Identification of Risk Factors in Hypertensive Patients
Contribution of Randomized Controlled Trials Through an Individual Patient Database

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Background—Predicting individual risk is needed to target preventive interventions toward people with the highest probability of benefit over a given time period. We assessed which prognostic factors should be used in predicting risk for hypertensive patients and in searching for treatment modifiers.

Methods and Results—Data from 24 390 hypertensive participants who constituted the control groups from 8 controlled trials (1726 deaths over 5 years) were analyzed in multivariate survival models. Outcomes were coronary heart disease death, stroke death, and cardiovascular death. We explored systematically the heterogeneity of results between trials. Left ventricular hypertrophy was electrocardiographically confirmed to be a powerful risk factor and should be included in risk scoring. Height, glomerular filtration rate, and serum uric acid deserve further exploration. Body mass index and heart rate were not confirmed as independent cardiovascular risk factors in this population. The association between male sex and coronary heart disease death was significantly stronger in British cohorts. The lack of prognostic value of diastolic blood pressure was explained by an interaction with age, with a positive association before 65 years and a negative association thereafter. Previous antihypertensive treatment was a significant risk factor.

Conclusions—Clinical trials provide valuable information for risk prediction. Carefully exploring the heterogeneity among trials is a way to assess the generalizability of findings. This approach, if systematically performed, should increase the ability to identify risk modifiers and to predict individual therapeutic benefit. (*Circulation*. 1999;100:e88-e94.)

Key Words: hypertension ∎ trials ∎ epidemiology ∎ stroke ∎ coronary disease

A rational prevention strategy against cardiovascular diseases includes targeting interventions toward people with a high probability of benefit from intervention.[1] The starting point of this approach is the hypothesis that the treatment effect model[2] of antihypertensive drugs is multiplicative. This means that the relative treatment effect estimates (relative risk, hazard ratio, and odds ratio) are the most generalizable, or stable, and that these estimates are constant over the risk levels. In such a situation, the predicted absolute benefit is simply obtained by multiplying the predicted risk without treatment by the relative treatment effect estimate. Such a simple method to predict treatment benefit has been proposed to regulate the prescription of antihypertensive drugs[3] in New Zealand.

The Individual Data Analysis of Antihypertensive Intervention Trials (INDANA) database includes baseline and follow-up characteristics of participants enrolled in randomized controlled trials that assessed the effect of blood pressure–lowering drugs on clinical outcomes. The main objective of the project is to identify and describe the profiles of responders and nonresponders to these drugs in terms of cardiovascular risk. These profiles will include the individual characteristics either linked to the risk (risk factors) alone or together with those modifying the treatment effect on a multiplicative scale. Under the assumption of a multiplicative treatment effect, absolute benefit is proportional to risk; thus, risk factors modify the size of the absolute benefit. This modification is called an arithmetic interaction, since the association disappears when one changes the treatment effect scale. Biological interactions are defined as the change in the size of treatment effect that cannot be explained by a simple change of scale, either multiplicative or additive. The

TABLE 1.   Trials and Events

Trial	Publication Year (Reference #)	Participants in Control Group, n	Covariates With Limited Availability						Cause of Death			
			Glomerular Filtration Rate	Uric Acid	ECG LVH	Ethnic Origin	Treatment History	Heart Rate	Coronary Heart Disease, n	Stroke, n	Cardiovascular Cause, n	All Causes, n
Coope	1986 (8)	465	Av	Av	Av	NA	Excluded	Av	28	15	50	70
EWPHE	1985 (7)	424	Av	Av	NA	NA	Av	NA	33	31	93	149
HDFP	1979 (9)	5455	Av	Av	Av	Av	Av	Av	148	52	240	421
UK-MRC1	1985 (5)	8654	NA	NA	Av	NA	Excluded	NA	97	27	139	253
UK-MRC2	1992 (6)	2213	Av	Av	Av	NA	Excluded	Av	110	42	180	315
MRFIT	1982 (4)	3993	Av	Av	Av	Av	Av	Av	74	9	95	169
SHEP	1991 (10)	2371	Av	Av	Av	Av	Av	Av	73	14	112	242
STOP	1991 (11)	815	Av	Av	NA	NA	NA	Av	20	15	41	63
Total		24 390							596	214	974	1726

Av indicates available; NA, not available; and STOP, Swedish Trial in Old Patients with Hypertension.

INDANA approach can also be defined as an attempt to refute the hypothesis of the multiplicative effect, through looking for biological interactions.

This approach includes 3 principal steps: (1) identifying the significant risk factors, which would be used as adjustment covariates in the following step; (2) identifying the factors modifying the treatment effect on a multiplicative scale, ie, biological interactions; and (3) exploring the impact of these interactions on the efficiency of treatment decisions. The first step led us to assess the prognostic impact of the main cardiovascular risk factors and some other characteristics, measured in the control groups of the trials included in INDANA. The pooled analysis of data from several cohorts from different sources enables us to explore the general value of results, through the heterogeneity of findings. If a given risk factor always yields the same association with a given event, without any significant change from one cohort to another, its prognostic value is likely to be general, or generalizable. The results of the first step are presented here. Its 2 objectives are as follows: (1) to assess which prognostic factors should be retained in treatment decision making because they predict cardiovascular outcomes and (2) to explore in a systematic way the generalizability of results through their heterogeneity across trials.

Methods

Participants

The data extracted from the INDANA database included participants from the control groups of 8 trials[4–11] (Table 1). The data from 3 other trials in the database have not been used: the Systolic Hypertension in the Elderly Program Pilot[12] (SHEP-Pilot) study did not offer baseline data other than age, sex, and blood pressure; the Veterans Administration–National Heart, Lung, and Blood Institute feasibility trial[13] (VA-NHLBI) had only a very small number of events; and because of the lack of follow-up after the first end point, the data from the Australian[14] trial are potentially biased when the terminating end points are analyzed separately.

In 3 of the remaining 8 trials, the data required to analyze survival without nonfatal outcomes were not available: in the European Working Party on High Blood Pressure in the Elderly trial[7] (EW-PHE), nonfatal outcomes were documented only when the participants were on treatment; in the Hypertension, Detection, and Follow-up Program[9] (HDFP) and in the Multiple Risk Factor

Intervention Trial[4] (MRFIT), only fatal events were accurately dated. Thus, the present study focuses on total and cause-specific mortality.

The main characteristics of each trial have been published previously,[15] and more details can be found in separate reports from each trial.

Outcomes

Among the 7 outcomes adopted in the INDANA protocol,[15] only the results concerning fatal cardiovascular outcomes are considered in the present study: fatal strokes, fatal coronary events, and cardiovascular mortality.

Potential Risk Factors

The independent covariates considered were measured at entry into each trial. Some were continuous: age (years), systolic and diastolic blood pressure (mm Hg), heart rate (bpm), body mass index (kg/m^2), height (m), serum total cholesterol (mmol/L), glomerular filtration rate (mL/min), and serum uric acid (mmol/L); others were dichotomous: sex (male 1, female 0); smoking status (current smoker 1, other 0); myocardial infarction history, stroke history, diabetes history, or antihypertensive treatment history (history 1, no history 0); presence of left ventricular hypertrophy criteria on ECG (present 1, absent 0); and ethnic origin (African American 1, other 0). Glomerular filtration rate was determined from serum creatinine, age, sex, and weight by the Cockroft formula[16]: $GFR = (140 - age) \times weight \times (1.228/creatinine) \times (0.85 + 0.15 \times sex)$, where age is given in years, weight in kilograms, and creatinine in millimoles per liter.

Most of the variables were collected during standardized clinical interview(s) and examination(s) (age, sex, ethnic origin, smoking status, cardiovascular history, height, and weight) and reflect the information one can observe in good clinical practice. Blood pressure measurements were always the basic inclusion criteria and thus were collected with a particular attention. Protocols of measurements varied greatly between trials in terms of their number, the use of random zero sphygmomanometer, and the time lapse between different measurements. ECG-defined left ventricular hypertrophy was the association of tall R waves (corresponding to Minnesota code 3.1) with abnormalities of repolarization (corresponding to Minnesota code 4.1 to 4.3 or 5.1 to 5.3). Laboratory data were gathered in various settings: in some trials, laboratory measurements were performed centrally for ECG and biochemistry; in others, these measurements were performed in the center for recruitment and follow-up.

Statistical Analysis

Hazard ratios associated with the presence of each covariate were computed through a Cox proportional hazards model[17] in univariate and multivariate approaches. Analyses were stratified by trials, which allowed us to take into account differences in risk across trials without any assumption of proportionality of hazards along time.
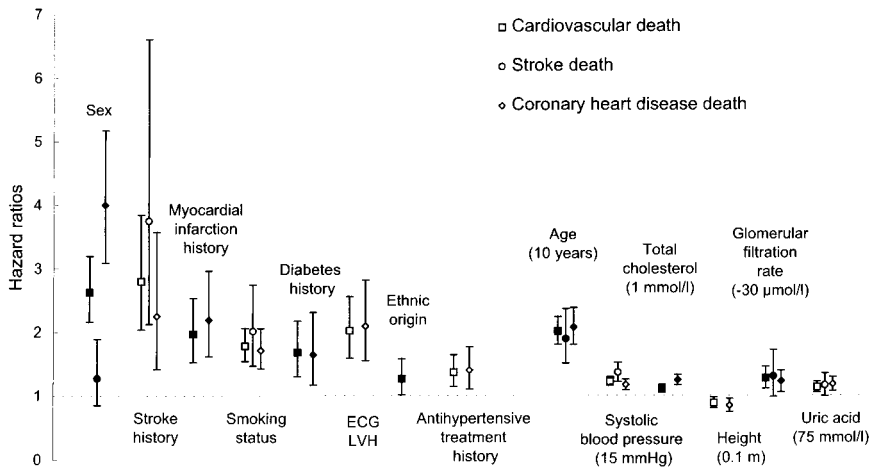
Figure 1. Prognostic importance of baseline characteristics in multivariate models. Hazard ratios between categories (categorical covariates are on left of figure) or corresponding to standard deviation increase (continuous covariates are on right of figure), computed in multivariate models, are given with their 95% confidence intervals. Hazard ratio >1 indicates a risk increase. Alternative use of solid and open symbols is for reading purposes only.

Because different approaches may select different sets of covariates, 3 different stepwise approaches were used to select covariates in multivariate models: backward and forward approaches and those based on best score, with $P=0.05$ as threshold to retain covariates.

A first model was parameterized on the basis of 11 covariates available in all trials, namely, age, sex, smoking status, systolic and diastolic blood pressure, stroke, myocardial infarction or diabetes history, body mass index, height, and serum total cholesterol. The results concerning these covariates are given from this model. Other models were built to explore the predictive value of 6 covariates that were not available for all trials (see Table 1 for the availability of covariates by trial), ie, glomerular filtration rate, serum uric acid, ethnic origin, left ventricular hypertrophy, history of antihypertensive treatment, and heart rate. The results of these models are given only for these covariates.

The heterogeneity of the prognostic role of a given covariate across trials was explored by testing the significance of the increase in fit of a model involving interaction terms between covariate and trials compared with the same model without these terms. When the increase in fit was significant, a backward stepwise procedure explored which trial(s) was responsible for the interaction. The significance threshold to keep an interaction in the model was 0.05.

The improvement of fit due to the inclusion of covariates in the full model was illustrated in comparing the observed risk among quartiles of predicted risk between 2 models: one including only sex and age as covariates and one also including the other significant covariates available in all trials.

The software used for data management and statistical analysis was SAS.[18]

Results

The number of participants included in the analysis was 23 415, among 24 390 included in the control groups of the trials considered (Table 1). This difference is related to missing values for baseline covariates (mainly serum cholesterol and body mass index). In addition, the data from MRFIT were included only for hypertensive participants, whose baseline diastolic blood pressure was >90 mm Hg. Standardized hazard ratios were estimated by using standard deviations computed on the pooled data and rounded in order to illustrate the specific importance of each risk factor in this population.

Results From the Full Multivariate Models

The hazard ratios for sex showed the only significant discrepancy between the 3 outcomes (Figure 1): whereas being a man was the strongest risk factor for coronary heart disease death, with a hazard ratio ≈4, there was no significant difference between men and women for stroke death. Some covariates did not reach significance for stroke death, possibly because of the relatively low numbers associated with stroke death: there was almost 3 times more coronary heart disease death than stroke death (Table 1). Stroke history was a risk factor for stroke and coronary heart disease death, whereas myocardial infarction history was a risk factor mainly for coronary heart disease death. The prognostic importance of left ventricular hypertrophy from ECG records appeared similar or greater than that of smoking status or diabetes. Compared with other people, African Americans had an increased risk of cardiovascular death. Having already been treated with antihypertensive drugs was also a significant risk factor.

For continuous covariates (Figure 1, right), age was by far the most important risk factor. Systolic blood pressure was better correlated with stroke than with coronary heart disease death. Total cholesterol was not associated with stroke death but with the 2 other outcomes (cardiovascular death and coronary heart disease death). A decrease in glomerular filtration rate and an increase in uric acid were associated with a greater risk for the 3 outcomes; the magnitude of this risk was similar to that of blood pressure and total cholesterol. Height was inversely correlated with the risk of coronary heart disease and cardiovascular death.

Three covariates were found not to be related to cardiovascular fatal outcomes: heart rate, body mass index, and diastolic blood pressure.

The gain in predictive power due to the addition of the other covariates to age and sex (Figure 2) is more impressive for myocardial infarction and cardiovascular death than for stroke death or all-cause death.

Heterogeneity of Prognostic Value of Each Risk Factor Between Trials

Nine covariates showed no significant heterogeneity for their prognostic roles across trials: smoking status, stroke history, antihypertensive treatment history, ethnic origin, total cholesterol, glomerular filtration rate, diastolic blood pressure, body mass index, and heart rate. The other 8 were associated with some differences between trials for at least one outcome. Concerning cardiovascular death, these differences are indicated on the right of Table 2. The trials in which the hazard
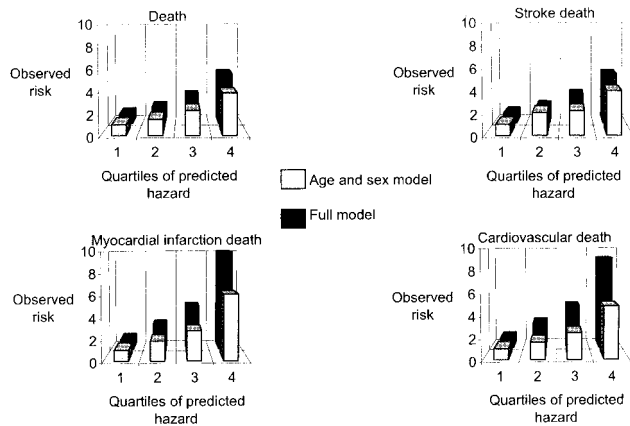
Figure 2. Efficiency of risk scoring. Full model: model adjusted on basis of age, sex, and other covariates significantly associated with risk. The relative observed risk (first quartile as reference) is shown for each quartile of predicted hazard, calculated either on age and sex model or on full model.

Figure 3. Changes in hazard ratios for height or sex differences according to model used. Left panel shows how adjusted model dramatically changes direction of results. Both panels illustrate heterogeneity of results across trials. Residual hazard ratio concerns trials that are not responsible for the heterogeneity.

ratio is significantly different from the others are listed. We give both the hazard ratio in the remaining trials (residual hazard ratio) and the ratio that is to be multiplied by the residual hazard ratio (added hazard ratio) to yield the specific hazard ratio in the trials showing a significant heterogeneity. For example, the hazard ratio of cardiovascular death for men compared with women was 2.63 for the population as a whole (Figure 3). However, this hazard ratio was only 1.57 (residual
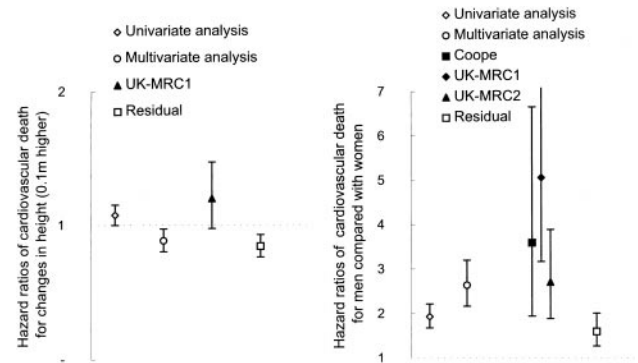
risk ratio) when the stronger effect of sex in the Coope[8] and UK Medical Research Council (UK-MRC)[5,6] trials was isolated. The hazard ratio computed was $2.28 \times 1.57 = 3.58$ for Coope, 5.04 for UK-MRC1, and 2.68 for UK-MRC2.

Discussion

In the present study, we demonstrate the first step of the modeling procedure to explore whether individual patient characteristics are associated with the intensity of the effect of

TABLE 2.   Risk Factors of Cardiovascular Death

Variable	Univariate Analysis		Multivariate Analysis			Interaction			
	Hazard Ratio	P	Hazard Ratio	95% CI	P	Trial	Added Hazard Ratio	P	Residual Hazard Ratio
Age (10 years)	2.04	0.0001	2.01	1.81–2.24	0.0001	EWPHE	1.52	0.002	1.91
Sex (males 1, females 0)	1.93	0.0001	2.63	2.16–3.19	0.0001	Coope	2.28	0.0091	1.57
						UK-MRC1	3.21	0.0001	...
						UK-MRC2	1.71	0.0038	...
Smoking status (current 1, other 0)	1.73	0.0001	1.78	1.54–2.06	0.0001				
Systolic blood pressure (15 mm Hg)	1.31	0.0001	1.22	1.16–1.29	0.0001				
Diastolic blood pressure (10 mm Hg)	1.10	0.0057							
Stroke history	3.62	0.0001	2.80	2.04–3.84	0.0001				
Myocardial infarction history	2.51	0.0001	1.97	1.52–2.53	0.0001	UK-MRC1	5.45	0.0001	1.73
Diabetes history	1.87	0.0001	1.68	1.30–2.17	0.0001				
Body mass index (5 kg/m^2)	0.84	0.0001							
Height (0.1 m)	1.07	0.0410	0.88	0.80–0.97	0.0109	UK-MRC1	1.42	0.0007	0.84
Total cholesterol (1 mmol/L)	1.05	0.0862	1.11	1.05–1.17	0.0003				
Glomerular filtration rate (-30 μmol/L)	1.79	0.0001	1.27	1.11–1.46	0.0006				
Uric acid (75 mmol/L)	1.25	0.0001	1.13	1.22–1.05	0.0010	HDFP	1.24	0.0001	0.99
						UK-MRC2	1.36	0.0012	...
Ethnic origin	1.31	0.0133	1.27	1.01–1.58	0.0374				
ECG-LVH	2.70	0.0001	2.02	1.59–2.56	0.0001	UK-MRC2	1.85	0.0212	1.76
Antihypertensive treatment history	1.46	0.0001	1.37	1.14–1.64	0.0007				
Heart rate (10 bpm)	0.98	0.5654							

ECG-LVH indicates ECG-defined left ventricular hypertrophy. Data in parentheses indicate variable increment or assigned value. Last 6 rows of table give results of models built on limited set of data because of lack of availability in all trials.

blood pressure–lowering drugs in terms of clinical outcome: we identified the significant risk factors for cause-specific cardiovascular death and explored the heterogeneity of our findings across trials.

Advantages of Multivariate Analysis

The comparison of results from univariate and multivariate analyses shows how taking into account other risk factors may modify the estimate of their association with risk. For example, stroke history adjusted with other risk factors multiplied the risk of cardiovascular death by 2.82, whereas univariate modeling suggested a stronger association (hazard ratio 3.62) (Table 2). On the other hand, an association may be revealed or reinforced after adjustment: an increase in 1 mmol/L of serum total cholesterol corresponded to a hazard ratio of 1.11 for cardiovascular death, which is highly significant, whereas the univariate approach did not retain cholesterol as a risk factor ($P=0.09$), with the estimated hazard ratio being 1.05 (Table 2). The most striking example of the effect of allowing for other covariates concerns height, which is positively and significantly correlated with coronary heart disease in the univariate approach but significantly and negatively correlated with the same outcome in the multivariate approach (Figure 3). This finding is explained by the fact that, on average, men are taller than women are and at higher risk of coronary heart disease. As a consequence, we must concentrate the discussion on results from multivariate analysis.

Limitations

The present study has several limitations: (1) It uses data from cohorts that were not specifically designed to assess the prognostic value of any of the studied characteristics, and the collection of baseline data was not standardized between trials. For example, blood pressure readings analyzed here were obtained most carefully and with more frequent measures than in traditional observational surveys, but the number of measurements used, and the time lapse between measurements, varied across trials. The resulting differences in measurement errors may explain a part of the heterogeneity of the association slopes between trials. This drawback may be prevented by prospectively planning the meta-analysis before the inception of the included trials (prospective meta-analyses[19,20]), which allows standardizing procedures across trials. (2) The average follow-up is 5 years, which is not very long compared with the usual longitudinal studies. It is planned to increase the follow-up duration for most trials included in the INDANA database for mortality data. (3) Many analyses have been performed; this increases the likelihood of significant positive results by chance. (4) Statistical modeling is simplistic and rigid compared with the complexity of biology. We could have increased the complexity of statistical models by including interaction terms to enhance the fit of the model to the data. However, such an approach may increase the singularity of the model and decrease the general value of the findings. Eventually, it may increase the gap between models and biological reality. Modeling should be seen here as an attempt to find out the best combination of risk factors that have the strongest and

the most general prognostic value. (5) The cohorts analyzed in the present study represent European and North American populations, with a reasonably large proportion of African American participants in HDFP[9] and SHEP[10]; it may not be appropriate to extrapolate the results to other populations. (6) The selection of people by blood pressure criteria and the selection procedure for clinical trials in general yield samples that are not representative of the general population. However, the variety of exclusion criteria between trials, with large inclusion criteria in one of the biggest trials (HDFP), leads to a very heterogeneous population for the present study. This fact enables us to explore efficiently the general value of each potential risk factor. (7) Although atrial fibrillation is a common risk factor for stroke, we are unable to account for its contribution because it was an exclusion criteria in most trials. This is unfortunate for several reasons: hypertension is a risk factor for atrial fibrillation, and both are powerful risk factors for stroke[21] (ischemic stroke for atrial fibrillation and both ischemic and hemorrhagic stroke for hypertension). The prevalence of both conditions increases with age, so that their association is frequent in the elderly. Antiplatelet and anticoagulant agents reduce the risk of stroke in atrial fibrillation but increase the risk of hemorrhage.[22] Unfortunately, there are no data regarding the respective benefit and a possible interaction between these treatments yet.

Complementary Analyses and Implications for Future Research

Our results confirm the prognostic impact of commonly identified cardiovascular risk factors[23] such as older age, male sex, current smoking, higher systolic blood pressure, diabetes, and history of cardiovascular disease. Diastolic blood pressure had no independent predictive value in multivariate models, ie, when systolic blood pressure was taken into account. Several explanations can be proposed: (1) Selecting people according to a narrow range of values for a given characteristic decreases the possibilities of assessing its prognostic value. (2) People in control groups were to be treated by blood pressure–lowering drugs if their blood pressure exceeded a given threshold. This procedure is likely to decrease the apparent prognostic value of blood pressure, but such reasoning is also applicable to systolic blood pressure. (3) There was a significant interaction between age and diastolic blood pressure for the occurrence of cardiovascular death. This suggested that diastolic blood pressure was associated with risk in younger people only. This association weakened with age and disappeared at ≈65 years, reversing thereafter. Being a man represented a higher risk of death, especially from coronary heart disease death. However, this association was stronger in the British cohorts, most of all in the UK-MRC1 study. This finding was not explained by differences in age or other common risk factors between studies, since they were taken into account. Thus, further study is required. Possibly, specific risk scores by geographical area and/or by sex could be established.

Cholesterol, height, and ECG-determined left ventricular hypertrophy were associated with all outcomes except stroke death. A negative association with hemorrhagic stroke[24] that masks the positive association with ischemic stroke probably

explains the lack of association between cholesterol and stroke.

Potentially modifiable risk factors are generally those of most interest as potential therapeutic targets. However, when risk factors are used to predict the risk of individuals, even those factors that are not modifiable should be taken into account, such as age, sex, and height. The negative correlation between height and cardiovascular mortality has already been described,[25,26] although findings have been inconsistent.[27] However, the significant qualitative heterogeneity of the association of height with coronary heart disease death we have observed puts into question its use in risk prediction. Epidemiological evidence has usually indicated an increase of cardiovascular risk with body mass index.[28,29] In the present study, body mass index was significantly (and negatively) associated only with all-cause death, without significant heterogeneity between trials. Testing the significance of an additional quadratic factor did not support a J- or U-shape relation to explain the lack of association with cardiovascular death.

Cardiovascular death is the most common cause of death among people with end-stage renal failure.[30] The independent prognostic value of glomerular filtration rate suggests that the effect of renal failure is not mediated by only the risk factors that were taken into account and that are associated with renal failure, such as age, high blood pressure, and high uric acid level. The hazard ratios associated with the increase in 1 SD of serum uric acid or serum total cholesterol are of the same magnitude. The significant association of serum uric acid with all outcomes raises the question of the possible therapeutic benefit from drugs that decrease its serum concentration. The presence of ECG-defined left ventricular hypertrophy doubled the hazard of coronary heart disease death and cardiovascular death. The prognostic importance of this information, so simple to obtain, was already shown in epidemiological studies, as in the Framingham study.[31] It should be included in any risk score that is used for deciding whether to prescribe any drug to prevent cardiovascular events.

The prognostic importance of previous antihypertensive treatment may reflect self-selection (or physician referral) of participants enrolled in clinical trials, ie, an unavoidable selection bias. That bias may also interact with the prognostic importance of blood pressure because of the remaining effect of previous drugs: the blood pressure measured would, in fact, be lower than the "real" blood pressure. However, the association between previous treatment and risk of death is stronger for coronary death than for stroke death, whereas the opposite would be expected if it were only due to a bias in blood pressure measurement. Ethnic origin had some impact on the risk of cardiovascular death but a greater impact on the risk of noncardiovascular death, which may reflect some confounding effect, such as that of socioeconomic status. The impact of ethnic origin was not apparent in the hypertensive participants of the MRFIT study.

Conclusions

We confirmed the prognostic importance of classic cardiovascular risk factors by analyzing pooled cohorts from control groups of clinical trials in hypertension. In addition, the prognostic value of a smaller height, a higher serum uric acid, or a lower glomerular filtration rate was strongly suggested and deserves to be explored further. However, quantitative and even qualitative disparities between cohorts for some risk factors, as seen elsewhere,[32] point to the need to assess whether a quantified hazard ratio for a given risk factor can be appropriately used in predicting the risk of people in various settings. Meta-analyses based on individual patient data from either observational studies[33] or controlled clinical trials, through multivariate modeling, constitute an appropriate tool to explore the general value of risk factors.

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Identification of Risk Factors in Hypertensive Patients: Contribution of Randomized Controlled Trials Through an Individual Patient Database

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