Management of Presumed Acute Kidney Injury during Hypertensive Therapy: Stay Calm and Carry on?

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Abstract

\textbf{Background:} Recent studies have demonstrated that intensive blood pressure control is associated with improved cardiovascular outcomes. Acute kidney injury (AKI), however, was more common in the intensive treatment group prompting concern in the nephrology community. \textbf{Summary:} Clinical trials on hypertension control have traditionally defined AKI by changes in serum creatinine. However, serum creatinine has several inherent limitations as a marker of kidney injury, with various factors influencing its production, secretion, and elimination. Urinary biomarkers of kidney injury and repair have the potential to provide insight on the presence and phenotype of kidney injury. In both the Systolic Blood Pressure Intervention Trial and the Action to Control Cardiovascular Risk in Diabetes study, urinary biomarkers have suggested that the increased risk of AKI associated with intensive treatment was due to hemodynamic changes rather than structural kidney injury. As such, clinicians who encounter rises in serum creatinine during intensification of hypertension therapy should “stay calm and carry on.” Alternative explanations for serum creatinine elevation should be considered and addressed if appropriate. When the rise in serum creatinine is limited, particularly if albuminuria is stable or improving, intensive blood pressure control should be continued for its potential long-term benefits. \textbf{Key Messages:} Increases in serum creatinine during intensification of blood pressure control may not necessarily reflect kidney injury. Clinicians should evaluate for other contributing factors before stopping therapy. Urinary biomarkers may address limitations of serum creatinine as a marker of kidney injury.

Introduction

The landscape of hypertension management has changed dramatically over the past 5 years. In 2014, the Eighth Joint National Committee guidelines recommended a blood pressure goal < 140/90 mm Hg among adults aged < 60 years (including those with chronic kidney disease [CKD]) and < 150/90 mm Hg among adults aged \geq 60 years [1]. One year later, the landmark Systolic Blood Pressure Intervention Trial (SPRINT) reported that intensive treatment (goal systolic blood pressure...
<120 mm Hg) was associated with a 25% lower risk of a composite cardiovascular outcome (95% CI 0.64–0.89) and 27% lower risk of all-cause mortality (95% CI 0.60–0.90) compared to standard treatment (goal systolic blood pressure <140 mm Hg) [2]. However, development of acute kidney injury (AKI), defined by changes in serum creatinine concentration, was 64% (95% CI 1.30–2.09) more likely in participants randomized to the intensive versus standard treatment group [3]. Despite this reported increase in AKI risk, hypertension guidelines have already begun to move toward lower blood pressure goals. For example, the American College of Cardiology and American Heart Association now recommend a blood pressure target <130/80 mm Hg for individuals with hypertension and any of the following: diabetes mellitus, CKD, or a 10-year atherosclerotic cardiovascular disease risk of ≥10% [4]. As such, clinicians are faced yet again with the age-old conundrum of whether to pursue more intensive blood pressure goals for their cardiovascular and mortality benefits but at the potential cost of worse kidney outcomes. This review aims to: (1) describe the limitations of serum creatinine as a marker of kidney injury; (2) discuss the utility of urinary biomarkers in discerning presumed from actual kidney injury in hypertension trials; and (3) propose an approach to managing presumed AKI during hypertension therapy.

**Pitfalls of Serum Creatinine as a Marker of Kidney Injury**

The ideal filtration marker is one that is freely filtered by the glomerulus and not secreted, reabsorbed, or metabolized by the renal tubule. In addition, the marker should be nontoxic, physiologically inert, and not bound to proteins. Considered the “gold standard,” inulin fulfills each of these criteria. However, the process of measuring inulin clearance is laborious, requiring an intravenous infusion and repeated sample collections [5]. Alternative filtration markers are therefore used in clinical practice, with the most common being serum creatinine. Creatinine, an endogenous 113 Dalton breakdown product of muscle metabolism, is less expensive and easier to measure compared to inulin. Freely filtered and not protein bound or metabolized by the kidneys, creatinine possesses many of the qualities of a good filtration marker but also has several important limitations. First, production of creatinine varies between and within individuals over time. Older adults, women, and Caucasians have diminished creatinine generation. Decreases in muscle mass (from malnutrition or amputation), increased dietary protein intake, or ingestion of creatine supplements can also influence creatinine production. Second, creatinine is secreted by the proximal tubules, which can lead to an overestimation of the glomerular filtration rate (GFR) [5, 6]. On the other hand, drugs known to inhibit creatinine secretion (e.g., trimethoprim, cimetidine, tyrosine kinase inhibitors, fibrates, and some antiretroviral medications) can increase serum creatinine levels without having an effect on GFR [6–11]. Third, extrarenal elimination of creatinine occurs in severe renal insufficiency (e.g., when serum creatinine >6 mg/dL) [5, 6, 12]. The mechanism is believed to be small intestinal bacterial overgrowth increasing creatinase activity and ultimately creatinine degradation [12].

There are also situations where a rise in serum creatinine does not reflect kidney injury but rather a change in glomerular hemodynamics. The classic example is after initiation of an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) in which an up to 30% rise in serum creatinine from baseline is generally considered acceptable [13]. In a study of patients with type 2 diabetes, hypertension, and CKD (mean estimated GFR [eGFR] ~40 mL/min/1.73 m²; urine albumin-to-creatinine ratio [UACR] >300 mg/g), initiation of losartan was associated with a greater acute fall in creatinine-based eGFR compared to placebo (2.3 vs. 1.6 mL/min/1.73 m², respectively; p = 0.03) in the first 3 months of treatment. Interestingly, in the losartan but not placebo group, participants with greater acute falls in eGFR (from baseline to 3 months) paradoxically had slower rates of long-term eGFR decline (from 3 months to the final visit; mean follow-up 3.4 years) [14]. In another study of patients with left ventricular dysfunction (mean eGFR 66 mL/min/1.73 m²), early worsening renal function (defined as a ≥20% decrease in eGFR within 2 weeks of initiating therapy) was independently associated with increased mortality in the placebo group (hazard ratio [HR] 1.4; 95% CI 1.1–1.8) but not the enalapril group (HR 1.0; 95% CI 0.8–1.3). Among participants who continued the study drug, the greatest survival advantage associated with enalapril therapy was observed in those who developed early worsening renal function (HR 0.66 comparing enalapril versus placebo; 95% CI 0.5–0.9) [15]. Other studies have demonstrated that withdrawal of an ACEI, even after years of therapy, can lead to a return in measured GFR toward baseline values [13, 16]. Taken together, the results of these studies suggest that an acute decline in eGFR that occurs following ACEI or ARB initiation...
may be a marker of therapeutic responsiveness rather than a safety concern [13–16].

In a post hoc analysis of SPRINT, Beddhu et al. [17] investigated the clinical implications of an early decline in eGFR attributed to intensive blood pressure control. Through causal mediation analyses, the investigators were able to parse out the indirect (mediated by change in eGFR from baseline to 6 months) and direct (mediated by pathways other than change in eGFR from baseline to 6 months) effects of the randomized treatment arms on trial outcomes. Although more individuals in the intensive treatment group developed an early eGFR decline ≥20% (10.3 vs. 4.4% comparing intensive vs. standard; \( p < 0.001 \)), this early decline in eGFR did not attenuate the cardiovascular or mortality benefits associated with intensive blood pressure control [17]. In post hoc analyses of the African American Study of Kidney Disease and Hypertension (AASK) and the Modification of Diet in Renal Disease (MDRD) trial, Ku et al. [18] reported that acute declines in eGFR < 20% (from baseline to 3 months for AASK; from baseline to 4 months for MDRD) were not associated with an increased risk of subsequent end-stage renal disease (ESRD) among participants randomized to the intensive treatment arms (MAP ≤92 mm Hg for AASK; MAP < 92 or < 98 mm Hg for MDRD). However, an acute eGFR decline ≥20% in the intensive treatment group was associated with 3.0-fold (AASK; 95% CI 1.95–4.77) and 1.6-fold (MDRD; 95% CI 1.09–2.24) higher risks for ESRD compared to an acute eGFR decline < 5%.

Interestingly, among participants randomized to the standard treatment group (MAP 102–107 mm Hg for AASK; MAP <107 and 113 mm Hg for MDRD), both acute eGFR declines of 5–20% and ≥20% were associated with 1.5–2.6-fold higher risks of ESRD (compared to acute eGFR decline <5%) [18]. These findings highlight the complicated relationship of blood pressure control, acute eGFR change, and cardiovascular and renal outcomes.

**Era of Urinary Biomarkers**

We previously described a conceptual model describing the potential limitations of using serum creatinine to define AKI (Fig. 1) [19]. In best-case scenarios, serum creatinine-based AKI definitions correctly identify the absence (no kidney injury) or presence (clinical acute tubular injury) of structural kidney injury. Conversely, serum creatinine-based AKI definitions may fail to detect structural kidney injury when present (subclinical AKI) or categorize patients as having AKI when no such damage exists (hemodynamic AKI). Subclinical AKI can transpire in a variety of settings. First, there is usually a 48–72-hour lag in serum creatinine elevation following kidney injury. During this time, patients may be exposed to additional nephrotoxic insults leading to further damage [19]. Second, ongoing kidney injury may be masked if uninjured nephrons are able to compensate for their injured counterparts and maintain GFR, a process known as renal reserve [19–21]. Third, serum creatinine concentrations may remain relatively stable despite ongoing kidney injury as a result of decreased creatinine production from low muscle mass or dilution from intravenous fluid administration [19]. Examples of hemodynamic AKI include inhibition of the renin-angiotensin aldosterone system (with ACEI or ARB), prerenal azotemia, cardiorenal syndrome, and hepatorenal syndrome. Drugs that inhibit creatinine tubular secretion also fall into this category [19]. Even when serum creatinine-based AKI definitions appropriately identify clinical acute tubular injury, they do not provide insight on the underlying cause of AKI or which segments of the nephron are affected.

With the advent of biomarker research, urinary biomarkers of kidney injury, function, inflammation, and repair have the potential to discern and characterize AKI beyond that of serum creatinine (Table 1). The presence of albuminuria, best quantified by a UACR, primarily reflects glomerular structure and injury [19, 22]. Nevertheless, a complex interplay of GFR and proximal tubule reabsorption exists such that if proximal tubule function is intact, then a decrease in GFR can reduce urine albumin excretion. Along these lines, once proximal tubule injury has occurred, excretion of urine albumin and other biomarkers of proximal tubule injury (e.g., kidney injury molecule-1 [KIM-1] and interleukin-18 [IL-18]) or function (\( \alpha_1 \)-microglobulin [A1M] and \( \beta_2 \)-microglobulin...
[B2M]) will increase [19, 22–26]. Uromodulin (UMOD) is produced in the Loop of Henle and is thought to protect against kidney ischemia and infection [22, 23, 27–29]. Neutrophil gelatinase-associated lipocalin (NGAL) largely signifies distal tubule injury, though may also be seen in proximal tubular dysfunction [22, 30]. Monocyte chemotactrant protein-1 (MCP-1) and anti-chitinase-3-like protein 1 (YKL-40) are markers of inflammation and repair, respectively [19, 23, 24]. To date, numerous studies have demonstrated that these biomarkers, alone or in combination, are associated with not only AKI but also incident CKD [23, 31], eGFR decline [28, 32, 33], ESRD [34–37], and mortality [28, 31, 34–47].

### Utility of Urinary Biomarkers in Hypertension Clinical Trials

Given that GFR is directly related to blood pressure, intensive lowering has the potential to lower GFR, especially if autoregulatory mechanisms are impaired [48]. Such hemodynamic changes are often accompanied by increases in serum creatinine. In this context, urinary biomarkers may help clarify whether structural kidney injury has occurred. In SPRINT (n = 9,361; 0% with diabetes), the intensive treatment group had a 66% higher risk of AKI, based on hospitalization records, compared to the standard treatment group. Among those without baseline CKD (n = 6,677), the intensive treatment group was 3.5-fold more likely to experience a ≥30% reduction in eGFR to <60 mL/min/1.73 m² compared to the standard treatment group (HR 3.49; 95% CI 2.44–5.10) [2]. Two subsequent studies utilized urinary biomarkers to further explore these potentially concerning findings [23, 49]. Employing a nested case-control study design, Zhang et al. [23] evaluated whether changes in 9 urinary biomarkers of kidney injury and repair (UACR, B2M, A1M, KIM-1, NGAL, IL-18, UMOD, MCP-1, and YKL-40) from baseline to 1 year differed by treatment arm and case-control status (162 incident CKD cases; 162 matched controls). Among participants randomized to intensive treatment, cases had a slightly greater increase in MCP-1 but significantly greater decreases in UACR, IL-18, and UMOD compared to controls. When considering cases only, the intensive treatment group had significantly greater decreases in UACR, B2M, A1M, UMOD, and YKL-40 compared to the standard treatment group [23]. In a longitudinal subgroup analysis of SPRINT participants with prevalent CKD (baseline eGFR <60 mL/min/1.73 m²; n = 978), Malhotra et al. [49] also found that compared to the standard treatment group, the intensive treatment group had a 7% lower eGFR at years 1 and 4 of follow-up. However, none of the 9 urinary biomarkers (UACR, B2M, A1M, KIM-1, NGAL, IL-18, UMOD, MCP-1, and YKL-40) examined were higher in the intensive versus standard treatment groups at either time point. In fact, UACR, B2M, A1M, IL-18 were 32, 29, 24, and 11% lower, respectively, at year 1 (Fig. 2) and UACR was 31% lower at year 4 when comparing the intensive to standard treatment groups (p < 0.05 for each) [49]. These findings provide support that the higher risk of AKI and eGFR decline observed in the intensive treatment arm of SPRINT were

### Table 1. Clinical correlates of urinary biomarkers of kidney injury, function, and repair beyond AKI

<table>
<thead>
<tr>
<th>Category</th>
<th>Biomarker</th>
<th>Clinical correlates beyond AKI</th>
</tr>
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<tbody>
<tr>
<td>Glomerular structure and injury</td>
<td>UACR</td>
<td>Incident CKD [23]; eGFR decline [33]; CVD [51, 52]; mortality [47, 51, 52]</td>
</tr>
<tr>
<td>Proximal tubular function</td>
<td>B2M</td>
<td>ESRD [36, 37, 53]; CVD [36, 37, 45]; mortality [36, 37, 43–45] eGFR decline [33]; CVD [39, 41, 42]; mortality [39, 41, 42]; allograft function [24]</td>
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<tr>
<td></td>
<td>A1M</td>
<td></td>
</tr>
<tr>
<td>Proximal tubular injury</td>
<td>KIM-1</td>
<td>Incident CKD [23]; ESRD [34]; CVD [40, 54]; mortality [34, 40, 54]</td>
</tr>
<tr>
<td></td>
<td>IL-18</td>
<td>Mortality [38, 46, 47]</td>
</tr>
<tr>
<td>Loop of Henle injury</td>
<td>UMOD*</td>
<td>eGFR decline [28]; CVD [42]; mortality [28]</td>
</tr>
<tr>
<td>Distal tubular injury</td>
<td>NGAL</td>
<td>CKD progression [55]; ESRD [35]; CVD [39]; mortality [35, 39, 40]</td>
</tr>
<tr>
<td>Inflammation and repair</td>
<td>MCP-1</td>
<td>Incident CKD [23]; eGFR decline [32]; CVD [41]; mortality [41]; allograft function [24]</td>
</tr>
<tr>
<td></td>
<td>YKL-40</td>
<td>Mortality [38]; allograft function [56]</td>
</tr>
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* Associated with lower risk.

AKI, acute kidney injury; CKD, chronic kidney disease; CVD, cardiovascular disease; ESRD, end-stage renal disease.
likely due to changes in renal plasma flow rather than structural kidney injury [23, 49].

The Action to Control Cardiovascular Risk in Diabetes study was another trial designed to clarify blood pressure goals for cardiovascular risk reduction but in patients with type 2 diabetes. As in SPRINT, 4,733 participants were randomized to intensive (goal systolic blood pressure <120 mm Hg) or standard (goal systolic blood pressure <140 mm Hg) treatment. Although there was no significant difference in risk of a composite cardiovascular outcome (HR 0.88; 95% CI 0.73–1.06) or all-cause mortality (HR 1.07; 95% CI 0.85–1.35), risk of stroke was lower in the intensive treatment group (HR 0.59; 95% CI 0.39–0.89). In terms of renal outcomes, the intensive treatment group had a lower frequency of macroalbuminuria but lower mean eGFR and more instances of eGFR <30 mL/min/1.73 m² compared to the standard treatment group [50]. Nadkarni et al. [32] expanded upon these findings by evaluating changes in eGFR and 5 urinary biomarkers (UACR, KIM-1, IL-18, MCP-1, and YKL-40) from baseline to year 2 of follow-up in a subset of Action to Control Cardiovascular Risk in Diabetes participants (n = 529). Despite a greater decline in eGFR in the intensive versus standard treatment group (17 and 9%, respectively), participants randomized to intensive treatment had greater decreases in UACR and IL-18. For the remaining urinary biomarkers, no significant differences were observed between the 2 groups (Fig. 2). Among participants developing incident CKD (n = 76 in the intensive treatment arm and n = 27 in the standard treatment arm), defined as a sustained decline in eGFR by 30% and to a level <60 mL/min/1.73 m², none of the 5 urinary biomarkers increased in the intensive treatment arm whereas IL-18 increased in the standard treatment arm [32]. Thus, in patients with diabetes at increased risk for cardiovascular disease, intensive blood pressure control does not appear to lead to structural kidney injury.

## Proposed Approach to Managing Presumed AKI during Hypertension Therapy

In SPRINT, the cardiovascular benefits of intensive blood pressure control were observed in patients with and without baseline CKD [2]. CKD itself is also an independent risk factor for cardiovascular disease [51]. Intensive blood pressure control should therefore be considered in all patients with hypertension and increased cardiovascular disease risk, including those with underlying CKD. In doing so, clinicians may encounter in-
creases in serum creatinine during attempts of intensifying hypertension therapy. In Figure 3, we propose an algorithm with which to approach such instances of “presumed AKI.” Briefly, we recommend checking a basic metabolic panel (BMP) and UACR prior to intensification of therapy. Approximately 1–2 weeks after reaching the goal blood pressure (e.g., systolic blood pressure < 120 mm Hg), a second BMP should be checked. If the serum creatinine has increased by < 20–30% of the baseline value, another BMP should be repeated in 2–3 weeks and if stable (i.e., < 20–30% above baseline) the current regimen can be continued. On the other hand, if the serum creatinine has increased by ≥20–30% of the baseline value, a UACR should be checked. If the UACR is stable or decreasing, then the rise in serum creatinine was likely a reflection of hemodynamic change and the current regimen can likely be continued. If the UACR is increasing, efforts should be made to identify concurrent nephrotoxins, recent initiation of drugs that decrease creatinine tubular secretion, or states of hypoperfusion. Once addressed, labs should be rechecked in 1–2 weeks. If the serum creatinine and UACR are stable and improving, then the current regimen can likely be continued with routine follow-up. If the serum creatinine or UACR remain elevated, the blood pressure goal should be raised (e.g., systolic blood pressure < 130–140 mm Hg) after close discussion with the patient. Lastly, if patients develop electrolyte abnormalities, dizziness, syncope, hypotension, bradycardia, recurrent falls, or other adverse effects of intensive blood pressure control, clinical judgment should be applied.

**Conclusion**

In summary, intensive blood pressure control is associated with cardiovascular benefits. During intensification of hypertension therapy, changes in glomerular he-

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**Fig. 3.** Proposed approach to managing serum creatinine elevations during hypertension management. * Consider checking cystatin C. Where available, urinary biomarkers of tubular injury (e.g., KIM-1, NGAL) can be checked in addition to urine albumin.

BP, blood pressure; BMP, basic metabolic panel; UACR, urine albumin-to-creatinine ratio; NSAIDS, nonsteroidal anti-inflammatory drugs.
modynamics may lead to increases in serum creatinine that do not necessarily reflect kidney tubular injury. Such instances of “presumed AKI” should not prompt immediate discontinuation of therapy, but rather efforts should be made to identify factors contributing to creatinine elevation. Clinicians should therefore think before acting so as not to deprive patients of potentially beneficial therapy. As the field of biomarker research continues to evolve, urinary biomarkers of tubular injury and repair may one day have a role in clinical practice to help clarify the presence or absence of structural kidney injury when serum creatinine falls short. In the meantime, UACR (in combination with sound clinical judgment) may prove satisfactory.

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References


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Presumed AKI and Hypertensive Therapy


