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Lynda A. Szczech, MD, MSCE; Christopher B. Granger, MD; Joseph F. Dasta, MSc, FCCM; Alpesh Amin, MD; W. Frank Peacock, MD; Peter A. McCullough, MD, MPH; John W. Devlin, PharmD; Matthew R. Weir, MD, MS; Jason N. Katz, MD; Frederick A. Anderson, Jr, PhD; Allison Wyman, MS; Joseph Varon, MD; for the Studying the Treatment of Acute Hypertension Investigators

Background—Little is known about the association of kidney dysfunction and outcome in acute severe hypertension. This study aimed to measure the association between baseline chronic kidney disease (estimated glomerular filtration rate), acute kidney injury (AKI, decrease in estimated glomerular filtration rate ≥25% from baseline) and outcome in patients hospitalized with acute severe hypertension.

Methods and Results—The Studying the Treatment of Acute Hypertension (STAT) registry enrolled patients with acute severe hypertension, defined as ≥1 blood pressure measurement >180 mm Hg systolic and/or >110 mm Hg diastolic and treated with intravenous antihypertensive therapy. Data were compared across groups categorized by admission estimated glomerular filtration rate and AKI during admission. On admission, 79% of the cohort (n=1566) had at least mild chronic kidney disease (estimated glomerular filtration rate <60 mL/min in 46%, <30 mL/min in 22%). Chronic kidney disease patients were more likely to develop heart failure ($P<0.0001$), non–ST-elevation myocardial infarction ($P=0.003$), and AKI ($P<0.007$). AKI patients were at greater risk of heart failure and cardiac arrest ($P\leq0.0001$ for both). Subjects with AKI experienced higher mortality at 90 days ($P=0.003$). Any acute loss of estimated glomerular filtration rate during hospitalization was independently associated with an increased risk of death (odds ratio, 1.05; $P=0.03$ per 10-mL/min decline). Other independent predictors of mortality included increasing age ($P<0.0001$), male gender ($P=0.016$), white versus black race ($P=0.003$), and worse baseline kidney function ($P=0.003$).

Conclusions—Chronic kidney disease is a common comorbidity among patients admitted with acute severe hypertension, and AKI is a frequent form of acute target organ dysfunction, particularly in those with baseline chronic kidney disease. Any degree of AKI is associated with a greater risk of morbidity and mortality. **(*Circulation*. 2010;121:2183-2191.)**

Key Words: epidemiology ■ hypertension ■ kidney ■ mortality

Both chronic kidney disease (CKD) and acute kidney injury (AKI) are associated with an increased risk of mortality.[1–3] The risks associated with abnormal kidney function are underscored by the poor outcomes of patients with end-stage renal disease (ESRD).[4] With greater awareness of the methods by which both conditions can be categorized and compared across studies, it is becoming more apparent that the risk associated with either abnormal serum creatinine or increases in serum creatinine manifest early and increase directly with a decline in kidney function.[5–7]

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Multiple studies further document the impact of chronic hypertension on kidney function, with hypertension as a cause of ESRD among a significant proportion of patients requiring dialysis.[2] However, the impact of acute severe hypertension on kidney function has not been explored fully. Knowledge of how outcomes vary among patients with acute severe hypertension and either CKD or AKI may enable us to identify high-risk groups that warrant increased clinical surveillance.

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From the Department of Medicine, Division of Nephrology, Duke University Medical Center, Durham, NC (L.A.S.); Duke Clinical Research Institute, Durham, NC (C.B.G.); College of Pharmacy, University of Texas, Round Rock (J.F.D.); UCIMC, Orange, Calif (A.A.); Emergency Department, The Cleveland Clinic, Cleveland, Ohio (W.F.P.); William Beaumont Hospital, Royal Oak, Mich (P.A.M.); School of Pharmacy, Northeastern University School of Pharmacy, Boston, Mass (J.W.D.); Division of Nephrology, University of Maryland School of Medicine, Baltimore (M.R.W.); Divisions of Cardiology and Pulmonary and Critical Care Medicine, University of North Carolina at Chapel Hill (J.N.K.); Center for Outcomes Research, University of Massachusetts Medical School, Worcester (F.A.A., A.W.); and University of Texas Health Science Center and St Luke's Episcopal Hospital, Houston (J.V.).

Correspondence to Lynda Anne Szczech, MD, MSCE, Duke University Medical Center, Box 3646, Durham, NC 27710. E-mail szcze001@mc.duke.edu

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This analysis is based on data from the Studying the Treatment of Acute Hypertension (STAT) registry, which enrolled patients admitted to hospital for acute severe hypertension. The study was undertaken to define the risk among patients with acute severe hypertension and AKI and the risk associated with both AKI and CKD on cardiovascular outcomes and mortality.

Methods

STAT is a US, hospital-based, retrospective observational study of the routine management practices and outcomes of patients with acute severe hypertension managed in the emergency or critical care settings (a setting with the capability of providing intravenous antihypertensive administration and arterial line blood pressure [BP] monitoring) and treated with intravenous antihypertensive therapy. Consecutive adults admitted with at least 1 BP measurement >180 mm Hg systolic and/or >110 mm Hg diastolic or >140/>90 mm Hg in patients with subarachnoid hemorrhage who were administered at least 2 antihypertensive boluses or were placed on continuous infusion therapy within 24 hours of hospitalization at 1 of 25 centers were enrolled. Antihypertensives included diltiazem, enalapril, esmolol, fenoldopam, hydralazine, labetalol, metoprolol, nicardipine, nitroglycerin, phentolamine, sodium nitroprusside, and verapamil. Exclusion criteria included hypertension therapy in the perioperative setting or during the peripartum period, therapy delayed >24 hours after hospitalization, nonintravenous administration of antihypertensive drugs, and patients receiving "comfort care measures" only.

Data on demographics, medical history, admitting information, in-hospital management, 90-day outcomes (readmission, death, and recurrent severe hypertension), and death up to 6 months after the index hospitalization were collected by trained data abstractors. The Social Security Death Index was used to determine survival at 6 months after presentation to hospital with the acute hypertensive event.

This study was conducted in accordance with the Health Insurance Portability and Accountability Act of 1996, with the approval of all local institutional review boards. It was done in compliance with the regulations of participating hospitals.

Definitions of Variables

Data on serum creatinine concentrations were collected at 4 points: up to 12 months before admission (when available), at admission, at peak creatinine, and at discharge when measured and available. Estimated glomerular filtration rate (eGFR) was calculated for each available serum creatinine measure with the Modification of Diet in Renal Disease formula.[8] For each patient, baseline kidney function was categorized according to the National Kidney Foundation Disease Outcomes Quality Initiative clinical practice guidelines[9] of >90 mL/min (normal kidney function), 60 to 89 mL/min (mild kidney disease), 30 to 59 mL/min (moderate), <30 mL/min (severe), or dialysis dependent. The group categorized with kidney function >90 mL/min included patients with or without kidney disease based on the presence or absence of proteinuria, respectively; no attempt was made to divide this group because of the potential impact of acute severe hypertension on the appearance of proteinuria at admission.

For each patient, the relative change in GFR was calculated by subtracting the lowest recorded eGFR from the earliest available eGFR (before or on admission) and dividing that by the earliest available measure. The latter was used to minimize the impact of an admission creatinine that is already elevated by early kidney injury. Change in kidney function from baseline to nadir GFR or severity of AKI was analyzed continuously and categorically. Change in kidney function was categorized with the RIFLE criteria (risk, injury, failure, loss, end-stage renal disease)[10] based on GFR. A difference of <25% from baseline to nadir was classified as no change in kidney function. As per the RIFLE criteria,[10] risk was defined as a GFR decrease of 25% to 50%; injury was defined as a decrease of 50% to 75%; and failure and more severe categories were defined as a loss of >75% and were combined because of the limited numbers of subjects and information available on the chronicity of their kidney injury. Patients with ESRD at baseline were not classified with these criteria and were analyzed separately.

Description of Analyses Performed

Patients were categorized according to baseline eGFR initially into levels of CKD and subsequently on the basis of loss of eGFR into levels of AKI. Categorical variables are reported as frequencies. Nominal variables were compared by use of the χ^2 test; dichotomous and ordinal variables were compared by use of the Mantel-Haenszel χ^2 test. Continuous variables are displayed as medians with 25th and 75th percentiles. To test for linear trends among continuous variables, each category of CKD was assigned its median value. A univariate linear regression on these values was then performed for each outcome; the P value for the slope is given in the tables. Similarly, each category of AKI was assigned its median value, again with a linear regression performed on these values. For continuous variables with nonnormal distributions, we performed linear trend tests on the untransformed variable and then a second time using a rank transformation (a nonparametric test that ensures that extreme values have no undue influence). In cases when results disagree, we report both results. Logistic regression was used to estimate the association between AKI and mortality risk in adjusted analyses. Candidate variables included in this model were age, gender, race, Hispanic ethnicity, diabetes mellitus, baseline eGFR, peripheral vascular disease, greatest decrement in eGFR during AKI, proteinuria, and the interaction between baseline eGFR and proteinuria.

All P values are 2 sided, and all confidence intervals are 95% intervals. Analyses were performed with SAS (version 9.1, SAS Institute Inc, Cary, NC).

Results

A total of 1566 patients were included in the STAT study between January 1, 2007, and April 6, 2008. Of these, 1542 had sufficient creatinine measurements available to evaluate the occurrence and severity of baseline CKD, and 1369 had sufficient creatinine measurements available to evaluate the occurrence and severity of AKI during the period of observation.

CKD at Baseline

Most of the patients (79%) had at least mild (stage II) CKD at baseline (Table 1), with the incidence of mild, moderate, and severe kidney disease being 32%, 23%, and 11%, respectively. A further 11% of patients were dialysis dependent on admission. In general, patients with more severe CKD at baseline presented with higher BP and were more likely to be of black race and to have comorbidities such as cardiac disease, hypertension, diabetes mellitus, and peripheral vascular disease (all $P<0.0001$).

During hospitalization, patients with worse baseline CKD were more likely to experience complications such as acute left ventricular dysfunction ($P<0.0001$) and non–ST-segment myocardial infarction ($P=0.003$; Table 2) and were less likely to experience intracranial hemorrhage (intracerebral, $P<0.001$; subarachnoid, $P<0.0001$). Subjects in each category of CKD experienced AKI; however, patients with the most severe CKD on admission were more likely to experience the greatest decrement in kidney function with AKI ($P=0.007$).

Table 1. Demographics and Baseline Medical History on Admission by CKD stage

	All Patients (n=1566)	eGFR >90 mL/min (n=322)	eGFR 60–89 mL/min (n=503)	eGFR 30–59 mL/min (n=366)	eGFR <30 mL/min (n=179)	ESRD (n=172)	*P*
Admission SBP, median (IQR), mm Hg	194 (172–216)	182 (157–204)	192 (170–212)	197 (175–220)	205 (190–224)	207 (188–227)	<0.0001
Admission DBP, median (IQR), mm Hg	105 (88–121)	104 (87–115)	105 (88–120)	102 (87–122)	110 (93–126)	110 (94–127)	0.002
Admission pulse, median (IQR), bpm	87 (74–102)	86 (74–102)	85 (74–102)	88 (74–102)	86 (76–102)	91 (75–105)	0.94
Age, median (IQR), y	58 (49–70)	55 (48–61)	60 (50–73)	66 (52–79)	59 (49–70)	53 (43–63)	<0.0001
Male gender, n (%)	800 (51)	190 (59)	249 (50)	173 (47)	84 (47)	91 (53)	0.07
Race, n (%)							<0.0001
White	531 (34)	119 (37)	187 (37)	145 (40)	41 (23)	35 (20)	
Black	878 (56)	165 (51)	272 (54)	190 (52)	121 (68)	112 (65)	
Other	126 (8.1)	31 (9.6)	36 (7.2)	23 (6.3)	15 (8.4)	19 (11)	
Hispanic/Latino	126 (8.1)	31 (9.6)	35 (7.0)	19 (5.2)	15 (8.4)	24 (14)	0.23
Medical history, n (%)							
Cardiac	626 (40)	71 (22)	184 (37)	175 (48)	88 (49)	98 (57)	<0.0001
Hypertension	1387 (89)	259 (80)	436 (87)	334 (91)	169 (94)	169 (98)	<0.0001
Diabetes mellitus	542 (35)	83 (26)	137 (27)	141 (39)	83 (46)	92 (53)	<0.0001
Peripheral vascular disease	166 (11)	17 (5.3)	39 (7.8)	43 (12)	29 (16)	36 (21)	<0.0001

DBP indicates diastolic BP; IQR, interquartile range; and SBP, systolic BP. *P* values are for the comparison of eGFR groups (excluding ESRD). Nominal variables were compared by use of the χ^2 test; dichotomous variables were compared by use of the Mantel-Haenszel χ^2 test. Continuous variables were tested for linear trend using linear regression.

AKI During Hospitalization

The change in kidney function for all patients was assessed relative to their own baseline value, and patients were categorized by severity of decline (Table 3). Of the entire cohort, 64% had a <25% decline in kidney function; 15% had an acute decline in between 25% and <50%; 4.2% developed kidney injury; and 3.6% developed renal failure.

There were few differences in baseline characteristics among subjects in the different categories of AKI. Subjects with the most severe kidney injury were slightly more likely to be of Hispanic ethnicity compared with those with lesser degrees of AKI ($P=0.008$). Other differences included a greater proportion of subjects with diabetes mellitus, peripheral vascular disease, and CKD among those with any degree of AKI compared with patients without a change in GFR ($P=0.015$, $P=0.002$, and $P<0.0001$, respectively). Only patients with severe AKI had a significantly different preadmission eGFR (30.1 versus 65.9 to 73.4 mL/min; $P<0.0001$). Although the downward trend in eGFR calculated on admission was more evident based on the degree of eventual AKI (68.9, 64.2, and 54.0 mL/min for <25%, 25% to <50%, and 50% to <75%, respectively), the category of patients with the most severe degree of injury was decreased most dramatically at 15.4 mL/min. Otherwise, no differences were seen in admission BP measurements, race, or presence of other preexisting comorbid conditions.

Few differences existed between types of antihypertensives taken at admission among subjects based on category of kidney injury. A greater proportion of patients with increasing severity of kidney injury received diuretics before admission ($P<0.001$). However, no differences were seen among categories of subjects with respect to the use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. Subjects with greater severity of kidney injury were more likely to receive β-blockers ($P=0.015$). With calcium channel blockers, a statistically significant difference existed among categories of patients by severity of kidney injury ($P=0.019$); however, this difference did not appear clinically meaningful.

In general, patients who experienced greater degrees of kidney injury also had a greater risk of other end-organ injury or dysfunction (Table 4). This included a greater risk of acute left ventricular dysfunction and cardiac arrest ($P\leq0.0001$ for both). Other adverse events that were more likely among subjects with AKI included the presence of moderate to severe bleeding, recurrent severe acute hypertension, and neurological decline ($P<0.001$, $P=0.001$, and $P<0.0001$, respectively).

With respect to treatment of the acute hypertensive episode, there were no differences among categories of subjects based on degree of kidney injury in the time to treatment with an intravenous agent or time to 10% decrease in systolic BP (Table 4). The duration of intravenous therapy and number of intravenous agents, however, were significantly greater among patients with greater degrees of AKI (both $P<0.0001$). Subjects with a greater severity of AKI had a higher in-hospital mortality rate and, among those discharged, a longer length of hospitalization ($P<0.0001$ for both; Table 5). Patients with a greater severity of AKI experienced an increased risk of rehospitalization for renal failure ($P=0.001$) or heart failure ($P=0.034$). Subjects with any AKI experienced a higher risk of mortality at 90 days ($P=0.003$; Figure 1).

Table 2. End-Organ Injury and Adverse Events During the Hospitalization for Accelerated Hypertension by CKD Stage

	All Patients (n=1566), n (%)	eGFR >90 mL/min (n=322), n (%)	eGFR 60–89 mL/min (n=503), n (%)	eGFR 30–59 mL/min (n=366), n (%)	eGFR <30 mL/min (n=179), n (%)	ESRD (n=172), n (%)	*P*
Cardiac							
Acute LV dysfunction	228 (15)	22 (6.8)	49 (9.7)	72 (20)	33 (18)	50 (29)	<0.0001
NSTEMI	88 (5.6)	11 (3.4)	19 (3.8)	32 (8.7)	13 (7.3)	13 (7.6)	0.003
STEMI	43 (2.8)	8 (2.5)	18 (3.6)	8 (2.2)	5 (2.8)	4 (2.3)	0.66
Unstable angina	50 (3.2)	7 (2.2)	19 (3.8)	17 (4.6)	1 (0.6)	5 (2.9)	0.80
Cardiac arrest/ventricular fibrillation	48 (3.1)	8 (2.5)	10 (2.0)	14 (3.8)	9 (5.0)	6 (3.5)	0.10
Cerebrovascular							
Ischemic stroke	95 (6.1)	16 (5.0)	31 (6.2)	31 (8.5)	7 (3.9)	10 (5.8)	0.84
Intracerebral hemorrhage	179 (11)	47 (15)	64 (13)	42 (11)	16 (8.9)	8 (4.7)	<0.001
Subarachnoid hemorrhage	186 (12)	78 (24)	67 (13)	28 (7.7)	11 (6.2)	1 (0.6)	<0.0001
Septicemia	27 (1.7)	8 (2.5)	3 (0.6)	6 (1.6)	4 (2.2)	6 (3.5)	0.22
Moderate to severe bleeding	69 (4.4)	15 (4.7)	20 (4.0)	11 (3.0)	13 (7.3)	10 (5.8)	0.28
AKI							0.007
No change in function (<25%)	1006 (64)	211 (66)	401 (80)	277 (76)	117 (65)	NA	
Decrement >25% and <50%	241 (15)	80 (25)	75 (15)	58 (16)	28 (16)	NA	
Decrement >50% and <75%	65 (4.2)	25 (7.8)	16 (3.2)	23 (6.3)	1 (0.6)	NA	
Decrement >75%	57 (3.6)	6 (1.9)	11 (2.2)	8 (2.2)	32 (18)	NA	
Mortality							
During hospitalization	108 (6.9)	20 (6.2)	27 (5.4)	34 (9.3)	15 (8.4)	10 (5.8)	0.38
Between discharge and 90 d	64 (4.7)	6 (2.2)	19 (4.2)	25 (7.8)	5 (3.3)	9 (5.8)	0.07
Mortality at 90 d (total)	172 (11)	26 (8.1)	46 (9.2)	59 (16)	20 (11)	19 (11)	0.07
Between 90 d and 6 mo*	40 (3.5)	10 (4.3)	7 (1.9)	9 (3.5)	5 (3.9)	9 (7.3)	0.11

LV indicates left ventricular; NSTEMI, non–ST-segment myocardial infarction. *P* values are for the comparison of eGFR groups (excluding ESRD) by use of the Mantel-Haenszel χ^2 test.

*Among the 1139 patients alive at 90 days and with valid Social Security number.

Subjects with worsening degrees of both baseline kidney function and severity of AKI experienced a greater risk of mortality at 90 days (Figure 2). In the multivariable model, any acute loss of eGFR during hospitalization was independently associated with an increased risk of death (odds ratio, 1.05; $P=0.026$ per 10-mL/min decline; Figure 3) when clinical and demographic factors associated with severity of AKI were controlled for. Other predictors of mortality included increasing age ($P<0.0001$), male gender ($P=0.02$), white versus black race ($P=0.003$), and poorer baseline kidney function ($P=0.002$).

Discussion

In this large multicenter study of patients hospitalized with acute severe hypertension, the presence of either CKD or AKI was associated with worse outcomes, including increased length of hospitalization. Even after accounting for baseline kidney dysfunction, the presence of AKI or an acute deterioration in kidney function during hospitalization is associated with morbidity and predicts mortality. This is the first study to demonstrate that this increase in risk begins with only a subtle decline in kidney function and increases progressively with severity of AKI. Although the association with other end-organ complications likely reflects the severity of the hypertensive episode, arguably AKI may have a more mechanistic relationship to increased mortality. Importantly, because kidney function was more severely impaired at baseline, there was a greater frequency and severity of subsequent AKI during the hospitalization. Finally, except for elevated creatinine concentration on admission, there were few identifying clinical factors among patients who developed severe AKI to distinguish them from patients with no or lesser degrees of kidney injury.

Although the association between CKD and outcomes in the setting of acute systolic hypertension has not been fully defined, these results are consistent with previous studies. Lip et al[11] demonstrated that patients presenting with accelerated hypertension whose blood urea nitrogen was >10 mmol/L and serum creatinine was >200 μmol/L had a worse survival. Although consistent with the results presented here, this study

Table 3. Demographics and Baseline Medical History on Admission by Degree of AKI

	Relative Change in GFR					
	<25% (n=1006)	25%–<50% (n=241)	50%–<75% (n=65)	≥75% (n=57)	*P*	Subjects With ESRD on Admission (n=172)
Age, median (IQR), y	59 (50–71)	61 (51–74)	62 (54–73)	56 (45–66)	0.46	53 (43–63)
Admission SBP, median (IQR), mm Hg	193 (170–214)	191 (170–213)	189 (170–216)	198 (176–214)	0.92	207 (188–227)
Admission DBP, median (IQR), mm Hg	105 (89–120)	104 (86–119)	105 (86–117)	112 (93–126)	0.88	110 (94–127)
Admission pulse pressure, mm Hg	87 (67–104)	90 (70–105)	85 (62–104)	87 (70–100)	0.79	97 (80–113)
Male gender, n (%)	522 (52)	109 (45)	37 (57)	28 (49)	0.55	91 (53)
Race, n (%)					0.13	
White	372 (37)	81 (34)	25 (38)	14 (25)		35 (20)
Black	552 (55)	128 (53)	32 (49)	35 (61)		112 (65)
Other	66 (6.6)	26 (11)	7 (11)	6 (11)		19 (11)
Hispanic/Latino	63 (6.3)	23 (9.5)	6 (9.2)	8 (14)	0.008	24 (14)
Medical history, n (%)						
Cardiac	375 (37)	91 (38)	31 (48)	20 (35)	0.55	98 (57)
Coronary artery disease	215 (21)	59 (24)	19 (29)	8 (14)	0.88	48 (28)
MI	126 (13)	32 (13)	10 (15)	5 (8.8)	0.87	27 (16)
Congestive heart failure	178 (18)	48 (20)	16 (25)	13 (23)	0.10	63 (37)
Prior hospitalization for heart failure	48 (4.8)	14 (5.8)	2 (3.1)	3 (5.3)	0.94	25 (15)
PCI	76 (7.6)	14 (5.8)	5 (7.7)	2 (3.5)	0.25	12 (7.0)
CABG	52 (5.2)	11 (4.6)	6 (9.2)	2 (3.5)	0.89	10 (5.8)
Hypertension	873 (87)	214 (89)	60 (92)	50 (88)	0.28	169 (98)
Diabetes mellitus	305 (30)	89 (37)	28 (43)	21 (37)	0.015	92 (53)
Prior neurological event	224 (22)	60 (25)	16 (25)	11 (19)	0.87	44 (26)
Peripheral vascular disease	82 (8.2)	25 (10)	12 (18)	9 (16)	0.002	36 (21)
Alcohol/tobacco use	382 (38)	79 (33)	24 (37)	17 (30)	0.13	75 (44)
Medications on admission, n (%)						
ACE inhibitor	291 (29)	83 (34)	16 (25)	17 (30)	0.71	79 (46)
Angiotensin receptor blocker	75 (7.5)	21 (8.7)	5 (7.7)	3 (5.3)	0.88	24 (14)
β-blocker	406 (40)	102 (42)	31 (48)	32 (56)	0.015	107 (62)
Calcium channel blocker	191 (19)	61 (25)	10 (15)	19 (33)	0.019	88 (51)
Diuretic (intravenous or oral)	270 (27)	87 (36)	25 (38)	24 (42)	<0.001	14 (8.1)
Kidney function, median (IQR)						
Last creatinine before admission, mg/dL	1.2 (0.9–1.7)	1.0 (0.8–1.6)	1.3 (0.8–1.5)	2.1 (1.0–6.0)	<0.0001	NA
Last eGFR before admission, mL/min	65.9 (42.2–84.0)	69.3 (43.7–96.3)	73.4 (52.9–101.8)	30.1 (10.5–77.4)	0.74* <0.0001†	NA
Admission creatinine, mg/dL	1.1 (0.9–1.5)	1.1 (0.9–1.6)	1.2 (0.9–1.8)	4.2 (2.5–8.5)	<0.0001	NA
Admission eGFR, mL/min	68.9 (47.5–87.1)	64.2 (42.3–88.1)	54.0 (40.1–91.8)	15.4 (6.9–27.1)	<0.0001	NA

SBP indicates systolic BP; IQR, interquartile range; DBP, diastolic BP; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; and ACE, angiotensin-converting enzyme. *P* values are for the comparison of relative change groups (excluding ESRD). Nominal variables were compared by use of the χ^2 test; dichotomous variables were compared by use of the Mantel-Haenszel χ^2 test. Continuous variables were tested for linear trend with linear regression.

*Nontransformed.

†Rank transformed.

does not allow the separation of risk associated with CKD on presentation from that associated with AKI accompanying a hypertensive event. Lip et al[12] further characterized this population of patients with acute severe hypertension as having a prevalence of "chronic renal failure" of 31.7% on admission. Chronic renal failure in their study was defined as a creatinine concentration >2.3 mg/dL. This study, however, had the same limitation; ie, it was unable to discern whether the elevation in creatinine was due to preexisting CKD or to AKI. In the analysis presented here, ≈80% of patients had a calculated eGFR in a range consistent with established CKD. In addition, ≈34% of patients had a significant change in kidney function qualifying as at least mild AKI.

Many previous studies demonstrate an increased risk of mortality among a broad spectrum of hospitalized patients who experience AKI. More recently, it has been recognized

Table 4. End-Organ Injury, Adverse Events, and Treatment Received During the Hospitalization for Accelerated Hypertension by Degree of AKI

	Relative Change in GFR					
	<25% (n=1006)	25%–<50% (n=241)	50%–<75% (n=65)	≥75% (n=57)	*P*	Subjects With ESRD on Admission (n=172)
Cardiac, n (%)						
Acute left ventricular dysfunction/PE	105 (10)	33 (14)	18 (28)	20 (35)	<0.0001	50 (29)
NSTEMI	53 (5.3)	10 (4.2)	5 (7.7)	7 (12)	0.08	13 (7.6)
STEMI	25 (2.5)	10 (4.2)	3 (4.6)	1 (1.8)	0.45	4 (2.3)
Unstable angina	28 (2.8)	11 (4.6)	3 (4.6)	2 (3.5)	0.26	5 (2.9)
Cardiac arrest/VF	18 (1.8)	13 (5.4)	3 (4.6)	7 (12)	<0.0001	6 (3.5)
Cerebrovascular, n (%)						
Ischemic stroke	67 (6.7)	11 (4.6)	4 (6.2)	3 (5.3)	0.41	10 (5.8)
Intracerebral hemorrhage	118 (12)	40 (17)	8 (12)	3 (5.3)	0.84	8 (4.7)
Subarachnoid hemorrhage	136 (14)	37 (15)	10 (15)	1 (1.8)	0.18	1 (0.6)
Septicemia, n (%)	8 (0.8)	5 (2.1)	5 (7.7)	3 (5.3)	<0.0001	6 (3.5)
Moderate to severe bleeding, n (%)	34 (3.4)	13 (5.4)	4 (6.2)	8 (14)	<0.001	10 (5.8)
Hypotension resulting from IV arterial hypertension treatment, n (%)	33 (3.3)	10 (4.2)	3 (4.6)	5 (8.8)	0.044	10 (5.8)
Recurrent severe acute hypertension, n (%)	268 (27)	86 (35)	26 (40)	21 (37)	0.001	42 (24)
Neurological decline, n (%)	43 (4.3)	20 (8.3)	8 (12)	8 (14)	<0.0001	9 (5.2)
Time from qualifying BP to start of IV, median (IQR), h*	1.3 (0.5–3.0)	1.2 (0.4–3.7)	1.4 (0.6–2.8)	1.2 (0.4–2.9)	0.85	1.3 (0.6–3.6)
Time from qualifying BP to 10% SBP decrease, median (IQR), h*	3.6 (1.5–8.5)	3.3 (1.6–11)	4.4 (1.7–14)	3.6 (1.6–8.5)	0.12	3.9 (1.7–11)
Total time of IV treatment, median (IQR), h*	5.5 (1.6–16)	7.7 (2.5–20)	11 (4.3–40)	17 (7.0–33)	<0.0001	7.0 (2.3–18)
IV drugs used, median (IQR), n*	2 (1–2)	2 (1–3)	2 (2–3)	2 (2–3)	<0.0001	2 (1–3)
Discharge creatinine, median (IQR), md/dL†	1.1 (0.8–1.5)	1.2 (0.9–1.9)	1.6 (1.1–2.2)	3.5 (1.6–4.6)	<0.0001	NA
Discharge eGFR, median (IQR), mL/min†	73.1 (50.5–95.2)	61.4 (36.4–84.7)	48.5 (30.7–78.8)	18.8 (11.7–39.4)	<0.0001	NA

PE indicates pulmonary embolism; NSTEMI, non–ST-segment myocardial infarction; VF, ventricular fibrillation; SBP, systolic blood pressure; and IQR, interquartile range. *P* values are for the comparison of relative change groups (excluding ESRD). Dichotomous variables were compared by use of the Mantel-Haenszel χ^2 test. Continuous variables were tested for linear trend with linear regression.

*Excludes patients with a presumptive primary admitting diagnosis of hemorrhagic stroke, subdural hematoma, or subarachnoid hemorrhage.

†Excludes patients who were dialysis dependent at discharge (n=1 for <25%, n=1 for 25% to <50%, n=0 for 50% to <75%, and 23 for ≥75%).

that even small reductions in kidney function are correlated with mortality.[13–16] Among studies of patients with acute severe hypertension, this study provides the first description that this risk begins to increase with more subtle relative changes in GFR of between 25% and 50% of the baseline value. It is noteworthy that there were a few differences in baseline clinical parameters on admission among patients categorized by their subsequent severity of AKI. This indi-

Table 5. Discharge Findings and 90-Day Follow-Up Information by Degree of AKI

	<25% (n=1006)	25%–<50% (n=241)	50%–<75% (n=65)	≥75% (n=57)	*P*	Subjects With ESRD on Admission (n=172)
Length of stay, median (IQR), d	4 (2, 8)	7 (4, 14)	9 (5, 18)	9 (6, 20)	<0.0001	3 (2, 7)
Mortality during hospitalization, n (%)	50 (5.0)	30 (12)	10 (15)	6 (11)	<0.0001	10 (5.8)
Readmission (by cause), n (%)*						
Any	270 (32)	65 (34)	20 (42)	16 (33)	0.26	81 (54)
Renal failure	23 (2.7)	4 (2.1)	2 (4.2)	7 (15)	0.001	35 (23)
Heart failure	28 (3.3)	5 (27)	6 (13)	3 (6.3)	0.034	13 (8.7)
Mortality between discharge and 90 d, n (%)†	32 (3.6)	14 (7.0)	4 (7.8)	5 (10)	0.003	9 (5.8)
Mortality between 90 d and 6 mo, n (%)‡	22 (2.9)	6 (3.7)	3 (8.3)	0 (0.0)	0.78	9 (7.3)

IQR indicates interquartile range. *P* values are for the comparison of relative change groups (excluding ESRD). Dichotomous variables were compared by use of the Mantel-Haenszel χ^2 test. Continuous variables were tested for linear trend with linear regression.

*Among the 1313 patients discharged alive and not lost to readmission follow-up.

†Among the 1369 patients discharged alive and whose vital status could be determined during follow-up.

‡Among the 1219 patients alive at 90 days and with valid Social Security number.

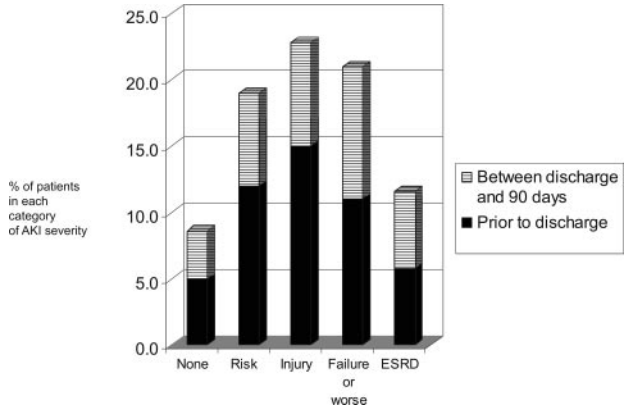

Figure 1. Mortality risk before discharge and at 90 days for subjects based on degree of AKI.

cates that vigilant surveillance of kidney function after admission is important to identify this higher-risk population. Furthermore, although the risk of mortality was increased, so were the risks of other significant clinical events such as acute heart failure, cardiac arrest, and bleeding episodes.

Our study has 2 important clinical implications. The first is that there appears to be a critical mass of functioning nephrons at baseline in the setting of hypertensive urgencies. This is partially reflected in the baseline eGFR compensating for any degree of organ injury or dysfunction to keep serum creatinine relatively unchanged in blood. In those with reduced eGFR at baseline, as a proxy for a reduced number of remnant nephron units, there is a likely loss of compensatory filtration in the setting of acute hypertension and hence the expression of AKI in terms of a rise in creatinine and fall in eGFR. The second is that markers of renal filtration such as creatinine are crude reflections of AKI as a disease process. Our study highlights the need for novel markers of AKI that give rapid specificity to renovascular, glomerular, and tubular injury before there is an elevation of filtered protein in the blood.[17] It is hoped that the development of these markers will lead to novel treatment strategies that not only lower BP but also result in improved renal and cardiac outcomes.

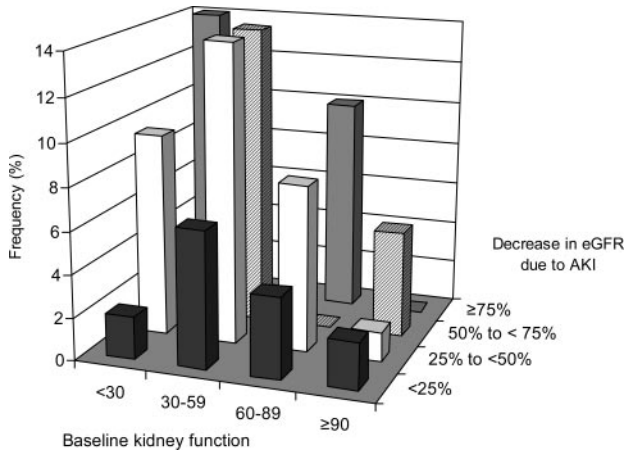

Figure 2. Mortality risk at 90 days based on the presence of CKD at baseline and AKI during hospitalization.

Study Limitations

The STAT registry is the largest observational cohort study to be conducted to date and provides data on a heterogeneous population of individuals presenting with acute severe hypertension. STAT is subject to certain inherent limitations and potential biases, including the collection of nonrandomized data and missing or incomplete information. Participating sites may not be representative of all US hospitals, and patients with acute hypertension likely differ by region. The study is subject to selection bias because the entry criteria required the physician to initiate intravenous antihypertensive therapy. We do not have complete information on follow-up, and we may underestimate the degree to which follow-up occurred. Although the enrollment of patients from multiple sites enhances power and generalizability compared with a single-center study, it introduces the complexities of comparison of serum creatinine measurements from multiple laboratories. Although the bias associated with this was minimized through the use of changes in kidney function relative to each individual's baseline, the effect of this misclassification bias cannot be obviated in the categorization of CKD stage and would bias any association between CKD and mortality toward the null. Additionally, the timing of the assessment of serum creatinine must also be considered. Even though all patients had a serum creatinine measurement on admission, those with elevated concentrations at that time point may reflect either the presence of preexisting CKD or the occurrence of incident AKI. To minimize the misclassification of these 2 different clinical scenarios, the earliest serum creatinine of either preadmission or admission was used as baseline. However, this does not obviate the impact of timing of changes in renal function on misclassification. Because both the Acute Kidney Injury Network and RIFLE criteria provide time frames for the changes in creatinine (48 hours and 7 days, respectively), our inability to fully define what changes occurred within those time frames likely introduced additional bias. This is compounded by the fact that a significant proportion of patients likely had CKD at baseline, and the time to comparable relative changes in creatinine among those with CKD is longer.[18] Finally, in terms of hospitalization, rehospitalizations at medical centers other than the participating sites would not be captured in this study and could potentially bias the strength of the association between AKI and rehospitalization demonstrated here toward the null.

Conclusions

This study demonstrates that an alteration in kidney function is associated with a greater risk of important outcomes, including mortality, additional end-organ injury, and increased length of stay, among patients admitted with acute severe hypertension. Thus, renal dysfunction should prompt careful monitoring of this population, and effective treatment may be especially important. Specifically, this higher-risk population who loses even small amounts of kidney function after admission is at greater risk of experiencing events such as acute left ventricular failure and cardiac arrest. However, in terms of designing directed surveillance techniques to address the risk associated with these events, other than

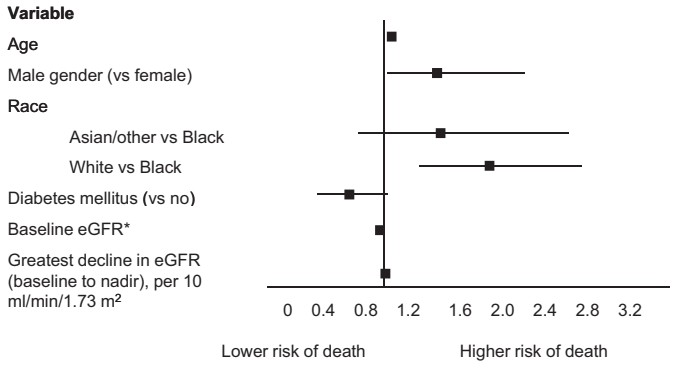

Figure 3. Logistic regression predicting death within 90 days. OR indicates odds ratio.

serum creatinine on admission, there are few clues available to the clinician to identify the patients at higher risk for AKI and adverse events. Until the kidney equivalent of the cardiac troponin is available to predict on presentation the occurrence of AKI, heightened awareness of AKI is required. Along with increased surveillance of serum creatinine, knowledge of the sensitivity of creatinine at lower ranges of measurement to changes in kidney function is needed to identify patients at highest risk for these poorer outcomes.

Appendix

STAT Steering Committee Members and Principal Investigators

Steering Committee: Alpesh Amin, Joseph F. Dasta, James Ferguson, Joel Gore, Christopher B. Granger, Kurt Kleinschmidt, Stephan A. Mayer, Alan S. Multz, W. Frank Peacock, Eric Peterson, Charles Pollack, Andrew F. Shorr, Gene Yong Sung, Joseph Varon, Matthew Weir.

Principal investigators: John Cienki, MD, Jackson Memorial Hospital, Miami, Fla; Lala Dunbar, MD, Louisiana State University Health Sciences Center/University Hospital, New Orleans, La; John Devlin, PharmD, Tufts–New England Medical Center, Boston, Mass; Deborah Diercks, MD, University of California Medical Center Davis; Icilma Fergus, MD, Harlem Hospital Center, New York, NY; James Froehlich, MD, University of Michigan Health System, Ann Arbor; Tony Gerlach, PharmD, Ohio State University Medical Center, Columbus, Ohio; Marc LaPointe, MD, Medical University of South Carolina, Charleston; Phillip Levy, MD, Detroit Receiving Hospital and Sinai Grace Hospital, Detroit, Mich; Chadwick Miller, MD, Wake Forest University Baptist Medical Center, Winston-Salem, NC; Richard Nowak, MD, Henry Ford Health System, Detroit, Mich; Brian O'Neil, MD, William Beaumont Hospital, Royal Oak, Mich; Noleen Ostapkovich, RN, Columbia University Medical Center, New York, NY; Namrata Patil, MD, Brigham and Women's Hospital, Boston, Mass; Jon Schrock, MD, MetroHealth Medical Center, Cleveland, Ohio; Adam Singer, MD, Stony Brook, Stony Brook, NY; Brian Tiffnay, MD, Chandler Regional Medical Center, Chandler, Ariz; Joseph Varon, MD, FACP, FCCP, FCCM, St Luke's Episcopal Hospital, Houston, Tex.

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CLINICAL PERSPECTIVE

Little is known about the association between kidney dysfunction and outcome in acute severe hypertension. Using data from the Studying the Treatment of Acute Hypertension (STAT) registry, this study examined the associations between both acute kidney injury and chronic kidney disease among patients with acute severe hypertension. On admission, 79% of the cohort had at least mild chronic kidney disease and were subject to a greater risk of heart failure, non–ST-elevation myocardial infarction, and acute kidney injury. Not surprisingly, acute kidney injury patients were also at greater risk of heart failure, cardiac arrest, and mortality at 90 days. However, quite notable is the fact that any acute loss of estimated glomerular filtration rate during hospitalization was independently associated with an increased risk of death (odds ratio, 1.05; $P=0.03$ per 10-mL/min decline). This study strongly supports the clinical need for early and frequent monitoring of kidney function to facilitate risk stratification among those admitted with acute severe hypertension. It also strongly supports research on whether treatment aimed at preventing or mitigating the severity of the acute kidney injury will lower the risk. The clinician should therefore be aware that patients with even a subtle decline in kidney function after admission are at higher risk for other cardiovascular events and tailor their therapy on a case-by-case basis.

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