

The natural history of prehypertension. A 20-year follow-up

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Abstract. – OBJECTIVE: According to the JNC7 report, prehypertension category includes subjects with systolic blood pressure between 120 and 139 mmHg and/or diastolic blood pressure between 80 and 89 mmHg that would be at risk for developing hypertension and its untoward sequelae as myocardial infarction and cerebrovascular disease. Moreover, ambulatory blood pressure monitoring made it possible to detect subjects with masked hypertension, who are at risk of greater target organ damage than those with normal ambulatory or home blood pressure.

The aim of this study was to evaluate the risk of cardiac, cerebral and vascular events in a group of prehypertensive subjects, with and without masked hypertension.

PATIENTS AND METHODS: We studied 204 consecutive asymptomatic prehypertensive subjects without history and signs of cardiovascular disease or diabetes. All the subjects underwent clinical evaluation, electrocardiogram, routine laboratory tests and ambulatory blood pressure monitoring. They were followed-up for a maximum of 237 months or until a cardiovascular event occurred.

RESULTS: Twenty-seven cardiovascular events (13.2%) occurred, including 4 abdominal aortic aneurysms. Age ($p<0.0001$), total cholesterol ($p=0.004$), smoking ($p=0.03$) and clinically overt hypertension development ($p=0.011$) were related to cardiovascular events. Prognosis was not related to masked hypertension.

CONCLUSIONS: The results of this study suggest that, in subjects with prehypertension, followed for 20 years, traditional cardiovascular risk factors and development of clinically overt hypertension could be more relevant than ambulatory hypertension in the prediction of an adverse outcome.

Key Words:

Prehypertension, Coronary heart disease, Stroke, Abdominal aortic aneurysm, Follow-up.

Introduction

In 2003 the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7) decided to create a new blood pressure (BP) category, called pre-hypertension (PHT). This category includes subjects with systolic BP (SBP) between 120 and 139 mmHg and/or diastolic BP (DBP) between 80 and 89 mmHg¹ that would be at risk for developing hypertension and its untoward sequelae as heart attack and stroke.

In particular, a meta-analysis including one million subjects demonstrated that cardiovascular (CV) disease and stroke increased in a log-linear proportion with both SBP and DBP values over 115/75 mmHg in individuals aged 40-89 years².

Therefore, early identification of healthy subjects at risk of developing CV disease seems an attractive issue; nevertheless, the rationale and relevance of diagnosing PHT have recently been called into question³. It can be estimated that up to one in three adults has PHT and, clearly, this means that effective CV prevention would be unfeasible, due to the large number of people to be included in the new entity. However, it should be reminded that PHT *per se* is not a disease, but a warning of CV risk requiring a preventive approach based on lifestyle changes: diet, physical activity, weight loss, decreased salt and alcohol intake. In fact, the risk of progressing to hypertension and developing CV disease is higher in individuals with BP 130 to 139/85 to 89 mmHg than in those with BP 120 to 129/80 to 84 mmHg.

It remains unclear whether mild BP elevation directly increases the risk of CV disease or whether other concurrent risk factors are responsible for

the increase⁴. Moreover, home and ambulatory BP monitoring (ABPM) enabled physicians to detect high out-of-office BP in subjects who have normal BP in clinic, a phenomenon called masked hypertension (MH) (5), a condition characterized by higher incidence of target organ damage than normal BP (6-9).

At the present time, there are no long-term prognostic data in subjects with PHT who were studied by ABPM. The aim of our work is to present a 20-year follow-up of prehypertensive subjects with and without MH.

Patients and methods

Patients

We studied 204 (101 M, 103 F, age 49.4±13.2 years) Caucasian consecutive asymptomatic subjects with PHT. Some of them had the following CV risk factors: cigarette smoking, overweight (body mass index, BMI >25 kg/m²) and dyslipidemia (Table I). They were members of the hospital staff, subjects examined for reasons other than hypertension or CV disease and without any relevant systemic disease and volunteers referred to our center by their family physicians for CV prevention screening. Subjects with history and/or clinical signs of CV disease, left ventricular hypertrophy, diabetes mellitus (fasting blood glucose >125 mg/dl or use of antidiabetic drugs) and kidney disease were excluded. All the subjects underwent clinical evaluation, ECG, routine laboratory tests, and ABPM.

Study subjects came to our center from the residential urban area of Rome, Italy.

The study was in accordance with the Second Declaration of Helsinki and was approved by the institutional Ethical Review Committees. Subjects gave informed consent.

Office BP Measurements

Clinic SBP and DBP readings were performed by a physician after 10 min of rest, using a mercury sphygmomanometer. Measurements were performed in triplicate, 2 minutes apart, and the average value was used as the BP for the visit. The arm with the major blood pressure was considered for measurements.

PHT was defined as clinic BP in the range of 120-139 mmHg for SBP and in the range of 80-89 mmHg for DBP in at least two visits. Development of clinically "overt" hypertension during the follow-up was defined as clinic BP

≥140 and/or 90 mmHg or prescription of anti-hypertensive medication, as judged by subjects' own family physicians or outpatient clinic specialists.

ABPM

ABPM was performed using Spacelabs 90207 recorders (Spacelabs, Redmond, WA, USA) on a day of typical activity, within 1 week from clinic BP measurement. ABPM recordings were obtained at 15-minute intervals from 6 a.m. to midnight, and at 30-minute intervals from midnight to 6 a.m. The ABPM parameters evaluated were average daytime (awake period), nighttime (asleep period), and 24-hour SBP and DBP. Awake and asleep periods were calculated from diary times. Recordings were automatically edited if SBP was >260 or <70 mmHg or if DBP was >150 or <40 mmHg and pulse pressure was >150 or <20 mmHg. Subjects included in this study had recordings of good technical quality (at least 70% of valid readings). The cutoff of 135/85 mmHg was used to define normal daytime BP. Thus, subjects with daytime BP ≥135 and/or 85 mmHg were diagnosed as having MH: 59 subjects (29.5%) in our casebook.

Dipper condition was defined as a decrease of nighttime mean BP of 10% or more than daytime mean BP.

Follow-up

Subjects were followed up in our Outpatient Clinic or by their family physicians. Subjects with MH were prescribed lifestyle changes as needed: diet, physical activity, weight loss, decreased salt and alcohol intake. Occurrence of composite CV events (CCVE) was recorded during follow-up visits or by telephone interview of the subject followed by a clinical visit. The follow-up reached 20 years (average 187.8±48.3 months). CCVE included fatal and non-fatal myocardial infarction, coronary revascularization (bypass surgery or percutaneous transluminal angioplasty), heart failure requiring hospitalization, fatal and non-fatal stroke, transient ischemic attacks (TIA), and development of abdominal aortic aneurysms (AAA).

The end-point of the study was represented by the occurrence of the first (in time) among the above mentioned CCVE. The development of clinically "overt" hypertension was considered an intermediate endpoint and the end of the study for the subjects who developed this condition.

Statistical Analysis

Statistical analysis was performed using the BMDP statistical software, release 7.0.¹⁰

Categorical data were presented as absolute frequencies and percent values. Quantitative measurements were expressed as mean±SD. The two groups of subjects (group A: no CCVE during follow-up; group B: CCVE during follow-up), were compared by chi-square test or Fisher's exact probability test (in case of two-by-two contingency tables) and by Mann-Whitney test for quantitative variables. Cox proportional hazards stepwise regression analysis was performed in order to evaluate the role of some covariates in CCVE development. The Kaplan-Meier method was used to estimate event free survival as a function of time in different subgroups of subjects based on: i) MH status at enrolment (yes vs. no), ii) clinical hypertension development at follow-up (yes vs. no), iii) smoking habit (smokers vs. no-smokers). Cases lost at follow-up were included in the analysis and considered censored at the time of the last observation.

A *p*-value of ≤ 0.05 was considered statistically significant.

Results

During the follow-up period, 27 subjects (13.2%) had CCVE: 5 subjects underwent myocardial revascularization; 5 subjects had fatal or non-fatal coronary events; 1 subject developed heart failure; 12 subjects had fatal or non-fatal cerebrovascular events and 4 subjects developed AAA. The intermediate endpoint of overt hypertension development was met by 87 subjects (42.6%) in the overall group, in 39.0% of subjects without CCVE and in 66.7% of subjects with CCVE (Table I). There was no difference in CCVE free survival between subjects with and without MH (Figure 1), while survival was poorer in subjects who developed overt hypertension in the follow-up (Figure 2). Subjects affected by CCVE were older, had significantly higher total cholesterol, were cigarette smokers and, as noted above, developed more clinically overt hypertension (Table I). Cardiac events (coronary events and heart failure) were predicted by age, BMI, total cholesterol, cigarette smoking and non-dipper condition (Table II). Cerebral and vascular events (strokes, TIA and AAA) were predicted by age and overt hypertension development in the follow-up (Table III).

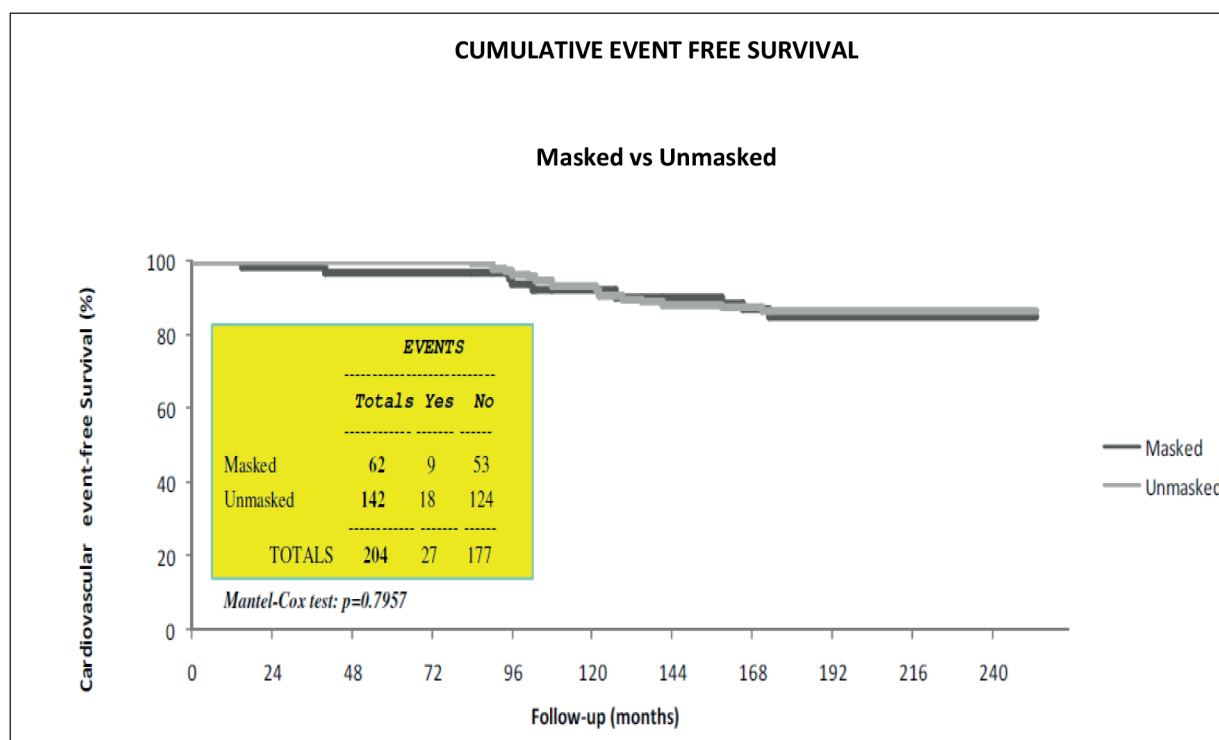


Figure 1. Event-free survival curves: Masked vs. Unmasked patients.

Table I. Characteristics and clinical data of the overall group of patients and grouped according to events development at follow-up.

Variables	All patients (n=204)	No events at follow-up (n=177)	Events at follow-up (n=27)	p
		mean + SD (%)	mean + SD n (%)	
Age (years)	49.4 + 13.2	48.1 + 13.1	58.4+ 9.8	<0.0001
Gender				0.4097
- F (0)	103 (50.5)	87 (49.2)	16	(59.3)
- M (1)	101 (49.5)	90 (50.8)	11	(40.7)
Body Mass Index (kg/m ²)	25.3 + 3.6	25.1 + 3.5	26.6 + 3.9	0.1085
Total Cholesterol	195.1+ 37.7	191.8 + 36.2	216.3 + 41.4	0.0041
Smoking	0.0302			
- No (0)	168 (82.4)	150 (84.7)	18	(66.7)
- Yes (1)	36 (17.6)	27 (15.3)	9	(33.3)
Systolic Office Blood Pressure (mmHg)	126.9 + 10.0	127.2 + 9.9	124.9 + 10.6	0.2572
Diastolic Office Blood Pressure (mmHg)	79.7+ 6.7	80.0 + 6.7	77.7 + 6.4	0.0555
24h Systolic ABP (mmHg)	122.7 + 11.8	122.8 + 11.7	122.2+ 12.8	0.5137
24h Diastolic ABP (mmHg)	75.8 + 8.2	75.9 + 8.2	75.6 + 8.5	0.8362
Systolic ABP daytime (mmHg)	126.2 + 11.4	126.3 + 11.1	125.3 + 13.3	0.3364
Diastolic ABP daytime (mmHg)	78.6 + 8.3	78.6 + 8.3	78.1 + 8.6	0.9038
Systolic ABP nighttime (mmHg)	109.5 + 14.7	109.4 + 14.8	110.2 + 14.4	0.7027

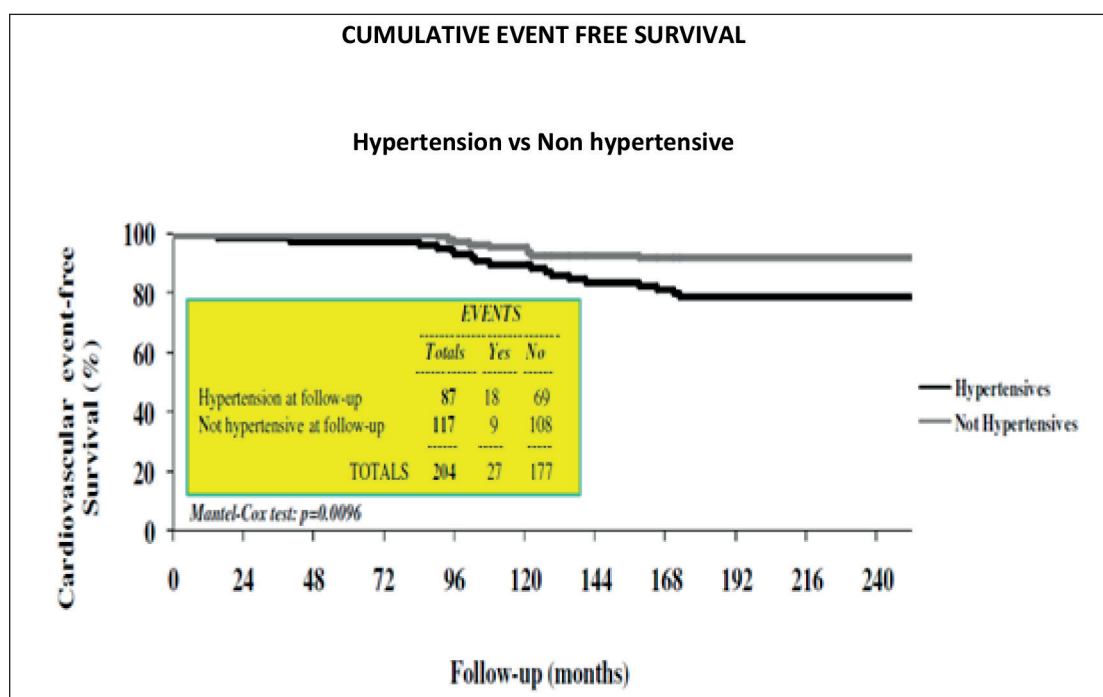


Figure 2. Event-free survival curves: Hypertensives vs. Non hypertensives at follow-up.

Discussion

In this prospective study, the occurrence of total CCVE (13.2%) was similar to large pop-

ulation surveys¹¹. The most frequent adverse outcomes were non-cardiac events. Similar results were found both in recent meta-analyses^{12,13} and in another Italian multicenter study

Table II. Predictive factors of cardiac events (n=11) at Cox proportional hazards stepwise regression analysis.

Variables	HR	95%CI	
		Lower	Upper
Age	1.0668	0.9973	1.1412
BMI	1.2308	1.0204	1.4843
Cholesterol	1.0163	1.0001	1.0328
NAPP	0.8579	0.7705	0.9551
Smoking (yes vs no)	7.2819	1.5309	34.6387
Dipper (no vs yes)	12.0768	2.3622	61.7442

HR, Hazard Ratio; CI, Confidence Interval

by Pierdomenico et al⁵. However, in our research prehypertensives diagnosed to have MH did not show a worse outcome than “unmasked” subjects (Figure 1). This finding also diverged from the results of Bobrie et al¹⁴ and Ohkubo et al¹⁵, where subjects with MH had an elevated mortality for stroke and other CCVE. On the contrary, the most relevant finding of our study is that clinically “overt” hypertension and other traditional CV risk factors (age, cholesterol and cigarette smoking) had a significant impact on CCVE free survival. Indeed, 18/27 (66.67%) CCVE occurred in prehypertensive subjects who developed hypertension in the follow-up vs. 9/27 (33.33%) CCVE recorded in subjects who

Table III. Predictive factors of cerebral and vascular (AAA) events (n=16) at Cox proportional hazards stepwise regression analysis.

Variables	HR	95%CI	
		Lower	Upper
Age	1.0967	1.0430	1.1531
Office Systolic BP	0.9534	0.9050	1.0044
HT (yes vs no)	4.0958	1.3021	12.8843

HT, hypertension development; CI, Confidence Interval.

remained prehypertensive until the end of the study. Moreover, 11 of these 18 subjects were also smokers (Figure 3).

As far as we know, there are no other reports on the incidence of AAA in prehypertensive subjects. In our casebook we recorded 4 cases of AAA in the follow-up (1.96%): 3 out of 4 developed hypertension in the follow-up and were not smokers. The last finding is remarkable, since that smoking is considered the main risk factor for AAA according to scientific guidelines¹⁶. We acknowledge that the main limitation of our findings is represented by the sample size of the study population. In fact, since that PHT is a low CV risk condition, it is necessary to follow up an elevated number of subjects for a long time span to achieve significant outcomes.

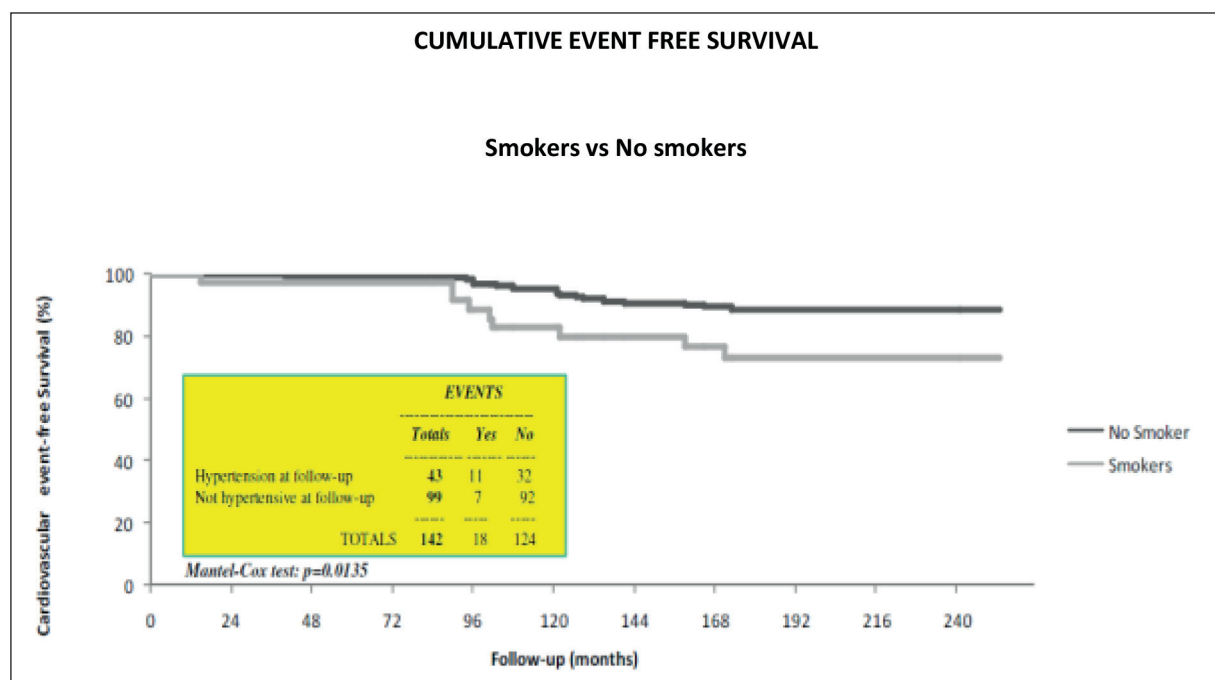


Figure 3. Event-free survival curves: Smokers vs. No smokers.

Conclusions

Our prospective study included 204 prehypertensive subjects who were followed-up until 20-years, thus totalling a 4.080 person-years investigation. As far as we know, there are no reported longer follow-up periods; thus, this extended time span of observation supports the relevance of our findings despite the absolute sample size.

It appears that in prehypertensive subjects the development of overt hypertension mediates, with and without the coexistence of other traditional CV risk factors, the occurrence of CCVE. This is not surprising as it could be inferred by the progression from high-normal BP to hypertension described by Vasan et al¹⁷ using the database of the Framingham Heart Study.

Conflict of Interest

The authors declare no conflicts of interest.

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