Effects of Dihydropyridine Calcium Channel Blockers, Angiotensin-Converting Enzyme Inhibition, and Blood Pressure Control on Chronic, Nondiabetic Nephropathies

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Abstract. Dihydropyridine-type calcium channel blockers (dihydropyridine CCB) adversely affect renal function in diabetes. The effects of dihydropyridine CCB on 24-h urinary protein excretion rate and GFR decline (ΔGFR) were prospectively evaluated in 117 nondiabetic patients with chronic, proteinuric nephropathies enrolled in the Ramipril Efficacy in Nephropathy study and randomized to angiotensin-converting enzyme inhibition (ACEI) or placebo plus conventional antihypertensive therapy. Sixty-three percent of patients were treated with dihydropyridine CCB. During follow-up, CCB-treated compared with no CCB patients had higher proteinuria (mean ± SEM: 4.8 ± 0.2 g/24 h versus 4.2 ± 0.2 g/24 h, respectively, \(P = 0.015\)) and mean arterial BP (MAP). The difference in proteinuria was significant in the placebo group (5.1 ± 0.2 g/24 h versus 4.3 ± 0.3 g/24 h, \(P = 0.02\)) but not in the ACEI group (4.4 ± 0.2 g/24 h versus 4.1 ± 0.2 g/24 h). Of note, CCB-treated patients had significantly less proteinuria (\(P = 0.028\)) in the ACEI group compared with placebo. CCB-treated versus no CCB patients had a faster ΔGFR in the overall study population and in the placebo group, but not in the Ramipril group. Proteinuria was comparable in CCB-treated and no CCB patients for MAP ≤ 100 mmHg, but was higher in CCB-treated patients for MAP >100 mmHg. Similarly, proteinuria was comparable in the placebo and in the ACEI group for MAP ≤ 100 mmHg, but was higher in the placebo group for MAP >100 mmHg. In CCB- and placebo-treated patients, a linear correlation (\(P = 0.006\) for both groups) was found between proteinuria and MAP values. MAP, proteinuria, and ΔGFR in patients given nifedipine versus those given other dihydropyridine CCB were comparable. Thus, in nondiabetic proteinuric nephropathies, dihydropyridine CCB may have an adverse effect on renal protein handling that depends on the severity of hypertension and is minimized by ACEI therapy or tight BP control. ACE inhibitors may electively limit proteinuria in patients on dihydropyridine CCB treatment and/or with uncontrolled hypertension.

In experimental animals and humans, interventions that reduce systemic hypertension effectively limit progression of chronic proteinuric nephropathies to renal insufficiency (1–3). However, several studies have demonstrated that among antihypertensive agents, angiotensin-converting enzyme inhibitors (ACEI) have a specific renoprotective effect (4–8). In particular, for comparable average reductions in BP, ACEI improved glomerular barrier permselectivity (9–11) and lower proteinuria (12–15) more than conventional therapy (diuretics and/or beta-blockers) or dihydropyridine calcium channel blockers (CCB), and were more renoprotective (5–8). Thus, in diabetes, nifedipine failed to decrease and actually even tended to increase urinary proteins at any level of BP control (16), whereas benzothiazepine-type or papaverine-type CCB, such as diltiazem or verapamil, were more consistently antiproteinuric (17,18). Different effects on preglomerular resistances and on glomerular barrier size-selectivity have been postulated to account for the heterogeneous response to the different types of CCB (19–25).

In the present study, we prospectively analyzed the impact of dihydropyridine CCB on urinary protein excretion rate and GFR decline (ΔGFR) in a large cohort of patients with nondiabetic chronic nephropathies and clinical proteinuria. These patients had been enrolled in the Ramipril Efficacy in Nephropathy (REIN) study (5), designed to formally address the hypothesis that glomerular protein traffic and its modification by an ACE inhibitor influenced the progression of chronic renal disease (26). The REIN study design randomly allocated patients to ACEI or placebo, plus non-ACEI antihypertensives when appropriate. Main efficacy variables have been ΔGFR and risk of end-stage renal failure. According to baseline urinary protein excretion rate, patients were separated a priori...
into two strata (stratum 1: 1.0 to 2.9 g/24 h; stratum 2: ≥3 g/24 h).

Materials and Methods

Study Design

A detailed description of the REIN study design and results have been published elsewhere (5,26). The active treatment and placebo were supplied by Hoechst (Frankfurt, Germany). Study participants were patients of either sex, between 18 and 70 yr old, with proteinuric chronic nephropathy (creatinine clearance 20 to 70 ml/min per 1.73 m² and urinary protein excretion >1 g/24 h over at least 3 mo). Patients provided signed written informed consent to study entry according to the Declaration of Helsinki.

According to baseline urinary protein excretion rate (estimated by the mean of two consecutive measurements 2 wk apart) before randomization and within each clinical center, patients were separated into two strata (stratum 1: 1.0 to 2.9 g/24 h; stratum 2: ≥3 g/24 h) and were then randomly assigned 1.25-mg capsules of Ramipril or placebo (identical appearance) on a 1:1 basis within each stratum. The study-drug dose was increased every 2 wk until “trough” diastolic BP (measured in the morning before study drug administration) was reduced to <90 mmHg. Antihypertensive agents (but not ACE inhibitors) were introduced (diuretics as first choice, centrally acting sympatholytic agents and vasodilators—including dihydropyridine-type CCB— as second and third choice, respectively), and their doses were adjusted to achieve and maintain diastolic BP <90 mmHg. In patients already receiving antihypertensive agents, the study-drug dose was increased, and the dose of the other antihypertensive drugs was progressively reduced to avoid symptomatic hypotension. In each patient, the broad aim was to adjust the dose of the study drugs to achieve and maintain target BP with the minimum dose of concomitant antihypertensive agents. ACE inhibitors or antagonists to angiotensin II receptor could not be added to the study drugs during the study period. Each patient was examined by a physician at baseline, every month during the first 3 mo after randomization, and every 6 mo thereafter. At each examination, arterial BP was measured in the sitting position in the morning and before ingestion of the antihypertensive drugs, and routine laboratory parameters, including 24-h urinary protein excretion rate, were evaluated. On each occasion, the ongoing antihypertensive therapy and any change in doses and drugs were carefully recorded. At baseline, at 1, 3, and 6 mo after randomization, and every 6 mo thereafter, patients had their GFR centrally evaluated at Mario Negri Institute for Pharmacological Research in Bergamo by the plasma clearance of nonradioactive iohexol (27).

Statistical Analyses

Dichotomous and polychotomous baseline characteristics were analyzed by Fisher’s exact test, and continuous variables were analyzed by Wilcoxon rank sum test. Data analysis was performed on patients who had three or more GFR measurements. A single-slope linear model was carried out to interpolate GFR evaluations. Comparisons between groups were done by unpaired t test or Wilcoxon rank sum test as appropriate. Correlation analysis was carried out by the Pearson correlation coefficient (r). Because of its skewed distribution, 24-h urinary protein excretion rate was log-transformed before evaluation. Data were expressed as mean ± SD, unless otherwise stated. All analyses were done using the SAS package (28).

Results

Baseline characteristics of the study population have been given in detail elsewhere (5). Of note, age, sex distribution, arterial BP, prevalence of the underlying renal diseases, baseline renal function, 24-h urinary protein excretion rate, lipid profile, and randomization to ACEI or placebo were comparable between CCB-treated and no CCB patients.

Overall, 74 patients (63%) were on dihydropyridine CCB. Four patients were on nondihydropyridine CCB and were not included in the analysis. Dosages of dihydropyridine CCB ranged from 20 to 120 mg/d (median 60 mg/d) for nifedipine and from 2.5 to 10 mg/d (median 5 mg/d) for amlodipine. Dosages of the ACEI Ramipril ranged from 1.25 to 5 mg/d (median 2.5 mg/d).

During follow-up, CCB-treated patients had higher levels of proteinuria compared with no CCB as for the overall population, and significantly higher mean arterial BP (MAP) (Figure 1). The difference in urinary protein excretion rate between CCB and no CCB patients was even higher in the placebo group, but was negligible in the ACEI group. In the ACEI group, no difference could be detected because CCB patients had significantly less proteinuria in the ACEI group than in the placebo group (Figure 1). MAP in the overall study population was significantly higher in CCB patients than in no CCB, and a comparable difference was found within the placebo and the ACEI groups (Figure 1). Differences in urinary protein excretion rate documented in the overall study population and in the placebo group were not accounted for by different levels of renal insufficiency. In particular, CCB-treated and no CCB patients had comparable GFR (mean ± SEM), both in the overall study population (39.5 ± 0.7 versus 41.8 ± 1.4 ml/min per 1.73 m²) and in the placebo group (40.5 ± 0.8 versus 40.6 ± 2.1 ml/min per 1.73 m²). The median dosages of

Figure 1. Mean ± SEM 24-h urinary protein excretion rate and mean arterial BP (M.A.P.) in patients treated with dihydropyridine calcium channel blockers (CCB) and no CCB patients in the overall study population and within the placebo and the angiotensin-converting enzyme inhibition (ACEI) group.
nifedipine and amlodipine were 30 mg/d and 2.5 mg/d for MAP \leq 100 \text{ mmHg}, and 60 mg/d and 5 mg/d for MAP 100 to 110 and >110 mmHg, respectively.

During follow-up, CCB-treated compared with no CCB patients also had a 30% faster GFR decline (mean ± SEM: 0.80 ± 0.10 versus 0.56 ± 0.13 ml/min per 1.73 m² per month, respectively), a difference that failed to achieve statistical significance. CCB-treated compared with no CCB had a higher ΔGFR in the placebo group (0.97 ± 0.16 versus 0.66 ± 0.22 ml/min per 1.73 m² per month, respectively), but such difference was minimized by ACEI (0.58 ± 0.11 versus 0.48 ± 0.15 ml/min per 1.73 m² per month, respectively).

Assessment of urinary protein excretion rate within three subgroups of patients assigned to three MAP ranges (lowest: \(\leq 100\) mmHg; middle: 100 to \(\leq 110\) mmHg; highest: >110 mmHg) showed that CCB-treated and no CCB patients in the lowest MAP range had comparable values. On the contrary, urinary protein excretion rate in CCB-treated compared with no CCB patients was significantly higher in the middle and in the highest MAP range (Figure 2). Of note, 24-h urinary protein excretion rate linearly correlated with MAP in CCB-treated \((r = 0.13, P = 0.006)\) patients, but was relatively independent from concomitant MAP in the no CCB group (Figure 2). As expected, within each MAP range, MAP pressures in CCB-treated and no CCB patients were comparable (Figure 2). Again, differences in urinary protein excretion rate documented for MAP > 100 mmHg were not accounted for by different levels of renal insufficiency in the two treatment groups. In particular, placebo- and ACEI-treated patients had comparable GFR (mean ± SEM) for MAP values of 100 to 110 mmHg (40.2 ± 1.5 versus 39.1 ± 1.6 ml/min per 1.73 m²) and >110 mmHg (40.6 ± 1.4 versus 40.0 ± 1.7 ml/min per 1.73 m²).

Among CCB-treated patients, patients given nifedipine or other dihydropyridine CCB had comparable MAP values (107.4 ± 6.8 versus 107.5 ± 7.3 mmHg), urinary protein excretion rates (5.2 ± 2.9 versus 4.7 ± 2.4 g/24 h), and LGFR (4.7 ± 2.4 ml/min per 1.73 m²). The median Ramipril dosages were 1.25 mg/d for MAP \(\leq 100\) mmHg and 2.5 mg/d for MAP 100 to 110 and >110 mmHg, respectively.

When the above comparisons within the same three MAP ranges were done between patients in the placebo and the ACEI group, again the two groups in the lowest MAP range were found to have a comparable urinary protein excretion rate. On the contrary, urinary protein excretion rate in the placebo group compared with the ACEI group was significantly higher in the middle and in the highest MAP range (Figure 3). Once again, 24-h urinary protein excretion rate linearly correlated with MAP in the placebo group \((r = 0.15, P = 0.006)\), but was relatively independent from concomitant MAP in the ACEI group (Figure 3). As expected, within each range, MAP values in CCB-treated and untreated patients were comparable, with a small, 2-mg difference documented only in the highest range (Figure 3). Again, differences in urinary protein excretion rate documented for MAP > 100 mmHg were not accounted for by different levels of renal insufficiency in the two treatment groups. In particular, placebo- and ACEI-treated patients had comparable GFR (mean ± SEM) for MAP values of 100 to 110 mmHg (40.2 ± 1.5 versus 39.1 ± 1.6 ml/min per 1.73 m²) and >110 mmHg (40.6 ± 1.4 versus 40.0 ± 1.7 ml/min per 1.73 m²).

**Discussion**

In the present study, we found that in renal patients chronic dihydropyridine CCB therapy compared with no CCB was associated with an excess in proteinuria that was minimized by tight BP control or concomitant ACEI therapy.
Because the same proportions of CCB-treated and no CCB patients were on ACEI or placebo during the study follow-up, randomization bias could not account for the difference in proteinuria. In addition, main baseline clinical characteristics were comparable, and glomerular and nonglomerular diseases were equally distributed in the two groups, which makes it extremely unlikely that differences in proteinuria and renal outcome were actually dependent on different underlying renal diseases.

Overall, patients treated with dihydropyridine CCB had more proteinuria and higher BP compared with no CCB patients. Subgroup analyses, however, found that the difference in proteinuria in the overall study population was almost completely accounted for by the placebo group, with urinary protein excretion rate virtually identical in CCB-treated and no CCB among patients randomized to ACEI. In addition, among CCB-treated patients, ACE inhibition therapy compared with placebo was associated with lower proteinuria despite a similar BP control. These findings led us to believe that the excess in proteinuria observed in CCB-treated patients was not the consequence of more severe hypertension and, in turn, that the antiproteinuric effect of ACEI in patients on dihydropyridine CCB did not depend on arterial BP reduction per se. Rather, the excess in proteinuria associated with CCB therapy and its prevention by concomitant ACEI therapy could be related to intrarenal changes—possibly hemodynamic in nature and/or acting on glomerular barrier permselectivity—that are mitigated or reversed by ACE inhibition. Whatever the mechanism(s) involved, evidence that ACEI limited proteinuria associated with dihydropyridine CCB suggests a novel indication for ACE inhibitors, i.e., to protect the kidney from chronic CCB effects in those patients who actually need or even depend on CCB therapy for achieving an adequate BP control or in those who have to take CCB for other concomitant illnesses, such as cardiac ischemic disease.

Finding higher BP in CCB-treated compared with no CCB patients raised the concern that differences in proteinuria between the two treatment groups could be accounted for by differences in arterial BP control and/or severity of hypertension rather than by a specific effect of calcium channel blockade. This potential bias, however, was extremely unlikely because CCB-treated patients had more proteinuria than patients on no CCB even for identical levels of MAP. Of note, however, the difference in proteinuria between CCB and no CCB progressively increased for increasing levels of arterial BP, peaking at MAP values of >110 mmHg. A similar trend was documented when comparing urinary protein excretion rate in patients on ACEI or placebo. For both comparisons, the difference increased for BP-dependent increases in proteinuria in CCB and in placebo patients, but not in no CCB or ACEI-treated patients. Of note, for MAP ≤ 100 mmHg, urinary protein excretion rate was comparable in the different treatment groups (CCB-treated versus no CCB and placebo versus Ramipril-treated patients). This finding reinforces the concept that tight BP control has per se an antiproteinuric effect that minimizes the specific and opposite effects on proteinuria of dihydropyridine CCB and ACE inhibitors.

These findings are in line with previous data in diabetes (12,29), showing that the degree of reduction in proteinuria depends on the level of BP control and that the different antihypertensive drugs have a comparable antiproteinuric effect when mean BP is reduced below 100 mmHg. As a result, in addition to ACE inhibition, targeting at a very tight BP control is another possibly complementary step to minimize the renal effects of chronic therapy with dihydropyridine CCB.

Before concluding that dihydropyridine CCB do accelerate disease progression in chronic, proteinuric nephropathies, some additional considerations appear appropriate. Although here CCB-treated compared with no CCB patients had more proteinuria and a faster GFR decline during follow-up, they also had more severe hypertension which, in turn, might have contributed to disease progression. On the other hand, differences in proteinuria and disease outcome in CCB-treated and no CCB patients cannot be accounted for by different levels of renal dysfunction at study entry, given comparable baseline GFR in the two groups. A confounding role of ACEI therapy is also unlikely, because a similar proportion of CCB-treated and no CCB patients were on Ramipril therapy during follow-up.

A still open question is whether the above renal effects apply to all CCB or are restricted to only dihydropyridine CCB. In diabetes, dihydropyridine CCB enhance urinary albumin excretion, but the nondihydropyridine CCB actually reduce albuminuria. Among the dihydropyridine CCB, nifedipine has been most frequently claimed to have an adverse effect on glomerular permeability and disease outcome (14,29–31). Due to the small proportion of patients on verapamil or diltiazem therapy in our series, we could not investigate the renal effects of nondihydropyridine CCB. On the contrary, more than 60% of our patients were on chronic treatment with dihydropyridine-type CCB, with nifedipine and other dihydropyridine-type CCB equally distributed in the study population. This allowed comparative analyses that consistently excluded any substantial difference in the renal effects of nifedipine and other most commonly used dihydropyridine CCB, such as amlodipine. This finding rules out a drug-specific effect of nifedipine and is more consistent with a specific untoward effect of the subclass of dihydropyridine CCB in patients with chronic, proteinuric renal disease.

Our data can be taken to suggest that dihydropyridine CCB adversely affect the glomerular barrier dysfunction of nondiabetic chronic nephropathies, which may contribute to accelerate the progression of the disease. This seems to be a specific effect that is exacerbated by uncontrolled hypertension and minimized by tight BP control and/or concomitant ACEI therapy. In line with previous data in diabetes, our findings are consistent with an untoward effect of dihydropyridine CCB in nondiabetic, chronic renal disease and suggest that their use should be confined to those very patients that fail to benefit from alternative, less dangerous treatments. This hypothesis, however, needs confirmation in a prospective randomized study that formally investigates the renal effects of dihydropyridine and nondihydropyridine CCB.

In conclusion, ACE inhibitors remain the best available
option to lower BP in proteinuric renal disease and may have an additional, elective indication for patients who have high values of urinary protein excretion either due to uncontrolled hypertension or concomitant dihydropyridine CCB.

Appendix

Organization of the REIN Study

Principal Investigators: G. Remuzzi, G. Tognoni. Study Coordinator: P. Ruggenenti. Independent Adjudicating Panel: L. Migone (chairman), E. Marubini (statistician), A. del Favero, G. Idoe, E. Geraci, U. Loi. Investigators and Institutions: N. Bossini, B.F. Viola, F. Scolari, R. Maiorca (Div. di Nefrologia e Dialisi, Spedali Civili, Brescia); F. Cofoano, G. Fellin, G. D’Amico (Div. di Nefrologia e Dialisi, Ospedale Provinciale S. Carlo Borromeo, Milano); D. Dissegna, A. Brendolan, G. La Greca (Div. di Nefrologia e Dialisi, Ospedale S. Bortolo, Vicenza); A. Feriozzi, E. Ancarani (Div. di Nefrologia e Dialisi, Ospedale Grande di Viterbo, Viterbo); E. Gandini, I. D’amato, A. Giangrande (Div. di Nefrologia e Dialisi, Ospedali Riuniti, Bergamo); F. Scanferba, G. Bazzato (Div. di Nefrologia e Dialisi, Ospedale Civile, Ivrea); G. Giannico, O. Vitale, C. Manno, F.P. Schena (Div. di Nefrologia e Dialisi, Policlinico, Bari); A. Mazzi, G. Garini, A. Borghetti (Istituto di Clinica Medica e Nefrologia, Parma); R. Pisoni, T. Bertani (Div.di Nefrologia e Dialisi, Ospedali Riuniti, Bergamo); F. Scanferla, G. Bazzato (Div. di Nefrologia e Dialisi Ospedale Provinciale Umberto I, Mestre); E. Oliva, C. Zoccali (Div. di Nefrologia Centro di Fisiologia Clinica del CNR, Reggio Calabria); G. Toti, S. Sisca, Q. Maggiore (Div. di Nefrologia e Dialisi, USL Zona 10H, Bagno a Ripoli); E. Pignone, R. Boero, (Div. di Nefrologia e Dialisi, Ospedale Zonale Giovanni Bosco, Torino); G. Piccoli (Cattedra di Nefrologia, Universita de Torino); R. Piperno, A. Rosati, M. Salvadori (U. O. Nefrologia e Dialisi, Ospedale di Niguarda, Milano); A. Borghetti (Istituto di Chimica Medica e Nefrologia, Parma); A. Gaspari, F. Arnoldi, O. Signorini, S. Ferrari, E. Guerini (Istituto di Ricerche Farmacologiche Mario Negri).

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