



ORIGINAL RESEARCH

Carotid Atherosclerosis Predicts Blood Pressure Control in Patients With Hypertension: The Campania Salute Network Registry

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BACKGROUND: The 2018 European Society of Cardiology/European Society of Hypertension arterial hypertension guidelines do not recommend routine carotid ultrasound as a tool to identify hypertension-mediated organ damage, unless clinically indicated. However, carotid plaque (CP) is a strong correlate of increased arterial stiffness, which influences blood pressure (BP) control over time. Thus, we assessed whether evidence of CP at first visit could predict BP control during follow-up.

METHODS AND RESULTS: From the CSN (Campania Salute Network) Registry, 6684 patients with hypertension had complete carotid ultrasound examination and were categorized by the presence of CP at baseline. Optimal BP control was defined as average BP <140/90 mm Hg and <135/85 during follow-up for office and home BP, respectively. At baseline, participants with CP (n=3061) were more likely to be men, to be older, to have diabetes, and to exhibit higher systolic BP, lower diastolic BP, worse lipid profile, and higher prevalence of left ventricular hypertrophy (all $P<0.0001$) than patients without CP. Optimal office BP control was adjudicated in 54% with and 62% without CP ($P<0.0001$), and optimal home BP in 51% with and 58% without CP ($P<0.01$). Presence of CP was significantly associated with the reduced probability of controlled office BP during follow-up (both $P<0.0001$), independently of significant effect of older age, male sex, higher baseline BP values, classes of medication, and presence of left ventricular hypertrophy, and only attenuated by duration of hypertension.

CONCLUSIONS: Presence of CP in treated patients with hypertension is associated with suboptimal BP control during follow-up, independently of worse metabolic profile and presence of left ventricular hypertrophy.

Key Words: atherosclerosis ■ high blood pressure ■ ultrasound ■ vascular disease

Routine carotid ultrasound is not recommended anymore, in the 2018 European Society of Cardiology/European Society of Hypertension guidelines for management of arterial hypertension,¹ as a tool to identify hypertension-mediated organ damage, unless clinically indicated. This is likely attributable to the high technical variability of the assessment,² to the lack of evidence that changes can be assessed

during clinically meaningful time frame, and to the fact that these changes have prognostic impact.^{3,4} However, presence of carotid plaque (CP) is a strong marker of atherosclerosis, characterized by increased deposition of arterial calcium and collagen associated with fraying of arterial elastin. The resultant reduction in arterial elasticity and compliance leads to a decrease of the lumen/wall ratio and increased arterial stiffness.⁵

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CLINICAL PERSPECTIVE

What Is New?

- This study demonstrated that presence of carotid plaque is associated with long-term blood pressure control in patients with hypertension.

What Are the Clinical Implications?

- Performing carotid ultrasound in patients with hypertension might be useful for the clinical management of high blood pressure.

Nonstandard Abbreviations and Acronyms

CP	carotid plaque
CSN	Campania Salute Network
HBP	home blood pressure
IMT	intima-media thickness
OBP	office blood pressure

These changes specially involve predominantly large arteries and the aorta, reducing distensibility and elastic recoil of conduit arteries. A faster velocity triggers a speedier reflected pressure wave, which, in turn, causes a ventricular-vascular mismatch, resulting in increased left ventricular (LV) afterload and systolic pressure,⁶ which favors the transition from systolic and diastolic hypertension to isolated systolic hypertension, a form much more difficult to treat.⁷ Thus, it is possible to speculate that presence of carotid atherosclerosis in patients with hypertension may impact on blood pressure (BP) control over time. Accordingly, this analysis was designed to assess whether the presence of CP at the time of the first visit in our outpatient clinic could predict BP control during follow-up in treated patients with hypertension.

METHODS

Patient Population

The CSN (Campania Salute Network) Registry is an open electronic registry, networking community hospital-based hypertension clinics, and general practitioners from the Campania region in Southern Italy to the Hypertension Research Center of Federico II University Hospital in Naples (ClinicalTrials.gov Identifier: NCT02211365).⁸ As previously reported in detail,⁹ recruited subjects are referred to the Hypertension Research Center for cardiovascular imaging and possible refinement of diagnosis and

treatment. The registry currently includes >15 000 patients with hypertension.

For the present analysis, patients with hypertension were selected on the basis of the following inclusion criteria:

1. Aged ≥ 18 years
2. Available follow-up >6 months
3. No prevalent coronary/cerebrovascular disease and atrial fibrillation
4. No prevalent valvular heart disease
5. Available baseline echocardiography and carotid ultrasound

Patients were followed up over a median of 69 months (interquartile range, 28–100 months).

The Federico II University Hospital Ethic Committee approved the database generation of the CSN Registry. All participants signed written informed consent for the possibility of using the data for scientific purposes.

Because of the sensitive nature of the data collected for this study, requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be sent to the CSN Registry study to attention of Prof. Raffaele Izzo (raffaele.izzo@unina.it).

Cardiovascular Risk Factor and Disease Assessment

Documented cardiovascular disease was defined at the first examination in the outpatient clinic and included previous myocardial infarction, angina pectoris, coronary or carotid revascularization procedures, stroke, transitory ischemic attack, or congestive heart failure. Auscultatory or oscillometric semiautomatic sphygmomanometers attended by physicians were used and validated periodically according to standardized protocols, using cuffs of appropriate size.¹⁰ Systolic and diastolic BP were measured after 5 minutes resting in the sitting position, 3 times at 1-minute interval, according to current guidelines¹ and standard procedures of CSN Registry. The average of the 2 last measurements was taken as the office BP (OBP). All patients were also invited to measure their BP at home (HBP) using validated device and according to current guidelines.¹ The patients were trained on BP measurement at home. All patients were invited to provide a validated device based on <https://www.stridebp.org/> list. Written instructions and a self-recording sheet were provided to ensure adequate pressure monitoring. Data included 2 HBP measurements (approximately at 7 AM and 7 PM), over a period of 7 days before the scheduled visit, with a minimum interval of 1 minute between measurements, and excluding the first measurement in each case. At each visit, HBP data were recorded if validated device was used.

According to our standard criterion, follow-up BP was considered optimally controlled when the average OBP values during follow-up visits was <140/90 mm Hg. Follow-up HBP was considered optimally controlled when the average HBP self-reported value was <135/85 mm Hg.¹ Isolated systolic hypertension was defined as systolic BP >140 mm Hg and diastolic BP <90 mm Hg.⁷ Obesity was defined as a body mass index ≥ 30 kg/m².¹¹ Fasting glucose and lipid profile were measured by standard methods. Diabetes was defined as history of diabetes, use of any antidiabetic medication, or presence of a fasting blood glucose ≥ 126 mg/dL, confirmed on 2 different occasions.¹² Estimation of creatinine clearance (estimated glomerular filtration rate) was done using Chronic Kidney Disease Epidemiology Collaboration equation, as previously reported.⁸

Echocardiography

Echocardiograms were performed using commercially available phased-array machines following a standardized protocol.^{13,14} LV hypertrophy was identified by prognostically validated sex-specific cutoff values for LV mass/height: >47 g/m^{2.7} in women and >50 g/m^{2.7} in men.^{1,15} LV end-diastolic dimension was ratiometrically normalized by height.¹⁵ Relative wall thickness was calculated as the ratio between posterior wall thickness and LV internal radius at end diastole and considered increased if ≥ 0.43 .¹

Carotid Ultrasonography

Carotid ultrasonography was performed using a commercially available ultrasound scanner equipped with a 7.5-MHz high-resolution transducer, following a previously published standardized protocol.¹⁶ The maximal carotid intima-media thickness (IMT) was estimated offline in up to 12 arterial walls, including the right and the left, near and far distal common carotid (1 cm), bifurcation and proximal internal carotid artery, according to the European Society of Cardiology/European Society of Hypertension guidelines.¹ According to previous studies, increased IMT was defined as IMT >0.9 mm and CP as a localized IMT ≥ 1.5 mm.¹⁶

Statistical Analysis

Statistical analysis was performed using IBM SPSS 23 (IBM Corporation, Armonk, NY). Data are presented as mean \pm 1 SD for continuous variables and as percentages for categorical variables. Patients were categorized into 2 groups according to the absence or the presence of CP at first visit. Analysis of variance and χ^2 distribution were used for exploratory statistics. As previously repeatedly reported,¹³ to account for therapy, single classes of antihypertensive medications, including renin-angiotensin system blockers

(ie, angiotensin-converting enzyme inhibitors and/or Angiotensin II receptor type 1 antagonists), calcium channel blockers, β -blockers, diuretics, and statins, were considered in the analysis according to their overall use during the individual follow-up, based on the frequency of prescriptions during the control visits. As previously reported, all medications prescribed for >50% of control visits in an individual patient during follow-up were considered as covariates in the multivariate logistic analyses.^{17,18}

Logistic regression analysis was used to assess the effect of CP on BP control during follow-up. The model was also adjusted for age, sex, diabetes, estimated glomerular filtration rate, presence of LV hypertrophy, baseline BP values, and therapy (classes of antihypertensive drugs and statins at baseline), with the addition of duration of hypertension in a second model. In an alternative model, CP was replaced with increased IMT. We also used continuous variables, IMT and LV mass index, instead of CP and LV hypertrophy. The null hypothesis was rejected at a 2-tailed $P < 0.05$, but attention was paid to the CI of odds ratios (ORs), as recently suggested.¹⁹

RESULTS

We selected a population sample of 6684 patients with hypertension (Figure 1), which included 2870 women and 3814 (or 57%) men, 1680 individuals with obesity (25%), and 674 patients with diabetes (10%). Probability to exhibit CP was significantly lower in women than in men (Table 1; $P < 0.001$), whereas obesity was similarly distributed in participants with or without CP. Participants with diabetes exhibited 2.6-fold higher probability of CP than participants without diabetes (95% CI, 2.24–3.14; $P < 0.0001$).

Participants with CP (N=3061) were prescribed more medications than those without plaque (N=3623) at the time of first visit at the Hypertension Center (Figure 2), a difference that was maintained during follow-up (both $P < 0.0001$).

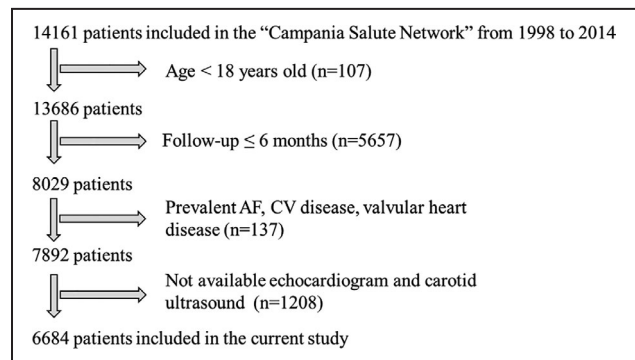


Figure 1. Selection of the study population. AF indicates atrial fibrillation; and CV, cardiovascular.

Table 1. Demographic Characteristic and Antihypertensive Therapy During Follow-Up of the Study Population

Variable	Carotid plaque	No carotid plaque	P value
	(n=3061)	(n=3623)	
Age, y	59±10	50±11	<0.001
Women, %	41	45	<0.001
Baseline systolic blood pressure, mm Hg	150±21	142±18	<0.001
Baseline diastolic blood pressure, mm Hg	87±12	89±11	<0.001
Baseline pulse pressure, mm Hg	57±16	51±13	<0.001
Mean systolic blood pressure during follow-up, mm Hg	139±13	135±11	<0.001
Mean diastolic blood pressure during follow-up, mm Hg	88±11	90±10	<0.001
Mean pulse pressure during follow-up, mm Hg	56±12	50±9	<0.001
Obesity, %	26	25	0.170
Diabetes, %	15	6	<0.001
Uncontrolled hypertension, %	46	38	<0.001
Isolated systolic hypertension, %	64	36	<0.001
Fasting glucose, mg/dL	103±26	96±18	<0.001
Estimated glomerular filtration rate, mL/min per 1.73 m ²	77±15	84±15	<0.001
Total serum cholesterol, mg/dL	209±41	203±37	<0.001
Serum triglycerides, mg/dL	140±75	130±75	<0.01
LV mass, g/m ^{2.7}	49±9	45±9	<0.001
LV hypertrophy, %	47	30	<0.001
RWT	0.39±0.04	0.38±0.04	<0.001
Anti-RAS during follow-up, %	87	79	<0.001
β-Blockers during follow-up, %	10	10	0.399
Calcium blockers during follow-up, %	12	9	0.005
Diuretics during follow-up, %	47	40	<0.001
Statins during follow-up, %	28	12	<0.001
Follow-up duration, mo	67±52	71±53	0.003

Data are given as mean±SD, unless otherwise indicated. LV indicates left ventricular; RAS, renin-angiotensin system; and RWT, relative wall thickness.

Table 1 shows that participants with CP were older and were more likely to be men and to have diabetes, with greater prevalence of isolated systolic hypertension, reduced kidney function, and worse lipid profile. They also exhibited greater LV mass index and higher relative wall thickness (all $P<0.001$). In this population sample, 59% of patients were optimally controlled, according to our criteria for OBP, 42.2% with and 57.7% without CP ($P<0.0001$).

Participants with CP presented with about 38% higher chance of uncontrolled OBP during follow-up (95% CI, 1.25–1.53; $P<0.001$) (Table 1). HBP was available in a subgroup of 6496 patients with mean value reported after the first visit of 131±8 mm Hg /81±6 mm Hg. Both baseline OBP and HBP were significantly higher in patients with CP compared with patients without CP (Figure 3). Optimal HBP was adjudicated in 51% with and 58% without CP ($P<0.01$). The presence of CP was associated with increased risk of uncontrolled HBP (OR, 1.16; 95% CI, 1.05–1.27; $P<0.01$). Participants with CP exhibited higher systolic and lower diastolic OBP at baseline, with a higher

pulse pressure, differences that were confirmed during follow-up (all $P<0.0001$; Table 1). All classes of antihypertensive medications, except β-blockers, were more prescribed in patients with than in those free of CP (all $P<0.0001$) (Table 1 and Figure 2).

After controlling for the significant effect of older age and male sex, presence of CP was significantly associated with increased probability of uncontrolled BP during follow-up ($P<0.0001$), an effect that was maintained after adjusting for significant effect of diabetes and reduced kidney function, baseline OBP values, classes of medication (less prescription of statin therapy and greater prescription of calcium channel blockers), and presence of LV hypertrophy (Table 2). Further adjusting model 3 for the self-reported duration of hypertension at first visit attenuated the effect of CP (OR, 1.12; 95% CI, 0.93–1.23; $P=0.06$; Table S1).

Replacing CP with clear-cut increased IMT (>0.9 mm) showed no association with optimal OBP control. However, the same analysis, repeated using continuous variables (IMT and LV mass index) exhibited

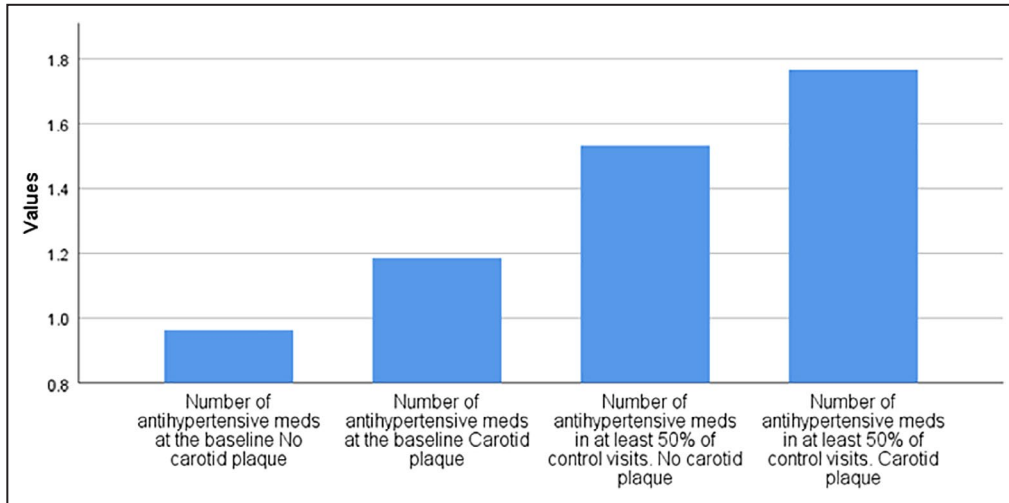


Figure 2. Number of antihypertensive medications (meds) at baseline and during follow-up.

results consistent with the effects of CP and LV hypertrophy (Figure 4 and Table S2).

No sex effect has been found as main mediator of the impact of CP on BP control.

DISCUSSION

Our study demonstrated that carotid atherosclerosis is a clinical sign jeopardizing the possibility of

long-term optimal BP control in treated patients with hypertension, suggesting that its identification might be of clinical relevance for tailoring intensity of initial antihypertensive treatment. The negative impact of CP on optimal BP control was also confirmed in a large subgroup of patients with available data on HBP. Once considered the self-reported duration of hypertension, the effect of CP was attenuated, reinforcing the idea that CP is an important proxy of the status of

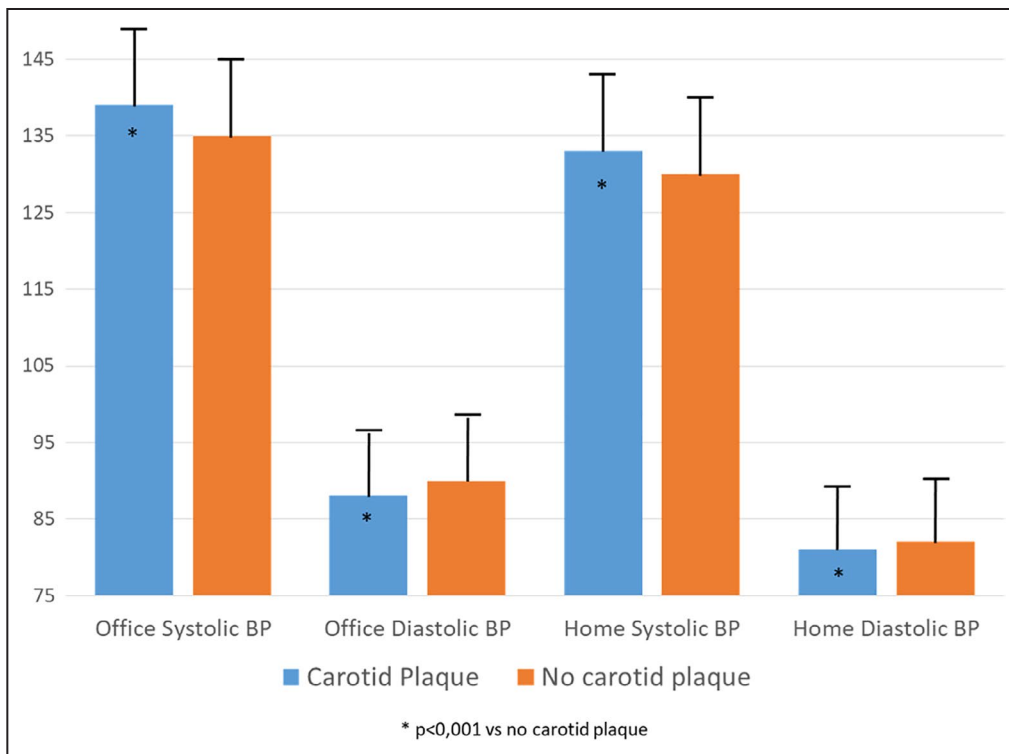


Figure 3. Mean office and home blood pressure (BP) during follow-up.

Table 2. Logistic Regression Analysis for Uncontrolled BP During Follow-Up Using CP as Covariate

Predictors	Model 1			Model 2		
	Significance	OR	95.0% CI	Significance	OR	95.0% CI
Age, y	0.01	1.01	1.001–1.01	0.670	0.998	0.99–1.05
Male sex	0.006	1.15	1.04–1.28	0.527	1.04	0.92–1.17
Carotid plaque (yes/no)	0.0001*	1.31*	1.18–1.47*	0.037*	1.15*	1.01–1.31*
Diabetes (yes/no)	0.032*	1.24*	1.02–1.51*
eGFR, mL/min per 1.73 m ²	0.512	1.01	0.99–1.01
Systolic BP, mm Hg	0.0001*	1.07*	1.06–1.08*
Diastolic BP, mm Hg	0.833	0.99	0.99–1.01
Anti-RAS (yes/no)	0.428	0.94	0.79–1.01
Diuretics (yes/no)	0.840	0.99	0.80–1.10
Calcium-channel blockers (yes/no)	0.0001*	1.44*	1.26–1.64*
Statins (yes/no)	0.0001*	0.69*	0.59–0.81*
LV hypertrophy (yes/no)	0.0001*	1.38*	1.22–1.57*

BP indicates blood pressure; CP, carotid plaque; eGFR, estimated glomerular filtration rate; LV, left ventricular; OR, odds ratio; and RAS, renin-angiotensin system.

*Significant predictors.

the arterial tree, in part related to the duration of the stimulus produced by high BP, and confirming that antihypertensive strategy should focus on early optimal control before hypertension-mediated organ damage consolidates and becomes irreversible.²⁰

With the present analysis, we provide new elements to orient decision in the management of patients with high BP. In particular, we demonstrated

that severe carotid atherosclerosis (as documented by the CP) is a sign indicating that BP control will be a difficult task. This awareness can help tailoring appropriate and possibly more aggressive antihypertensive treatment since beginning of therapy, and program more frequent follow-up visits to rapidly titrate doses of medications and optimize antihypertensive therapy as soon as possible.

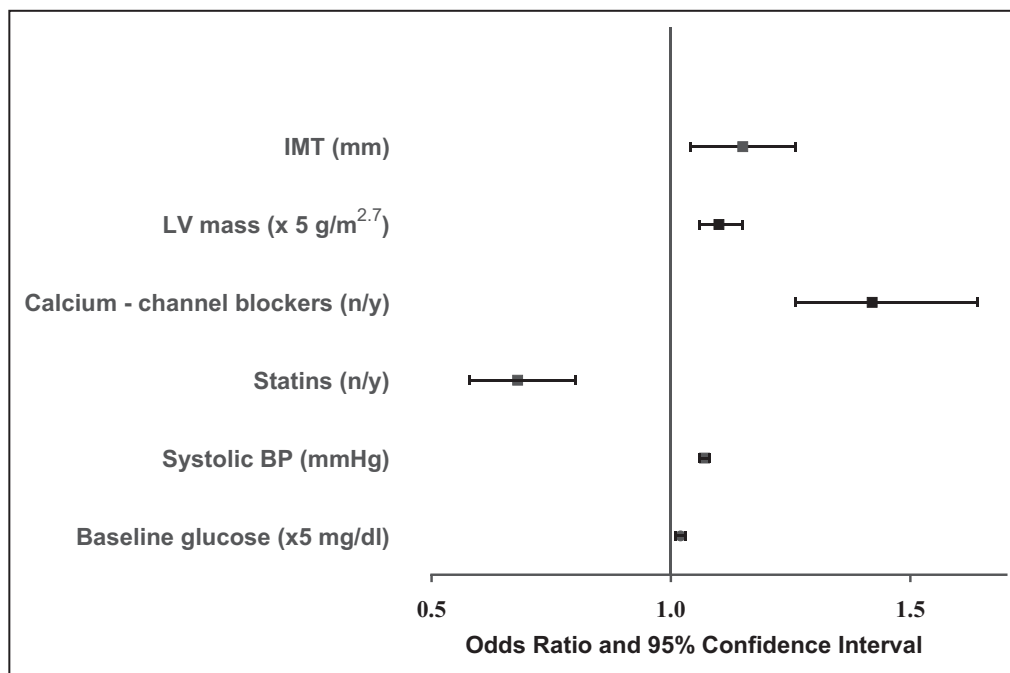


Figure 4. Main determinants of uncontrolled blood pressure (BP) during follow-up using continuous variables.

IMT indicates intima-media thickness; LV, left ventricular; n, no; and y, yes.

Effective BP control is of paramount importance to prevent cardiovascular morbidity and mortality. Data worldwide suggest that, despite the progressive improvement during past decades,²¹ optimal BP control is still achieved in <50% of patients despite the large number of available antihypertensive medications. The evidence that carotid atherosclerosis is another characteristic of patients with high risk of poor BP control during follow-up is added to the other characteristics that we have shown in previous analyses, including LV hypertrophy, increased arterial stiffness, and metabolic abnormalities.^{22–24}

The provided evidence that morphologic signs of atherosclerosis, paralleling functional signs (high arterial stiffness), are linked with uncontrolled hypertension despite treatment, parallels the observation that in young and middle-aged patients with stroke, presence of CP is strongly associated with uncontrolled BP during follow-up.^{25,26}

Carotid atherosclerosis is one of the main determinants of development of isolated systolic hypertension, a condition in which optimal BP control and normalization of systolic BP is difficult, further reinforcing the concept that early identification of patients at high risk of uncontrolled BP is critically important.²⁷

Our study suggests that categorization of IMT using a commonly adopted cut point is less useful to predict probability of uncontrolled BP, probably attributable to lack of specificity, which is, in contrast, maximized when clear-cut CP is found. This is in line with recommendation from American College of Cardiology/American Heart Association and European Society of Cardiology for cardiovascular disease prevention.^{28,29} In contrast, however, there is a clear association between IMT as a continuous variable and probability of suboptimal BP control, as shown in Figure 4, which is more consistent with results of recent meta-analyses on prognosis associated with IMT.^{30,31} In a meta-analysis of 37 197 subjects, the risk for incident acute myocardial infarction or stroke was increased by 15% or 18% per 10 μm of IMT, respectively,³⁰ corresponding to a more recent meta-analysis of 100 667 individuals showing that decrease in carotid IMT of 10 $\mu\text{m}/\text{year}$ is associated with 16% reduced cardiovascular risk.³¹

Increased IMT represents the hemodynamic adaptation to high shear stress, in a pathophysiologic process in which development of plaque represents the highest level of evolution (worsening) of arterial disease. Thus, CP is probably the end point of this evolution³² and is probably irreversible, as clinical trials suggest.³³ Under this perspective, the more modest association of IMT is clearly related to the larger basis of affected patients, whereas CP captures selected individuals with advanced vascular disease.

In our study, less use of statin therapy is associated with uncontrolled BP over time, in line with recent findings by Spannella et al.³⁴ One of the main indications

for prescription of statin therapy is the presence of CP. Thus, carotid ultrasound study in patients with hypertension might be important to increase prescription rate of statins, which could also help control BP.³⁵ Aggressive treatment of atherosclerosis, beyond BP control, in patients with concomitant hypertension and carotid atherosclerosis might be important for stroke prevention.³⁶ Recent evidence suggests that combined presence of hypertension and CP hampers cardiovascular risk of patients in general population studies and thus patients with hypertension might be conveniently screened for the presence of CP, especially when the phenotypical profile suggests high probability, and actively treated with lipid-lowering medications.³⁷ The earlier the treatment is initiated, the more likely it will be successful in reducing the burden of cardiovascular disease.³⁸

Attenuation, but not elimination, of the effect of CP by duration of hypertension (Table S1) strongly suggests that prolonged exposition to high BP might induce irreversible changes in the arterial tree that hamper efficacy of antihypertensive therapy, generating a vicious cycle. There is evidence that consolidated hypertension-mediated organ damage can become irreversible, suggesting that prevention might be more effective than therapy to control structural consequences of arterial hypertension.³⁹

Limitations

The CSN Registry is an observational registry, which can be influenced by bias, a limitation that is difficult to eliminate despite the extensive multivariable adjustment that we perform.^{40,41} In particular, despite the adjustment for baseline BP values in the logistic regression model, we could not determine any exact cause-effect relationship between presence of CP and baseline BP values. Despite that, the main clinical message of our article is to give priority to the assessment of CP in patients with hypertension at first visit to tailor the intensity of antihypertensive and statin treatment for long-term BP control.

Accurate assessment of adherence to antihypertensive treatment is not available in our database, and we cannot exclude its effect in the relationship between CP and BP control.

CONCLUSIONS

Our study demonstrated that presence of carotid atherosclerosis, as marker of hypertension-mediated arterial tree damage, is a main predictor of long-term suboptimal BP control in treated patients with hypertension. CP is more sensitive than the commonly used cutoff for increased IMT in the identification of patients with hypertension who require closer clinical

surveillance for optimal control of OBP and HBP and atherosclerosis.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Material

Tables S1–S2

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Supplemental Material

Table S1. Logistic regression analysis for uncontrolled BP during FU, including reported duration of hypertension. Significant predictors (i.e. OR not crossing 1) are highlighted in bold.

Predictors	Model		
	Sig.	OR	95.0% CI
Age (years)	0.09	0.99	0.98 - 1.01
Male sex	0.78	1.02	0.90-1.15
Carotid Plaque (y/n)	0.06	1.12	0.93-1.23
Diabetes (y/n)	0.08	1.19	0.98-1.46
eGFR (ml/min/1.73m ²)	0.35	1.00	0.99-1.06
Systolic BP (mmHg)	0.001	1.07	1.06-1.07
Diastolic BP (mmHg)	0.93	1.00	0.99-1.07
Anti-RAS (y/n)	0.26	0.91	0.77-1.07
Diuretics (y/n)	0.36	0.94	0.85-1.07
Calcium -channel blockers (y/n)	0.001	1.34	1.16-1.53
Statins (y/n)	0.001	0.69	0.58-0.80
LV hypertrophy (y/n)	0.001	1.36	1.19-1.54
History of hypertension (years)	0.001	1.03	1.02-1.04

BP blood pressure, LV left ventricle, RAS renin angiotensin system.

Table S2. Logistic regression analysis for uncontrolled BP during FU. Significant predictors are highlighted in bold.

Predictors	Model 1			Model 2		
	Sig.	HR	95.0% CI	Sig.	HR	95.0% CI
Age (years)	0.0001	1.01	1.001-1.02	0.99	1.00	0.99-1.05
Male sex	0.02	1.13	1.02-1.25	0.242	1.07	0.95-1.21
Increase IMT (n/y)	0.30	1.09	0.93-1.28	0.775	0.967	0.81-1.16
Diabetes (n/y)	-----	-----	-----	0.025	1.25	1.02-1.51
eGFR (ml/min/1.73m ²)	-----	-----	-----	0.534	1.01	0.99-1.01
Systolic BP (mmHg)	-----	-----	-----	0.0001	1.07	1.06-1.08
Diastolic BP (mmHg)	-----	-----	-----	0.681	0.99	0.99-1.01
Anti-RAS (n/y)	-----	-----	-----	0.486	0.94	0.79-1.01
Diuretics (n/y)	-----	-----	-----	0.673	0.97	0.80-1.10
Calcium -channel blockers (n/y)	-----	-----	-----	0.0001	1.42	1.26-1.64
Statins (n/y)	-----	-----	-----	0.0001	0.69	0.59-0.81
LV hypertrophy (n/y)	-----	-----	-----	0.0001	1.39	1.22-1.58

BP blood pressure, LV left ventricle, RAS renin angiotensin system.