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Risk profiles and prognosis of treated and untreated hypertensive men and women in a population-based longitudinal study *The Reykjavik Study*

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The aim was to examine the risk profiles and prognosis of treated and untreated hypertensive subjects and examine to what degree confounding by indication was present in a population-based cohort study with up to 30-year follow-up. The study population consisted of 9328 men and 10 062 women, aged 33–87 years at the time of attendance from 1967 to 1996. The main outcome measures were myocardial infarction (MI), cardiovascular disease (CVD) mortality and all-cause mortality. Comparing the risk profiles between treated and untreated subjects entering the study showed significantly higher values for some risk factors for treated subjects. During the first 10 years, hypertensive men without treatment, compared with those treated, had a significantly lower risk of suffering MI, CVD and all-cause mortality, hazard ratio (HR) 0.72 (95% CI; 0.57, 0.90), 0.75 (95% CI; 0.59, 0.95) and 0.81 (95% CI; 0.61, 0.98), respectively. No significant differences in outcome were seen during the following 20 years. In identically defined groups of women, no significant differences in mortality were seen between groups. Subgroup analysis, at two stages of the study 5 years apart, revealed that some cardiovascular risk factors had a higher prevalence in hypertensive men who were treated at the later stage, compared with those who remained untreated ($P = 0.004$). In conclusion, hypertensive treated men had a worse prognosis during the first 10 years of follow-up than untreated ones, which is most likely due to worse baseline risk profile. Hypertensive men that were treated at a later stage had a worse risk profile than those not treated at a later stage.

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Introduction

Hypertension is a serious risk factor for many common causes of morbidity and mortality, including stroke, myocardial infarction (MI), congestive heart failure and end-stage renal disease.[1–3] This disorder affects about a quarter of the adult population in industrialized societies.[4,5] Several clinical trials have confirmed the benefit of treatment in preventing cardiovascular morbidity and mortality, particularly stroke and coronary artery disease.[6,7] Other trials have not shown benefit from treatment of coronary artery disease and all-cause mortality.[8,9] Most clinical trials have been carried out on selected groups of patients and individuals, where the highest-risk individuals are usually excluded.[10–12] Thus, the documented effects of treatment in a trial may have less general validity than is often assumed.[12] Therefore, epidemiological studies are important in considering the effect of treatment in the community. Only a few epidemiological studies have been carried out, where the aim was to assess the possible benefits of long-term treatment (>5 years) of hypertension.[12–14]

An inherent problem in comparing the outcome of nonrandomized treatment groups, such as treated and untreated hypertensives, in an epidemiological setting is the complexity of the treatment indication that may be affected by associated risk factors. The prognosis of the treated patients may be different from that in the untreated subjects. The indication

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for drug use may confound comparison so that it looks as if the treatment induces the disease rather than curing it. One term suggested for this biased observation is confounding by indication.[15–17] The objectives of the present study were to examine thoroughly the risk profiles and prognosis of treated and untreated hypertensive men and women and to examine the effects of antihypertensive treatment in the community. The aims were also to compare the risk score of hypertensive subjects before they were treated, in those who were treated later *vs* those who remained untreated, in order to examine to what degree confounding by indication was present.

Methods

The Reykjavik Study, initiated in 1967, is a prospective, population-based study that includes participants from Iceland's capital city, Reykjavik, and adjacent communities. In 1968, the population of the area was around 104 000, close to half the total population of Iceland at that time. The study cohort (30 795 participants, 14 923 men and 15 872 women) was selected from the National Roster, a computerized, continuously updated population register established in 1953, based on a compulsory, lifetime personal identification number. The cohort was divided into six comparable groups and examined in six successive stages between 1967 and 1996. The design of the study and invitation to participate has previously been described in detail.[18,19] Some of the groups were invited to attend more than once. The men attended 18 495 times and women 18 281 times, a response rate of 70.9% for men and 70.1% for women.[18,19] Loss to follow-up during the whole study was $<0.5\%$.[19] Every participant received an invitation letter that included standardized questions about health and social factors, including the Rose chest pain questionnaire.[20] The participants in the present study are the men (2792) and women (2642) that fulfilled the set criteria from all stages of the Reykjavik Study.

Examinations

Participants came in a fasting state to the clinic. After 5 min rest, the supine blood pressure was measured, on two occasions, between 0830 and 1030 hours, by a nurse, and 10–14 days later between 1100 and 1330 hours, by a physician. The subjects were not instructed to be fasting at the second blood pressure measurement. The instruments used were mercury sphygmomanometers of the type 'Erkameter' wall-model (Erka, Germany). The cuffs had a rubber bladder 15 cm × 32 cm, and the total length of the cuff was 66 cm. The same types of cuffs and instruments were used throughout the study. The procedure followed in measuring blood pressure was according to WHO recommendations.[21] The diagnosis of hypertension was based on the mean of two measurements: systolic blood pressure $\geqslant 160$ mmHg and/or diastolic blood pressure $\geqslant 95$ mmHg. Subjects on antihypertensive medication were considered to be hypertensive.

A standardized 12-lead resting electrocardiogram was recorded and read according to the Minnesota code.[22] Subjects were classified as having suffered a definite symptomatic MI if hospital records fulfilled the MONICA criteria for definite MI.[23] If the subject's electrocardiograph (ECG) fulfilled the criteria for definite MI (Minnesota codes 1:1: 1-1:3:6, 4:1-4:4, 5:1-5:4), but there was no history or symptoms of heart attack, the participant was classified as having had an unrecognized or silent MI.[18] From the outset of the study, the same personnel have delivered the examining questionnaires, and the same physician (NS) has read and coded the ECGs. Quality control of the ECG coding has been through the World Health Organization Reference Centre for ECG coding at the Hungarian Institute of Cardiology in Budapest. Blood chemistry, fasting blood glucose from a capillary blood sample and lipid profiles were measured using the standard techniques of each time period since 1967.[24,25]

Follow-up procedures

After entering the study, subjects were followed for up to 30 years (up to 1998) through the National Roster, using the International Classification of Diseases (ICD-9). The following endpoint categories were used in this study: fatal and nonfatal MI ICD-9: 410–414; total cardiovascular disease (CVD) mortality ICD-9: 390–459; and all-cause mortality ICD-9: 001–999.

Statistics

First, a composite risk score based on results from the first visit of all attendants (9328 men and 10 062 women) was computed for each gender and each of the following endpoints: fatal and nonfatal MI, total CVD and all-cause mortality. The composite risk between treated and untreated hypertensive subjects at first visit was compared. The composite risk scores were calculated by forming the sum of products of beta coefficients from Cox regression, using all measurements at first visit and each individual's values of the risk factors

$$\text{composite risk score} = \sum (\beta_i \text{Var}_i)$$

for each person, where the beta coefficient (β_i) is the natural logarithm of relative risk for variable i and Var_i is the value of variable number i for each person. The established risk factors used were calendar year, age, total cholesterol, fasting glucose, left ventricular hypertrophy, serum triglycerides, protein- or glucosuria, smoking and manifestations of previous coronary heart disease (known and

unrecognized infarct, angina and ST-T changes).[11,26] Blood pressure and its treatment were not included in the composite risk score, being the main variables under study. When the composite risk score for MI was calculated, subjects with previous MI were omitted. The survivor functions adjusted to mean values of composite risk score of each of the groups treated and not treated (for hypertension) were computed. This was done in order to evaluate the profile of risk from established risk factors for each group without regard to blood pressure and antihypertensive treatment.

Second, the hazard ratio (relative risk) was analysed for three endpoints: MI (fatal and nonfatal), total CVD mortality and all-cause mortality. Ordinary Cox regression[27] was applied except when the risk period was bisected, and then time-dependent Cox regression was used, adjusted for composite risk score. Two hypertensive groups were compared: hypertensive subjects who were not treated and hypertensive subjects who were treated. The composite risk score was included in the regression for adjustment. The risk period of 30 years was divided into two intervals, 0–10 years and 11–30 years, in order to analyse changes in hazard ratio due to regression dilution bias.[28]

Third, a subgroup analysis was performed for hypertensive men and women who later were treated *vs* those who remained untreated. This was carried out to compare the risk profile between two groups before they were treated with antihypertensive medication.

Subjects used in the analysis attended the study twice, were hypertensive on both visits, untreated on the first visit, and either treated or not treated on the second visit. In this analysis only stages II–III of the Reykjavik Study were used, 1970–1975 for men and 1971–1976 for women. The average time between the stages was 5 years (range 3–6.4 years) for men and 6 years (range 4–7.7 years) for women. Subjects present at both stages II and III were included. CVD risk factors of both subgroups were compared at stage II when neither group was receiving treatment. The CVD composite risk score and a survivor function were calculated for the subgroups. The software package used was SPIDA.[29]

Results

The analysis included 2792 hypertensive men, or 29.9% of male attendants, and 2642 hypertensive women, or 26.3% of female attendants, all diagnosed on their first visit to the clinic. The number of endpoints reached for men was about twice the number for women during follow-up (Table 1).

Risk profiles of treated *vs* untreated hypertensives

When comparing characteristics at the first examination, distinct differences were found between hypertensive subjects without treatment and those who were treated. A similar pattern for men and women was seen (Table 2). Subjects who were hypertensive and treated at the first examination entered the study later than those who were hypertensive and untreated. The average age was significantly higher for the treated men and women than for hypertensive subjects without treatment. After adjusting for age and the year of entry into study, systolic/diastolic blood pressure was significantly lower ($P<0.0001$) at the first visit for treated men and women than for the group not treated. After adjusting for age and the year of entry into study, previous MI was more prevalent among the hypertensive men (7.7%) and women (2.4%) who were treated than for the groups not treated (5.1% for men and 1.2% for women; $P=0.011$ and 0.022, respectively). The difference in composite risk between treated and untreated subjects entering the study was significantly in favour of those untreated (Table 3), mostly due to a higher prevalence of

Table 1 Number of subjects and endpoints in the Reykjavik Study 1967–1998

	Number of subjects	*(%)*	*Number of endpoints*					
			Fatal and nonfatal MI	*(%)*	*CVD mortality*	*(%)*	*All-cause mortality*	*(%)*
Men	9328							
Hypertensive	2792	(29.9)[a]						
treated	692	(24.8)[b]	222	(32.1)	211	(30.5)	355	(51.3)
not treated	2100	(75.2)	630	(30.0)	635	(30.2)	1086	(51.7)
Women	10062							
Hypertensive	2642	(26.3)[a]						
treated	1196	(45.3)[b]	184	(15.4)	199	(16.6)	381	(31.9)
not treated	1446	(54.7)	227	(15.7)	250	(17.3)	544	(37.6)

MI = myocardial infarction; CVD = cardiovascular disease.
[a]29.9% of the men were hypertensive *vs* 26.3% of the women; the difference was significant, $P<0.001$.
[b]24.8% of the hypertensive men were treated *vs* 45.3% of the women, the difference was significant, $P<0.001$.
Mean follow-up time for fatal and nonfatal MI was 18.7 years for men and 19.2 years for women.
Mean follow-up time for CVD and all-cause mortality was 19.7 years for men and 19.6 years for women.

Table 2 Characteristics at first examination of hypertensive men and women

	Hypertensive men				*Hypertensive women*			
	treated		*not treated*		*treated*		*not treated*	
Characteristics	*Mean*	*(s.d.)*	*Mean*	*(s.d.)*	*Mean*	*(s.d.)*	*Mean*	*(s.d.)*
Number of subjects	692		2100		1196		1446	
Year entering study	1980	(6.9)	1974	(5.7)	1982	(7.6)	1975	(7.3)
Age (years)	59.8	(9.5)	53.9	(9.0)	61.6	(10.1)	56.2	(9.5)
Total cholesterol (mmol/l)	6.3	(1.1)	6.5	(1.1)	6.9	(1.2)	7.0	(1.3)
Triglycerides (mmol/l)	1.6	(1.1)	1.4	(0.8)	1.4	(0.8)	1.1	(0.5)
Fasting glucose (mmol/l)	4.8	(1.1)	4.8	(1.0)	4.7	(1.2)	4.5	(0.8)
BMI (kg/m^2)	27.6	(3.8)	26.9	(3.7)	28.6	(5.2)	26.4	(4.7)
Systolic blood pressure (mmHg)	157.1	(22.4)	161.6	(16.6)	155.3	(22.5)	166.3	(16.3)
Diastolic blood pressure (mmHg)	95.8	(11.7)	100.2	(8.6)	89.6	(11.3)	97.4	(8.9)
	%	Cases	%	Cases	%	Cases	%	Cases
Protein- or glucosuria	10.0	(69)	3.5	(73)	2.6	(31)	2.3	(33)
Left ventricle hypertrophy	6.5	(45)	5.4	(114)	1.4	(17)	1.4	(20)
Previous MI	7.4	(51)	2.6	(55)	2.5	(30)	0.6	(9)
Previous unrecognized infarction	1.3	(9)	0.6	(12)	1.3	(15)	0.7	(10)
Angina	5.2	(36)	2.3	(49)	5.3	(63)	3.7	(54)
ST-T changes	16.0	(111)	9.4	(197)	12.8	(153)	12.2	(176)
Current smokers	35.8	(248)	48.7	(1022)	25.9	(309)	31.6	(457)
Former smokers	40.2	(278)	27.6	(580)	19.9	(238)	15.8	(228)

Table 3 Risk profile and predicted 10-year survival of treated and untreated hypertensive men and women without regard to blood pressure and antihypertensive treatment

	Men			*Women*		
	MI	*CVD*	*All-cause*	*MI*	*CVD*	*All-cause*
Composite risk score[a] *for*						
hypertensive[b] treated	5.49	5.49	5.09	7.74	7.48	5.29
hypertensive not treated	5.06	4.91	4.55	7.21	6.85	4.80
Difference	0.44	0.58	0.53	0.53	0.62	0.49
P-value[c]	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Predicted 10-year survival[d] *for*						
hypertensive treated (%)	84.2	88.1	82.1	93.7	94.6	89.6
hypertensive not treated (%)	88.9	92.3	88.4	95.8	96.7	93.0
Difference (%)	−4.7	−4.2	−6.3	−2.1	−2.1	−3.4

[a]Composite risk score at baseline was comprised of risk factors significantly predictive in the Cox model for all-cause mortality, CVD mortality and MI. The risk factors used were year of entry into study, age, total cholesterol, fasting glucose, left ventricular hypertrophy, serum triglycerides, protein- or glucosuria, smoking, known infarct, silent infarct, angina and ST-T changes. Known and silent infarct were not included in composite risk score for MI.
[b]Hypertension was defined at first visit as systolic blood pressure (BP) $\geqslant$ 160 mmHg and/or diastolic BP $\geqslant$ 95 mmHg.
[c]*P*-values are from the *t*-test.
[d]Predicted 10-year survival is taken from a calculated survivor function (which is adjusted for the mean values of the baseline composite risk scores). This was done in order to evaluate the profile of risk from established risk factors for each group without regard to blood pressure and antihypertensive treatment.
MI = myocardial infarction, fatal and nonfatal; CVD = cardiovascular disease mortality; All-cause = all-cause mortality.

established coronary heart disease among the treated, compared with those not treated.

Hazard for treated *vs* untreated hypertensives

During the first 10 years, hypertensive men without treatment, compared with those treated, had a significantly lower risk of suffering an MI, a lower risk of CVD mortality and a lower risk of all-cause mortality (Table 4), even when a composite risk score was taken into account. During the period of 11–30 years, the risk was between 0.89 and 1.09 (Table 4). The risk over the first 10 years of cardiovascular mortality and all-cause mortality was close to one for women, but the risk of suffering MI was 0.81 for hypertensive women without treatment, compared with those treated. The risk

Table 4 Hazard ratio (HR) for hypertensive[a] men, not treated (2100) *vs* treated (692), and hypertensive women, not treated (1446) vs treated (1196), using Cox regression, adjusting for composite risk score[b], the Reykjavik Study, 1967–1998

		Men		*Women*	
Endpoints	*Follow-up years*	*HR[c] (RR)*	*95% CI[d]*	*HR[c] (RR)*	*95% CI[d]*
All-cause mortality	0–10	0.81	(0.66, 0.98)	0.92	(0.72, 1.17)
	11–30	0.89	(0.74, 1.07)	0.95	(0.78, 1.15)
	0–30	0.85	(0.74, 0.97)	0.93	(0.80, 1.09)
CVD mortality	0–10	0.75	(0.59, 0.95)	0.96	(0.70, 1.32)
	11–30	0.96	(0.76, 1.22)	0.81	(0.62, 1.06)
	0–30	0.85	(0.72, 1.01)	0.87	(0.71, 1.07)
MI (fatal and nonfatal)	0–10	0.72	(0.57, 0.90)	0.81	(0.58, 1.12)
	11–30	1.09	(0.82, 1.43)	0.91	(0.68, 1.21)
	0–30	0.86	(0.72, 1.02)	0.86	(0.69, 1.07)

[a]Hypertension was defined at first visit as systolic blood pressure (BP) $\geqslant$ 160 mmHg and/or diastolic BP $\geqslant$ 95 mmHg.
[b]Composite risk score was comprised of risk factors significantly predictive in the Cox model for all-cause mortality, CVD mortality and MI. The risk factors used were year of entry into study, age, total cholesterol, fasting glucose, left ventricular hypertrophy, serum triglycerides, protein- or glucosuria, smoking, known infarct, silent infarct, angina and ST-T changes. Subjects with a history of known or silent MI were not included in composite risk score for MI.
[c]HR, which is equivalent to relative risk (RR), was calculated using Cox regression, with the hypertensive treated controlled group as a reference category. The time periods used were 0–10, 11–30 and 0–30 years of follow-up.
[d]CI denotes confidence interval.

over the 11- to 30-year period for hypertensive women without treatment, compared with those treated, of MI, CVD mortality and all-cause mortality was not significantly different from 1.

Risk profiles of hypertensive men and women who were later treated *vs* those who were not later treated

The risk profile for the two groups was examined at first attendance for men and women (Table 5). The average age for hypertensive men who were treated later was 50.5 years and 52.3 years for hypertensive men who were not treated later ($P = 0.005$). The average age for women in the two groups was identical, 51.3 years. There was no difference in examination year between the two groups for men and women, respectively. As can be seen in Table 5, hypertensive men and women who were treated later had significantly higher systolic/diastolic blood pressure, a difference of 15.3/6.5 mm Hg and 9.4/5.5 mmHg, respectively, compared with hypertensive men and women who were not treated later. Hypertensive women who were treated later had significantly fewer cases of angina at first visit than hypertensive men and women who were not treated later. Hypertensive men who were treated later had a higher prevalence of ST-T changes and protein and/or glucosuria than hypertensive men who were not treated later. The difference in frequency of ST-T changes and protein- or glucosuria was not significant between hypertensive women who were treated later and hypertensive women who were not treated later. The composite risk score for CVD mortality was significantly higher for the hypertensive men who were treated later than for those who were not treated later, a difference of 0.33 ($P = 0.004$). For women the difference was −0.059 and not significant ($P = 0.73$).

Discussion

In this longitudinal study we found that during the first years of follow-up, hypertensive men who were not treated were at significantly lower risk of coronary heart disease than hypertensive, treated men. This was not seen for women. When entering the study, the risk profiles for hypertensive men and women on treatment were significantly worse than for hypertensive men and women who were not treated. Subgroup analysis showed higher blood pressure and a higher level of some cardiovascular risk factors in hypertensive men who were treated later, compared with hypertensive men who were not treated later. The decision to treat seems to have been affected by the baseline risk profile, that is there was confounding by indication.

The results from the whole follow-up might suggest that antihypertensive treatment was not beneficial, or that there was confounding by indication in the study. During the first years of follow-up, hypertensive men who were not treated were significantly less likely than treated men to suffer fatal or nonfatal MI, and had lower CVD mortality and all-cause mortality. When looking at the risk within 2-year periods during the first 10 years for men (data not shown), the risk of MI, CVD mortality

Table 5 The subgroups 'hypertensive later treated' were hypertensive subjects without treatment at first attendance in the study and treated for hypertension at a second attendance (about 5 years later). The subgroups 'hypertensive later not treated' were hypertensive subjects without treatment at first and second attendance

	Hypertensive men					*Hypertensive women*				
	treated later		*not treated later*			*treated later*		*not treated later*		
Characteristics	*Mean*	*(SEM)*	*Mean*	*(SEM)*	P-*value*	*Mean*	*(SEM)*	*Mean*	*(SEM)*	P-*value*
Number of subjects	136		442			86		83		
Year entering study	1971	(0.02)	1971	(0.04)	0.83	1973	(0.05)	1973	(0.05)	0.54
Age (years)	50.5	(0.31)	52.3	(0.54)	0.005	51.3	(0.72)	51.3	(0.62)	1.0
Total cholesterol (mmol/l)	6.42	(0.08)	6.57	(0.05)	0.13	6.86	(0.13)	6.86	(0.99)	0.99
Triglycerides (mmol/l)	1.33	(0.06)	1.43	(0.04)	0.05	1.08	(0.05)	1.11	(0.05)	0.98
Fasting glucose (mmol/l)	4.90	(0.11)	4.66	(0.04)	0.05	4.51	(0.10)	4.40	(0.06)	0.36
Systolic blood pressure (mmHg)	177.6	(1.66)	162.3	(0.71)	0.0001	176.7	(1.96)	167.3	(1.54)	0.0002
Diastolic blood pressure (mmHg)	107.8	(0.91)	101.3	(0.36)	0.0001	103.5	(0.93)	98.0	(0.88)	0.0001
	%	*Cases*	*%*	*Cases*	*P-value*	*%*	*Cases*	*%*	*Cases*	*P-value*
Protein and/or glucosuria	8.1	(11)	2.0	(9)	0.002	2.4	(2)	2.5	(2)	0.65
Left ventricle hypertrophy	6.6	(9)	5.0	(22)	0.60	1.2	(1)	1.2	(1)	0.76
Previous MI	2.2	(3)	0.7	(3)	0.29	0.0	(0)	0.0	(0)	
Previous unrecognized infarction	0.0	(0)	0.2	(1)	1.0	1.2	(1)	0.0	(0)	1.0
Angina	0.7	(1)	2.3	(10)	0.43	0.0	(0)	9.6	(8)	0.01
ST-T changes	17.7	(24)	5.0	(22)	0.0007	11.6	(10)	10.8	(9)	0.93
Current smokers	41.1	(56)	46.6	(206)		22.1	(19)	25.3	(21)	
Former smokers	36.0	(49)	27.4	(121)	0.15[a]	16.3	(14)	21.1	(17)	0.61[a]
				(SEM)	*P*-value				*(SEM)*	*P*-value
Difference in composite risk score for CVD mortality[b]			0.33	(0.12)	0.004			−0.06	(0.33)	0.73
Difference in predicted 10-year survival[c] (%)			1.4					−0.2		

[a]*P* for trend.
[b]Difference in composite risk score: hypertensive later treated − hypertensive later not treated (same method used as in Table 3).
[c]Difference in predicted 10-year survival taken from a calculated survivor function: hypertensive later treated − hypertensive later not treated (same method used as in Table 3).
P-values from *t*-test, χ^2 and Fisher's exact test as appropriate.

and all-cause mortality for the treated men started off significantly higher and then gradually reached that of the untreated ones. This was not seen for women. A possible explanation is that there were fewer endpoints among hypertensive women than men. This gave wider confidence intervals for the hazard ratios, especially for the first 10 years of follow-up, and made interpretation of results for the women less reliable. If we assume that worse prognosis during the first 10 years for the treated men were due to worse baseline risk profile (confounding by indication), then the results for 11–30 years, which show no significant difference in relative risk between treated and untreated men, may either indicate a late benefit of treatment for the men or it could be a weakening of the effect of difference in baseline risk profile over time.

When subjects entered the study, various risk factors for CVD mortality were more severe among hypertensive treated men and women than among hypertensive men and women that were not treated, including previous MI, previously unrecognized infarction and angina. Also, when entering the study, the composite risk score for all three endpoints was significantly higher for treated subjects. This consistent difference in composite risk score strongly suggests confounding by indication. Patients with more ominous risk profiles were more likely to be treated with antihypertensive drugs, regardless of differences in blood pressure values. This kind of prescription habit has been recommended in both European and American guidelines of antihypertensive treatment, since the objective of antihypertensive treatment is to lower overall risk.[30]

Confounding by indication was further shown in the subgroup analysis for men, but apart from higher blood pressure, this was not found in women. For example, we could not adjust for the pretreatment blood pressure values, which were considerably higher in hypertensive men and women who were treated later than in hypertensive subjects who were not treated later, as was shown in the subgroup analysis.

The subgroup analysis also showed a higher level of some cardiovascular risk factors (ST-T changes, protein or glucose in urine) in hypertensive men who were treated later than in those who were not treated later, resulting in significantly higher cardiovascular disease risk scores in those who were treated later. On the other hand, angina was significantly more prevalent among hypertensive women who were not treated later. This was not the case when comparing treated and untreated subjects upon entry to the study, which showed a higher prevalence of angina among treated subjects than among untreated ones. There is no obvious explanation for this finding, but the number of endpoints was small.

This is an observational study where treatment is not randomly assigned and confounding by indication is strongly suggested. In spite of attempts to account for multiple confounders in the Cox model, a complete correction cannot be accomplished, resulting in residual confounding at baseline. This could explain why the treated men have worse prognosis during the first years after baseline compared to the untreated men even after statistically adjusting for the differences in baseline risk profiles. Even after adjusting for known risk factors, a residual confounding may occur because of measurement error or unmeasured or unknown risk factors.[31]

The analysis of the whole cohort is limited to a single examination when subjects entered the study. It cannot control for changes in compliance or a shift of subjects between categories during the study period. Although we adjust for the year of entry into the study, the possibility of crossover is clearly present. During follow-up, hypertensive subjects without treatment at entry into the study may have been treated later, especially since treatment of hypertension was getting more common.[24] Additionally, in the present study there was systematic referral of hypertensive individuals to physicians.[32] This causes some misclassification that underestimates the true effect of treatment and results in bias toward the null.

In conclusion, hypertensive treated men had a worse prognosis during the first 10 years of follow-up than untreated ones, which is most likely due to a worse baseline risk profile among the treated men. Hypertensive men who were treated at a later stage had a worse risk profile than those who were not treated at a later stage.

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