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Original Investigation

Estimated GFR and the Effect of Intensive Blood Pressure Lowering After Acute Intracerebral Hemorrhage

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Background: The kidney-brain interaction has been a topic of growing interest. Past studies of the effect of kidney function on intracerebral hemorrhage (ICH) outcomes have yielded inconsistent findings. Although the second, main phase of the Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT2) suggests the effectiveness of early intensive blood pressure (BP) lowering in improving functional recovery after ICH, the balance of potential benefits and harms of this treatment in those with decreased kidney function remains uncertain.

Study Design: Secondary analysis of INTERACT2, which randomly assigned patients with ICH with elevated systolic BP (SBP) to intensive (target SBP $<$ 140 mm Hg) or contemporaneous guideline-based (target SBP $<$ 180 mm Hg) BP management.

Setting & Participants: 2,823 patients from 144 clinical hospitals in 21 countries.

Predictors: Admission estimated glomerular filtration rates (eGFRs) of patients were categorized into 3 groups based on the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) creatinine equation: normal or high, mildly decreased, and moderately to severely decreased ($>$90, 60-90, and $<$60 mL/min/1.73 m^2, respectively).

Outcomes: The effect of admission eGFR on the primary outcome of death or major disability at 90 days (defined as modified Rankin Scale scores of 3-6) was analyzed using a multivariable logistic regression model. Potential effect modification of intensive BP lowering treatment by admission eGFR was assessed by interaction terms.

Results: Of 2,623 included participants, 912 (35%) and 280 (11%) had mildly and moderately/severely decreased eGFRs, respectively. Patients with moderately/severely decreased eGFRs had the greatest risk for death or major disability at 90 days (adjusted OR, 1.82; 95% CI, 1.28-2.61). Effects of early intensive BP lowering were consistent across different eGFRs ($P = 0.5$ for homogeneity).

Limitations: Generalizability issues arising from a clinical trial population.

Conclusions: Decreased eGFR predicts poor outcome in acute ICH. Early intensive BP lowering provides similar treatment effects in patients with ICH with decreased eGFRs.

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INDEX WORDS: Kidney function; estimated glomerular filtration rate (eGFR); chronic kidney disease (CKD); dialysis; hemodialysis; stroke; intracerebral hemorrhage (ICH); cerebral hemorrhage; stroke; cerebrovascular disease; systolic blood pressure; intensive blood pressure lowering treatment; INTERACT2.

Patients with cerebrovascular disease often have chronic kidney disease (CKD), chiefly defined as reduced estimated glomerular filtration rate (eGFR) or increased urinary albumin excretion, because of shared risk factors and pathophysiologic mechanisms affecting the brain and kidney.[1] Although mounting evidence indicates an association between reduced kidney function and adverse outcomes in patients with acute stroke, much of these data pertain to those with ischemic or undifferentiated stroke.[2-4] Thus, the

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prognostic significance of kidney function in patients with acute intracerebral hemorrhage (ICH), the most serious type of stroke, remains uncertain. Although the second, main phase of the Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT2) did not demonstrate a significant reduction in the combined primary outcome of 90-day death or major disability by intensive blood pressure (BP) treatment at the conventional $P < 0.05$ level, it showed improved secondary functional recovery, as measured by changes across all levels of the modified Rankin Scale (mRS) scores. These findings have led to revisions of guidelines,[5,6] but concerns persist over the potential for harm from such treatment (eg, in patients with poor kidney function). The objectives of this study were to elucidate the prognostic significance of decreased eGFR in more than 2,600 participants in INTERACT2[5] and assess whether it modifies the treatment effect of early intensive BP lowering.

METHODS

Study Design and Patient Characteristics

This was a post hoc analysis of the INTERACT2 study population, the details of which are outlined elsewhere.[5] In brief, INTERACT2 was an international, multicenter, open, blinded end point–assessed, randomized, controlled trial involving 2,839 patients with acute spontaneous ICH within 6 hours of onset and elevated systolic BP (SBP; 150-220 mm Hg). Participants were randomly assigned to receive intensive (target SBP < 140 mm Hg within 1 hour) or contemporaneous guideline-recommended (target SBP < 180 mm Hg) BP-lowering therapy using locally available agents according to standardized protocols. Patients were excluded if they had a structural cerebral cause for the ICH, were in a deep coma (defined as Glasgow Coma Scale scores of 3-5), had a massive ICH with an expected poor prognosis, or early surgery to evacuate the hematoma was planned. The study protocol was approved by an appropriate ethics committee at each hospital site, and written informed consent was obtained from each participant or his or her legal surrogate.

Demographic and clinical characteristics were recorded at the time of enrollment. Initial laboratory parameters, including serum creatinine, were measured at hospital presentation/admission. Assessment of kidney function was based on eGFR calculated using the CKD-EPI (CKD Epidemiology Collaboration) creatinine equation.[7] Because creatinine level was not standardized to isotope-dilution mass spectrometry, the INTERACT2 creatinine level was reduced by 5% for calculations using the CKD-EPI equation.[8] Participants were categorized into 3 groups of eGFRs: normal or high, mildly decreased, and moderately to severely decreased (>90, 60-90, and <60 mL/min/1.73 m^2, respectively).[9] BP was measured in the nonparetic arm with the patient supine using an automated device or manual sphygmomanometer with an appropriate size cuff. Baseline BP was measured twice with an interval of 2 or fewer minutes and the mean of the 2 measurements was used. Achieved BP in the hyperacute phase was measured at 1, 6, 12, 18, and 24 hours postrandomization; mean values of these 5 measurements were calculated. A diagnostic computed tomographic (CT) scan was obtained for all participants according to standardized techniques at baseline and at a mean of 24 ± 3 (standard deviation) hours in a subset of patients where this was routine or for a substudy evaluating hematoma growth. For each CT scan, uncompressed digital CT images were collected in Digital Imaging and Communications in Medicine (DICOM) format on a CD-ROM identified only with the patient's unique study number. Hematoma and perihematomal edema volumes were independently assessed by trained neurologists (S.S., C.D., Y.C.) who were blinded to clinical and treatment details and date and sequence of scan using computer-assisted multislice planimetric and voxel threshold techniques.[10,11]

Outcomes

For these analyses, the primary clinical outcome was death or major disability at 90 days (defined by mRS scores of 3-6).[12] Secondary clinical outcomes were, separately, death and major disability (mRS scores of 6 and 3-5, respectively) at 90 days. CT outcomes in a subset of patients were absolute 24-hour hematoma and perihematomal edema growth volumes.

Statistical Analysis

Baseline characteristics of patients in predefined groups were summarized as mean ± standard deviation or median with interquartile range for continuous variables and as number (percent) for categorical variables, with comparisons made using Wilcoxon or χ^2 tests. Associations between baseline eGFR and clinical outcomes were examined using categorical and ordinal logistic regression, using normal or high eGFR as the reference group and adjusted for potential confounders including: age, Chinese region, any history of ischemic stroke, acute coronary syndrome, hypertension, diabetes mellitus, prior use of antithrombotics and a statin, log-transformed time from onset to randomization, baseline SBP, baseline National Institutes of Health Stroke Scale score (<14 and ≥14), baseline hematoma volume (≤10, 11-20, and >20 mL), location (lobar and nonlobar) of ICH, intraventricular extension of ICH, and randomly assigned group. We further tested potential effect modification by antithrombotic therapy on the relationship between kidney function and the primary outcome using interaction terms. Stratified analyses of antithrombotic users versus non–antithrombotic users were also carried out in logistic regression models. Heterogeneity of the treatment effect of intensive BP lowering between eGFR groups was also examined with the use of interaction terms. Effects of eGFR levels on mean achieved SBP during the initial 24 hours in each treatment arm were assessed by analysis of covariance adjusted for the same covariates except for randomized intensive BP lowering. The association between eGFR and 24-hour absolute growth of hematoma and perihematomal edema volumes was also determined using analysis of covariance; the 24-hour hematoma growth model was adjusted for recurrent ICH, warfarin use, time from onset to baseline CT scan, categorized baseline hematoma volume, and intraventricular extension of ICH.[10] The 24-hour perihematomal edema growth model was adjusted for time from onset to CT scan, categorized baseline ICH volume, intraventricular extension of ICH, and 24-hour hematoma growth.[11] Data are reported as odds ratios (ORs) and 95% confidence intervals (CIs). A 2-tailed $P < 0.05$ was regarded as indicating statistical significance. All analyses were performed using SAS software (version 9.3; SAS Institute Inc).

RESULTS

A total of 2,623 patients with recorded admission creatinine level and 90-day clinical outcome were included in this study (Fig S1, available as online supplementary material). Characteristics for those included and excluded were broadly similar (Table S1). Of those included, 1,431 (55%), 912 (35%), and 280 (11%) patients had normal/high, mildly decreased, and moderately/severely decreased

eGFR, respectively. There were 9 patients who had received dialysis within 7 days of the hospital admission. In comparison to those with normal/high eGFRs, patients with decreased eGFRs tended to be older and were recruited from countries outside China. Patients with decreased eGFRs were more likely to have had a history of ischemic stroke, acute coronary syndrome, hypertension, and diabetes mellitus and to have used antithrombotics and statins prior to ICH. Furthermore, they had higher SBP, National Institutes of Health Stroke Scale score, and ICH score values, with a greater proportion of intraventricular extension of ICH at admission and required a higher number of BP-lowering agents compared with patients with normal/high eGFRs (Table 1).

Table 1. Patient Characteristics According to Admission eGFR Categories

	Normal or High eGFR: >90 mL/min/1.73 m^2	Mildly Decreased eGFR: 60-90 mL/min/1.73 m^2	Moderately/Severely Decreased eGFR: <60 mL/min/1.73m^2	*P*
No. of patients	1,431	912	280	
Demographics				
Age, y	59 ± 11	70 ± 12	71 ± 14	<0.001
Male sex	900 (63)	568 (62)	172 (61)	0.9
Ethnicity				
Chinese ethnicity	1,073 (75)	518 (57)	154 (55)	<0.001
African ethnicity	16 (1)	8 (1)	4 (1)	0.7
Medical history				
ICH	118 (8)	70 (8)	26 (9)	0.7
Ischemic stroke	130 (9)	105 (12)	28 (10)	0.2
Acute coronary syndrome	27 (2)	34 (4)	15 (5)	0.001
Hypertension	1,020 (71)	663 (73)	223 (80)	0.02
Diabetes mellitus	125 (9)	108 (12)	54 (19)	<0.001
Medications				
Antihypertensives	566 (40)	468 (51)	161 (58)	<0.001
Antithrombotics	105 (7)	160 (18)	61 (22)	<0.001
Statin	65 (5)	97 (11)	32 (11)	<0.001
Clinical features				
Time from onset to randomization, h:min	3:41 [2:45-4:44]	3:47 [2:54-4:42]	3:38 [2:53-4:44]	0.6
SBP, mm Hg	178 ± 16	180 ± 17	183 ± 18	<0.001
DBP, mm Hg	103 ± 14	99 ± 15	100 ± 16	<0.001
ICH score	1 (0-1)	1 (0-2)	1 (0-2)	<0.001
NIHSS ≥ 14[a]	444 (31)	315 (35)	119 (43)	<0.001
GCS ≤ 9[b]	101 (7)	87 (10)	26 (9)	0.08
Serum creatinine, mg/dL	0.65 ± 0.15	0.89 ± 0.17	1.90 ± 1.60	<0.001
Baseline CT findings				
Hematoma volume, mL[c]	11.5 [6.1-19.8]	10.0 [5.0-18.7]	10.5 [5.8-19.6]	0.04
Hematoma location[d]				0.03
Lobar	108 (8)	108 (13)	28 (11)	
Deep	1,113 (85)	692 (81)	206 (81)	
Brainstem	46 (4)	22 (3)	8 (3)	
Cerebellum	43 (3)	30 (4)	12 (5)	
Intraventricular extension of ICH[c]	329 (25)	261 (31)	92 (36)	<0.001
Perihematomal edema volume, mL[e]	1.8 [0.9-3.6]	1.8 [0.8-3.7]	2.4 [1.0-4.9]	0.1
Randomized intensive BP lowering	708 (49)	453 (50)	132 (47)	0.7
Treatment with ≥2 BP-lowering agents	645 (45)	448 (49)	145 (52)	0.04

Note: Values for categorical variables are given as number (percentage); values for continuous variables, as mean ± standard deviation or median [interquartile range].

Abbreviations: BP, blood pressure; CT, computed tomography; DBP, diastolic blood pressure; eGFR; estimated glomerular filtration rate; GCS, Glasgow Coma Scale; ICH, intracerebral hemorrhage; NIHSS, National Institutes of Health Stroke Scale; SBP, systolic blood pressure.

[a]NIHSS scores can range from 0 (normal, no neurologic deficit) to 42 (coma with quadriplegia).

[b]GCS scores can range from 3 (deep coma) to 15 (normal, alert).

[c]There were 195 total patients with missing baseline CT data.

[d]There were 207 total patients with missing information for baseline hematoma location.

[e]There were 1,827 total patients with missing information for baseline perihematomal edema volume.

Admission eGFR was associated with the primary combined clinical outcome of death or major disability and with the secondary clinical outcome of major disability alone. Compared with patients with normal/high eGFRs, those with moderately/severely decreased eGFRs had worse 90-day outcomes (adjusted OR, 1.82; 95% CI, 1.28-2.61; Table 2; Fig 1) and greater risk for major disability (adjusted OR, 1.51; 95% CI, 1.12-2.05; Table 2). However, moderately/severely decreased eGFR was not significantly associated with death (adjusted OR, 1.08; 95% CI, 0.70-1.67; Table 2). Ordinal logistic regression analyses using all levels of mRS scores[12] showed similar results (adjusted OR, 1.49; 95% CI, 1.15-1.93 for moderately/severely decreased eGFRs; P for trend = 0.01; Fig 1). Furthermore, our results did not show evidence of effect modification by antithrombotic use for the primary outcome of death or major disability ($P = 0.6$). Stratified analyses revealed statistically significant associations between admission eGFR and the primary outcome of death and major disability among non–antithrombotic users and associations for outcomes of death and major disability separately among antithrombotic users (Table S2).

There was no evidence of heterogeneity in the effect of early intensive BP-lowering treatment on the primary poor outcome (death or major disability at 90 days) across the 3 eGFR groups ($P = 0.5$ for homogeneity; Fig 2). Table S3 shows a significant inverse trend between mean achieved 24-hour SBP and categories of eGFR in the treatment group (P for trend < 0.001).

A substantial number of patients were missing 24-hour CT imaging data. There were 923 patients with available hematoma growth data and 798 with perihematomal edema growth data (Fig S1). As shown in Table S4, there is no significant association between decreased eGFR and 24-hour hematoma and perihematomal edema growth (adjusted P for trend = 0.3 for both).

DISCUSSION

This study shows that reduced kidney function on admission is an independent predictor of poor outcome in patients with acute ICH, but this does not appear to be due to an effect of hematoma or perihematomal edema growth. However, there was no evidence of heterogeneity in the beneficial effect of early intensive BP lowering according to different eGFRs.

There is increasing awareness of the influence of kidney function on the outcome from acute stroke,[2-4,13,14] with previous studies being largely consistent in showing that reduced kidney function has independent significance in ischemic or undifferentiated stroke.[2-4] However, studies of the relationship between kidney function and outcomes in ICH are limited.[14-18] A multicenter study of 113,059 patients with ICH in the United States reported an association between kidney dysfunction and higher in-hospital mortality,[18] which confirmed results of other small studies of this

Table 2. Association Between Admission eGFR and Clinical Outcomes at 90 Days

		Univariable		Multivariable	
Outcome/Admission eGFR	No. of Events (%)	OR (95% CI)	P for trend	OR (95% CI)	P for trend
Death or major disability					
Normal or high eGFR[a]	661/1,431 (46)	1.00 (reference)	<0.001	1.00 (reference)	0.007[d]
Mildly decreased eGFR[b]	529/912 (58)	1.61 (1.36-1.90)		1.04 (0.83-1.31)	
Moderately/severely decreased eGFR[c]	200/280 (71)	2.91 (2.20-3.85)		1.82 (1.28-2.61)	
Death					
Normal or high eGFR[a]	124/1,431 (9)	1.00 (reference)	<0.001	1.00 (reference)	0.8[d]
Mildly decreased eGFR[b]	138/912 (15)	1.88 (1.45-2.43)		0.96 (0.69-1.34)	
Moderately/severely decreased eGFR[c]	49/280 (18)	2.24 (1.56-3.20)		1.08 (0.70-1.67)	
Major disability					
Normal or high eGFR[a]	537/1,431 (38)	1.00 (reference)	<0.001	1.00 (reference)	0.03[d]
Mildly decreased eGFR[b]	391/912 (43)	1.25 (1.06-1.48)		1.01 (0.82-1.24)	
Moderately/severely decreased eGFR[c]	151/280 (54)	1.95 (1.51-2.52)		1.51 (1.12-2.05)	

Abbreviations: CI, confidence interval; eGFR; estimated glomerular filtration rate; OR, odds ratio.

[a]eGFR >90 mL/min/1.73 m^2.

[b]eGFR of 60-90 mL/min/1.73 m^2.

[c]eGFR <60 mL/min/1.73 m^2.

[d]Adjusted for age, Chinese ethnicity, history of ischemic stroke, acute coronary syndrome, hypertension, diabetes mellitus, prior use of antithrombotics and statin, log-transformed time from onset to randomization, baseline systolic blood pressure, baseline National Institutes of Health Stroke Scale score (<14 and ≥14), hematoma volume (≤10, 11-20, and >20 mL) and location (lobar and nonlobar), intraventricular extension of intracerebral hemorrhage, and randomly assigned group.

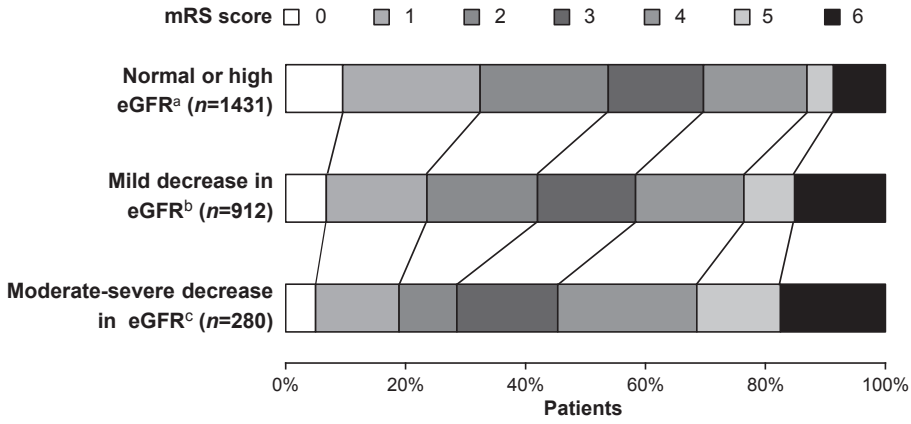

Figure 1. Baseline estimated glomerular filtration rate (eGFR) and modified Rankin Scale (mRS) score at 90 days. Crude odds ratios (ORs) of ordinal logistic regression analysis, 1.65 (95% confidence interval [CI], 1.43-1.92) for group with mildly decreased eGFR; and 2.58 (95% CI, 2.05-3.24) for the group with moderately/severely decreased eGFR in comparison to the normal- or high-eGFR group (P for trend < 0.001). Adjusted ORs of ordinal logistic regression analysis, 1.04 (95% CI, 0.88-1.23) for the group with mildly decreased eGFR; and 1.49 (95% CI, 1.15-1.93) for the group with moderately/severely decreased eGFR in comparison to thw normal- or high-eGFR group (P for trend $= 0.01$). [a] >90 mL/min/1.73 m^2. [b]60-90 mL/min/1.73 m^2. [c]<60 mL/min/1.73 m^2.

topic.[14-17] Nonetheless, these studies did not include data related to imaging findings[16-18] or functional outcome[14,15,18] and lacked the ability to fully adjust for confounding variables due to small sample sizes.[14-17] Our study largely overcomes these limitations by being based on a large population of well-characterized patients from a wide range of hospitals across 21 countries, and we also adjusted for various important confounders, such as ICH volume, ICH location, and baseline clinical status, that are components of the predictive ICH and the Functional Outcome in Patients with Primary Intracerebral Hemorrhage (FUNC) scores,[19,20] thus strengthening the evidence of an association between reduced kidney function and poor functional outcome in ICH.

The exact mechanisms underlying the relationship between reduced kidney function and poor outcomes after stroke are unknown, although some studies have proposed that it relates to effects on the initial size and growth of hematoma and perihematomal edema.[15,17] However, we have been unable to show a significant association between eGFR and 24-hour growth in hematoma and perihematomal edema volume. Because patients with decreased eGFRs are generally older, premorbid frailty related to aging is a plausible contributing factor to poor outcomes irrespective of ICH dynamics.[21,22] Other explanations include measures of brain frailty such as mild cognitive impairment and co-occurring depression, which is common in patients with CKD due to their high symptom

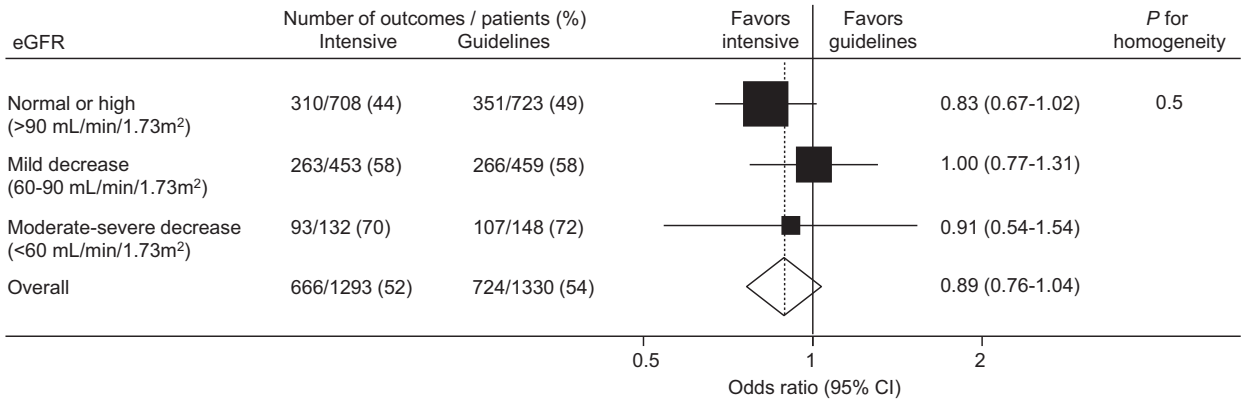

Figure 2. Effect of early intensive blood pressure lowering on death or major disability at 90 days by baseline estimated glomerular filtration rate (eGFR). Solid boxes represent estimates of treatment effect on risk for outcomes. Centers of the boxes are placed at the estimate of the effect; areas of the boxes are proportional to the reciprocal of the variance of the estimates. Horizontal lines represent 95% confidence interval (CIs); diamonds, estimates and 95% CIs for overall effects in total participants. INTERACT2 (Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial) had a reported odds ratio (OR) of 0.87 (95% CI, 0.75-1.01; $P = 0.06$) for the primary outcome of death or major disability with intensive treatment. Ordinal logistic regression analysis showed significantly lower modified Rankin Scale scores with intensive treatment (OR for greater disability, 0.87; 95% CI, 0.77-1.00; $P = 0.04$).[5]

burden and poor quality of life,[23,24] that could adversely affect rehabilitation potential and functional outcomes after stroke.[25-27] Prior studies have also shown that receiving maintenance hemodialysis is an independent indicator for poor functional outcome and mortality after stroke, possibly related to the presence of other comorbid conditions.[28,29] Finally, decreased erythropoietin production leading to anemia in patients with CKD[30] may contribute to secondary cerebral injury caused by neuronal tissue hypoxia, metabolic distress, and cell energy dysfunction.[31,32]

Decreased eGFR is a surrogate marker of cerebral small-vessel disease and is strongly associated with vascular risk factors.[1,33] We speculated that moderately/severely decreased eGFR indicates altered cerebral regulation from more advanced cerebral small-vessel disease.[1,23-35] In patients with stable cerebral autoregulation, decreases in cerebral perfusion pressure trigger compensatory vasodilation of resistance arterioles to preserve cerebral blood flow.[36] Conversely, autoregulatory failure may occur at higher cerebral perfusion pressures in patients with long-standing hypertension with altered cerebral autoregulation.[36] In the present analysis, the overall treatment effect was homogeneous across all eGFRs and the data do not show a deleterious effect of intensive BP lowering in groups with decreased eGFRs. Thus, our study supports findings of no relationship between the magnitude of BP reduction and perihematomal cerebral blood flow in patients with moderate ICH.[37] Intriguingly, the beneficial effect of intensive BP lowering appears to be marginally more pronounced in the group with normal or high eGFRs. This trend may be attributed to variations in achieved SBP during the initial 24 hours between eGFR groups due to possible BP treatment resistance in patients with decreased eGFRs (as evidenced by the higher number of BP-lowering agents required)[38,39] and/or more cautious BP reduction management by physicians in more vulnerable patients.

We recognize that this study has some limitations, such as the inability to obtain information for kidney-specific factors, for example, proteinuria prior to ICH onset. Information for possible causes of poor ICH outcomes in patients with decreased eGFRs, such as premorbid physical and cognitive function, depression symptoms, and baseline hemoglobin levels or anemia condition, was also unavailable. Due the limited number of hemodialysis patients in the study, we were also unable to assess its contribution to the prognosis of ICH. Furthermore, the present study includes patients from around the world and thus the CKD-EPI equation, which was developed using a sample of North American and European populations, may have led to overestimation of baseline kidney function measurements (especially in the Asian population) and biased results toward the null. Finally, because the data are derived from a clinical trial population in which patients with a poor prognosis and large hematoma were excluded, there may be concerns of the generalizability of the findings.

In summary, these analyses of the INTERACT2 database highlight the adverse prognostic significance of decreased admission eGFRs in patients with ICH, which appears independent of an effect of hematoma or perihematomal edema growth. However, early intensive BP-lowering treatment provides broadly consistent effects, even in patients with ICH with decreased eGFRs.

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SUPPLEMENTARY MATERIAL

Table S1: Characteristics of included and excluded patients.

Table S2: Association between eGFR and clinical outcome by antithrombotic use.

Table S3: Mean achieved SBP within 24 h after treatment randomization.

Table S4: Association between eGFR and 24-h hematoma and perihematomal edema growth.

Figure S1: Patient flow chart.

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