Chronic Allograft Nephropathy in the Rat Is Improved by Angiotensin II Receptor Blockade But Not by Calcium Channel Antagonism

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Abstract. Functional and structural changes of chronic renal allograft failure share similarities with other chronic nephropathies with low nephron number. In models of reduced nephron number, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers prevented proteinuria and retarded renal lesions. This study investigates whether blockade of angiotensin II activity prevented chronic allograft injury in the Fisher 344 → Lewis rat kidney transplant model, and compares its effect with that of calcium channel blockers, the main antihypertensive agents used in transplant patients to control BP. Transplanted rats received either no treatment (control), the type 1 angiotensin II receptor antagonist losartan, or the calcium channel blocker lacidipine. Rats received cyclosporine for the first 10 d posttransplant to prevent acute rejection.

In past 20 yr, there have been significant advances in the ability to control acute rejection through more effective immunosuppressive regimens, but these improvements have had little impact on the rates of decline of long-functioning grafts (1). The leading cause of the gradual deterioration of renal function in kidney transplant recipients is an ill-defined process termed "chronic rejection," which accounts for the fact that the half-life of allografts has remained constant at 8.5 yr after transplant, although short-term results of organ survival have significantly improved (2,3). Apparently, the natural history of the process has not been modified by the continuing maintenance immunosuppression or even by the better and more selective immunosuppressive regimens now available, indicating that a number of other factors beside immunologic ones may adversely affect long-term graft function (4–6).

In "chronic rejection," kidney biopsy shows segmental glomerulosclerosis, tubular atrophy, interstitial fibrosis, and arteriosclerosis. Thus, functional and structural changes of chronic renal allograft failure share similarities with those observed in other forms of chronic progressive renal disease, in which inadequate functioning nephron mass has been considered the key event (6,7). Therefore, it has been suggested that the term "chronic rejection" actually encompasses a process of progressive deterioration of renal function, at least in part depending on a lower than normal number of functioning nephrons (7). Indeed, transplantation of a single kidney theoretically supplies half the number of nephrons commonly available to a healthy person. This implies an increased workload per nephron to maintain body homeostasis (8). The transplanted kidney is also subject to further reduction in the pool of functioning nephrons due to surgical and ischemic injury, acute rejection, and chronic cyclosporin A (CsA) toxicity (1,6).

The role of inadequate nephron supply in long-term renal allograft failure was recently documented in the Fisher 344 → Lewis rat model of kidney transplant, which mimics the progressive functional and structural changes that occur in chronic allograft rejection in humans, as shown by the development of proteinuria and glomerulosclerosis, tubulointerstitial injury, and vascular obliteration seen on histologic examination of the graft (9). In this model, increasing the renal mass by orthotopic renal allotransplantation in Lewis recipients that still maintained one native kidney prevented renal damage and glomerular dysfunction (10). Thus, similar to other rat models of disease progression, such as renal mass ablation (11) and streptozotocin diabetes (12), the low initial nephron number
and further nephron losses in the graft may set in motion compensatory hemodynamic changes, ultimately leading to glomerular injury (7).

In other models of reduced nephron number, angiotensin-converting enzyme (ACE) inhibitors and angiotensin II (AngII) receptor blockers reduced glomerular hypertension, prevented proteinuria, and retarded renal lesions, thus protecting against renal function deterioration (13). The possibility of a common pathogenic mechanism for progressive renal disease in all of these models suggests that therapies already found effective in slowing the progression of several immune and nonimmune renal diseases unrelated to transplantation can also limit chronic renal allograft dysfunction.

Therefore, we investigated whether blockade of AngII activity by a specific type 1 AngII receptor antagonist prevented chronic allograft injury in the Fisher 344 → Lewis kidney transplant model. In addition, because most human allograft recipients are given calcium channel blockers to control their BP (14), the same experimental model was used to test for comparison of the effect of a calcium antagonist, taking special care to maintain a comparable level of BP control in the two treatment groups throughout the whole study period.

Materials and Methods

Animals

Inbred male rats weighing 150 to 250 g were used in all experiments (Charles River Italia, Calco, Italy). Lewis rats (LEW RT1) acted as recipients, Fisher 344 (F344, RT1) as donors. These animals differ partially at class I, class II, and various non-MHC genes. Animal care and treatment were carried out in accordance with institutional guidelines, in compliance with national and international laws and policies (EEC Council Directive 86/609, OIJ 358, December 1987; Guide for the Care and Use of Laboratory Animals, U.S. National Research Council 1996). Animals had free access to standard rat chow and to tap water.

Renal Transplantation and Experimental Groups

Orthotopic kidney transplantation was performed as described previously (9). Donor animals were anesthetized with leptoßen (1 ml/kg, intramuscularly). The left kidney was prepared by freeing the ureter from the attachments. The renal artery was separated from the renal vein by blunt dissection. The donor kidney and ureter were removed en bloc and flushed with normal saline solution containing 1000 U/ml heparin. Then the kidney was placed in an iced saline solution until transplant.

Recipient were prepared by removal of the left kidney. An anastomosis was created between the recipient and the donor renal artery as well as renal vein with end-to-end anastomosis. The vascular clamps were released as soon as the vascular anastomoses were completed, with an ischemia time of 20 to 30 min. Donor and recipient ureters were attached end-to-end. The native right kidney was removed on the 11th postoperative day.

Three groups of allograft animals were studied: group 1 (n = 8) were control untreated rats; group 2 (n = 10) were rats given the nonpeptide AngII receptor antagonist losartan (30 mg/kg per d; Merck, Sharpe, and Dohme, Rome, Italy) in the drinking water; and group 3 (n = 10) were given the calcium channel blocker lacidipine (1 mg/kg per d, Glaxo-Wellcome, Verona, Italy) by gavage. A fourth group consisted of eight Lewis recipients of syngeneic F344 grafts. All animals received CsA (5 mg/kg per d, intramuscularly; Novartis, Milan, Italy) for the first 10 d after transplantation to prevent early acute rejection (9). Rats were followed for 6 mo. Doses of all antihypertensive drugs were adjusted as needed to achieve a comparable level of systolic BP control throughout the study. Renal function, as serum creatinine, was monitored before transplantation, on day 11 posttransplant, and monthly thereafter. At the same time points, animals were placed in individual metabolic cages for 24-h urine collection and determination of urine output and protein excretion. Systolic BP was measured serially in conscious rats by the tail-cuff method (15). The animals were acclimated to their restraint device and were warmed for 10 min before BP was measured in triplicate. Frequent interim BP measurements were made to ensure continuing BP control.

At the end of the 6-mo follow-up, whole kidney function studies were done as described previously (9). The rats were anesthetized with thiopental sodium (100 mg/kg, intraperitoneally), placed on a temperature-regulated table, and tracheotomized. A PE-50 tubing catheter was inserted into the left femoral artery for subsequent periodic blood sampling and continuous BP monitoring with an electronic transducer connected to a writing recorder (Battaglia Rangoni, Bologna, Italy). A catheter was also placed in the left femoral vein for infusion of clearance markers. Urine was collected by ureter cathe-terization. On completion of the surgery, a bolus of 4% inulin and 0.2% p-aminohippurate (PAH) solution in normal saline was infused as priming load, followed by a sustained infusion of the same solution using a syringe pump, at the rate of 1.2 ml/h. After 60 min equilibration, three timed clearance periods of 30 min each were started. Arterial blood samples were obtained at the midpoint of each clearance period for evaluation of plasma inulin and PAH concentration.

After the clearance studies, the kidneys were removed; fixed in phosphate-buffered formalin (10%); stained with Masson's trichrome, with hematoxylin and eosin, and by the periodic acid-Schiff technique; and prepared for histologic examination. The frequency of focal and segmental sclerosis and hyalinosis was determined by examining all glomerular profiles contained within one or two coronal sections from each kidney, and expressed as a percentage of the total number of glomeruli counted. Tubular changes (atrophy and casts) and interstitial fibrosis and inflammation, and vascular changes were semiquantitatively graded from 0 to 4+. Kidney tissue specimens were analyzed by the same pathologist blinded to the nature of the experimental groups.

Analytical Assay

Inulin and PAH concentrations in plasma and urine samples were measured by previously described methods (16,17). GFR and renal plasma flow, measured as inulin and PAH clearances, were calculated using standard formulas. Protein concentration in 24-h urine samples was measured by the Coomassie blue G-dye binding method (18).

Statistical Analyses

All results are expressed as mean ± SD. Data were analyzed by one-way or two-way ANOVA, as appropriate. The significance of differences between individual group means, after ANOVA, was established using the Tukey–Cicchetti test for multiple comparisons (19). Values for urinary protein excretion, which were not normally distributed, were log-transformed before statistical analysis. Survival curves were compared by log-rank test. Estimates of renal injury from morphologic studies were compared with the Wilcoxon rank sum test for nonparametric data adjusted by Bonferroni. Statistical significance was defined as P < 0.05.
Results

At the beginning of the study, body weights were comparable in the four groups. During follow-up, all of the rats gained weight, with no differences between the groups. Figure 1 shows animal survival in the four experimental groups. Five out of eight of the animals in group 1 (control) died of end-stage renal failure 31, 36, 120, 134, and 139 d posttransplant (survival at 6 mo: 37.5%). Treatment with losartan (group 2) improved survival and all animals were alive at the end of 6-mo follow-up ($P < 0.003$ versus control). By contrast, only 60% of transplanted rats given lacidipine (group 3) survived the entire 6-mo observation period and the remainder died of end-stage renal insufficiency 72, 88, 127, and 174 d after surgery ($P < 0.03$ versus losartan). In the latter group, animal survival was numerically but not significantly higher than in controls. All rats who received syngeneic grafts (group 4) survived up to the end of the study period.

Urinary protein excretion rate in the four groups is illustrated in Figure 2. The development and time course of proteinuria in group 1 followed a pattern previously described in this model (9). Thus, in most of these untreated animals, urinary protein excretion rate started to rise from baseline from day 30 posttransplant. Then, proteinuria progressively increased, reaching an average of 122 mg/24 h at the end of the observation period.

In contrast, in group 2 given losartan, urinary protein excretion values remained quite constant until day 120 postsurgery, when they began to rise, reaching 56 mg/24 h at the end of the follow-up ($P < 0.05$ versus control). In group 3, given lacidipine, urinary protein excretion began to rise above baseline values from day 30 postsurgery, and continued rising progressively thereafter. In this group, mean protein excretion values at the end of the 6-mo follow-up (131 mg/24 h), although numerically higher, were not significantly different from untreated control rats. Also, in group 4 of untreated animals receiving a syngeneic kidney graft, urinary protein excretion tended to increase, starting from day 120 postsurgery up to an average value of 45 mg/24 h at the end of the 6-mo observation period.

Systolic BP (SBP) in group 1 (controls) remained somewhat elevated starting from day 90 posttransplant (139 ± 6 mmHg), but did not attain overtly hypertensive levels (Basal: 121 ± 6 mmHg; day 180: 141 ± 17 mmHg). In group 2, losartan adequately controlled SBP, which remained within the established normal range throughout the study (Basal: 122 ± 8 mmHg; day 180: 118 ± 13 mmHg). Similarly, in group 3 rats given lacidipine, SBP was maintained in the normal range, not significantly different from the losartan-treated animals for the entire 6-mo observation period (Basal: 121 ± 8 mmHg; day 180: 135 ± 8 mmHg).

Table 1 shows the time course of serum creatinine concentrations in the four groups in animals that were alive at a given time point posttransplant. In all allograft groups, there was invariably a tendency for serum creatinine to increase on day 11 posttransplant. This was less evident in animals receiving the syngeneic kidney graft. After a transient recovery, serum creatinine in untreated group 1 rats showed a further slight increase with time. This was not seen in most of animals given losartan, in which serum creatinine remained quite stable up to

![Figure 1. Animal survival in the four experimental groups of transplanted animals during the 6-mo observation period (losartan versus control, $P < 0.05$; losartan versus lacidipine, $P < 0.03$).](image-url)
Figure 2. Serial values of urinary protein excretion rate during the 6-mo follow-up in control, losartan- and lacidipine-treated transplanted rats, as well as in syngeneic grafted animals. Values are mean ± SD. *P < 0.05 versus losartan and syngeneic grafts at the same time point.

Table 1. Time course of serum creatinine in the four groups of transplanted rats

<table>
<thead>
<tr>
<th>Group</th>
<th>Serum Creatinine (mg/dl)*</th>
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<tbody>
<tr>
<td></td>
<td>Basal</td>
</tr>
<tr>
<td>Control</td>
<td>0.63 ± 0.10</td>
</tr>
<tr>
<td>(n = 8)</td>
<td>(n = 8)</td>
</tr>
<tr>
<td>Losartan</td>
<td>0.66 ± 0.14</td>
</tr>
<tr>
<td>(n = 10)</td>
<td>(n = 10)</td>
</tr>
<tr>
<td>Lacidipine</td>
<td>0.67 ± 0.13</td>
</tr>
<tr>
<td>(n = 10)</td>
<td>(n = 10)</td>
</tr>
<tr>
<td>Syngeneic graft</td>
<td>0.68 ± 0.08</td>
</tr>
<tr>
<td>(n = 8)</td>
<td>(n = 8)</td>
</tr>
</tbody>
</table>

* All surviving animals at a given time point. Values are mean ± SD.

b P < 0.05 versus basal for each group.

c P < 0.05 versus losartan at day 180.

d P < 0.05 versus lacidipine at day 180.

6 mo posttransplant. In lacidipine-treated rats, there was a slight increase in serum creatinine in animals surviving up to 5 mo posttransplant.

As shown in Figure 3, animals treated with losartan had a higher GFR than untreated allograft rats who survived the 6-mo follow-up, but the values did not reach statistical significance. In animals given lacidipine who reached the end of the study, GFR was only slightly but not significantly lower than in losartan-treated rats, and comparable to values in syngeneic grafted rats. At variance in rats treated with losartan, renal plasma flow was significantly higher (5.71 ± 2.02 ml/min) than in lacidipine-treated animals (3.58 ± 1.01 ml/min) and in syngeneic grafted rats (2.94 ± 1.00 ml/min), but not in control (3.36 ± 0.92 ml/min).

Figure 3. GFR, as inulin clearance, measured at the end of the study in animals from the four experimental groups who survived the 6-mo follow-up. Values are mean ± SD.
Table 2. Glomerular and tubulointerstitial injury in the four groups of transplanted rats at the end of the 6-mo follow-up*

<table>
<thead>
<tr>
<th>Group</th>
<th>Glomerulosclerosis (%)</th>
<th>Tubular Casts (score)</th>
<th>Interstitial Inflammation (score)</th>
<th>Interstitial Fibrosis (score)</th>
<th>Vascular Changes (score)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>67&lt;sup&gt;b,c&lt;/sup&gt;</td>
<td>2&lt;sup&gt;b,c&lt;/sup&gt;</td>
<td>3&lt;sup&gt;b,c&lt;/sup&gt;</td>
<td>2&lt;sup&gt;b,c&lt;/sup&gt;</td>
<td>2&lt;sup&gt;b,c&lt;/sup&gt;</td>
</tr>
<tr>
<td>(50 to 100)</td>
<td>(2 to 3)</td>
<td>(2 to 3)</td>
<td>(2 to 3)</td>
<td>(2 to 2)</td>
<td></td>
</tr>
<tr>
<td>Losartan</td>
<td>2&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>(0 to 10)</td>
<td>(0 to 1)</td>
<td>(0 to 1)</td>
<td>(0 to 1)</td>
<td>(0 to 1)</td>
<td></td>
</tr>
<tr>
<td>Lacidipine</td>
<td>12&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>(4 to 20)</td>
<td>(1 to 3)</td>
<td>(1 to 3)</td>
<td>(1 to 3)</td>
<td>(0 to 2)</td>
<td></td>
</tr>
<tr>
<td>Syngeneic graft</td>
<td>0</td>
<td>0.2</td>
<td>0.2</td>
<td>0.1</td>
<td>0</td>
</tr>
<tr>
<td>(0 to 0)</td>
<td>(0 to 1)</td>
<td>(0 to 1)</td>
<td>(0 to 0)</td>
<td>(0 to 0)</td>
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</tr>
</tbody>
</table>

* Values are mean (range).
<sup>b</sup> P < 0.05 versus syngeneic graft.
<sup>c</sup> P < 0.05 versus losartan.
<sup>d</sup> P < 0.05 versus lacidipine.

Table 2 reports the histologic findings in the animals that survived 6 mo. The extent of focal and segmental glomerulosclerosis corresponded well with proteinuria. The kidney allografts from untreated animals showed marked glomerular injury, with sclerosis involving 67% of the glomeruli. Sclerosis was strikingly limited in rats given losartan, the mean (2%) being significantly lower than in control group. In lacidipinetreated animals, glomerulosclerosis (12%) was numerically, but not significantly, lower than in controls. Moreover, in these animals glomerular lesions were significantly higher than in rats receiving losartan, despite similar systemic BP values. No glomerulosclerosis was found in syngeneic grafted animals. In control rats, numerous tubular casts were found (Table 2). In animals given losartan but not lacidipine, a reduction in tubular casts was observed. Similarly, in untreated rats tubulointerstitial injury was severe (Table 2). Losartan administration largely preserved tubulointerstitial structure, with only mild mononuclear cell infiltrates and interstitial fibrosis. In contrast, marked interstitial infiltrates and interstitial fibrosis were found in allografts from lacidipine-treated animals. Only one of the syngeneic grafts showed mild tubulointerstitial inflammation. Vascular changes were prominent in control rats, but virtually absent in animals given losartan. In lacidipine-treated rats, vascular abnormalities were numerically lower than in controls, but the difference did not reach statistical significance. No vascular lesions were shown in untreated syngeneic grafts.

**Discussion**

The first observation of the present study is that in most of our kidney allograft rats, a transient increase in serum creatinine concentration occurred 11 d posttransplant, probably as a result of a mild acute graft rejection process. Ischemic damage and/or cyclosporine toxicity may also have contributed to mild deterioration of renal function, because at the same time point serum creatinine also increased in rats receiving syngeneic kidneys. Though transient, these processes may have further reduced the number of functioning nephrons, suggesting that crossing the immune barrier may accelerate injury in allografts, through the early episode of acute rejection, together with the contribution of ischemia and cyclosporine treatment. The reduction in nephron supply per unit of recipient body mass may trigger a rapidly progressive course of hemodynamically mediated glomerular injury (6). Thus, in this model of chronic allograft rejection, micropuncture studies showed that glomerular capillary hydraulic pressure and plasma flow were higher than in syngeneic animals, independent of systemic BP (20,21). Furthermore, glomerular capillary pressure rose as early as 6 wk posttransplant (21), suggesting that it may be an early aspect of chronic rejection which, in conjunction with the immune-based insult, culminates in glomerulosclerosis and eventual deterioration of renal function, as extensively shown in other experimental models of renal mass ablation (11,12).

Here, we found that daily treatment with the AngII receptor blocker losartan in transplanted Fisher 344 → Lewis rats largely prevented the development of proteinuria and preserved glomerular structure, as documented by urinary protein excretion and histologic features, which were similar to those in animals receiving syngeneic graft and followed for the same period of time after transplant. These findings are in harmony with a recent report that in the same model, the ACE inhibitor cilazapril or the AngII receptor blocker L-158,809 reduced urinary protein excretion, decreased glomerulosclerosis, and improved graft survival (22). Very similar results have been obtained in other models of renal disease progression, such as the remnant kidney model and streptozotocin-induced diabetes, in which both ACE inhibitors and AngII receptor antagonists limited proteinuria and glomerular lesions (11,12,23–25). In these models, the beneficial effect of inhibiting the renin-angiotensin system was attributed to their property of normalizing glomerular hypertension (26).

At variance with losartan, the calcium channel blocker lacidipine failed to prevent proteinuria in rats with chronic rejection. The extent of the glomerular and extraglomerular lesions in chronically rejecting allografts (day 180) removed from recipients treated with lacidipine, despite being numerically lower than in untreated controls, allows us to infer that a longer
follow-up period will almost certainly be associated with increased graft loss. Animal survival compared with untreated animals was significantly prolonged by losartan, but not by lacidipine, although both treatment regimens were equally effective in controlling systemic BP. Thus, blockade of the renin-angiotensin system is more effective than calcium channel blockers in reducing renal injury and retarding the progression of renal disease in the rat model of chronic allograft rejection.

Previous studies with calcium channel blockers in experimental renal disease of nontransplanted models gave conflicting results. In the remnant kidney, verapamil afforded protection in some studies (27), but not in others (28). Nifedipine and other dihydropyridine derivatives have been more successful in preventing glomerular injury in rats with systemic hypertension and progressive renal disease (29,30), although not without exception (31). Diltiazem and its derivatives have also given variable findings with respect to renal protection (32,33). Other studies found that despite adequate reduction in systemic BP, neither verapamil (34) nor nifedipine (35) limited the development of albuminuria or structural injury in experimental diabetes.

Previous studies (11,12,29,30,35–37) found that in experimental animals, drugs that successfully prevented glomerular injury consistently normalized glomerular hypertension. It remains to be established whether the marginal effect of lacidipine on chronic transplant nephropathy depends on its failure to normalize glomerular hemodynamics.

Besides hemodynamics, when the glomerular permselective property is lost, the increased glomerular ultrafiltration of proteins leads to an abnormal amount of proteins in the ultrafiltrate that is largely reabsorbed by proximal tubular cells with congestion of cell organelles and subsequent accumulation of proteins and lysosomal enzymes into the interstitial space (13). This form of tubular cell activation upregulates genes of inflammatory and vasoactive substances that, in the long term, contribute to renal scarring (13). There is now plenty of evidence that drugs which restore normal glomerular permselectivity retard the progression of renal disease. Thus, in experimental models of chronic renal disease, ACE inhibitors (23) and AngII receptor blockers (24) ameliorate glomerular membrane functional properties by reducing membrane pore size and concomitantly increasing the hydraulic permeability of the glomerular capillary wall and reducing renal injury. Similar findings have been obtained in patients with proteinuric diabetic and nondiabetic renal diseases (38–41). It is possible that amelioration of glomerular permeability contributed to the observed better effect of losartan compared with lacidipine in the present study.

There is also evidence that AngII may affect tissue remodeling independent of its effect on BP or hemodynamic parameters (42), through its growth factor properties (43). As shown in rats, AngII infusion indeed exerts a growth-stimulatory effect on the kidney in vivo with proliferation of mesangial cells and vascular smooth muscle cells and changes in the tubulointerstitial architecture with increased collagen IV deposition (44). Moreover, evidence supporting the inhibitory effect of ACE inhibition (45,46) or AngII receptor blockade (47,48) on intimal hyperplasia in nontransplanted models as well as on graft coronary artery disease has been recently reported. Taken together, these findings suggest that the antiproliferative effect of blocking AngII biological activity could also have contributed to the renoprotective effect of losartan in the present model of chronic allograft nephropathy.

Calcium antagonists are the most commonly used drugs for the treatment of posttransplant hypertension in human renal allograft recipients (14,49) and are generally administered with the aim of antagonizing cyclosporine vasoconstriction (50). Indeed, the effect of calcium antagonists in reducing the tone of afferent arterioles counteracts the vasoconstrictive effect of cyclosporine on preglomerular arterioles (50–52), and may reduce the long-term renal toxicity of cyclosporine. In a human study, we found that renal transplant patients given lacidipine for 7 d were completely protected from the acute renal hypoperfusion and fall in GFR that invariably occur a few hours after cyclosporine dosing (53). However, although most reports suggest that calcium channel blockers are beneficial in the early posttransplant period (50,54–56), there are still no data about the effect of this treatment on renal allograft outcome in the long term.

Our present findings of clear superiority of an AngII antagonist over a calcium channel blocker in the progressive nephropathy of experimental transplantation indicate a novel way to protect the transplant kidney from progressive renal function deterioration. These data also question seriously the current attitude of most clinicians of treating hypertension in human recipients of renal allograft with calcium antagonists. Blocking the activity of AngII instead is probably the most correct approach in this setting. Clinical trials should start soon to validate the above assumption.

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References