Primary care

Effects of low dose ramipril on cardiovascular and renal outcomes in patients with type 2 diabetes and raised excretion of urinary albumin: randomised, double blind, placebo controlled trial (the DIABHYCAR study)

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Abstract

Objective To investigate whether a low dose of the angiotensin converting enzyme (ACE) inhibitor ramipril lowers cardiovascular and renal events in patients with type 2 diabetes who have microalbuminuria or proteinuria.

Design Randomised, double blind, parallel group trial comparing ramipril (1.25 mg/day) with placebo (on top of usual treatment) for cardiovascular and renal outcomes for at least three years.

Setting Multicentre, primary care study conducted mostly by general practitioners in 16 European and north African countries.

Participants 4912 patients with type 2 diabetes aged >50 years who use oral antidiabetic drugs and have persistent microalbuminuria or proteinuria (urinary albumin excretion ≥ 20 mg/l in two consecutive samples), and serum creatinine ≤ 150 µmol/l.

Main outcome measures The primary outcome measure was the combined incidence of cardiovascular death, non-fatal myocardial infarction, stroke, heart failure leading to hospital admission, and end stage renal failure.

Results Participants were followed for 3 to 6 (median 4) years. There were 362 primary events among the 2443 participants taking ramipril (37.8 per 1000 patient years) and 377 events among the 2469 participants taking placebo (38.8 per 1000 patient years; hazard ratio 1.03 (95% confidence interval 0.89 to 1.20, P = 0.65)). None of the components of the primary outcome was reduced. Ramipril lowered systolic and diastolic blood pressures (by 2.43 and 1.06 mm Hg respectively after two years) and favoured regression from microalbuminuria (20-200 mg/l) or proteinuria (>200mg/l) to normal level (<20 mg/l) or microalbuminuria (P < 0.07) in 1868 participants who completed the study.

Conclusions Low dose (1.25 mg) ramipril once daily has no effect on cardiovascular and renal outcomes of patients with type 2 diabetes and albuminuria, despite a slight decrease in blood pressure and urinary albumin. The cardiovascular benefits of a daily higher dose (10 mg) ramipril observed elsewhere are not found with an eightfold lower daily dose.

Introduction

People with type 2 diabetes develop severe cardiovascular and renal diseases prematurely, especially those with high urinary albumin excretion (microalbuminuria or proteinuria).[1 2] The association of high urinary albumin excretion with poor cardiovascular prognosis in diabetes is well known.[3] Inhibition of the renin-angiotensin system in patients with type 1 and type 2 diabetes reduces high urinary albumin excretion[4–6] and improves renal outcome[7] in addition to lowering blood pressure. A high dose (10 mg a day) of the angiotensin converting enzyme (ACE) inhibitor ramipril improved the cardiovascular prognosis of a broad range of patients at high cardiovascular risk, including people with type 2 diabetes.[8–10]

The contribution of the fall in blood pressure to these beneficial effects of ACE inhibitors is still debated.[11 12] Low dose ramipril (1.25 mg a day), without measurable effect on blood pressure, reduced urinary albumin excretion in people with type 1 diabetes and microalbuminuria and left ventricular hypertrophy in hypertensive patients.[13 14] The DIABHYCAR (non-insulin-dependent diabetes, hypertension, microalbuminuria or proteinuria, cardiovascular events, and ramipril) study was established to test whether 1.25 mg ramipril daily would reduce cardiovascular and renal morbidity and mortality in normotensive or hypertensive patients with type 2 diabetes and microalbuminuria or proteinuria.[15]

Methods

Study design and patients

The study protocol is described elsewhere.[15] In brief, DIABHYCAR was a randomised, double blind, parallel group trial that compared the cardiovascular and renal outcomes for patients taking ramipril (1.25 mg once daily, usually in the morning) versus those taking placebo, plus their usual treatment (both groups). Eligible participants were older than 50 years, had type 2 diabetes (defined on the basis of receiving current treatment with at least one oral antidiabetic agent), and had urinary albumin excretion ≥20 mg/l, in two successive random urine samples. The principal exclusion criteria were a serum creatinine

P+ *A table giving baseline characteristics for normotensive and hypertensive participants is on bmj.com*

concentration >150 μmol/l; treatment with insulin, an ACE inhibitor, or an angiotensin II receptor blocker; documented congestive chronic heart failure; myocardial infarction during the past three months; urinary tract infection; and previous intolerance to an ACE inhibitor. The study was conducted mostly by general practitioners in 16 countries in Europe and north Africa (Austria, Belgium, Croatia, the Czech Republic, France, Germany, Greece, Hungary, Morocco, the Netherlands, Slovenia, Spain, Switzerland, Tunisia, Turkey, and the United Kingdom). All participants provided written informed consent.

End points
The primary end point of the study was the combined incidence of cardiovascular death (including sudden death), non-fatal acute myocardial infarction, stroke, heart failure requiring admission to hospital, and end stage renal failure (defined as requirement for haemodialysis or kidney transplant). These outcomes were also analysed separately. Secondary end points were fatal and non-fatal acute myocardial infarction, stroke, heart failure, and end stage renal failure, death from any cause, any revascularisation procedure (angioplasty, stenting, or bypass grafts) on coronary or other arterial vessels, transient neurological ischaemic episodes, doubling of the serum creatinine concentration (assessed annually), loss of vision in one eye, and amputation above the metatarsophalangeal joint. The investigators examined the participants every six months for at least three years. All primary and secondary end points were adjudicated according to standard definitions by a central end point committee, whose members were blinded to the treatment group assignment.[15]

Randomisation
Participants were randomly assigned to ramipril or its matched placebo by using a centralised telephone randomisation procedure stratified by centre and balanced by blocks of two treatments, using a computer generated random number list.

Biological methods
For the French participants glycated haemoglobin (HbA_{1c}) was assayed by HPLC (Bio-Rad Diamat Analyzer, Bio-Rad, Richmond, California, USA; range of normal values 4.0-5.6%) at the biochemistry laboratory, University Hospital, Angers, France. For other participants, HbA_{1c} was assayed locally and adjusted to the values of the French laboratory. Serum creatinine and blood glucose concentrations were assayed locally. Urinary albumin excretion was measured in the French laboratory by nephelometry (assay sensitivity 2 mg/l, intra-assay and interassay variability 4% and 5% respectively). Patients were selected for inclusion if they had a urinary albumin excretion ≥20 mg/l on two consecutive occasions: this two sample strategy predicts persistently high urinary albumin excretion with a specificity of >98%.[15 16] For logistical reasons, urinary albumin excretion at end of the study was measured once only in French participants who had completed the study.

At each examination, the local investigators measured blood pressure once, using a mercury sphygmomanometer and with the patient sitting.

Statistical analysis
Assuming an annual incidence of the primary end point of 6.7%, we initially estimated that 4000 subjects, followed for three years, would be sufficient to allow us to detect a 20% relative risk reduction of the primary end point with a power of 90%. Owing to a lower than expected incidence of the primary end point, the steering committee decided in September 1997 to extend the follow up to up to six years and to increase the recruitment (in

accordance with the recommendations of the independent data and safety committee).

Efficacy was analysed according to the intention to treat approach. Cumulative survival curves were constructed by means of the Kaplan-Meier procedure, and the log rank test was used to evaluate differences between groups. Only the first event in each participant was considered as a primary end point. If further events occurred—for example, a myocardial infarction after a stroke—these were classified as secondary end points. All significance levels are two tailed. The type I error rate for testing the primary end point was set at 0.048 at the final analysis to account for the two interim analyses performed after the first 200 and 400 primary outcomes had been adjudicated. The hazard ratio of the primary end point in the ramipril versus placebo groups and its 95% confidence interval were obtained by adjustment of a Cox model to a single covariate, the allocated treatment. For other end points, relative risks and their 95% confidence intervals were calculated. We used χ^2 tests for comparisons of proportions.

The data are given as means (with standard deviation) or median (with 95% confidence interval) values. All statistical analyses were performed with the SAS statistical software (version 6.2).

Results

Recruitment and follow up
From February 1995 to April 1998, 3973 investigators in the 16 participating countries screened 25 468 people with type 2 diabetes for high urinary albumin excretion: 19 520 did not meet this inclusion criterion—a proportion similar to that seen in other studies,[16] and a further 1011 did not consent to participate. The remaining 4937 people—with type 2 diabetes and high urinary albumin excretion—were randomised. Twenty investigators (who had included 25 participants) were excluded from the study by the steering committee in September 1998 because they provided no data after randomisation and refused site visits. Among the remaining 4912 participants, 2443 were assigned to receive ramipril 1.25 mg a day and 2469 to receive placebo. Table 1 shows the characteristics of participants at entry.

We report data collected up to 31 March 2001. The trial ended prematurely for 838 (17%) participants: 678 (14%) withdrew and refused to be followed up subsequently (344 (14%) taking ramipril and 334 (14%) taking placebo); and 160 (3.2%) were lost to follow up (62 (2.5%) taking ramipril and 98 (4.0%) taking placebo), and their primary end point status is unknown. These participants were censored at the time of discontinuation.

The median duration of follow up was 47 months (1st quarter 38 months, 3rd quarter 60 months). In all, 138 (2.8%) participants (70 (2.9%) assigned to take ramipril, 68 (2.8%) to take placebo) never started the study treatment. At one year, 2043 of the 2377 (85.9%) surviving participants in the ramipril group and 2111 of the 2415 (87.4%) surviving participants in the placebo group were still taking study drugs. At the end of the study, 1250/1209 (59.3%) surviving participants in the ramipril group and 1265/2145 (59.0%) surviving participants in the placebo group were still taking study drugs. In all, 4074 (82.9%) participants were followed to 31 March 2001, died, or presented with a non-fatal primary end point (fig 1).

Primary and secondary end points

Primary

There were 739 primary end point events (in 15.0% of the participants) during the study, 362 (14.8%, 37.8 per 1000 patient
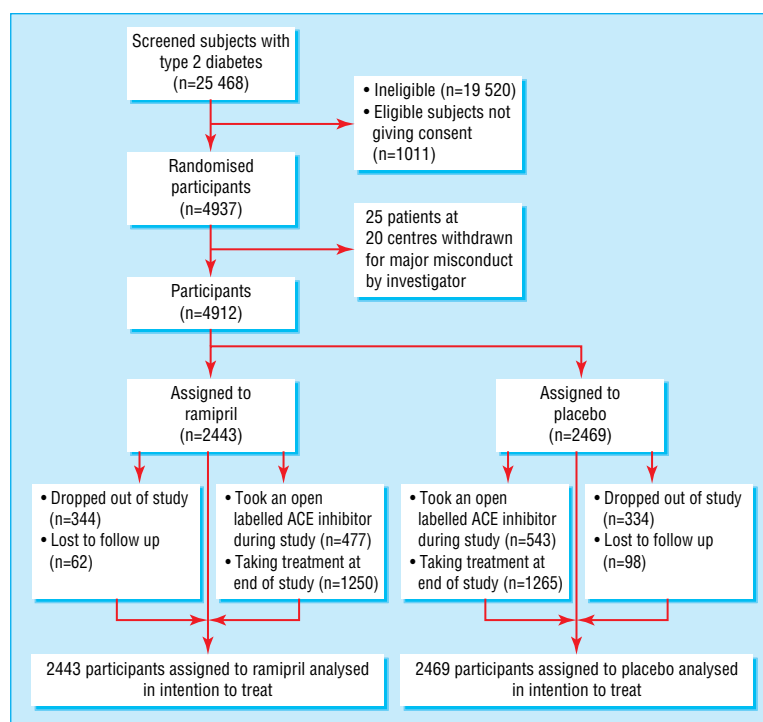
Fig 1 Chart showing flow of participants through study. ACE=angiotensin converting enzyme inhibitor

years) in the ramipril group and 377 (15.3%, 38.8 per 1000 patient years) in the placebo group (hazard ratio 1.03, 95% confidence interval 0.89 to 1.20, P = 0.65) (fig 2). We found no difference between the two groups for each of the components of the primary end point (table 2). There were 137 primary end point events among the 1065 (12.9%) normotensive participants taking ramipril and 137 (12.3%) among the 1112 normotensive participants taking placebo (relative risk 1.044, 95% confidence

interval 0.837 to 1.303). There were 225 (16.3%) primary end point events among 1378 hypertensive participants taking ramipril and 240 (17.7%) among the 1357 hypertensive participants taking placebo (0.923; 0.782 to 1.09).

Secondary
We found no effect of the study treatment on the secondary end points (table 2).

Adverse events
More participants stopped taking ramipril than placebo because of coughing (3.3% *v* 0.9%). Two participants developed angio-oedema (one taking ramipril, related to treatment, and one taking placebo, not related to treatment). Table 3 shows the adverse events experienced by participants during the study.

Other analyses
More participants taking placebo than ramipril took angiotensin II receptor antagonists or ACE inhibitors other than ramipril during the study (543 (22.9%) *v* 477 (20.0%); log rank test P = 0.05).

Table 1 Baseline characteristics of the 4912 randomised participants, according to treatment group. Values are numbers (percentages) of patients unless stated otherwise

	Ramipril (n=2443)		Placebo (n=2469)	
Sex (male, female)	1701,	742	1731,	738
Mean (SD) age (years)	65.2	(8.4)	65.0	(8.3)
Mean (SD) body mass index (kg/m^2)	29.2	(4.5)	29.2	(4.7)
Mean (SD) fasting blood glucose (mmol/l)	9.7	(3.1)	9.9	(3.3)
Mean (SD) HbA$_{1c}$ (%)	7.85	(1.82)	7.79	(1.81)
Mean (SD) diabetes duration (years)	9.8	(7.3)	9.8	(7.5)
Mean (SD) systolic blood pressure (mm Hg)	145.8	(15.0)	145.1	(15.2)
Mean (SD) diastolic blood pressure (mmHg)	82.4	(8.7)	82.2	(8.5)
Hypertensive*	1378	(56.4)	1357	(55.0)
Smoker (≥1 cigarette/day)	371	(15.2)	385	(15.6)
Alcohol consumption (≥1 glass/day)	1123	(46.0)	1135	(46.0)
Mean (SD) serum creatinine (μmol/l)	89.2	(20.7)	89.2	(19.6)
Microalbuminuria (20-200 mg/l†)	1792	(73.4)	1835	(74.3)
Proteinuria (≥200 μg/l†)	651	(26.6)	634	(25.7)
Previous myocardial infarction	137	(5.6)	158	(6.4)
Peripheral vascular disease	218	(8.9)	285	(11.5)
Previous stroke	107	(4.4)	100	(4.1)
Previous retinopathy	126	(5.2)	120	(4.9)
No previous cardiovascular disease	1895	(77.6)	1816	(73.6)
Drug treatment:				
Antihypertensive agents	1158	(47.4)	1184	(48.0)
Lipid lowering agents	727	(29.8)	674	(27.3)
Antiplatelets	447	(18.3)	472	(19.1)

*Blood pressure >140/90 mm Hg and/or taking antihypertensive drugs.
†Mean of two determinations.
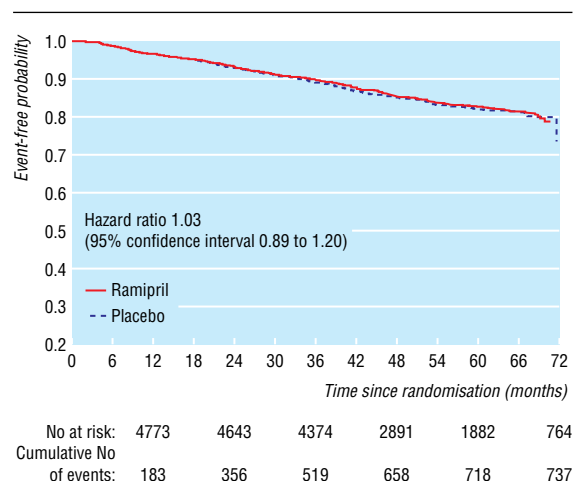
Fig 2 Incidence of the primary end point according to treatment group

Table 2 Incidence of primary end point (combined and in its separate components) and secondary end points, according to treatment group. Values are numbers (percentages) of participants in whom events occurred, unless stated otherwise

	Ramipril (n=2443)	Placebo (n=2469)	Relative risk (95% confidence interval)	P value
Primary end point				
Combined	362 (14.8)	377 (15.3)	0.97 (0.85 to 1.11)	0.66
Cardiovascular death*	141 (5.8)	133 (5.4)	1.07 (0.85 to 1.35)	0.58
Myocardial infarction (non-fatal)	52 (2.1)	59 (2.4)	0.89 (0.61 to 1.29)	0.57
Stroke (non-fatal)	89 (3.6)	84 (3.4)	1.07 (0.80 to 1.44)	0.70
Heart failure (non-fatal)†	76 (3.1)	91 (3.7)	0.84 (0.62 to 1.14)	0.27
End stage renal failure‡	4 (0.2)	10 (0.4)	0.40 (0.13 to 1.30)	0.18
Secondary end points				
Total mortality	334 (13.7)	324 (13.1)	1.04 (0.90 to 1.20)	0.57
Cardiovascular death§	179 (7.3)	175 (7.1)	1.03 (0.85 to 1.26)	0.77
Myocardial infarction (fatal and non-fatal)	61 (2.5)	78 (3.2)	0.79 (0.57 to 1.10)	0.16
Stroke (fatal and non-fatal)	118 (4.8)	116 (4.7)	1.03 (0.80 to 1.32)	0.83
Heart failure(fatal and non-fatal)†	85 (3.5)	102 (4.1)	0.84 (0.64 to 1.12)	0.22
End stage renal failure (fatal and non-fatal)‡	11 (0.5)	12 (0.5)	0.93 (0.41 to 2.10)	0.85
Revascularisation procedures (cardiac or peripheral)	179 (7.3)	201 (8.1)	0.90 (0.74 to 1.09)	0.29
Transient neurological ischaemic episode	22 (0.9)	21 (0.9)	1.06 (0.58 to 1.92)	0.85
Loss of vision of one eye	8 (0.3)	8 (0.3)	1.01 (0.38 to 2.69)	0.98
Doubling of serum creatinine	48 (2.0)	60 (2.4)	0.81 (0.56 to 1.12)	0.27
Amputation beyond metatarsophalangeal joint	28 (1.1)	26 (1.1)	1.09 (0.64 to 1.85)	0.75

Different numbers of the same event appear as primary or as secondary end points because only the first event in one participant is a component of the primary end point. However, a participant might have had several other events later. These are added to the numbers of secondary end points
*Including sudden death (77 events (3.2%) in the ramipril group and 77 (3.1%) in the placebo group) and death of unknown origin (32 (1.3%) events in the ramipril group and 30 (1.2%) in the placebo group).
†Requiring hospital admission or the intervention of a mobile coronary care unit.
‡Requiring haemodialysis or kidney transplantation.
§Death from a cardiovascular cause, sudden death, or death from an unknown cause.

At one year, compared with baseline values, systolic and diastolic blood pressure in those taking ramipril had fallen by 1.89 mm Hg and 1.34 mm Hg respectively, whereas in those taking placebo systolic blood pressure had risen by 0.22 mm Hg and diastolic pressure had fallen by 0.33 mm Hg (intergroup differences: systolic 2.12 (95% confidence interval 1.19 to 3.05); diastolic 1.01 (0.45 to 1.57)).

At two years, compared with baseline values, systolic and diastolic blood pressure had fallen by 2.52 mm Hg and 1.89 mm Hg respectively in those taking ramipril and by 0.09 mm Hg and 0.83 mm Hg respectively in those taking placebo (intergroup differences: systolic 2.43 (1.43 to 3.44); diastolic 1.06 (0.46 to 1.65)).

At final evaluation, compared with baseline values, systolic and diastolic blood pressure had fallen by 3.61 mm Hg and 2.37 mm Hg respectively in those taking ramipril and by 2.32 mm Hg and 1.98 mm Hg respectively in those taking placebo (intergroup differences: systolic 1.54 (0.34 to 2.75); diastolic 0.30 (−0.40 to 0.99)).

We found no differences between the two groups for blood glucose concentration and body weight (data not shown).

Between the first and the last examination, serum creatinine concentration increased comparably in the ramipril and placebo groups, by 8 μmol/l (standard deviation 37) and 9 μmol/l (SD 43) respectively. The urinary albumin excretion was measured in 1868 French participants (935 taking ramipril, 933 taking placebo) at the end of follow up. There was a trend towards more regression from proteinuria (urinary albumin excretion >200 mg/l) and microalbuminuria (20-200 mg/l) to normal (urinary albumin excretion <20 mg/l) or microalbuminuria among those taking ramipril than those taking placebo (27% v 23%; relative reduction in risk 14% (95% confidence intervals −4% to 28%), χ^2 test, 1 df, P<0.07).

Table 3 Numbers (percentages) of participants who experienced adverse events during study

	Ramipril group (n=2443)	Placebo group (n=2469)
Non-serious adverse events	154 (6.3)	98 (4.0)
Most frequent:		
Cough	80 (3.3)	21 (0.9)
Hypertension	8 (0.3)	12 (0.5)
Vertigo	8 (0.3)	6 (0.2)
Diarrhoea	7 (0.3)	6 (0.2)
Headache	4 (0.2)	5 (0.2)
Serious adverse events	1055 (43.2)	1097 (44.4)
Most frequent:		
Inadequate control of diabetes	339 (13.9)	346 (14.0)
Cardiac failure	70 (2.9)	72 (2.9)
Atrial fibrillation	60 (2.5)	48 (1.9)
Hypertension	51 (2.1)	54 (2.2)
Angina pectoris	35 (1.4)	61 (2.5)
Adverse events (serious or not) leading to discontinuation of treatment	609 (24.9)	554 (22.4)

Discussion

The DIABHYCAR study was set up after two small short term studies had shown that two cardiovascular risk markers, microalbuminuria and left ventricular hypertrophy, were similarly reduced by 1.25 mg and 5 mg ramipril, once daily, whereas blood pressure was decreased by the 5 mg dose only.[13 14] Other multicentre studies among people with type 1 and 2 diabetes have confirmed that 1.25 mg a day of ramipril reduced microalbuminuria as effectively as 5 mg a day.[17–19]

The hypothesis tested in the DIABHYCAR study was that 1.25 mg of ramipril would reduce cardiovascular risk, in parallel to a fall in urinary albumin excretion, and without any decrease in blood pressure. Results were not as expected. Blood pressure in the ramipril group decreased minimally but significantly; urinary albumin excretion improved slightly; and the cardiovascular risk was not reduced. Therefore, the DIABHYCAR study

shows that a low dose of ramipril—1.25 mg a day for three years or more—does not reduce the high cardiovascular risk of patients with type 2 diabetes with high urinary albumin excretion, mostly recruited by general practitioners. By comparison with the HOPE and MICRO-HOPE studies,[8–10] this absence of cardiovascular protection by low dose ramipril suggests that a marked inhibition of the renin-angiotensin system is required to reduce the cardiovascular risk associated with type 2 diabetes and raised urinary albumin excretion.

The absence of cardiovascular prevention in high risk subjects by 1.25 mg ramipril once a day—whereas a 10 mg dose was effective—suggests a dose dependency of the cardioprotective effect of this ACE inhibitor. The same interpretation may apply to all other blockers of the renin-angiotensin system, which differ by their pharmacokinetics and pharmacological properties.

Comparison with HOPE and MICRO-HOPE studies

Several of our results show that this low ramipril dose did have a biological effect, however. We detected the expected effects of an ACE inhibitor. The differences in systolic (2.43 mm Hg) and diastolic (1.06 mm Hg) blood pressure between the ramipril and placebo group are of the same magnitude as the differences in the MICRO-HOPE study (2.4 mm Hg, 1.0 mm Hg). In the MICRO-HOPE study the relative reduction in urinary albumin excretion induced by a 10 mg/day dose of ramipril was 22%[9] whereas in the DIABHYCAR study the reduction was 14% for a 1.25 mg/day dose. This reduction was measured in a subgroup of French patients who survived and completed the trial, which underestimates the actual effect because of the exclusion by death of the patients with the most serious illnesses. The increased incidence of cough in the group taking ramipril also confirms—through the presence of an expected adverse effect—the biological efficacy of the 1.25 mg ramipril dose.

The differences between the results of DIABHYCAR and those of HOPE and MICRO-HOPE cannot be explained solely by differences in the study populations. All the patients with type 2 diabetes recruited from February 1995 to April 1998 for the DIABHYCAR study had a permanent high urinary albumin excretion, and therefore a high cardiovascular risk, but only 22% had a previous cardiovascular disease. Conversely, only 30% of the diabetic patients recruited in the HOPE and MICRO-HOPE[11] studies from December 1993 to June 1995 had an abnormal urinary albumin excretion in a single sample, but 68% had a previous cardiovascular disease. Thus, DIABHYCAR is more of a primary prevention trial and HOPE and MICRO-HOPE are secondary prevention trials, although all participants had high cardiovascular risk. The difference in the study population probably explains why there were fewer end points events (particularly myocardial infarctions) in DIABHYCAR than in MICRO-HOPE. However, as the risk reduction induced by a 10 mg/day dose of ramipril in the diabetic participants of the HOPE and MICRO-HOPE studies was of the same magnitude regardless of whether the patients had previous cardiovascular disease, the difference in the proportions of patients with previous cardiovascular disease in DIABHYCAR and in the HOPE study is not a likely explanation of the differences in their results.[9]

Several factors may contribute to a dilution of the effect of low dose ramipril in comparison with placebo. To have a sufficient number of events, 16 countries and a large number of general practices participated, thereby increasing heterogeneity of both clinical care (especially the timing and routine methods of blood pressure measurements) and duration of previous exposure to risk factors (hypertension, diabetes, hypercholesterolaemia) and treatments. Retrospectively, the study had a 90% power to detect a 20% difference in the combined end point between the groups, with an α risk of 0.048. However, some usual difficulties of long term trials were more prominent in DIABHYCAR than in MICRO-HOPE. Although only 2.8% of patients were lost to follow up, 59.3% of patients taking ramipril were still taking the drug at the end of DIABHYCAR compared with 65% at the end of MICRO-HOPE. In addition, 20-23% of the participants were exposed to a blocker of the renin-angiotensin system at some time during DIABHYCAR, whereas this occurred in only 12-15% of the patients during MICRO-HOPE.

Dose dependency of ACE inhibitors for cardiovascular and renal protection

We still consider, however, that the use of low dose ramipril may explain most of the striking difference between MICRO-HOPE (25% relative risk reduction of the combined primary outcome, 95% confidence interval 13% to 36%, P < 0.004) and DIABHYCAR (3%, 95% confidence intervals − 11 to 20%, P = 0.65), when interpreted within the context of what is already known on the cardiovascular and renal protective effects of ACE inhibitors and angiotensin II antagonists, and more specifically of ramipril.

Experiments in rabbits have shown that atheromatous lesions were successfully prevented by a high dose of trandolapril, whereas a low dose had no effect,[20] although plasma ACE activity was inhibited similarly. As for clinical investigation, the SECURE study has shown a strong dose dependency of atherosclerosis progression, as estimated from carotid intima-media thickness measured by B mode carotid ultrasound; a 2.5 mg dose of ramipril did not affect it more than placebo, whereas ramipril 10 mg daily did.[21] Along the same lines, Parving et al have shown a dose-response effect of the protection from ongoing kidney damage by the angiotensin receptor blocker, irbesartan, at 150 mg and 300 mg daily.[22]

That cardiovascular and renal protection by an ACE inhibitor is dose-dependent has important implications for current clinical care and for research on prevention of cardiovascular disease by the inhibition of the renin-angiotensin system. It means that patients treated by once daily, usual doses of ACE inhibitors in hypertension trials may have experienced a lower cardiovascular benefit than could have been safely achieved if ACE inhibitors had been used at higher doses. The benefit to risk ratio of high doses of other ACE inhibitors, of angiotensin II antagonists,[23] or of the two types of drugs combined certainly deserves further investigation.

Despite the well known difficulties of interpretation generated by the results of "negative" randomised trials, we conclude that our results, interpreted in the context of other experimental and clinical data, show that high doses of ramipril—and possibly other blockers of the renin-angiotensin system—are preferable to low doses in the prevention of cardiovascular and renal events in patients at high risk of cardiovascular events.

What is already known on this topic

Albuminuria (both microalbuminuria and proteinuria) is an independent predictor of premature cardiovascular events in people with type 2 diabetes

Angiotensin converting enzyme (ACE) inhibitors at low doses reduce albuminuria and blood pressure in these people

The ACE inhibitor ramipril at high dose (10 mg a day) reduces cardiovascular risk in people with type 2 diabetes and albuminuria

What this study adds

Ramipril at low dose (1.25 mg a day) did not prevent cardiovascular events in people with type 2 diabetes and albuminuria, although it slightly reduced their albuminuria and blood pressure

Thus, high dose ramipril can be recommended for cardiovascular protection of these people with type 2 diabetes and albuminuria

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