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Hypertension and Chronic Kidney Disease Progression: Why the Suboptimal Outcomes?

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Abstract

Current therapeutic interventions to retard the progression of chronic kidney disease have yielded disappointing outcomes despite adequate renin-angiotensin system blockade. The parameters to gauge the adequacy of blood pressure control need to be reassessed because clinic blood pressure constitutes a poor gauge of such control. The biologically relevant parameter for hypertensive target organ damage is total blood pressure burden, and reliance on isolated clinic blood pressure measurements per se does not accurately reflect the total blood pressure burden. This is particularly relevant to the population with chronic kidney disease in whom masked daytime or nocturnal hypertension and blood pressure lability are both widely prevalent and more difficult to control. Consequently, it is possible that the limited success currently being achieved in preventing or attenuating chronic kidney disease progression may be attributable in part to suboptimal 24-hour blood pressure control. Recent data and analyses also indicate that blood pressure variability, instability, episodic and nocturnal blood pressure elevations, and maximum systolic blood pressure may constitute additional strong predictors of the risk of target organ damage independently of mean systolic blood pressure. Accordingly, we suggest that future research should include the development of safe and effective strategies to achieve around-the-clock blood pressure control in addition to targeting mechanisms that reduce intrarenal blood pressure transmission or interrupt subsequent downstream pathways. Meanwhile, more aggressive use of patient education and home blood pressure monitoring with selection of longer-acting antihypertensive agents or nocturnal dosing should be considered to improve the current suboptimal results.

Keywords

Ambulatory blood pressure monitoring; Antihypertensive agents; Blood pressure lability; Masked hypertension; Renal autoregulation

Chronic kidney disease, regardless of cause, tends to progress, albeit at varying rates. Blockade of the renin-angiotensin system and aggressive blood pressure control are the mainstays of current management guidelines to retard the progression of most chronic

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kidney diseases, including diabetic nephropathy, with additional specific therapy for associated comorbidities.^{1,2} Nevertheless, despite the apparently successful application of this strategy, rather disappointing outcomes were reported recently for the extended follow-up of the African-American Study of Kidney Disease and Hypertension (AASK) cohort.^{3,4} During a follow-up of 8 to 12 years, adverse renal outcomes (doubling of serum creatinine, development of end-stage renal disease, or death) occurred in 280 of 733 nonproteinuric patients and in 285 of 357 proteinuric patients (baseline urine protein to creatinine ratio of > 0.22, ~300 mg/d).

These poor outcomes may be due in part to the enhanced genetic susceptibility for chronic kidney disease progression in African Americans because of the wide prevalence of genetic variants in this population associated with a high risk for focal segmental glomerular sclerosis and nondiabetic end-stage renal disease.⁵⁻⁷ These genetic traits may render the renal disease in such patients less amenable to renin-angiotensin system blockade or other antihypertensive therapy. However, it is worth noting that the overall glomerular filtration rate decline of < 2 mL/min/1.73 m² per year achieved in the AASK trial is substantially better than that in other trials in racially unselected, albeit more proteinuric populations,^{2,8} particularly in those with diabetic nephropathy, who tend to exhibit the most rapid rates of progression for reasons that remain to be precisely identified.⁹⁻¹¹ Consequently, the poor outcomes in the AASK trial cannot be entirely attributable to an increased genetic susceptibility per se of African-American patients. Because continued chronic kidney disease progression in such patients may be mediated at least in part by factors or mechanisms that are independent of both renin-angiotensin system and blood pressure,^{12,13} the question arises if the AASK trial results represent the best that currently can be achieved in combating chronic kidney disease progression with renin-angiotensin system blockade and antihypertensive therapy in our present state of knowledge. Indeed, efforts to further enhance renin-angiotensin system blockade beyond that achieved by the generally recommended doses of individual agents by combining multiple renin-angiotensin system blockers have not only failed to improve outcomes but also may have contributed to excess adverse events.¹⁴⁻¹⁶

BLOOD PRESSURE TARGETS IN CHRONIC KIDNEY DISEASE

Available clinical trial data also indicate that further lowering of blood pressure targets to less than 130 mm Hg systolic may not be sufficient to achieve significant additional reductions in adverse outcomes, except perhaps in some selected subsets of patients.^{4,17,18} Although a large body of observational data does indicate that lower blood pressure levels are associated with better renal outcomes,^{1,2} 3 major clinical trials in adult patients with chronic kidney disease (Modification of Diet in Renal Disease [MDRD],¹⁹ Renoprotection in Patients with Nondiabetic Chronic Renal Disease 2,²⁰ and AASK^{3,4}) have not been able to demonstrate such benefits of lower blood pressure goals, except in smaller subsets of proteinuric patients (AASK, MDRD).^{4,18} Of note, even with the greater benefits of lower blood pressure targets in proteinuric patients, adverse renal outcomes still occurred in 136 of 181 proteinuric individuals assigned to the lower blood pressure goals in the AASK trial,⁴ consistent with the overall poorer outlook in proteinuric patients.^{2,8,18} Despite these apparently discouraging results, several considerations, including the pathophysiology of hypertensive renal injury and the results of ambulatory blood pressure monitoring in such patients, suggest that it may be possible to achieve significant additional improvements in ameliorating the blood pressure-dependent component of chronic kidney disease progression.

PATHOPHYSIOLOGY OF HYPERTENSIVE RENAL DAMAGE

The primary pathologic processes in hypertensive states that result in the progressive loss of glomerular capillaries and filtration capacity in chronic kidney disease can be broadly separated into ischemia or barotrauma-mediated pathways.^{21,22} In the absence of malignant hypertension, ischemia-dependent pathways likely predominate in essential hypertension. Because renal autoregulation is preserved, glomerular capillaries are protected from direct barotrauma and significant proteinuria is usually not seen. Nevertheless, the more slowly progressive vascular pathology of benign nephrosclerosis eventually results in glomerular ischemia and nephron loss, particularly in certain susceptible individuals and populations. By contrast, significant reductions of functional renal mass in chronic kidney disease states are associated with afferent arteriolar vasodilation, impaired autoregulation, and increased transmission of systemic blood pressure to glomerular capillaries with resultant glomerular barotrauma, proteinuria, glomerulosclerosis, and more rapid progression.

SUSCEPTIBILITY TO HYPERTENSIVE RENAL INJURY

Chronic kidney disease and diabetes also may enhance the susceptibility of glomerular capillaries to injury at any given glomerular pressure via mechanisms that remain poorly defined but likely include potential stresses induced by glomerular hypertrophy responses.²¹ It also may be important to emphasize that the ambient glomerular capillary pressures are a function of not only the systemic blood pressure and the autoregulatory afferent arteriolar responses to it but also the prevailing efferent arteriolar resistance that in turn is dependent on neurohormonal inputs, including angiotensin II and nitric oxide.^{21,23,24} In fact, the postulated blood pressure-independent renoprotective superiority of the renin-angiotensin system blockade has been in part ascribed to its potential efferent vasodilatory effects.^{8-11,21,24} Although widely accepted, the magnitude of such effects of renin-angiotensin system blockade in chronic kidney disease states as yet remains to be established.^{21,24,25} In any event, patients with chronic kidney disease are likely to differ in their susceptibility to hypertensive injury because of differences in underlying pathology, renal hemodynamics, and autoregulatory capacity (genetic or acquired). Such differences are expected to alter the threshold level of blood pressure that significantly affects chronic kidney disease progression and the slope of the relationship between increases in blood pressure level and renal damage.²⁶ Given these considerations, the observed nonlinear interactions among blood pressure, proteinuria, and chronic kidney disease progression are not unexpected, and although proteinuria is clearly heterogeneous in its pathogenesis, it may nevertheless serve as a surrogate marker of increased glomerular capillary pressure or its responsiveness to blood pressure reductions in those with chronic kidney disease. Thus, it is not surprising that greater relative risk reductions with lower blood pressure targets have been seen in proteinuric patients compared with nonproteinuric patients or that reductions in proteinuria during antihypertensive therapy correlate better with renal risk reduction than the magnitude of the blood pressure reductions per se.^{4,8,20,26,27}

BLOOD PRESSURE LABILITY AND GLOMERULAR TRANSMISSION

In this context, it is important to emphasize the dynamic and around-the-clock nature of such enhanced glomerular blood pressure transmission and glomerular capillary injury. Blood pressure is fundamentally labile even in normotensive states, and it is the intact autoregulatory mechanisms that prevent the normally occurring blood pressure fluctuations from reaching the glomeruli.^{23,28} Therefore, when autoregulation is impaired, there is a greater transmission of such blood pressure lability to the renal microvasculature, and glomerular pressure exposure may not be normalized even if overall normotension is achieved with antihypertensive therapy.²⁹ Given that blood pressure lability is further

exaggerated in hypertensive states, such data also suggest that isolated blood pressure measurements are likely to be more limited in providing an index of the total glomerular blood pressure exposure in those with chronic kidney disease.^{21,25,28,29} It is for such reasons that direct and continuous rather than isolated tail-cuff blood pressure measurements have been recommended for the investigations of hypertensive renal damage in experimental animal models.³⁰ Such considerations also indicate that even with optimal blood pressure control, it may not be possible to completely eliminate glomerular barotrauma and some chronic kidney disease progression in such patients. However, an examination of the blood pressure data in AASK and other chronic kidney disease trials indicate that the actual blood pressure control being achieved is considerably suboptimal.

AMBULATORY BLOOD PRESSURE MONITORING AND BLOOD PRESSURE CONTROL

Although overall blood pressure goals were claimed to have been largely successfully achieved in the AASK trial, this was entirely based on isolated clinic blood pressure measurements.^{3,4} Ambulatory blood pressure monitoring performed at entry into the cohort phase of the study showed that overall blood pressure was inadequately controlled during daytime or nighttime in 80% of the participants.³¹ Moreover, an unexpectedly high prevalence (70%) of masked hypertension (elevated day or nighttime blood pressure levels but controlled clinic blood pressure levels) was seen in the more than 60% of patients who had achieved clinic blood pressure control. Remarkably, 40% of the patients also demonstrated a reverse dipping pattern with a nighttime systolic blood pressure that averaged approximately 14 mm Hg higher than their clinic systolic blood pressure. The AASK investigators have recently expressed valid concerns regarding conclusions reached on the basis of “achieved blood pressure” versus “intention to treat” analyses.³² However, as also has been noted by others, the implications of the more problematic issues of the failure of the clinic blood pressure per se in the AASK study to accurately reflect the most biologically relevant parameter for target organ damage (total blood pressure burden) were not seriously addressed.³³ Nevertheless, despite the well-recognized limitations of office/clinic blood pressure measurements as a surrogate measure of the “true blood pressure load” on the vasculature, they have remained the primary blood pressure index used in clinical trials because of considerations of cost, convenience, practicality, and potential translatability to clinical practice.^{25,34}

ADDITIONAL LIMITATIONS OF TRADITIONAL CLINIC BLOOD PRESSURE MEASUREMENTS

Concerns about the conclusions based on isolated and limited clinic blood pressure measurements have been further magnified by the recent data and analysis that indicate that blood pressure variability, instability, episodic and nocturnal blood pressure elevations, and maximum systolic blood pressure may be additional strong predictors of the risk of target organ damage independently of mean systolic blood pressure.^{35,36} Although such associations have thus far been most clearly defined for stroke, there is evidence that at least some of these variables may be relevant for chronic kidney disease progression.^{29,37} Indeed, it is possible that the limited success that is currently being achieved in preventing chronic kidney disease progression may be attributable in part to the fact that masked daytime or nocturnal hypertension and blood pressure lability are both more prevalent and more difficult to control in those with chronic kidney disease.^{31,38} Therefore, given the likelihood that target organ damage is the result of total cumulative exposure to elevated blood pressures, better outcomes may be obtained by achieving blood pressure targets throughout the 24-hour period than by further lowering clinic blood pressure target pressures.

Although clinical trial data showing that therapies specifically addressed to these aspects of blood pressure control can further reduce target organ damage have only just started to appear,^{39,40} both observational and experimental data, as well as biological plausibility, support the advisability of such goals and future research targeted at approaches to attain these goals. Although the recent National Institute for Clinical Excellence guidelines have recommended a wider use of ambulatory blood pressure monitoring during the initial assessment of hypertensive patients, this has been questioned in the United States.^{41,42} In any event, ambulatory blood pressure monitoring is currently not feasible in routine clinical practice to monitor blood pressure control or the development of masked hypertension. Nevertheless, it may be possible to achieve improvements in blood pressure control through more aggressive promotion of patient education and their enlistment as active participants in their own management, including home blood pressure monitoring. Also, the use of longer-acting antihypertensive agents, appropriate combinations or nocturnal dosing, and more aggressive diuretic therapy may help reduce the prevalence or severity of nocturnal hypertension and regulate around-the-clock blood pressure control in those with chronic kidney disease^{39,40,43,44} (see below). Ambulatory blood pressure monitoring could then be considered in patients who fail to exhibit reduction in proteinuria or in the rate of renal function decline despite “apparent” clinic blood pressure control.

PHARMACOKINETICS OF ANTIHYPERTENSIVE AGENTS AND BLOOD PRESSURE CONTROL

A greater consideration of the pharmacokinetic profiles of antihypertensive agents also may help achieve these goals of preserving normal circadian rhythms and obviating or minimizing intermittent and fluctuating blood pressure control. The trough-to-peak ratio is a well-established parameter for characterizing the therapeutic profile of an antihypertensive drug, thereby constituting a basis for therapeutic decisions.^{45,46} This measurement arose from deliberations of the Food and Drug Administration in vetting the attributes of newly submitted antihypertensive drugs that were being adjudicated for approval.⁴⁵ The recommended trough-to-peak is approximately 50% to 60%, although some have recommended higher ratios. Although initially conceived as a regulatory requirement, trough-to-peak ratios provide the clinician with a useful index to gauge the duration of a drug’s antihypertensive response and consequently to select drugs within each antihypertensive class.^{45,46} The use of newer sustained-delivery systems, such as the spheroidal oral drug absorption system, the “coat core” formulation, drug delivery systems with osmotic pumps (gastrointestinal therapeutic systems), and the chronotherapeutic oral drug absorption system, may provide additional tools to help achieve such goals.

CALCIUM CHANNEL BLOCKERS AND PROGRESSION OF PROTEINURIC KIDNEY DISEASE

These considerations also are likely relevant to the efforts to define the relative merits of different antihypertensive classes or agents for preventing target organ injury, the focus of much recent investigation. For instance, the dihydropyridine calcium channel blockers are effective in preventing stroke, a superiority that has recently been attributed in part to their ability to reduce blood pressure variability.^{35,36} However, it is of note that despite this putative advantage, the dihydropyridine calcium channel blockers have been noted to be relatively ineffective in reducing proteinuria or slowing chronic kidney disease progression despite their effectiveness in blood pressure lowering.^{21,47,48} To illustrate, unlike the benefits of lower blood pressure targets in proteinuric patients seen in the AASK and MDRD trials,¹⁸ the addition of felodipine to a ramipril-based regimen in proteinuric patients with chronic kidney disease in the Renoprotection in Patients with Nondiabetic Chronic

Renal Disease 2 trial failed to provide any additional renal benefits despite further reduction in systolic blood pressure of 4.1 mm Hg.²⁰ Likewise, in proteinuric patients with diabetic nephropathy in the Irbesartan in Diabetic Nephropathy Trial, the amlodipine-treated group had a mean arterial pressure that was 3.3 mm Hg lower than the placebo control group, yet the expected renoprotection from the lower blood pressure was not seen.¹⁰ Indeed, in the AASK trial, the hard outcomes of end-stage renal disease or death were significantly more frequent in the dihydropyridine calcium channel blocker group despite a 2 mm Hg lower systolic blood pressure.⁴⁹ These differences likely stem from the fact that unlike stroke, chronic kidney disease progression (loss of glomerular filtration area) is largely a consequence of micro- and not macrovascular pathology. Calcium channel blockers impair autoregulation and thereby enhance pathologic microvascular blood pressure transmission.^{21,28,50} This may in large part account for their inferiority to renin-angiotensin system blockade as renoprotective antihypertensive agents. With the use of blood pressure radiotelemetry in experimental proteinuric models, the dihydropyridine calcium channel blockers have been demonstrated to result in greater glomerulosclerosis at any given blood pressure elevation compared with untreated or renin-angiotensin system blockade-treated animals, as would be predicted from their adverse effects on renal autoregulation.^{28,50}

FUTURE DIRECTIONS

Investigations are needed to help identify mechanisms to improve renal autoregulatory capacity and glomerular blood pressure transmission, as well as favorably modulate the downstream cellular and molecular pathways initiated in response to the microvascular barotrauma. Meanwhile, given the rather disappointing outcomes with the current management approach based on clinic blood pressure monitoring, development of alternative strategies addressed to comprehensive blood pressure control seems likely to yield more success than therapies targeted to greater renin-angiotensin system blockade or even lower clinic blood pressure targets per se while we await the development of effective supplemental therapies directed to additional targets.^{12,13}

CONCLUSIONS

Current therapeutic interventions to retard the progression of chronic kidney disease have yielded disappointing outcomes despite adequate renin-angiotensin system blockade. Blood pressure reduction constitutes a major facet of current therapeutic regimens, but the parameters currently used to gauge the adequacy of blood pressure control (ie, clinic blood pressure) need to be reassessed. The biologically relevant parameter for hypertensive kidney damage is the total blood pressure burden that the kidneys are exposed to, and isolated clinic blood pressure measurements per se do not provide an accurate reflection of such blood pressure burden. Consequently, it is possible that the limited success currently being achieved in preventing or attenuating chronic kidney disease progression may be due in part to the fact that masked daytime and nocturnal hypertension and blood pressure lability are both widely prevalent and more difficult to control in those with chronic kidney disease. In accord with this formulation, recent data and analyses indicate that blood pressure variability, instability, episodic and nocturnal blood pressure elevations, and maximum systolic blood pressure may constitute additional strong predictors of the risk of target organ damage independently of mean systolic blood pressure. Accordingly, we suggest that future research should include the development of safe and effective strategies to achieve around-the-clock blood pressure control in addition to targeting mechanisms that reduce intrarenal blood pressure transmission or interrupt subsequent downstream pathways. Meanwhile, more aggressive use of patient education and home blood pressure monitoring with selection of longer-acting antihypertensive agents or nocturnal dosing should be considered to improve the current suboptimal results. Finally, to the extent that elevated blood pressure

does not constitute the sole determinant of chronic kidney disease progression, additional investigative efforts should focus on identifying other nonhemodynamic mechanisms of renal disease progression and developing newer treatment strategies to counter them.

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CLINICAL SIGNIFICANCE

- Chronic kidney disease is associated with impaired renal autoregulation that promotes glomerular barotrauma.
- Poor 24-hour blood pressure control likely contributes to suboptimal renal outcome in clinical trials.
- Consideration of pharmacokinetic profiles of antihypertensive agents, use of combinations, or nocturnal dosing may help achieve better 24-hour blood pressure control.