Why cardiovascular mortality is higher in treated hypertensives versus subjects of the same age, in the general population

Athanase Benetos, Frédérique Thomas, Kathryn E. Bean and Louis Guize

Objective **The aim of the present study was to assess whether increased cardiovascular mortality in treated hypertensives could be explained by high blood pressure levels, or by the presence of associated risk factors and/or associated diseases.**

Design **The study sample consisted of 8893 treated hypertensive men and women from the Investigations Préventives et Cliniques cohort, and 25 880 gender-matched and age-matched untreated subjects from the same cohort. Vital status was obtained for an 8–12 year period.**

Results **Treated hypertensive subjects had higher systolic blood pressure (SBP) (+ 15 mmHg) and higher diastolic blood pressure (+ 9 mmHg), and a higher prevalence of associated risk factors and diseases. Treated hypertensives compared with untreated subjects presented a two-fold increase in the risk ratio (RR) for cardiovascular mortality [RR, 1.96; 95% confidence interval (CI), 1.74–2.22] and coronary mortality (RR, 1.99; 95% CI, 1.63–2.44). Adjustment for unmodifiable risk factors decreased the excess cardiovascular risk observed in treated subjects only slightly: RR, 1.77; 95% CI, 1.56–2.00 for cardiovascular mortality; and RR, 1.76; 95% CI, 1.44–2.16 for coronary mortality. After additional adjustment for modifiable associated risk factors, the increased mortality in treated subjects persisted: RR, 1.52; 95% CI, 1.33–1.74 for cardiovascular mortality; and RR, 1.49; 95% CI, 1.19–1.86 for coronary mortality. Only after additional adjustment for SBP were cardiovascular mortality and coronary mortality similar in the two groups of subjects: RR, 1.06; 95% CI, 0.92–1.23; and RR, 1.06; 95% CI, 0.85–1.35, respectively.**

Conclusions **The increased cardiovascular mortality in treated hypertensive subjects as compared with untreated subjects is mainly due to high SBP levels under treatment. This result suggests that the excess risk found in treated hypertensives may be drastically reduced if SBP were brought under control.** ***J Hypertens*** **21:1–6 © 2003 Lippincott Williams & Wilkins.**

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Centre d'Investigations Préventives et Cliniques (IPC), Paris, France.

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Correspondence and requests for reprints to Athanase Benetos, MD, PhD, Centre d'Investigations Préventives et Cliniques, 6/14 rue La Pérouse, 75116 Paris, France.
Tel: +33 1 53 67 35 10; fax: +33 1 47 20 44 58; e-mail: benetos@ipc.asso.fr

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Introduction

Population studies have shown that treated hypertensive patients have an increased risk of cardiovascular complications compared with normotensive individuals [1,2]. There may be several reasons for this. One of these reasons may be uncontrolled blood pressure (BP) in most treated hypertensive subjects. Observational studies from several countries have demonstrated that among treated hypertensives, the proportion of those who are well controlled is less than 30% [3–6]. We recently showed that cardiovascular disease (CVD) mortality in poorly controlled treated hypertensive men [systolic blood pressure (SBP) $>$ 140 mmHg] was twice as high as in well-controlled treated hypertensive men [7]. Another reason for the high-risk profile in treated hypertensives as compared with the rest of the general population is that treated patients have a higher prevalence of modifiable associated risk factors such as dyslipidemia, diabetes, excess weight and other metabolic disturbances, and target organ damage even before starting therapy. Finally, this excess in CVD risk may be related to the presence of unmodifiable factors such as family and personal history of cardiac disease, which are also more frequent in treated hypertensive subjects.

The crucial question is whether the excess in CVD risk found in treated hypertensives can be prevented or whether it is inevitable due to the presence of unmodifiable risk factors. Determining the respective roles of these different risk factors on the excess CVD risk in treated hypertensives may answer this question.

The aims of the present study were to assess whether treated hypertensive subjects presented an excess of

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CVD mortality as compared with subjects without antihypertensive treatment (both normotensive and hypertensive), and to quantify the respective roles of BP levels, and of modifiable and unmodifiable risk factors in CVD mortality in treated hypertensives. The study sample consisted of 8893 treated hypertensive men and women from the Investigations Préventives et Cliniques (IPC) cohort, and 25 880 gender-matched and age-matched untreated subjects (including subjects with low and high BP levels) from the same cohort.

Methods

The IPC population

Subjects were examined at the IPC center (Centre d'Investigations Préventives et Cliniques). This medical center, which is subsidized by the French national health care system (Sécurité Sociale — Caisse Nationale d'Assurance Maladie), provides all working and retired persons and their families with a free medical examination every 5 years. It is one of the largest medical centers of this kind in France, having carried out approximately 20 000–25 000 examinations per year since 1970 for people living in the Paris area [7,8].

In the present analysis, we compared treated hypertensives with gender-matched and age-matched untreated normotensive and hypertensive subjects. Both groups were chosen from subjects who had had a health check-up at the IPC Center between 1978 and 1988. This population was composed of 221 814 subjects (12 513 men and 96 301 women). All treated hypertensive men ($n = 4712$) and women ($n = 4181$) were included. Each treated subject was matched with three untreated subjects of the same gender and age ($\pm$ 1 year). In a few cases, especially among the oldest subjects, only two control subjects instead of three were included due to an insufficient number of untreated subjects of the same age. Thus, the analysis included 13 982 untreated men and 11 898 untreated women.

For the entire study period, all subjects were examined with the same protocol and under the same conditions. All complementary examinations [electrocardiogram (ECG), biological tests, etc.] were realized at the IPC center the same day as the clinical check-up.

Supine BP was measured three times in the right arm, after a 10-min rest period, using a manual sphygmomanometer. The mean of the final two measurements was calculated. A self-administered questionnaire containing dichotomous (yes or no) questions regarding tobacco use (current consumption of more than 10 cigarettes/day) and physical activity ($\geq$ 2 h/week) was administered. Personal and family history of CVD were also assessed with a self-administered questionnaire. Diabetes was defined as personal history or treatment for diabetes.

All subjects fasted for at least 12 h before the examination. Blood was drawn before all other examinations. For all patients and for the entire period of 1978–1988, total cholesterol and triglycerides were measured in the laboratory at the IPC center, with a Technicon SMA 12 (Technicon, London, UK).

ECG measurements were also recorded. Left ventricular hypertrophy (LVH) was defined from the ECGs that all examined patients had (Sokolow index $>$ 35 mm).

The IPC center received approval from the national ethics committee (Comité National d'Informatique et des Libertés) to conduct these analyses. All subjects included in this study gave their informed consent at the time of the examination. Based on the national statistics on mortality, our cohort presented a 30% lower mortality rate than the general French population. This may be explained by the fact that people who come for a health check-up are generally healthy and motivated. Interestingly, when compared with the national data, the distribution of the different causes of mortality in our cohort was identical to that of the general population.

For all screened subjects, vital status was obtained for an 8–12 year period (mean 11.4 $\pm$ 0.4), which extended from the time of inclusion until the end of December 1997. These data were obtained from the mortality records at the Institut National de Statistiques et d'Etudes Economiques, following a previously established procedure [7,8]. To validate this procedure, we took a sample of 250 subjects and compared our data with those found at the city halls. An error was found in only two cases ($<$ 1%).

Causes of mortality, taken from death certificates, were provided by Institut National de la Santé et de la Recherche Médicale's Department of Mortality Studies (Unit SC 8). Causes of death were codified according to the *International Classification of Disease* (eighth revision until 1978 and ninth revision thereafter). Cardiovascular-related deaths were coded 390-459, and 798 (sudden death). The subgroup of coronary deaths was coded 410-414 and 798.

Data analysis

Differences in clinical characteristics and mortality rates between treated and untreated subjects were studied using either a Student *t* test or a chi-square test.

Survival curves for CVD and coronary heart disease (CHD) mortality were assessed in treated and untreated individuals and after classifying subjects according to their BP levels. Differences in survival probability were tested using a log-rank test.

Analyses were carried out to evaluate risk ratios (RR) and 95% confidence intervals (CIs) for CVD and CHD mortality in treated and untreated subjects using a Cox proportional hazard regression analysis. Four different models were used. In Model A, treated subjects were compared with age-matched and gender-matched untreated individuals. In Model B, we included unmodifiable variables (personal history of heart attack or heart failure, family history of hypertension or sudden death before the age of 60). In Model C, target organ damage and 'potentially' modifiable risk factors (total cholesterol, tobacco, diabetes, LVH, physical exercise, triglycerides, expiratory volume ratio, heart rate, serum creatinine) were added. In Model D, additional adjustment for BP levels [SBP, diastolic blood pressure (DBP) or pulse pressure (PP) alone, and SBP and DBP together] were included.

P values less than 5% were considered as significant.

All statistical analyses were carried out using the SAS statistical software package.

Results

BP levels and presence of risk factors in treated and untreated subjects

Treated subjects, as compared with age-matched and gender-matched untreated subjects, had significantly higher mean values of SBP, DBP and PP, and a higher incidence of diabetes and tachycardia, but they had a lower percentage of tobacco consumption (Table 1). They also had an increased prevalence of LVH (detected by ECG), higher serum creatinine, higher serum triglyceride levels and an increased prevalence of personal history of heart attack. Finally, treated hypertensives had a higher prevalence of family history of hypertension, diabetes mellitus and sudden death.

CVD mortality in treated versus untreated subjects: the role of associated risk factors

During the follow-up period, 837 treated hypertensives and 1480 untreated subjects died (Table 1). Figure 1 shows lower survival curves for CVD and CHD mortality in treated hypertensive subjects as compared with untreated subjects ($P < 0.001$). The differences in CVD and CHD survival curves between the two groups became more accentuated as follow-up increased.

Figure 2 shows lower survival curves for CVD and CHD mortality after classifying treated and untreated subjects in groups according to BP levels (normal versus high). As expected, patients with high BP levels had higher CVD ($P < 0.0001$) and CHD ($P < 0.0001$) mortality as compared with those with low BP levels, independent of the presence or absence of antihypertensive treatment. Among those with normal BP levels, CVD mortality was slightly higher in treated subjects ($P = 0.03$) whereas CHD mortality did not differ ($P = 0.68$). In the groups with high BP levels, those under treatment were at higher risk of CVD ($P < 0.001$) and CHD ($P < 0.001$) mortality as compared with untreated subjects with high BP levels. It is important to note that in the groups of high BP, treated subjects as compared with untreated hypertensive subjects had more elevated SBP (157 ± 16 mmHg versus 150 ± 12 mmHg, $P < 0.001$), DBP (96 ± 10 mmHg versus 91 ± 9 mmHg, $P < 0.01$) and PP (61 ± 12 mmHg versus 59 ± 10 mmHg, $P < 0.05$) levels.

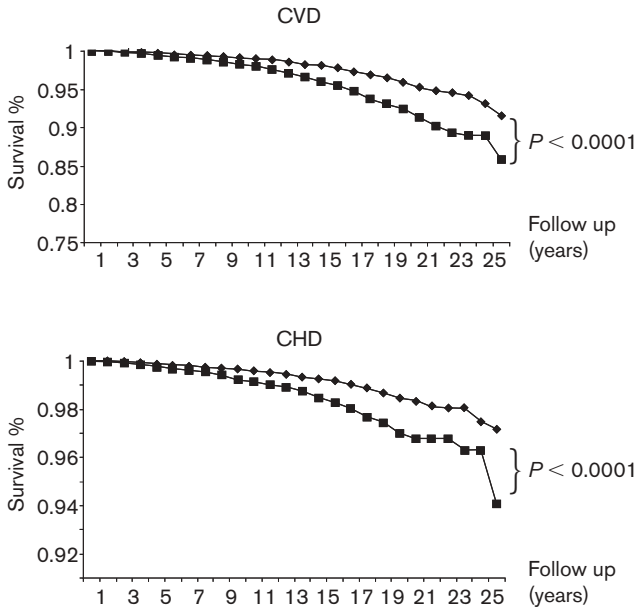
The Cox regression analysis showed that treated hyper-

Table 1 Mean values (± standard deviation) in untreated and treated hypertensive subjects

	Untreated	Treated	*P*
Number (% men)	25 883 (54%)	8898 (53%)	
Cardiovascular disease mortality rates[a]	18.2 (658)	34.4 (428)	0.001
Coronary heart disease mortality rates[b]	6.6 (240)	12.6 (157)	0.001
Age (years)	52.2 ± 10.4	52.5 ± 15.1	Not significant
Height (cm)	166 ± 9.23	165.2 ± 9.2	Not significant
Weight (kg)	67.8 ± 12.6	71.8 ± 13.9	0.001
Systolic blood pressure (mmHg)	136 ± 16.0	151.1 ± 18.8	0.001
Diastolic blood pressure (mmHg)	83.4 ± 10.5	92.6 ± 11.7	0.001
PP (mmHg)	52.3 ± 10.1	58.5 ± 12.4	0.001
Total cholesterol (g/l)	229 ± 42	233 ± 43	Not significant
Left ventricular hypertrophy (%)[c]	1.5	3.3	0.001
Triglycerides (mg/l)	110 ± 76.5	130 ± 90.5	0.001
Serum creatinine (mg/l)	9.7 ± 1.7	10.0 ± 2.1	0.001
Heart rate > 80 beats/min (%)	18.6	21.2	0.001
Current smokers (%)	20.6	17.6	0.001
Diabetes (%)[d]	7.7	13.3	0.001
Physical exercise (%)	25.6	17.1	0.001
History of cardiovascular disease (%)	4.4	9.3	0.001
Family history of cardiovascular disease (%)	24.6	30.6	0.001

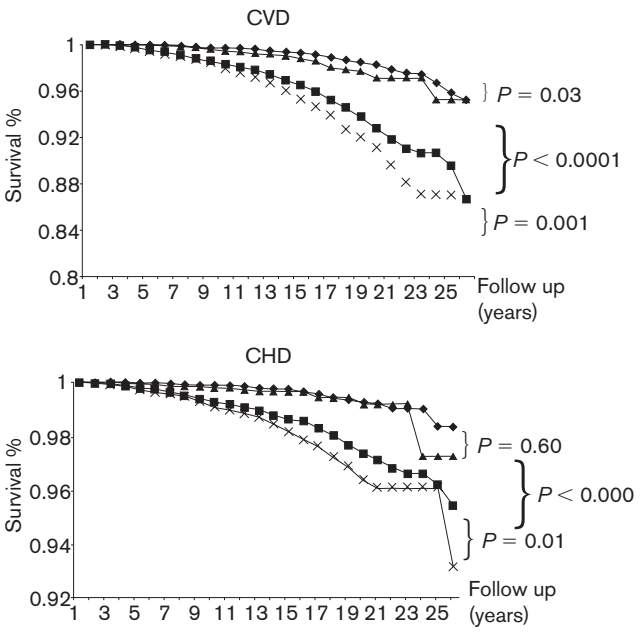
[a]Cardiovascular deaths per 10,000 patient-years. [b]Coronary deaths per 10 000 patient-years; absolute number of deaths are indicated in parentheses. [c]Left ventricular hypertrophy was evaluated with electrocardiogram. [d]Personal history of diabetes reported by the patient. PP, pulse pressure.

Fig. 1



Survival curves for cardiovascular disease (CVD) mortality (upper panel) and coronary heart disease (CHD) mortality (lower panel) in treated (■) versus untreated subjects (◆). The log-rank test showed that for both CVD and CHD mortalities, the difference was statistically significant ($P < 0.001$).

Fig. 2



Survival curves for cardiovascular disease (CVD) (upper panel) and coronary heart disease (CHD) (lower panel) mortality after classifying treated and untreated subjects in groups according to blood pressure (BP) levels (normal versus high). (◆) Untreated, BP < 140/90 mmHg; (■) untreated, BP ⩾ 140/90 mmHg; (▲) treated, BP < 140/90 mmHg; (×) treated, BP ⩾ 140/90 mmHg. CVD mortality and CHD mortality were higher in groups with BP ⩾ 140/90 mmHg independently of the presence or absence of treatment ($P < 0.001$).

tensive subjects had an almost two-fold increase in CVD and CHD mortality compared with age-matched untreated subjects (Fig. 3, model A). Differences in CVD mortality remained the same even after excluding subjects who had died during the first 2 years of follow-up (data not shown).

Adjustment for unmodifiable risk factors (personal and family history of CVD disease) decreased the excess risk of CVD and CHD mortality in treated hypertensive subjects, but mortality was still approximately 75% greater as compared with the untreated subjects (Fig. 3, Model B). After additional adjustment for total cholesterol, tobacco smoking, diabetes, LVH, physical activity, triglycerides, expiratory volume capacity, heart rate and serum creatinine, treated hypertensive subjects still had an excess in CVD and CHD mortality of about 50% ($P < 0.001$) (Fig. 3, Model C).

Subsequently, we evaluated the possible contribution of BP levels to the increase in CVD and CHD mortality in treated hypertensives. Adding SBP to Model C canceled the difference in CVD mortality and CHD mortality between treated and untreated subjects (Fig. 3, Model D). Interestingly, when both SBP and DBP were introduced into the model they were both significant determinants of CVD mortality, but SBP was positively correlated (RR for 10 mmHg, 1.37; 95% CI, 1.31–1.43) and DBP was negatively correlated (RR for 10 mmHg, 0.84; 95% CI, 0.78–0.91). SBP was also positively correlated with CHD mortality (RR for 10 mmHg, 1.27; 95% CI, 1.16–1.37) whereas DBP was not (RR for 10 mmHg DBP, 1.01; 95% CI, 0.88–1.16). When PP, instead of SBP, was added to Model C, the difference between treated and untreated subjects was also non-significant (CVD: RR, 1.10; 95% CI, 0.88–1.33; and CHD: RR, 1.08; 95% CI, 0.85–1.32).

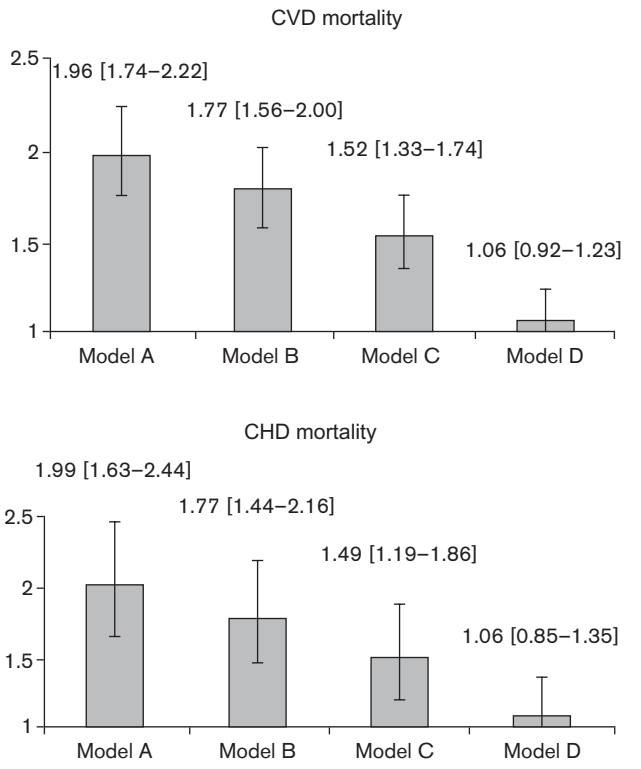
We also did a Cox regression analysis by first adjusting for SBP. Following this adjustment the difference between treated and untreated subjects decreased from 96% to 14% for CVD mortality ($P = 0.05$), and from 99% to 16% ($P = 0.08$) for CHD mortality (Table 2). Adding DBP to the model did not modify these numbers. After supplementary adjustments for associated risk factors, the difference in CVD and CHD risk between the two populations disappeared.

Similar results were found when men and women were studied separately (data not shown).

Discussion

This study shows that 'everyday' treated hypertensive subjects have a two-fold increase in total cardiovascular mortality as compared with untreated age-matched and

Fig. 3



Risk ratios (RR) (95% confidence intervals) for cardiovascular disease (CVD) mortality (upper panel) and coronary heart disease (CHD) mortality (lower panel) in treated versus untreated subjects. Model A, unadjusted RR, treated versus age-matched and gender-matched untreated subjects. Model B, adjusted for unmodifiable CVD risk factors (personal history of heart attack and heart failure, family history of hypertension, and sudden death before the age of 60). Model C, includes Model B plus modifiable CVD risk factors (total cholesterol, tobacco consumption, diabetes, left ventricular hypertrophy, physical exercise, triglycerides, expiratory volume ratio, heart rate, serum creatinine). Model D, includes Model C, plus adjustment for systolic blood pressure.

gender-matched subjects. There are at least three possible reasons for the increased mortality in treated hypertensives as compared with the general population: (1) an elevated prevalence of unmodifiable CVD risk factors (personal and family history of CVD); (2) a higher prevalence of modifiable CVD risk factors; and (3) elevated levels of BP in treated subjects as compared with in the rest of the study population.

The present study shows that uncontrolled BP levels, which is the case for the large majority of treated hypertensives, is the major determinant in increased mortality among these subjects, as compared with a general population. In this study, the predominant role of BP has been demonstrated by using different analyses. Survival curves (Fig. 2) showed that control of BP was the main determinant of CVD and CHD mortality. The multivariate analysis presented in Figure 3 showed that SBP was the most significant determinant of the excess in cardiovascular deaths. The contribution of SBP seems to be even greater when this variable was introduced first in the multivariate analysis, as presented in Table 2. This difference can most probably be explained by the fact that SBP levels are correlated with most of the associated risk factors, and therefore multivariate analyses cannot quantify the exact impact of each variable. Taken together these results confirm a major role of SBP levels in the excess risk observed in treated hypertensive individuals.

The role of associated modifiable and unmodifiable risk factors in determining cardiovascular risk in hypertensives has been pointed out in several studies and in international guidelines [9–11]. In a recent analysis of the Hypertension Optimal Treatment study, the authors concluded that each of the associated risk factors was found to significantly increase residual risk in patients with a good BP control [12].

The fact that our study shows that the main determinant of increased CVD risk was high BP is not in opposition to the earlier results. Actually, as shown in our analyses, a significant part of the excess of the CVD risk in treated hypertensives was related to a higher prevalence of associated risk factors. The relatively modest contribution of the modifiable risk factors can be explained by the fact that the levels of some of these factors in treated hypertensives were similar (e.g. total cholesterol) or even lower (tobacco smoking) than in untreated subjects. The most striking difference between the two populations was the higher BP levels in treated subjects. In the present study, the majority of treated hypertensives had high BP levels, confirming previous reported results of insufficient BP control with treatment [3–6]. More than 50% of the excess in CVD mortality may be explained almost entirely by the presence of high SBP levels, observed in treated hypertensives (plus 15 mmHg as compared with untreated

Table 2 Risk ratios (95% confidence intervals) for cardiovascular disease mortality and coronary heart disease mortality in treated subjects as compared with untreated subjects

	Cardiovascular disease	Coronary heart disease
Model 1, unadjusted risk ratios	1.96 (1.74–2.22)	1.99 (1.63–2.44)
Model 2, adjusted for systolic blood pressure	1.14 (0.99–1.30)	1.16 (0.94–1.44)
Model 3, adjusted for systolic and diastolic blood pressures	1.17 (1.03–1.34)	1.17 (0.94–1.45)
Model 4, Model 3 + risk factors	1.06 (0.92–1.23)	1.06 (0.85–1.35)

subjects). Interestingly, when SBP and DBP were simultaneously introduced in the analyses, the latter either had no significant value or it was negative, corroborating previously reported results [13].

Limitations of the present analysis

One of the limitations of this analysis is that a number of untreated subjects included in this study, especially among those with high BP values, may have received treatment later on, just as a number of treated subjects may have stopped their treatment. This dilution phenomenon, which is very common in such observational studies [14], can only underestimate the differences between treated and untreated subjects.

It may also be that single BP measurements exaggerate BP values and overestimate the percentage of uncontrolled treated subjects and the prevalence of hypertensives among untreated subjects. However, this study clearly shows that, under these circumstances, which are the same as those faced by physicians in their everyday clinical practice, SBP and PP values are strong indicators of subsequent CVD mortality in both treated and untreated subjects.

Finally, the fact that treated hypertensive subjects have increased CVD mortality does not contest the possible beneficial effects of antihypertensive treatment in reducing CVD morbidity and mortality as shown in a large number of controlled studies. Treated subjects had higher BP levels and a higher prevalence of target organ damage before starting drug therapy. It is therefore possible that the same subjects would have higher mortality rates if they remained untreated and that a partial reduction in BP levels, as observed in this study, could have some beneficial effects on a patient's prognosis.

Clinical implications and conclusions

In a recent study [7] we reported that, among treated hypertensive men, high levels of SBP were an important determinant of CVD mortality. The present report provides additional information by comparing CVD mortality in treated hypertensive men and women with both untreated hypertensive and normotensive men and women. The main contribution of our study is to show that the excess risk in CVD mortality in treated hypertensives is mainly related to the presence of high SBP. Therefore, CVD excess may be drastically reduced with more effective treatment, which would mean better control of SBP levels.

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