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Cardiovascular Mortality in Hypertensive Men According to Presence of Associated Risk Factors

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Abstract—To evaluate the risk of cardiovascular disease (CVD) mortality in hypertensive men according to the presence of associated risk factors (ARFs). The population was composed of 29 640 normotensive men without ARFs (reference group) and 60 343 hypertensive men (with and without ARFs) who had a standard health checkup at the Centre d'Investigations Préventives et Cliniques between 1978 and 1988. Mortality data for a mean period of 14 years were analyzed. The following ARFs were considered: total cholesterol ≥2.5 g/L, personal history of diabetes, smoking (current smokers), body mass index >28 kg/m^2, and heart rate >80 bpm. CVD risk related to the presence of isolated hypertension (assessed in hypertensive subjects without ARFs versus the reference group) increased linearly from 15% at the age of 30 years to 134% at the age of 80 years. In hypertensive subjects, one additional ARF increased CVD risk by 56% (47% to 65%, $P<0.01$) in younger subjects but only by 4% (−8% to 17%, P=NS) in older subjects. The role of hypercholesterolemia and tobacco smoking in CVD mortality was significantly higher in hypertensive subjects aged <55 years than in hypertensive subjects aged ≥55 years ($P<0.01$), whereas the roles of tachycardia and obesity were not affected by age. In younger hypertensive subjects, evaluation of CVD risk and therapeutic strategies should target ARFs. In older subjects, the presence of high blood pressure levels seems to be the major determinant of CVD risk. **(*Hypertension*. 2001;37:1256-1261.)**

Key Words: hypertension, essential ■ risk factors ■ blood pressure ■ mortality

Much of the focus in the management of hypertension has been centered on reducing blood pressure (BP) to the normal range in hopes that this would decrease cardiovascular disease (CVD) morbidity and mortality associated with high BP.[1,2]

It has been shown that antihypertensive treatment only partially reverses the risk of cardiovascular complications, especially coronary complications, in hypertensive individuals.[3,4] These results can be explained by the fact that hypertension-related complications, especially coronary heart disease, are determined by a large number of associated risk factors (ARFs), especially metabolic parameters, that are very often altered in both treated and untreated hypertensive individuals. Several studies have reported that hypertensive subjects consistently have higher levels of total cholesterol, body mass index (BMI), heart rate (HR), glycemia, and triglycerides.[5,6] In a previous report, it was observed that hypertension usually occurs in conjunction with other metabolically linked risk factors and that 13% of men and 20% of women present an isolated hypertension.[6] In the Framingham study, it was observed that clusters of ≥3 of these ARFs occurred 4 times as often as expected by chance.[5] Among individuals with hypertension, ≈40% of the coronary events in men and ≈68% of the coronary events in women are attributable to the presence of ≥2 ARFs. Only 14% of coronary events in hypertensive men and 5% of coronary events in hypertensive women occurred in the absence of additional risk factors. The risk of cardiovascular events among hypertensive patients varies greatly depending on the number of these coexisting risk factors.[7,8] Therefore, increased CVD risk in hypertensive patients may due to the presence of both high BP and ARFs.

The latest international recommendations for BP management clearly indicate that among subjects with hypertension, CVD risk depends on both the BP levels and the presence of ARFs.[2,9] However, the respective roles of BP elevation and ARFs in increased CVD risk may be modified by age. As age increases, the prevalence of hypertension, especially systolic hypertension, dramatically increases.[10] Moreover, aging influences several other risk factors, leading to an accumulation of these risk factors in the elderly.

In the present study, we evaluated the impact of ARFs in cardiovascular mortality in younger and older hypertensive men. Subjects were classified into 2 age groups. For each age group, we compared CVD mortality in 3 groups of hypertensive men according to the number of ARFs (no ARF, 1 to 2 ARFs, and ≥3 ARFs) with CVD mortality in low-risk subjects of the same cohort (normotensive men with no ARFs). We also evaluated whether the role of each risk factor was modified by age.

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TABLE 1. Characteristics of Men According to Presence of Hypertension and ARFs in 2 Age Groups

	Reference Group (Normotensive Men Without ARFs)	Hypertensive Men (All)	Hypertensive Men Without ARFs	Hypertensive Men With 1 or 2 ARFs	Hypertensive Men With ≥3 ARFs
Men age <55 y					
Subjects, n	22 147	42 765	12 450	26 321	3994
Age, y	36.7 (8.9)	40.5 (9.1)	39.1 (9.4)	40.7 (9.1)	43.0 (7.8)
BMI, kg/m^2	23.2 (2.2)	25.2 (3.4)	24.0 (2.2)	25.4 (3.4)	28.1 (3.9)
SBP, mm Hg	125 (7)	145 (11)	143 (9)	145 (11)	150 (14)
DBP, mm Hg	76 (6)	90 (9)	89 (8)	90 (9)	93 (10)
PP, mm Hg	49 (7)	55 (10)	54 (9)	55 (10)	56 (10)
Total cholesterol, g/L	1.96 (0.3)	2.25 (0.4)	2.02 (0.3)	2.29 (0.4)	2.70 (0.4)
Subjects treated for hypertension, %	...	5.9%	5.3%	6.0%	7.4%
CVD deaths, n (%)	60 (2.2)	479 (19.7)	56 (4.5)	307 (11.7)	116 (29.0)
Men age ≥55 y					
Subjects, n	2496	12 785	3348	8148	1289
Age, y	58.8 (4.5)	60.0 (5.7)	60.7 (6.4)	59.8 (5.6)	58.9 (4.4)
BMI, kg/m^2	24.1 (2.2)	26.1 (3.2)	24.7 (2.0)	26.2 (3.3)	28.8 (3.7)
SBP, mm Hg	126 (7)	150 (15)	148 (14)	150 (15)	154 (16)
DBP, mm Hg	78 (5)	92 (9)	91 (9)	92 (9)	95 (11)
PP, mm Hg	48 (6)	58 (11)	57 (11)	58 (11)	60 (11)
Total cholesterol, g/L	2.12 (0.25)	2.37 (0.4)	2.14 (0.24)	2.42 (0.42)	2.67 (0.37)
Subjects treated for hypertension, %	...	16.8%	16.8%	16.3%	18.9%
CVD deaths, n (%)	45 (18.0)	737 (57.6)	183 (54.7)	441 (54.1)	113 (87.7)

Values are mean (SD), unless indicated otherwise. ARFs were as follows: hypercholesterolemia (≥2.5 g/L or treatment), personal history of diabetes, tobacco smoking (current smokers), obesity (BMI >28 in men), and HR >80 bpm.

Methods

Population

Subjects were examined at the Centre d'Investigations Préventives et Cliniques (IPC Center), a medical center that is subsidized by the French national health care system (Securité Sociale, Caisse Nationale d'Assurance Maladie) and that provides all working and retired individuals and their families with a free medical checkup every 5 years. It is one of the biggest medical centers of this kind in France, having carried out ≈15 000 examinations per year from 1970 to 1978 and ≈25 000 per year thereafter for people living in the Paris area. Clinical and biological data were obtained during the standard health checkup at the IPC Center, and the same procedures were used for all subjects. The study population was composed of all the hypertensive men (systolic BP [SBP] ≥140 mm Hg or diastolic BP [DBP] ≥90 mm Hg or antihypertensive treatment, n=60 343) who had a health checkup at the IPC Center during the period of January 1978 to December 1988. Normotensive men (SBP <140 mm Hg and DBP <90 mm Hg, without treatment for hypertension) with no modifiable CVD risk factors (defined in the next paragraph) who were examined at the IPC Center during the same period were used as the reference population (n=29 640). If a person had ≥1 examination, the first examination was used for analysis. For all variables and for both younger and older subjects, the percentage of missing values was <1%. All clinical and biological parameters used to determine the presence of risk factors were assessed the day of the examination.

Supine BP was measured 3 times in the right arm by use of a manual sphygmomanometer after a 10-minute rest period. The mean of the last 2 measurements was calculated. The first and the fifth Korotkoff phases were used to define SBP and DBP. A self-administered questionnaire containing dichotomous (yes or no) questions regarding tobacco use (current consumption of >10 cigarettes per day) and a personal history of diabetes was administered. HR was measured with an ECG, and results were inserted into the database in 1 of the following classes: HR <60 bpm, 60 bpm≤HR≤80 bpm, 80 bpm<HR≤100 bpm, and HR >100 bpm. Biological parameters were measured under fasting conditions. Plasma cholesterol was measured with a Technicon SMA 12.

Associated cardiovascular risk factors considered for this analysis were as follows: hypercholesterolemia (total cholesterol ≥2.5 g/L), personal history of diabetes, tobacco consumption (current smoker, ie, >10 cigarettes per day), obesity (BMI >28 kg/m^2), and HR >80 bpm.

To study the respective roles of hypertension and ARFs in CVD mortality, hypertensive subjects were divided into 3 groups. The first group had no other associated CVD risk factors. The second group had 1 or 2 cardiovascular ARFs. The third group had at least 3 cardiovascular ARFs. The CVD mortality in these 3 groups was compared with the CVD mortality in normotensive subjects without ARFs (reference group).

To assess age-dependent differences in the effects of hypertension and ARFs, subjects were separated into 2 age groups: younger subjects (aged <55 years) and older subjects (aged ≥55 years). The role of age was also assessed for the entire population by studying the interactions of age and hypertension and of age and ARFs on CVD mortality (see data analysis).

Mortality Data

Deceased subjects were identified from the mortality records of the Institut National de Statistiques et d'Etudes Economiques (INSEE). A patient from our cohort was classified as deceased when he had the same first name, last name, gender, and date of birth as a person recorded in the INSEE mortality records. By use of this matching procedure, the identification error was <1%. Only subjects with all 4 of these criteria were classified as deceased. Individuals matching for gender, last name, and only 1 of the other 2 criteria were excluded from the study. Mortality data were recorded for a period of 0 to 18 years (mean, 14 years). Follow-up ended in December 1996. Causes of mortality, taken from the death certificates, were provided by

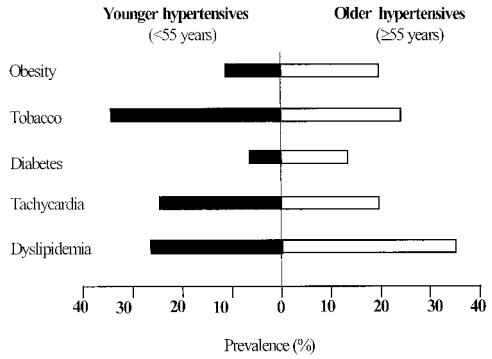

Figure 1. Prevalence of ARFs in younger and older hypertensive subjects. The following ARFs were considered: hypercholesterolemia (≥2.5 g/L or treatment), personal history of diabetes, tobacco smoking (current smokers), obesity (BMI >28 in men), and HR >80 bpm.

INSERM's Department of Mortality (Unit SC 8). Causes of death were codified according to the International Classification of Disease (8th revision before 1978 and 9th revision thereafter). The codes 390 to 459, 785, 798, and 799 were used to identify all cardiovascular deaths.

Data Analysis

A multivariate analysis was used to compare biological and clinical parameters in each group, after adjustment for age. The prevalence of tobacco consumption, diabetes, tachycardia (HR >80 bpm), and treated hypertension in the different groups was compared by a χ^2 test. Mortality rates were compared by a univariate analysis with no adjustment. A χ^2 test was used to compare mortality rates in each group.

Cox regression models were used to determine the role of age and other risk factors in younger and older hypertensive subjects.

A multivariate analysis using a Cox regression model was used to evaluate risk ratios in each group compared with the normotensive group (reference group). Age was included in the model. The interaction between age and hypertension (age×isolated hypertension) and age and ARFs (age×ARFs) were also included in the Cox regression model. To illustrate these interactions, we calculated CVD mortality risk from coefficients estimated by the Cox regression analysis at different ages: hypertensive men without other ARFs were compared with normotensive men for the age×isolated interaction, and hypertensive men with 2 other ARFs were compared with hypertensive men without other ARFs for the age×ARF interaction.

All statistical analyses were carried out by use of the SAS statistical software package. The present study received approval from the Comité National de l'Informatique et des Libertés. All study participants gave their informed consent for their data to be used for epidemiological studies.

Results

Prevalence of ARFs in Younger and Older Hypertensive Men

The main characteristics of the different groups, classified according to age and the presence of ARFs, are presented in Table 1. Among younger hypertensive men, 29% had no ARFs, whereas among older hypertensive men, 26% had no ARFs. In younger hypertensive men, tobacco smoking (35.7%), hypercholesterolemia (27.6%), and accelerated HR (25.5%) were the most common ARFs. In older hypertensive men, hypercholesterolemia was the most common ARF (36.2%), followed by smoking (25.5%). Among the different ARFs, diabetes increased the most with age (6.8% in younger versus 14% in older hypertensive men) (Figure 1).

In both younger and older men, SBP, DBP, and pulse pressure (PP) increased in hypertensive subjects with ARFs. In younger subjects, the percentage treated for hypertension increased with the number of ARFs. This was not observed in older subjects.

CVD Mortality in Younger and Older Hypertensive Men According to the Number of ARFs

Compared with the reference group, younger men with isolated hypertension had unadjusted CVD mortality rates, which were twice as high ($P<0.005$) (Table 1). However, because of the low mortality rates in these 2 groups, CVD survival probability curves showed very little difference between subjects with isolated hypertension and normotensive control subjects (Figure 2, left panel). CVD mortality rates increased dramatically in the presence of ARFs; there was a 5-fold increase in the group with 1 to 2 ARFs and a 15-fold increase in the group with >2 ARFs ($P<0.001$ versus normotensive subjects). These results are also shown in Figure 2 (left panel). Survival probability decreased significantly when hypertension was associated with other risk factors.

In older subjects, compared with the reference group, unadjusted CVD mortality rates showed a 3-fold increase in the group with isolated hypertension and in the group with 1 to 2 ARFs ($P<0.001$ versus reference group). In the group with >2 ARFs, CVD mortality rates showed a 4.5-fold increase versus rates in the reference group ($P<0.001$). Figure 2 (right panel) also illustrates these results. Older subjects with isolated hypertension had a significantly lower

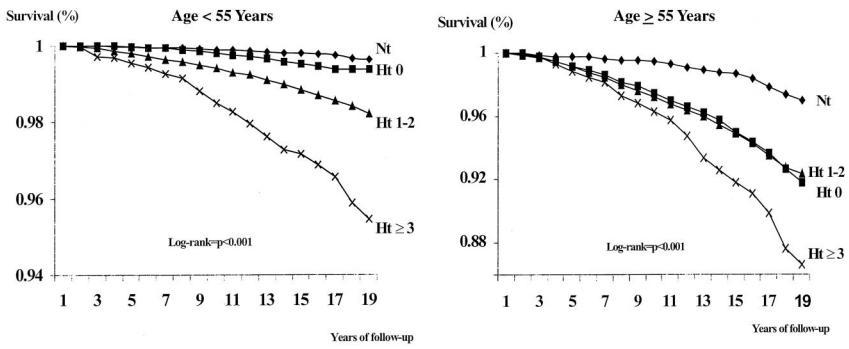

Figure 2. Survival probability for CVD mortality in younger (left) and older (right) men according to the presence of hypertension and ARFs. Nt indicates normotensive subjects; Ht 0, hypertensive subjects without ARFs; Ht 1-2, hypertensive subjects with 1 or 2 ARFs; and Ht ≥3, hypertensive subjects with ≥3 ARFs.

TABLE 2. Age-Adjusted Risk Ratios for CVD Mortality According to Presence of Hypertension and ARFs in 2 Age Groups

	Age <55 y		Age ≥55 y	
	Risk Ratio	95% CI	Risk Ratio	95% CI
Normotensive men	1	...	1	...
Hypertensive men without ARFs	1.74	1.20–2.52	2.03	1.45–2.84
Hypertensive men with 1 or 2 ARFs	4.11	3.10–5.44	2.72	2.00–3.70
Hypertensive men with ≥3 ARFs	9.73	7.02–13.48	5.34	3.78–7.56

CVD survival probability compared with the reference group, whereas hypertensive subjects with 1 or 2 ARFs did not show any further decrease in survival probability. Survival probability showed a more important decrease for hypertensive subjects with >2 ARFs.

Similar results were obtained when age-adjusted relative risk for CVD mortality was assessed (Table 2). Compared with normotensive subjects, younger hypertensive subjects with no ARFs had a higher risk of CVD mortality. In this age group, the presence of ARFs dramatically increased CVD mortality risk. In men aged >55 years, however, the increase in CVD risk was observed even in those hypertensive subjects without any other ARFs. The presence of ARFs had little effect on CVD risk in this age group.

Respective Roles of BP Increase and ARFs in CVD Mortality

Our analysis showed that in hypertensive men, the risk of CVD mortality related to the addition of 1 ARF was 1.56 (95% CI 1.47 to 1.65) in younger subjects and 1.04 (95% CI 0.92 to 1.17) in older subjects. After adjustment for SBP and DBP, in hypertensive men, the risk related to the increment of 1 associated risk factor was 1.55 (95% CI 1.43 to 1.68) in younger men and 1.03 (95% CI 0.91 to 1.15) in older men. A significant interaction between age and isolated hypertension was observed for CVD mortality ($P<0.005$), implying that the role of hypertension increased with age. As illustrated in Figure 3, CVD risk related to the presence of isolated hypertension (isolated hypertensive subjects versus reference group) was 1.15 (95% CI 0.89 to 1.49) at the age of 30 years and 2.34 (95% CI 2.27 to 2.41) at the age of 80 years. By contrast, the effect of ARFs on CVD mortality significantly decreased with age (negative interaction, $P<0.0001$). Thus, as shown in Figure 4, whereas at the age of 30 years, the CVD risk for hypertensive subjects with 2 ARFs compared with subjects with isolated hypertension was 4.50 (95% CI 3.57 to 5.63), at the age of 80 years, the CVD risk related to the presence of 2 ARFs was 1.26 (95% CI 1.22 to 1.30).

We also evaluated the respective roles of each of the different ARFs in younger and older subjects by using a Cox analysis (Table 3). As expected, in both groups, age was a significant determinant of CVD mortality, but its role was more important in older than in younger subjects ($P<0.01$). The role of hypercholesterolemia and tobacco smoking in CVD mortality was significantly higher in younger than in older hypertensive subjects ($P<0.01$). Tachycardia and diabetes showed the same trends, but differences between age groups were not significant. However, obesity was a significant independent determinant only in older hypertensive subjects.

Discussion

The main result of the present study is that in men, the CVD risk related to hypertension increases with age, whereas the risk related to associated risk factors is more important in younger than in older hypertensive subjects. Thus, the risk in younger hypertensive men depends primarily on the number of ARFs, whereas the risk in older hypertensive men is

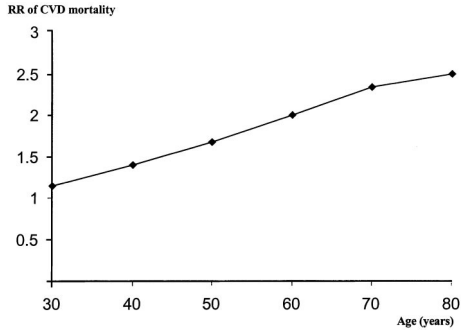

Figure 3. Estimated relative risk (RR) for CVD mortality related to presence of isolated hypertension according to age (RR in hypertensive subjects without ARFs vs normotensive subjects without ARFs).

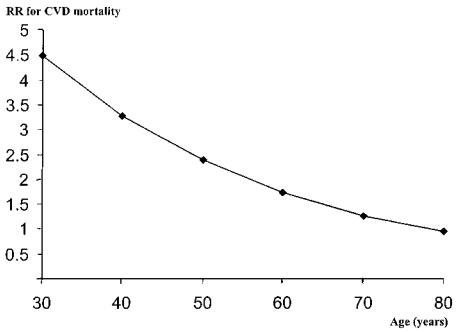

Figure 4. Estimated RR for CVD mortality related to presence of ARFs in hypertensive subjects according to age (RR in hypertensive subjects with 2 ARFs vs hypertensive subjects without ARFs).

TABLE 3. RR (95% CI) for CVD Risk Factors in Younger and Older Hypertensive Men

	Younger Hypertensive Men, RR (95% CI)	Older Hypertensive Men, RR (95% CI)
Age (1 y)	1.08 (1.06–1.09)*	1.11 (1.10–1.12)*
Hypercholesterolemia (yes/no)	1.80 (1.50–2.16)*	1.18 (1.02–1.38)†
Diabetes (yes/no)	1.41 (1.07–1.84)†	1.25 (1.03–1.51)†
Obesity (yes/no)	1.14 (0.93–1.41)	1.28 (1.08–1.51)†
Current smoker (yes/no)	2.37 (1.97–2.84)*	1.45 (1.23–1.70)*
Tachycardia (yes/no)	1.48 (1.22–1.78)‡	1.32 (1.11–1.56)‡

RR indicates relative risk.
*$P<0.001$, †$P<0.05$, and ‡$P<0.01$.

primarily dependent on BP and much less on the presence of ARFs.

Prevalence of Risk Factors in Younger and Older Hypertensive Men

Several studies have shown that hypertensive subjects compared with normotensive subjects invariably have a higher incidence of obesity, diabetes, hypercholesterolemia, and increased HR.[11] We recently reported that in a French population composed of 92 641 men examined recently (1992 to 1997) at the IPC Center, 72% presented at least 1 modifiable associated CVD risk factor, and among them, >7% presented at least 3 ARFs.[12] The results of the present study show that in a population studied between 1978 and 1988, the prevalence of ARFs is very similar.

In the present study, we observed that the percentage of hypertensive subjects with ARFs increases only slightly in older subjects compared with younger subjects (74% versus 71%, respectively). This is due to the fact that some risk factors (such as diabetes mellitus and hypercholesterolemia) dramatically increase with age, whereas others (such as tobacco smoking and tachycardia) are more frequent in younger hypertensive men.

Role of Hypertension in CVD Risk in Younger and Older Hypertensive Men

The most important difference between the 2 age groups concerns the impact of hypertension and the different ARFs on CVD mortality. Our analysis shows that the role of hypertension increases with age. Aging increases the hemodynamic patterns of BP change due to an increase in large artery stiffness, and borderline isolated hypertension becomes the dominant form of hypertension.[10,13] In the present study, when compared with younger hypertensive subjects, older hypertensive subjects had higher SBP and PP but the same DBP. Several studies have shown that SBP and PP are major risk factors, primarily in older subjects.[14–16] The influence of SBP and PP levels on CVD mortality have been observed in subjects up to 85 years of age.[17,18] The present study clearly shows that the risk related to hypertension increases with age. Because the prevalence of high SBP and PP increases with age, our results point out that the risk attributable to SBP and PP dramatically increases in older subjects.

By contrast, the role of ARFs seems to be much less important in older hypertensive men, despite the increase in the prevalence of most ARFs with age. Actually, with the exception of obesity (which plays a more important role in older subjects) and HR (whose role remains almost unchanged in older subjects), all other ARFs play a less important role in older than in younger hypertensive subjects. A number of studies reported that the effect of several major risk factors, especially cholesterol, decreased in older persons, losing its predictive value for CVD morbidity and mortality.[19,20] Although this decrease, especially for tobacco smoking, can be attributed to natural selection, the fact that the risk for some ARFs is unchanged or even increases in older hypertensive subjects leads to the conclusion that the mechanisms responsible for arterial alterations are modified by age.

Another hypothesis is that chronic treatment of risk factors can modify their role on CVD mortality, especially in older subjects, for whom treatment of risk factors is more common. One of the limitations of the present study (subjects examined between 1978 and 1988) is that no information was available concerning treatment for cholesterol or diabetes. This information has been available in our database only since 1992. Therefore, we were able to evaluate the percentage of treated subjects among those who had a standard health checkup at the IPC Center during 1992. Among subjects with hypercholesterolemia, it was observed that 11.2% of the younger subjects and 29.2% of the older subjects were treated. For diabetes, the percentage of treated subjects was 22.4% and 32.6% in younger and older subjects, respectively (unpublished data from the IPC Center, 1992–1998). However, we do not believe that this can explain the decrease in the role of ARFs in older subjects. If that were the case, a decrease in the role of hypertension should also have been observed in older subjects. Actually, among older subjects, the proportion of hypertensive subjects who were treated was almost 3 times as high as the proportion of younger hypertensive subjects who were treated. Thus, the difference of the effect of ARFs between the 2 age groups could not be entirely explained by the difference in treatment.

Clinical Implications and Conclusions

The recent recommendations for the management of hypertensive subjects suggest that BP levels and ARFs should be considered for risk stratification and therapeutic efficacy. Our results show that this approach is more adapted to younger subjects than to older ones. In younger hypertensive subjects,

evaluation of CVD risk and therapeutic strategies should target associated risk factors. In older subjects, the presence of high BP levels seems to be the major determinant of CVD risk.

Acknowledgments

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