KDIGO Controversies Conference on Acute Kidney Injury
- Public Review Comments -

As of January 17, 2019
Industry comments are highlighted in blue

Cécile Couchoud (REIN Registry, France)

Please consider the Following publication: Nephrol Dial Transplant. 2018 Dec 1;33(12):2218-2227. doi: 10.1093/ndt/gfy137. Outcomes of acute kidney injury depend on initial clinical features: a national French cohort study. Riffaut N, Moranne O, Hertig A, Hannedouche T, Couchoud C.

Angel de Francisco (University of Cantabria, Spain)

In the Breakout Group 4: Nephrotoxins (Contrast) we need to discuss cancer patient as a risk factor and ESUR 10 guidelines which are based in weak recommendations score. Cancer Patients as a Risk Factor: Why does the cancer patient have a high risk factor for Acute Renal Lesion after contrast and should not be excluded?

1. The cancer patient has a higher risk of AKI
• Christiansen, C.F, Johansen MB, Langeberg WJ y cols., Incidence of acute kidney injury in cancer patients: a Danish population-based cohort study. Eur J Intern Med, 2011. 22(4): p. 399-406.
• Salahudeen AK, Doshi SM, Pawar T y cols Incidence rate, clinical correlates, and outcomes of AKI in patients admitted to a comprehensive cancer center. Clin J Am Soc Nephrol, 2013. 8(3): p. 347-54.
• Chertow, G.M., Burdick E, Honour M, y cols Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. J Am Soc Nephrol, 2005. 16(11): p. 3365-70.

2. Frequent CKD in the oncological patient, especially in those in which cancer is more frequent with ages> 65 years.

• Society, A.C., Cancer Treatment & Survivorship Facts & Figures 2016-2017. Atlanta: American Cancer Society; 2016.
• Otero A, de Francisco ALM, Gayoso P, García F; EPIRCE Study Group. Prevalence of chronic renal disease in Spain: results of the EPIRCE study. Nefrologia. 2010;30(1):78-86.
• Janus N, Launay-Vacher V, Byloos E, y cols .Cancer and renal insufficiency results of the BIRMA study. Br J Cancer 103: 1815–1821, 2010.
• Canter D, Kutikov A, Sirohi M,y cols Prevalence of baseline chronic kidney disease in patients presenting with solid renal tumors Urology. 2011 ;77(4):781-5.
• Nakamura Y, Tsuchiya K, Nitta K, Ando M. Prevalence of anemia and chronic kidney disease in cancer patients: clinical significance for 1-year mortality Nihon Jinzo Gakkai Shi. 2011;53(1):38-45.(abstract)
• De Francisco ALM, Fernandez E, Cruz JJ, y cols Under-recognized renal insufficiency in hospitalized patients: implications for care. Eur J Intern Med. 2010 ;21(4):327-32.

3. Frequent associations with Nephrotoxic treatments 50% of anti-cancer drugs are predominantly excreted in the urine and 80% of patients receive drugs potentially nephrotoxic and / or for which the dose must be adjusted The presence of pre-existing renal insufficiency may limit the use of otherwise active regimens that may be curative.
• Janus N, Launay-Vacher V, Byloos E, y cols Cancer and renal insufficiency results of the BIRMA study. Br J Cancer 103: 1815–1821, 2010 In patients with exposure to contrast media one week before the administration of cisplatin, the risk of AKI-CP was significantly higher than in patients without such exposure
• Sendur MA, Aksoy S, Yaman S y cols Administration of contrast media just before cisplatin-based chemotherapy increases cisplatin-induced nephrotoxicity. J BUON, 2013. 18(1): p. 274-80.

4. Frequency of studies with contrast media in cancer patients. The recommendations for the staging and monitoring of cancer treatments require the performance of studies with iodinated contrast very frequently. In colorectal cancer, CT with a thoraco-abdominal contrast is recommended every 3-6 months for two years and then every 6-12 months for 5 years In lung cancer for diagnosis and staging, chest CT with contrast (and PET with CT or brain MRI) is recommended, which should be performed annually
• Labianca R et al Early colon cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up Ann Oncol. 2013 Oct;24 Suppl 6:vi64-72.
• NCCN Colon cancer guidelines V2 2016.
www.nccn.org/professionals/physician_gls/default.aspx
• Kauczor HU, Bonomo L, Gaga M y cols ,ESR/ERS white paper on lung cancer screening. Eur Radiol 2015 25(9):2519-31.
• Vansteenkiste J, De Ruysscher D, Eberhardt WE, y cols Guidelines Working Group. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013 Oct;24 Suppl 6:vi89-98.
• ESUR 10 We should discuss many recommendations without evidence

It is postulated that many IA administrations are similar to the IV for the kidney because the contrast arrives diluted) In our opinion:
- No evidence is provided to justify the differentiation of primary or secondary renal exposure (theoretical assumption)
- Does not consider factors related to the patient, their comorbidity and the type of procedure.
- It contradicts and omits the high evidence of the risk of AKI in contrast exposure by the intra-arterial coronary route, which reflects the guidelines in cardiology
- Does not consider that this risk can also be transferred to patients undergoing CT with contrast, as has been demonstrated in patients with risk factors other than renal
- Lowering of renal risk omitting non-renal risk factors:
- GFR <45ml / min / 1.73m2 in intra-arterial administration with direct renal exposure or in patients in ICU.
- GFR <30ml / min / 1.73m2 in intra-arterial or iv administration with secondary renal exposure

José António Lopes (Centro Hospitalar Lisboa, Portugal)

In fact, the AKI definition, the mechanistic pathways, the management and knowledge of impact on prognosis have all evolved in the current decade and justify this conference.

Greg Knoll (The Ottawa Hospital, Canada)

Is post-transplant delayed graft function in scope? Many of the issues being discussed in the non-transplant setting (e.g. nomenclature, diagnosis, fluid management etc) are also critical, unresolved issues in the transplant setting. Thanks.

George Bakris (University of Chicago, USA)

This looks reasonable. However, this guideline has caused a great deal of confusion with the general medical literature and definitions have been inter mixed between 50% increase in creatinine and 0.3 which restricted to hospitalized heart failure patients-BIG mistake to intermingle these even the original author of the 2000 paper Krumholtz has said this is probably not correct. Moreover, people are using the 0.3 mg change in creatinine to signal AKI in the outpatient setting. I don't care how clear you are, as a guideline writer I think you need to be honest with the data and restrict this to heart failure. Moreover, I have attached some recent papers (included at the end of this document) that clearly are NOT AKI but hemodynamic changes that are being called AKI-This confusion needs to end and only you can help.
Best Wishes, George

Peter McCullough (Baylor University Medical Center, USA)

1) Insert a section on worsened renal function in the setting of acute heart failure with a vetting of whether this is AKI or azotemia related to delayed plasma refill

2) Insert mention of Iodine-125–Tagged Albumin in acute heart failure and the studies conducted to date as an aid in management

3) Insert a section on AKI and the progression of CKD

4) Insert mention of hyperkalemia as a complication of AKI and provide information on its epidemiology, prevention, and management

Andrew Crannage (St. Louis College of Pharmacy, USA)

The scope appears appropriate, would ask that emphasis be placed on prevention as still an area of need and has been confirmed in recent studies.

Rinaldo Bellomo (Austin Hospital, Australia)

Breakout group 1: topic 3: discuss role of follow-up to determine the best time to measure recovery. Should it be at 3 months? Later?

Breakout group 2: discuss the combination of clinical models with biomarkers

Breakout group 3: discuss the effect of fluid bolus on renal function and what technology can be used to monitor fluid removal

Breakout group 4: discuss ACE inhibitors and the timing of their re-start after AKI

Breakout group 5: discuss the criteria for cessation of RRT

Mark Murphy (Irish Kidney Association (IKA), Ireland)

The IKA is a kidney Patient Association, and is made up of patients with a chronic condition. The AKI patients don't end up in our type of organisation unless their acute condition turns into a chronic condition. So we don't have much to offer on this topic.
Regards,
Mark Murphy

Thomas Golper (Vanderbilt University Medical Center, USA)

In the US it matters greatly whether terms like AKI versus ATN are used. There should be included criteria for the use of the terms. For example, ATN is very likely in many critically ill pts who are properly resuscitated and renal dysfunction worsens after several days. Yet AKI, while true, affects coding and payment much differently for the hospital.

Cibele Rodrigues (Pontifícia Universidade Católica de São Paulo, Brazil)

1- Agree with the scope and I want to make a suggestion. Acute kidney injury is common in kidney transplant recipients and there's no breakout group about this topic. It's a challenging work. Certain features and risk factors are specific to kidney allografts like rejection, drug toxicity, recurrence of kidney disease, infections, urinary tract obstruction, vascular thrombosis, and so on.

2- We all know that most physicians alter therapy depending on changes in serum creatinine, and this often represents delayed intervention, but that's what is possible in our country (and many others). Various AKI biomarkers have been discovered and validated but they are not available in the clinical setting.

Kianoush Kashani (Mayo Clinic, USA)

Group 2: - Clinical models:
• Computational vs. bedside calculated
• Discrete vs continuous - Diagnosis and monitoring: It may be as of interest to at least partly focus on monitoring measures that are kidney focused not CV hemodynamic variables: e.g., intraabdominal pressures, contrast-enhanced US, non-invasive kidney elastography, kidney

perfusion pressure, continuous GFR monitoring, urinary sodium, ammonium, oxygen monitoring, microcirculation, etc. - "Which patients should be followed up?" could be expanded to: "who, where, how, what should be monitored after AKI?"

Group 4: one potentially important topic would be the relationship between chemotherapies and AKI (particularly new biologicals). Would it be possible to dedicate a question to Onco-AKI?

Group 5: Risk prediction for the need to initiate RRT may be a good addition

Andrew Davenport (University College London, UK)

Dear John, there are problems with definition

1. descriptive based on changes serum creatinine/urine - we need to consider underlying etiology
2. same % change in serum creatinine does not result in equivalent injury or chance of recovery or later risk of end stage kidney failure
3. need to review treatment options PD vs IHD/F vs CRRT - as we have have now learned how to deliver more efficient PD
4. need to consider effects of RRT and drug clearances - particularly antibiotics

Clarissa Havel (RPh-on-the-go, USA)

Timely review and good questions of aki, mirrors the ACCP board re-certification of BCPS for pharmacists. The KDIGO notes on the Acute Kidney Injury are consistent with the pharmacotherapy for Board Re-certification.
Sincerely,
Clarissa Havel, PharmD, BCPS

Fan Fan Hou (Nanfang Hospital, China)

Suggestion for some additional topics:

Breakout Group 1: Diagnostic Criteria

1. What is the appropriate diagnostic criteria for pediatric AKI? Is it possible to incorporate reference change value of serum creatinine into the diagnosis of pediatric AKI?
2. How to diagnose acute-on-chronic kidney injury?

Breakout Group 2: Prognostication
1. What is the impact of AKI on long-term mortality?
2. How to identify patients who are at high risk of AKI to CKD progression? Any available biomarkers?

Breakout Group 4: Nephrotoxins
Any newly found nephrotoxic drugs (PPIs/H2RAs)?

Breakout Group 5: Renal Replacement Therapy
What criteria should be used to stop RRT?

Mehmet Sukru Sever (Istanbul School of Medicine, Turkey)

Many thanks in advance for this excellent work. Just 3 suggestions; can you also comment on:
1. Indications /non-indications for biopsy
2. Fluid policy during resolution of AKI
3. AKI in transplant setting.

Ken Say (U.S. Public Health Service, Indian Health Service, USA)

Regarding nephrotoxins: Is there enough evidence to support stronger warnings/labeling for OTC and RX NSAIDs and AKI risk? Risk is not well defined or articulated in the recommended patient information from the FDA. Is the risk significant enough to merit more focus on patient education/clinical intervention especially during times of acute illness (dehydration, volume depletion) and/or in combination with other medications such as ACEI/ARBs, diuretics? See link to NHS UK campaign for sick day guidance. Agree with risk statements against stopping diuretics and anti-hypertensives, but is evidence sufficient for stronger recommendations to stop/limit/avoid NSAIDs during acute illness? https://www.thinkkidneys.nhs.uk/aki/wp-content/uploads/sites/2/2018/01/Think-Kidneys-Sick-Day-Guidance-2018.pdf

Rolando Claure-Del Granado (Universidad Mayor de San Simon, Bolivia)

Is sufficient evidence now available to warrant a change in the definitions/classification/staging system for AKI? I think yes it is, I would recommend that subclinical AKI should be addeed to the new definitions and urinary microscopy should be considered for this nomenclature. How should existing (or new) definitions of AKI be implemented at the bedside, in research? Using back calculation of MDRD should be included for determining a baseline sCr in every patient What are the roles for risk-stratification of patients for AKI? A consideration should be made on adaptations to the RAI for adult population (I have some research on this area) How should patients be followed after AKI? Recommendations should be made about a follow up plan, I think after 7 days, at day 30 and day 90. In light of current evidence what can be recommended for prevention and management of contrast-associated AKI? There is still a population with CKD at higher stages like 4 that would beneffit from profilaxis strategies, recommendation should be made about individualazed risk assessment and type of profilaxis that should be used. A risk score should be propossed not only for patients Post-PCI (the only one available) Is there sufficient evidence to classify potential nephrotoxins in a clinical useful way? You must include herbs as potential toxins!!!

Hassan Shora (Port-Said University, Egypt)

The conference scope is comprehensive. We need to add important area of coverage such as dilemma in management of acute cardiorenal syndrome, implications of systems and precision nephrology for AKI management including complex deep neural networks analysis and clinical descision support system for AKI. The controversial use of myoglobin as a biomarker of AKI in rhabdomyolysis.

Ikechi Okpechi (University of Cape Town, South Africa)

Dear KDIGO,
The scope and contents of this controversies conference is broad and detailed. I have no further additions to make.
Kind regards,
Ike

Hassan Aleid (King Faisal Specialist Hospital, Saudi Arabia)

1. Wish to see a chapter on AKI-transplant
2. Potential promising therapy

Eisei Noiri (University of Tokyo, Japan)

Knowledge Gaps: Is this the timing to change creatinine and urine output definition to further (depending on clinical scenario, etc)? The difference of therapeutic considerations to AKI stage (ex. Stage 1 vs 2 and 3) have to be stated as a scope of care bundle. Renal angina index (RAI) was recently proved the efficacy to detect persistent AKI in pediatric ICU cohort using concise combination of creatinine-increase and clinical condition. However, use of RAI in adult ICU is not well established. HSCT in above mentioned RAI often cause AKI in adult but such clinical data is not well accumulated, though knowing the occurrence of AKI after HSCT on survival. This will be partly because of the missing link between hematologist and nephrologist or intensivist. Potential monitoring device for longer creatinine clearance (functional) or biomarker (injury) monitoring should be stated in the manuscript as future perspective. The adsorption modality to sepsis including septic AKI such as PMX-DHP and Cytosorb should be mentioned based on the current clinical evidence and perspective. Biomarkers approved for clinical use (NephroCheck, NGAL, L-FABP, Cystatin C, NAG, etc) should be discussed for their characteristics in terms of strong and weak points for proper use and interpretation. The definition of radiocontrast media induced AKI is still the same as before in cardiology area. AKI evaluation approach to newly up-coming treatment such as TAVI and TAVR in cardiology, hematological new drugs (…mibs, immune checkpoint inhibitors), CAR-T should be discussed and suchlike.

Paul Stevens (East Kent Hospitals University NHS Foundation Trust, UK)

Breakout Group 1: Question 1. Metabolomic profiling is just starting to take off in assessment of estimated GFR and may have advantages in areas where eGFR based on creatinine is unreliable, worth considering for AKI too

Breakout Group 3: Question 3. Might ask one of these questions a slightly different way ie what are the predictors of CKD in patients recovered from AKI?

Breakout Group 4: Question 2. criteria for classification could also be vascular, glomerular, tubular - for example certain nephrotoxins are vasoactive, some may cause thrombotic microangiopathy, others are tubulotoxic or lead to interstitial nephritis etc

Finally, don't forget about AKI prevention/early identification in primary care

Charles Tomson (Retired nephrologist, UK)

I strongly encourage KDIGO to differentiate between true 'nephrotoxins' and drugs that may affect glomerular haemodynamics and/or systemic BP and thus have some effect on GFR, such as ACEI and ARB; these drugs may actually protect against tubular injury. The question of whether or not to continue or discontinue these drugs during sepsis, hypotension, and other precipitants of AKI is open, and should be a topic for review. Calling them 'nephrotoxic' pre-supposes that they should be stopped during AKI. The previous guideline failed to give clear guidance on this. Even if the evidence base is limited on when/whether to continue these drugs (for instance, depending on the indication - HFrEF vs proteinuric kidney disease vs 'standard' early onset hypertension) clear guidance should be given on whether/when they should be discontinued, and even more importantly, when they should be restarted.

Eugen Mota (University of Medicine and Pharmacy Craiova, Romania)

AKI is an important clinical syndrome associated with poor clinical outcomes for hospitalised patients. The current diagnostic approach of AKI is based on an acute decrease of GFR, as reflected by an acute rise in sCr levels and/or a decline in urine output over a given time interval. Recently several biomarkers have been proposed for the diagnosis of AKI and these are in various stages of development and validation. Nevertheless, it is not clear, if a single or multiple biomarker approach is necessary to diagnose the complicated and multifactorial aspects of AKI. However, in addition to the analytical difficulties associated with each specific biomarker, there is also an issue concerning the appropriate reference point, and more specifically about using sCr as the standard, for the clinical evaluation of these biomarkers. It is known that sCr is insensitive to acute changes of renal function and levels can vary widely with age, gender, muscle mass, diet, medications and hydration status. Moreover it is not a direct marker of tubular damage, but rather a marker of GFR, and substantial increases in sCr can be observed in renal hypo-perfusion even when the kidneys are structurally intact, resulting in pre-renal azotaemia. For these reasons sCr is considered an 'imperfect "gold standard"'for the diagnosis of AKI. Another issue with sCr is that in most clinical situations its true baseline value

is not known, which makes the evaluation of patients very difficult. Moreover, given the phenotypic variability of AKI (different clinical phenotypes with distinct underlying pathophysiologies), it is not clear. Essentially AKI is a term used to describe the clinical syndrome that occurs when renal function is acutely decreased to a point that the body accumulates waste products and becomes unable to maintain electrolyte, acid-base and water balance.The pathophysiology of AKI is multifactorial and complex. The most common cause of AKI is ischaemia, which can occur for a number of reasons. AKI is also very common in the setting of sepsis. In sepsis the circulation is hyperdynamic and blood flow is altered, albeit not necessarily in the ischaemic range, and GFR drops rapidly. The pathophysiology of septic-AKI is very complex and involves inflammation, oxidative stress microvascular dysfunction and amplification of injury via secretion of cytokines by tubular cells. Kidney and cardiac disease are not only common but often coexist. Both acute and chronic cardiac disease can contribute directly to acute and/or chronic worsening of renal function and vice versa. The term cardiorenal syndrome (CRS) is often used to describe this condition and represents an important model for the exploration of the pathophysiology of cardiac and renal dysfunction. Recently a consensus definition/classification scheme has been proposed for the CRS. According to this definition, five subtypes of the CRS exist. Each subtype's etymology reflects the primary and secondary pathology, cardiac and renal as well as dysfunction secondary to systemic disease. It is important to distinguish hepatic dysfunction as a result of AKI as distinct from the well-recognised hepatorenal syndrome (HRS). Liver injury often correlates with severity of kidney injury. Ischaemic AKI induces oxidative stress and promotes inflammation apoptosis and tissue damage to hepatocytes. On the other hand the concept of HRS is very well recognised; it is a reversible functional renal impairment that occurs in patients with advanced liver cirrhosis or in patients with fulminant hepatic failure. It is characterised by a marked decrease in GFR and renal blood flow in the absence of other causes of renal injury. HRS is not uncommon and occurs in approximately 40% of patients with advanced cirrhosis. Maintenance of volume homeostasis and correction of biochemical abnormalities remain the primary goals of AKI treatment. Dietary changes are an important facet of AKI treatment. Restriction of salt and fluid becomes crucial in the management of oliguric renal failure, in which the kidneys do not adequately excrete either toxins or fluids. Pharmacologic treatment of AKI has been attempted on an empiric basis, with varying success rates. Considerable advances have been made in refining the definition of this syndrome and in the elucidation of the underlying pathophysiologic mechanisms of the different clinical phenotypes. It is obvious that all clinical phenotypes of AKI cannot fit into a single pathophysiologic pathway. AKI facilitates organ cross-talk and distant organ injury. These innovations will aid in the design of epidemiologic studies and randomised trials of preventive and therapeutic interventions.

Josee Bouchard (University of Montreal, Canada)

Dear Drs Kellum and Ostermann,
Please find comments and suggestions below.

Breakout Group 1: Nomenclature & Diagnostic Criteria
-would suggest including discussion on issues with the diagnosis of AKI with CKD stage 4/5
-for the best way to define renal recovery, what would be the optimal period of time, and whether it would be during or after hospitalization if not community-acquired AKI

Breakout Group 2: Risk Stratification
-for "How should patients be followed after AKI?" comments on the role of nuclear medicine exams to measure GFR in some populations

Breakout Group 4: Nephrotoxins
1. "what can be recommended for prevention and management of contrast-associated AKI?" need to/how to optimize fluid administration: i.e. amount of fluid to be administered/benefit of targeting a specific LVEDP value?

Breakout Group 5: Renal Replacement Therapy
-issues with therapeutic trials with RRT and other therapeutic agents for prevention and treatment of AKI

Wish you both a successful and Happy New Year,
Sincerely,
Josee Bouchard

Norbert Lameire (University Hospital Gent, Belgium)

General remarks:
The guideline should not forget that it should address not only AKI in the critically ill (although this is of course very important) but also the probably more frequent “community AKI”. In addition, the KDIGO guidelines are global and not only trying to provide guidance to the high tech and sophisticated clinical hospital possibilities in high income countries. The clear distinction definition between AKD and AKI should be discussed. As far as can be derived from the ADQI definitions (see Chawla et al Nature Reviews Nephrology) is AKD an “ a posteriori” diagnosis ; i.e. an “extended AKI” ; what is the impact of AKID on epidemiology and coding of

AKI? How to apply the present and future KDIGO AKI definition to severe acute glomerular, interstitial and vascular kidney diseases? "Transient AKI" is formulated as opposite of "recurrent" AKI. We believe that the dichotomy between "transient" and "intrinsic" AKI is more important. In the section on biomarkers the necessity of adequate and objective studies on the "added value" of biomarkers vis à vis the traditional diagnostic approach to AKI should be discussed. What is the significance of the diagnosis of "subclinical" AKI since it is a concept that is based on "inadequate" measurement and interpretation of glomerular filtration.

Additional remarks:
- Breakout group 1: 1h: definition of community vs hospital acquired AKI; hospital acquired AKI= ICU + non ICU? should be regarded as separate entities; community acquired: not hospitalized or AKI before 48h after hospitalization?, AKI on admission? 2b: urinary output in ml/kg/h but what weight should be used? ideal weight (in fluid overloaded ICU patients), actual weight? 3: remaining question: at what time point should AKI recovery be assessed?

- Breakout group 2: who should do the follow-up of post AKI patient? Post AKI clinic? General nephrology department?

- Breakout group 3: how to define and clinical diagnosis of fluid overload?

- Breakout group 4: Role for measuring peak and trough serum levels of certain potentially nephrotoxic drugs? Is there a role of biomarkers to early detection of nephrotoxicity?

- Breakout group 5: Dosing of antibiotics across different RRT modalities It can be suggested that the KDIGO AKI guideline should include separate sections on Cardio renal, hepato- renal, oncology AKI and AKI in pregnancy.

These suggestions are formulated after discussion of the topic in the renal division of the Ghent University Hospital between Norbert Lameire, Raymond Vanholder, Wim Van Biesen and Jill Vanmassenhove.

Jose Perez (Baylor College of Medicine, USA)

Nomenclature & Diagnostic Criteria
-With the increasing evidence of AKI in the ICU settings, prompt diagnosis and prompt interventions to minimize risk of further kidney injury is of the utmost importance. Having appropriate nomenclature for AKI/AKD/CKD/NKD is appropriate for research and for bedside

care. Often times in our clinical practice at our academic institution, nephrology is consulted late in the care of these critically ill patients where we are often limited in our options for the care of these patients. Serum Creatinine is and imperfect marker for detecting severe AKI. Prompt diagnosis is of the utmost importance in the care of these patients. Education amongst physicians, not only nephrologist, but Critical Care, Medicine, Surgery etc will promptly identify these patients and allow for appropriate intervention.

Risk Stratification

-Patients and their families want to know what type of prognosis they have regarding their kidney health. Many patients will need long term follow up, however when a kidney injury occurs, having solid data would be beneficial in helping guide the care of these patients. Those patients in poverty-stricken areas may also be at high risk of ongoing kidney injury given their socioeconomic risk factors. Having an understanding of what environmental conditions play in the recovery of kidney injury will also be beneficial.

Fluid Management

-Fluid management plays a crucial role in the care of patients with kidney injury. Having an understanding of appropriate ways of monitoring fluid levels within the patient is an area that is often debated amongst the care providers from different specialties (cardiology vs critical care vs nephrology). Should alkaline fluid also be a question regarding the composition of IVF preparation?

Nephrotoxins

-Contrast associated AKI remains debatable, with recent large meta-analysis demonstrating no increased risk of AKI in those pts with and without contrast imagining. However, many clinicians still fear the risk associated with contrast in those patients with underlying CKD. Having a risk classification for nephrotoxins is beneficial (similar to those risk classifications for medications given during pregnancy). However, there are too many variables in the toxicity of potential nephrotoxins such as age and body size of patient, underlying risk factors, underlying kidney disease.

Renal Replacement Therapy

-RRT initiation remains a debatable topic amongst nephrologists and colleagues in other subspecialties. The timing and modality of RRT also plays a large role in the care of those patients with AKI. In our clinical practice, we have multiple hospitals including a public county-based hospital and multiple private hospital. Within these institutions, there are significant differences in resources including access to CRRT vs other dialysis modalities. Within these institutions, our practice differs in that within the private hospital with easy access to

modalities and nursing, physicians are more likely to initiate CRRT when compared to patients within the county system where nursing and dialysis machines may be more limited. Late start dialysis is the general practice within the county where as in our private hospitals, we generally initiate earlier.

YusukeTsukamoto (Itabashi Chuo Medical Center, Japan)

1. In most of clinical fields (at least in Japan), etiology of AKI is still classified into pre-renal, renal parenchymal and post-renal. And FENa and FEUN are often misused. I would suggest to validate this classification measure. Is this still useful?

2. In polyuric phase of AKI, it is not easy to decide the timing of cessation of fluid replacement. What is the good indicator to diagnose recovery of concentration disorder during polyuria?

Andrew Levey (Tufts Medical Center, USA)

I'm pleased to see that there will be continuing discussion regarding nomenclature regarding the overlap of AKI and AKD and their continuum with CKD. I'd also like the group to consider re-naming RRT to be KRT, to be consistent with other English-language preferred kidney disease nomenclature.

Marty Lefkowitz (Novartis Pharmaceuticals Corporation)

The program would benefit by the inclusion of a section on clinical trials (inclusion criteria, endpoints, consideration for trials in different types of AKI (eg, CIN, cardiac surgery, sepsis) for the prevention / treatment of AKI.

Maurizio Gallieni (University of Milano, Italy)

I have a strong interest in the topics of breakout group 4 on Nephrotoxins. During the recent KDIGO Controversies Conference on Onconephrology, the nephrotoxic effects of cancer treatment, as well as the issue of repeated contrast media use during cancer follow-up, have been debated and there is a need for more research and guidance on AKI in this fragile patient population. The presence in breakout group 4 of an expert in onconephrology could be of relevance. Again in breakout group 4, question 1 on contrast media should be expanded with a

re-evaluation of the role of iso-osmolar versus low-osmolar CM, which was addressed in the 2012 AKI KDIGO guidelines. The single and cumulative dose of CM in determining CM associated AKI should be addressed. A question on different approaches in intra-arterial versus intravenous administration of CM could be another important issue with available evidence (they have different effects). The main unanswered questions are, in my view, those related to the use of CM in patients with advanced CKD (Stage 4, 5, and 5D), because the lower observed toxicity with IV administration of CM could allow a more open use of radiological exams which are now denied (maybe inappropriately) while, on the other hand, it could turn out that CM associated kidney damage is indeed a relevant issue in advanced CKD patient and we should still apply measures which proved ineffective in patients with higher GFR. The issue of preservation of residual renal function is also quite relevant, in relation to the need for CM radiological exams at the beginning of dialysis and for the evaluation of idoneity to a kidney transplant. A simple question that could be added is the following: which is the best approach to the use of contrast media in patients with advanced CKD. Finally, the issue of renal replacement therapy in the critically ill cancer patient is an issue worth discussing in breakout group 5.

Lynne Sykes (Salford Royal Foundation Trust, UK)

Dear Colleagues,
Please let me bring to your attention the following work on acute kidney injury that we have completed and published from Salford Royal NHS Foundation Trust. The first "A narrative review of the impact of interventions in acute kidney injury" outlines the recent evidence on interventions and their impact on AKI mortality and critical care admission. The second "Reducing acute kidney injury incidence and progression in a large teaching hospital" details our own highly effective quality improvement project in Salford Royal NHS Foundation Trust, the generalisability and the challenges faced.

A narrative review of the impact of interventions in acute kidney injury (www.ncbi.nlm.nih.gov/pmc/articles/PMC6061256/) Sykes L, Nipah R, Kalra P, Green D. A narrative review of the impact of interventions in acute kidney injury. J Nephrol. 2017;31(4):523-535.

"The NCEPOD of 2009 has been a great motivator by creating improved public awareness of AKI, increasing its profile in the NHS, and by provoking the introduction of financial incentives. This narrative review supports the growing body of evidence that grouped interventions can create an impact on the progression and severity of, and mortality from, AKI. Overall success

appears to be due to a combination approach of an e-alert and an AKI bundle, supported by overarching education and an AKI nurse to create a failsafe within the system.
• The e-alert must be timely and appropriately intrusive to trigger actions such as the completion of an AKI bundle.
• All healthcare workers, from healthcare assistants, nurses and doctors both undergraduate and postgraduate, should undergo AKI education with a focus on risk recognition, the unwell patient and task prioritisation.
• There must be a redundancy built into the system, be it AKI nurses or dedicated pharmacist review, to mitigate for human factors and ensure that alerts translate into action."

Reducing acute kidney injury incidence and progression in a large teaching hospital (https://bmjopenquality.bmj.com/content/7/4/e000308) Sykes L, Sinha S, Hegarty J, et al Reducing acute kidney injury incidence and progression in a large teaching hospital BMJ Open Qual 2018;7:e000308. doi: 10.1136/bmjoq-2017-000308

"A number of acute hospitals have now demonstrated impactful successes in AKI reduction using traditional service improvement and QI methodologies. Almost all appear to have centred on a dedicated AKI nurse model plus e-alerting with supporting changes. This project adds value by highlighting another approach that does not require a new post with resultant rolling costs and risks. We believe that as our approach concentrated on embedding improved recognition and actions across the MDT, it has had the benefit of having increased our efficacy in acute care in our front-line teams."

We have two further manuscripts currently under consideration of peer review which present difference aspects of AKI. The first looks at the impact of AKI in specific medical and surgical diagnoses, and the risks for critical care admission and mortality. The second looks at effect of AKI in patients with chronic kidney disease and the effect on mortality, renal replacement therapy and further episodes of AKI.

I would be grateful if you were able to consider the former and would also be very pleased to attend and discuss the work and its implications. I am currently working as a clinical research fellow in AKI and quality improvement, and as a general medical registrar part of my renal and general medical training. I have co-chaired sessions on AKI at the UK Kidney Week for the last 2 years and presented and co-chaired at the Royal Society of Medicine AKI Frontiers day last year.

Many thanks,
Lynne Sykes

Barbara Philips (Brighton and Sussex Medical School, UK)

The scope of work is comprehensive and should lead to good recommendations. I have a comment for group 4. Could we consider the impact of AKI on drug dosing decisions particularly for drugs which are concentration dependent for effect? Initially dosing for such drugs may need to be the same or even increased from normal at the start of therapy to achieve sufficient concentration but then require modification according to renal function. This can be complex but we need to move away from the automatic reduction in drug dose often precipitated by the development of AKI. This is to take in to account changes in Vd, protein binding as well as factors such as renal replacement therapy and augmented renal clearance in early AKI recovery. It is unlikely we could deal with this subject comprehensively but I think the concepts and issues should be acknowledged.

Zhiyong Peng (Zhongnan Hospital of Wuhan University, China)

1. Fluid management
What is the relationship between fluid overload and AKI? Is it association or causation? Patients with fluid overload are always complicated with shock or other critical illness, and AKI may be induced by shock or other critical illness. Fluid overload may be an associative phenomenon.

2. AKI diagnosis
The current criterion for AKI, serum creatinine, mainly reflects the GFR. However, the pathology of AKI occurs in tubules. The secretion of small molecules by the proximal tunnels represents a vital function for clearing endogenous solute from the circulation. Despite its central importance, this tubular secretory clearance is rarely measured. Can we consider it in our future AKI diagnosis?

Mauricio Berdugo (bioMerieux)

We would like to thank the KDIGO committee for the opportunity to submit our comments for the scope of review for the upcoming KDIGO Guideline Controversies Conference. It is our hope that our comments will not only serve for review purposes, but will also serve as a reference for collaboration, with the shared goal of improving patient care. bioMerieux is committed to improving the health and care of patients around the world through research collaborations, educational initiatives and our portfolio of diagnostic tests and services in the fields of infectious disease, antimicrobial resistance, sepsis and acute kidney injury.

We found the scope of work and proposed questions to be relevant and comprehensive. We will therefore focus our comments on several areas of importance to bioMerieux's mission to improve care and outcomes of patients at risk for AKI. Though our subsidiary Astute Medical, we have invested intense effort over the past decade working with our academic collaborators to discover, develop, and validate (including FDA clearance) novel AKI biomarkers, and importantly, to work with our clinical collaborators to develop and validate protocols for how clinicians can use these biomarkers in routine clinical practice to improve patient outcomes. The 2012 KDIGO AKI Guideline played a critical role in these efforts and we are delighted the Guideline will be reviewed for revision given the substantial progress that has been made since 2012 in managing patients at risk for AKI.

The role of biomarkers has been extensively studied and has advanced significantly since publication of the 2012 Guideline. The only biomarker test to date to have gained FDA clearance for routine clinical use in the United States ([TIMIP-2]*[IGFBP7]) was published for the first time in 2013[1]. This unique biomarker test detects kidney stress that can lead to AKI has been approved for use in the United States and the European Union as an aid in the risk assessment for acute kidney injury. Since 2013, multiple publications have described performance and validation of the test in large multicenter studies of heterogeneous cohorts of critically ill patients as well as specific cohorts such as cardiac surgery[1-6] . Most importantly, randomized controlled trials [7-8] and quality initiatives for pragmatic routine use of the test [9] have published showing that use of the test in conjunction with protocols based on the KDIGO recommendations for patients at high risk of AKI can improve AKI outcomes.

Another important question to answer is whether there is sufficient evidence now available to warrant a change in the definitions/classification/staging system for AKI, related to the AKI/AKD/CKD continuum, early diagnosis of AKI remains a challenge for clinicians. Existing recommendations of acute kidney injury emphasize the importance of early intervention, risk assessment, and prevention. Guidelines recommend using a multi-parameter approach including clinical indicators of functional decline such as raised SCr levels, estimated glomerular filtration rate (eGFR), reduced urine output and other factors such as age, use of nephrotoxic drugs and comorbidities to identify at-risk patients. Increased SCr levels and reduced urine output are consequences of an earlier injury to the kidney and may not manifest for up to 48 hours after the injury has occurred; this can potentially cloud or delay the diagnosis of AKI and the kidney can rapidly progress to a more severe stage of AKI or even to CKD. Tissue Inhibitor of Metalloproteinase 2 and Insulin-like Growth Factor Binding Protein 7 ([TIMP-2]*[IGFBP-7]) levels rise rapidly early in the process of stress/injury to kidney cells, and thus in conjunction with the existing KDIGO diagnostic criteria, may help the clinician make a more timely and accurate assessment or diagnosis of the patient.

In one multicenter study of a large cohort of critically ill patients, AKI was clinically adjudicated by an expert panel of three critical care nephrologists who based their adjudication on KDIGO criteria, but considered numerous other patient clinical variables and could overrule the KDIGO criteria for any patient based on their expert judgement. In this analysis, [TIMP-2]*[IGFBP7] correlated to clinically adjudicated AKI better than to KDIGO criteria. Furthermore, in difficult cases where adjudicators overruled KDIGO criteria, the biomarker test discriminated well, providing evidence that [TIMP-2]*[IGFBP7] can add useful information to existing KDIGO criteria for assessing and diagnosing patients. In another study involving measurement of renal functional reserve prior to and 90 days after cardiac surgery [10], investigators found that patients who had a positive [TIMP-2]*[IGFBP7] test 4 hours after surgery but never developed AKI had significantly reduce renal functional reserve at 90 days. The results provide evidence that the test detects significant kidney stress/injury events that can lead to permanent kidney damage but that are not always manifest through the current KDIGO diagnostic criteria. The test therefore can be complimentary to the current diagnostic criteria that are based solely on SCr and urine output. Also peri-operative elevated values [[TIMP-2]•[IGFBP7] levels "may be superior to help identify patients at highest risk for subsequent decrease of RFR after cardiac surgery compared with postoperative time points [10].

In terms of the roles of biomarkers for risk-stratification and monitoring of patients for AKI, according to peer-reviewed literature, kidney stress can be monitored utilizing the combination urinary biomarker, [TIMP-2]*[IGFBP-7] . It is an in vitro diagnostic test used to measure tubular cell stress before acute kidney injury occurs in critically ill patients; this test identifies kidney stress much faster than the commonly used markers of serum creatinine and urine output. Based on most recent literature, TIMP-2/IGFBP-7 can be monitored pre-operatively, intraoperatively, or post-operatively. The main points from the evidence summarized in this briefing are from 3 validation and diagnostic accuracy studies (n=1,262) and 2 randomized controlled trials (n=397). The evidence shows that an increase in urinary TIMP2 and IGFBP7 in the critically ill a predictor of acute kidney injury.

Lastly, the role of biomarkers may also play a role in defining the criteria for classification of AKI caused by nephrotoxins. According to Griffin et al, the ability of [TIMP-2/IGFBP-7] to help the clinician identify early risk for AKI in critically ill patients may allow the clinician to identify kidney stress induced by nephrotoxins, therefore aiding the clinician in reducing the dose of the nephrotoxic drug, thus avoiding progression of kidney disease. [11]

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Dustin Dunham (GE Healthcare - Life Sciences, Pharmaceutical Diagnostics)

Thank you for encouraging submission statements regarding scope of work for the 2019 KDIGO Controversies Conference on Acute Kidney Injury. We would like to submit the below topics and literature for consideration with special attention to Breakout Group 4: Nephrotoxins,

specifically regarding the prevention, management, and relative impact of contrast-associated AKI:

The exact pathophysiology of contrast-induced acute kidney injury (CI-AKI) is not well defined, however includes a complex cascade of events resulting in both ischemic and chemotoxic injury to the proximal renal tubules. Subclinical CI-AKI may occur in every patient exposed to iodinated contrast media (CM). Because there is a robust tubular repair capability, this process may not have any clinical consequences in healthy subjects. However, in patients with chronic kidney disease (CKD), especially those with underlying diabetes mellitus, who have a reduced number of functioning nephrons and an impaired ability to regenerate tubular epithelial cells, routine cardiac procedures using average doses of iodinated contrast can cause CI-AKI that is clinically important[1].

While several recent publications have questioned the true incidence of CI-AKI, particularly after intravenous administration of CM, the burden of acute renal events post-contrast enhanced procedures is categorical, particularly in higher-risk patients and complex procedures. There is strong correlation between the volume of contrast media administered and the incidence of AKI[2]. AKI occurring over course of percutaneous coronary intervention (PCI) has been associated with increased risk of bleeding, myocardial infarction, and death both in-hospital[3] and post-discharge[4]. Acute kidney injury in-turn perpetuates hospital readmission rates[5] and CI-AKI also leads to significant financial burden[6].

Susceptible patient populations such as oncology settings are further prone to poorer prognostic implications of AKI which is associated with prolonged hospital length of stay, increased hospitalization cost, and increased morbidity & mortality[7]. Recent retrospective review of 29 million inpatient visits suggests that acute renal events are more common in patients undergoing contrast enhanced computed tomography (CECT) versus those who do not, further that cancer patients are more prone to developing renal events versus non-cancer patients, and that adverse events parallel underlying degree of renal insufficiency and stages of CKD[8]. Serial insult in oncology patients due to CM-enhanced follow up examinations may further impact renal functional reserve (RFR), causing subclinical AKI to eventually develop into clinically relevant AKI[9].

Due to the frequency and poor prognostic implications posed by AKI, short-term adverse events, long-term adverse events, and potential financial burden, we recommend that comprehensive mitigation strategies be developed and employed. Further, AKI should be considered an important quality metric for healthcare systems as it is of strong clinical

relevance, measurable with persistent gap, actionable, and prevention of AKI results in improved downstream outcomes.

With regard to prevention strategies, the 2012 KDIGO Clinical Practice Guideline for the Evaluation and Management of CKD references avoidance of high osmolar agents, further, analysis of evidence indicates that wherever possible, isosmolar agents should be used in people with CKD at high risk for CI-AKI[10]. This recommendation is mirrored in a recent retrospective, propensity-score matched analysis where intravenous administration of isosmolar contrast media for CECT was not an independent risk factor for AKI, dialysis, or mortality among patients at the highest perceived risk of postcontrast AKI[11]. It also strongly parallels other key curricula noting the potential relative renal protective benefit of isosmolar contrast media evident within the American Society of Nephrology's Onco-Nephrology Curriculum[12], Geriatric Nephrology Curriculum[13], and recently published consensus statement addressing CT related risk factors in oncology patients[14].

The above isosmolar recommendations may be further substantiated given recent contributions to the literature, including several meta-analyses[15,16,17] and systematic review[17] that were published after the 2012 KDIGO AKI Guideline, which reveal favorable risk reduction with isosmolar vs low-osmolar contrast, most notably within intra-arterial procedures versus intravenous administration. Procedural complexity and patient comorbidities are critical factors in the development of CI-AKI and efforts should be made to better explore and understand susceptible groups. A recent prospective, blinded, randomized control trial assessing cancer patients undergoing CECT suggested a more favorable safety profile with isosmolar contrast versus a low-osmolar comparator[18]. Robust real-world data has additionally rendered some potential external validation to findings from clinical trials for more complex procedures and at-risk patients such as those undergoing percutaneous cardiovascular intervention. McCullough et al data mined over 333,00 patient visits to better understand trends in contrast media utilization and prevalence of major adverse renal and cardiovascular events (MARCE). Results suggest that clinicians tend to utilize isosmolar contrast in older, sicker, and more comorbidity compromised patients and that after adjustment, isosmolar contrast was associated with 9.32% relative risk reduction in MARCE rate and 50% decrease in renal composite endpoint (events requiring dialysis) compared to low-osmolar contrast media[19].

Given the totality of data and recent supplementary evidence, we suggest that selection of isosmolar contrast media be considered as a recommendation for high-risk patients/procedures to complement a comprehensive multiprong mitigation strategy encompassing individual risk

assessment, peri-procedural hydration, judicious use of contrast in highest risk patients, withholding nephrotoxic medications when amenable, etc.

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Thank you for your review and consideration.

Best regards,
Dustin M Dunham, DC, BCMAS Global Medical Leader - Cardiology Medical Affairs
Jeannette Rautenbach, MD Global Medical Leader - Radiology Medical Affairs

Tina Abdelnour (Edwards Lifesciences)

All comments specific to Fluid Management Breakout (page 7):
Consider "Hemodynamic" Management, rather than just fluid, considering the large body of evidence that Intraoperative & Postoperative Hypotension are also strongly associated with postoperative AKI

Literature supporting Association of Hypotension with AKI:
1. Walsh M, et al. 2016 Anesthesiology Relationship between Intraoperative Mean Arterial Pressure and Clinical Outcomes after Noncardiac Surgery: Toward and Empirical Definition of Hypotension
2. Salmasi V, et al. 2016 Anesthesiology Relationship between Intraoperative Hypotension, Defined by Either Reducation from Baseline or Absolute Thresholds, and Acute Kidney & Myocardial Injury after Noncardiac Surgery: A Retrospective Cohort Analysis
3. Sun L, et al. 2015 Anesthesiology Association of Intraoperative Hypotension with Acute Kidney Injury after Elective Noncardiac Surgery
4. Gu, et al. 2017 Intern J Cardiology Association between intraoperative hypotension and 30-day mortality,major adverse cardiac events, and actue kidney injury after non-cardiac surgery: A meta-analysis of cohort studies
5. Hallqvist L, et al. 2018 Europ J Anesth Observational choort Intraoperative hypotension is associated with acute kidney injury in noncardiac surgery
6. Haase-Fielitz, A. et al 2017 Blood Purif Perioperative Hemodynamic Instability and Fluid Overload are Associated with Increasing Acute Kidney Injury Severity and Worse Outcome after Cardiac Surgery
7. Aronson S, et al. 2013 Anesthesiology Research & Practice The Association of Postcardiac Surgery Acute Kidney Injury with Intraoperative Systolic Blood Pressure Hypotension

8. Lehman L, et al. 2010 Computing in Card Hypotension as a Risk Factor for Acute Kidney Injury in ICU Patients
9. Futier JAMA 2017 Effect of Individualized versus Standard Blood Pressure Management Strategies on Postoperative Organ Dysfunction Among High-Risk Patients Undergoing Major Surgery: a Randomized Controlled Trial

Consider literature to support hemodynamic monitoring to implement Goal-Directed Fluid Therapy, as many of the 50+ RCTs demonstrated improvement in AKI rates with a goal-directed approach. The recent RELIEF trial also demonstrated that under-resuscitation in surgical patients worsens kidney outcomes

1. Chong, et al. EJA 2018 Does goal-directed haemodynamic therapy and fluid therapy improve peri-operative outcomes? A systematic review and meta-analysis.
2. Calvo-Vecino BJA 2018 Effect of goal-directed haemodynamic therapy on postoperative complications in low-moderate risk surgical patients: a randomised controlled trial (FEDORA trial)
3. Myles NEJM 2018 Restrictive versus Liberal Fluid Therapy for Major Abdominal Surgery Makaryus, Miller BJA 2018 Current concepts of fluid management in enhanced recovery pathways
4. Pinsky COCC 2016 Postoperative Hemodynamic Instability & Monitoring

Michael Joannidis (Medical University Innsbruck, Austria)

Group 3: Topic 3: also would ask who should follow up patients after AKI

Group 5: Topic 1: Criteria for initiation of RRT should also include biomarkers as a subtopic

Effects of Intensive Blood Pressure Treatment on Acute Kidney Injury Events in the Systolic Blood Pressure Intervention Trial (SPRINT)

Michael V. Rocco, Kaycee M. Sink, Laura C. Lovato, Dawn F. Wolfgram, Thomas B. Wiegmann, Barry M. Wall, Kausik Umanath, Frederic Rahbari-Oskoui, Anna C. Porter, Roberto Pisoni, Cora E. Lewis, Julia B. Lewis, James P. Lash, Lois A. Katz, Amret T. Hawfield, William E. Haley, Barry I. Freedman, Jamie P. Dwyer, Paul E. Drawz, Mirela Dobre, Alfred K. Cheung, Ruth C. Campbell, Udayan Bhatt, Srinivasan Beddhu, Paul L. Kimmel, David M. Reboussin, and Glenn M. Chertow, on behalf of the SPRINT Research Group

Background: Treating to a lower blood pressure (BP) may increase acute kidney injury (AKI) events.

Study Design: Data for AKI resulting in or during hospitalization or emergency department visits were collected as part of the serious adverse events reporting process of the Systolic Blood Pressure Intervention Trial (SPRINT).

Setting & Participants: 9,361 participants 50 years or older with 1 or more risk factors for cardiovascular disease.

Interventions: Participants were randomly assigned to a systolic BP target of <120 (intensive arm) or <140 mm Hg (standard arm).

Outcomes & Measurements: Primary outcome was the number of adjudicated AKI events. Secondary outcomes included severity of AKI and degree of recovery of kidney function after an AKI event. Baseline creatinine concentration was defined as the most recent SPRINT outpatient creatinine value before the date of the AKI event.

Results: There were 179 participants with AKI events in the intensive arm and 109 in the standard arm (3.8% vs 2.3%; HR, 1.64; 95% CI, 1.30-2.10; $P < 0.001$). Of 288 participants with an AKI event, 248 (86.1%) had a single AKI event during the trial. Based on modified KDIGO (Kidney Disease: Improving Global Outcomes) criteria for severity of AKI, the number of AKI events in the intensive versus standard arm by KDIGO stage was 128 (58.5%) versus 81 (62.8%) for AKI stage 1, 42 (19.2%) versus 18 (14.0%) for AKI stage 2, and 42 (19.2%) versus 25 (19.4%) for AKI stage 3 ($P = 0.5$). For participants with sufficient data, complete or partial resolution of AKI was seen for 169 (90.4%) and 9 (4.8%) of 187 AKI events in the intensive arm and 86 (86.9%) and 4 (4.0%) of 99 AKI events in the standard arm, respectively.

Limitations: Trial results are not generalizable to patients with diabetes mellitus or without risk factors for cardiovascular disease.

Conclusions: More intensive BP lowering resulted in more frequent episodes of AKI. Most cases were mild and most participants had complete recovery of kidney function.

Trial Registration: Registered at ClinicalTrials.gov with study number NCT01206062.

Complete author and article information (including a list of the members of the SPRINT Research Group) provided before references.

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The Systolic Blood Pressure Intervention Trial (SPRINT), sponsored by the National Institutes of Health (NIH), was a study of blood pressure (BP) control in persons without diabetes mellitus at increased risk for developing cardiovascular disease (CVD).[1] The relative hazard of the primary composite end point in SPRINT, which included myocardial infarction, acute coronary syndrome not resulting in myocardial infarction, stroke, acute decompensated heart failure, or death from cardiovascular causes, was significantly lower in the intensive arm (goal systolic BP [SBP] < 120 mm Hg) compared to the standard arm (goal SBP < 140 mm Hg).[2] In addition, all-cause mortality was significantly lower in the intensive BP-lowering arm of the trial.

The frequency of serious adverse events (SAEs) in SPRINT was not significantly different between the 2 arms of the trial. SAEs that were anticipated to be higher in the intensive arm of the trial were a priori ascertained by the clinical sites and the SPRINT Safety Officer. Conditions of interest that were more frequent in the intensive arm included hypotension, syncope, electrolyte abnormalities, and acute kidney injury (AKI), typically noted in association with hospitalization.[2] The goals of our detailed examination of AKI in SPRINT were to: (1) identify predictors of AKI resulting in either a hospitalization or emergency department (ED) visit, (2) adjudicate each of the reported AKI events, (3) determine the severity of and recovery from these events, and (4) explore effect modification of intensive versus standard BP lowering on AKI within each of the 6 predefined participant subgroups. Changes in kidney function that were noted based on SPRINT clinic laboratory results that did not result in a hospitalization or ED visit are described in 2 other publications.[3,4]

Methods

Study Population

SPRINT was a randomized controlled open-label trial sponsored by the National Heart, Lung, and Blood Institute (NHLBI), with cosponsorship by the National Institute of Diabetes and Digestive and Kidney Diseases, the National Institute of Neurological Diseases and Stroke, and the National Institute on Aging. The trial was approved by institutional review boards at participating study sites; all participants provided written informed consent. Participants from 102 clinical sites were randomly assigned to a target goal SBP of <120 mm Hg (intensive arm, n = 4,678) or <140 mm Hg (standard arm, n = 4,683). The design, eligibility, full trial protocol, sample size calculations, and interim analysis and stopping rules have been previously reported.[1,2] The SPRINT cohort included participants 50 years or older with SBPs ≥ 130 mm Hg, without a history of diabetes or stroke, and with increased risk for cardiovascular events, defined by 1 or more of the following: clinical or subclinical CVD other than stroke; chronic kidney disease (CKD), excluding polycystic kidney disease; 10-year risk for CVD ≥ 15% on the basis of the Framingham risk score; or age 75 years or older. Persons with diabetes mellitus, polycystic kidney disease, screening urine protein excretion > 1 g/d or equivalent, symptomatic heart failure, ejection fraction < 35%, or stroke were excluded from the trial. Participant enrollment into SPRINT occurred November 2010 to March 2013.

Study Outcomes

Demographic data were collected at baseline, including self-reported race and ethnicity. Six prespecified subgroups of interest for all outcomes included the following: CVD at baseline (yes vs no), CKD at baseline (yes vs no), sex, race (black vs nonblack), age (<75 vs ≥75 years), and tertiles of baseline SBP (≤132, >132-<145, and ≥145 mm Hg). The presence of CKD at randomization was defined as estimated glomerular filtration rate of 20 to 59 mL/min/1.73 m^2 using the isotope-dilution mass spectrometry (IDMS)-traceable 4-variable MDRD (Modification of Diet in Renal Disease) Study equation; this definition defined the CKD cohort in SPRINT.[5]

Clinical and laboratory data were obtained at baseline and every 3 months thereafter. Serum creatinine was measured in a central laboratory by an enzymatic procedure using a Roche analyzer and was IDMS-traceable for calibration. Urine albumin was measured by an immunoturbidometric method using a Roche analyzer. Urine albumin was quantified along with urine creatinine in random spot urine specimens, with urine albumin-creatinine ratio (in mg/g) used to account for urine concentration. AKI was defined using modified KDIGO (Kidney Disease: Improving Global Outcomes) criteria[6] incorporating only serum creatinine concentration to assess for AKI stage (ignoring the component of urine output, which was not uniformly measured). These modified KDIGO criteria include the following AKI stages and serum creatinine definitions: stage 1, increase ≥ 0.3 mg/dL or increase of 1.5- to 2.0-fold from baseline; stage 2, increase greater than 2.0- to 3.0-fold from baseline; and stage 3, increase greater than 3.0-fold from baseline or ≥4.0 mg/dL with an acute increase of 0.5 mg/dL or need for renal replacement therapy.

At quarterly study visits, a structured interview was used to query participants about hospitalizations in the prior 3 months, as well as specific outcomes of interest, such as initiation of dialysis therapy.[2] SAEs were also identified between visits if study staff were informed of them by participant report, electronic medical record notification, or other mechanism. SAEs were defined as events that were fatal or life-threatening, resulted in significant or persistent disability, or required or prolonged a hospitalization or medical events that the investigator judged to be a significant hazard or harm to the participant and required medical or surgical intervention to prevent hospitalization, death, or persistent disability. For selected SAEs, including AKI (as either the primary reason for hospitalization or a part of the hospitalization), clinic staff were required to obtain medical records of the event for review by the medical safety officer, including ED notes for ED visits and the admission history and physical and discharge summary for hospitalizations. The medical safety team at the Coordinating Center reviewed the medical records from hospitalizations and ED visits and from SAE reports, and the team recorded AKI if it was noted on admission or occurred during a hospitalization or ED visit and was reported in the hospital discharge summary as a primary or main secondary diagnosis. If the discharge summary did not list AKI as a primary or secondary diagnosis, the record was not reviewed to determine whether an AKI event may have occurred but was not listed explicitly. In some cases, these records included all laboratory creatinine values obtained during the admission, whereas in other cases, only creatinine values recorded in the discharge summary and/or the admission note and/or progress notes were used to ascertain the occurrence and severity of AKI. The Medical Dictionary for Regulatory Activities (MedDRA) was used to classify safety events. Coding was performed at the Coordinating Center, and up to 3 codes were assigned to each safety event.

All SAEs and ED visits classified as involving an AKI event by the safety team were reviewed in a blinded fashion by 2 nephrologists or physician experts in outcomes adjudication to determine baseline and peak creatinine values, modified KDIGO stage of AKI, the underlying primary cause of the AKI, and whether it was thought that SPRINT participation caused or contributed to the event. Baseline creatinine concentration was defined as the most recent SPRINT outpatient creatinine value before the date of the AKI event. Disagreements regarding baseline and peak creatinine values, AKI stage, or whether SPRINT participation caused or contributed to the event were resolved by a single third adjudicator (M.V.R.). After

blinded adjudication, 54 of 402 events were not thought to represent AKI by modified KDIGO criteria. Therefore, the rest of this study reports on the 348 events adjudicated as AKI.

Recovery of kidney function was determined by comparing the peak recorded serum creatinine value with the lowest outpatient SPRINT creatinine value obtained in the subsequent 365 days. Recovery was classified as complete (recovery to within 20% of pre-AKI serum creatinine concentration),[7,8] partial (recovery to within 30% of pre-AKI serum creatinine value),[9] or nonrecovery (no decline in serum creatinine or a decline not reaching the "within 30% of baseline value" threshold).

Statistical Analyses

Statistical analyses were conducted at the Coordinating Center using SAS software, version 9.4 (SAS Institute Inc). Baseline characteristics were compared among participants who did and did not have AKI during the trial with use of t test or Wilcoxon rank sum test for continuous variables and χ^2 test for discrete or categorical variables. Continuous variables are presented as either mean ± standard deviation if normally distributed or median with 25th to 75th percentile if not normally distributed.

Time until first occurrence of AKI was compared between the 2 study arms with the use of the intention-to-treat approach for all randomly assigned participants. We used Cox proportional hazards regression, with 2-sided tests at the 5% level of significance, with stratification by clinical site.

An assessment for nonproportionality of hazards was made with the addition of the interaction between log (time) and the intervention.[10] Follow-up time was censored at the time of the final event ascertainment. Interactions between treatment effect and prespecified subgroups were assessed using a likelihood ratio test for interaction. Baseline variables thought to be related to time to the development of AKI were assessed first in univariate models and then added as a group to the primary analysis model.

In exploratory analyses, participants with multiple AKI events were analyzed according to data obtained at the first occurrence of AKI to determine whether these variables were predictive of recurrence. These exploratory analyses used time from the first episode of AKI to first recurrence, with censoring time set at the participant's last visit. The association of AKI events with primary and secondary end points was evaluated using the Cox proportional hazards model, with a time-varying covariate for the first AKI episode.

Results

Overview

The SPRINT cohort consists of 9,361 participants who were followed up for a mean of 3.26 years before the BP intervention was stopped early on August 20, 2015,

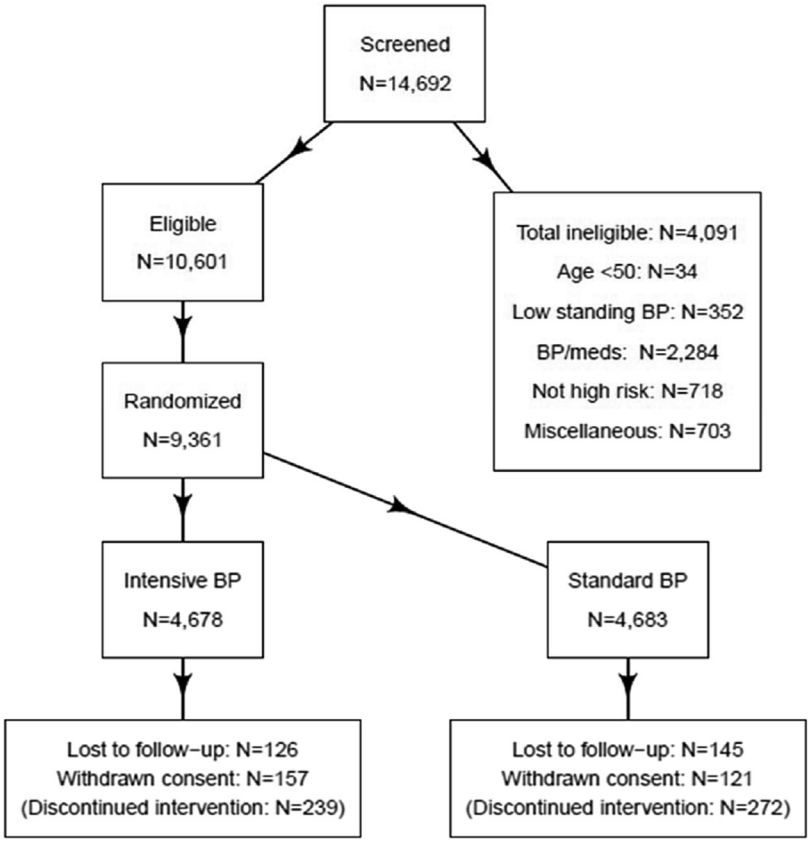

Figure 1. CONSORT (Consolidated Standards of Reporting Trials) diagram. Abbreviation: BP, blood pressure.

after the NIH accepted the recommendation of the Data and Safety Monitoring Board due to benefit in the intensive arm on the primary outcome (Fig 1).[2] This study reports on AKI events occurring through August 20, 2015.

Incidence and Correlates of Adjudicated AKI Events

There were 348 AKI events in 288 (3.0%) participants. Baseline characteristics of study participants, stratified by the presence or absence of at least one AKI event, are shown in Table 1. Baseline characteristics associated with time to the development of AKI included age 75 years or older, male sex, CKD at trial entry, higher urine albumin-creatinine ratio, presence of CVD, higher Framingham risk score, and in at least 1 treatment group, also race/ethnicity, smoking status, and SBP and/or diastolic BP. Of 288 participants with an AKI event, 248 (86.1%) had a single AKI event during the course of the trial, 30 (10.4%) had 2 events, 5 (1.7%) had 3 events, and 5 (1.7%) had 4 or more events. AKI events were typically mild because AKI stage 1 was the most common AKI stage. Based on modified KDIGO criteria, numbers of AKI events in the intensive versus standard arm by KDIGO stage were 128 (58.5%) versus 81 (62.8%) in stage 1, 42 (19.2%) versus 18 (14.0%) in stage 2, and 42 (19.2%) versus 25 (19.4%) in stage 3 ($P = 0.5$ for comparison of stages of AKI by randomized arm; AKI events by CKD cohort in Table 2). Dialysis was required infrequently by participants in the intensive (n = 8) and standard (n = 6) arms (Table 3) and end-stage kidney disease subsequently developed in 2 intensive-arm and 3 standard-arm participants. No participant underwent kidney transplantation for irreversible AKI.

Cause of and Risk Factors for AKI Events

The most common proximate cause of AKI events in both arms of the trial was dehydration and/or

Table 1. Baseline Clinical Characteristics by Occurrence of AKI

	Intensive Treatment			Standard Treatment		
Baseline Characteristics	No AKI (n = 4,499)	AKI (n = 179)	*P*	No AKI (n = 4,574)	AKI (n = 109)	*P*
Age ≥ 75 y	1,250 (27.8%)	67 (37.4%)	0.005	1,268 (27.7%)	51 (46.8%)	<0.001
Age, y	67.8 ± 9.3	70.7 ± 10.0	<0.001	67.8 ± 9.4	71.4 ± 10.7	<0.001
Female sex	1,635 (36.3%)	49 (27.4%)	0.01	1,619 (35.4%)	29 (26.6%)	0.06
Race or ethnic group			0.002			0.5
African American	1,307 (29.1%)	72 (40.2%)		1,386 (30.3%)	37 (33.9%)	
Hispanic	493 (11.0%)	10 (5.6%)		474 (10.4%)	7 (6.4%)	
Other	97 (2.2%)	1 (0.6%)		77 (1.7%)	1 (0.9%)	
White	2,602 (57.8%)	96 (53.6%)		2,637 (57.7%)	64 (58.7%)	
CKD	1,233 (27.5%)	97 (54.5%)	<0.001	1,245 (27.4%)	71 (65.1%)	<0.001
Serum creatinine, mg/dL	1.1 ± 0.3	1.4 ± 0.5	<0.001	1.1 ± 0.3	1.4 ± 0.5	<0.001
eGFR, mL/min/1.73 m^2	72.2 ± 20.4	59.8 ± 24.4	<0.001	72.1 ± 20.4	55.6 ± 19.9	<0.001
Urinary ACR, mg/g	40.3 ± 161.8	139.1 ± 407	<0.001	37.0 ± 126.7	203.8 ± 544	<0.001
CVD[a]	889 (19.8%)	51 (28.5%)	0.004	902 (19.7%)	35 (32.1%)	0.001
Subclinical	155 (3.4%)	6 (3.4%)	0.9	151 (3.3%)	3 (2.8%)	0.8
Clinical	734 (16.3%)	45 (25.1%)	0.002	751 (16.4%)	32 (29.4%)	0.003
Smoking status			0.07			0.002
Never	1,986 (44.3%)	64 (35.8%)		2,042 (44.8%)	30 (27.5%)	
Former	1,892 (42.2%)	85 (47.5%)		1,934 (42.4%)	62 (56.9%)	
Current	609 (13.6%)	30 (16.8%)		584 (12.8%)	17 (15.6%)	
BMI, kg/m^2	29.9 ± 5.8	30.0 ± 5.8	0.9	29.8 ± 5.7	29.7 ± 6.3	0.8
SBP, mm Hg	139.6 ± 15.7	142.1 ± 17.1	0.03	139.6 ± 15.4	141.6 ± 16.6	0.2
DBP, mm Hg	78.3 ± 11.8	77.1 ± 13.5	0.2	78.1 ± 12.0	75.8 ± 13.0	0.05
SBP tertile			0.2			0.1
≤132 mm Hg	1,534 (34.1%)	49 (27.4%)		1,522 (33.3%)	31 (28.4%)	
>132-<145 mm Hg	1,429 (31.8%)	60 (33.5%)		1,518 (33.2%)	31 (28.4%)	
≥145 mm Hg	1,536 (34.1%)	70 (39.1%)		1,534 (33.5%)	47 (43.1%)	
Fasting glucose, mg/dL	98.8 ± 13.6	100.3 ± 16.5	0.2	98.8 ± 13.3	99.3 ± 15.1	0.7
Statin use	1,896 (42.5%)	82 (45.8%)	0.4	2,020 (44.6%)	56 (51.4%)	0.2

Note: Values for categorical variables are given as count (percentage); for continuous variables, as mean ± standard deviation. Conversion factors for units: creatinine in mg/dL to μmol/L, ×88.4; glucose in mg/dL to mmol/L, ×0.05551.

Abbreviations: ACR, albumin-creatinine ratio; AKI, acute kidney injury; BMI, body mass index; CKD, chronic kidney disease; CVD, cardiovascular disease; DBP, diastolic blood pressure; ECG, echocardiogram; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure.

[a]Subclinical CVD includes ≥50% stenosis of a coronary, carotid, or lower-extremity artery; abdominal aortic aneurysm ≥ 5 cm with or without repair; coronary artery calcium score ≥ 400 Agatston units; low ankle-brachial index (≤0.90); left ventricular hypertrophy by computer ECG reading, ECG report, or other cardiac imaging procedure. Clinical CVD includes myocardial infarction; acute coronary syndrome with or without ECG changes at rest, ECG changes on graded exercise test, or positive cardiac imaging study; coronary revascularization; carotid endarterectomy or carotid stenting; and peripheral arterial disease with revascularization.

Table 2. Severity of AKI Events in Non-CKD and CKD Cohorts

	Intensive Arm		Standard Arm	
	Participants[a]	Events	Participants[a]	Events
Non-CKD cohort[b]				
AKI stage 1	35 (43%)	42 (43%)	19 (50%)	22 (50%)
AKI stage 2	19 (23%)	24 (25%)	6 (16%)	6 (14%)
AKI stage 3	22 (27%)	25 (26%)	13 (34%)	16 (36%)
Unknown stage	6 (7%)	6 (6%)	0 (0%)	0 (0%)
CKD cohort[c]				
AKI stage 1	70 (72%)	86 (70%)	52 (73%)	59 (69%)
AKI stage 2	14 (14%)	18 (15%)	9 (13%)	12 (14%)
AKI stage 3	13 (13%)	17 (14%)	5 (7%)	9 (11%)
Unknown stage	0 (0%)	1 (1%)	5 (7%)	5 (6%)

Note: Values are given as count (percentage).
Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease.
[a]In participants with multiple events, only the first AKI event is shown.
[b]P=0.2 for comparison of stages of AKI by randomly assigned arm, excluding unknowns (all events); P = 0.5 for comparison of stages of AKI by randomly assigned arm, excluding unknowns (first events).
[c]P=0.8 for comparison of stages of AKI by randomly assigned arm, excluding unknowns (all events); P = 0.5 for comparison of stages of AKI by randomly assigned arm, excluding unknowns (first events).

intravascular volume depletion, followed by hypotension (Table 3). In both the CKD and non-CKD cohorts, 10.0% of cases of AKI in the intensive arm and 2.3% of cases in the standard arm were thought to be secondary to the intervention. By multivariable analysis, risk factors for time to development of an AKI event included older age, nonwhite race, lower baseline estimated glomerular filtration rate, and presence of CVD at baseline (Table 4).

Effects of Intensive BP Lowering on AKI by Prespecified Subgroups

There were 179 participants with AKI events in the intensive arm and 109 in the standard arm (3.8% vs 2.3%). The hazard ratio (HR) for AKI in the intensive versus standard arms was 1.64 (95% confidence interval [CI], 1.30-2.10; Fig 2). The effects of the intervention on AKI rate were consistent across the prespecified subgroups (baseline CVD, baseline CKD, sex, race, age, and baseline SBP; Fig 3). There were no significant interactions between treatment and subgroup (P value range, 0.06-0.9).

Post-AKI Events

Among participants with sufficient data to determine recovery, complete or partial resolution of AKI was seen for 169 (90.4%) and 9 (4.8%) of the 187 AKI events in the intensive arm and 86 (86.9%) and 4 (4.0%) of the 99 AKI events in the standard arm, respectively. Only 14 (5.6%) events required dialysis for the treatment of AKI and 50% of these participants subsequently became dialysis independent.

Exploratory analyses were conducted to examine the risk for events following AKI. When including first AKI event as a time-varying covariate in a Cox model accounting for randomized group, AKI events were found to be associated with higher risks for both the primary SPRINT outcome (501 events in the no-AKI group [5.5%] vs 61 events in the AKI group [21.2%]; HR, 2.0 [95% CI, 1.2-3.1]; $P = 0.004$) and death from any cause (320 events in the no-AKI group [3.5%] vs 45 events in the AKI group [15.6%]; HR, 5.6 [95% CI, 4.0-7.8]; $P < 0.001$). Causes of death by randomly assigned arm are shown in Table 5.

Discussion

In SPRINT, participants randomly assigned to the intensive BP-lowering arm had significantly lower rates of the trial's primary composite end point, as well as lower rates of death and no difference in the total number of SAEs compared with participants randomly assigned to the standard arm. These benefits were offset by a subset of SAEs that were more common in participants in the intensive treatment arm, including AKI. Of participants who developed AKI in either arm of the trial, AKI stage, as assessed by modified KDIGO criteria, was in the lowest stage of severity for >50% of AKI events. AKI events were mainly attributed to volume depletion and in ~90% of persons in either study arm resulted in complete or partial recovery of kidney function. The need for dialytic therapy for the treatment of AKI was exceedingly rare (0.15%). Moreover, the rate of development of AKI in SPRINT was steady throughout the trial; specifically, AKI was not more common during the initial year, when participants generally experienced the most active titration of antihypertensive medications (Fig 2). We hypothesize that the increased frequency of AKI events in the intensive arm may have been due to the lower baseline SBP that resulted in increased risk for BP falling below the autoregulatory threshold for kidney perfusion when a volume-depleting illness and/or hypotension occurred.

Episodes of AKI, including those not severe enough to require dialysis, have consistently been shown to associate

Table 3. Changes in Kidney Function During and After the AKI Event Among Participants Stratified by Treatment Arm and Presence or Absence of CKD at Baseline

	Intensive Arm		Standard Arm	
	Non-CKD (n = 82)	CKD (n = 97)	Non-CKD (n = 38)	CKD (n = 71)
No. of events	97	122	44	85
Participant required RRT	4 (4.1%)	4 (3.3%)	2 (4.5%)	4 (4.7%)
Participant discharged on RRT	4 (4.1%)	1 (0.8%)	0 (0.0%)	2 (2.4%)
Participant developed ESRD	0 (0.0%)	2 (1.6%)	0 (0.0%)	3 (3.5%)
Participant died in hospital during this event	3 (3.1%)	1 (0.8%)	1 (2.3%)	3 (3.5%)
AKI was primary reason for admission	30 (30.9%)	37 (30.3%)	14 (31.8%)	22 (25.9%)
AKI developed after admission to hospital	3 (3.1%)	9 (7.4%)	3 (6.8%)	6 (7.1%)
ATN developed or was present during hospitalization	36 (37.1%)	31 (25.4%)	14 (31.8%)	18 (21.2%)
AKI developed during a cardiac event	7 (7.2%)	10 (8.2%)	1 (2.3%)	10 (11.8%)
AKI developed during a CHF event	4 (4.1%)	7 (5.7%)	4 (9.1%)	6 (7.1%)
AKI developed after patient had a fall	9 (9.3%)	13 (10.7%)	2 (4.5%)	11 (12.9%)
AKI developed due to dehydration or intravascular volume depletion	60 (61.9%)	77 (63.1%)	28 (63.6%)	61 (71.8%)
AKI developed due to hypotension	43 (44.3%)	42 (34.4%)	10 (22.7%)	25 (29.4%)
AKI developed postoperatively	1 (1.0%)	4 (3.3%)	1 (2.3%)	2 (2.4%)
AKI developed due to a septic event	7 (7.2%)	15 (12.3%)	7 (15.9%)	11 (12.9%)
AKI developed due to contrast nephropathy	2 (2.1%)	1 (0.8%)	2 (4.5%)	2 (2.4%)
AKI developed due to obstruction	6 (6.2%)	9 (7.4%)	2 (4.5%)	3 (3.5%)
AKI developed due to medications	25 (25.8%)	37 (30.3%)	10 (22.7%)	17 (2.0%)
SPRINT intervention was responsible for this episode of AKI	10 (11.1%)	12 (10.2%)	2 (4.7%)	1 (1.3%)

Note: Unless otherwise indicated, values are given as number (percentage).
Abbreviations: AKI, acute kidney injury; ATN, acute tubular necrosis; CKD, chronic kidney disease; CHF, congestive heart failure; ESRD, end-stage kidney disease; RRT, renal replacement therapy; SPRINT, Systolic Blood Pressure Intervention Trial.

with increased risk for in-hospital mortality.[11-13] In this trial, we found that AKI was associated with increased risk for the primary SPRINT outcome and for death from any cause. Moreover, AKI has the potential to cause significant morbidity because AKI can contribute to progressive CKD and, in some instances, end-stage kidney disease.[14-16] Risk factors for AKI include the presence of CKD and older age, subgroups that were specifically recruited into SPRINT. Thus, during protocol development for SPRINT, it was recognized that the acute decrease in estimated glomerular filtration rate that had been seen in previous hypertension trials[17,18] could adversely affect kidney function in SPRINT participants, both on a long-term basis and by increasing the risk for AKI events. The paucity of AKI events in SPRINT that resulted in longer-term deterioration of kidney function allays this latter concern. In addition, although participants in the intensive arm had increased risk for AKI events, participants in the intensive arm still had reduced risk for the primary SPRINT outcome and all-cause mortality compared with those in the standard arm.[2] These findings help in interpreting the risk-benefit ratio of the SPRINT results and are important to consider when developing clinical guidelines for the management of hypertension.

Table 4. Multivariable Predictors of Time to Development of AKI

Baseline Variables	HR (95% CI)	*P*
Male sex	1.86 (1.43-2.44)	<0.001
Black race	2.08 (1.62-2.66)	<0.001
eGFR (per 10 mL/min/1.73 m^2 greater)	0.71 (0.66-0.75)	<0.001
CVD subgroup	1.48 (1.14-1.90)	0.003
Senior subgroup	1.52 (1.18-1.95)	0.001
ACE-inhibitor use	1.20 (0.95-1.51)	0.1
ARB use	1.30 (0.62-2.39)	0.4
Diuretic use	0.98 (0.77-1.24)	0.9
Randomly assigned to intensive arm	1.64 (1.30-2.09)	<0.001

Abbreviations: ACE, angiotensin-converting enzyme; AKI, acute kidney injury; ARB, angiotensin receptor blocker; CI, confidence interval; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio.

Comparison of the SPRINT AKI results with other hypertension trials is difficult for several reasons. First, a minority of hypertension trials provide information on the incidence of AKI.[19] Second, persons with CKD, a major risk factor for AKI, have often been excluded from hypertension trials.[20] Furthermore, there is no consensus regarding how to define recovery of kidney function after AKI; a recent meta-analysis demonstrated that there was a broad range of definitions, including variability in the timing of post-AKI creatinine measurements and in the thresholds used for recovery based on serum creatinine concentrations.[21] We chose to report recovery of kidney function using 2 different definitions. UK guidelines adopted a return of serum

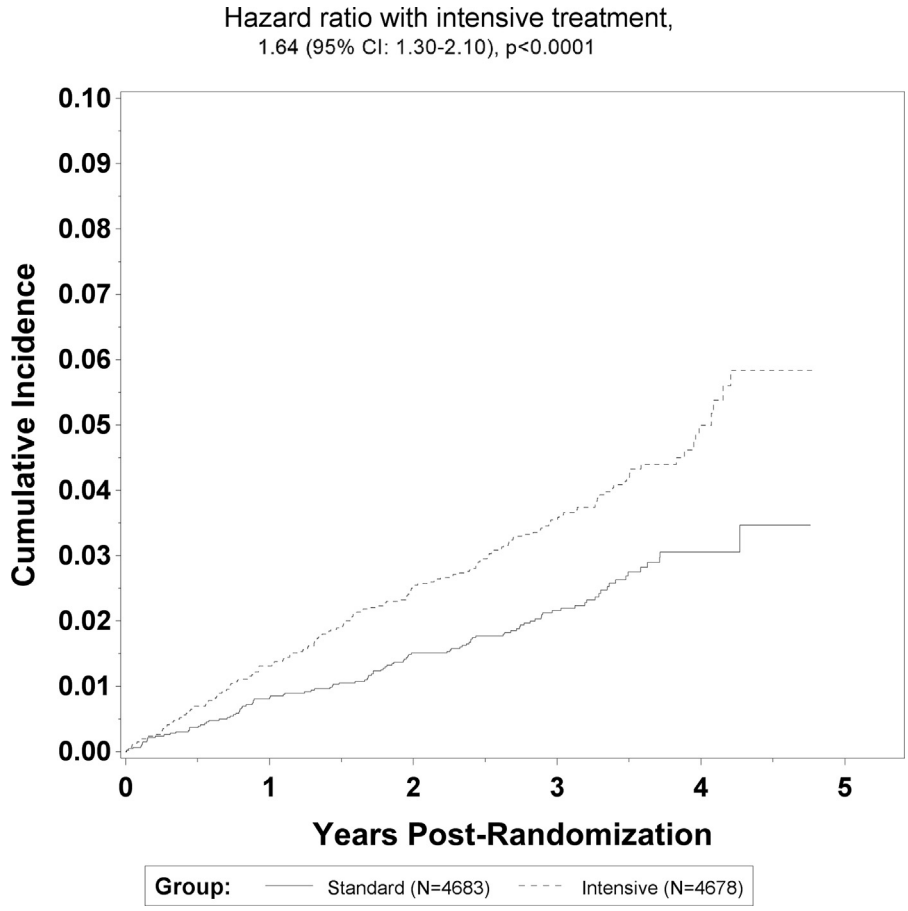

Figure 2. Cumulative hazard plot for acute kidney injury. Abbreviation: CI, confidence interval.

creatinine concentration to within 20% of baseline as a definition of recovery; the Program to Improve Care in Acute Renal Disease (PICARD) used the same definition.[7,8] Other investigators proposed a threshold of recovery to within 30% of the baseline serum creatinine concentration and cite increased risk for CKD if recovery does not occur.[9]

There are several strengths of these analyses, including the large sample size; inclusion of participants with risk factors for AKI, including CKD at baseline and older age; wide separation between achieved BPs in the trial arms; and capture of major diagnoses from virtually all hospitalizations. There are also important limitations to these analyses. First, serum creatinine data—in the hospital and thereafter—were relatively sparse and collected based on the trial protocol (monthly for 3 months, then biannually), rather than based on clinical indications. In other words, post-discharge serum creatinine determinations were not uniformly obtained. Second, site staff were unblinded and could have looked more carefully for AKI events in records of participants randomly assigned to the arm with intensive BP lowering. Third, although adjudicators were blinded to treatment assignment, in some cases, they may have been able to infer the treatment assigned to individual participants. Fourth, AKI events that were managed in the outpatient setting were not captured in this analysis; however, it is likely that these events were not severe enough to warrant either a hospital admission or evaluation in an ED. Note that data for changes in kidney function based on SPRINT laboratory data only will be the subject of 2 additional studies. Thus, the AKI prevalence reported here is likely an underestimation of the true AKI incidence in the trial, but captures all AKI events of sufficient severity to be associated with a hospitalization. Finally, these results are generalizable to only the study population and thus should be extrapolated cautiously to other patient populations, including those with diabetes mellitus or polycystic kidney disease, persons at low risk for cardiovascular events, and institutionalized patients.

In sum, more intensive BP lowering in persons with hypertension at high risk for CVD resulted in an increase in risk for AKI, although episodes of AKI were generally mild and largely reversible. Patients and physicians who undertake more intensive BP-lowering strategies should be alert for the risk for AKI, particularly among older

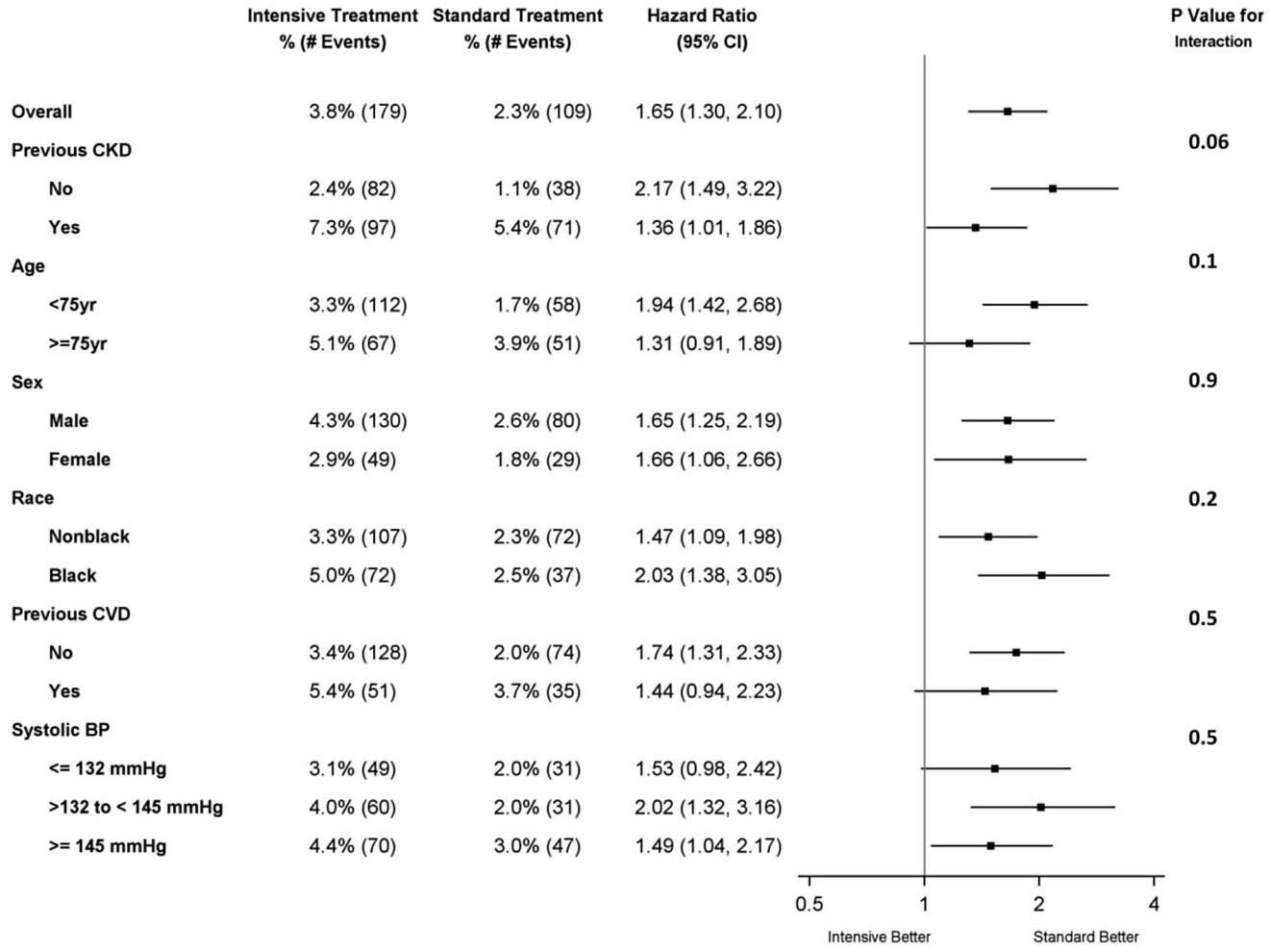

Figure 3. Forest plot of acute kidney injury. The dashed vertical line represents the hazard ratio for the overall study population. Box sizes are proportional to the precision of the estimates (with larger boxes indicating a greater degree of precision). The subgroup of no previous chronic kidney disease (CKD) includes some participants with unknown CKD status at baseline. Black race includes Hispanic black and black as part of a multiracial identification. Abbreviations: BP, blood pressure; CI, confidence interval; CVD, cardiovascular disease.

patients and patients with CKD. However, for patients thought to benefit in terms of CVD prevention, fear of AKI should not preclude an intensive BP-lowering strategy.

Table 5. Causes of Death for 45 Participants With Any AKI Event Who Died

Cause of Death	Intensive Arm	Standard Arm
CHF	3	2
Cancer	10	3
MI/coronary heart disease	0	1
Other noncardiac/nonstroke death	7	8
Stroke	1	1
Sudden cardiac death	0	1
Unclassifiable	2	3
Still under adjudication	1	0
Accident/injury/suicide/homicide	2	0
Total	26	19

Note: Values are given as number of participants.
Abbreviations: AKI, acute kidney injury; CHF, congestive heart failure; MI, myocardial infarction.

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Annals of Internal Medicine ORIGINAL RESEARCH

Kidney Damage Biomarkers and Incident Chronic Kidney Disease During Blood Pressure Reduction

A Case–Control Study

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Background: Whether the increased incidence of chronic kidney disease (CKD) during intensive systolic blood pressure (SBP) lowering is accompanied by intrinsic kidney injury is unknown.

Objective: To compare changes in kidney damage biomarkers between incident CKD case participants and matched control participants as well as between case participants in the intensive (<120 mm Hg) versus the standard (<140 mm Hg) SBP management groups of SPRINT (Systolic Blood Pressure Intervention Trial).

Design: Nested case–control study within SPRINT.

Setting: Adults with hypertension without baseline kidney disease.

Participants: Case participants (n = 162), who developed incident CKD during trial follow-up (128 in the intensive and 34 in the standard group), and control participants (n = 162) without incident CKD, who were matched on age, sex, race, baseline estimated glomerular filtration rate, and randomization group.

Measurements: 9 urinary biomarkers of kidney damage were measured at baseline and at 1 year. Linear mixed-effects models were used to estimate 1-year biomarker changes.

Results: Higher concentrations of urinary albumin, kidney injury molecule-1, and monocyte chemoattractant protein-1 at baseline were significantly associated with greater odds of incident CKD (adjusted odds ratio per doubling: 1.50 [95% CI, 1.14 to 1.98], 1.51 [CI, 1.05 to 2.17], and 1.70 [CI, 1.13 to 2.56], respectively). After 1 year of blood pressure intervention, incident CKD case participants in the intensive group had significantly greater decreases in albumin–creatinine ratio (ACR), interleukin-18, anti–chitinase-3-like protein 1 (YKL-40), and uromodulin than the matched control participants. Compared with case participants in the standard group, those in the intensive group had significantly greater decreases in ACR, β_2-microglobulin, α_1-microglobulin, YKL-40, and uromodulin.

Limitation: Biomarker measurements were available only at baseline and 1 year.

Conclusion: Incident CKD in the setting of intensive SBP lowering was accompanied by decreases, rather than elevations, in levels of kidney damage biomarkers and thus may reflect benign changes in renal blood flow rather than intrinsic injury.

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The association of lower blood pressures with substantial cardiovascular and mortality benefit is well established (1–3). SPRINT (Systolic Blood Pressure Intervention Trial) was a pivotal randomized controlled trial demonstrating that intensive systolic blood pressure (SBP) reduction to less than 120 mm Hg decreased rates of major cardiovascular events and all-cause mortality compared with standard management to less than 140 mm Hg (4). Despite these benefits, a notable harm was a more than 3-fold incidence of chronic kidney disease (CKD) in the intensive versus the standard group. Nonetheless, recent guidelines by the American College of Cardiology and American Heart Association lowered blood pressure targets for hypertension diagnosis and management (5). These policy changes may dramatically increase the incidence of CKD at the population level and pose an important public health concern. However, in the setting of intensive blood pressure lowering, kidney function decline measured by creatinine levels may be a benign manifestation of reduced renal blood flow. Thus, uncertainty remains regarding whether incident CKD that develops during intensive blood pressure lowering is accompanied by intrinsic kidney injury or instead reflects hemodynamic changes.

To address this question, we designed a nested case–control study of incident CKD case participants and matched control participants within SPRINT. We used a panel of urinary biomarkers of kidney damage measured at baseline and at 1 year of follow-up. Our aims were to determine whether baseline biomarker concentrations were associated with incident CKD, whether changes in urinary biomarkers were associated with risk for incident CKD, and whether the extent of biomarker changes differed between participants with CKD that developed during intensive versus standard SBP management. We hypothesized that biomarker changes among CKD case participants in the intensive

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group would represent benign changes in renal blood flow rather than intrinsic tissue injury.

METHODS

Study Design and Population

SPRINT was a randomized, controlled, open-label study of intensive (targeting <120 mm Hg) versus standard (targeting <140 mm Hg) SBP therapy in persons at high cardiovascular risk and without diabetes (4). A total of 9361 participants were enrolled between November 2010 and March 2013 at 102 sites in the United States and Puerto Rico. Among these participants, 2646 (28%) had baseline CKD, defined as an estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73 m^2 by the Modification of Diet in Renal Disease (MDRD) equation. Full details of the study protocols are published elsewhere (6).

Among participants without CKD at baseline, the SPRINT protocol defined incident CKD as a reduction in eGFR of 30% or more from baseline, on the basis of the MDRD equation, and an eGFR less than 60 mL/min/1.73 m^2 confirmed on 2 serial measurements at least 3 months apart. During a mean SPRINT follow-up of 3.26 years, incident CKD developed in 162 participants, 128 in the intensive and 34 in the standard group. Of the 162 incident CKD cases, 26.5% (n = 43) were diagnosed by the 1-year follow-up visit, whereas the remaining cases were diagnosed afterward. In the SPRINT Kidney Tubule Health ancillary project, we defined baseline CKD by using the CKD Epidemiology Collaboration equation with both cystatin C and creatinine (resulting in 2503 cases of baseline CKD), which accounts for the modest difference in the number of incident CKD cases in our study (n = 162) relative to the original publication (n = 154). For each incident CKD case participant, we used prevalent control sampling to select 1 matched control participant in whom CKD had not developed by the end of follow-up. We used a hierarchical matching scheme prioritizing the following factors, in order—randomization group, age (within 5 years), sex, race, and baseline eGFR (within 5 mL/min/1.73 m^2)—to account for these potential confounders. One control participant could not be matched on race after being matched on randomization group, eGFR, and age. The SPRINT Research Group approved the study protocol, which complies with the Declaration of Helsinki.

Measurement of Urinary Biomarkers of Kidney Damage

Our panel included the following 9 urinary biomarkers: albumin–creatinine ratio (ACR), interleukin-18 (IL-18), kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), monocyte chemoattractant protein-1 (MCP-1), anti–chitinase-3-like protein 1 (YKL-40), β_2-microglobulin (β_2M), α_1-microglobulin (α_1M), and uromodulin. These proteins have been well studied in kidney disease as direct markers of kidney damage, particularly in the settings of drug nephrotoxocity (7, 8) and acute kidney injury (9–11). In general, the biomarkers reflect glomerular injury (ACR), tubular injury and fibrosis (IL-18, KIM-1, NGAL, and MCP-1), tubular injury repair (YKL-40), proximal tubular dysfunction (β_2M and α_1M), and loop of Henle protein production (uromodulin).

We used urine specimens collected from CKD case and control participants at randomization (baseline) and at the 1-year follow-up visit. All specimens were stored continuously at −80 °C, without previous freeze–thaw, until measurement. Biomarkers were measured at the University of Vermont Laboratory for Clinical Biochemistry Research. Urinary biomarkers from both baseline and 1 year were measured contemporaneously to minimize the influence of laboratory drift. Biomarkers were measured simultaneously by using multiplex immunoassays from Meso Scale Discovery—except for α_1M, which was measured by using the BN II nephelometer assay (Siemens). Urinary creatinine was measured by using a Cobas c 311 clinical analyzer (Roche Diagnostics). Details regarding assay methods are shown in Appendix Tables 1 and 2 (available at Annals.org). Biomarker concentrations below the lower limit of detection were imputed with a value calculated by subtracting a small number from the limit of detection. Laboratory personnel were blinded to clinical information about the participants, and specimens were evaluated in random order. Except for urinary ACR and α_1M, all biomarkers were measured in duplicate, and results were averaged to improve precision.

Covariates

In addition to matching factors, covariates examined included baseline and 1-year SBP and diastolic blood pressure; number of antihypertensive medications used; angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker use; and baseline total and high-density lipoprotein cholesterol concentrations, body mass index, history of clinical cardiovascular disease, history of chronic heart failure, and smoking status. Covariates were selected on the basis of evidence from previous studies (12) and were collected as part of the parent trial. Our prespecified analytic plan included statistical adjustments for baseline covariates that differed between case and control participants within each intervention group.

Statistical Analysis

First, we summarized baseline characteristics in CKD case and matched control participants, stratified by intervention group, and tested for differences by using univariate conditional logistic regression models. Next, we compared baseline biomarker concentrations between case and matched control participants in our overall study sample, as well as stratified by intervention group, by fitting separate conditional logistic regression models for each biomarker, adjusting for baseline SBP and urinary creatinine levels. Because of their skewed distributions, biomarker concentrations were summarized by using geometric means and SEs. All models, except those for ACR, were adjusted for $\log_2$-transformed urinary creatinine concentrations to account for urine tonicity.

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We assessed the potential for bias due to the choice of prevalent control sampling at the end of follow-up rather than incidence density sampling. To account for these potential control selection biases, we used the semiparametric weighted estimator proposed by Landsman and Graubard (13). We then recalculated the associations between biomarkers at baseline and case–control status by using sample weights. Case participants were assigned a weight of 1, because all participants with incident CKD were included in the sample. Initial weights for control participants were calculated at each distinct CKD onset time as the inverse probability of selection after inclusion of subsequent case participants as potential control participants to simulate incidence density sampling. After rescaling these weights by dividing them by their mean value, we calibrated them to the predicted weights by using the matching factors. This process resulted in the model-adjusted weights for the logistic regression analyses.

Next, we compared 1-year changes in each biomarker between case and control participants, stratified by intervention group. We also compared 1-year changes among case participants in the intensive group versus those in the standard group. Although comparing control participants between intervention groups was not part of our prespecified analytic plan, these data were included for completeness. We examined 1-year changes by modeling the difference (1-year minus baseline) in $\log_2$-transformed biomarker concentrations by using linear mixed-effects models, adjusting for baseline SBP and both linear and quadratic terms for $\log_2$-transformed urinary creatinine concentrations. To account for the matched study design, we included case–control pair ID as a random effect and adjusted for the matching variables (age, race, sex, and eGFR). Only participants with complete data for case–control pairs were included in these analyses, which resulted in varying sample sizes across the biomarkers. Predicted (least-squares) means of the change in biomarker and associated 95% CIs were back transformed to estimate the mean ratio of 1-year to baseline levels. Associated Wald tests for differences in the predicted mean changes were used to test significance. The mean changes in each biomarker and the comparisons between groups were presented graphically for ease of communication. We used an interaction term to evaluate whether relative biomarker changes between case and control participants were statistically different between the intervention and standard groups.

P values less than 0.05 were considered statistically significant for all analyses without adjustment for multiple comparisons, because biomarkers were hypothesized to be mutually reinforcing rather than a series of independent tests (14). All analyses were performed with SAS, version 9.4 (SAS Institute), particularly the LOGISTIC procedure for conditional logistic regression analyses and the MIXED procedure for linear mixed-effects models.

Role of the Funding Source

This ancillary study was funded by the National Institute for Diabetes and Digestive and Kidney Diseases (NIDDK). The funding source had no involvement in study design, analysis, or production of the final manuscript.

RESULTS

After control participants were matched to incident CKD case participants on age, sex, race, baseline eGFR, and randomization group, additional baseline characteristics and cardiovascular risk factors were well balanced between the case participants and their matched controls (**Table 1**). The only exception was baseline SBP, which was significantly higher among the case than the control participants within both intervention groups. At 1 year after randomization, persons with incident CKD in both intervention groups had significantly higher serum creatinine concentrations and lower eGFRs than their respective matched controls. In addition, persons in the intensive group were prescribed greater numbers of antihypertensive medications, including angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers, at 1 year than those in the standard group. Within the intensive group, the CKD case participants were prescribed significantly more antihypertensive medications and had significantly lower diastolic blood pressures at 1 year than their matched controls.

At baseline, the 9 kidney biomarkers were only weakly intercorrelated (**Appendix Table 3**, available at Annals.org); moderate correlations were observed for only 2 biomarker pairs (α_1M and β_2M [$r = 0.53$], and KIM-1 and MCP-1 [$r = 0.49$]), whereas the other pairwise comparisons showed weak associations. We evaluated the association between baseline biomarker concentrations and incident CKD case status, adjusting for baseline SBP and urinary creatinine levels (**Table 2**). Higher ACR and urinary KIM-1 and MCP-1 concentrations were each significantly associated with greater odds of incident CKD. These results were not affected by reweighting of the matched control participants to the broader cohort of non–case participants (**Appendix Table 4**, available at Annals.org). In stratifying by intervention group, we observed similar effect sizes in each group, although the associations were not statistically significant in the standard group (**Appendix Table 5**, available at Annals.org).

The 1-year biomarker concentrations among case and control participants in each intervention group are presented in **Appendix Table 6** (available at Annals.org). We compared the 1-year relative changes in each biomarker between case and control participants and found that persons with incident CKD in the intensive group had relative declines in ACR, IL-18, YKL-40, and uromodulin that differed significantly from the relative changes in matched control participants (**Figure**). In the intensive group, the 1-year relative changes in KIM-1, NGAL, β_2M, and α_1M levels did not differ significantly between case and control participants, and MCP-1 rel-

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Table 1. Characteristics of Incident CKD Case Participants and Matched Control Participants in SPRINT at Baseline and Year 1, by Randomization Group*

Characteristic	Intensive Group (n = 128 Pairs)			Standard Group (n = 34 Pairs)		
	Case Participants	Control Participants	*P* Value†	Case Participants	Control Participants	*P* Value†
Baseline						
Mean age (SD), *y*	67 (9)	67 (9)	‡	68 (8)	68 (9)	‡
Female, *n (%)*	45 (35)	45 (35)	‡	14 (41)	14 (41)	‡
Race, *n (%)*			‡			‡
African American	41 (32)	42 (33)		13 (38)	13 (38)	
Caucasian	71 (56)	67 (52)		18 (53)	18 (53)	
Hispanic/other	16 (13)	19 (15)		3 (9)	3 (9)	
Mean eGFR (SD), *mL/min/1.73 m²*			‡			‡
MDRD study equation	80 (15)	79 (17)		75 (9)	74 (12)	
CKD-EPI cystatin C equation	80 (14)	80 (14)		77 (12)	77 (12)	
Mean blood pressure (SD), *mm Hg*						
Systolic	146 (19)	140 (15)	0.007	151 (14)	140 (15)	0.009
Diastolic	80 (14)	80 (11)	0.92	80 (13)	78 (11)	0.34
Mean serum creatinine level (SD)			0.17			0.42
μmol/L	83 (16)	84 (17)		86 (14)	88 (16)	
mg/dL	0.94 (0.18)	0.95 (0.19)		0.97 (0.16)	0.99 (0.18)	
Mean total cholesterol level (SD)			0.53			0.80
mmol/L	5.05 (1.22)	4.97 (1.04)		5.00 (1.14)	5.05 (0.83)	
mg/dL	195 (47)	192 (40)		193 (44)	195 (32)	
Mean HDL cholesterol level (SD)			0.26			0.67
mmol/L	1.40 (0.41)	1.35 (0.36)		1.48 (0.39)	1.53 (0.36)	
mg/dL	54 (16)	52 (14)		57 (15)	59 (14)	
Mean body mass index (SD), *kg/m²*	30 (6)	31 (6)	0.66	28 (5)	30 (6)	0.40
History of clinical CVD, *n (%)*	24 (19)	24 (19)	1.00	7 (21)	5 (15)	0.57
History of CHF, *n (%)*	2 (1.6)	2 (1.6)	1.00	0 (0)	0 (0)	–
ACE inhibitor or ARB use, *n (%)*	54 (42)	51 (40)	0.71	10 (29)	10 (29)	1.00
Mean antihypertensives (SD), *n*	1.8 (1.1)	1.7 (1.1)	0.52	1.7 (1.0)	1.8 (1.1)	0.71
Current smoker, *n (%)*	18 (14)	15 (12)	0.58	7 (21)	3 (9)	0.18
Year 1						
Serum creatinine level§						
Mean (SD)			<0.001			0.006
μmol/L	111 (24)	88 (18)		119 (73)	88 (17)	
mg/dL	1.25 (0.27)	0.99 (0.20)		1.35 (0.83)	0.99 (0.19)	
Mean change from baseline (SD)			<0.001			0.008
μmol/L	27 (19)	4 (11)		35 (73)	0.88 (8)	
mg/dL	0.31 (0.22)	0.04 (0.12)		0.39 (0.83)	0.01 (0.09)	
Mean eGFR by MDRD study equation (SD), *mL/min/1.73 m²*§	58 (12)	75 (15)	<0.001	59 (19)	74 (15)	0.004
Mean blood pressure (SD), *mm Hg*‖						
Systolic	119 (14)	121 (12)	0.25	140 (15)	133 (13)	0.077
Diastolic	66 (11)	70 (10)	0.002	76 (13)	76 (9)	0.74
ACE inhibitor or ARB use, *n (%)*‖	114 (92)	92 (74)	<0.001	25 (74)	18 (53)	0.083
Mean antihypertensives (SD), *n*‖	3.3 (1.2)	2.7 (0.9)	<0.001	2.3 (1.1)	1.9 (1.4)	0.19

ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; CHF = congestive heart failure; CKD = chronic kidney disease; CVD = cardiovascular disease; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; MDRD = Modification of Diet in Renal Disease; SPRINT = Systolic Blood Pressure Intervention Trial.
* Percentages may not sum to 100 due to rounding.
† Calculated using a univariate conditional logistic regression model.
‡ Matching factor; no test was performed.
§ n = 123 pairs for the intensive group and 33 pairs for the standard group.
‖ n = 124 pairs for the intensive group.

atively increased in case participants. In the standard group, no significant differences in 1-year relative changes were observed between case and control participants for any biomarker. We tested for interactions comparing the case–control differences between the 2 intervention groups and found none to be statistically significant (**Appendix Table 7**, available at Annals.org).

At 1 year, the case participants in the standard group had higher values of all 9 biomarkers compared with those in the intensive group, but the difference was statistically significant only for YKL-40 (P = 0.01) (**Appendix Table 6**). We compared the 1-year relative changes in each biomarker between CKD case participants in the intensive group and those in the standard group, adjusting for baseline SBP and urinary creatinine levels, and found significant differences for ACR, β_2M, α_1M, YKL-40, and uromodulin (**Figure**). Among case participants, values of all 5 of these biomarkers were lower at 1 year in the intensive group and were either higher or unchanged in the standard group.

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To determine whether use of renin–angiotensin-aldosterone system inhibitors influenced the decrease in ACR, we stratified the case participants in the intensive group by users (n = 90) and nonusers (n = 19) of angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers during follow-up until CKD diagnosis. The median reduction in ACR was near unity among these 2 groups (−33% [interquartile range, −66% to 25%] vs. −46% [interquartile range, −86% to 41%], respectively). Among case participants in the standard group, the change in ACR differed substantially by use of these medications: −16% (interquartile range, −68% to 44%) among 23 users versus 85% (interquartile range, 54% to 159%) among 10 nonusers.

DISCUSSION

In this case–control study nested within a trial of persons with hypertension and without CKD at baseline, we used a diverse panel of urinary biomarkers to characterize intrinsic kidney damage among incident CKD case participants in the setting of intensive SBP reduction to less than 120 mm Hg. Our findings demonstrate that despite substantial eGFR declines in participants who developed CKD during SPRINT's first year, incident CKD cases in the setting of intensive blood pressure lowering were not characterized by intrinsic kidney damage; rather, these participants had less injury overall than matched control participants without CKD. In contrast, incident CKD case participants in the standard study group had relatively higher levels of 5 of the 9 biomarkers we evaluated compared with those in the intensive group. These data support the notion that eGFR declines in the setting of intensive blood pressure lowering are generally manifestations of benign changes in renal blood flow.

Although participants did not have clinically diagnosed CKD at baseline, we found that baseline urinary ACR and urinary KIM-1 and MCP-1 concentrations were associated with incident CKD during follow-up. Compared with the baseline characteristics of control participants, those of matched participants with future incident CKD otherwise were distinguished only by higher SBP. These findings suggest that urinary biomarkers may identify persons with subclinical kidney injury who may be at increased risk for subsequent eGFR changes. These findings are consistent with studies in other settings that reported associations of ACR, KIM-1, and MCP-1 with incident CKD and kidney function decline (15–17).

Our comparisons of 1-year biomarker changes also are consistent with previous clinical trials reporting that eGFR declines have divergent associations with cardiovascular disease and mortality, depending on whether they occur during intensive versus standard SBP management (18–22). For example, a post hoc analysis of the SPS3 (Secondary Prevention of Small Subcortical Strokes) trial found that early eGFR declines within the intensive SBP reduction group were not associated with adverse cardiovascular outcomes, in contrast to eGFR declines within the standard care group, which portended greater cardiovascular risk (23). Likewise, analyses of the MDRD and AASK (African American Study of Kidney Disease and Hypertension) trials found that participants randomly assigned to more intensive SBP lowering had initial elevations in creatinine levels, but lower long-term mortality risk, relative to participants assigned to less intensive management (24, 25). These investigators hypothesized that blood pressure treatment decreases renal blood flow and reduces hydrostatic pressure gradients across the glomerular capillaries, in turn benignly decreasing creatinine clearance and eGFR. Building on these findings, our results suggest that blood pressure lowering may even alleviate hypertensive kidney injury, regardless of changes in serum creatinine levels.

Although we measured a panel of biomarkers to broadly characterize kidney damage, highlighting the unique physiologic domains these biomarkers represent is important. For example, serum albumin, α_1M,

Table 2. Comparison of Baseline Biomarker Concentrations in Incident CKD Case Participants and Matched Control Participants in Both Randomization Groups of SPRINT Combined

Baseline Urinary Biomarker Concentration	Pairs, *n*	Geometric Mean (±SE)		OR (95% CI)*	*P* Value
		Case Participants	Control Participants		
ACR, *mg/g*	150	18.2 ± 1.9	10.5 ± 0.85	1.50 (1.14–1.98)	0.004
IL-18, *pg/mL*	158	36.9 ± 2.7	34.4 ± 2.5	1.30 (0.93–1.79)	0.12
KIM-1, *pg/mL*	158	595.9 ± 59.7	546.2 ± 55.8	1.51 (1.05–2.17)	0.027
NGAL, *ng/mL*	157	25.9 ± 2.5	28.1 ± 2.6	0.96 (0.71–1.30)	0.80
MCP-1, *pg/mL*	158	160.2 ± 13.4	148.4 ± 13.5	1.70 (1.13–2.56)	0.012
YKL-40, *pg/mL*	158	660.8 ± 68.8	590.8 ± 53.3	1.18 (0.90–1.56)	0.23
β_2M, *mg/L*	154	0.078 ± 0.009	0.077 ± 0.007	0.95 (0.74–1.22)	0.68
α_1M, *mg/L*	157	4.98 ± 0.61	4.14 ± 0.52	1.18 (0.90–1.56)	0.23
Uromodulin, *μg/mL*	157	9.95 ± 0.58	10.34 ± 0.67	1.04 (0.77–1.40)	0.80

α_1M = α_1-microglobulin; ACR = albumin–creatinine ratio; β_2M = β_2-microglobulin; CKD = chronic kidney disease; IL-18 = interleukin-18; KIM-1 = kidney injury molecule-1; MCP-1 = monocyte chemoattractant protein-1; NGAL = neutrophil gelatinase-associated lipocalin; OR = odds ratio; SPRINT = Systolic Blood Pressure Intervention Trial; YKL-40 = anti–chitinase-3-like protein 1.
* Per SD increase in $\log_2$-transformed biomarker concentrations. All models except that for ACR were adjusted for $\log_2$-transformed urinary creatinine concentrations. All models were adjusted for baseline systolic blood pressure.

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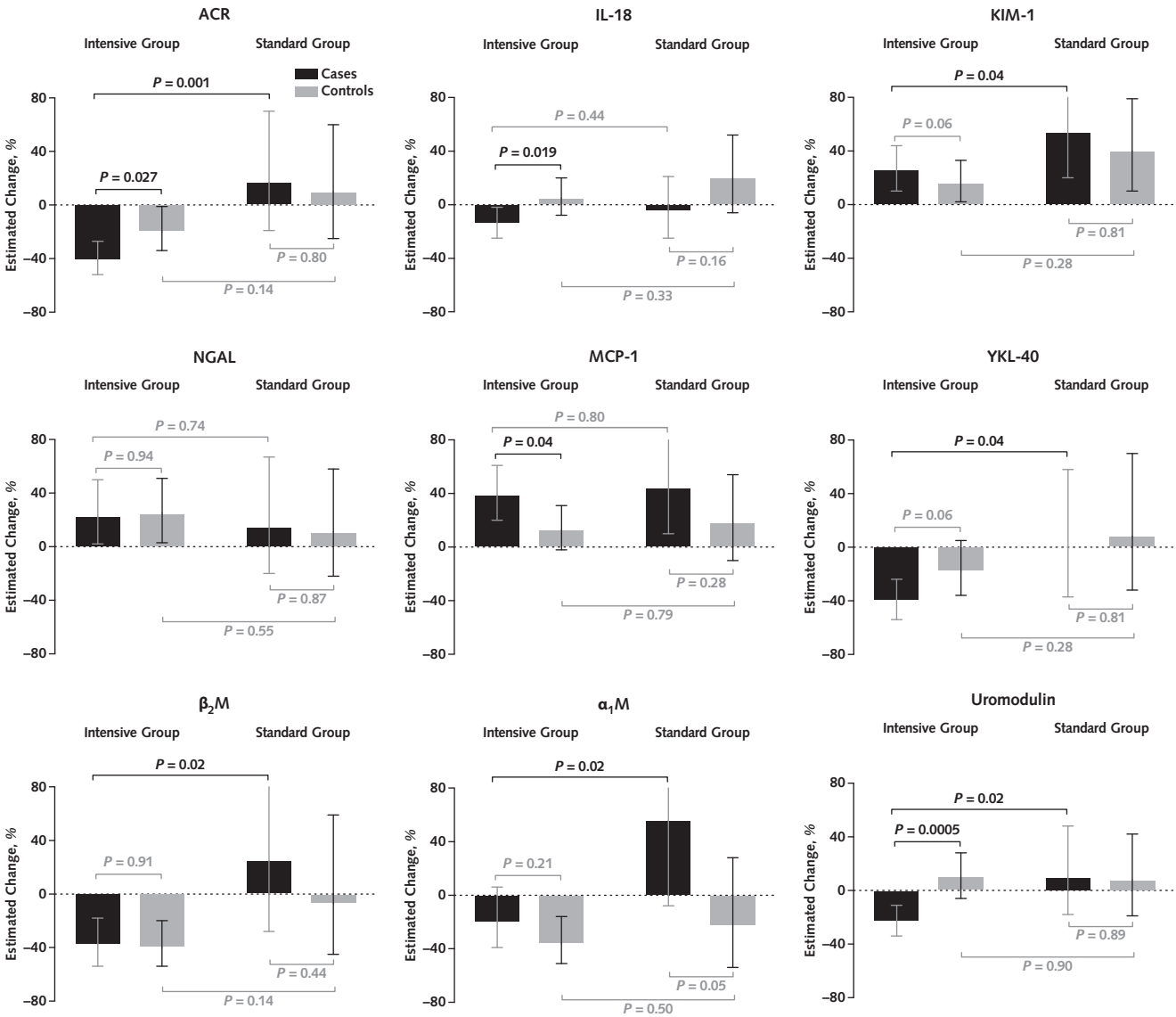
Figure. One-year percentage changes in levels of 9 urinary biomarkers among incident CKD case participants (*black bars*) and matched control participants without CKD (*gray bars*), stratified by randomization group, in SPRINT.



The intensive group had 128 case participants, and the standard group had 34. In each intervention group, 1 control participant was matched to each case participant on age (within 5 y), sex, race, and baseline eGFR (within 5 mL/min/1.73 m^2). The 1-y changes were estimated from separate linear mixed models for each biomarker, with adjustment for $\log_2$-transformed urinary creatinine levels and systolic blood pressure. Error bars denote the 95% CIs. The *y*-axes are truncated at ±80%. The 95% CI upper bounds for several biomarkers among case participants in the standard group were truncated: The 95% CI upper bounds of 1-y changes in KIM-1, MCP-1, β_2M, and α_1M extend to 97%, 89%, 114%, and 163%, respectively. Brackets with *P* values represent comparisons of 1-y changes between respective groups at bracket tails. *P* values less than 0.05 were considered statistically significant. The numerical values of the 1-y change and 95% CIs are presented in **Appendix Table 6**. The dotted lines represent baseline. ACR = albumin–creatinine ratio; α_1M = α_1-microglobulin; β_2M = β_2-microglobulin; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; IL-18 = interleukin-18; KIM-1 = kidney injury molecule-1; MCP-1 = monocyte chemoattractant protein-1; NGAL = neutrophil gelatinase-associated lipocalin; SPRINT = Systolic Blood Pressure Intervention Trial; YKL-40 = anti–chitinase-3-like protein 1.

and β_2M are systemic proteins filtered at the glomerulus and reabsorbed by the proximal tubules. Urinary concentrations of these proteins decreased significantly in the case participants in the intensive group versus those in the standard group at 1 year (26–28). These relative decreases among case participants in the intensive group may be a direct reflection of reduced renal blood flow and glomerular filtration of these proteins in the setting of intensive blood pressure lowering, independent of renin–angiotensin–aldosterone system inhibitor use. In contrast, the relative elevations among case participants in the standard group may represent impaired tubular absorption of these proteins, a manifestation of true intrinsic kidney damage.

The other 6 biomarkers are produced largely within the kidney and released into urine, and 2 of these biomarkers differed significantly in the compari-

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sons of case participants between the 2 randomization groups: YKL-40 and uromodulin decreased in the case participants in the intensive group and remained unaltered or increased in those in the standard group. YKL-40 is produced largely by kidney tubular cells and signifies kidney tubular injury and repair (29, 30). The relative decreases in YKL-40 levels suggest that participants with incident CKD in the setting of intensive blood pressure lowering had less tubular damage than matched control participants and less than case participants in the standard group. However, this pattern was not observed for other traditional markers of tubular injury (for example, IL-18, KIM-1, NGAL, and MCP-1).

The relative decreases in uromodulin levels among case participants in the intensive group that differed significantly from elevations among case participants in the standard group were unexpected. Uromodulin, which is produced in the thick ascending limb of the loop of Henle and the distal tubule, is believed to protect against CKD. When measured at a single time point, higher uromodulin levels were associated with less CKD progression in a previous study (31), although baseline uromodulin levels were not associated with the odds of incident CKD in our current study. We expected to observe relative elevations in uromodulin levels among case participants in the intensive group. However, dynamic changes in uromodulin were not evaluated in previous studies. A possibility exists that lower renal blood flow may lead to a decreased requirement for uromodulin production or secretion. Nonetheless, we acknowledge that this finding may be discrepant with our overall hypotheses. Future studies are necessary to examine the dynamic changes of uromodulin in response to treatments that influence kidney health and its association with outcomes.

Strengths of this study include the matched case–control design in a randomized trial setting, which minimized potential confounding. The SPRINT study involved 102 centers across the United States and Puerto Rico, closely followed the participants, and collected creatinine measurements and longitudinal urine samples frequently, which provided a unique opportunity to investigate kidney changes in the context of intensive blood pressure reduction.

We also acknowledge several important limitations. Although the biomarker results exhibit a consistent pattern overall, we cannot explain the biological mechanisms of some of the changes specifically. For example, KIM-1 and NGAL were significantly increased to a similar magnitude in comparisons of case versus control participants. We are uncertain why these biomarkers would increase during follow-up, and to our knowledge, no previous study measured them repeatedly in a similar cohort. In addition, our study lacked power to compare case and control participants who received standard therapy, because only 34 incident CKD cases occurred in this group. This may explain the absence of significant differences in baseline biomarkers in case participants in the standard group as well as significant differences in the 1-year changes between case and control participants in this group. Because we measured biomarkers only at baseline and at year 1, we do not have biomarker concentrations from the precise time of CKD diagnosis. Most incident CKD end points occurred after the 1-year biomarker measurements; thus, concentrations may have been different if measured at the time of incident CKD diagnosis. However, the mean eGFR decline at 1 year was significantly greater among case than control participants in the intensive group (20 vs. 4 mL/min/1.73 m^2) and in the standard group (16 vs. 0 mL/min/1.73 m^2), so the eGFR had already decreased substantially among the incident CKD case participants at the time of biomarker measurement. If the substantial eGFR declines found among case participants in the intervention group had been associated with intrinsic kidney injury, we should have detected elevations in biomarker concentrations at 1 year. Finally, our findings may not be generalizable to all persons with hypertension, particularly those with diabetes or proteinuria greater than 1 g/d, who were excluded from SPRINT.

Two important and distinct roles for urinary biomarkers emerge from our findings: identifying persons susceptible to CKD by using the baseline concentrations and using changes in the biomarkers to evaluate longitudinal changes in kidney health. The biomarkers that provided baseline prediction of CKD, a potential proxy of kidney reserve, were not the same as those that reflect responses to blood pressure changes. An eventual biomarker panel in clinical care will warrant a collection of proteins that achieve both these objectives. Future work should investigate whether urinary biomarkers can prognosticate and distinguish persons with true tubular injury accompanying eGFR changes in CKD, similar to the use of these biomarkers in acute kidney injury (32, 33).

In conclusion, the perception of a tradeoff between cardiovascular benefits and kidney harms during intensive blood pressure lowering may be misguided. We found that participants with incident CKD in the setting of intensive SBP treatment did not have elevations in kidney damage biomarkers in the first year of treatment; instead, they had relative declines in several biomarkers compared with both matched control and CKD case participants in the standard group. These findings suggest that eGFR reductions observed in the setting of intensive blood pressure lowering are mostly hemodynamic in nature, even among persons who may be inappropriately labeled as having a new diagnosis of CKD. We also demonstrate the limitations of serum creatinine and the potential utility of urinary biomarkers for monitoring kidney health during hypertension treatment, when changes in renal blood flow may confound the clinical interpretation of changes in serum creatinine levels. Ultimately, these findings, in conjunction with the lower cardiovascular disease and mortality risk reported in SPRINT, should reassure clinicians who embark on evidence-based intensive blood pressure lowering for their patients.

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Note: All components of the SPRINT study protocol were designed and implemented by the investigators. The investigative team collected, analyzed, and interpreted the data. All aspects of manuscript writing and revision were carried out by the coauthors.

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Reproducible Research Statement: *Study protocol:* See the **Supplement** (available at Annals.org). *Statistical code:* Available from Mr. Craven (e-mail, tcraven@wakehealth.edu). *Data set:* Available from SPRINT Coordinating Center (e-mail, pnance@wakehealth.edu).

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Appendix Table 1. Urinary Biomarker Assay Information for MSD Multiplex Panels

Assays	Dilution	Standard Range	Minimum Detectable Concentration	Manufacturer-Defined "Normal" Range
Albumin	1:251	0.0488-200 ng/mL	0.141 ng/mL	Undetectable-48 757 ng/mL
IL-18	1:10	0.64-10 000 pg/mL	0.161 pg/mL	NA
KIM-1	1:10	1.28-20 000 pg/mL	0.19 pg/mL	NA
NGAL	1:251	0.0024-10.00 ng/mL	0.0029 ng/mL	4.20-225.00 ng/mL
MCP-1	1:10	0.64-10 000 pg/mL	0.071 pg/mL	1.95-1173 pg/mL
YKL-40	1:10	3.20-50 000 pg/mL	0.346 pg/mL	NA
β_2M	1:251	0.0049-20.00 ng/mL	0.0061 ng/mL	38.00-1130.00 ng/mL
Uromodulin	1:251	0.0244-100.00 ng/mL	0.026 ng/mL	347.00-7846.00 ng/mL

β_2M = β_2-microglobulin; CKD = chronic kidney disease; IL-18 = interleukin-18; KIM-1 = kidney injury molecule-1; MCP-1 = monocyte chemoattractant protein-1; MSD = Meso Scale Discovery; NA = not available; NGAL = neutrophil gelatinase-associated lipocalin; YKL-40 = anti–chitinase-3-like protein 1.

Appendix Table 2. Urinary Biomarker Assay Information for Non-MSD Assays

Assay	Instrument	Method	Detectable Range
α_1M	BN II nephelometer	Immunochemical	5-80 mg/L
Creatinine	Cobas c 311	Enzymatic	1.1-610 mg/dL

α_1M = α_1-microglobulin; MSD = Meso Scale Discovery.

Appendix Table 3. Spearman Correlations of Baseline Biomarker Concentrations

Variable	ACR	α_1M	β_2M	Uromodulin	Il-18	KIM-1	MCP-1	YKL-40	NGAL
ACR	1								
α_1M	0.36	1							
β_2M	0.27	0.53	1						
Uromodulin	0.01	0.16	0.21	1					
IL-18	0.23	0.21	0.09	−0.08	1				
KIM-1	0.25	0.03	0.08	−0.003	0.23	1			
MCP-1	0.27	0.05	0.07	−0.01	0.24	0.49	1		
YKL-40	0.21	0.08	0.28	−0.04	0.36	0.11	0.17	1	
NGAL	0.19	0.03	0.19	0.08	0.41	0.21	0.20	0.43	1

ACR = albumin–creatinine ratio; α_1M = α_1-microglobulin; β_2M = β_2-microglobulin; IL-18 = interleukin-18; KIM-1 = kidney injury molecule-1; MCP-1 = monocyte chemoattractant protein-1; NGAL = neutrophil gelatinase-associated lipocalin; YKL-40 = anti–chitinase-3-like protein 1.

Appendix Table 4. Baseline Biomarker Concentrations Among Incident CKD Case Participants and Matched Control Participants in Both Randomization Groups of SPRINT Combined: Comparison of Results of Unweighted and Weighted LR Analyses

Biomarker	Pairs, *n*	Unweighted LR Analysis*		Weighted LR Analysis	
		OR (95% CI)†	*P* Value	OR (95% CI)†	*P* Value
ACR, *mg/g*	150	1.50 (1.14-1.98)	0.004	1.58 (1.16-2.15)	0.004
IL-18, *pg/mL*	158	1.30 (0.93-1.79)	0.12	1.29 (0.94-1.77)	0.11
KIM-1, *pg/mL*	158	1.51 (1.05-2.17)	0.027	1.54 (0.99-2.40)	0.058
NGAL, *ng/mL*	157	0.96 (0.71-1.30)	0.80	0.89 (0.67-1.19)	0.43
MCP-1, *pg/mL*	158	1.70 (1.13-2.56)	0.012	1.70 (1.10-2.62)	0.018
YKL-40, *pg/mL*	158	1.18 (0.90-1.56)	0.23	1.10 (0.86-1.42)	0.44
β_2M, *ng/mL*	154	0.95 (0.74-1.22)	0.68	0.95 (0.74-1.21)	0.66
α_1M, *mg/L*	157	1.18 (0.90-1.56)	0.23	1.14 (0.84-1.53)	0.40
Uromodulin, *µg/mL*	157	1.04 (0.77-1.40)	0.80	0.91 (0.66-1.25)	0.55

ACR = albumin–creatinine ratio; α_1M = α_1-microglobulin; β_2M = β_2-microglobulin; CKD = chronic kidney disease; IL-18 = interleukin-18; KIM-1 = kidney injury molecule-1; LR = logistic regression; MCP-1 = monocyte chemoattractant protein-1; NGAL = neutrophil gelatinase-associated lipocalin; OR = odds ratio; SPRINT = Systolic Blood Pressure Intervention Trial; YKL-40 = anti–chitinase-3-like protein 1.

* See Table 2.

† Per SD increase in $\log_2$-transformed biomarker concentrations. All models except for ACR adjust for $\log_2$-transformed urinary creatinine concentrations. All models adjust for baseline systolic blood pressure.

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Appendix Table 5. Comparison of Baseline Biomarker Concentrations Among Incident CKD Case Participants and Matched Control Participants in SPRINT, by Randomization Group

Biomarker	Intensive BP Group					Standard BP Group				
	Pairs, *n*	Geometric Mean (±SE)		OR (95% CI)*	*P* Value	Pairs, *n*	Geometric Mean (±SE)		OR (95% CI)*	*P* Value
		Case Participants	Control Participants				Case Participants	Control Participants		
ACR, *mg/g*	118	19.3 ± 2.4	10.6 ± 1.01	1.55 (1.13-2.11)	0.006	32	14.9 ± 2.8	10.2 ± 1.4	1.39 (0.67-2.88)	0.38
IL-18, *pg/mL*	124	37.0 ± 3.3	36.6 ± 3.1	1.20 (0.85-1.69)	0.30	34	36.5 ± 4.2	27.7 ± 3.8	2.65 (0.85-8.24)	0.092
KIM-1, *pg/mL*	124	621.3 ± 72.4	601.0 ± 70.8	1.47 (0.98-2.20)	0.062	34	511.8 ± 97.9	384.8 ± 74.4	1.58 (0.66-3.79)	0.30
NGAL, *ng/mL*	124	25.3 ± 2.7	28.5 ± 3.1	0.96 (0.69-1.33)	0.80	33	28.3 ± 6.2	26.3 ± 4.7	0.90 (0.40-2.00)	0.79
MCP-1, *pg/mL*	124	163.3 ± 15.2	154.7 ± 16.6	1.78 (1.12-2.83)	0.014	34	149.2 ± 28.3	127.5 ± 20.4	1.09 (0.41-2.89)	0.87
YKL-40, *pg/mL*	124	641.6 ± 68.6	627.1 ± 66.1	1.13 (0.84-1.53)	0.41	34	735.9 ± 213.2	475.2 ± 78.3	1.36 (0.58-3.20)	0.48
β_2M, *ng/mL*	121	78.5 ± 9.5	83.0 ± 9.1	0.89 (0.66-1.20)	0.45	33	77.7 ± 20.0	58.5 ± 10.4	1.17 (0.70-1.93)	0.55
α_1M, *mg/L*	124	5.12 ± 0.69	4.51 ± 0.64	1.15 (0.84-1.58)	0.39	33	4.48 ± 1.24	3.01 ± 0.81	1.45 (0.78-2.70)	0.24
Uromodulin, *μg/mL*	124	10.3 ± 0.70	10.6 ± 0.83	1.10 (0.79-1.52)	0.58	33	8.8 ± 1.0	9.4 ± 0.80	0.84 (0.41-1.73)	0.63

ACR = albumin–creatinine ratio; α_1M = α_1-microglobulin; β_2M = β_2-microglobulin; BP = blood pressure; CKD = chronic kidney disease; IL-18 = interleukin-18; KIM-1 = kidney injury molecule-1; MCP-1 = monocyte chemoattractant protein-1; NGAL = neutrophil gelatinase-associated lipocalin; OR = odds ratio; SPRINT = Systolic Blood Pressure Intervention Trial; YKL-40 = anti–chitinase-3-like protein 1.
* Based on SD increase in $\log_2$-transformed biomarker concentrations. All models except those for ACR adjust for $\log_2$-transformed urinary creatinine concentrations. All models adjust for baseline systolic BP.

Appendix Table 6. One-Year Biomarker Concentrations Among Incident CKD Case Participants and Matched Control Participants in SPRINT, Overall and by Randomization Group

Biomarker	Intensive BP Group			Standard BP Group			Overall		
	Pairs, *n*	Geometric Mean (±SE)		Pairs, *n*	Geometric Mean (±SE)		Pairs, *n*	Geometric Mean (±SE)	
		Case Participants	Control Participants		Case Participants	Control Participants		Case Participants	Control Participants
ACR, *mg/g*	99	11.2 ± 1.3	9.3 ± 1.0	30	13.3 ± 3.0	11.1 ± 2.2	129	11.6 ± 1.2	9.7 ± 0.9
IL-18, *pg/mL*	121	33.6 ± 2.9	36.9 ± 3.3	34	43.0 ± 6.6	34.5 ± 4.9	155	35.5 ± 2.7	36.4 ± 2.8
KIM-1, *pg/mL*	121	819.2 ± 88.3	634.9 ± 76.4	34	977.3 ± 165.1	560.8 ± 93.2	155	851.5 ± 78.3	617.9 ± 62.2
NGAL, *ng/mL*	120	32.4 ± 3.5	32.8 ± 3.9	32	40.8 ± 8.5	29.6 ± 6.2	152	34.1 ± 3.2	32.1 ± 3.3
MCP-1, *pg/mL*	121	244.8 ± 23.5	162.6 ± 18.7	34	275.8 ± 48.6	152.6 ± 27.3	155	251.3 ± 21.2	160.4 ± 15.7
YKL-40, *pg/mL*	121	427.1 ± 59.3	506.3 ± 60.9	34	948.8 ± 295.0	610.3 ± 115.2	155	508.9 ± 66.3	527.5 ± 54.1
β_2M, *ng/mL*	110	56.5 ± 9.0	56.4 ± 6.3	29	92.9 ± 24.5	58.7 ± 14.1	139	62.7 ± 8.6	56.9 ± 5.8
α_1M, *mg/L*	120	4.14 ± 0.64	2.92 ± 0.42	32	7.52 ± 2.00	2.52 ± 0.71	152	4.70 ± 0.64	2.83 ± 0.36
Uromodulin, *μg/mL*	119	8.4 ± 0.54	11.1 ± 0.70	32	10.1 ± 1.22	9.8 ± 1.02	151	8.8 ± 0.49	10.8 ± 0.59

ACR = albumin–creatinine ratio; α_1M = α_1-microglobulin; β_2M = β_2-microglobulin; BP = blood pressure; CKD = chronic kidney disease; IL-18 = interleukin-18; KIM-1 = kidney injury molecule-1; MCP-1 = monocyte chemoattractant protein-1; NGAL = neutrophil gelatinase-associated lipocalin; SPRINT = Systolic Blood Pressure Intervention Trial; YKL-40 = anti–chitinase-3-like protein 1.

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Appendix Table 7. Comparisons of 1-Year Changes in Biomarker Concentrations Among Incident CKD Case Participants and Matched Control Participants in SPRINT, by Randomization Group

Biomarker	Intensive Group			Standard Group			*P* Value				
	Pairs, *n*	Change (95% CI), %*		Pairs, *n*	Change (95% CI), %*		Case Participants vs. Case Participants	Case Participants vs. Control Participants			Control Participants vs. Control Participants
		Case Participants	Control Participants		Case Participants	Control Participants		Intensive Group	Standard Group	Interaction	
ACR	99	−41 (−52 to −27)	−20 (−34 to −1)	30	17 (−19 to 70)	10 (−25 to 60)	0.001	0.027	0.80	0.20	0.14
IL-18	121	−14 (−25 to −2)	5 (−8 to 20)	34	−5 (−25 to 21)	20 (−6 to 52)	0.44	0.019	0.16	0.89	0.33
KIM-1	121	26 (10 to 44)	16 (2 to 33)	34	54 (20 to 97)	40 (10 to 79)	0.14	0.37	0.58	0.94	0.17
NGAL	120	23 (2 to 50)	25 (3 to 51)	32	15 (−20 to 67)	11 (−22 to 58)	0.74	0.94	0.87	0.85	0.55
MCP-1	121	39 (20 to 61)	13 (−2 to 31)	34	44 (10 to 89)	18 (−10 to 54)	0.80	0.04	0.28	0.99	0.79
YKL-40	121	−40 (−54 to −24)	−18 (−36 to 5)	34	0 (−37 to 58)	8 (−32 to 70)	0.04	0.06	0.81	0.49	0.28
β_2M	110	−38 (−54 to −18)	−40 (−54 to −20)	29	25 (−28 to 114)	−7 (−45 to 59)	0.02	0.91	0.44	0.52	0.14
α_1M	120	−20 (−39 to 6)	−36 (−51 to −16)	32	56 (−8 to 163)	−23 (−54 to 28)	0.02	0.21	0.05	0.24	0.50
Uromodulin	119	−23 (−34 to −11)	10 (−6 to 28)	32	10 (−18 to 48)	8 (−19 to 42)	0.02	0.0005	0.89	0.08	0.90

ACR = albumin–creatinine ratio; α_1M = α_1-microglobulin; β_2M = β_2-microglobulin; CKD = chronic kidney disease; IL-18 = interleukin-18; KIM-1 = kidney injury molecule-1; MCP-1 = monocyte chemoattractant protein-1; NGAL = neutrophil gelatinase-associated lipocalin; SPRINT = Systolic Blood Pressure Intervention Trial; YKL-40 = anti–chitinase-3-like protein 1.

* Changes estimated from linear mixed models with $\log_2$ (biomarker) as the outcome. All models except those for ACR adjust for $\log_2$-transformed urinary creatinine concentrations. All models adjust for baseline systolic blood pressure.

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Creatinine Bump Following Antihypertensive Therapy
Think Before You Act

George L. Bakris, Rajiv Agarwal

See related article, pp 1337–1344

A small subset of people manifests significant increases in their serum creatinine when blood pressure (BP) is reduced to guideline levels. In this issue of the journal, Collard et al[1] evaluate whether the extent of increase in serum creatinine affected the combined end point of all-cause mortality, major cardiovascular events, and renal outcomes in the ACCORD-BP trial (Action to Control Cardiovascular Risk in Diabetes Blood Pressure). Before we discuss this study, it is essential to understand why this creatinine increase after BP reduction occurs.

The kidney is a regulatory organ driven by BP and can autoregulate its internal pressure within a certain range of systemic BPs between 90 and 180 mm Hg when the kidney is healthy.[2] However, during disease, responses can become maladaptive. This maladaptive autoregulatory response manifests itself as more substantial than expected increases in serum creatinine when substantial reductions in BP occur. These increase in serum creatinine, however, are generally not in the range of acute kidney injury (AKI), that is, >50% increases from the baseline, but can be as high as 30% to 35% after BP reduction.[3]

Given that the dysfunction of autoregulation plays a significant part in allowing changes in creatinine to occur it is essential to understand the provenance of this problem. The most common contributors of impaired autoregulation are antihypertensive medications specifically, calcium antagonists and loop diuretics with partial impairment by renin-angiotensin system (RAS) inhibitors.[4] Most patients with diabetes mellitus or chronic kidney disease (CKD) require multiple medications—from at least 2 different classes—to achieve lower BP goals per guidelines thus, exposing some patients to increases in serum creatinine. Poor vascular compliance, identified clinically by pulse pressures of >70 mm Hg, is associated with impaired intrarenal flow, in part, related to lower levels of nitric oxide and associated with reduced kidney function.[5] Moreover, tubuloglomerular feedback is also not fully functional when kidney function is reduced.[6] Hence, normal myogenic reflexes needed to maintain glomerular filtration rate are reduced. Thus, there are many reasons to expect more significant changes in serum creatinine in people with more advanced CKD or preexisting vascular disease.

Taken together, these changes in the physiological function of the kidney explain why the increment in serum creatinine decline is related to the magnitude of systolic BP reduction and is magnified by RAS blockers. Hence, it would be misleading and inappropriate to view a hemodynamic resetting of kidney function as injury.

Many large epidemiological studies, as well as some smaller studies, demonstrate that increases in serum creatinine up to 30%, within a few weeks after initiation or intensification of antihypertensive therapy, are not associated with adverse renal outcomes or faster declines in kidney function.[7–9] The renal outcome defined by Collard et al[1] of changes in serum creatinine in the context of predefined cardiovascular outcomes in ACCORD-BP was not a predefined outcome in the initial ACCORD-BP trial, but one created by the authors. The renal outcome was defined as an increase in serum creatinine to ≥3.3 mg/dL in the absence of an acute reversible cause, renal transplantation or dialysis initiation. In each group, the extent of BP lowering was related to the increment in serum creatinine increase. Furthermore, the number of subjects with an increase in serum creatinine of <10%, 10% to 30%, and >30% from baseline to 4 months were related to the composite cardiorenal outcome using a proportional hazards model. The authors report that the cardiorenal outcome was not dependent on an increase in serum creatinine concentration irrespective of the group. Therefore, they suggest that an increase in serum creatinine can be ignored when intensifying antihypertensive therapy. These are critically important observations and support earlier systematic reviews documenting similar observations.[7–9]

There are many strengths and some weaknesses of this article. Strengthens of the article include its uniqueness to evaluate the question of increases in serum creatinine in a cohort of patients with diabetes mellitus. Most data evaluating increases in serum creatinine after BP lowering are mainly derived from studies in nondiabetic patients.[7,10–12] Moreover, in some studies, of early-stage CKD, an early and sustained fall in estimated glomerular filtration rate portend a better kidney outcome.[7,9–11] The article also has some weaknesses, one that cardiovascular outcomes were not predefined in the context of serum creatinine changes in the initial ACCORD-BP trial and

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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second, there are no data on whether antihypertensive therapy was reduced in response to a robust increase in serum creatinine. Changes in medication or dose may have influenced the outcome interpretation.

Collard et al[1] make several important points worth emphasizing. First, the reduction in BP from baseline to 4 months was strongly related to the increase in serum creatinine. Second, the increase in serum creatinine concentration to >30% was more strongly related to an increase in all-cause mortality and cardiovascular mortality in the intensive BP reduction group only. Conversely, similar increases in serum creatinine were more strongly related to an increase in renal outcomes in the standard BP reduction group. In our opinion, it seems that competing risks of renal failure and all-cause mortality neutralized the overall effect of >30% increase in serum creatinine concentration with the composite cardiorenal outcome.

The notion that competing risks are operative has been demonstrated previously in a cohort of patients with CKD, where a lower systolic BP is a promoter of all-cause mortality but a protector from end-stage renal disease.[13] Since the authors do not report whether antihypertensive therapy was reduced in response to an increase in serum creatinine, we cannot, even in an observational data set analyzed from a randomized trial, begin to answer the question of whether antihypertensive therapy could be reduced or not.

Given the limitations of these analyses, it is prudent to stick to what experts consider to be best practice. If a patient has an increase in serum creatinine of >30% after initiation or intensification of antihypertensive therapy, one should evaluate the circumstances surrounding these changes. They should assess whether this change was indeed kidney injury, or a hemodynamic change reflecting underlying volume depletion or related to poor vascular compliance or intrarenal vascular disease. Thus, for each case the clinical risks and benefits of continuing or reducing antihypertensive therapy should be performed.

Multiple reports attest to the safety of limited, increases in serum creatinine of up to 30% after BP is reduced significantly, regardless of RAS blocker use.[7,9–11,14] The earliest review of this topic noted a strong association between increases in serum creatinine of up to 30% that stabilize within 2 months of starting a RAS inhibitor and correlate with long-term renal preservation.[7] This relationship holds for people with serum creatinine values of >1.4 mg/dL (>124 mmol/L). The only reason to reduce RAS blockade in this study was hyperkalemia.[7] A 10-year follow-up study in almost 19 000 patients with stage 3b CKD notes a 0.2% incidence of serum creatinine increases by 50% or more associated with RAS blockers.[8] None developed renal failure requiring dialysis and dehydration, infection and heart failure were the most common settings, where this elevation occurred. Lastly, a population-based cohort study using electronic health records in Denmark examined >122 000 patients and noted 2078 (1.7%) with creatinine increases of 30% or more.[15] These people were at higher risk for cardiovascular events and death, however a higher proportion was elderly, had preexisting cardiorenal comorbidity, and used nonsteroidal anti-inflammatory drugs, loop or potassium-sparing diuretics, all of which predispose to serum creatinine elevations with BP lowering as discussed earlier.

The most recent prospective trial to shed light on renal and cardiovascular outcomes associated with serum creatinine elevations is the SPRINT (Systolic Blood Pressure Intervention Trial), a multicenter, randomized study with 9361 participants that demonstrated reduced cardiovascular events in the group randomized to a BP <120 mm Hg compared with 140 mm Hg in patients with CKD.[16] Rocco et al[14] evaluated the incidence of AKI among the entire SPRINT cohort. There were 179 participants with AKI events in the intensive arm and 109 in the standard arm (3.8% versus 2.3%; hazard ratio, 1.64; 95% CI, 1.30–2.10; $P<0.001$).[14] Of 288 participants with an AKI event, 248 (86.1%) had a single AKI event with 58.5% a mild stage 1 AKI. Complete or partial resolution of AKI was seen for 169 (90.4%) of 187 AKI events in the intensive arm. Moreover, when markers for AKI were examined in SPRINT there was no evidence that any established marker for kidney injury was increased, hence, this was a hemodynamic change.[17]

In short, data from clinical trials indicate that people with CKD garner a cardiovascular risk reduction at BP levels <130/80 mm Hg, despite increases in serum creatinine of ≤30% above baseline. In most cases, this is a hemodynamic effect that can be mitigated by ensuring the patient is not taking agents that affect renal autoregulation and ensuring the patient is volume replete. In most cases, the easiest way to assess volume is measure orthostatic drop in systolic arterial pressure.

Despite the availability of observational data in thousands of patients, population effects often are insufficient to guide treatment decisions in individuals. Medicine is involved, and complex conditions will require multifactorial decision-making that can best be made by well-informed physicians. What we learn from the ACCORD analysis is that a rise in serum creatinine of >30% is a marker of future nonrenal morbidity and mortality. What we do about it is a matter of clinical judgment.

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Creatinine Rise During Blood Pressure Therapy and the Risk of Adverse Clinical Outcomes in Patients With Type 2 Diabetes Mellitus

A Post Hoc Analysis of the ACCORD-BP Randomized Controlled Trial

Didier Collard, Tom F. Brouwer, Ron J.G. Peters, Liffert Vogt, Bert-Jan H. van den Born

See Editorial Commentary, pp 1274–1276

Abstract—Lowering blood pressure may affect renal function. Current guidelines state that reducing antihypertensive therapy should be considered in patients with a >30% serum creatinine increase after initiation of antihypertensive therapy. We examined the association between a serum creatinine increase and adverse clinical outcomes in the ACCORD-BP trial (Action to Control Cardiovascular Risk in Diabetes Blood Pressure), were patients with type 2 diabetes mellitus were randomized to intensive (target systolic blood pressure <120 mm Hg) and standard antihypertensive (<140 mm Hg) treatment. The primary outcome was a combined end point consisting of all-cause mortality, major cardiovascular events, and renal failure. Patients were stratified into 3 groups according to serum creatinine increase between baseline and 4 months (<10%, 10%–30%, >30%). A total of 4733 patients, aged 62.2 years, 52% men with a mean estimated glomerular filtration rate 81.5 mL/min per 1.73 m^2 were included. Follow-up was available for 4446 patients, 2231 were randomized to intensive and 2215 to standard therapy. Kaplan-Meier analysis showed no association between a serum creatinine increase and the composite end point in the intensive (P=0.20) and the standard treatment group (P=0.17). After adjusting for possible confounders, a >30% serum creatinine increase was associated with a higher risk of clinical adverse outcomes in both treatment groups, but to a similar extent. These data suggest that a >30% serum creatinine increase that coincides with lower blood pressure values should not directly lead to a reduction in antihypertensive medication in patients with type 2 diabetes mellitus.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00000620.

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Diabetic nephropathy is a highly frequent complication in patients with diabetes mellitus, an independent predictor of cardiovascular mortality and morbidity,[1,2] and the leading cause of renal failure in most developed countries.[3] Blood pressure (BP)-lowering treatment is effective in reducing the risk of diabetic nephropathy and for the prevention of renal function decline.[4,5] However, intensive BP-lowering treatment is also associated with a decrease in renal function. The initial rise in serum creatinine after BP-lowering treatment may be interpreted as reversal of hyperfiltration associated with uncontrolled hypertension. In this situation, the loss of renal function after initiation of therapy reflects the hemodynamic effect of a lower perfusion pressure on glomerular filtration rate, but not a loss of functional nephrons.[6] An important concern, however, is that the increase in creatinine is caused by ischemic nephropathy as a result of inadequate renal perfusion. Therefore, current guidelines recommend to monitor renal function after initiation of therapy. A serum creatinine increase up to 20% or 30% is generally accepted,[7–9] but it is recommended that withdrawal of therapy should be considered if creatinine levels increase by >30%.[10] This is supported by evidence from a recent cohort study in a primary care population showing that even a small creatinine increase by 10%–20% after starting an angiotensin receptor blocker (ARB) or angiotensin-converting enzyme (ACE) inhibitor is associated with an increased incidence of adverse cardiorenal outcomes during 10-year follow-up.[11]

Patients with type 2 diabetes mellitus are potentially prone to the development of renal hypoperfusion because of the higher frequency of micro- and macrovascular diseases

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and an impaired renal autoregulation.[12–14] This may pose patients with diabetes mellitus and an increase in serum creatinine at increased risk for adverse clinical outcomes during intensive BP-lowering treatment. The ACCORD-BP trial (Action to Control Cardiovascular Risk in Diabetes Blood Pressure) was a prospective randomized control trial of intensive, a target systolic BP (SBP) <120 mm Hg, versus standard (target SBP <140 mm Hg) BP-lowering therapy in patients with type 2 diabetes mellitus at high risk for cardiovascular events. Because of its design using different BP-lowering thresholds, the ACCORD study provides a unique opportunity to assess whether the rise in creatinine during BP-lowering treatment is a sign of preexisting renal damage or points toward ischemic nephropathy caused by hypoperfusion. In the present post hoc analysis, we assessed whether the serum creatinine increase during intensive BP-lowering treatment is associated with more adverse clinical outcomes compared with standard therapy.

Methods

Study Design and Patient Eligibility

All data used for this study has been made publicly available at the Biolincc repository and can be requested at https://biolincc.nhlbi.nih.gov/studies/accord/. The ACCORD trial was a randomized control trial conducted from January 2001 to June 2009 at 77 clinical sites in the United States and Canada, which enrolled 10 251 high-risk patients with type 2 diabetes mellitus, who were randomized to either intensive or standard glycemia control. Inclusion ended in 2005. Using a 2 by 2 factorial design a subgroup of 4733 participants was assigned to intensive or standard BP-lowering treatment in the ACCORD-BP trial. ACCORD-BP was designed to have 94% power to detect a 20% reduction in the rate of cardiovascular events in the intensive treatment group. The design, rationale, main results, and safety outcomes of this study have been published elsewhere.[15,16] Participants were eligible if they had a diagnosis of type 2 diabetes mellitus, had glycated hemoglobin level of 7.5% or more, and were older than 40 years with cardiovascular disease or older than 55 years with anatomic evidence of a substantial amount of atherosclerosis, albuminuria, left ventricular hypertrophy, or at least 2 additional risk factors for cardiovascular disease (dyslipidemia, hypertension, smoking, or obesity). Patients with a serum creatinine level of >1.5 mg/dL were excluded. For inclusion in the BP trial, participants were required to have an SBP between 130 and 180 mm Hg with 3 or fewer antihypertensive medications, and a 24-hour protein excretion rate of <1.0 g. This trial was sponsored by the National Heart, Lung and Blood Institute, and the protocol was approved by the institutional review board of each participating center and by an independent review committee of the National Heart, Lung and Blood Institute. The use of the data set for the present analysis was approved by the institutional review board of Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands, and the data were obtained via the National Heart, Lung and Blood Institute.

Trial Intervention

Participants were randomly assigned to an SBP target of <120 mm Hg (intensive treatment group) and an SBP of <140 mm Hg (standard treatment group). The allocation was performed centrally using permuted blocks through the study's website. Participants and physicians were not blinded to treatment strategy. In the intensive treatment group, visits were scheduled once a month for the first 4 months and every 2 months thereafter. In the standard treatment group, visits were in month 1, month 4, and every 4 months thereafter. At each visit, BP mediation could be titrated or switched to reach the target SBP according to the protocol. No specific medication was required and treatment strategies of normal clinical practice could be applied. At each 4-month visit information about study outcome and adverse events were obtained. During the first year, at 4 months intervals, serum creatinine was determined, after this information was obtained on yearly basis. The planned average follow-up was 5.6 years.

Outcomes

For the present analysis, we used the occurrence of adverse clinical outcomes, defined as the composite of the first major cardiovascular event, renal failure, or death because of any cause as primary outcome measure. After the definitions used in ACCORD, a major cardiovascular event was defined as a nonfatal myocardial infarction, a nonfatal stroke or cardiovascular death. Renal failure was defined as renal transplantation, initiation of dialysis, or a rise in serum creatinine >3.3 mg/dL in the absence of an acute reversible cause. Secondary outcomes were the individual components of the primary outcome and the original primary outcome, a major cardiovascular event. All clinical end points were adjudicated by a committee blinded to the treatment assignment.

Statistical Analysis

After previous publications,[17,18] we chose to stratify patients into 3 groups according to their initial increase in serum creatinine (<10%, 10%–30%, >30%). As initial increase, we used the difference between serum creatinine at baseline and 4 months after randomization. Kaplan-Meier analysis was used to investigate the relation between serum creatinine increase and the primary end point. For the primary and secondary outcomes, Cox-regression analysis was performed. In the crude model, correction was performed for age and sex. An additional term for baseline renal function and baseline SBP was added to the model. Renal function was calculated using the Chronic Kidney Disease Epidemiology Collaboration formula, taking ethnicity into account.[19] Use of medication was determined from the ACCORD-BP trial medication logbook. For the medication and the difference in SBP between baseline and 4 months, the value at 3 or 6 months was used if the value at 4 months was missing. Baseline characteristics were compared between the different strata and treatments groups using the appropriate tests (χ^2, ANOVA, Kruskal-Wallis). All statistical analyses were conducted with R version 3.4.3 using the Survival version 2.41–3 and Tableone version 0.9.2 packages (Vienna, Austria). The figures were created using Graphpad Prism, version 7 (California).

Results

Baseline Characteristics

A flowchart of participants included in the present analysis is presented in Figure 1. Of the 2362 participants randomized to intensive therapy, 2231 (94.5%) were included in the present analysis. Of the 2371 participants randomized to standard therapy, 2215 (93.4%) were included. Exclusion of participants was because of missing creatinine data. An overview of the baseline characteristics stratified according to treatment group and creatinine increase is given in Table 1. The >30% stratum (n=259; 11.6%) in the intensive treatment group was more than twice as high compared with the standard treatment group (n=122; 5.5%). SBP decreased by 15.9 mm Hg in the intensive treatment group and by 6.0 mm Hg in the standard treatment group between baseline and 4 months. Compared with subjects without a significant increase in serum creatinine, subjects with a >30% increase had a more profound decrease in SBP. In patients with a <10% increase in serum creatinine, SBP decreased by 12.7 mm Hg in the intensive and 4.1 mm Hg in the standard treatment group, whereas in those with a >30% increase in creatinine SBP decreased by

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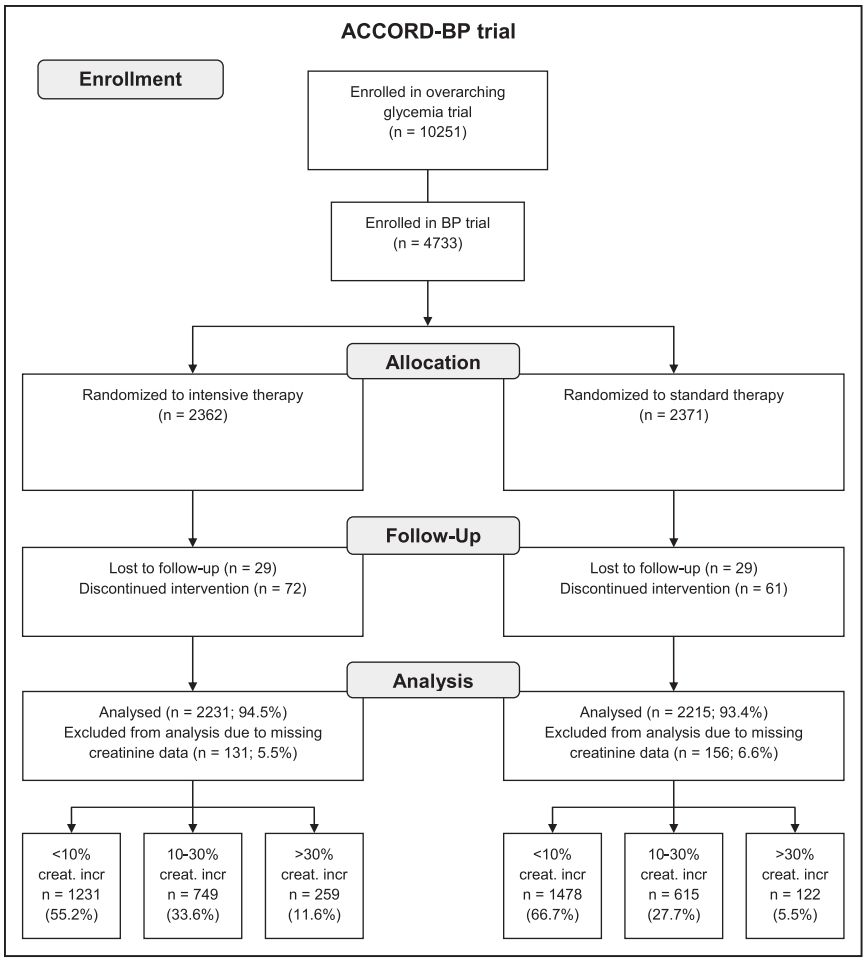

Figure 1. Flowchart of the post-hoc analysis of the ACCORD-BP trial (Action to Control Cardiovascular Risk in Diabetes Blood Pressure). Creat. incr. indicates the creatinine increase between baseline and 4 months.

25.4 and 16.3 mm Hg, respectively. Subjects with a >30% increase had a higher SBP and diastolic BP at baseline, had a higher estimated glomerular filtration rate (eGFR), a higher Framingham-risk score and higher urinary-to-albumin ratio. In the intensive treatment group, more patients received an ACE inhibitor or ARB after 4 months than in the standard treatment group, except for the >30% stratum, where the use of ACE inhibitors or ARBs was 94.6% in the intensive and 90.1% in the standard treatment group. At the last study visit, delta SBP with baseline and the use of ACE inhibitors or ARBs remained similar, with a difference of −22.1 and −12.3 mm Hg between the intensive and standard treatment group in the >30% stratum and an 89.6% and 83.6% use of ACE inhibitors or ARBs. The differences in baseline characteristics between the standard and intensive treatment group according to creatinine increase are given in Table I in the online-only Data Supplement.

Primary and Secondary Outcomes

After a mean follow-up of 4.9 years, 306 of the subjects developed an event in the intensive treatment group compared with 333 in the standard treatment group. Kaplan-Meier analysis is shown in Figure 2. When stratified to creatinine increase, 161 subjects in the <10% stratum, 105 subjects in the 10%–30% stratum, and 40 subjects in the >30% stratum developed an adverse clinical event in the intensive treatment group, whereas in the standard treatment group, 228 subjects in the <10% stratum, 82 subjects in 10%–30% stratum, and 23 subjects in the >30% stratum had an event. In both the intensive and standard treatment group no significant association was found between an increase in serum creatinine and the primary outcome (P=0.20 for the intensive and P=0.17 for the standard treatment group).

Cox-regression analysis performed to estimate the hazard ratio using the crude model, taking only age and sex into account, yielded the same results and showed no significant association between serum creatinine increase and the primary outcome in both treatment groups (Table 2). In the secondary outcome analysis, a serum creatinine increase was associated with an increased hazard ratio for all-cause mortality and cardiovascular mortality in the intensive treatment group, while in the standard treatment group, no such association was found. However, in the standard treatment group, a >30% serum creatinine increase was associated with an increased hazard ratio for adverse renal events, while in the intensive treatment group, a serum creatinine rise was not associated with adverse renal outcomes. Additional correction for SBP and eGFR at baseline, resulted in a significant association between a >30% serum creatinine increase and adverse clinical outcomes with an adjusted hazard ratio of 1.47 (95% CI, 1.03–2.11) and 1.57 (95% CI, 1.01–2.43) in the intensive and the standard treatment group, while no significant association was present for the 10% to 30% strata. Further analysis showed that the difference between the crude

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Table 1. Baseline Characteristics

Characteristics	Intensive			Standard			*P* Value
	<10%	10%–30%	>30%	<10%	10%–30%	>30%	
No. of subjects	1231	741	259	1478	615	122	
Age, mean (SD), y	62.55 (6.61)	62.84 (6.48)	62.82 (6.48)	62.66 (6.72)	62.99 (6.80)	61.70 (6.97)	0.41
Women, n (%)	588 (47.8)	328 (44.3)	138 (53.3)	680 (46.0)	294 (47.8)	66 (54.1)	0.08
Race or ethnic group, n (%)							0.36
Black	298 (24.2)	166 (22.4)	56 (21.6)	331 (22.4)	159 (25.9)	30 (24.6)	
Hispanic	79 (6.4)	43 (5.8)	11 (4.2)	101 (6.8)	46 (7.5)	6 (4.9)	
Other	120 (9.7)	78 (10.5)	26 (10.0)	175 (11.8)	49 (8.0)	15 (12.3)	
White	734 (59.6)	454 (61.3)	166 (64.1)	871 (58.9)	361 (58.7)	71 (58.2)	
SBP, mm Hg, mean (SD)	137.0 (15.4)	140.5 (15.9)	143.8 (18.0)	137.8 (15.0)	141.4 (15.4)	146.2 (16.9)	<0.001
DBP, mm Hg, mean (SD)	75.2 (10.2)	76.7 (11.0)	77.5 (10.4)	75.6 (10.2)	76.4 (10.0)	77.8 (11.4)	0.001
History of cardiovascular disease, n (%)	399 (32.4)	257 (34.7)	89 (34.4)	479 (32.4)	207 (33.7)	51 (41.8)	0.33
Framingham 10-y risk of cardiovascular death, median (IQR)*	30.83 (20.81, 43.19)	33.21 (23.11, 46.79)	34.15 (24.87, 46.89)	29.78 (20.90, 42.44)	32.01 (21.67, 45.58)	33.74 (22.82, 44.57)	0.001
Smoker, n (%)	163 (13.2)	105 (14.2)	27 (10.4)	194 (13.1)	80 (13)	17 (13.9)	0.79
Body mass index, mean (SD), kg/m^2	32.16 (5.59)	32.27 (5.55)	32.61 (5.54)	31.98 (5.36)	32.16 (5.23)	33.05 (5.52)	0.24
Serum creatinine, mg/dL, mean (SD)	0.95 (0.24)	0.84 (0.20)	0.81 (0.25)	0.94 (0.24)	0.83 (0.19)	0.79 (0.24)	<0.001
eGFR, mL/min per 1.73 m^2, mean (SD)	77.79 (17.97)	86.00 (15.38)	86.85 (18.86)	78.77 (17.48)	86.43 (15.03)	88.86 (18.11)	<0.001
Ratio of urinary albumin, mg, to creatinine, g, median (IQR)	13.00 (7.00, 37.00)	16.00 (7.50, 49.00)	21.00 (10.00, 84.00)	14.00 (7.00, 43.50)	16.00 (7.00, 50.50)	20.00 (9.25, 83.75)	<0.001
Total cholesterol, mg/dL, mean (SD)	193.80 (43.77)	192.76 (45.24)	202.15 (51.43)	190.47 (41.51)	189.83 (44.70)	202.76 (59.18)	<0.001
Total HDL, mg/dL, mean (SD)	46.26 (13.15)	46.32 (13.17)	45.05 (13.72)	47.03 (14.21)	45.60 (13.66)	43.12 (12.61)	0.01
Aspirin use, n (%)	674 (55.0)	395 (53.4)	136 (52.7)	780 (53.0)	308 (50.7)	58 (47.5)	0.45
Statin use, n (%)	763 (62.2)	496 (67.0)	168 (65.1)	983 (66.8)	395 (65.0)	80 (65.6)	0.19
ACE inhibitor/ARB use at 4 mo, n (%)	1132 (92.0)	699 (94.3)	245 (94.6)	1159 (78.5)	494 (80.5)	109 (90.1)	<0.001
ΔSBP baseline and 4 mo, mm Hg, mean (SD)	−12.7 (17.1)	−18.0 (17.8)	−25.4 (18.8)	−4.1 (16.8)	−8.6 (16.5)	−16.3 (20.9)	<0.001

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; DBP, diastolic blood pressure, eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; IQR, interquartile range; mo, months; and SBP, systolic BP.

*Only for patients without a history of cardiovascular disease. To convert the values for creatinine to millimoles per liter, multiply by 88.4. To convert the values the values for cholesterol and HDL to millimoles per liter, multiply by 0.02586. To convert the values for ratio of urinary albumin to creat to mg/mmol, multiply by 0.113.

and the fully adjusted model was mainly driven by baseline eGFR: a lower eGFR was associated with an increased hazard ratio for adverse clinical outcomes. The results of the Cox-regression using the fully adjusted model for the primary and secondary outcomes are shown in Table II in the online-only Data Supplement. Additional adjustment for allocation to glycemic treatment arm did not materially change the association between the increase in serum creatinine and adverse clinical events.

Discussion

Our results show that, when stratified to initial serum creatinine increase, intensive BP treatment does not lead to an increased risk of adverse clinical outcomes compared with standard therapy in patients with type 2 diabetes mellitus. However, in both treatment groups, patients with a >30% serum creatinine increase had a significantly higher risk for adverse outcomes compared with the other strata when adjusted for potential confounders. This suggests that a serum creatinine rise after initiation of antihypertensive therapy is a marker to identify high-risk patients, but that intensive therapy itself does not lead to a further increase in the risk for adverse outcomes. Our results suggest that in patients with diabetes mellitus treatment decisions about the benefits of intensive BP-lowering therapy should not be influenced by an initial serum creatinine increase and that a >30% rise in serum creatinine should alert the clinician to an increased risk for adverse outcomes, but may not necessarily mean that BP-lowering medication needs to be reduced.

Meta-analyses have shown that intensive BP-lowering treatment reduces cardiovascular morbidity and mortality in chronic kidney disease (CKD) patients with and without diabetes mellitus.[20,21] Therefore, current guidelines emphasize the importance to achieve lower BP goals, but this carries an

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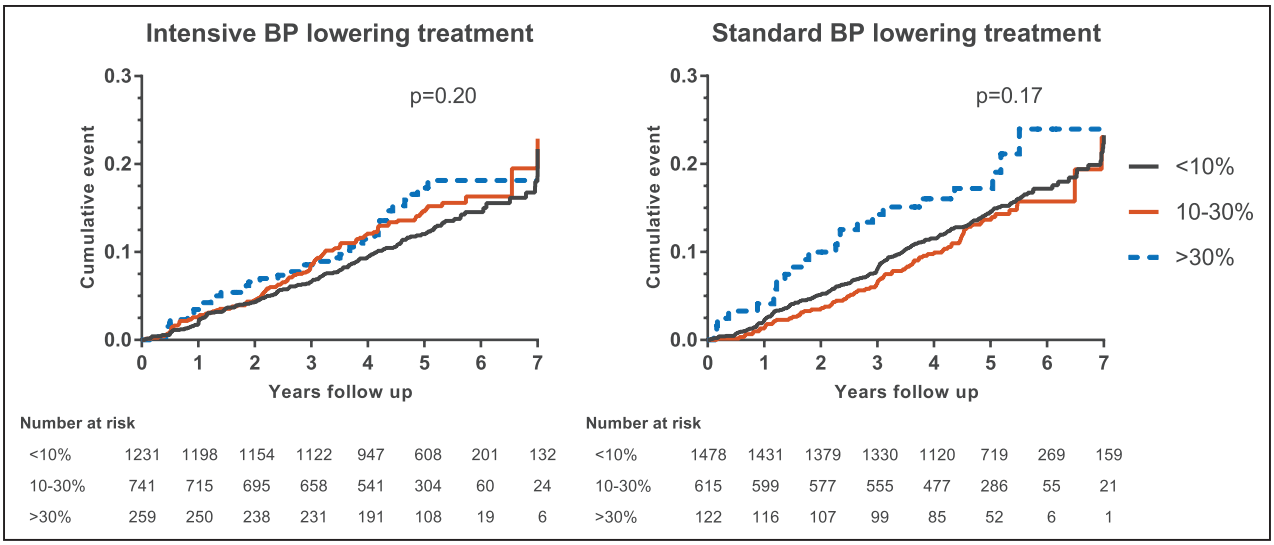

Figure 2. Kaplan-Meier analysis of initial serum creatinine increase versus adverse clinical outcomes, intensive (**left**) versus standard (**right**) BP lowering treatment.

increased concern of iatrogenic ischemic kidney damage as a result of hypoperfusion.[8] Evidence that a >30% rise in creatinine may be harmful is derived from an earlier meta-analysis of randomized trials showing that in patients with preexisting renal insufficiency a serum creatinine increase by >30% is rare and may point toward hypoperfusion.[10] In the present post hoc analysis, we found no association between a serum creatinine increase and adverse renal events in the intensive treatment group. In the standard treatment group, however, a >30% creatinine increase was associated with an increased risk of renal failure. This difference may be explained by the fact that in the standard treatment group other causes for a decrease of renal function than the initiation of antihypertensive therapy were more likely leading to a serum creatinine elevation at higher SBP targets.

A previous analysis of the ONTARGET (Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial) and TRANSCEND trial (Telmisartan Randomized Assessment Study in ACE Intolerant Participants With Cardiovascular Disease) showed an increased risk of adverse renal and cardiovascular outcomes in patients with a >12.7% decrease in renal function after treatment with an ACE inhibitor or ARB.[22] A similar finding was also observed in a recent study, which showed that a serum creatinine increase larger than 10% after initiation of an ACE inhibitor or ARB was associated with increased cardiorenal and mortality risk in a UK primary care population.[11] The results from the present study confirm these findings by showing that a serum creatinine increase of >30% is associated with a higher risk of cardiorenal events and death. However, they also illustrate that the increased risk of cardiovascular and renal complications is independent of the attained BP level. This supports the hypothesis that a decline in renal function as a result of antihypertensive therapy should not be interpreted as harmful.

Our findings are in line with an earlier post hoc analysis from the AASK (African American Study of Kidney Disease and Hypertension) and MDRD trial (Modification of Diet in Renal Disease) that examined the effects of intensive BP-lowering treatment in CKD patients without diabetes mellitus. Here, a >20% decline in renal function during intensive BP therapy was associated with an increased risk for renal failure, while in the standard treatment arm a >5% decline was already predictive for renal failure.[17] A post-analysis of the RENAAL trial (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan) found that the initial fall in eGFR after initiation of an ARB in diabetic patients attenuated the decrease in eGFR on the long term, but that the initial change in eGFR was associated with more renal events, the risk being higher in the placebo than the ARB treatment group.[18] As the target SBP in the RENAAL trial was <140 mm Hg, this finding is in line with the findings of our analysis and those by Ku et al[17] supporting that an increased risk of adverse renal outcomes is present in patients with a creatinine increase during BP-lowering therapy, but may be protective in the long run.

Our data are in apparent contrast with an earlier analysis of the SPRINT (Systolic Blood Pressure Intervention Trial) and ACCORD trials that reported an increased risk of CKD in patients receiving intensive BP-lowering treatment with and without diabetes mellitus.[23] However, both in the original and our post hoc analysis of the ACCORD trial, no evidence for an increased risk for renal failure was found in the intensive group compared with the standard group. Because Beddhu et al[23] defined incident CKD as an eGFR decrease of ≥30%, it is conceivable that the increase in renal events was merely a reflection of the reversal of hyperfiltration during antihypertensive treatment. Similar, an analysis of acute kidney injury in the SPRINT trial by Rocco et al[24] showed an increased risk for acute kidney injury in the intensive compared with the standard treatment group. However, acute kidney injury was already defined as a rise >0.3 mg/dL or increase >1.5-fold from baseline. The notion that hyperfiltration is implicated in the serum creatinine rise after antihypertensive treatment is supported by a subgroup analysis in patients with CKD in SPRINT that showed no

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Table 2. Results of Cox-Regression Analysis for Primary and Secondary Outcomes

End Point	Intensive (event rate)	HR	L95	U95	*P* Value	Standard (Event Rate)	HR	L95	U95	*P* Value
Primary outcome										
<10%	13.1%	1.00				15.4%	1.00			
10%–30%	14.2%	1.16	0.90	1.48	0.25	13.3%	0.91	0.70	1.17	0.45
>30%	15.4%	1.32	0.94	1.88	0.11	18.9%	1.47	0.96	2.27	0.08
All-cause mortality										
<10%	4.9%	1.00				5.6%	1.00			
10%–30%	5.8%	1.34	0.90	1.99	0.14	5.7%	1.11	0.75	1.66	0.60
>30%	9.7%	2.37	1.48	3.80	<0.001	5.7%	1.29	0.59	2.79	0.52
Nonfatal MI										
<10%	5.5%	1.00				6.6%	1.00			
10%–30%	5.4%	1.02	0.69	1.52	0.91	5.0%	0.81	0.54	1.21	0.30
>30%	3.5%	0.70	0.35	1.40	0.31	9.0%	1.64	0.87	3.06	0.12
Nonfatal stroke										
<10 %	1.4%	1.00				2.6%	1.00			
10%–30%	1.5%	1.13	0.53	2.42	0.76	2.1%	0.83	0.44	1.57	0.57
>30%	0.8%	0.62	0.14	2.70	0.53	0.8%	0.35	0.05	2.58	0.31
Renal failure										
<10%	2.7%	1.00				2.8%	1.00			
10%–30 %	2.2%	0.83	0.46	1.52	0.55	1.8%	0.68	0.35	1.32	0.26
>30%	3.5%	1.47	0.70	3.08	0.31	6.6%	2.62	1.23	5.61	0.013
CV mortality										
<10%	1.5%	1.00				2.2%	1.00			
10%–30%	3.0%	2.36	1.26	4.43	0.008	1.6%	0.82	0.40	1.67	0.59
>30%	3.9%	3.16	1.45	6.91	0.004	4.1%	2.46	0.95	6.35	0.06
Major CV events										
<10%	7.9%	1.00				10.4%	1.00			
10%–30%	9.6%	1.30	0.96	1.77	0.09	8.0%	0.80	0.58	1.10	0.17
>30%	7.7%	1.09	0.67	1.77	0.73	13.1%	1.51	0.90	2.53	0.12

HR is adjusted for age and sex. L95 and U95 indicate the 95% CI. Less than 10%, 10%–30%, >30% indicate the different creatinine increase strata. CV indicates cardiovascular; HR, hazard ratio; and MI, myocardial infarction.

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difference between eGFR reduction after 6 months between the standard and intensive BP targets.[25]

The strength of our study is that ACCORD-BP was a large randomized control trial of high-risk patients with type 2 diabetes mellitus who were prone to develop adverse events. This allowed us to determine the contribution of the BP-lowering therapy to the increased risk in patients with an initial serum creatinine increase. The limitation is that this is a post hoc analysis, and the study was not originally powered to answer this question. Most patients received an ACE inhibitor or ARB as part of their BP-lowering treatment, but the choice of medication was left at the discretion of the physician. We, therefore, cannot conclude from our data if the effect observed is primarily the result of lower BP or a result of the use of specific antihypertensive medication. Finally, the ACCORD-BP study only included patients with type 2 diabetes mellitus and although the association between an increase in serum creatinine and increased risk of adverse clinical outcomes is also observed in other populations, effects of intensive BP-lowering treatment may be different.

In conclusion, a >30% serum creatinine increase during BP-lowering treatment in patients with type 2 diabetes mellitus is associated with a higher risk of adverse clinical outcomes, irrespective of whether standard or intensive BP-lowering therapy is used. However, when stratified to initial serum creatinine increase, intensive BP-lowering treatment does not lead to a higher risk of adverse clinical outcomes compared with standard therapy. Furthermore, there was no association between incidence of renal failure and initial serum creatinine increase in the intensive treatment group. Only during standard therapy, a >30% creatinine

increase was associated with an increased hazard ratio for renal failure.

Perspectives

Current guidelines state that reducing antihypertensive therapy should be considered in patients with a >30% serum creatinine increase. This is based on studies showing that an initial serum creatinine increase during antihypertensive therapy is associated with an increased risk for all-cause mortality, cardiovascular events, and renal failure. This post hoc analysis of the ACCORD-BP trial shows that an initial >30% serum creatinine increase is associated with adverse clinical outcomes, but does not lead to a higher risk of cardiovascular and renal outcomes in patients receiving intensive treatment compared with standard antihypertensive therapy. These data suggest that a serum creatinine increase that coincides with a lower BP should not be interpreted as harmful and lead to a reduction in BP-lowering medication. Further research should focus on whether there is an optimal cutoff value for serum creatinine increase after BP-lowering treatment related to the difference in blood pressure.

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Disclosures

None.

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Novelty and Significance

What Is New?

- An initial increase in serum creatinine by >30% during antihypertensive therapy is associated with adverse clinical outcomes, irrespective of whether standard or intensive therapy is used.

What Is Relevant?

- Acute lowering of blood pressure has been shown to increase creatinine and may lead to concerns of iatrogenic kidney damage.
- Our data suggest that an initial serum creatinine increase after better blood pressure control may not always be indicative that reduction of blood pressure lowering medication is necessary.

Summary

This post hoc analysis of the ACCORD-BP trial (Action to Control Cardiovascular Risk in Diabetes Blood Pressure) shows that when stratified to serum creatinine increase intensive antihypertensive treatment does not lead to a higher risk of adverse clinical outcomes compared with standard therapy in patients with type 2 diabetes mellitus.

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