Blood-pressure control for renoprotection in patients with non-diabetic chronic renal disease (REIN-2): multicentre, randomised controlled trial

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Summary

Background **In chronic nephropathies, inhibition of angiotensin-converting enzyme (ACE) is renoprotective, but can further renoprotection be achieved by reduction of blood pressure to lower than usual targets? We aimed to assess the effect of intensified versus conventional blood-pressure control on progression to end-stage renal disease.**

Methods **We undertook a multicentre, randomised controlled trial of patients with non-diabetic proteinuric nephropathies receiving background treatment with the ACE inhibitor ramipril (2·5–5 mg/day). We randomly assigned participants either conventional (diastolic <90 mm Hg; n=169) or intensified (systolic/diastolic <130/80 mm Hg; n=169) blood-pressure control. To achieve the intensified blood-pressure level, patients received add-on therapy with the dihydropyridine calcium-channel blocker felodipine (5–10 mg/day). The primary outcome measure was time to end-stage renal disease over 36 months' follow-up, and analysis was by intention to treat.**

Findings **Of 338 patients who were randomised, three (two assigned intensified and one allocated conventional blood-pressure control) never took study drugs and they were excluded. Over a median follow-up of 19 months (IQR 12–35), 38/167 (23%) patients assigned to intensified blood-pressure control and 34/168 (20%) allocated conventional control progressed to end-stage renal disease (hazard ratio 1·00 [95% CI 0·61–1·64]; p=0·99).**

Interpretation **In patients with non-diabetic proteinuric nephropathies receiving background ACE-inhibitor therapy, no additional benefit from further blood-pressure reduction by felodipine could be shown.**

Introduction

In diabetic and non-diabetic chronic nephropathies, high blood pressure is a major determinant of disease progression, and blood-pressure reduction is renoprotective.[1] Reducing blood pressure with drugs that inhibit the renin-angiotensin system has the additional benefit of lowering glomerular hypertension,[2] which in turn, ameliorates glomerular-sieving properties.[3] In animals, at comparable levels of blood-pressure control, angiotensin-converting-enzyme (ACE) inhibitors or angiotensin-II-receptor blockers are more renoprotective than conventional antihypertensive drugs.[2–4] Work done in patients accords with this finding.[5–10] In individuals with non-diabetic renal disease, the Ramipril Efficacy In Nephropathy (REIN) trial[5–7] showed that—at comparable levels of blood-pressure control—the ACE inhibitor ramipril slowed decline in glomerular filtration rate (GFR) and reduced progression to end-stage renal disease by 50% compared with conventional drugs.

Can blood-pressure reduction to levels lower than in the REIN study (diastolic <90 mm Hg) help to further retard or even prevent dialysis? Results of the Modification of Diet in Renal Disease study[11,12] showed that in patients with non-diabetic proteinuric renal disease, targeting treatment at blood-pressure levels of 125/75 mm Hg or less reduced GFR decline more effectively than if the target was 140/90 mm Hg.[11] However, 48% of patients in the lower blood-pressure group received ACE-inhibitor therapy versus 28% in the usual blood pressure group.[12] Thus, the benefit recorded in the low blood-pressure group was affected by use of ACE inhibitors. In the African American Study of Kidney Disease and Hypertension (AASK),[9] targeting antihypertensive therapy at a mean blood pressure of 92 mm Hg, compared with usual targets of 102–107 mm Hg, did not slow progression of hypertensive nephrosclerosis. In this study, an identical proportion of patients in the usual or lower blood-pressure group was on ACE-inhibitor therapy.[9] A meta-analysis of 11 randomised trials of ACE-inhibitor therapy in 1860 people with non-diabetic chronic kidney disease showed that systolic blood-pressure reduction to less than 120 mm Hg did not offer additional renoprotection compared with targets of 120–130 mm Hg, and reduction to 110 mm Hg or less even accelerated progression of renal disease.[13] Thus, the additional benefit of blood-pressure reduction to lower than the original REIN study targets[5–7] remains questionable and might even create safety issues, particularly in the setting of concomitant ACE-inhibitor therapy.[13] With this background, the REIN-2 trial was designed to establish whether, on top of ACE inhibition, further blood-pressure lowering could be of benefit in chronic kidney disease. Our primary objective was to

assess the effect of intensified versus conventional blood-pressure control on progression to end-stage renal disease. Secondary aims were to compare the effects of two different levels of blood-pressure control on GFR decline, residual proteinuria, and fatal and non-fatal cardiovascular events, and to investigate the relations between achieved blood-pressure reduction and main outcome variables.

Participants and methods

Participants

Between June, 1999, and June, 2003, we screened men and women (age 18–70 years) who had non-diabetic nephropathy and persistent proteinuria and who had not received ACE-inhibition therapy for at least 6 weeks for inclusion in our study. We defined persistent proteinuria as urinary protein excretion exceeding 1 g per 24 h for at least 3 months without evidence of urinary-tract infection or overt heart failure (New York Heart Association class III–IV). Patients with proteinuria of 1–3 g per 24 h were included if their creatinine clearance was less than 45 mL/min per 1·73 m^2; those with a proteinuria of 3 g per 24 h or more were included if their creatinine clearance was less than 70 mL/min per 1·73 m^2. Exclusion criteria were: treatment with corticosteroids, non-steroidal anti-inflammatory drugs, or immunosuppressive drugs; acute myocardial infarction or cerebrovascular accident in the previous 6 months, severe uncontrolled hypertension, evidence or suspicion of renovascular disease, obstructive uropathy, type 1 diabetes mellitus, collagen disease, cancer, higher serum amino-transferase concentrations, or chronic cough, history of allergy, or poor tolerance to ACE inhibitors or dihydropyridine calcium-channel blockers; drug or alcohol abuse; pregnancy; breastfeeding; and ineffective contraception. The ethics committee and institutional review board of all hospitals involved approved the protocol for this study. Every participant gave written informed consent.

Procedures

After 6 weeks' washout from ACE inhibitors, angiotensin-II-receptor antagonists, and dihydro-pyridine calcium-channel blockers, we asked eligible patients to submit three consecutive 24-h urine samples within 2 weeks for baseline evaluation. This assessment included measurement of arterial blood pressure, serum creatinine, creatinine clearance, 24-h urinary protein (mean of three consecutive samples), sodium, and urea excretion. We recommended a low-sodium diet and a daily protein intake of about 0·8 g/kg, and we did not make any changes to diet during the study. Treatment with thiazide or loop diuretics, but not potassium-sparing diuretics, was adjusted as deemed appropriate to maintain fluid and sodium balance. To maintain diastolic blood pressure at less than 90 mm Hg, we allowed use of antihypertensive drugs, apart from ACE inhibitors, angiotensin-II-receptor antagonists, and dihydropyridine calcium-channel blockers.

After the baseline evaluation, eligible patients entered a 6-week run-in period. We gave participants ramipril 2·5 mg/day after previous diuretic therapy had been withdrawn for at least 24 h. The ramipril dose was up-titrated after a week to 5 mg/day and concomitant antihypertensive therapy was down-titrated to maintain diastolic blood pressure at less than 90 mm Hg—ie, maximum tolerated dose of ramipril, minimum dose of concomitant antihypertensive drugs.

At the end of the run-in phase, we repeated the baseline evaluations and measured the GFR (prerandomisation assessment). We randomly assigned patients to either conventional blood-pressure control (diastolic blood pressure <90 mm Hg, irrespective of systolic blood pressure) or to intensified blood-pressure control (systolic blood pressure <130 mm Hg, diastolic blood pressure <80 mm Hg)[14] to be achieved with a long-acting dihydropyridine calcium-channel blocker that does not directly inhibit the renin-angiotensin system.[15] We randomised patients with the minimisation method,[16,17] which considered the following factors: site, previous treatment with an ACE inhibitor or an angiotensin-II-receptor antagonist (1, yes for <36 months; 2, yes for ⩾36 months; 3, no), previous participation in the REIN study (yes/no), and level of proteinuria (⩾3 g per 24 h or ⩾1 to <3 g per 24 h). An updated registration of treatment assignment for each factor was required and in case of equal sums, a simple randomisation list was considered. The randomisation process was centrally administrated by the treatment assignment secretariat. Because of the nature of the study—ie, two different targets of blood-pressure control—investigators and patients were both aware of the allocation.

Patients assigned conventional blood-pressure control continued their treatment with ramipril and concomitant antihypertensive drugs. Those allocated intensified blood-pressure control received felodipine 5 mg/day as an add-on to their previous treatment with ramipril and concomitant antihypertensive drugs. We up-titrated the felodipine dose after a week to 10 mg/day according to blood-pressure response. In both arms, we allowed up-titration and down-titration of concomitant treatments to maintain the target blood pressure and to avoid symptomatic hypotension. Changes in the ramipril dose were avoided throughout the study period. The broad aim was to have comparable ramipril doses in the two arms, so the only difference would be in blood-pressure control. In both arms, to achieve and maintain the target blood pressures we allowed use of diuretics (first choice), β blockers, α/β blockers, antiadrenergic drugs such as clonidine, prazosin or methyldopa, non-dihydropyridine calcium-channel blockers such as verapamil and diltiazem (second choice), and

vasodilators such as minoxidil or hydralazine (third choice). ACE inhibitors other than ramipril and angiotensin-II-receptor antagonists were forbidden, as were dihydropyridine calcium-channel blockers different from felodipine.

We measured blood pressure 1 week, 2 weeks, and 3 months after randomisation, and every 3 months thereafter. Additional measurements were done within 1 week after any change in antihypertensive therapy and whenever deemed clinically appropriate. The blood pressure measurement was the mean of three values taken 2 min apart, after 5 min rest in the sitting position, on the same arm by a standard sphygmomanometer. We followed up all patients even if target blood pressure was not achieved. GFR studies were restricted to centres that, a priori, could do all the planned measurements in all randomised patients. We assessed GFR centrally (at Mario Negri Institute for Pharmacological Research, Bergamo, Italy) by plasma clearance of non-radioactive iohexol.[18] At least three measurements, including baseline, were needed to calculate the rate of GFR decline (ΔGFR). We measured complete blood-cell count, concentration in serum of lipids, calcium, phosphate, and uric acid before randomisation and every 6 months. Serum creatinine, creatinine clearance, 24 h urinary protein (mean of three consecutive samples), sodium, and urea excretion, were also measured at these times and at month 3.

Statistical analysis

This was a superiority study undertaken to test the hypothesis that treatment targeted to reduce blood pressure to lower-than-usual levels might be more renoprotective than treatment targeted to maintain usual blood-pressure levels. The primary outcome measure was time to end-stage renal disease over 36 months' follow-up. Based on the outcome of patients included in the REIN study and randomised to ramipril treatment,[5–7] the incidence of end-stage renal disease in patients allocated conventional blood-pressure control was estimated to be 8% per year. A 50% reduction (from 8% per year to 4% per year) was predicted in patients allocated intensified blood-pressure control. To give the study the power ($1-\beta=0\cdot80$) to detect as significant ($\alpha=0\cdot05$, two-tailed test) a 50% difference in the cumulative incidence of end-stage renal disease between the two treatment groups, 160 patients in each group had to complete the study. Screening of patients was continued until 320 people had been randomised. At this time, 18 patients were already in the run-in phase: they completed the run-in and were randomised. Thus, 338 patients (169 per group) were randomised.

All analyses were undertaken independently at the Mario Negri Institute for Pharmacological Research. Analyses were done by intention-to-treat on the full analysis set, which included all randomised patients apart from three who never took the study drugs and were not followed up. We tabulated summary statistics by arm and according to proteinuria (<3 g per 24 h or $\geqslant3$ g per 24 h). Risk of progression to end-stage renal disease in the two arms was compared univariately with the log-rank test and was assessed multivariately by proportional-hazards regression (SAS PROC PHREG, version 8; SAS Institute, Cary, NC, USA), including the following baseline covariates: sex, age, mean arterial pressure, concentration in serum of creatinine, and log-transformed 24-h proteinuria. We plotted Kaplan-Meier curves for the two arms.

Rate of GFR decline was compared univariately with the Wilcoxon rank-sum test and multivariately by multiple regression (SAS PROC REG, version 8), including the above-mentioned covariates. We compared blood pressures and log-transformed proteinuria by ANCOVA. For explorative reasons, the mean arterial pressure during follow-up instead of the baseline value was also assessed. Concomitant antihypertensive therapy was described in an analysis, without inferential statistics.

An independent adjudicating panel was appointed to monitor ethical and statistical issues and, in particular, to assess the safety and efficacy profiles of the two study groups at predefined interim analyses. Interim analyses were planned after the last randomised patient had completed 6-month follow-up and every year thereafter up to study end. The statistical stopping rule was based on the Haybittle and Peto approach[19] (overall two-sided $\alpha=0\cdot05$). The independent adjudicating panel was updated on the results of the interim analyses and on the incidence of major events (deaths, serious adverse events, major cardiovascular events), and had authority to stop the study at any time for safety, efficacy, or futility. Moreover, the study protocol established a priori that if any interim analysis showed a highly significant difference in ΔGFR between the two study groups in favour of intensified blood-pressure control ($p<0\cdot001$) or of conventional blood-pressure control ($p<0\cdot01$), the study had to be stopped prematurely for efficacy and safety reasons, respectively. Statistical stopping rules were detailed in the statistical plan. We used a difference in favour of intensified blood-pressure control[20] of less than 25% to stop the trial for futility.

Role of the funding source

The REIN-2 trial was an independent academic study designed, undertaken, and monitored by the Mario Negri Institute for Pharmacological Research. Aventis Pharma SA (France) supplied ramipril and Simesa SpA (Italy) supplied felodipine. The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

The first interim analysis, done as per protocol, showed that, despite more effective blood-pressure reduction in the intensified blood-pressure control arm, the cumulative incidence of end-stage renal disease, rate of GFR decline, and residual proteinuria were similar in the two arms. Moreover, none of the above outcome variables was affected to any great extent. On the basis of these findings, the independent adjudicating panel stated that the study had to be stopped for futility. All data recorded in the database at the time the study was stopped were included in the present analysis.

338 patients were randomly assigned either conventional or intensified blood-pressure control, and, of these, 335 were followed up for a median of 19 months (IQR 12–35; figure 1). The follow-up period was similar for the two groups. Baseline characteristics were balanced between groups (table 1). An identical proportion of patients (84%) was on ramipril 5 mg/day in the two arms; the remaining patients were on ramipril 2·5 mg/day. These doses were not modified throughout the study period. About two-thirds of patients in the intensified blood-pressure control arm were on felodipine 10 mg/day at different visits during the follow-up period; the remainder were on felodipine 5 mg/day. Table 2 shows concomitant treatments with diuretics and other blood-pressure-lowering drugs at baseline and follow-up.

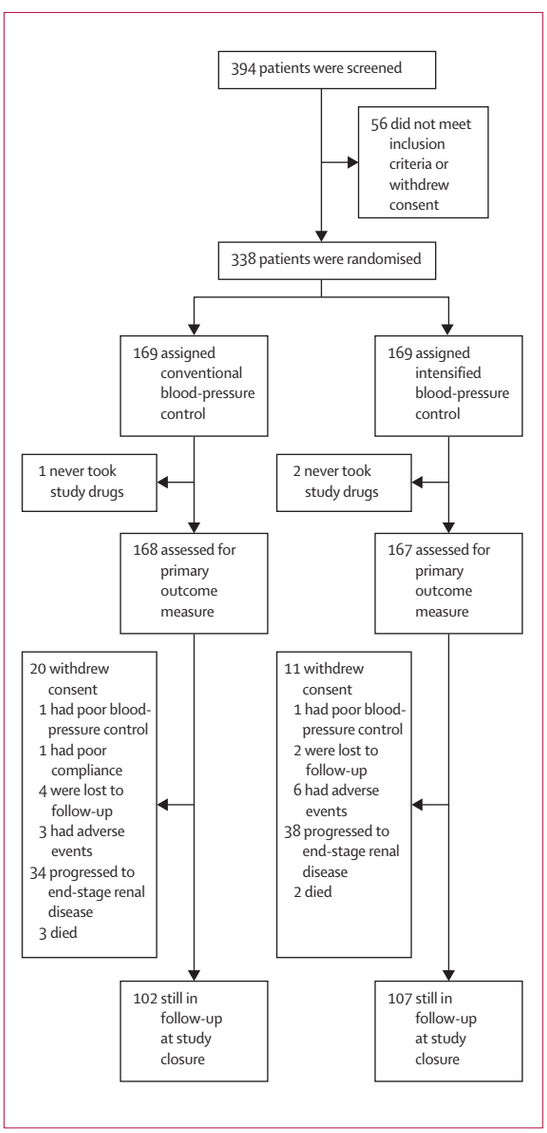


Figure 1: **Trial profile**

Blood pressure fell from 137/84 mm Hg before randomisation to 130/80 mm Hg throughout follow-up ($p<0·0001$ for both systolic and diastolic blood pressure) in the intensified blood-pressure control group and from 136/84 mm Hg to 134/82 mm Hg in the conventional control arm ($p=0·02$ for systolic blood pressure and $p=0·03$ for diastolic blood pressure). Mean systolic blood pressure throughout follow-up was 129·6 mm Hg (SD 10·9) in the intensified blood-pressure control group and 133·7 mm Hg (12·6) in the conventional control arm ($p=0·0019$); diastolic blood pressure was 79·5 mm Hg (5·3) and 82·3 mm Hg (7·1), respectively ($p<0·0001$). Thus, a mean systolic and diastolic separation of about 4·1 mm Hg and 2·8 mm Hg was maintained throughout the study. Overall, in the intensified blood-pressure control group, mean blood pressure fell from 101·9 mm Hg (10·4) before randomisation to 96·2 mm Hg (6·1) throughout follow-up ($p<0·0001$) and from 101·4 mm Hg (11·4) to 99·5 mm Hg (7·5) in the conventional control arm ($p=0·014$). Thus, a mean separation of about 3·0 mm Hg was maintained throughout the study (figure 2).

38 (23%) of 167 patients in the intensified-control arm and 34 (20%) of 168 in the conventional-control group progressed to end-stage renal disease (figure 3). After adjustment for the prespecified baseline covariates, the hazard ratio for this disorder was 1·00 (95% CI 0·61–1·64; $p=0·99$). In patients with baseline proteinuria of 3 g per 24 h or greater, the hazard ratio adjusted for the same baseline covariates was 1·09 (0·55–2·19; $p=0·81$), and in those with baseline proteinuria of 1–3 g per 24 h, the hazard ratio was 1·06 (0·51–2·20; $p=0·89$). On multivariate analysis, male sex ($p=0·002$), high serum creatinine ($p<0·0001$), proteinuria ($p<0·0001$) and mean arterial blood pressure ($p=0·02$) were independently associated with an increased risk of end-stage renal disease. When baseline systolic and diastolic blood pressure was included in the model instead of mean arterial pressure, high systolic blood pressure was associated ($p=0·001$) with an increased risk of the disorder, whereas diastolic blood pressure had no predictive value ($p=0·26$). Age and treatment group had no predictive value. Male sex, concentration in serum of creatinine, and proteinuria

	Overall		Proteinuria <3 g per 24 h		Proteinuria ≥3 g per 24 h	
	Conventional blood-pressure control (n=168)	Intensified blood-pressure control (n=167)	Conventional blood-pressure control (n=106)	Intensified blood-pressure control (n=109)	Conventional blood-pressure control (n=62)	Intensified blood-pressure control (n=58)
Demography						
Age (years)	53·1 (15·8)	54·6 (14·7)	53·7 (13·6)	55·3 (13·8)	52·0 (19·0)	53·1 (16·3)
Men (%)	127 (76%)	124 (74%)	78 (74%)	81 (74%)	49 (79%)	43 (74%)
Blood pressure						
Systolic (mm Hg)	136·4 (17·0)	137·0 (16·7)	134·3 (16·0)	135·4 (17·7)	139·9 (18·3)	139·9 (14·4)
Diastolic (mm Hg)	83·9 (10·4)	84·3 (9·0)	83·7 (9·9)	83·6 (9·8)	84·2 (11·3)	85·7 (7·1)
Mean (mm Hg)	101·4 (11·4)	101·9 (10·4)	100·6 (11·0)	100·8 (11·4)	102·7 (12·1)	103·8 (7·9)
Renal function						
GFR (mL/min per 1·73 m^2)	34·1 (18·1)	35·9 (18·6)	35·9 (20·8)	32·9 (14·1)	31·1 (12·6)	41·7 (24·4)
Creatinine clearance (mL/min per 1·73 m^2)	38·9 (21·7)	38·6 (17·9)	38·6 (19·7)	36·2 (16·4)	39·5 (25·0)	43·3 (19·9)
Serum creatinine (μmol/L)	2·7 (1·1)	2·7 (1·1)	2·7 (1·1)	2·8 (1·2)	2·7 (1·0)	2·5 (1·0)
Urinary protein excretion (g/day)	2·9 (1·9)	2·8 (2·0)	1·8 (0·7)	1·7 (0·7)	4·9(1·8)	4·9 (1·9)
Urinary urea excretion (g/day)	20·7 (9·3)	20·2 (7·5)	20·9 (7·1)	19·9 (6·5)	20·4 (12·3)	20·6 (9·1)
Urinary sodium excretion (mEq/day)	179·1 (70·7)	166·2 (65·0)	174·2 (72·3)	162·0 (65·1)	187·4 (67·6)	174·5 (64·6)
Biochemistry						
Serum cholesterol (mmol/L)	216·5 (45·7)	218·5 (41·7)	205·3 (40·4)	211·2 (39·1)	236·6 (48·1)	232·6 (43·3)
Serum triglycerides (mmol/L)	177·8 (127·8)	181·5 (125·9)	166·9 (109·6)	178·0 (133·4)	197·4 (154·3)	188·2 (110·9)
Serum potassium (mEq/L)	4·7 (0·5)	4·7 (0·6)	4·6 (0·5)	4·6 (0·6)	4·7 (0·6)	4·7 (0·6)

Data are mean (SD) or number of participants (%).

Table 1: **Baseline characteristics overall and according to baseline proteinuria**

remained significant when changes in systolic, diastolic, or mean blood pressure (follow-up *vs* baseline) were included in the model instead of basal mean arterial pressure.

173 patients (93 in the intensified control arm and 80 in the conventional control group) had at least three GFRs available (including baseline) for slope analysis. Throughout the study period, the median rate of GFR decline in the intensified blood-pressure control arm was 0·22 mL/min per 1·73 m^2 per month (IQR 0·06–0·55) and with conventional control it was 0·24 mL/min per 1·73 m^2 per month (0·0001–0·56; p=0·62). In patients with baseline proteinuria of less than 3 g per 24 h, median GFR decline was slower than in those with proteinuria of 3 g per 24 h or greater (0·19 mL/min per 1·73 m^2 per month [–0·01 to 0·44] *vs* 0·49 mL/min per 1·73 m^2 per month [0·11–0·98]; p=0·001]. In participants with proteinuria of less than 3 g per 24 h, median GFR decline was similar in the intensified-control arm and in the conventional-control group (0·18 mL/min per 1·73 m^2 per month [0·03–0·49] *vs* 0·21 mL/min per 1·73 m^2 per month [–0·03 to 0·40]; p=0·89); in those with proteinuria of 3 g per 24 h or greater, GFR decline was also fairly similar (0·51 mL/min per 1·73 m^2 per month [0·16–1·05] *vs* 0·39 mL/min per 1·73 m^2 per month [0·03–0·98]; p=0·39).

After adjustment for the prespecified baseline covariates, the standardised β coefficient for ΔGFR was –0·08 (p=0·27) for the comparison between the two arms. In patients with baseline proteinuria of 3 g per 24 h or greater, β adjusted for the same baseline covariates was –0·15 (p=0·26), and in those with proteinuria of 1–3 g per 24 h it was –0·03 (p=0·71).

By multivariate analysis including predefined baseline covariates, concentration in serum of creatinine (p=0·02) and proteinuria (p=0·0006) independently predicted the rate of GFR decline, whereas sex, age, baseline mean arterial pressure, and study arm had no significant predictive value. Serum creatinine and proteinuria also retained predictive value when changes in systolic, diastolic, or mean blood pressure (follow-up

	Baseline		Follow-up	
	Conventional blood-pressure control (n=168)	Intensified blood-pressure control (n=167)	Conventional blood-pressure control (n=168)	Intensified blood-pressure control (n=167)
Any	109 (65%)	99 (59%)	103 (61%)	93 (56%)
Diuretics	84 (50%)	78 (47%)	73 (43%)	68 (41%)
Sympatolytic drugs	56 (33%)	39 (23%)	48 (29%)	32 (19%)
β blockers	40 (24%)	45 (27%)	37 (22%)	43 (26%)
Non-dihydropyridine calcium-channel blockers	14 (8%)	5 (3%)	12 (7%)	3 (2%)
Other	9 (5%)	4 (2%)	5 (3%)	2 (1%)

Data are number of participants (%).

Table 2: **Concomitant treatments at baseline and throughout follow-up**

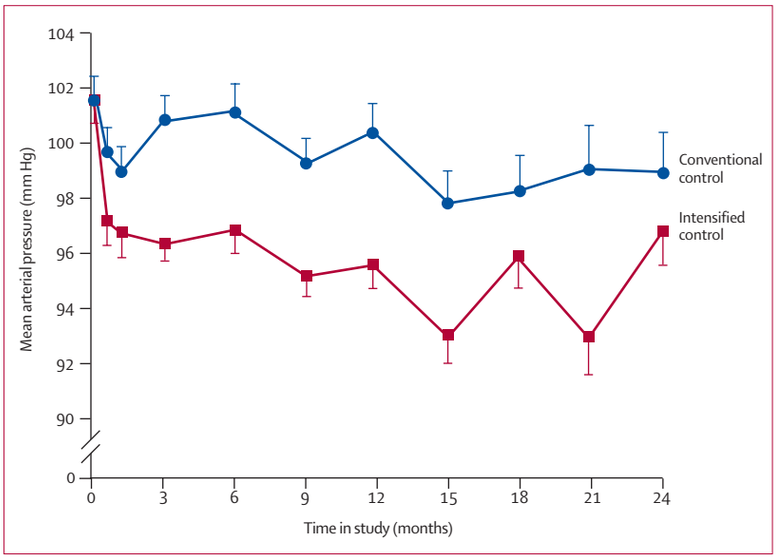
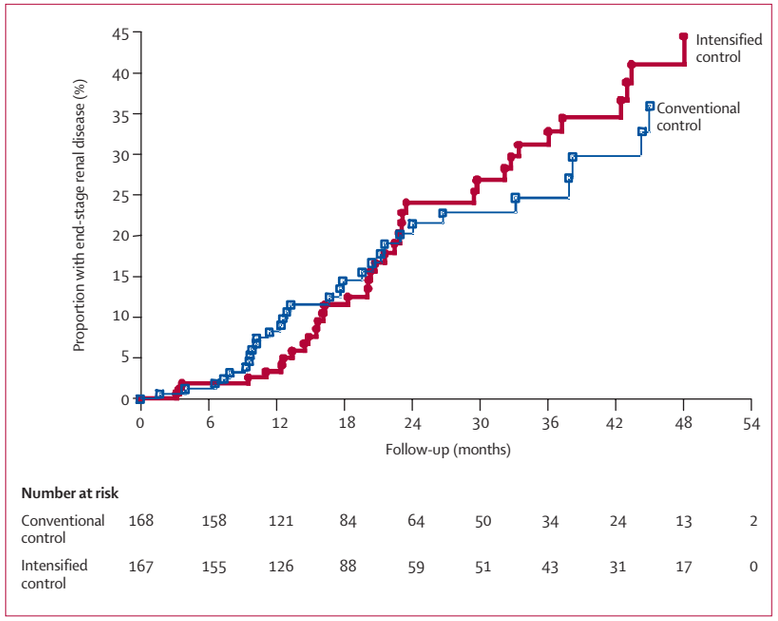


Figure 2: **Mean arterial pressure in each study arm**
Error bars are SE.

vs baseline) were included in the model instead of basal mean arterial pressure. Changes in systolic, diastolic, or mean blood pressure were not associated with ΔGFR.

Throughout the study period the median rate of decline in creatinine clearance was similar in the intensified and conventional blood-pressure control arms (0·26 mL/min per 1·73 m^2 per month [IQR 0·03–0·53] *vs* 0·25 mL/min per 1·73 m^2 per month [0·0001–0·75]; p=0·59). Throughout the study, urinary protein excretion was similar in both arms.



Number at risk

Conventional control	168	158	121	84	64	50	34	24	13	2
Intensified control	167	155	126	88	59	51	43	31	17	0

Figure 3: **Proportion of patients with end-stage renal disease in each study arm**

Five patients died during the study, three in the conventional blood-pressure control group (one myocardial infarction, one stroke, and one cancer) and two in the intensified-control group (one myocardial infarction and one death from unknown causes). 25 non-fatal serious adverse events arose in the conventional-control group (including myocardial infarction, congestive heart failure, stroke, and cancer) and 37 in the intensified-control group (including myocardial infarction, acute coronary syndrome, acute congestive heart failure, stroke, transient ischaemic attack, and cancer). No case of severe hyperkalaemia was reported.

Discussion

We have shown that in patients with non-diabetic, proteinuric chronic nephropathies, intensified blood-pressure control with ramipril and felodipine reduced blood pressure more effectively than did conventional control with ramipril alone and was safe. However, this intensified regimen compared with conventional ACE inhibition alone had no additional benefits for residual proteinuria, GFR decline, and progression to end-stage renal disease. By multivariate analyses, further blood-pressure reduction and add-on felodipine treatment had no independent beneficial effect on disease outcome. Altogether, these data suggest that further blood-pressure reduction below usual targets with felodipine given with a fixed ACE-inhibitor dose does not confer additional renoprotection. They also extend previous evidence that dihydropyridine calcium-channel blockers,[21] unlike ACE inhibitors[5–10] or angiotensin-II-receptor antagonists,[22,23] do not offer additional renoprotection.

In patients with type 1 diabetes and overt nephropathy,[24] blood-pressure differences were similar to those we achieved in our present study and led to less proteinuria in the lower blood-pressure group, an effect that could suggest slower progression of kidney disease in the long term. In the above study,[24] however, patients in the intensified blood-pressure control group were given a two-fold higher dose of ramipril (about 6 mg/day *vs* 3 mg/day) than those in conventional-control arm. Actually, a pooled analysis—including our present study and three previous trials of intensified blood-pressure control in patients with diabetic[24] or non diabetic[9,12] proteinuric nephropathies—showed that more effective inhibition of the renin-angiotensin system, rather than more effective blood-pressure reduction, is the key component of intensified treatments aimed to maximise renoprotection (table 3).

Although experimental[25,26] and human[8,27] studies have so far failed to show any specific benefit of calcium-channel blockade on progression of chronic nephropathies,[28,29] since the introduction of nifedipine in the early 1970s,[30] dihydropyridine calcium-channel blockers have been launched as part of standard

	Patients	Achieved mean arterial pressure during follow-up (mm Hg)		Main outcomes (intensified *vs* conventional blood-pressure control)		
		Intensified control	Conventional control	End-stage renal disease	ΔGFR	Proteinuria
Comparable ACE-inhibitor therapy in intensified and conventional blood-pressure control arms						
Wright[9]	Non-diabetics	92	102	Similar	Similar	Similar
Present study	Non-diabetics	96	100	Similar	Similar	Similar
Intensified ACE-inhibitor therapy in intensified blood-pressure control group						
Lewis[24]	Diabetics	91	97	Similar	Similar	Reduced
Peterson[12]	Non-diabetics	94	100	Reduced	Reduced	Reduced

Table 3: **Main outcome data for patients with proteinuric chronic nephropathies included in randomised trials of intensified and conventional blood-pressure control**

treatment for reduction of blood-pressure in patients with chronic kidney disease. About 70% of proteinuric participants in the AASK study were on calcium-channel blocker therapy, whereas only 40% were on ACE inhibitors.[8,9] A similar proportion was recorded in 1500 patients with type 2 diabetes and overt nephropathy entering the RENAAL trial,[21] and similar figures are expected in the general population of patients with chronic kidney disease.[31]

Altogether, these findings show that intensified blood-pressure control by combined therapy with an ACE inhibitor and dihydropyridine calcium-channel blocker is not effective. Different strategies aimed at more effective inhibition of the renin-angiotensin system might help in prevention of progression in chronic renal disease. A role for add-on therapy with angiotensin-II-receptor antagonists in addition to ACE inhibitors has been established.[32] Findings of other studies have shown that loop or thiazide diuretics increase the antiproteinuric effect of renin-angiotensin system inhibition without hyperkalaemia.[33] Of diuretic drugs, aldosterone antagonists have received particular attention over the past few years because of their beneficial effects in heart failure[34] and nephropathy of type 2 diabetes.[35] However, no long-term outcome data are available for kidney survival, and their use in combination with renin-angiotensin system blockade is contraindicated because of a substantial excess of life-threatening hyperkalaemia.[36]

In conclusion, in patients with non-diabetic proteinuric nephropathies and background ACE inhibitor therapy, further blood-pressure reduction by dihydropyridine calcium-channel blocker therapy offers no additional protection against renal disease progression.

Contributors

P Ruggenenti and G Remuzzi participated in all stages of the study, made the initial interpretation of the study findings, and prepared the first draft of the report and the final manuscript. A Perna and M Ganeva did statistical analyses. M Lesti and M Turturro monitored all phases of the study. B Ene-Jordache prepared the database and contributed to data management. G Loriga, E Perticucci, I Nediyalkov Chakarski, D Leonardis, G Garini, A Sessa, C Basile, M Alpa, R Scanziani, G Sorba, and C Zoccali contributed to patients' recruitment and management. All authors critically revised the first draft and approved the final manuscript.

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Conflict of interest statement

We declare that we have no conflict of interest.

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