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ORIGINAL ARTICLE

Prolonged Time-to-antihypertensive Therapy Worsens Organ Damage and Blood Pressure Control in Arterial Hypertension

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Abstract

Introduction Delay in arterial hypertension (AH) diagnosis and late therapy initiation may affect progression towards hypertensive-mediated organ damage (HMOD) and blood pressure (BP) control.

Aim We aimed to assess the impact of time-to-therapy on BP control and HMOD in patients receiving AH diagnosis.

Methods We analysed data from the Campania Salute Network, a prospective registry of hypertensive patients (NCT02211365). At baseline visit, time-to-therapy was defined as the interval between the first occurrence of BP values exceeding guidelines-directed thresholds and therapy initiation; HMOD included left ventricular hypertrophy (LVH), carotid plaque, or chronic kidney disease. Optimal BP control was considered for average values < 140/90 mmHg. Low-risk profile was defined as grade I AH without additional cardiovascular risk factors.

Results From 14,161 hypertensive patients, we selected 1,627 participants who were not on antihypertensive therapy. This population was divided into two groups based on the median time-to-therapy (≤ 2 years $n = 1{,}009$, > 2 years $n = 618$). Patients with a time-to-therapy > 2 years had higher risk of HMOD (adjusted odds ratio, aOR:1.51, 95%, CI:1.19–1.93, $p < 0.001$) due to increased risks of LVH (aOR:1.43, CI:1.12–1.82, $p = 0.004$), carotid plaques (aOR:1.29, CI:1.00-1.65, $p = 0.047$), and chronic kidney disease (aOR:1.68, CI:1.08–2.62, $p = 0.022$). Time-to-therapy > 2 years was significantly associated with uncontrolled BP values (aOR:1.49, CI:1.18–1.88, $p < 0.001$) and higher number of antihypertensive drugs (aOR:1.68, CI:1.36–2.08, $p < 0.001$) during follow-up. In low-risk subgroup, time-to-therapy > 2 years did not impact on BP control and number of drugs.

Conclusions In hypertensive patients, a time-to-therapy > 2 years is associated with HMOD and uncontrolled BP.

Keywords Arterial hypertension · Blood pressure control · Hypertensive-mediated organ damage

1 Introduction

Arterial hypertension (AH) represents a global disease burden, being the cause of the development of hypertension-mediated organ damage (HMOD), which involves functional and morphological alterations in multiple organs [1–3]. Current guidelines for AH management recommend initiating drug treatment, along with lifestyle interventions, in patients presenting with grade 2 and 3, or in patients with grade 1 and high cardiovascular (CV) risk. More controversial, however, is the correct timing for initiating antihypertensive therapy in patients with grade 1 AH and low CV risk [3, 4]. Nonetheless, the initiation of therapy for AH implies, primarily, patients' awareness and medical recognition of the hypertensive status, as clinical manifestations

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related to AH could be initially vague [5]. In addition, blood pressure (BP) values can be highly variable, and AH diagnosis may require further assessments and additional time to be confirmed [3]. Thus, all these components could lead to a substantial delay in starting antihypertensive therapies, potentially impacting on BP control and on HMOD [3, 4].

In this study, we leveraged data from the Campania Salute Network, an observational, prospective registry, to analyse the impact of history of AH and delayed time-to-therapy on BP control and HMOD in a large cohort of hypertensive patients with long-term follow-up.

2 Methods

2.1 Study Population

The Campania Salute Network is a prospective registry, which adhered to the relevant ethical guidelines and received approval from the Federico II University Hospital Ethic Committee (ClinicalTrials.gov Identifier: NCT02211365), as previously described in detail [6–8]. All patients gave written informed consent to participate in clinical studies.

AH diagnosis was based on elevated BP values exceeding guidelines-directed thresholds. Out of 14,161 patients included in the registry from 1990 to 2014, 1,627 hypertensive patients were selected, based on the following inclusion criteria: (a) patients who presented to our observation with a history of hypertension, testified either by the patient's blood pressure diaries or by records from the general practitioner, which was confirmed at our first visit and but not assuming any antihypertensive therapy before enrolment; (b) available follow-up ≥ 6 months; (c) available echocardiographic and carotid ultrasound assessment at baseline evaluation; (d) age ≥ 18 years. Patients already under antihypertensive therapy at baseline visit ($n = 9{,}424$), without available follow-up ≥ 6 months ($n = 2223$), without available echocardiographic and carotid ultrasound assessment at baseline ($n = 781$) and with age < 18 years ($n = 106$) were excluded (Supplemental Fig. 1).

Time-to therapy was calculated as the time elapsing form the diagnosis of AH to the start of the therapy. At baseline and each follow-up visit, systolic and diastolic BP and heart rate were collected using a semiautomatic oscillometric sphygmomanometer with cuffs of appropriate size, and were measured after 5 min resting in the sitting position, 3 times at 1 min interval, according to current guidelines on AH [3]. The average of the two last measurements was taken as the office BP recorded. The calibration of the devices was performed by yearly checks from the manufacturer. Optimal office BP control during the follow up was defined for average values $< 140/90$ mmHg during the follow-up visits, in accordance with ESC/ESH guidelines for management of AH [3, 4].

Obesity was established for values of body mass index ≥ 30 kg/m^2. Lipid profile and fasting glucose were measured by standard methods. Diabetes was defined as the use of any specific antidiabetic treatment, history of diabetes, or for values of fasting plasma glucose > 126 mg/dL confirmed on two different occasions [9].

Glomerular filtration rate was assessed by the chronic kidney disease epidemiology collaboration (CKD-EPI) equation, as previously described [10]. The subgroup of patients with a low risk profile ($n = 329$) according to ESC/ESH guidelines [3, 4] and thus including patients with grade 1 AH (systolic BP 140–159 mmHg and/or diastolic BP 90–99 mmHg) and without other CV risk factors was also further analysed.

2.2 Cardiovascular Ultrasound Assessment

Cardiac and carotid ultrasound assessment was performed using commercially available phased-array machines by a standardized protocol at the Hypertension Outpatient Clinic of the Federico II University Hospital [11, 12]. All measurements were obtained according to the latest consolidated convention and according to the standard of our laboratory [13, 14]. Echocardiographic exams were digitally recorded and read offline by a trained expert reader under the supervision of a senior faculty member, using dedicated workstations.

Left ventricular (LV) mass was estimated from a necropsy-validated formula and normalized for height in meters to the power of 2.7 (LV mass index) [15, 16]. LV hypertrophy (LVH) was defined for values of LV mass index > 47 g/m$^{2.7}$ in women and > 50 g/m$^{2.7}$ in men [17, 18]. Relative wall thickness was measured as the ratio between posterior wall thickness and LV internal radius at end-diastole [13]. LV systolic function was assessed by LV ejection fraction [19, 20].

Carotid ultrasound was assessed in supine position. The intima–media thickness was measured as the distance between lumen-intima and media-adventitia interface in up to 2 arterial walls, on both near and far walls of distal common carotid (1 cm), bifurcation and proximal internal carotid artery of both sides and carotid plaques were identified for intima–media thickness values > 1.5 mm [21].

As sites with HMOD at baseline visit, we considered the presence of LVH, carotid plaques and/or CKD-EPI $\geq$ III.

2.3 Statistical Analysis

The study population was divided in two groups according to time-to-therapy value; the threshold for time-to-therapy

was derived from the best threshold of the Youden index of the receiving operating characteristic (ROC) curves for HMOD outcome variables considering time-to-therapy as a continuous variable.

Data were summarized by presenting the mean (±SD) for continuous variables and absolute frequency (percentage) for categorical variables. Difference between means for continuous variables were calculated using the Student's t test or Mann-Whitney as appropriate, while differences between proportions for categorical variables were calculated using Chi-square or Fisher's exact test as appropriate. Associations between the factors and HMOD outcome variables were evaluated using binary logistic regression models. For the determinants of BP control a binary logistic regression model was also performed, whereas for the determinants of the number of antihypertensive drugs taken during follow-up a multinomial logistic regression was used. For all analyses, variables that resulted significant at the univariate models were added to multivariate regression models. Analyses were performed with R statistical software version 4.3.0. A two-tailed p-value < 0.05 was considered as threshold for statistical significance.

Table 1 Baseline and ultrasound characteristics of the study population divided into two groups according to the time-to-therapy

Variables	Time-to-therapy ≤2 years, *N* = 1,009	Time-to-therapy > 2 years, *N* = 618	*p*-value
Age (years)	49 (11)	53 (11)	**< 0.001**
Female Sex	391 (39%)	268 (43%)	0.066
Systolic BP (mmHg)	144 (17)	144 (18)	0.731
Diastolic BP (mmHg)	92 (10)	90 (11)	**0.003**
Current smoking (%)	229 (23%)	118 (19%)	0.226
Obesity	191 (19%)	156 (25%)	**0.003**
Body mass index (kg/m^2)	27.1 (3.9)	27.8 (4.0)	**< 0.001**
Diabetes	56 (5.6%)	58 (9.4%)	**0.003**
Time-to-therapy (years) [IQR]	0.6 [0.2–1.0]	5.0 [4.0–8.0]	**< 0.001**
Serum total Cholesterol (mg/dL)	204 (39)	206 (37)	0.496
Serum HDL-Cholesterol (mg/dL)	51 (13)	50 (12)	0.164
Serum LDL-Cholesterol (mg/dL)	128 (37)	130 (35)	0.443
Serum triglycerides (mg/dL)	128 (68)	133 (79)	0.212
LV end-diastolic diameter (cm)	4.97 (0.35)	4.99 (0.39)	0.273
LV end-diastolic diameter index (cm/m2)	2.95 (0.18)	2.99 (0.20)	**< 0.001**
LV mass index (g/m$^{2.7}$)	45 (8)	48 (9)	**< 0.001**
LV Relative wall thickness	0.38 (0.04)	0.38 (0.04)	0.079
LV ejection fraction (%)	66.3 (3.7)	66.2 (3.9)	0.724
CKD-EPI ≥ III	42 (4.2%)	52 (8.4%)	**< 0.001**
Carotid plaque	299 (29.6%)	251 (40.6%)	**< 0.001**
LVH	277 (27.4%)	248 (40.1%)	**< 0.001**

BP = blood pressure, CKD-EPI, chronic kidney disease epidemiology collaboration equation, LV = left ventricular, LVH = left ventricular hypertrophy

3 Results

The study population, including 1,627 patients, was divided into two groups according to the threshold of 2 years (n = 1,009 with time-to-therapy ≤ 2 years and n = 618 with time-to-therapy > 2 years). This threshold corresponded to the best threshold of the Youden index for HMOD outcome variables considering time-to-therapy as a continuous variable and at the same time corresponded to the median value of this parameter in the study population.

The median of the follow-up period was 4.7 years, IQR [2.4–8.7].

Baseline clinical and ultrasound characteristics of the two study groups are summarised in Table 1. Patients with time-to-therapy > 2 years were older, more often diabetic and obese, with higher values of LV relative wall thickness and LV mass index and presented a higher prevalence of HMOD at baseline in terms of LVH, carotid plaques and CKD-EPI ≥ III.

Variables associated with each HMOD site (LVH, carotid plaques and CKD-EPI ≥ III at baseline) were evaluated by univariate and multivariate binary logistic regressions.

At baseline, a time-to-therapy > 2 years was significantly associated with any type of HMOD (adjusted odds ratio aOR 1.51, 95% confidence intervals, CI 1.19–1.93, p < 0.001). In particular, time-to-therapy > 2 years was significantly associated with LVH (aOR, 1.43, 95% CI, 1.12–1.82, p = 0.004), carotid plaque (aOR 1.29, 95%CI 1.00-1.65, p = 0.047), and CKD-EPI ≥ III (aOR 1.68, 95%CI 1.08–2.62, p = 0.022) (Table 2; Fig. 1). In addition, aging was a common determinant of all types of HMODs. Female sex was associated with a higher risk of LVH, whereas male sex with a higher risk of carotid plaques.

The follow-up duration was comparable in the 2 groups. During follow-up, patients with time-to-therapy > 2 years achieved a significant lower rate of optimal BP control, received a higher number of antihypertensive drugs, such as renin-angiotensin system inhibitors, diuretics and dihydropyridine calcium channel blockers and developed a higher rate of HMOD in terms of LVH, carotid plaques and CKD-EPI ≥ III (Table 3). Time-to-therapy > 2 years resulted significantly associated to both uncontrolled BP values (aOR 1.49, CI 1.18–1.88, p < 0.001) (Table 4) and higher number of antihypertensive drugs administered during follow-up (aOR 1.68, CI 1.36–2.08, p < 0.001) (Table 5).

Table 2 Binary logistic regressions in the pooled study population to analyse determinants of HMOD

	Univariate		Multivariate	
	OR (95% CI)	P	aOR (95% CI)	p
Any HMOD				
Age (years)	1.09 (1.08 to 1.11)	**< 0.001**	1.10 (1.08 to 1.11)	**< 0.001**
Female Sex	0.92 (0.75 to 1.12)	0.398		
Time-to-therapy				
≤ 2 years	—		—	
> 2 years	1.98 (1.61 to 2.43)	**< 0.001**	1.51 (1.19 to 1.93)	**< 0.001**
Systolic BP (mmHg)	1.02 (1.01 to 1.02)	**< 0.001**	1.01 (1.00 to 1.02)	**0.004**
Diastolic BP (mmHg)	0.99 (0.98 to 1.00)	0.138		
Current smoking (%)	1.10 (0.87 to 1.40)	0.416		
Body mass index (kg/m2)	1.11 (1.08 to 1.14)	**< 0.001**	1.10 (1.07 to 1.14)	**< 0.001**
Diabetes	3.14 (2.03 to 5.05)	**< 0.001**	2.04 (1.20 to 3.60)	**0.011**
Serum total Cholesterol (mg/dL)	1.00 (1.00 to 1.01)	**< 0.001**	1.00 (0.99 to 1.00)	0.252
Serum HDL-Cholesterol (mg/dL)	1.00 (0.99 to 1.01)	0.786		
Serum LDL-Cholesterol (mg/dL)	1.00 (1.00 to 1.01)	**< 0.001**	1.01 (1.00 to 1.01)	0.135
Serum triglycerides (mg/dL)	1.00 (1.00 to 1.00)	**< 0.001**	1.00 (1.00 to 1.00)	**0.039**
LV ejection fraction (%)	0.91 (0.89 to 0.94)	**< 0.001**	0.92 (0.89 to 0.95)	**< 0.001**
LVH				
Age (years)	1.05 (1.04 to 1.06)	**< 0.001**	1.05 (1.04 to 1.06)	**< 0.001**
Female Sex	1.16 (0.93 to 1.43)	0.182	1.34 (1.05 to 1.71)	**0.019**
Time-to-therapy				
≤ 2 years	—		—	
> 2 years	1.80 (1.45 to 2.23)	**< 0.001**	1.43 (1.12 to 1.82)	**0.004**
Systolic BP (mmHg)	1.02 (1.01 to 1.02)	**< 0.001**	1.01 (1.01 to 1.02)	**< 0.001**
Diastolic BP (mmHg)	1.00 (0.99 to 1.01)	0.794		
Current smoking (%)	0.91 (0.70 to 1.18)	0.481		
Body mass index (kg/m^2)	1.19 (1.15 to 1.22)	**< 0.001**	1.20 (1.16 to 1.24)	**< 0.001**
Diabetes	2.30 (1.56 to 3.39)	**< 0.001**	1.46 (0.94 to 2.28)	0.089
Serum total Cholesterol (mg/dL)	1.00 (1.00 to 1.00)	0.374		
Serum HDL-Cholesterol (mg/dL)	0.99 (0.99 to 1.00)	0.111		
Serum LDL-Cholesterol (mg/dL)	1.00 (1.00 to 1.00)	0.674		
Serum triglycerides (mg/dL)	1.00 (1.00 to 1.00)	0.053		
LV ejection fraction (%)	0.88 (0.86 to 0.91)	**< 0.001**	0.88 (0.85 to 0.91)	**< 0.001**
Carotid plaque				
Age (years)	1.09 (1.08 to 1.11)	**< 0.001**	1.09 (1.07 to 1.11)	**< 0.001**
Female Sex	0.68 (0.54 to 0.85)	**< 0.001**	0.53 (0.41 to 0.70)	**< 0.001**
Time-to-therapy				
≤ 2 years	—		—	
> 2 years	1.66 (1.33 to 2.06)	**< 0.001**	1.29 (1.00 to 1.65)	**0.047**
Systolic BP (mmHg)	1.01 (1.00 to 1.02)	**0.006**	1.01 (1.00 to 1.02)	**0.015**
Diastolic BP (mmHg)	0.98 (0.97 to 0.99)	**< 0.001**	0.98 (0.96 to 0.99)	**0.005**
Current smoking (%)	1.14 (0.89 to 1.46)	0.309		
Body mass index (kg/m^2)	1.00 (0.97 to 1.03)	0.995		
Diabetes	2.45 (1.65 to 3.67)	**< 0.001**	1.45 (0.92 to 2.28)	0.106
Serum total Cholesterol (mg/dL)	1.01 (1.00 to 1.01)	**< 0.001**	1.01 (1.00 to 1.01)	0.144
Serum HDL-Cholesterol (mg/dL)	1.00 (1.0 to 1.01)	0.503		
Serum LDL-Cholesterol (mg/dL)	1.01 (1.00 to 1.01)	**< 0.001**	1.00 (0.99 to 1.01)	0.948
Serum triglycerides (mg/dL)	1.00 (1.00 to 1.00)	**0.012**	1.00 (1.00 to 1.00)	0.387
LV ejection fraction (%)	0.96 (0.93 to 0.98)	**0.002**	0.97 (0.94 to 1.00)	**0.049**
CKD-EPI ≥ III				
Age (years)	1.09 (1.06 to 1.11)	**< 0.001**	1.08 (1.06 to 1.11)	**< 0.001**
Female Sex	1.65 (1.09 to 2.52)	**0.018**	1.41 (0.91 to 2.19)	0.121
Time-to-therapy				

Table 2 (continued)

	Univariate		Multivariate	
	OR (95% CI)	P	aOR (95% CI)	p
≤ 2 years	—		—	
> 2 years	2.13 (1.40 to 3.26)	**< 0.001**	1.68 (1.08 to 2.62)	**0.022**
Systolic BP (mmHg)	1.01 (1.00 to 1.02)	**0.028**	1.01 (1.00 to 1.02)	0.170
Diastolic BP (mmHg)	0.99 (0.97 to 1.01)	0.152		
Current smoking (%)	0.83 (0.47 to 1.38)	0.488		
Body mass index (kg/m^2)	0.94 (0.88 to 0.99)	**0.034**	0.94 (0.88 to 1.00)	**0.038**
Diabetes	1.82 (0.89 to 3.40)	0.075		
Serum total Cholesterol (mg/dL)	1.00 (1.00 to 1.01)	0.150		
Serum HDL-Cholesterol (mg/dL)	1.00 (0.99 to 1.02)	0.672		
Serum LDL-Cholesterol (mg/dL)	1.00 (1.00 to 1.01)	0.099		
Serum triglycerides (mg/dL)	1.00 (1.00 to 1.00)	0.676		
LV ejection fraction (%)	1.00 (0.95 to 1.06)	0.950		

Abbreviations as in Table 1

A further analysis was performed in the subgroup of patients presenting at the baseline visit with a low risk profile (grade I AH and without other cardiovascular risk factors). In this subgroup of patients, time-to-therapy > 2 years did not reach the statistical significance as determinant of both BP control and number of antihypertensive drugs administered during follow-up (Supplemental Tables 1 and Supplemental Table 2, respectively).

4 Discussion

In the present study, performed in a real-life scenario, we found that: (1) patients affected by AH who waited a period > 2 years before starting an appropriate antihypertensive therapy, were more susceptible to have HMOD in terms of LVH, carotid plaques and CKD-EPI ≥ III; (2) after adjusting for possible confounders, time-to-therapy > 2 years resulted significantly associated with HMODs; (3) during follow-up, a time-to-therapy > 2 years was significantly associated with uncontrolled BP values and a higher number of antihypertensive drugs; (4) in patients with a low risk profile, a time-to-therapy > 2 years did not impact on BP control and number of antihypertensive drugs administered during the follow-up.

AH is responsible for CV and cerebrovascular complications and is often defined as a 'silent killer', since patients could remain asymptomatic for several years. Without symptoms, hypertensive patients are poorly motivated in searching for a clinical visit and in adhering to treatment [22]. The harmful impact of AH on both morphology and function of the cardiovascular system depends not only on the high blood pressure values but also on the duration of which patients are exposed to these elevated blood pressure levels [3, 23]. Thus, time plays a relevant role throughout the whole patient's journey. Several factors, including both scarce patients' awareness and doctors' recognition, possibly vague symptoms, highly variable BP values requesting additional analyses for confirming diagnosis, could delay the recognition of the hypertensive status [5, 24]. In addition, adherence to antihypertensive therapy could be also influenced by socio-economic status, patients' compliance, frailty. Thus, regardless of the cause, the time interval between the finding of elevated BP values exceeding guidelines-directed thresholds and initiation of antihypertensive therapy could be increased.

In the current study, we demonstrated that patients who waited longer before initiating antihypertensive therapy were more likely to present with metabolic impairment and additional CV risk factors, such as obesity and diabetes. In addition, time-to-therapy > 2 years resulted independently associated with HMODs in terms of LVH, carotid plaques, or CKD-EPI ≥ III at baseline. Indeed, all three sites of HMOD at baseline visit were more often present in AH patients with prolonged time-to-therapy.

In addition to a longer time-to-therapy, aging emerged as a common factor influencing the risk of HMOD. The impact of age on the development of various affected areas in HMOD is well-documented in the literature [25].

Our study suggests that sex could also play a role in determining HMOD, with males and females potentially exhibiting susceptibility in different affected areas, as previously indicated [26]. The association observed between female sex and left ventricular hypertrophy (LVH) may stem from several factors. One possible explanation is that females may become aware of their cardiovascular risk later than males, possibly due to a perception of protection from estrogens' effects. Additionally, there may be an unconscious bias within the medical community, where cardiovascular risk is often perceived primarily as a male issue, potentially leading to delays in therapeutic interventions for female patients [27, 28]. Our study further clarifies

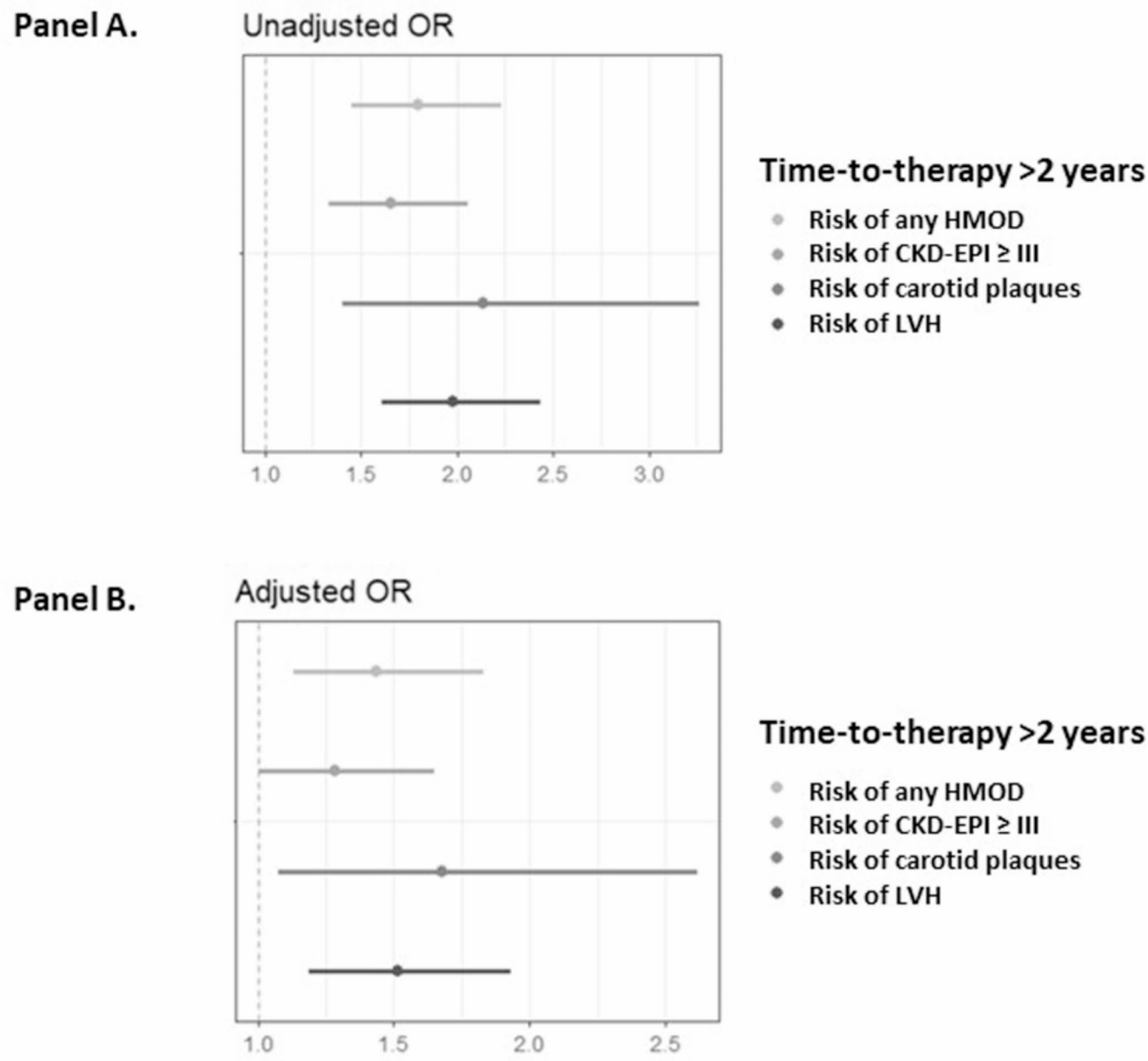

Fig. 1 Unadjusted (panel **A**) and adjusted (panel **B**) odds ratio describing the risk of any HMOD, CKD-EPI ≥ III, carotid plaques and LVH in patients with a time-to-therapy > 2years. CKD-EPI, chronic kidney disease epidemiology collaboration; HMOD, hypertension-mediated organ damage; LVH, left ventricular hypertrophy; OR, odds ratio

that carotid atherosclerosis, as HMOD, was predominant in male sex, as suggested by previous observations [29], while renal injury was comparable in both sexes, conceivably because it occurred in later stages of hypertensive disease. Other important factors for the development of any HMOD were increased levels of baseline systolic and diastolic BP, elevated body mass index, altered metabolic status of patients, as suggested by previous evidence [2, 3]. Nonetheless, a time-to-therapy > 2 years, despite all those significant determinants, remained independently and significantly associated with the presence of all the HMOD districts exanimated, thus representing a possible modifiable risk factor that should be promptly and adequately addressed.

In addition, time-to-therapy > 2 years also represented a determinant of BP control, since patients with prolonged time-to-therapy hardly controlled BP values during follow-up and the number of antihypertensive drugs administered occurred to be significantly higher, thus this group of patients had possibly an increased risk to develop resistant hypertension. Indeed, it is noteworthy that the role of the combination of antihypertensive drugs does not only have a substantial impact in reducing BP values, but it may also

Table 3 Data of the study population during the follow-up

Variables	Time-to-therapy ≤2 years, *N* = 1,009	Time-to-therapy >2 years, *N* = 618	*p*-value
Optimal BP control	628 (63%)	339 (55%)	**0.004**
Mean systolic BP	136 (11)	137 (12)	**0.014**
Mean diastolic BP	85 (7)	85 (7)	0.265
LVH at the end of follow up	307 (31%)	270 (45%)	**< 0.001**
CKD-EPI ≥ III at the end of follow up	46 (5.0%)	55 (8.9%)	**0.013**
Carotid plaques at the end of follow up	428 (48%)	320 (58%)	**< 0.001**
LV Ejection Fraction (%)	66.5 (3.7)	66.1 (4.0)	0.057
Number of drugs	1.48 (0.65)	1.72 (0.77)	**< 0.001**
renin-angiotensin system inhibitors drugs	811 (80%)	529 (86%)	**0.007**
Betablockers	252 (25%)	160 (26%)	0.680
dihydropyridine calcium channel blockers	152 (15%)	142 (23%)	**< 0.001**
Diuretics	360 (36%)	297 (48%)	**< 0.001**
Statins	132 (14%)	90 (15%)	0.354
Antiplatelet therapy	95 (9.6%)	108 (18%)	**< 0.001**

Abbreviations as in Table 1

Table 5 Multinomial logistic regression to investigate determinants of number of drugs during follow-up

	Univariate		Multivariate	
	OR (95% CI)	*P*	aOR (95% CI)	*p*
Age (years)	1.02 (1.01 to 1.03)	**< 0.001**	1.01 (1.00 to 1.02)	**0.005**
Female Sex	1.09 (0.89 to 1.33)	0.403		
Time-to-therapy				
≤ 2 years	-		-	
> 2 years	1.82 (1.49 to 2.23)	**< 0.001**	1.68 (1.36 to 2.08)	**< 0.001**
Systolic BP (mmHg)	1.01 (1.00 to 1.02)	**< 0.001**	1.01 (1.00 to 1.02)	**0.003**
Diastolic BP (mmHg)	1.01 (1.00 to 1.02)	0.207		
Current smoking (%)	1.27 (1.00 to 1.61)	0.051		
Body mass index (kg/m^2)	1.05 (1.03 to 1.08)	**< 0.001**	1.04 (1.01 to 1.06)	**0.009**
Diabetes	1.27 (0.87 to 1.86)	0.219		
Serum total Cholesterol (mg/dL)	1.00 (1.00 to 1.00)	0.775		
Serum HDL-Cholesterol (mg/dL)	1.00 (0.99 to 1.00)	0.384		
Serum LDL-Cholesterol (mg/dL)	1.00 (1.00 to 1.00)	0.466		
Serum triglycerides (mg/dL)	1.00 (1.00 to 1.00)	**< 0.001**	1.00 (1.00 to 1.00)	**0.003**
LV ejection fraction (%)	0.97 (0.94 to 0.99)	**0.016**	0.98 (0.95 to 1.01)	0.115

Abbreviations as in Table 1

Table 4 Binary logistic regression to investigate determinants of BP control during follow-up

	Univariable		Multivariable	
	OR (95% CI)	*P*	aOR (95% CI)	*p*
Age (years)	1.00 (0.99 to 1.01)	0.491		
Female Sex	0.96 (0.78 to 1.17)	0.666		
Time-to-therapy				
≤ 2 years	-		-	
> 2 years	1.35 (1.10 to 1.66)	**0.004**	1.49 (1.18 to 1.88)	**< 0.001**
Systolic BP (mmHg)	1.07 (1.06 to 1.08)	**< 0.001**	1.06 (1.05 to 1.07)	**< 0.001**
Diastolic BP (mmHg)	1.06 (1.05 to 1.07)	**< 0.001**	1.01 (1.00 to 1.02)	0.107
Current smoking (%)	0.92 (0.72 to 1.18)	0.528		
Body mass index (kg/m^2)	1.03 (1.00 to 1.06)	**0.022**	1.02 (0.99 to 1.05)	0.235
Diabetes	1.14 (0.77 to 1.67)	0.513		
Serum total Cholesterol (mg/dL)	1.00 (1.00 to 1.00)	0.348		
Serum HDL-Cholesterol (mg/dL)	1.00 (0.99 to 1.00)	0.454		
Serum LDL-Cholesterol (mg/dL)	1.00 (1.00 to 1.00)	0.133		
Serum triglycerides (mg/dL)	1.00 (1.00 to 1.00)	**0.045**	1.00 (1.00 to 1.00)	**0.032**
LV ejection fraction (%)	0.99 (0.96 to 1.02)	0.501		

Abbreviations as in Table 1

have some additional effects involving both metabolic and anti-inflammatory actions that hinder CV damage and the progression towards HMOD [30, 31]. Thus, a delay in starting antihypertensive therapy could promote those further detrimental effects related to AH.

There is ongoing debate about the optimal timing to begin antihypertensive therapy in patients with a low risk profile, defined as those with grade I AH without additional CV risk factors [3, 4]. The present study corroborates previous findings, showing that a time-to-therapy > 2 years did not impact on BP control and number of drugs administered during the follow-up, thus suggesting that close follow-up evaluations could be advisable for this subgroup of patients [32].

While vigilant monitoring may be an acceptable strategy for patients with a low-risk profile, it is imperative to

promptly initiate antihypertensive therapy in patients with AH who exhibit high-risk characteristics. Achieving this objective necessitates heightened awareness in both patients and healthcare providers. In addition, implementation and support of effective screening for CV risk factors could be a relevant strategy for this purpose. The time spent before initiating antihypertensive treatment emerges as a substantial modifiable risk factor that should be promptly addressed to mitigate CV impairment associated with AH.

4.1 Study Limitations

The results of the present study derive from a retrospective study, based on an observational registry. Nonetheless, the design of a prospective or a randomised trial for the evaluation of the time-to-therapy in AH would not be ethically appropriate, considering the demonstrated importance of introducing antihypertensive therapy to hinder progression of hypertensive disease [33, 34]. Therefore, the use of an observational real-life registry, such as the current one, can still yield valuable information in these circumstances.

The present study did not investigate additional sites of HMOD, such as brain magnetic resonance abnormalities or retinopathy, but findings regarding LVH, carotid plaques, and renal impairment offer a comprehensive overview of its extent. While acknowledging potential additional confounding factors like low socio-economic status, marital status and frailty associated with the studied variables, our research focuses on investigating the impact of delayed time-to-therapy on HMOD and BP control within a large cohort of hypertensive patients, rather than exploring the causes of therapeutic inertia.

5 Conclusions

Initiating antihypertensive drugs more than 2 years after the onset of hypertension in high-risk profile patients is an independent risk factor for persistent uncontrolled BP over time and HMOD. Thus, delayed time-to-therapy represents a relevant modifiable risk factor that should be adequately and timely addressed to hinder the progression of hypertensive damage. Both patients' awareness and physicians' active screening are essential for this aim.

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Data Availability All data described in the manuscript are available from the corresponding author upon reasonable request.

Declarations

Conflict of Interest There is no conflict of interest.

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