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Real-life appraisal on blood pressure targets achievement in adult outpatients at high cardiovascular risk

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ESC score

Abstract *Background and aim:* Although hypertension guidelines highlight the benefits of achieving the recommended blood pressure (BP) targets, hypertension control rate is still insufficient, mostly in high or very high cardiovascular (CV) risk patients. Thus, we aimed to estimate BP control in a cohort of patients at high CV risk in both primary and secondary prevention.
Methods and results: A single-center, cross-sectional study was conducted by extracting data from a medical database of adult outpatients aged 40–75 years, who were referred to our Hypertension Unit, Rome (IT), for hypertension assessment. Office BP treatment targets were defined according to 2018 ESC/ESH guidelines as: a)<130/80 mmHg in individuals aged 40–65 years; b)<140/80 mmHg in subjects aged >65 years. Primary prevention patients with SCORE <5% were considered to be at low-intermediate risk, whilst individuals with SCORE ≥5% or patients with comorbidities were defined to be at very high risk. Among 6354 patients (47.2% female, age 58.4 ± 9.6 years), 4164 (65.5%) were in primary prevention with low-intermediate CV risk, 1831 (28.8%) in primary prevention with high-very high CV risk and 359 (5.6%) in secondary prevention. In treated hypertensive outpatients, uncontrolled hypertension rate was significantly higher in high risk primary prevention than in low risk primary prevention and secondary prevention patients (18.4% vs 24.4% vs. 12.5%, respectively; $P < 0.001$). In high risk primary prevention diabetic patients only 10% achieved the recommended BP targets.
Conclusions: Our data confirmed unsatisfactory BP control among high-risk patients, both in primary and secondary prevention, and suggest the need for a more stringent BP control policies in these patients.

Introduction

Arterial hypertension is the major preventable risk factor for cardiovascular (CV) disease and CV death. Over the last decades, successful progress has been obtained in hypertension treatment due to the scientific evidences demonstrating that lowering blood pressure (BP) to the recommended BP targets can significantly reduce CV morbidity and mortality [1].

A large number of effective pharmacological (i.e. combination therapies) and lifestyle (dietary sodium restriction, weight reduction, regular physical activity, smoking

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cessation etc.) strategies have been promoted to ensure effective BP control [2–4]. However, despite the efforts made by physicians and scientific societies, recent clinical surveys showed that overall BP control rates remain relatively poor and still unsatisfactory in Europe and worldwide [5–8]. Early and effective BP control has relevant implications in reducing the risk of CV events, both in primary and secondary prevention, thus uncontrolled hypertension might be viewed as a major determinant for the persistently high burden of CV disease [9].

In 2017, the SPRINT trial showed that targeting systolic BP to less than 120 mmHg in high-risk patients is associated with even lower rates of fatal and non-fatal CV events and death from any cause than those observed with conventional systolic BP target [10]. Further analyses from other randomized controlled clinical trials, support not only the importance of achieving traditional BP control, but also the need of adopting in the clinical practice more intensive BP targets, especially in individuals at increased risk of developing major CV outcomes, in order to reduce the burden of hypertension-related CV diseases. Thus, based on the available evidence, in 2018 European guidelines have redefined the BP treatment targets to be achieved under pharmacological therapy in hypertensive patients with comorbidities, thus suggesting more ambitious BP goals [11].

Given these considerations, the aim of this study was to investigate the rates of BP control in a large cohort of high CV risk patients who were referred to an excellence hypertension center, and to evaluate the potential differences in BP control rate between primary and secondary prevention groups. Secondary aim was to analyse the clinical variables which may predict the achievement of the recommended BP treatment targets, in order to identify those patients who may benefit of more strictly medical control. Finally, ddespite current guidelines [11] did not provide formal ambulatory blood pressure monitoring (ABPM) treatment targets, we further analysed data from 24-h ABPM of high-risk treated hypertensive patients.

Methods

Methodology of the study

The methodology of the study protocol has been previously described [12,13]. Briefly, this is a single-center, cross-sectional, observational study designed to evaluate the rate of BP control in high-risk hypertensive adult outpatients, who were consecutively evaluated at the Hypertension Unit of Sant'Andrea Hospital, University of Rome Sapienza, in Rome, Italy, from February 2004 to April 2020.

To be included in the study, patients had to fulfil the following inclusion criteria: 1) adult individuals aged more than 40 years and less than 75 years; 2) valid clinic systolic and diastolic BP levels; 3) valid data for age, gender, total cholesterol levels, and smoking habit; 4) signature of informed consent for study participation. In addition, the following exclusion criteria were considered: 1) secondary hypertension or true resistant hypertension; 2) recent (less than 6 months) history of acute CV diseases, including at least one of the following: coronary artery disease (CAD), transient ischemic attack (TIA), stroke, congestive heart failure, severe valve disease, or peripheral artery disease; 3) any neurological or psychiatric disease which may at least, in part, affect the BP assessment or the signature of the informed consent.

Once identified, patients were stratified according to the presence or absence of previous CV events including myocardial infarction, transient ischemic attack, or stroke (secondary and primary CV prevention, respectively). Primary prevention patients with ESC Score $<5\%$ were considered to be at low-intermediate CV risk whilst individuals with ESC score $\geq 5\%$ were defined to be at high-very CV high risk.

Collected information included anthropometric data, blood test parameters, antihypertensive therapy, CV risk factors and comorbidities. Clinical systolic and diastolic BP, home BP levels and 24-h BP levels, when available, were also extracted.

The study conformed to the Declaration of Helsinki and its subsequent modifications, and was authorized by the reference Ethical Committee. As applied in previous studies, the confidentiality of the data was carefully and strictly protected.

Cardiovascular risk estimation

CV risk was calculated by using the European SCORE (Systematic COronary Risk Evaluation) risk equation in those outpatients without previous cardiovascular events [14] The SCORE system estimates the 10 year risk of a first fatal CV event, in relation to age, sex, smoking, total cholesterol and systolic BP [14]. Since the study population was composed by adult Caucasian individuals, the low-risk score charts have been applied [14]. The use of SCORE is recommended for estimate CV risk for treatment decisions in hypertensive patients who are not already at high or very high risk (Class of recommendation I, Level of evidence B) [14] and it applied to patients aged between 40 and 65 years; however, the system has been also adapted for older patients [15]. According to guidelines [11], patients with valid SCORE risk have been stratified, as follows: 1) low CV risk (SCORE $<1\%$); 2) moderate CV risk (SCORE $\geq 1\%$ - $<5\%$); 3) high CV risk (SCORE $\geq 5\%$ - $<10\%$); 4) very high CV risk (SCORE $\geq 10\%$). In the present study, primary prevention population was stratified in two groups according to ESC score as follows: individuals with ESC Score $<5\%$ were considered to be at low (intermediate) CV risk whilst patients with ESC score $\geq 5\%$ were defined to be at high (very high) CV risk.

Blood pressure measurements

Office attended BP measurements were performed according to recommendations by European guidelines [11]. Sequential clinic BP measurements (1–2 min apart), using an adequate bladder cuff, were performed in all patients in

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a quiet room, after 10 min of rest, on the left arm and with the participant in supine position, by using an automated oscillometric device (Omron 705 IT). The average of three consecutive BP measurements was considered as clinic BP value.

ABPM was performed according to clinician indications, by an oscillometric device (Spacelabs 90207, Spacelabs Inc., Redmond, Washington, USA). Automatic BP readings were obtained every 15 min during the day-time and every 30 min during the night over 24 h. Each patient was instructed not to alter her/his usual schedule during the monitoring period, asked to avoid unusual physical exercise, to maintain the arm still during BP measurements and to record daily activities and sleep time on a diary. A minimum of 70% valid BP measurements were required for considering valid the monitoring. Average values for the 24-h, day-time and night-time systolic and diastolic BP levels and heart rate were reported. BP thresholds considered as goal for optimal treatment target were: <130/80 mmHg over 24 h.

Clinical BP treatment targets were initially set as <140/90 mmHg in the overall population sample. According to the recent 2018 European hypertension guidelines [11], the following office BP treatment targets were defined: a) systolic BP $\leq$ 130 mmHg and diastolic BP < 80 mmHg in individuals aged 18–65 years; b) systolic/diastolic BP < 140/80 mmHg in those aged >65 years.

For the purposes of the present analysis, the last available clinic BP levels were used from those available in our medical database during the predefined observational period, as previously described [12,13].

Definition of cardiovascular risk factors and comorbidities

Based on anthropometric data, calculation of body mass index (BMI) was made and it was expressed as body weight in kilograms divided by the square of height in meters (kg/m2).

Diagnosis of hypertension was defined in the presence of systolic BP levels $\geq$140 mmHg and/or diastolic BP levels $\geq$90 mmHg in untreated subjects or in the presence of stable ($\geq$6 months) antihypertensive drug treatment [11]. Diagnosis of hypercholesterolemia was made in the presence of total cholesterol levels $\geq$190 mg/dl or low-density lipoprotein (LDL) cholesterol levels $\geq$130 mg/dl, while hypertriglyceridemia for triglyceride levels $\geq$150 mg/dl or stable lipid-lowering drug treatment in both conditions [16]. Diabetes was defined in the presence of plasma glucose levels $\geq$126 mg/dl or in the presence of glucose-lowering therapy [17].

Coronary artery disease (CAD), including non-fatal myocardial infarction (MI), was defined according to the presence of the two of the following three items: symptoms (e.g. chest pain) 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 (new persistent ST-segment) elevation or pathological Q waves in two contiguous leads [18]. The diagnosis of CAD may also include other coronary events, for example acute coronary syndrome, recurrent angina and coronary revascularization [18].

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 [19]. Transient ischaemic attack was defined as a neurological event with the signs and symptoms of stroke, but which resolve within a short period of time (typically less than 24 h) [20].

Statistical analysis

Patients' characteristics are presented as number and percentage for dichotomous variables and mean $\pm$ standard deviation (SD) of the mean for continuous variables. Normal distribution of data was assessed using histograms and Kolmogorov–Smirnov test. Continuous variables were tested with either t-Student or ANOVA tests, whereas dichotomous variables were tested by chi square test. All tests were two-sided, and a P value of less than 0.05 was considered statistically significant. All calculations were generated using SPSS, version 20.0 for MacOs (SPSS Inc., Chicago, Illinois).

Results

Study population

From an overall sample of 8906 individuals we selected data from 6354 patients (47.2% female, age 58.4 $\pm$ 9.6 years, BMI 27.1 $\pm$ 4.6 kg/m2, clinic BP 142.5 $\pm$ 18.2/89.4 $\pm$ 13.2 mmHg), among whom 4164 (65.5%) were in primary prevention with low-intermediate CV risk, 1831 (28.8%) in primary prevention with high-very high CV risk and 359 (5.6%) in secondary prevention. General characteristics of the study population are reported on Table 1.

Primary prevention patients at low-intermediate risk were significantly younger (55.1 $\pm$ 8.6 vs 65.0 $\pm$ 7.9 years; P < 0.001), more frequently female (56.9% vs. 39.7%; P < 0.001) and showed significantly lower prevalence of major CV risk factors compared to those at high risk. In particular, smoking habit resulted significantly more frequent in high risk primary prevention patients than in those at low risk (21.6% vs 16.0% P < 0.001).

In the secondary prevention group, 165 (46%) had a previous MI, 189 (52.6%) had a previous TIA or stroke, and only 5 patients (1,4%) had both CV events. Compared to high risk primary prevention patients, those with previous CV event were significantly younger (62.8 $\pm$ 8.7 vs 65.0 $\pm$ 7.9 years) and showed significantly higher prevalence of major CV risk factors, including obesity, dyslipidaemia and diabetes (p < 0.001 for all comparison). No significant differences regarding gender and smoking habit were observed between these two groups.

With regard to metabolic parameters, we observed significantly lower LDL-C levels in secondary prevention patients compared to those at high risk in primary

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Table 1 General characteristics of the study population.

Parameters	Overall Sample	Primary Prevention			Secondary Prevention	
		Pts with low-intermediate risk (%)	Pts with high-very high risk (%)	P value vs low-intermediate risk	Pts with comorbidities %	P value vs High-very high risk
Outpatients (%)	6354 (100.0)	4164 (65.5)	1831 (28.8)	–	359 (5.6)	–
Female (%)	2996 (47.2)	2139 (51.4)	702 (38.3)	<0.001	155 (43.2)	0.086
Age (years)	58.4 ± 9.6	55.1 ± 8.6	65.0 ± 7.9	<0.001	62.8 ± 8.7	<0.001
BMI (kg/m2)	27.1 ± 4.6	27.0 ± 4.7	27.2 ± 4.4	0.071	27.9 ± 4.8	0.012
Smoke (%)	586 (17.9)	298 (16.0)	244 (21.6)	<0.001	44 (15.9)	0.038
Obesity (%)	4116 (64.8)	2623 (63.0)	1222 (66.8)	0.005	271 (75.5)	0.001
Dyslipidaemia (%)	1732 (27.3)	807 (19.4)	689 (37.7)	<0.001	236 (65.7)	<0.001
Diabetes (%)	676 (10.6)	332 (8.0)	257 (14.1)	<0.001	87 (24.2)	<0.001
Glucose (mg/dl)	99.6 ± 22.3	96.3 ± 24.	100.3 ± 21.1	0.004	105.5 ± 24.4	0.020
TOT-C (mg/dl)	199.6 ± 27.9	189.8 ± 34.7	204.6 ± 36.8	<0.001	184.9 ± 47.2	<0.001
HDL-C (mg/dl)	52.8 ± 14.9	54.5 ± 15.9	52.4 ± 14.3	0.033	51.7 ± 16.8	0.668
LDL-C (mg/dl)	123.9 ± 45.8	119.5 ± 66.7	127.2 ± 35.6	0.014	108.3 ± 43.9	<0.001
TG (mg/dl)	122.3 ± 67.2	109.4 ± 70.3	126.4 ± 66.3	<0.001	127.0 ± 59.3	0.925
BUN (mg/dl)	30.7 ± 14.5	28.3 ± 14.0	31.4 ± 14.4	0.003	33.1 ± 15.8	0.332
Creatinine (mg/dl)	0.95 ± 0.4	0.9 ± 0.4	1.0 ± 0.4	0.011	1.0 ± 0.3	0.691
Uric Acid (mg/dl)	5.7 ± 1.6	5.2 ± 1.4	6.1 ± 1.7	0.002	5-7±1.8	0.342
eGFR (ml/min)	95.8 ± 108.1	91.7 ± 91.6	97.8 ± 124.3	0.573	98.8 ± 61.0	0.951

BMI, body mass index; TOT-C, total cholesterol; HDL-C, high density lipoprotein cholesterol; LDL-C, high density lipoprotein cholesterol; TG, triglycerides; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate.

prevention (108.3 ± 43.9 vs 127.2 ± 35.6 mg/dl; P < 0.001). On the other hand, both HDL-C and triglycerides levels did not significantly differ among groups, despite patients in secondary prevention received significantly more antihypertensive, antiplatelet, and lipid-lowering drugs compared to those without previous CV event (P < 0.001 for all comparisons).

Blood pressure levels and control in low risk and high risk primary prevention patients

BP levels in the overall study population and in treated and untreated individuals are reported in Table 2. Proportions of treated hypertensive patients achieving the recommended office and 24-h BP treatment targets are illustrated in Fig. 1. As illustrated, the majority of patients received combination therapies with at least two or three antihypertensive agents; in particular, most treated hypertensive outpatients received fixed combination therapies based on ACE inhibitors plus either HCTZ (5.8%) or CCB (3.5%) or both (0.5%), or ARB plus either HCTZ (24.8%) or CCB (5.1%), or beta-blocker plus diuretics (2.8%); these combination therapies were used alone or with other antihypertensive drug classes.

High risk primary prevention patients showed significantly higher office (151.4 ± 19.6 vs. 138.8 ± 16.0 mmHg; P < 0.001), 24-h (135.0 ± 12.5 vs. 127.4 ± 12.2 mmHg; P < 0.001), and home (137.8 ± 15.9 vs. 135.8 ± 16.7) systolic BP levels than those recorded in low risk primary prevention patients. Conversely, diastolic BP values resulted lower in the former than in the latter group, at both office (88.3 ± 11.9 vs. 90.2 ± 11.8 mmHg, P < 0.001), 24-h (79.6 ± 9.4 vs. 80.3 ± 9.1 mmHg; P = 0.017), and home (82.3 ± 10.2 vs. 85.1 ± 10.9 mmHg; P < 0.001) BP measurements.

In the setting of primary prevention, proportion of treated hypertensive patients was significantly higher in high risk than that in low risk group (73.5% vs. 51.9%; P < 0.001), with predominant adoption of combination therapies in the former than in the latter group (27.6% vs. 13.8%; P < 0.001). Among treated hypertensive outpatients, both office (136.8 ± 15.9 vs. 150.6 ± 19.5; P < 0.001), 24-h (126.5 ± 12.6 vs. 134.2 ± 13.6 mmHg; P < 0.001) and home (134.3 ± 17.3 vs. 136.9 ± 16.7; p = 0.001) systolic BP levels were significantly lower in low risk than in high risk patients. No significant difference has been observed regarding office and 24-h diastolic BP levels between the two groups. Similar findings were observed in untreated individuals.

Overall, in primary prevention 16.8% of treated outpatients achieved the recommended office BP targets and 34.5% the 24-h BP targets (Fig. 1a). In particular, proportion of treated patients with controlled office BP was 18.4% in the low risk group and 12.5% in the high risk group (P < 0.001). Similarly, 41.2% of low risk patients achieved the 24-h BP targets compared to 30.6% of high risk patients (P < 0.001).

Blood pressure levels and control in primary prevention high risk patients and secondary prevention patients

Patients in secondary prevention showed significantly lower office (140.9 ± 20.3/85.6 ± 27.3 vs. 151.4 ± 19.6/88.3 ± 11.9 mmHg; P < 0.001) and 24-h (129.1 ± 14.6/

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Table 2 Office and 24-h blood pressure levels and control in overall sample and treated and untreated hypertensive patients.

Parameters	Overall Sample	Primary Prevention			Secondary Prevention	
		Pts with low-intermediate risk (%)	Pts with high-very high risk (%)	P value vs low-intermediate risk	Pts with comorbidities %	P value vs High-very high risk
Clinic Systolic BP (mmHg)	142.5 ± 18.2	138.8 ± 16.0	151.4 ± 19.6	<0.001	140.9 ± 20.3	<0.001
Clinic Diastolic BP (mmHg)	89.4 ± 13.2	90.2 ± 11.8	88.3 ± 11.9	<0.001	85.6 ± 27.3	0.002
Home Systolic BP (mmHg) (n = 3430)	136.6 ± 16.7	135.8 ± 16.7	137.8 ± 15.9	0.001	137.6 ± 20.2	0.858
Home Diastolic BP (mmHg) (n = 3430)	83.9 ± 10.8	85.1 ± 10.9	82.3 ± 10.2	<0.001	81.8 ± 11.7	0.526
24 h Systolic BP (mmHg) (n = 5684)	129.4 ± 13.1	127.4 ± 12.2	135.0 ± 12.5	<0.001	129.1 ± 14.6	<0.001
24 h Diastolic BP (mmHg) (n = 5684)	79.9 ± 9.3	80.3 ± 9.1	79.6 ± 9.4	0.017	77.1 ± 9.9	<0.001
Treated outpatients	3819 (60.1)	2162 (51.9)	1346 (73.5)	<0.001	311 (86.6)	<0.001
Monotherapy (%)	1239 (19.5)	803 (19.3)	379 (20.7)		57 (15.9)	
Dual Therapy (%)	1338 (21.1)	786 (18.99)	462 (25.2)		90 (25.1)	
Combo Therapy (%)	1242 (19.5)	573 (13.8)	505 (27.6)		164 (45.7)	
Clinic Systolic BP (mmHg)	142.0 ± 18.8	136.8 ± 15.9	150.6 ± 19.5	<0.001	141.1 ± 20.3	<0.001
Clinic Diastolic BP (mmHg)	87.1 ± 13.8	87.5 ± 11.4	86.9 ± 11.5	0.114	85.5 ± 29.0	0.175
24 h Systolic BP (mmHg)	129.2 ± 13.6	126.5 ± 12.6	134.2 ± 13.6	<0.001	129.1 ± 15.0	<0.001
24 h Diastolic BP (mmHg)	78.7 ± 9.5	78.9 ± 9.4	78.7 ± 9.4	0.625	76.9 ± 10.0	<0.001
24 h BP < 130/80 mmHg (%) (2725)	1164 (42.7)	820 (47.2)	235 (30.6)	<0.001	109 (49.1)	<0.001
Home BP < 135/85 (mmHg)	848 (22.2)	432 (20.0)	349 (25.9)	<0.001	67 (21.5)	0.108
Untreated outpatients	2535 (39.9)	2002 (48.1)	485 (26.5)	<0.001	48 (13.4)	<0.001
Clinic Systolic BP (mmHg) (n = 205)	143.3 ± 17.3	140.9 ± 15.7	153.5 ± 19.6	<0.001	139.1 ± 18.1	<0.001
Clinic Diastolic BP (mmHg)	92.8 ± 11.7	93.0 ± 11.6	92.4 ± 11.9	0.252	86.2 ± 10.2	0.001
24 h Systolic BP (mmHg) (n = 2433)	129.9 ± 12.5	128.3 ± 11.8	136.8 ± 13.2	<0.001	136.8 ± 13.2	0.001
24 h Diastolic BP (mmHg)	81.6 ± 8.8	81.6 ± 8.7	81.5 ± 9.2	0.872	78.8 ± 9.3	0.075
24 h BP < 130/80 mmHg (%) (2286)	746 (32.6)	656 (34.9)	78 (21.2)	<0.001	12 (32.4)	0.090
Home BP < 135/85 (mmHg)	273 (10.8)	203 (10.1)	61 (12.6)	0.118	9 (18.8)	0.227

BP, blood pressure.

77.1 ± 9.9 vs. 135.0 ± 12.5/79.6 ± 9.4 mmHg; P < 0.001) systo-diastolic BP levels compared to those recorded in high risk primary prevention patients. No significant difference were observed regarding home BP levels (137.6 ± 20.2/81.8 ± 11.7 vs. 137.8 ± 15.9/82.3 ± 10.2 mmHg) between the two groups.

Proportion of treated hypertensive patients was significantly higher in secondary prevention than in primary prevention (86.6% vs. 73.5%; P < 0.001), with a higher proportion of patients on combination therapies (45.7% vs. 27.6%; P < 0.001). As a consequence, both office (141.1 ± 20.3 vs. 150.6 ± 19.5 mmHg; P < 0.001) and 24-h (129.1 ± 15.0 vs. 134.2 ± 13.6 mmHg; P < 0.001) systolic BP levels were significantly lower in secondary prevention than in primary prevention; conversely, home systolic BP was significantly lower in the latter than in the former group (137.0 ± 16.0 vs. 138.1 ± 19.1; p < 0.001). No significant difference has been observed regarding home (81.4 ± 9.9 vs. 81.9 ± 11.1 mmHg; P = 0.567) and office (85.5 ± 29.0 vs. 86.9 ± 11.5 mmHg; P = 0.175) diastolic BP levels between the two groups, whereas 24-h diastolic BP levels were lower in secondary than in primary prevention group (76.9 ± 10.0 vs. 78.7 ± 9.4 mmHg; P < 0.001).

As shown in Fig. 1a, among treated outpatients, only 24.1% of patients in secondary prevention achieved the recommended office BP targets and 38.0% achieved the 24-h BP targets. Both these proportions were significantly higher than those achieved by high risk patients in primary prevention (P < 0.001 for both comparisons).

Blood pressure levels and control in hypercholesterolemic patients in primary and secondary prevention

There were 19.4% patients with hypercholesterolemia in the low risk primary prevention group, 37.7% in the high risk primary prevention group, and 65.7% in the secondary prevention group (P < 0.001), among whom 96.3%, 95.9%, and 95.4% received at least one lipid-lowering drug, and 27.4%, 45.4%, and 71.4% were treated with antihypertensive drugs, respectively. Proportions of hypercholesterolemic patients who achieved the recommended BP targets under BP lowering drugs were 39% in the low risk primary

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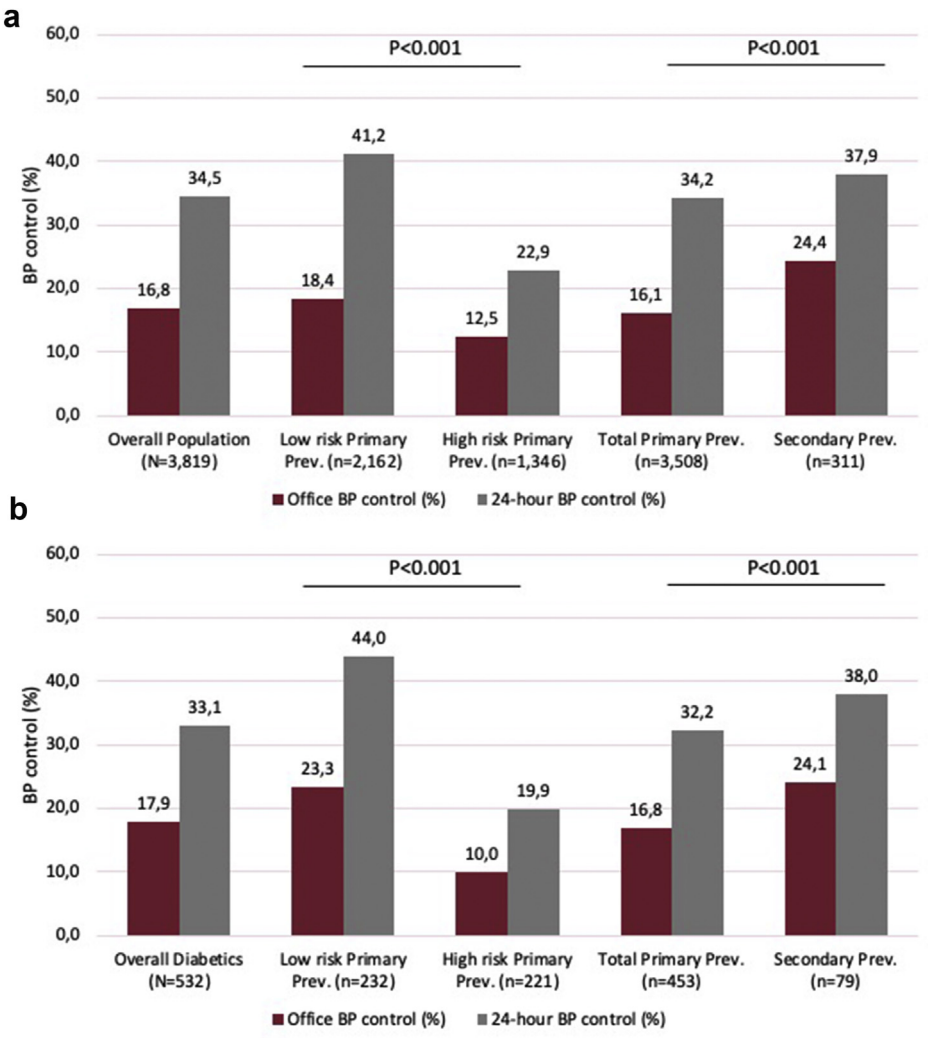

Figure 1 a. Proportions of treated outpatients achieving the recommended BP targets according to 2018 ESC/ESH guidelines in the overall population (**Panel A**) and in diabetic patients (**Panel B**). In the figure: BP, blood pressure.

prevention group, 56.5% in the high risk primary prevention group, and 76.3% in the secondary prevention group ($P < 0.001$).

Blood pressure levels and control in diabetic patients in primary and secondary prevention

In the subgroup of diabetic individuals, proportions of hypertensive outpatients under drug treatment showed a trend toward increase, being 69.9% in the low risk group, 86% in the high risk group of primary prevention and 90.8% in the secondary prevention group ($P < 0.001$), with increasing proportions of dual and triple combinations therapies in these latter groups compared to low risk primary prevention individuals.

Systolic BP levels were significantly higher in diabetic primary prevention patients at high risk compared to those at low risk at both office (157.6 ± 21.4 vs. 139.31 ± 8.1 mmHg; $P < 0.001$) and 24-h ambulatory (137.7 ± 15.5 vs. 129.3 ± 13.5 mmHg; $P < 0.001$) BP measurements. They also showed significantly higher office (157.6 ± 21.4 vs. 148.0 ± 22.9 mmHg; $P < 0.001$) and 24-h (137.7 ± 15.5 vs133.6 ± 17.0 mmHg; $P < 0.001$) compared to those patients in secondary prevention. Similar trend was observed for office diastolic BP levels, which resulted significantly higher in high risk primary prevention patients compared to those at low risk or those in secondary prevention (86.8 ± 12.3 vs. 86.0 ± 11.9 vs. 82.6 ± 12.8 mmHg, respectively: $P < 0.001$). Of note, no significant differences among groups were observed for home (81.8 ± 9.8 vs. 84.6 ± 14.2 vs. 82.0 ± 12.4, respectively; $P = 0.092$) and 24-h (77.2 ± 9.5 vs. 77.3 ± 8.9 vs. 74.7 ± 9.7, respectively; $P = 0.081$) diastolic BP levels.

As illustrated in Fig. 1b, 17.9% of treated diabetic outpatients achieved the recommended office BP targets and 33.1% the 24-h BP targets. In particular, proportion of treated diabetic patients with controlled office BP was 23.3% in the low risk group and 10.0% in the high risk group ($P < 0.001$); in addition, 44.0% of low risk diabetic patients achieved the 24-h BP targets compared to 19.9% of high risk patients ($P < 0.001$). These proportions for secondary prevention patients were 24.1% for office BP and

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Table 3 Univariate and multivariate analyses of predictive factors for BP control in treated outpatients.

Parameters	Univariate analysis	P value	Multivariate Analysis	P value
	OR (95% CI)		OR (95% CI)	
Age (years)	1.044 (1.034–1.055)	<0.001	1.037 (1.026–1.047)	<0.001
Male Gender	0.660 (0.556–0.782)	<0.001	0.683 (0.574–0.813)	<0.001
Diabetes	0.916 (80.720–1.164)	0.472	–	–
Obesity	0.978 (0.814–1.174)	0.810	–	–
Hypercholesterolemia	1.705 (1.437–2.023)	<0.001	1.414 (1.180–1.693)	<0.001
Smoke	0.847 (0.633–1.135)	0.266	–	–
HTN therapy (num.)	1.157 (1.074–1.246)	<0.001	1.080 (1.000–1.167)	0.050
Secondary prevention	1.685 (1.281–2.215)	<0.001	1.317 (0.989–1.755)	0.060
SCORE[a]	0.978 (0.968–0.989)	<0.001	0.950 (0.936–0.964)	<0.001

HTN, hypertension.
[a] Primary prevention group.

38.0% for 24 hour BP, which resulted significantly higher than those observed in high risk primary prevention patients ($P < 0.001$ for both comparisons).

Univariate and multivariate analyses for blood pressure control

Univariate and multivariate for predictive factors for BP control for treated hypertensive patients both in primary and in secondary prevention are reported in Table 3. Ageing, hypercholesterolemia (defined as total cholesterol levels ≥190 mg/dl or LDL cholesterol levels ≥130 mg/dl), intensity of hypertensive therapies (i.e. number of BP lowering drugs) and female gender resulted to be independent predictors of the achievement of the recommended office BP targets. Furthermore, in primary prevention patients, high SCORE risk value showed to be an independent predictor of lack of achieving the recommended BP control.

Discussion

In the present study we estimated the BP control rates in a relatively large cohort of hypertensive patients at different CV risk profile. In this sample we were able to demonstrate a high prevalence of treated uncontrolled hypertension among high CV risk categories, both in primary and secondary prevention, in whom effective BP control should be mandatory for reducing hypertension-related CV morbidity and mortality. The study also showed for the first time that out-of-office BP control, as defined by home, 24-h, day-time and night-time BP within the recommended therapeutic thresholds, was persistently poor over the entire 24-h period in those patients at high or very high CV risk.

Real-life estimations of the proportions of treated hypertensive patients reaching the recommended BP therapeutic targets are relatively difficult, because of several intrinsic limitations may exist, such as missing data on pill counts, serum or urine levels of drugs or metabolites, administrative records for drug prescriptions. Previous clinical studies proposed various potential factors for traying to explain the persistently low rate of office BP control in high or very high risk populations. Among these, one of the main obstacle may be represented by the suboptimal adherence to prescribed antihypertensive medications, possibly due to high number of prescribed pills, mostly in the setting of high risk primary prevention or secondary prevention.

In these high risk categories of hypertensive patients, therapeutic adherence to antihypertensive medications is reported to be highly variable, ranging from 84% [21] to approximately 31% [22], and depending not only on different criteria applied by various clinical studies or individual global CV risk profile, but also on the applied therapeutic regimen (fixed or free combination therapies).

A great proportion of high-risk hypertensive patients require three or more drugs to achieve the recommended BP therapeutic goals [23]. It has been demonstrated that double or triple-combination therapies, especially in fixed formulations, are able to promote effective and sustained BP control, with high level of adherence and without a significant increase in adverse events with respect to monotherapy [23]. Indeed, in our analysis the majority of patients received combination therapies with at least two or three antihypertensive agents; in particular, most treated hypertensive outpatients received fixed combination therapies based on ACE inhibitors or ARB plus either HCTZ or CCB. These combination therapies have proven to be effective and safe in lowering BP levels an reducing the incidence of hypertension-related CV diseases [24–27].

Therapeutic adherence could be also increased by ameliorating patient-physician communication about the importance of treatment, investigating possible adverse effects, preventing drugs withdrawal and, especially in older individuals, involving family members in at-home care [28]. Beyond these relevant aspects, particular attention should be also devoted in properly assessing individual CV risk, especially in young primary prevention patients affected by type 2 diabetes, since it has been recognized that global CV risk is often underestimated in this group of high risk individuals.

Many studies reported low rate of BP control in diabetic patients. A recent study showed a rate of 18.5% of diabetic patients achieving the BP office target <140/85 mmHg and only 13.9% the 24-h BP target, despite the vast majority

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(about 72%) of patients were on combination therapies with at least two antihypertensive drugs [29]. Similarly, in our analysis we observed that about 18% of diabetic patients achieved the recommended office BP targets, and 33% the 24-h BP targets, with higher percentages in primary prevention patients at low risk in and in those in secondary prevention. This seems to suggest a better adherence to the therapeutic recommendations from international guidelines in those patients at very high CV risk (i.e. those in secondary prevention), whilst lesser attention seems to be devoted to those patients in primary prevention, even in the presence of diabetes and/or high CV risk profile. Indeed, in our analysis, presence of diabetes was not recognized as an independent predictor for the achievement of the recommended BP treatment targets at multivariate analysis.

Our results are in line with previous published study [30], which demonstrated not only the unsatisfactory but also the increased proportions of treated uncontrolled hypertensive patients consequently to introduction of new lower office BP treatment targets by current hypertension guidelines [11] compared to previous ones [31]. In our study untreated patients correspond to about 39.9% of patients and they are mostly in the low risk primary prevention group (48.1%) but with a consistent proportion also in high risk groups (39.9%). This is probably due to the fact that, in particular individuals without previous CV event are “perceived” to be at low-to-moderate risk profile receiving non-pharmacological interventions (i.e. life-style changes, diet, weight reduction, etc). These findings highlight the need to further promote antihypertensive treatment strategies, in order to improve the BP control rates and achieve the recommended BP treatment targets in both primary and secondary high CV risk patients.

Study limitations

The present study has some potential limitations that should be acknowledged. First of all, patients included in the present analysis were consecutively enrolled in a single excellence center for hypertension management and control over a long observational period. During this time, several sets of guidelines and recommendations from national and international societies have been produced, furthermore single−pill combination therapy has been proposed and widely prescribed in the last few years. This may have at least, in part, influenced the observed rate of BP control, though the last available BP levels were extracted from our database and considered for the analysis, as well as the last BP thresholds recommended by guidelines [11] were adopted. Secondly, we have no sufficient information on therapeutic adherence since we have not routinely applied questionnaire or executed serum levels of drugs analyses which could may help to understand the reason of low rate of BP target achievement. Finally, the inclusion of very high risk patients with comorbidities, who received antihypertensive therapies for CV protection, may have generated potential bias that should be considered when interpreting our findings.

Conclusions

Our study confirmed that BP control is still unsatisfactory in high and very high risk hypertensive patients, despite the adoption of dual or triple combination therapies. According to our findings, and in line with the recommendations of current European guidelines [11], it is necessary to implement both pharmacologic and non-pharmacologic antihypertensive strategies, in order to reach the recommended BP targets, achieve an effective and sustained BP control and reduce the burden of hypertension-related CV diseases and CV death. Therefore, physicians should place more attention on the achievement of BP levels goal in all hypertensive patients, in particular in those at high CV risk, even in primary prevention, with the aim of improving BP control in daily clinical practice.

Declaration of competing interest

None declared.

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