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Journal of Human Hypertension (2010) 24, 19–26

www.nature.com/jhh

ORIGINAL ARTICLE

Residual cardiovascular risk in treated hypertension and hyperlipidaemia: the PRIME Study

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Although pharmacological treatments of hypertension and dyslipidaemia are both associated with a reduction in cardiovascular risk, little is known about the degree of cardiovascular risk remaining in treated individuals, by assessing the levels of their risk factors achieved, that is their 'residual cardiovascular risk'. We then used the data from the Prospective Epidemiological Study of Myocardial Infarction (PRIME), which involved 9649 men aged 50–59 years, from France and Northern Ireland with a 10-year follow-up, to test the presence of specific residual cardiovascular risks of coronary heart disease, stroke, total of fatal and non-fatal cardiovascular events and cardiovascular mortality, in patients treated with antihypertensive agents or lipid-lowering agents. In the whole cohort, a total of 796 patients developed a fatal or non-fatal cardiovascular event. Antihypertensive drug use at baseline was significantly associated (RR = 1.50, 95% CI: 1.25–1.80) with total cardiovascular event risk, but not lipid-lowering drug use, after adjusting for classic risk factors (age, smoking, total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure and diabetes). Similar results were obtained for coronary heart disease (RR = 1.46, 95% CI: 1.18–1.80), stroke (RR = 1.75, 95% CI: 1.14–2.70) and cardiovascular death (RR = 1.62, 95% CI: 1.02–2.58), but neither for total death (RR = 1.15, 95% CI: 0.89–1.48) nor for non-cardiovascular death (RR = 1.00, 95% CI: 0.74–1.36). For any cardiovascular end point, residual risks did not globally differ according to the antihypertensive drug class prescribed at baseline. In conclusion, treatment with antihypertensive agents, but not with lipid-lowering agents, was associated with a sizeable residual cardiovascular risk, suggesting that more efficient risk reduction strategies in hypertension should be developed as a priority.
Journal of Human Hypertension (2010) **24,** 19–26; doi:10.1038/jhh.2009.34; published online 28 May 2009

Keywords: epidemiology; risk prediction; antihypertensive agents; population

Introduction

Management of individual patients requires the integration of the results of both observational and interventional epidemiology.[1] In the field of hypertension, observational epidemiology clearly demonstrates that hypertensives have an increased risk of developing cardiovascular complications.[2] In addition, blood pressure decrease is associated with a reduction in major cardiovascular complications: coronary heart disease (CHD), stroke, congestive heart failure and cardiovascular mortality.[3] To improve hypertensive treatment, we should remember that although antihypertensive treatment reduces cardiovascular risk, it cannot completely reverse the hypertension-induced risk of morbid events. Therefore, antihypertensive treatment cannot be considered effective if only part of the cardiovascular events attributable to hypertension is prevented. Conventional therapeutic trials do not furnish this information because patients are highly selected. Other sources of evidence are needed to determine the proportion of hypertension-induced cardiovascular events prevented by antihyper-

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Received 10 February 2009; revised 1 April 2009; accepted 2 April 2009; published online 28 May 2009

tensive drugs as they are prescribed and monitored in the population. Little is known about the cardiovascular risk of patients receiving antihypertensive treatment, taking into account the levels of risk factors achieved, that is their 'residual cardiovascular risk'. Some data support a residual cardiovascular risk in treated hypertensives, even in patients with controlled blood pressure levels.[4–10]

Residual cardiovascular risk is important at the public health level to implement new guidelines, and at the epidemiological level to built more realistic prediction models, taking into account both the current level of the risk factor and type of drug treatment. The confirmation of an important residual cardiovascular risk in hypertension or in hypercholesterolaemia would bear important clinical implications, opening discussions on earlier treatment, more intensive treatment and the need for developing new drugs.

In an earlier PRIME (Prospective Epidemiological Study of Myocardial Infarction) Study paper, we demonstrated a sizeable residual coronary risk in treated hypertensives after a 5-year follow-up. The 10-year follow-up might give enough power to test the presence of specific residual cardiovascular risks, not only of CHD, but also of stroke, total of fatal and non-fatal cardiovascular events and cardiovascular mortality. Furthermore, because hypercholesterolaemia might behave similarly, we also tested the presence of a residual cardiovascular risk associated with lipid-lowering drugs.

Methods

Cohort recruitment, examination methods and the protocol for the analysis of fatal and non-fatal coronary and cerebrovascular events have been described previously,[7,11,12] and only the main details are given below.

Population sampling

The PRIME Study was established in 1991 in the populations of four WHO MONICA Collaborating Centres in Belfast (UK), and Lille, Strasbourg and Toulouse (France) (see Appendix). The target was to recruit 2500 men, aged 50–59 years, in each centre and to follow them over 10 years. The sample was recruited to broadly match the social class structure of the background population. The recruitment frame was based on industry, various employment groups, health screening centres and general practice. Approval from the appropriate local ethics committees was obtained and subjects who accepted to participate gave their written consent at examination.

Personal history and examination

Self-administered questionnaires relating to demographic, socioeconomic factors and diet were completed at home by the participants and checked by the survey staff with the subjects at the clinic. Data on educational level, occupational activity, personal and family history, tobacco and alcohol consumption, drug intake and physical activity were collected by the staff. During the examination, a questionnaire on personal medical history was completed along with the London School of Hygiene Cardiovascular (Rose) Questionnaire for Chest Pain on Effort and Possible Infarction,[13] and a standard 12-lead electrocardiogram was recorded. Questionnaires were designed in French and rigorously translated into English. Anthropometric measurements included height and weight without shoes.

Subjects were considered free of coronary disease at entry if they had no history of myocardial infarction and/or angina pectoris diagnosed by a physician; no electrocardiographic evidence of myocardial infarction, defined as major or moderate Q-wave coding using the Minnesota system[11] and no positive answer to the Rose questionnaire.[13] Subjects were considered free of cerebrovascular disease at entry if they had no history of stroke or transient ischaemic attack.

All subjects receiving antihypertensive, lipid-lowering or antidiabetic therapy were included in the present analysis. Antihypertensive agents were divided into β-blockers, diuretics, angiotensin-converting enzyme (ACE) inhibitors, calcium channel antagonists (CCAs), α-blockers and centrally acting agents, the latter two were grouped together in the analysis because of small numbers. Subjects taking drug combinations were included in the analysis as if they were taking the drugs separately. Lipid-lowering agents were divided into fibrates and statins.

Blood pressure was measured once with an automatic device (Spengler SP9) at the end of the examination after a 5 min rest in the sitting position and before blood was drawn. A standard cuff size was used, but a large cuff was available when necessary. To minimize systematic between-centre differences, we circulated and recalibrated devices every 3 months at the coordinating centre in Paris.

Blood samples were processed within 4 h of venesection. Plasma for lipid analysis[11] was sent each week at 4 °C to the Central Laboratory in Lille, France.

Follow-up

Subjects were contacted annually by letter and asked to complete a clinical event questionnaire to be returned to the centre in a prepaid envelope. If the subject did not comply, phone contact was established with him or with his general practitioner. For all subjects reporting a possible event, clinical information was sought directly from the hospital or general practitioners' notes. Death certificates were checked for supporting clinical and postmortem information on cause of death. When necessary, the circumstances of death were

obtained from the practitioner or the family. Subjects who could not be contacted at the 10th year of surveillance or who refused to participate any longer in the study at any time of follow-up represented 4.9% of the total cohort, 286 subjects from France (3.0%) and 190 from Northern Ireland (2.0%).

A medical committee was established, comprising one member from each PRIME Centre, and independent cardiologists and neurologists. Its task was to provide an independent validation of coronary and stroke events during follow-up. In summary, myocardial infarctions, coronary deaths and stroke events were defined according to MONICA criteria.[14] Angina pectoris was diagnosed only as a first-ever event with the presence of chest pain at rest and/or on exertion, with an angiographic coronary stenosis over 50% or a positive exercise test if no angiography was undertaken. From available clinical data including imaging, strokes were classified as ischaemic or intracerebral haemorrhagic or of unknown origin. All data on death causes including death certificates were reviewed and the main cause was given a PRIME code according to ICD 9th Revision. Deaths with a code 410–441 or 798.1 were considered as cardiovascular deaths.

Statistical analysis

Statistical analysis was conducted using SAS software (SAS Institute, Cary, NC, USA). Univariate comparisons were performed using the χ^2-test and the Student's *t*-test. Different end-point predictions (all-cause death, cardiovascular death, CHD, stroke, fatal or non-fatal cardiovascular event and non-cardiovascular death) were assessed by Cox regression models. In prediction models, each drug class was coded as a (0–1) variable whatever be the mode of treatment (combined or not). Moreover, conventional factors, apart from blood pressure and lipid-lowering therapy, were systematically introduced as covariates: centre, age, tobacco consumption, total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, body mass index, systolic blood pressure and treatment for diabetes. However, because body mass index and triglyceride levels showed no independent association with risk, they were excluded from the final analysis. Comparison of the relative risks associated with each treatment was performed with a Cox likelihood ratio test (model with antihypertensive treatments combined versus a model with all treatment classes separately) by a χ^2-test with four degrees of freedom. Results were expressed as mean ± s.d. or as a percentage. Statistical significance was assessed for $P<0.05$.

Results

Table 1 shows the clinical, biological and pharmacological characteristics of coronary- and cerebrovascular-free subjects at inclusion, in France and in Northern Ireland. The prevalence of antihypertensive, lipid-lowering and oral antidiabetic agent use was lower in Northern Ireland than in France ($P<0.001$ for all).

Table 1 Clinical, biological and pharmacological characteristics of PRIME subjects at inclusion, according to the recruiting country

Parameter	*Northern Ireland (n = 2382)*	*France (n = 7267)*
Age (years)	54.7 ± 2.9	54.9 ± 2.9
Current smokers (%)	31	26
Tobacco (g per day)	4.7 ± 9.7	3.1 ± 7.7
Ex-smokers (%)	34	46
Body mass index (kg m^{-2})	26.2 ± 3.4	26.7 ± 3.4
Systolic blood pressure (mm Hg)	134 ± 20	134 ± 18
Diastolic blood pressure (mm Hg)	82 ± 12	84 ± 12
Total cholesterol (g l^{-1})	2.27 ± 0.39	2.20 ± 0.37
HDL cholesterol (g l^{-1})	0.46 ± 0.12	0.50 ± 0.13
Triglycerides (g l^{-1})	1.73 ± 1.08	1.41 ± 0.97
Antihypertensive agents (%)	9.0	14.3
β-Blockers (%)	5.0	5.3
Diuretics (%)	2.6	4.7
ACE inhibitors (%)	1.5	5.9
CCAs (%)	2.1	2.9
Others (%)	0.2	0.8
Lipid-lowering agents (%)	0.9	11.0
Fibrate drugs (%)	0.6	7.3
Statin drugs (%)	0.3	3.7
Antidiabetic agents (%)	0.8	2.5
Sulphonylurea drugs (%)	0.3	1.5
Biguanide drugs (%)	0.1	1.4
Insulin (%)	0.5	0.2

Abbreviations: ACE, angiotensin-converting enzyme; CCA, calcium channel antagonists; HDL, high-density lipoprotein.

In 9649 subjects who were free of coronary and cerebrovascular diseases at entry, 537 deaths were recorded over the 10-year follow-up, 22.7% of them from cardiovascular causes. Six hundred and forty-eight first coronary events occurred; of these, 356 were first angina pectoris and 315 hard coronary events (myocardial infarctions and CHD deaths). One hundred and thirty-eight patients developed a first stroke over the 10-year follow-up, among them 80% being from ischaemic cause. In the whole cohort, a total of 796 patients presented a fatal or non-fatal cardiovascular event during the 10-year follow-up (Table 2).

In an initial analysis of fatal or non-fatal cardiovascular events in the whole cohort, antihypertensive drug use was significantly and positively associated (RR = 1.50, 95% CI: 1.25–1.80) with risk, but lipid-lowering drug use was not (RR = 1.00, 95% CI: 0.77–1.30) adjusting for classic risk factors (age, smoking, total cholesterol, HDL cholesterol, systolic blood pressure and diabetes), which were all statistically significant predictors (Table 3a). Similar results were obtained for CHD (RR = 1.46, 95% CI: 1.18–1.80), stroke (RR = 1.75, 95% CI: 1.14–2.70) and cardiovascular death (RR = 1.62, 95% CI: 1.02–2.58), but neither for total death (RR = 1.15, 95% CI:

Table 2 Total deaths, cardiovascular death, coronary heart disease incidence, stroke incidence and the total of fatal or non-fatal cardiovascular events during the follow-up, according to the recruiting country

Parameters	*Northern Ireland* (n = *2382*)	*France* (n = *7267*)	*All subjects* (n = *9649*)
Total deaths, n (%)	171 (7.2)	366 (5.0)	537 (5.6)
Non-cardiovascular deaths, n (%)	121 (5.1)	294 (4.0)	415 (4.3)
Cardiovascular deaths, n (%)	50 (2.1)	72 (1.0)	122 (1.3)
Cardiovascular deaths among total deaths (%)	29.2	19.7	22.7
CHD incidence, n (%)	235 (9.9)	413 (5.7)	648 (6.7)
Angina, first event, *n* (%)	120 (5.0)	236 (3.2)	356 (3.7)
MI, CHD death, *n* (%)	126 (5.3)	189 (2.6)	315 (3.3)
Stroke incidence, n (%)	48 (2.0)	90 (1.2)	138 (1.4)
Ischaemic, *n* (proportion)	38 (79)	72 (80)	110 (80)
Fatal or non-fatal cardiovascular events, n (%)	282 (11.8)	514 (7.1)	796 (8.2)

Abbreviations: CHD, coronary heart disease; MI, myocardial infarction.

Table 3 Relative risks of end points according to drug-use groups, centre and classical risk factors being covariates

Parameters	*Total death* (n = *537*)	*CV death* (n = *122*)	*CHD* (n = *648*)	*Stroke* (n = *138*)	*Fatal or non-fatal CV event* (n = *796*)	*Non-CV death* (n = *415*)
(a) Overall analysis						
Antihypertensive agents (0–1)	1.15	1.62*	1.46***	1.75**	1.50***	1.00
	(0.89–1.48)	(1.02–2.58)	(1.18–1.80)	(1.14–2.70)	(1.25–1.80)	(0.74–1.36)
Lipid-lowering agents (0–1)	0.80	0.72	1.09	0.68	1.00	0.83
	(0.56–1.14)	(0.34–1.55)	(0.82–1.45)	(0.34–1.35)	(0.77–1.30)	(0.56–1.23)
(b) Separate analysis by antihypertensive drug classes						
β-Blockers (0–1)	1.06	0.64	1.36*	1.26	1.37**	1.23
	(0.73–1.52)	(0.28–1.48)	(1.03–1.79)	(0.68–2.32)	(1.07–1.76)	(0.82–1.85)
Diuretics (0–1)	1.18	1.84	1.03	1.17	1.10	0.96
	(0.81–1.72)	(0.99–3.40)	(0.73–1.45)	(0.59–2.33)	(0.81–1.49)	(0.59–1.55)
ACE inhibitors (0–1)	1.27	2.08*	1.17	2.39**	1.30	1.01
	(0.89–1.81)	(1.15–3.77)	(0.85–1.62)	(1.40–4.06)	(0.98–1.72)	(0.64–1.59)
CCAs (0–1)	0.98	1.14	1.60**	1.28	1.65**	0.92
	(0.61–1.59)	(0.49–2.66)	(1.13–2.25)	(0.58–2.81)	(1.22–2.24)	(0.51–1.65)
Others (0–1)	1.62	3.04	1.90	1.76	1.49	1.11
	(0.72–3.64)	(0.95–9.71)	(0.94–3.83)	(0.43–7.19)	(0.74–2.99)	(0.35–3.46)
Heterogeneity of effects,	1.80	6.91	1.69	4.23	1.55	0.99
χ^2-test 4 d.f.	NS	NS	NS	NS	NS	NS
(c) Separate analysis by lipid-lowering drug classes						
Fibrate drugs (0–1)	0.84	0.76	0.95	0.77	0.93	0.87
	(0.56–1.25)	(0.32–1.78)	(0.67–1.33)	(0.37–1.62)	(0.68–1.26)	(0.55–1.36)
Statin drugs (0–1)	0.73	0.66	1.42	0.76	1.24	0.76
	(0.39–1.38)	(0.16–2.70)	(0.95–2.13)	(0.24–2.41)	(0.84–1.83)	(0.38–1.55)

Abbreviations: ACE, angiotensin-converting enzyme; CCA, calcium channel antagonist; CHD, coronary heart disease; CV, cardiovascular.
*$P<0.05$; **$P<0.01$; ***$P<0.001$.
A, adjustments were made on age, centre, tobacco consumption, diabetes, systolic blood pressure, total cholesterol and HDL cholesterol. B, adjustments were made on same parameters as A+lipid-lowering agents. C, adjustments were made on same parameters as A+antihypertensive agents.

0.89–1.48) nor for non-cardiovascular death (RR = 1.00, 95% CI: 0.74–1.36). When all antihypertensive drug classes were entered simultaneously into the same Cox models, β-blocker use was associated with both CHD and fatal or non-fatal cardiovascular events (RR = 1.36, 95% CI: 1.03–1.79 and RR = 1.37, 95% CI: 1.07–1.76, respectively), CCA use was also associated with both CHD and fatal or non-fatal cardiovascular events (RR = 1.60, 95% CI: 1.13–2.25 and RR = 1.65, 95% CI: 1.22–2.24, respectively), ACE inhibitors were associated with both cardiovascular death and stroke event risks (RR = 2.08, 95% CI: 1.15–3.77 and RR = 2.39, 95% CI: 1.40–4.06, respectively); finally, diuretic use was marginally associated with risk of cardiovascular death (RR = 1.84, 95% CI: 0.99–3.40) (Table 3b). It must be noted however that, for every end point, the specific RRs attached to the various drug classes were not globally statistically different (all $P>0.05$, Table 3b). Finally, there was no significant residual risk with lipid-lowering agents for any end point, either in the overall analysis (Table 3a) or in the drug class analysis (Table 3c).

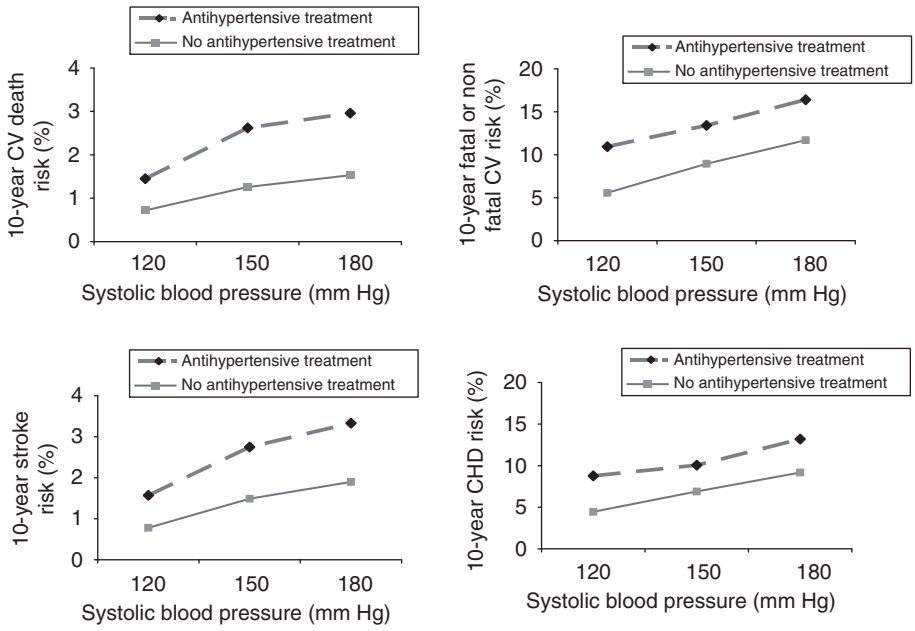

Figure 1 Relation between systolic blood pressure and 10-year risks of cardiovascular (CV) death, fatal or non-fatal cardiovascular event, stroke and coronary heart disease in patients with and without antihypertensive treatment. The relations were adjusted on centre, age, tobacco consumption, diabetes, total cholesterol and high-density lipoprotein (HDL) cholesterol. Residual cardiovascular risks were statistically significant in treated patients for all events studied ($P<0.05$ for all).

Adjusted 10-year rates of cardiovascular death, fatal or non-fatal cardiovascular, stroke and CHD events by tertiles of systolic blood pressure (<140, 140–160 and >160 mm Hg) in patients with and without antihypertensive treatment were plotted, using multivariate logistic regression adjusted for the classic cardiovascular risk factors (Figure 1).

Discussion

The salient finding in our study was that treatment by antihypertensive agents, either alone or in combination, but not by lipid-lowering agents, was associated with an increased residual cardiovascular risk in middle-aged men in primary cardiovascular prevention, after adjusting for classic risk factors, including systolic blood pressure and cholesterol levels. These findings applied to all the components of cardiovascular risk: coronary event, stroke, fatal or non-fatal cardiovascular events and cardiovascular mortality, but not non-cardiovascular mortality and total mortality. The drug treatment studied in this population was that which prevailed during the recruiting phase, that is years 1991–1993.

Antihypertensive agents

The increased residual cardiovascular risk associated with antihypertensive drug use in the present analysis cannot reflect a suboptimal blood pressure achieved in treated subjects, because all analyses were adjusted for the level of blood pressure on inclusion. Thus, the most likely explanation for our results is that the cardiovascular risk attributable to hypertension cannot be entirely reversed by antihypertensive drugs, at least in men in their fifties. This hypothesis has already been put forward by others. Andersson *et al*.[4] reported that treated hypertensive Swedish men had increased CHD mortality despite continuous good blood pressure control. Glynn *et al*.[5] developed cardiovascular risk prediction models using two large clinical trial cohorts (the Physicians' Health Study and the Women's Health Study). They reported, after adjustment for classic risk factors, including systolic and diastolic blood pressures, a 20% increase in cardiovascular risk associated with antihypertensive drug use. In the third report of the National Cholesterol Education Program Expert Panel, the presence of antihypertensive treatment was accepted as a cardiovascular risk factor.[6] Similarly, in three recently published papers, treatment by antihypertensive agents was associated with a significant increased residual cardiovascular risk, after adjusting for classic risk factors, including systolic blood pressure.[8–10] According to Hippisley-Cox *et al*.,[9] failure to take into account the presence of antihypertensive treatment would lead to a significant underestimation of cardiovascular risk in the population. From a pathophysiological point of view, this explanation is supported by numerous publications relating partly nonreversible modifications of cardiovascular structures and functions in hypertensives, even when correctly treated, such as cardiac hypertrophy, cardiac fibrosis, diastolic dysfunction, arterial stiffness, arterial fibrosis, arterial enlargement, endothelial dysfunction, vascular

inflammation, glomerular sclerosis, renal impairment and so on.[15]

Finally, another possible explanation for this residual cardiovascular risk could involve the addition of a drug-specific deleterious effect *per se* to an incomplete reversal of hypertension-attributable cardiovascular risk. This might result in an absolute risk difference that would not depend on blood pressure levels achieved, leading to a parallel relationship in blood pressure/risk in presence or in absence of antihypertensive therapy. Although partial reversal of the cardiovascular risk attributable to hypertension would be dependent on the blood pressure regulation achieved, the lower the achieved blood pressure, the lower the residual risk. Nevertheless, such an interpretation is speculative and our data cannot tease out the true underlying mechanisms.

For any cardiovascular end point, residual risk did not globally differ according to the antihypertensive drug class prescribed at entry, although this was close to the limit of significance for cardiovascular death. Nevertheless, it is interesting to observe that (1) CHD event risk was statistically significant in the presence of β-blockers in the contemporary era of increasing evidence against β-blockers as a first-line antihypertensive agents;[16] (2) CHD event risk was also statistically significant in the presence of CCAs, a drug class that was recently shown to be inferior to ACE inhibitors in CHD prevention;[17] (3) CHD being the major component of fatal or non-fatal cardiovascular events in this population, β-blockers and CCAs were also the two classes of antihypertensive drugs significantly associated with a residual risk; (4) stroke risk was statistically significant in the presence of ACE inhibitors, a drug class that was recently shown to be inferior to CCAs in cerebrovascular prevention;[17] (5) cardiovascular mortality risk was nearly statistically significant in the presence of diuretics, a class that was incriminated in sudden death;[18] (6) cardiovascular mortality was statistically significant in the presence of ACE inhibitors. This result is at variance with results of the major therapeutic trials, which have shown that ACE inhibitors cover a cardiovascular protective effect equal or superior to other antihypertensive classes,[19] although the largest therapeutic trial ever performed concluded on the global superiority of a thiazide diuretic (Chlorthalidone) over an ACE inhibitor (Lisinopril).[20]

Lipid-lowering agents

In this analysis, no residual risks were found for lipid-lowering agents, suggesting that some form of complete risk reversibility, at least observed at the population level, might be achieved through treatment of hyperlipidaemia, essentially by fibrates or statins prescribed in 50-year-old men. Interestingly, no evidence in favour of a risk-lowering effect associated with statin use for a given post-intervention level of total cholesterol and HDL cholesterol was observed. Such a finding seems to conflict with small pathophysiological studies focusing on intermediate end points,[21] but is in accordance with more objective epidemiological evidence.[22] Nevertheless, because only 2.9% of the population was treated with a statin, the power to demonstrate such a beneficial effect is very low.

Methodological limitations

Because cardiovascular benefits have been shown for antihypertensive drugs in severe, moderate and mild hypertension, placebo groups in controlled trials are no longer ethical, and the investigation of residual cardiovascular risk requires observational epidemiological studies in large studies, such as PRIME. Similar observations can be made for lipid-lowering agents. Observational studies have certain strengths, mainly their population-based prospective design, which generally introduces less selection bias than case–control studies, and its long follow-up, leading to a larger number of morbid events and deaths and increased power in the statistical analysis. However, because antihypertensive and lipid-lowering drug treatments were not randomly assigned, uncontrolled confounding factors cannot be excluded, and causal interpretation is uncertain. Another major limitation of our analysis concerns the fact that analyses were based on the treatment received at the beginning of the observation period, without allowing for treatment modification over the 10-year follow-up. Furthermore, because the patients' characteristics in the PRIME Study were based upon a unique medical visit at entry, statistical analyses were adjusted on the levels of cardiovascular risk factors, including blood pressure, at inclusion, but not during the period of follow-up; this might have confounded the relationship. Moreover, the finding of a residual cardiovascular risk associated with antihypertensive drug use in the present study cannot be extrapolated to groups other than middle-aged men with no cardiovascular history at baseline. These limitations seem important concerning the validity of the analysis of the antihypertensive drug class effects, because antihypertensive treatment are frequently modified in usual care; it might be less important when considering antihypertensive treatment as a whole, because the majority of hypertensives remain on treatment for long periods.

Finally, this analysis has shown that treatment with antihypertensive agents, but not with lipid-lowering agents, was associated with a significant residual cardiovascular risk in middle-aged men over a follow-up period of 10 years. These observational data cannot discriminate between a deleterious effect of the antihypertensive agents *per se* and an incomplete reversal of the cardiovascular risk attributable to antihypertensive drugs, or both. Interventional and observational epidemiology will

need to be considered in the future to understand more fully the role of residual risk in hypertensive outcomes and the differential effects of each drug class. It is therefore important to consider the presence of antihypertensive treatment in individual cardiovascular risk assessment, as subjects on treatment represent an increasing proportion of the population. Above all, the present results should stimulate the testing of similar hypotheses in other big international prospective cohorts to check their robustness and validity, in conjunction with the results of large prevention trials.

What is known about topic?

- Treatment for hypertension and/or hyperlipidaemia in not taken into account in the computation of cardiovascular risk of individuals.
- Evidence for (or against) the claimed preventive effects of some drug classes above (or below) those ascribable to the risk factor reduction is presently lacking at the epidemiological level.

What this study adds?

- In this analysis of the PRIME cohort data, we show that a sizeable cardiovascular risk is associated with the use of antihypertensive drugs, after adjusting for classic risk factors, including systolic blood pressure and cholesterol levels.
- These findings applied to all the components of cardiovascular risk: coronary event, stroke, fatal or non-fatal cardiovascular events and cardiovascular mortality, but not non-cardiovascular mortality and total mortality.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

We thank the following organizations that allowed the recruitment of the PRIME subjects: the Health screening Centres organized by the Social Security of Lille (Institut Pasteur), Strasbourg, Toulouse and Tourcoing; Occupational Medicine Services of Haute-Garonne, of the Urban Community of Strasbourg; the Association Interentreprises des Services Médicaux du Travail de Lille et environs; the Comité pour le Développement de la Médecine du Travail; the Mutuelle Générale des PTT du Bas-Rhin; the Laboratoire d'Analyses de l'Institut de Chimie Biologique de la Faculté de Médecine de Strasbourg; the Department of Health (NI) and the Northern Ireland Chest Heart and Stroke Association. We also thank the members of the event validation committees: Professor Louis Guize, Dr Caroline Morrison, Dr Marie-Thérèse Guillanneuf, Professor Maurice Giroud; and the Alliance Partnership Programme for its financial support. Pierre Ducimetière had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Appendix

The PRIME Study Group
The PRIME Study is organized under an agreement between INSERM and the Merck Sharp and Dohme-Chibret Laboratory, with the following participating laboratories:

- The Strasbourg MONICA Project, Laboratoire d'Epidemiologie et de Sante Publique, EA1801, Strasbourg, F-67085, France; Universite Louis Pasteur, Faculte de Medecine, Strasbourg, F-67085, France (D Arveiler and B Haas).
- The Toulouse MONICA Project, INSERM U558, Departement d'Epidemiologie, Universite Paul Sabatier-Toulouse Purpan, Toulouse, France (J Ferrières and JB Ruidavets).
- The Lille MONICA Project, INSERM U744, Lille, France; Institut Pasteur de Lille, Lille, France; Université de Lille 2, Lille, France (P Amouyel and M Montaye).
- The Department of Epidemiology and Public Health, Queen's University Belfast, Belfast, Northern Ireland (A Evans, J Yarnell and F Kee).
- The Department of Atherosclerosis, INSERM U545, Lille, France; Institut Pasteur de Lille, Lille, France; Université de Lille 2, Lille, France (G Luc and JM Bard).
- The Laboratory of Haematology, INSERM U626, Marseille, Hôpital La Timone, Marseille, France (I Juhan-Vague and P Morange).
- The Laboratory of Endocrinology, INSERM U563, Toulouse, France (B Perret).
- The Vitamin Research Unit, The University of Bern, Bern, Switzerland (F Gey).
- The Nutrition and Metabolism Group, Centre for Clinical and Population Sciences, Queen's University Belfast, Belfast, Northern Ireland (J Woodside and I Young).
- The DNA Bank, INSERM U525, Paris, France (F Cambien).
- The Coordinating Center, INSERM U780, Villejuif, F-94807, France; University Paris-Sud, Faculty of Medicine, Villejuif, F-94807, France (P Ducimetiere and A Bingham).