Role of Remission Clinics in the Longitudinal Treatment of CKD

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ABSTRACT

Heavy proteinuria is a major determinant of progression to ESRD for patients with chronic nephropathies and reducing proteinuria should be a key target for renoprotective therapy. In the Remission Clinic, we applied a multimodal intervention to target urinary proteins in 56 consecutive patients who had >3 g proteinuria/d despite angiotensin-converting enzyme inhibitor therapy. We compared the rate of GFR decline and incidence of ESRD in this cohort with 56 matched historical reference subjects who had received conventional therapy titrated to a target BP. During a median follow-up of 4 yr, the monthly rate of GFR decline was significantly lower in the Remission Clinic cohort (median 0.17 versus 0.56 ml/min per 1.73 m²; P < 0.0001), and ESRD events were significantly reduced (3.6 versus 30.4% reached ESRD). Follow-up BP, cholesterol, and proteinuria were lower in Remission Clinic patients than in reference subjects, such that disease remission or regression was achieved in up to 50% of patients who would have been otherwise expected to progress rapidly to ESRD on conventional therapy. Proteinuria reduction independently predicted a slower rate of GFR decline and ESRD incidence, but response to treatment differed depending on the underlying disease. Regarding safety, no patient was withdrawn because of hyperkalemia. In summary, multidrug treatment titrated to urinary protein level can be safely and effectively applied to normalize proteinuria and to slow the loss of renal function significantly, especially among patients without type 2 diabetes and with otherwise rapidly progressing chronic nephropathies.


After pioneering studies in the early 1980s showing that antihypertensive therapy slows GFR decline in patients with type 1 diabetic nephropathy,1 arterial hypertension has been identified as a major determinant of renal disease progression, and lowering the BP has become the main strategy for nephroprotection for all patients with chronic kidney disease (CKD). In addition to arterial hypertension, however, increased urinary protein excretion soon emerged as another important factor associated with the tendency of renal function to decline over time2,3 with heavy (i.e., >3 g/24 h) proteinuria invariably predicting progression to ESRD within months.2–5 In the 1990s, the Ramipril Efficacy In Nephropathy (REIN) studies found that in patients with nondiabetic chronic nephropathies, short-term reduction in proteinuria predicted a slower GFR decline and a reduced risk for progression to ESRD in the long term.6–9 Finding that this effect was independent of achieved BP control provided evidence for a specific renoprotective effect of protein-
Concomitant diuretic and antihypertensive therapy to target serum K+ < 6 mEq/L and blood pressure <130/80 mmHg

Atorvastatin (10-20 mg/day)
Vorapaxir (90-120 mg/day)
Losartan (20-100 mg/day)
Ramipril (5-10 mg/day), controlled protein (0.9 g/kg/day) diet

Start Remission Clinic

*Up-titration and combined therapy if serum K+ < 6.0 mEq/L.

Figure 1. Algorithm describing the key steps of the Remission Clinic intervention protocol.

Table 1. Baseline characteristics of patients included in the Remission Clinic program according to residual proteinuria achieved on follow-up or as a whole (overall) and in matched reference patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Proteinuria (g/24 h)</th>
<th>Overall (n = 56)</th>
<th>Reference Patients (n = 56)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥1.0 (n = 30)</td>
<td>≥0.3 and &lt;1.0 (n = 14)</td>
<td>&lt;0.3 (n = 12)</td>
</tr>
<tr>
<td>Male gender</td>
<td>27 (90.0)</td>
<td>11 (78.6)</td>
<td>10 (83.3)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>56.3 ± 14.7</td>
<td>49.9 ± 16.7</td>
<td>51.2 ± 14.4</td>
</tr>
<tr>
<td>Diabetes</td>
<td>14 (46.7)%</td>
<td>3 (21.4)</td>
<td>1 (8.3)</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>144.3 ± 21.9</td>
<td>145.1 ± 23.1</td>
<td>141.3 ± 21.9</td>
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<tr>
<td>DBP (mmHg)</td>
<td>85.0 ± 13.5</td>
<td>86.5 ± 10.7</td>
<td>85.1 ± 9.1</td>
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<tr>
<td>Mean BP (mmHg)</td>
<td>104.8 ± 13.7</td>
<td>106.0 ± 13.6</td>
<td>103.8 ± 10.5</td>
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<tr>
<td>Body weight (kg)</td>
<td>79.9 ± 12.4</td>
<td>83.9 ± 18.2</td>
<td>79.5 ± 12.8</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>257.4 ± 68.3</td>
<td>267.5 ± 56.8</td>
<td>252.8 ± 88.0</td>
</tr>
<tr>
<td>Potassium (mEq/L)</td>
<td>4.5 ± 0.4</td>
<td>4.4 ± 0.6</td>
<td>4.0 ± 0.5</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>14.0 ± 2.2</td>
<td>13.7 ± 1.5</td>
<td>13.7 ± 1.7</td>
</tr>
<tr>
<td>eGFR (ml/min per 1.73 m²)</td>
<td>73.2 ± 32.5</td>
<td>80.7 ± 33.7</td>
<td>60.1 ± 29.1</td>
</tr>
</tbody>
</table>

Data are N (%), or mean ± SD, or mean ± SD and median (IQR).

aP < 0.01 versus patients with 24-h proteinuria <0.3 and ≥0.3 and ≤1.0 g.
bP < 0.001 versus overall.

There are several options for reducing proteinuria, taken as the key target of renoprotective therapy. The integrated use of different treatments against the same target, such as uncontrolled cell or viral replication, has dramatically improved the outcome of severe diseases such as cancer and AIDS. By analogy, a multimodal intervention strategy using all available tools to target urinary proteins seems a rational approach to maximizing renoprotection in patients with chronic renal disease.20 Experimental data in rat models support this notion.21 Finding that such multimodal intervention normalized proteinuria and stabilized the GFR in a young girl with heavy proteinuria and rapidly worsening renal function while on standard therapy with antihypertensive dosages of an ACEI offered additional clinical support to this assumption.22 Thus, we formalized this approach in an intervention protocol, the “Remission Clinic” program (Figure 1),20 implemented through an informatic support (http://clinicalweb.marionegri.it/remission/) and applied to all consecutive patients who were referred to our Outpatient Clinic because of chronic renal disease.

Antiproteinuric effect that is further enhanced by a low-sodium diet and the addition of a diuretic.14–16 Moreover, ACEI and ARB have an (at least) additive effect on urinary proteins, and the two drugs in combination reduce urinary protein excretion more effectively than single RAS blockade by each agent alone, even without further BP reduction.17 Nondihydropyridine calcium channel blockers (CCB) and hydroxymethyl-glutaryl CoA inhibitors (statins) may also reduce proteinuria regardless of their effect on BP18 or serum lipids,19 respectively.
and heavy proteinuria despite therapy. Then, in the setting of a matched-cohort study, we compared their outcome with that of historical reference patients on conventional therapy titrated to BP. We had three aims: (1) To test the feasibility of this approach in everyday hospital practice; (2) to assess the possibility to normalize heavy proteinuria resistant to standard therapy; and (3) to test formally the hypothesis that normalizing urinary proteins may halt progression, even in most severe forms of chronic renal disease. Secondarily, we evaluated whether the underlying renal disease affected response to treatment and which factors could explain different outcomes in considered disease subgroups.

RESULTS

Baseline Characteristics, GFR Decline, and Progression to ESRD in Patients and Reference Patients

Baseline characteristics of patients and reference patients were similar, with the exception of a significant excess of those with diabetes among patients (Table 1). Over a median (interquartile range [IQR]) follow-up of 60 (36 to 72) and 39 mo (20 to 55), respectively, median (IQR) change in estimated GFR (ΔeGFR) was significantly (P < 0.0001) slower in patients (−0.56 ml/min per 1.73 m² [−1.07 to −0.23]) than in reference patients (−0.17 ml/min per 1.73 m² [−0.32 to −0.01]) than in reference patients. Two (3.6%) patients and 17 (30.4%) reference patients progressed to ESRD (hazard ratio [HR] 0.092; 95% confidence interval [CI] 0.021 to 0.401; P = 0.0015; Figure 2). The excess risk in reference patients was significant (HR 0.027; 95% CI 0.004 to 0.173; P = 0.0001) even after adjustment for gender, age, and baseline serum creatinine and proteinuria. Sensitivity analyses performed after curtail the follow up at 39 mo (i.e., the median follow-up of the reference patients) showed that over a median (IQR) follow-up of 39 mo (36 to 39 mo) in patients and 38 mo (20 to 39 mo) in reference patients, the unadjusted HR (0.091; 95% CI 0.012 to 0.721; P = 0.0232) and adjusted HR (0.038; 95% CI 0.003 to 0.514; P = 0.0139) for ESRD were similar to those observed throughout the whole study period. Compared with baseline, follow-up systolic (SBP) and diastolic BP (DBP), serum cholesterol, and proteinuria decreased more consistently in patients than in reference patients (Figure 3).

Comparative Analyses According to Achieved Ranges of Proteinuria

Residual 24-h proteinuria was persistently ≥1 g, decreased to ≥0.3 and < 1 g, or decreased to <0.3 g in 30 (53.6%), 14 (25.0%), and 12 patients (21.4%) and in 50 (89.3%), three
(5.4%), and three (5.4%) reference patients, respectively (P = 0.0001 for trend; Figure 4). In nine (16.1%) patients compared with 16 (28.6%) reference patients, residual 24-h proteinuria was >3 g. Median (IQR) ΔGFR was significantly different in patients with 24-h proteinuria ≥1 g (−0.28 ml/min per 1.73 m²/mo [−0.42 to −0.17]) compared with those with 24-h proteinuria ≥0.3 and <1 g (−0.08 ml/min per 1.73 m²/mo [−0.27 to 0.09]; P = 0.011) and with those with 24-h proteinuria <0.3 g (<0.04 ml/min per 1.73 m²/mo [−0.11 to 0.02]; P = 0.001; Figure 5). Baseline characteristics (Table 1) and BP control (Figure 4) in these subgroups were similar, with the exception of a significantly higher prevalence of patients with type 2 diabetes in those with residual 24-h proteinuria ≥1 g.

Comparative Analyses between Patients with and without Diabetes

At baseline, patients with compared to those without diabetes were significantly older (66.4 ± 9.6 versus 47.5 ± 13.5 yr; P < 0.0001) and heavier (83.5 ± 13.4 versus 79.6 ± 14.4 kg; P = 0.35) and had higher SBP (Table 2). Gender distribution (16 [88.9%] men among patients with diabetes versus 32 [84.2%] among patients without diabetes), DBP, proteinuria, and eGFR were similar in the two groups, whereas total cholesterol tended to be higher in patients without diabetes (Table 2).

At 6- and 12-mo follow-up versus baseline, proteinuria decreased by 34.5 and 41.6%, respectively, in patients with diabetes and by 31.7 and 50.7% in those without. From month 12 to the end of the observation period, proteinuria was relatively stable in those with diabetes but continued to decrease progressively in those without (Figure 6). Only one (5.5%) of the 18 patients with diabetes compared with 11 (28.9%) of the 38
without achieved the proteinuria target of <0.3 g/24 h (P = 0.08). In three (16.7%) additional patients with diabetes and 11 (28.9%) without, 24 h proteinuria decreased to <1 g but >0.3.

Thus, in four (22.2%) patients with diabetes compared with 22 (57.9%) without, residual proteinuria was <1 g/24 h (P = 0.021). Six (33.3%) patients with diabetes and six (15.8%) without had a residual proteinuria >3.0 g/24 h. After inclusion into the Remission Clinic, the BP decreased in both groups, but, on follow-up, SBP was significantly higher in those with diabetes (Figure 7), whereas DBP was comparable between groups. ΔeGFR was significantly faster in patients with than without diabetes (−0.29 [−0.49 to −0.10] versus −0.11 ml/min per 1.73 m²/mo [−0.27 to −0.01]; P = 0.049). Serum cholesterol decreased more in patients without than with diabetes (Table 2).

Within the subgroup with residual proteinuria >1 g/24 h, proteinuria reduction at 6- and 12-mo follow-up versus baseline (−30.1 and −32.7%, respectively, versus 0.7 and −24.4%; P > 0.15 for both comparisons) and ΔeGFR (−0.31 [−0.66 to −0.19] versus −0.23 ml/min per 1.73 m²/mo [−0.42 to −0.10]; P = 0.22) were not significantly different in those with or without diabetes.

Table 2. Main clinical characteristics of the study group according to the presence of diabetes at baseline (month 0) and at various time points after inclusion in the Remission Clinic program

<table>
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<tr>
<th>Characteristic</th>
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<th>12</th>
<th>24</th>
<th>36</th>
<th>48</th>
<th>60</th>
<th>72</th>
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<td></td>
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<tr>
<td>diabetic</td>
<td>157.5±25.1</td>
<td>156.1±18.9</td>
<td>151.8±17.6</td>
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<td>143.9±23.8</td>
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<td><strong>DBP (mmHg)</strong></td>
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<td>diabetic</td>
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<td>102.5±9.5</td>
<td>96.3±9.8</td>
<td>94.3±13.9</td>
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<td><strong>Body weight (Kg)</strong></td>
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<td>212.3±30.7</td>
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<tr>
<td><strong>Potassium (mEq/L)</strong></td>
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</tr>
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<td>4.8±0.6</td>
<td>4.8±0.6</td>
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</tr>
<tr>
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<td></td>
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<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
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<td>(g/24 h)</td>
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<td></td>
<td></td>
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<td>2.8±2.0</td>
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<td>1.4±1.4</td>
<td>1.3±1.2</td>
<td>0.9±1.1</td>
</tr>
</tbody>
</table>

*Data are mean ± SD.

P < 0.05, *P = 0.01, †P ≤ 0.001, and ‡P < 0.0001, diabetes versus nondiabetes adjusted for baseline values by analysis of covariance.

P < 0.05, †P ≤ 0.01, ‡P ≤ 0.001, and †‡P ≤ 0.0001, time visit versus baseline.

Outcomes of Patients without Diabetes According to the Underlying Renal Disease

The proteinuria target of 0.3 g/24 h was achieved by eight (47.1%) of the 17 patients with IgA, one (14.3%) of the seven
with idiopathic membranous nephropathy (IMN), and two (14.3%) of the 14 with other nondiabetic nephropathies. BP control in these subgroups was similar (data not shown). Those with IMN showed a trend to faster GFR decline than patients with other nondiabetic renal diseases.

Disease Progression before and after Inclusion into the Remission Clinic Program

Twenty-four patients had at least three eGFR values available for slope analyses before inclusion into the Remission Clinic. All of them were on continued ACEI therapy since at least 1 yr. In these patients considered as a whole, \( \Delta eGFR \) was 3.8-fold faster \( (P = 0.008) \) before \( (-0.60 \text{ ml/min per 1.73 m}^2/\text{mo} [-1.55 \text{ to } -0.22]) \) than after \( (-0.16 \text{ ml/min per 1.73 m}^2/\text{mo} [-0.28 \text{ to } -0.05]) \) inclusion into the Remission Clinic program (Figure 8). Before inclusion, both arterial BP and 24-h urinary protein excretion showed a trend to increase over time. This trend reversed after inclusion into the Remission Clinic program, and both BP and proteinuria progressively decreased throughout the whole study period (Figure 7). After inclusion into the Remission Clinic program, \( \Delta eGFR \) did not significantly change in the six patients with diabetes \( (-0.58 [-1.57 \text{ to } -0.30] \text{ versus } -0.45 \text{ ml/min per 1.73 m}^2/\text{mo} [-0.69 \text{ to } -0.22]; P = 0.32) \), whereas it significantly decreased by 5.5-fold (from \( -0.60 [-1.53 \text{ to } -0.14] \) to \( -0.11 \text{ ml/min per 1.73 m}^2/\text{mo} [-0.23 \text{ to } -0.04]; P = 0.015 \)) in the 18 patients with nondiabetic kidney disease.

Projected Progression to ESRD

Patients versus Matched Control Subjects. On the basis of each individual eGFR at baseline and \( \Delta GFR \) measured on follow-up, no patient without ESRD during the observation period was projected to progress to ESRD within expected lifetime (75 yr for men; 80 yr for women), as compared with three reference patients who were projected to progress to ESRD \( (eGFR <10 \text{ ml/min per 1.73 m}^2) \) over 14, 22, and 34 yr, respectively, after the end of the active observation period.

Pre- versus Postinclusion into the Remission Clinic. On the basis of each individual eGFR at baseline and \( \Delta GFR \) measured before inclusion into the Remission Clinic, patients were projected to progress to ESRD \( (GFR 10 \text{ ml/min per 1.73 m}^2) \) over a median (IQR) of 7.5 yr (4.4 to 11.2). Progression to ESRD was projected within expected lifetime (75 yr for men; 80 yr for women) in 15 (63%) patients. On the basis of each individual eGFR at baseline and \( \Delta GFR \) measured after inclusion into the Remission Clinic, these patients were projected to progress to ESRD over 19.0 yr (8.9 to 35.0). Thus, progression to ESRD

Figure 7. SBP and DBP (top) and 24-h urinary protein excretion (bottom) at different time points after inclusion in the Remission Clinic in patients with or without diabetes.

Figure 8. SBP and DBP (top), 24-h urinary protein excretion (middle), and eGFR (bottom) at different time points before and after inclusion in the Remission Clinic in the 24 patients with at least three eGFR values available for slope analyses before inclusion.
was projected within expected lifetime in seven (29%) patients. Thus, on average, projected time to ESRD was postponed by approximately 12 yr, and the number of patients predicted to progress to ESRD over their expected lifetime was reduced by almost two-fold.

On the basis of their GFR decline before inclusion into the Remission Clinic, two of the six patients with diabetes were projected to progress to ESRD. This figure did not change after inclusion, as well as the projected time to ESRD (before 7.5 yr [4.8 to 9.0]; after 5.6 yr [4.1 to 8.5]). On the contrary, among patients with nondiabetic kidney disease, the number of those projected to progress to ESRD within their expected lifetime decreased from 13 (72.2%) before to 5 (27.8%) after inclusion into the Remission Clinic program. In parallel, the projected time to ESRD increased from 7.8 (4.4 to 21.0) to 28.8 yr (18.5 to 40.5). Thus, the number of patients predicted to progress to ESRD was reduced by 2.5-fold, and expected progression was postponed by 21 yr.

Safety
No patients, either with or without diabetes, had acute renal function deterioration, severe hyperkalemia refractory to diuretic therapy, acid-base control, potassium-binding exchange resins, or any other serious adverse event possibly related to treatment. Serum potassium levels transiently exceeded 5.5 mEq/L in seven patients and five reference patients and 6 mEq/L in one patient and one reference patient. In all patients, serum potassium promptly normalized by adjustment of the dosage of diuretics and/or correction of metabolic acidosis or hyperglycemia. One patient and one reference patient received potassium-binding resins. One patient reported a disturbing cough while on ramipril therapy, but the symptom recovered with dosage reduction to 2.5 mg/d and he was maintained in the Remission Clinic. No patients withdrew verapamil because of bradycardia or atrioventricular block or withdrew statins because of muscle or liver toxicity. On follow-up, serum potassium slightly increased in both patients and reference patients versus baseline and at different visits was similar in the two groups or was 0.1 to 0.2 mEq/L higher in reference patients than in patients. Hemoglobin concentration was stable and similar in the two groups (data not shown).

DISCUSSION
In this long-term, matched-cohort study of 112 patients with severe CKD and high risk for progression to ESRD, we found that a multidrug treatment titrated to urinary proteins—the Remission Clinic program—compared with a conventional regimen titrated to BP significantly slowed GFR decline and reduced the risk for terminal kidney failure by 8.5-fold. During 7 yr of observation, only two patients who were treated according to the Remission Clinic protocol progressed to ESRD, compared with 17 reference patients who were receiving conventional therapy. Moreover, on the basis of individual GFR at inclusion and rates of GFR decline observed on follow-up, no other patient was projected to progress to ESRD within expected lifetime, whereas three additional reference patients were projected to need renal replacement therapy within 14, 22, and 34 yr after the end of the active observation period, respectively. These effects were associated with more effective BP, serum cholesterol, and urinary protein reduction in patients who were treated according to the Remission Clinic approach compared with reference patients on conventional therapy. Twenty-six patients achieved disease regression or remission (24-h proteinuria <0.3 g and <1 g, with improving or stable GFR). On the contrary, only a small minority of reference patients achieved disease remission or regression and were therefore protected from eventual progression to ESRD. Of note, no patient or reference patient with 24-h proteinuria <1 g died, had cardiovascular events, or progressed to ESRD. All of these events were confined to those with residual 24-h proteinuria ≥1 g. Serum potassium was similar in the two cohorts, and no patient withdrew from the Remission Clinic because of refractory hyperkalemia or other serious adverse events. Thus, (1) a standardized, multidrug, sequential treatment targeting urinary proteins can be safely and effectively applied in everyday clinical practice; (2) by this approach, heavy proteinuria can be normalized, even in cases resistant to standard therapy; and (3) reduction of proteinuria to normal range translates into stabilization of kidney function and effective prevention of ESRD.

Role of BP Control and Proteinuria Reduction
Conceivably, both intensified BP control and more effective proteinuria reduction—possibly in addition to better control of hypercholesterolemia—contributed to the additional protection against disease progression conferred by the Remission Clinic compared with the conventional approach. Within the Remission Clinic population, however, finding that BP reduction was similar in patients with residual 24-h proteinuria <0.3 g, ≥0.3 g and <1 g, or ≥1 g ruled out the possibility that different outcomes were explained by different BP control in the three groups. Indeed, in a multivariable context, proteinuria reduction was the only follow-up variable associated with the rate of GFR decline and the risk for ESRD, and the slowest progression was observed in patients achieving the lowest proteinuria. Of note, proteinuria reduction had a highly significant predictive value even after adjustments for BP control at inclusion and BP changes on follow-up. Along the same line, analyses by tertiles of achieved BP control and residual proteinuria showed that increasing proteinuria was consistently associated with increasing rate of progression and risk for ESRD. Consistently with data from the Modification of Diet in Renal Disease (MDRD) trial, achieved BP control had an appreciable impact on progression in those with highest residual proteinuria. This confirms that in proteinuric chronic nephropathies, reducing proteinuria is the most efficient way to slow progression and that intensified BP control may confer additional renoprotection in particular in those with heavy proteinuria despite RAS inhibitor therapy. The finding that,
in addition to ESRD events, fatal and nonfatal cardiovascular events all were confined to patients with residual 24-h proteinuria of \( \geq 1 \) g extends previous evidence that proteinuria reduction may translate into a reduced cardiovascular risk in the long term.\(^{24}\) Regardless of the independent role of BP and proteinuria may translate into a reduced cardiovascular risk in the long term.\(^{24}\) Regardless of the independent role of BP and proteinuria reduction, our data provide convincing evidence that a multifactorial, intensified treatment targeting all treatable risk factors is more renoprotective than regular standard care.

**Role of Diabetes**

On follow-up, mean GFR decline was two-fold faster in patients with than without diabetes. Indeed, the Remission Clinic approach slowed GFR decline by 8.4-fold, delayed the projected time to ESRD by 21 yr, and reduced the risk for kidney failure within patient expected lifetime by 2.5-fold in those with nondiabetic kidney disease but had no appreciable effects in those with type 2 diabetes. All fatal and nonfatal cardiovascular events were restricted to patients with diabetes. These different outcomes were likely explained by the different effect on urinary proteins that were significantly reduced in those with nondiabetic chronic nephropathies but were only marginally affected in those with diabetic kidney disease.

Notably, diabetes was the only baseline covariate with an independent predictive value, the presence of diabetes being associated with faster GFR decline. The association, however, was NS when follow-up changes in proteinuria were introduced into the multivariate model. Consistently, GFR decline on follow-up depended on the amount of residual proteinuria, and, at comparable levels of proteinuria, there were no appreciable differences in GFR decline between patients with and without diabetes. Thus, diabetes was a predictor of faster progression to the extent that it was associated with a less effective reduction in proteinuria. Actually, despite intensified and multiphasologic treatment, follow-up SBP largely exceeded the target in most patients with diabetes, and this, at least in part, might have offset the antiproteinuric effect of RAS inhibition in this population. Refractory systolic hypertension is a frequent problem that further enhances the excess renal and cardiovascular risk in patients with type 2 diabetes, in particular in those with renal insufficiency.\(^{25}\) Conversely, failure to reduce proteinuria effectively in these patients extended previous evidence that the specific antiproteinuric effect of RAS inhibitor therapy is limited in patients with type 2 diabetes and severe renal insufficiency and heavy proteinuria.\(^{26}\) Actually, unlike in patients with type 1 diabetic nephropathy\(^{27–29}\) or nondiabetic CKD,\(^{6–8}\) in those with type 2 diabetes and advanced nephropathy, ACEI did not appreciably ameliorate the sieving function of the glomerular barrier\(^{26}\) and, conceivably, failed to protect the kidney from the chronic toxicity of ultrafiltered proteins,\(^{30}\) which translated into less effective renoprotection in the long term.\(^{31,32}\) A possible explanation is that at the stage of overt nephropathy (heavy proteinuria and decreased GFR), renal structural changes in patients with type 2 diabetes are so advanced and diffuse to prevent pharmacologic treatments from achieving the desired effect on proteinuria and disease progression.\(^{36}\) This is consistent with finding that in the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL), losartan decreased by almost 50% the risk for ESRD in those with baseline proteinuria/creatininuria ratios <2000 mg/g but had no significant effect in those with more severe proteinuria.\(^{33}\) These findings combined with consistent evidence from several trials\(^{24,34–36}\) of a remarkable renoprotective effect of RAS inhibitor therapy in earlier stages of renal disease should be taken to emphasize the importance of early intervention in patients with type 2 diabetes.

**Role of Different Underlying Nondiabetic Renal Diseases**

Within the limitations of comparative analyses between relatively small subgroups, data showed that patients with IMT tended to a less consistent reduction in proteinuria and a faster GFR decline than those with IgA nephropathy or other nondiabetic renal diseases. This was most likely explained by the fact that in these cases, progression was sustained not only by the nephrotoxicity of protein traffic\(^{20}\) but also by the underlying immunologic process. Conceivably, those with residual, nephrotic-range proteinuria despite conservative therapy might benefit the most from treatments aimed at attenuating the activity of the disease.\(^{57}\) This does not seem to apply to those with IgA nephropathy, who, consistent with data from previous studies,\(^{38,39}\) showed a high rate of proteinuria remission and a remarkably good long-term outcome with conservative therapy alone. These findings might help in the design of future intervention trials in different chronic nephropathies associated with heavy proteinuria.

**Regression and Remission of Nondiabetic CKD**

The REIN Follow-Up study showed that ACEI therapy improved or stabilized the GFR in patients with nondiabetic chronic nephropathies and heavy proteinuria; the effect, however, was restricted to a limited subgroup.\(^{8}\) Here we showed that with the Remission Clinic approach, the response rate to renoprotective therapy was remarkably increased, with protection against renal disease progression being achieved in a large proportion of patients. We did not explore whether improved clinical outcome was also associated with improved renal pathology. Experimental data, however, suggested that this is a reasonable possibility.\(^{40–44}\) In a genetic model of progressive nephropathy, combined therapy with ACEI and ARB in addition to normalize urinary proteins reduced glomerular sclerosis, in particular in glomeruli that had less severe lesions to start with.\(^{45,46}\) This remodeling of glomerular architecture suggests some form of regeneration of the capillary network.\(^{45,46}\) Actually, three-dimensional reconstruction studies of the glomerular tuft showed that RAS inhibitor therapy enlarged the volume of intact capillaries by up 40%—structural changes that allowed the kidney to regain function with time.\(^{47}\) Glomerular remodeling also was observed in 10 patients with type 1 diabetes after 10 yr of normoglycemia induced by pancreatic transplantation.\(^{48}\) Thus, amelioration of kidney function and, pos-
sibly, structure is achievable in humans, although, admittedly, only in a proportion of cases. Efforts should aim at identifying more effective strategies allowing achievement of this target in all patients, in particular in those with most severe disease predicted to progress rapidly to ESRD because of heavy proteinuria or type 2 diabetes. In this perspective, the Remission Clinic approach is a valuable strategy that can be safely and effectively applied to “real-life” patients seen in hospital practice. Of note, because of the concern of severe hyperkalemia, in particular in the setting of everyday clinical practice, no patient was treated with aldosterone antagonists. Whether aldosterone blockade may further enhance the protective effect of the Remission Clinic approach against the development of kidney failure, without unacceptably increasing the risk for life-threatening hyperkalemia, remains to be addressed.

Safety
Treatment was safe and well tolerated in all patients, with no patient withdrawing from the Remission Clinic program because of drug-related serious adverse events. Despite combined treatment with high-dosage ACEI and ARB, serum potassium levels transiently exceeded 5.5 mEq/L in a small minority of patients (and in a similar proportion of reference patients) and promptly normalized by adjustment of the dosage of diuretics and/or correction of metabolic acidosis or hyperglycemia. Only one patient, as well as one reference patient, required the administration of potassium-binding resins. Hemoglobin concentration was stable over time with no patient requiring erythropoietin supplementation for symptomatic anemia. Atorvastatin therapy—at the relatively low dosages we used in our patients—was also well tolerated and in no case had to be withdrawn because of liver, muscle, or kidney toxicity. Thus, provided treatment is cautiously and gradually up-titrated in parallel with close BP and serum potassium monitoring and strategies to prevent hyperkalemia are implemented, the Remission Clinic approach can be safely applied to patients with CKD, including those with type 2 diabetes.

Limitations
A possible limitation of this study is that allocation to treatment was not randomized and that patients and reference patients were identified among different populations in different clinical settings; however, the matched-cohort design we used is a well-established approach that may be worth considering as an alternative to randomized clinical trials. provided a good matching for major prognostic variables is achieved and the standard of care and monitoring are similar in considered cohorts. On this regard, it is important to note that our reference patients were identified among patients included in randomized clinical trials, who were therefore monitored and treated according to optimized and standardized protocols. Standards of data recording were also at least as good as those for the Remission Clinic patients. Moreover, in our study, the two cohorts were very well comparable not only for the matching parameters (gender, age, and baseline 24-h urinary protein excretion) but also for the other considered variables at baseline, with the only exception of the prevalence of diabetes that happened to be higher in patients than in reference patients. The finding that the multidrug compared with the conventional approach remarkably slowed the rate of GFR decline and almost fully prevented progression to ESRD despite the higher proportion of patients at increased risk in the Remission Clinic cohort provided additional evidence of the robustness of our data. Patients and reference patients were recommended a low-sodium diet with a controlled (0.8 g/kg body wt per d) protein content and were invited to refrain from smoking.

Another possible limitation is that some reference patients were not referred to our nephrology unit and, at least in theory, might have received suboptimal treatment. Sensitivity analyses, however, showed no center effect appreciably affecting the study findings. The follow-up tended also to be longer for patients than for reference patients. This, however, cannot explain the excess of events in reference patients. The robustness of the findings was confirmed by sensitivity analyses curtailed at 39 mo of follow-up showing a large excess of events in reference patients similar to that observed throughout the whole observation period.

Finally, the sample size and the total number of events were relatively small. This, however, reflected the rarity of the clinical condition under evaluation here. Conversely, the power to detect the observed difference on ESRD events was 93%, which is above the 80% threshold usually taken as a standard for between-group comparative analyses.

In conclusion, a multimodal regimen titrated to urinary proteins achieved disease remission or regression in up to 50% of patients who had severe CKD and were otherwise expected to progress rapidly to ESRD while on conventional therapy titrated just to BP control. Provided patients are closely monitored and treatment is cautiously up-titrated according to tolerability, this approach might be safe even in day-to-day hospital practice. Conceivably, because proteinuria is a strong cardiovascular risk factor and its reduction is cardioprotective, achieving disease remission or regression should also help to reduce the excess cardiovascular morbidity associated with chronic proteinuric nephropathies. Thus, the Remission Clinic approach seems to be a valuable option to limit renal and cardiovascular events in this clinical setting; however, novel and more effective intervention strategies are needed for those with type 2 diabetes and heavy proteinuria, who, despite intensified treatment with available medications, remain at very high risk for poor renal and cardiovascular outcomes.

CONCISE METHODS
In this matched-cohort study, we compared GFR decline and progression to ESRD in all consecutive patients included in the Remission Clinic from January 1999 to November 2004 and in reference patients matched 1:1 by gender, age, and urinary protein excretion identified among the 140 patients who were enrolled from 1992 to 2003 in REIN6,7 and REIN 250 studies and had been allocated to the active
treatment arm with the ACEI ramipril. All patients had 24-h proteinuria ≥3 g for ≥6 mo. Those with indication to immunosuppressive therapy, such as idiopathic FSGS, IMN (since April 2001, when we started treating IMN with anti-B cell mAb), rapidly progressive glomerulonephritis, or any active immune disease were excluded, as well as those who were expected to have spontaneous remissions, such as those with minimal-change disease or with IMN and previous spontaneous or treatment-induced remissions. Clinical and laboratory parameters were recorded in an ad hoc database. GFR was estimated (eGFR) by the Cockroft-Gault formula.51

Treatment
Only patients with 24-h proteinuria persistently ≥3 g for ≥6 mo despite continued treatment with full antihypertensive dosages of an ACEI or an ARB entered the Remission Clinic and were treated according to a sequential, stepwise, multimodal treatment protocol titrated to urinary proteins (Figure 1). Reference patients received a conventional antihypertensive treatment including single-drug RAS inhibition with a standard antihypertensive ACEI dosage (ramipril 5 mg/d), as described previously,6,7,50 and a statin according to cardiovascular risk.52 Both patients and reference patients were recommended low-sodium and controlled (0.8 g/kg body wt per d) protein intake and to refrain from smoking.

In patients, each step of the Remission Clinic protocol was implemented according to a predefined sequence until 24-h proteinuria was reduced to <0.3 g or the protocol had to be stopped because of safety/tolerability reasons (see the Safety Evaluations and Stopping Rules section). A fixed dosage (5 mg/d) of an ACEI (ramipril) was prescribed, and treatment with other ACEI, ARB, aldosterone antagonists, or other potassium-sparing diuretics was withdrawn. When tolerated, the ramipril dosage was up-titrated to 10 mg/d. At 1 mo, a fixed dose (50 mg/d) of an ARB (losartan) was added on and, when tolerated, was up-titrated to 100 mg/d. Then patients were maintained on dual RAS blockade; adjustments in ramipril (dosage range 2.5 to 20 mg/d) and losartan (dosage range 50 to 200 mg/d) dosages were allowed according to BP control and tolerability. At 3 mo, those who had a heart rate >60 bpm and were not receiving a β blocker were prescribed a fixed dosage (80 mg/d) of a nondihydropyridine CCB (verapamil) that, when tolerated, was up-titrated to 120 mg/d. Three months later, a fixed dosage (10 mg/d) of atorvastatin was prescribed and, when tolerated, was up-titrated to 20 mg/d (dosages never reported to induce tubular proteinuria). Then patients were seen every 3 to 6 mo. Adjustments of antihypertensive agents were allowed to target ≤120/80 mmHg without inducing symptomatic hypotension. Thiazide (if serum creatinine ≤1.4 mg/dl) or loop (if serum creatinine >1.4 mg/dl) diuretics were first-line therapy to target BP, prevent hyperkalemia, and/or control edema. Antiadrenergic agents were second-line therapy, whereas dihydropyridine CCB were used for safety reasons in those with BP >130/90 mmHg despite the other treatments.53 Minoxidil was considered as rescue therapy.

Monitoring
In both patients and reference patients, parameters considered at baseline were evaluated at 1 and 2 mo and every 3 to 6 mo thereafter. Additional safety visits were performed 7 to 10 d after inclusion and after any treatment modification. Aspartate aminotransferase, alanine aminotransferase, and creatine phosphokinase serum levels were measured 1 mo after the prescription of atorvastatin and every 3 to 6 mo thereafter. Outcome data were retrieved from all patients up to progression to an end point (ESRD or death) or to last available follow-up.

Safety Evaluations and Stopping Rules
Stopping rules for safety/tolerability reasons included symptomatic hypotension and/or DBP <70 mmHg,6; acute (between two consecutive steps) serum creatinine increase >30%,6; serum potassium >6.0 mEq/L despite restricted potassium intake, optimized control of metabolic acidosis and hyperglycemia (in diabetics), and treatment with diuretics and/or potassium-binding resins; sinus bradycardia or delayed atrioventricular conduction in those on verapamil; and serum aspartate aminotransferase, alanine aminotransferase, or creatine phosphokinase increases above the double of upper normal limit in those on statin. When a stopping point was reached, treatment was back-titrated to the previous step and the clinical and/or laboratory abnormality was monitored up to resolution. Serum potassium values >5.5 mEq/L and the use of potassium-binding resins were recorded for comparative safety analyses between patients and reference patients.

Targets and Outcomes
The steps of the Remission Clinic protocol were implemented until the proteinuria target of 0.3 g/24 h was achieved. Additional treatments were indicated to target BP <120/80 mmHg, glycosylated hemoglobin ≤7.5% (in patients with diabetes), and total cholesterol ≤200 mg/dl.52 Treatment of reference patients targeted a DBP of ≤90 mmHg, regardless urinary proteins.6,7,50 For both groups, three categories of response to treatment were defined:20 (1) Residual 24-h proteinuria persistently ≥1 g, (2) reduction of 24-h proteinuria to ≥0.3 g and <1 g (in two consecutive visits), and (3) reduction of 24-h proteinuria to <0.3 g (in two consecutive visits). Primary and secondary efficacy variables were the rate of eGFR decline (ΔeGFR) and ESRD, respectively.

Statistical Analyses
Baseline characteristics were compared by Wilcoxon rank sum, χ2, or Fisher’s exact test as appropriate. ΔeGFR was calculated using a single slope linear model for each patient who had at least three eGFR values. GFR slopes were compared by Wilcoxon rank sum test, analysis of covariance, or paired t test, as appropriate. Baseline covariates and “on follow-up” variables as potential predictors of GFR slopes were selected on the basis of a priori clinical considerations. Multiple linear regression included the independent variables that were significantly (P < 0.05) associated with ΔeGFR at the univariate approach. The relative importance of different independent variables was evaluated by means of the standardized β coefficient. Cochran-Armitage test was used to check for possible trends. On follow-up, data of proteinuria, BP, and lipid profile were compared by analysis of covariance including the baseline measurement in the model. The risk for progression to ESRD was compared by means of the log-rank test and, in a multivariable context, by the proportional-hazards regression
model (SAS PROC PHREG). The event curves were based on the Kaplan-Meier method. Proteinuria was log-transformed before statistical analysis. All analyses were performed using SAS software (release 9; SAS Institute, Cary, NC). Data were expressed as mean (SEM), median (IQR), or n (%), unless otherwise stated.

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DISCLOSURES

This was an academic, independent, internally funded study. P.R., A.P., and G.R. have been involved in the design and conduct of independent randomized clinical trials of ARB in diabetic and nondiabetic CKD coordinated by the Mario Negri Institute for Pharmacological Research. G.R. is a member of the steering committee of company-funded randomized clinical trials of ARB in diabetes and CKD.

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