dl or stable lipid-lowering drug treatment in both conditions [21]. Diagnosis of hyperuricemia was set according to criterion proposed by the Uric acid Right foR heArt Healt (URRAH) study (serum uric acid [SUA] ≥ 5.6 mg/dl in both sexes) [22]. Diabetes was defined in the presence of fasting plasma glucose levels ≥ 126 mg/dl or in the presence of glucose-lowering therapy [23].

Cardiac hypertension-mediated organ damage (HMOD) was defined by ECG or echocardiographic evidence of left ventricular hypertrophy (LVH). In particular, ECG-LVH was defined for one of the following criteria: (1) Sokolow-Lyon index > 35 mm; (2) Cornell Voltage > 28 mm in males and > 20 mm in females; (3) R wave in aVL in 11 mm. Additionally, Echo-LVH was defined for LVM indexed by height^2.7 > 50 g/m^2.7 in males and > 47 g/m^2.7 in females. LV concentric remodelling was set for relative wall thickness (RWT) ≥ 0.43. Thus, concentric LVH was defined for above normal values of both RWT and LVM indexed by height^2.7, whilst eccentric LVH for abnormal values of LVM indexed by height^2.7 with RWT < 0.43. Vascular HMOD was defined for PWV ≥ 10 m/sec or PP ≥ 60 mmHg. Renal HMOD was defined for eGFR < 60 ml/min/1.73 m², or MAU ≥ 30 mg/lt, or urinary albumin/creatinine ratio (UACR) > 30 mg/g.

6 Cardiovascular Risk Stratification

Global CV risk stratification was performed according to SCORE2 [17] risk algorithm for those patients aged 40–65 years and according to SCORE2-OP [16] for those aged 65 years or more. In both cases, risk estimation was performed in patients without comorbidities, as defined by the presence of atherosclerotic cardiovascular disease (ASCVD). Since

data on glycated haemoglobin and duration of diabetes were not available in our database, SCORE2-Diabetes [24] cannot be calculated for patients with treated hypertension and diabetes. To avoid underestimation of individual CV risk profile, SCORE2 risk was not calculated in patients with diabetes, who were considered at high CV risk profile.

Previous ASCVD included non-fatal myocardial infarction (MI) and non-fatal stroke or transient ischemic attack (TIA). Non-fatal MI was defined according to the presence of the two of the following three criteria: typical symptoms lasting longer than 15 min, transient increase in serum concentrations of enzymes indicating cardiac damage (more than twice the upper limit of normal) and electrocardiographic changes typical of myocardial ischemia [25, 26]. The diagnosis of MI may also include acute coronary syndrome, recurrent angina and coronary revascularization [27].

Non-fatal stroke was defined as a neurological deficit with sudden onset and persistence of symptoms for more than 24 h or leading to death with no apparent causes other than vascular ones [28]. Transient ischaemic attack (TIA) was defined as a neurological event with the signs and symptoms of stroke, but which go away within a short period of time (typically last 2 to 30 min) [29].

6.1 Statistical Analysis

All data were collected in a protected database managed by authorized personnel and stored in password-accessible dedicated personal computers. Baseline characteristics of patients are presented as number and percentage for dichotomous variables and mean ± standard deviation of the mean for continuous variables. Normal distribution of data was assessed using histograms and Kolmogorov-Smirnov test. Differences between continuous variables were assessed using either t-Student or ANOVA tests and statistical correction for multiple comparisons among groups (Bonferroni) was applied. Categorical variables were compared among groups by the chi-square test. To account for potential confounding related to baseline risk profile and treatment indication, logistic regression models were built to identify factors predicting ARB prescriptions. In Model 1, we included dichotomous variables potentially related to the use of ARB-based therapy, including sex, obesity, dyslipidaemia, diabetes, comorbidities (ASCVD), uncontrolled office (>=140/>=90 mmHg) or out-of-office (>=130/>=80 mmHg) hypertension, presence or absence of antihypertensive combination therapy and concomitant medications. Comorbidities were defined as the presence of ≥1 of the following: established CAD, stroke or TIA, and chronic kidney disease. In Model 2, we included continuous variables, such as age, BMI, office and out-of-office systolic/diastolic BP values, eGFR, SCORE2 risk, and number of antihypertensive drugs. Collinearity among BP variables was assessed prior to multivariable analyses. All tests were two-sided, and a P value<0.05 was considered statistically significant; where applicable, Bonferroni correction was applied for multiple comparisons. All calculations were generated using SPSS, version 27.0 (SPSS Inc., Chicago, Illinois) for MacOs.

7 Results

The overall database included 11,168 adult participants. Of these, 252 records were excluded due to paediatric, gestational or secondary forms of hypertension, 4,580 records due to screening (untreated) hypertension, 104 records due to partial or poor quality of the BP data, and 306 with office BP values exceeding 190/120 mmHg. We further excluded from the analysis patients treated with dual RAAS blocking agents, and those treated with drugs poorly represented in our population. Thus, we obtained a final sample of 5,677 adult outpatients with treated hypertension (46.3% females, mean age 63.6±13.1 years, BMI 27.4±4.8 kg/m2, office BP 140.6±17.5/85.5±11.5 mmHg, 24-hour BP 128.7±13.7/77.2±9.7 mmHg, SCORE2 5.4±4.3%), among whom 3,002 (52.9%) were treated with ARBs, 1,712 (30.2%) were treated with ACE inhibitors, and 963 (17.0) were treated with other drugs, including calcium channel blockers, diuretics, beta blockers, mineralocorticoid receptor antagonists, or alpha-blockers. A flow-chart for patients' selection is illustrated in Fig. 1.

General characteristics of the study population are reported in Table 1. Patients treated with ARBs were more frequently males ($P < 0.001$) and were significantly older ($P < 0.001$) than those treated with other drugs. CV risk factors were more frequently represented in the ARB-treated patients, as demonstrated by higher prevalence of obesity or overweight ($p < 0.001$), dyslipidaemia ($P < 0.001$), and diabetes ($P = 0.001$) compared to that recorded in patients treated with both ACE inhibitors and other drugs. They also showed higher values of SCORE2 [17] or SCORE2-OP [16] risk than those treated with ACE inhibitors or other drugs, although this difference did not achieve statistical significance.

No significant differences among groups were observed for glucose, lipid, uric acid and renal parameters, except for significantly lower values of TOT-C ($P=0.022$) and LDL-C ($P=0.008$) levels in patients treated with ARBs than in those treated with other drugs. This was paralleled with significantly higher proportions of patients receiving lipid ($P<0.001$) and glucose ($P=0.019$) lowering therapies

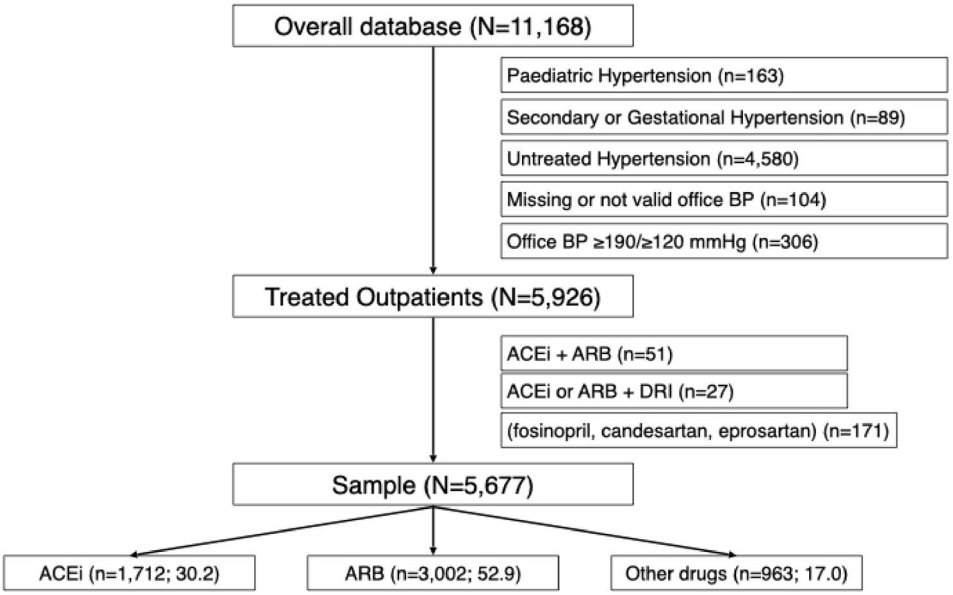


Fig. 1 Schematic representation of patients' selection according to inclusion and exclusion criteria. In the figure: BP, blood pressure: ACEi: angiotensin-converting enzyme inhibitors; ARBs: angiotensin receptor blockers; DRI: direct renin inhibitors

Table 1 General characteristics of the study population, stratified according to reference treatment groups

Parameters	Total	ARB	ACEi	Others	*P* value
Outpatients (%)	5,677 (100.0)	3,002 (52.9)	1,712 (30.2)	963 (17.0)	–
Female (%)	2,631 (46.3)	1,347 (44.9) #	767 (44.8) #	517 (53.7)	<0.001
Age (years)	63.6±13.1	64.5±12.3 #	63.3±12.7 #	61.4±15.5	<0.001
BMI (kg/m2)	27.4±4.8	27.7±4.8 #	27.3±4.7 #	26.5±4.9	<0.001
BSA (m2)	1.85±0.3	1.87±0.3 #	1.86±0.3 #	1.81±0.3	<0.001
Smoking (%)	677 (11.9)	369 (12.3)	188 (11.0)	120 (12.4)	0.346
Obesity (%)	1,383 (24.4)	794 (26.4) *#	392 (22.9) #	197 (24.4)	<0.001
Hyperuricemia (%) (*n*=756)	350 (46.3)	205 (45.5)	82 (50.0)	63 (44.7)	0.554
Dyslipidaemia (%)	2,514 (44.3)	1,417 (47.2) *#	738 (43.1) #	359 (37.2)	<0.001
Diabetes (%)	936 (16.5)	543 (18.1) *#	261 (15.2) #	132 (13.7)	0.001
Resistant HTN (%)	467 (8.2)	326 (10.9) *#	129 (7.5) #	12 (1.2)	<0.001
ASCVD (%)	824 (14.5)	432 (14.4) #	285 (16.6) #	107 (11.1)	<0.001
LVEF (%) (*n*=1,062)	66.6±10.1	66.9±9.9*	64.8±10.2	67.5±10.6	0.014
SCORE2 (%) (*n*=1,438)	5.4±4.3	5.5±4.3	5.3±4.1	5.0±4.6	0.390
Glucose (mg/dl) (*n*=1,856)	102.4±38.9	102.4±39.3	104.9±46.5	98.6±20.4	0.112
TOT-C (mg/dl) (*n*=1,915)	187.3±41.9	186.2±41,8	186.3±42.9	193.6±40.9	0.022
HDL-C (mg/dl) (*n*=1,915)	52.7±14.0	53.0±14.2	52.0±13.4	52.3±14.1	0.453
LDL-C (mg/dl) (*n*=1,915)	113.3±37.9	111.6±37.4	114.1±39.9	119.3±36.6	0.008
TG (mg/dl) (*n*=1,915)	118.1±61.4	117.8±61.4	118.7±58.8	118.4±64.1	0.962
Creatinine (mg/dl) (*n*=1,928)	1.00±0.5	0.99±0.5	1.01±0.7	1.03±0.5	0.450
SUA (mg/dl) (*n*=756)	5.5±1.5	5.5±1.5	5.5±1.5	5.4±1.4	0.529
LLT (%)	2,022 (35.6)	1,152 (38.4) *#	593 (34.6) #	277 (28.8)	<0.001
GLT (%)	619 (10.9)	358 (11.9)	175 (10.2)	86 (8.9)	0.019
ASA (%)	1,769 (31.2)	957 (31.9)	567 (33.1)	245 (25.4)	<0.001

ACEi: angiotensin-converting enzyme inhibitors; ARBs: angiotensin receptor blockers; BMI: body mass index; BSA: body surface area; HTN: hypertension; ASCVD: atherosclerotic cardiovascular disease; LVEF: left ventricular ejection fraction; TOT-C: total cholesterol; LDL-C: low-density lipoporotein cholesterol; HDL-C: high density lipoprotein cholesterol; TG: triglycerides; SUA: serum uric acid; LLT: lipid-lowering therapy; GLT: glucose-lowering therapy; ASA: acetyl salicylic acid

* < 0.001 vs. ACEi; # < 0.001 vs. Other Drugs

in the ARB-treated group as compared to those reported in patients treated with ACE inhibitors or other drugs.

Patients treated with ACE inhibitors presented more frequently comorbidities ($P<0.001$), lower (yet within the normal range) left ventricular ejection fraction ($P=0.014$) and received more frequently aspirin ($P<0.001$) than those treated with other drugs, though no significant differences were observed as compared to the ARB group.

8 Distribution of Antihypertensive Therapies and Blood Pressure Treatment Targets

The distribution of the different antihypertensive therapies is reported in Table 2. Patients treated with ARBs were less frequently treated with monotherapies than those treated with either ACE inhibitors or with other drugs ($P<0.001$). At

Table 2 Distribution of different antihypertensive treatment strategies and office and out-of-office BP control in the overall population and in reference treatment groups

Parameters	Total	ARB	ACEi	Others	*P* value
Average drugs (num)	2.2 ± 1.1	2.4 ± 1.1 *#	2.1 ± 1.0 #	1.4 ± 0.7	< 0.001
Monotherapy	1,842 (32.4)	656 (21.9) *#	528 (30.8)	658 (68.3)	< 0.001
Dual Therapy	1,937 (34.1)	1078 (35.9) #	641 (37.4) #	218 (22.6)	< 0.001
Triple Therapy	1,231 (21.7)	805 (26.8) *#	360 (21.0) #	66 (6.8)	< 0.001
Quadruple Therapy	504 (8.9)	347 (11.6) *#	139 (8.1) #	18 (1.9)	< 0.001
> 4 Drugs	162 (2.9)	116 (3.9) *#	43 (2.5) #	3 (0.3)	< 0.001
Office BP < 140/90 mmHg (%)	2,234 (39.4)	1,190 (39.6)	671 (39.2)	373 (38.7)	0.871
Office BP < 130/80 mmHg (%)	827 (14.6)	429 (14.3)	262 (15.3)	136 (14.1)	0.584
24-hour BP < 130/80 mmHg (%)	2,010 (43.2)	1,061 (43.7)	640 (44.4)	309 (39.4)	0.056

ARBs: angiotensin receptor blockers; ACEi: angiotensin-converting enzyme inhibitors; BP: blood pressure

* < 0.001 vs. ACEi; # < 0.001 vs. Other Drugs

the same time, they received significantly more antihypertensive agents (2.4 ± 1.1 vs. 2.1 ± 1.0 vs. 1.4 ± 0.7; $P < 0.001$) and were more frequently treated with triple ($P < 0.001$), quadruple ($P < 0.001$), or more complex ($P < 0.001$) combination regimens of antihypertensive drugs than patients treated with either ACE inhibitors or other drugs, as illustrated in Fig. 2.

As shown in Table 3, there were no significant differences among groups for office and out-of-office BP values, except for average office systolic BP values, which tended to be slightly higher in patients treated with ARBs than in those treated with ACE Inhibitors ($P = 0.05$) whereas night-time diastolic BP levels resulted significantly lower in patients treated with either ARBs or ACE inhibitors as compared to those treated with other drugs ($P = 0.009$). Of note, systolic ($P = 0.014$) and diastolic ($P = 0.023$) nocturnal dipping was significantly more pronounced in patients treated with ARBs than in those reported in the other treatment groups.

There were no significant differences among groups regarding the proportions of patients with office BP levels within the recommended therapeutic targets of office BP < 140/90 mmHg ($P = 0.871$), < 130/80 mmHg ($P = 0.584$), nor for 24-hour BP < 130/80 mmHg ($P = 0.056$).

Prescriptive options for selected classes of antihypertensive drugs according to different hypertension phenotypes is illustrated in Fig. 3. ARBs represented the most frequently used drug class across all hypertension phenotypes ($P < 0.001$), mostly in those patients with isolated systolic hypertension and systolic-diastolic hypertension, followed by ACE inhibitors and other drugs.

Proportions of patients treated with single-pill combination therapies are shown in Fig. 4. Fixed combination therapies with either ACE inhibitors or ARBs plus thiazide or thiazide-like diuretics were frequently used before the publication of 2013 ESH/ESC [30] hypertension guidelines [30], though they showed a trend toward reduction after the publication of 2013 ESH/ESC [30] and, mostly, 2018 ESC/ESH [31] hypertension guidelines. On the other hand, fixed combination therapies with either ACE inhibitors or ARBs plus CCBs showed a progressive, and significant increase after the publication of 2013 ESH/ESC [30] and, mostly, 2018 ESC/ESH [31] hypertension guidelines.

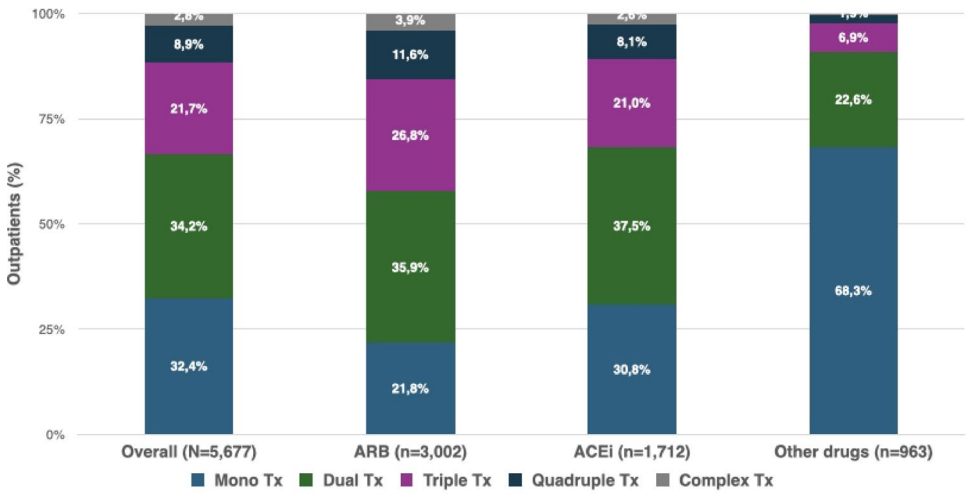


Fig. 2 Treatment complexity according to reference study drug class. In each drug class proportions of patients under monotherapies, dual, triple, quadruple, or complex (5-6 drugs) combination therapies are illustrated. In the figure: ACEi: angiotensin-converting enzyme inhibitors; ARBs: angiotensin receptor blockers

Table 3 General characteristics of the study population, stratified according to reference treatment group

BP values	Total	ARB	ACEi	Others	*P* value
Office SBP (mmHg)	140.6 ± 17.5	141.4 ± 17.6 *	139.7 ± 17.1	140.0 ± 17.9	0.004
Office DBP (mmHg)	85.5 ± 11.5	85.3 ± 11.4	85.6 ± 11.6	86.3 ± 11.4	0.057
24-hour SBP (mmHg)	128.7 ± 13.7	128.9 ± 13.8	128.2 ± 13.3	129.3 ± 13.9	0.189
24-hour DBP (mmHg)	77.2 ± 9.7	77.3 ± 10.0	76.8 ± 9.5	77.8 ± 9.4	0.061
Daytime SBP (mmHg)	131.9 ± 14.0	132.2 ± 14.2	131.2 ± 13.5	132.1 ± 14.2	0.080
Daytime DBP (mmHg)	80.1 ± 10.2	80.2 ± 10.4	79.6 ± 10.0	80.5 ± 9.8	0.081
Night-time SBP (mmHg)	119.8 ± 15.4	119.7 ± 15.6	119.3 ± 14.9	120.9 ± 15.7	0.061
Night-time DBP (mmHg)	69.0 ± 9.9	68.9 ± 10.2 #	68.6 ± 9.4 #	70.0 ± 9.9	0.009
Dipping SBP (%)	9.0 ± 7.8	9.3 ± 7.9 #	8.9 ± 7.4	8.4 ± 7.9	0.014
Dipping DBP (%)	13.5 ± 8.4	13.8 ± 8.3 #	13.5 ± 8.3	12.9 ± 8.4	0.023

Univariate and multivariate analysis for identifying predictors of the use of ARB-based therapy. In model 1, dichotomous covariates have been included in the logistic regression analysisARBs: angiotensin receptor blockers; ACEi: angiotensin-converting enzyme inhibitors; SBP: systolic blood pressure; DBP: diastolic blood pressure

* < 0.001 vs. ACEi; # < 0.001 vs. Other Drugs

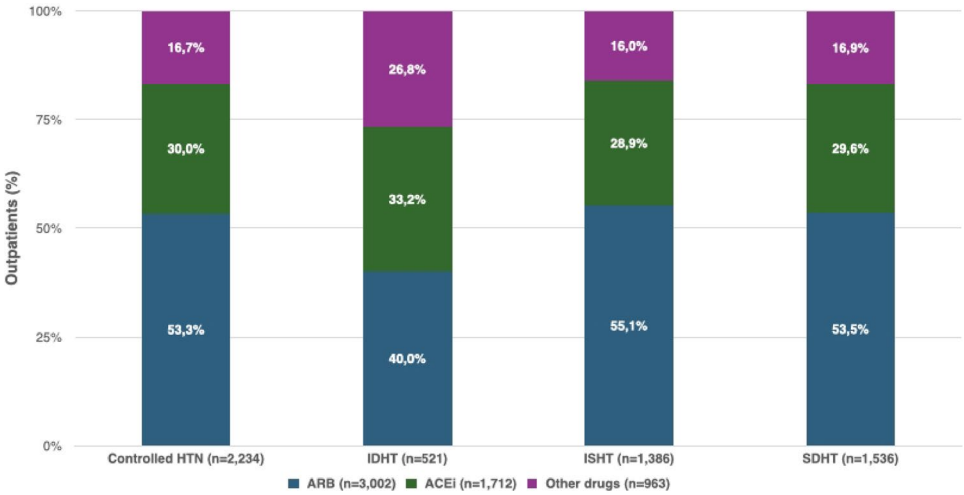


Fig. 3 Proportions of patients treated with either ARBs, ACE inhibitors or other drugs, according to different hypertension phenotypes. Office blood pressure levels were used to identify different hypertension phenotypes in adult treated hypertensive outpatients. In the figure: ACEi: angiotensin-converting enzyme inhibitors; ARBs: angiotensin receptor blockers; HTN: hypertension; IDHT: isolated diastolic hypertension; ISHT: isolated systolic hypertension; SDHT: systolic-diastolic hypertension

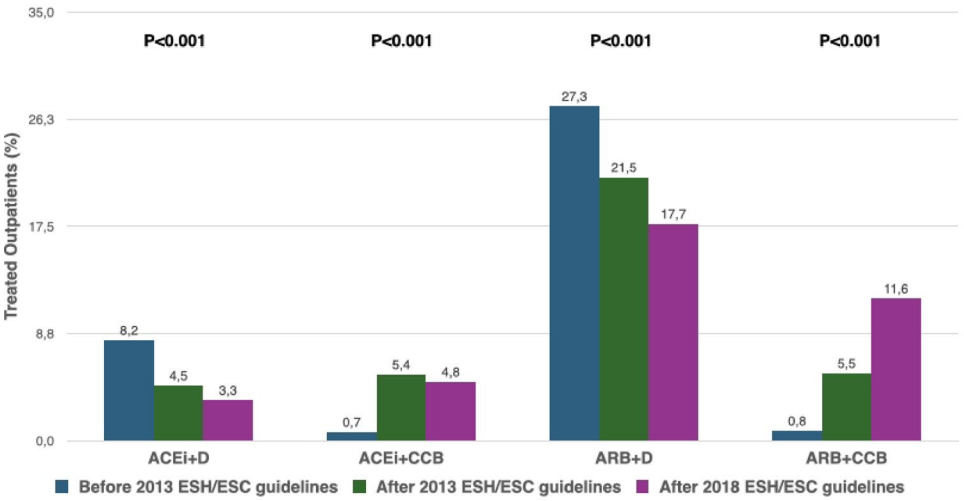


Fig. 4 Proportions of patients treated with single-pill (fixed) combination therapies based with either ARBs, or ACE inhibitors plus thiazide or thiazide diuretics or calcium-channel blockers, before and after the publication of 2013 ESH/ESC guidelines and 2018 ESC/ESH guidelines on hypertension. In the figure: ACEi: angiotensin-converting enzyme inhibitors; ARBs: angiotensin receptor blockers; D: thiazide or thiazide-like diuretics; CCB: calcium-channel blockers; ESH: European Society of Hypertension; ESC: European Society of Cardiology

8.1 Subgroup Analysis of Patients Treated with ARB-based Therapies

In the ARB-based treatment group, 655 (21.8%) patients were on monotherapy, 1,079 (35.9%) on dual, 805 (26.8%) on triple, and 347 (11.6%) on quadruple combination therapy, while 116 (3.9%) patients received 5–6 antihypertensive drugs.

Among ARBs, olmesartan was the most frequently prescribed agent in this cohort (44.8%), followed by valsartan

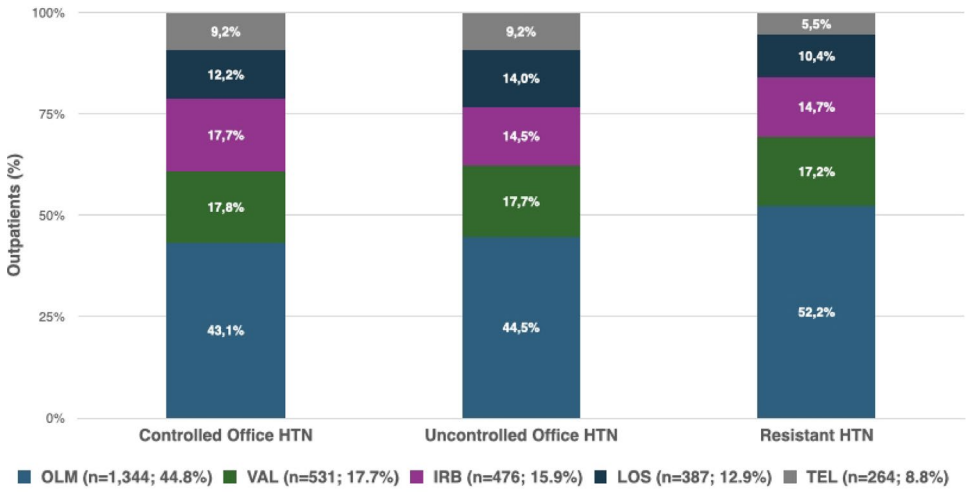


Fig. 5 Distribution of different molecules within the ARB class according to hypertension strata. In the figure: HTN: hypertension; OLM: Olmesartan; VAL: valsartan; IRB: irbesartan; LOS: losartan; TEL: telmisartan

Table 4 Univariate and multivariate analysis for identifying predictors of the use of ARB-based therapy. In model 1, dichotomous covariates have been included in the logistic regression analysis

Model 1	Univariate		Multivariate	
Covariates	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Obesity	1.274 (1.127–1.439)	<0.001	1.1418 (1.011–1.304)	0.033
Dyslipidaemia	1.286 (1.158–1.429)	<0.001	1.159 (0.978–1.374)	0.089
Diabetes	1.282 (1.113–1.478)	<0.001	1.053 (0.905–1.225)	0.506
Comorbidities	0.979 (0.844–1.135)	0.778	–	–
Combination therapies	2.848 (2.538–3.197)	<0.001	2.761 (2.457–3.103)	<0.001
Uncontrolled Office BP	1.026 (0.922–1.142)	0.637	–	–
Uncontrolled Out-of-office BP	0.957 (0.852–1.075)	0.455	–	–
Lipid-lowering Tx	1.292 (1.158–1.441)	<0.001	0.976 (0.817–1.167)	0.790
Aspirin	1.074 (0.959–1.202)	0.216	–	–

OR: odds ratio; CI: confidence interval

(17.7%), irbesartan (15.9%), losartan (12.9%), and telmisartan (8.8%). Olmesartan resulted as the most frequently used compound among patients under monotherapies (44.1%), followed by valsartan (17.1%), irbesartan (14.2%), losartan (13.0%), and telmisartan (11.7%). A similar distribution was observed also in patients receiving combination therapies, in whom olmesartan-based therapies resulted to be the most frequently used (45.0%), followed by valsartan (17.9%), irbesartan (16.3%), losartan (12.9%), and telmisartan (8.0%).

The distribution of the different ARBs according to hypertension stratification is reported in Fig. 5. Proportions of patients treated with olmesartan increased from patients with controlled hypertension to those with uncontrolled hypertension and in those with resistant hypertension. Proportions of patients treated with valsartan remained substantially unchanged across these same categories, whereas those of patients treated with irbesartan, losartan, and telmisartan tended to be used progressively less in relation to the increasing complexity of the patients.

8.2 Univariate and Multivariate Analyses

Results of logistic regression analyses are reported in Tables 4 and 5. In model 1 (panel A), at univariate analysis obesity, dyslipidaemia, diabetes, presence of combination therapy and concomitant medications with lipid-lowering agents resulted predictors for the ARB prescription. At multivariate analysis, only obesity [OR 95% CI: 1.1418 (1.011–1.304); $P=0.033$] and combination therapy [OR 95% CI: 2.761 (2.457–3.103); $P<0.001$] resulted to be independent predictors for the use of ARB-based antihypertensive strategy. In model 2 (panel B), age, BMI, office systolic BP, and number of antihypertensive medications resulted associated with the use of ARBs at univariate analysis. At multivariate analysis, all these covariates, including age [OR 95% CI: 1.005 (1.000-1.009); $P=0.030$], BMI [OR 95% CI: 1.015 (1.004–1.027); $P=0.011$], and office systolic BP [OR 95% CI: 1.003 (1.000-1.007); $P=0.030$] resulted associated with the use of ARB-based antihypertensive strategy, with number of antihypertensive medications [OR 95% CI: 1.574 (1.489–1.663); $P<0.001$] thus emerging as the strongest, independent predictors of the use of ARBs in our population sample.

Table 5 Univariate and multivariate analysis for identifying predictors of the use of ARB-based therapy. In model 2, continuous covariates have been included in the logistic regression analysis

Model 2	Univariate		Multivariate	
Covariates	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age (years)	1.011 (1.007–1.015)	<0.001	1.005 (1.000-1.009)	0.030
BMI (kg/m2)	1.028 (1.016–1.039)	<0.001	1.015 (1.004–1.027)	0.011
Office SBP (mmHg)	1.005 (1.002–1.008)	<0.001	1.003 (1.000–1.007)	0.030
Office DBP (mmHg)	0.996 (0.991–1.000)	0.067	–	–
24-hour SBP (mmHg)	1.001 (0.997–1.006)	0.524	–	–
24-hour DBP (mmHg)	1.001 (0.995–1.007)	0.725	–	–
eGFR	1.000 (0.999–1.001)	0.411	–	–
Risk SCORE2 (%)	1.018 (0.993–1.043)	0.169	–	–
Antihypertensive drugs (num)	1.612 (1.528–1.701)	<0.001	1.574 (1.489–1.663)	<0.001

OR: odds ratio; CI: confidence interval; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate

9 Discussion

The present study provides a comprehensive characterization of adult outpatients with hypertension and high CV risk profile, who were referred to a tertiary hypertension center over a 20-year period, and treated with the currently recommended therapeutic strategies, including either ARBs, ACE inhibitors, or other antihypertensive drug classes. The study offers unique insights into real-world practice of a high-volume hypertension center, by analysing prescribing patterns, as well as hypertension phenotypes and control associated with different antihypertensive therapies. Several important observations emerged at a deep analysis of patients' features driving the choice among the therapeutic options. First of all, ARB-based therapies resulted the most frequently used in a setting of an excellence hypertension center. Indeed, patients receiving ARBs were more frequently characterized by a higher burden of risk factors and comorbidities, received more complex antihypertensive regimens, exhibited slightly higher office BP values, and presented more frequently with difficult-to-treat or resistant hypertension and markers of HMOD.

Our findings highlight the complexity of therapeutic decision-making in hypertension management and underscore the importance of contextual clinical factors that extend beyond BP control alone. At the same time, they require caution in attributing mechanistic or causal interpretations to cross-sectional associations, particularly in the light of the role of potential concomitant confounding factors linked to the indication and the inherent selection bias typical of tertiary referral populations.

In unadjusted analyses, patients receiving ARBs presented with a more complex clinical profile, as evidenced by higher prevalence of obesity, dyslipidaemia, and diabetes, as well as greater burden of HMOD. These associations are consistent with previous reports showing that ARBs are widely prescribed in patients with metabolic disorders, possibly due to their neutral or even favourable safety profile, neutrality or benefit on glucose metabolism, lower incidence of adverse effects and better tolerability compared with other drugs including ACE inhibitors [32–34]. Nevertheless, the magnitude of several observed differences in the present cohort requires careful interpretation. In spite of the statistical significance, which may be partly due to the large sample size, some of the recorded differences in BP values, metabolic parameters, or nocturnal dipping were numerically small and may have marginal clinical meaning. In our sample, office systolic BP was approximately 1–2 mmHg higher in patients on ARBs compared with those on ACE inhibitors, and nocturnal systolic dipping differed by less than 1% point across drug groups. These findings, while statistically detectable, cannot be interpreted as evidence of differential efficacy or chronobiological modulation across drug classes. Instead, they likely reflect underlying differences in referral patterns, previous treatment history, or physician preference in more complex or treatment-resistant cases.

Patients in the ARB group received a greater number of antihypertensive agents and had a higher proportion of resistant hypertension. This pattern suggests that ARBs may have been preferentially selected for patients requiring combination therapies or for those who had previously discontinued ACE inhibitors due to intolerance. The higher frequency of combination therapies among ARB-treated patients, particularly the widespread use of ARB plus CCB regimen, is consistent with recommendations from 2023 ESH hypertension guidelines [1], endorsing RAAS blockade as a foundational component of the combination treatment strategies. It should be also noted that dual or triple combination therapies based on ARBs have proven to reduce office and 24-hour ambulatory BP levels and achieve the recommended therapeutic targets in numerous randomized, controlled, clinical trials [35–37], independently by demographic, anthropometric, and clinic parameters, as well as by previous background monotherapies [38–40].

However, after adjustment for age, metabolic comorbidities, renal function, office and out-of-office BP, and global CV risk profile, the number of antihypertensive agents did not independently predict the use of ARBs. This finding

reinforces the importance of distinguishing between treatment complexity as a marker of disease severity and treatment class as a deliberate therapeutic choice. Real-world prescribing is strongly influenced by prior tolerance, physician's attitudes, experience and familiarity, and clinical appraisal of comorbidities, making it unlikely that antihypertensive drug class selection can be attributed to isolated clinical variables.

Our findings support the clinical equivalence between ARBs and ACE inhibitors in terms of BP control, even if ARBs were predominantly used in our target population. Although current hypertension guidelines [1, 2] consider ARBs and ACE inhibitors broadly interchangeable for most compelling indications, the preferential use of ACE inhibitors in secondary prevention has been deeply rooted in clinical culture since the seminal HOPE [41] and EUROPA [42] clinical trials. After these trials, long-standing clinical practice and guideline endorsements have historically supported the use of ACE inhibitors in high-risk patients, particularly in those with established ASCVD, including chronic CAD or cerebrovascular disease, heart failure, or diabetic nephropathy. Thus, physicians may perceive ARBs as more suitable for patients with metabolic comorbidities or difficult-to-treat hypertension, whereas ACE inhibitors may be preferred in high-risk profiles due to their longer track record and robust evidence base in high-risk populations.

It is important to emphasize that the observed association does not imply inferior efficacy of ARBs in high-risk patients. On the contrary, large, randomized, controlled, clinical trials [43–46] and meta-analyses [47, 48] indicate that ARBs provide CV protection comparable to ACE inhibitors, with better tolerability and lower risk of cough and angioedema. Therefore, the present findings likely reflect traditional prescribing attitudes rather than clinical differences.

Another interesting result of our analysis is the progressive changes reported for prescriptions of fixed combination therapies before and after the publication of the latest sets of hypertension guidelines. 2013 ESH/ESC [30] and, mostly, 2018 ESC/ESH [31] guidelines strongly support the use of single pill combination therapies for the clinical management of hypertension, in order to improve patients' adherence to prescribed medications and attained BP control. In addition, 2018 ESC/ESH guidelines [31] firstly supported the use of fixed combination therapies based on RAAS blocking agents plus either thiazide or thiazide-like diuretics or CCBs as first-line therapies for uncomplicated hypertension. The same therapeutic approach has been recently confirmed by both 2023 ESH [1] and 2024 ESC [2] guidelines. To the best of our knowledge, this is the first evidence demonstrating a significant and consistent shift from single-pill combination therapies with diuretics towards those with CCBs, in high-risk patients with hypertension followed in a setting of real-world practice of a high-volume hypertension center. This trend toward increase in the use of fixed combinations therapies based on either ACE inhibitors or ARBs plus CCBs might be considered in the light of the positive results of such therapeutic approach in reducing HMOD [49, 50] and risk of CV complications [51, 52] in patients with hypertension.

Although 24-hour ABPM provides crucial insight into out-of-office BP profile, the differences observed in daytime and night-time BP, dipping patterns, and pulse pressure among treatment groups were modest. The interpretation of ABPM data must also consider methodologic limitations: the ABPM protocol applied daytime–nighttime windows independent of the actual time of device placement, potentially introducing misclassification for patients with unconventional sleep–wake schedules or nonstandard monitoring start times. Given these considerations, it would be inappropriate to infer differential chronobiological effects of ARBs, ACE inhibitors, or other drug classes from the present retrospective data. Only randomized crossover or prospective clinical studies on chronotherapy could adequately test such hypotheses.

Several limitations must be acknowledged. First, the cross-sectional design precludes causal inference. Associations between drug classes and clinical characteristics cannot be interpreted as treatment effects. Secondly, confounding factors influencing the choice are substantial: ARBs may be preferentially prescribed to specific patient profiles based on history of intolerance, perceived metabolic benefits, or physician preference and attitudes. Third, SCORE2 calculations were not available for diabetic patients, who were automatically classified as high risk. This approach, although consistent with guidelines' structure, limits comparability of absolute risk values across subgroups. Fourth, substantial collinearity was observed between office and out-of-office systolic BP values, as well as between BP and BMI, which may affect model stability. Fifth, referral bias is unavoidable: a tertiary hypertension center receives a disproportionate number of complex and treatment-resistant hypertension, limiting generalizability to primary care populations. Finally, the cohort reflects a tertiary referral hypertension center, thus the observed results may not be generalized to unselected primary care populations.

Despite these limitations, our current study provides a unique example of how analysis of large population samples referred to a specialized hypertension center can implement and reinforce data obtained in the rigid design and structure of randomized controlled trials or in the more heterogeneous environment of GPs registries. The study's large sample size, long observational window, and availability of detailed ABPM, metabolic, and therapeutic data provide a

robust description of antihypertensive prescribing patterns of a specialized hypertension center in the context of real-world practice.

9.1 Clinical Implications

Given the observational and cross-sectional nature of the study, the associations observed cannot be interpreted as causal, do not imply superiority or differential efficacy of ARBs over other antihypertensive drug classes, and should be considered as descriptive of real-world prescribing patterns rather than as a basis for direct therapeutic decision-making. Our findings suggest that ARBs are frequently used in patients with metabolic comorbidities and more complex hypertension, consistent with their documented efficacy and favourable tolerability profile. The study also shows that Among ARBs, olmesartan was the most frequently prescribed agent in this cohort, reflecting local prescribing patterns in a real-world outpatient setting. This higher frequency of olmesartan use observed in the present study should be interpreted as a descriptive finding related to real-world prescribing habits rather than as evidence of comparative effectiveness among ARBs. Given the repeatedly and consistently demonstrated equivalence of ARBs and ACE inhibitors in BP reduction and CV protection and the superior tolerability and persistence on treatment of ARBs, their underutilization in high-risk CV patients requires further analysis. Future implementation studies should explore whether educational interventions or updated risk-stratified treatment algorithms could mitigate such discrepancies. Moreover, the modest differences observed in ABPM parameters reinforce the notion that drug class selection should prioritize global CV protection, tolerability, and HMOD protective properties rather than minor hemodynamic variations on BP reductions.

10 Conclusions

In conclusion, ARBs are the most prescribed antihypertensive drugs in the practice context of a high-volume specialized center. High risk hypertensive outpatients treated with ARBs in this large real-world cohort exhibit a more complex clinical profile, greater therapeutic burden, and slightly different hemodynamic features. After multivariable adjustment, office systolic BP values, individual risk factors (ageing and obesity), and complex therapeutic regimens appear to be the predominant independent determinant of ARB prescription. Our current findings underscore the multifaceted nature of antihypertensive prescribing and highlight opportunities for improving alignment between clinical practice and current evidence regarding the use of RAAS inhibitors across CV risk strata.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40292-026-00784-7.

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Declarations

Conflict of interest G.T. has received honoraria from Menarini Italia and Menarini International for acting as a speaker in national and international symposia. MV has received honoraria for speaker bureau or Advisory Board from Astra Zeneca, Menarini International, Neopharmed, Novartis, Servier and he is supported by a Grant of the Italian Ministry of Health ("Ricerca Corrente"). Other authors have no conflict of interest to disclose to the present manuscript.

Ethical Approval The present study was approved by the local Ethical Committee.

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