Accelerated Surgery Versus Standard Care in Hip Fracture (HIP ATTACK-1): A Kidney Substudy of a Randomized Clinical Trial

To the Editor:

Acute kidney injury (AKI) is a lesser-known complication of hip fracture that may come about owing to decreased kidney perfusion and heightened inflammation from trauma, pain, bleeding, and fasting.[1,2] Approximately 15%-20% of patients undergoing surgery for a hip fracture develop AKI, with 0.5%-1.8% receiving dialysis.[3-5] A strategy of accelerating the time to surgery after a hip fracture was recently compared with standard care in HIP ATTACK-1 (ClinicalTrials.gov identifier NCT02027896), a multinational randomized clinical trial.[6,7] Enrollment occurred March 2014 through May 2019, and 2,970 patients from 69 hospitals in 17 countries were randomized. Compared with standard care, accelerated medical assessment and surgical repair did not significantly lower the risk of the 2 co–primary outcomes (mortality and major perioperative complications), although it did decrease the risk of delirium, moderate-to-severe pain, and urinary tract infection, and resulted in faster mobilization and a shorter hospital stay.[7]

We conducted a prespecified kidney substudy of HIP ATTACK-1 to examine the effect of accelerated surgical treatment versus standard care on AKI in patients with a hip fracture.[8] Eligibility criteria for the main trial and the kidney substudy are provided in Table S1, and substudy methods are detailed in Item S1; minor changes in substudy execution compared to the published protocol[8] are summarized in Table S2. Briefly, eligible patients aged ≥45 years who presented to the emergency department with a hip fracture were randomly allocated (1:1) to receive accelerated surgical repair or standard care. The primary outcome of the substudy was AKI, defined as an Scr increase (from the prerandomization value) of ≥0.3 mg/dL (26.5 μmol/L) within 48 hours after randomization, or an increase of ≥50% within 7 days after randomization.[9] Six secondary definitions of AKI (listed in Item S1) were also examined.

Of 2,970 patients randomized in HIP ATTACK-1, 2,445 (82%) were included in the substudy (Figure S1). Baseline characteristics of patients in the substudy are shown in Table 1 (corresponding data for the main trial are in Table S3). The baseline, prerandomization Scr was obtained at the time of hospital admission for 99% of patients and before the hospital admission for 1%. The accelerated surgery group had surgery earlier than the standard care group and the mean between-group difference in the time from hip fracture diagnosis to surgery was 18 (95% CI, 15-20) hours.

AKI occurred in 13.5% (163/1,204) in the accelerated surgery group and in 14.9% (179/1,203) in the standard care group (postrandomization Scr was missing in 38 [1.6%] patients and was imputed using fully conditional specification for the primary analysis as described in Item S1). The relative risk (RR) was 0.91 (95% CI, 0.74-1.13), and the absolute risk difference was 1.3% (95% CI, −1.5% to 4.1%; Table 2). Results were similar in sensitivity analyses (Tables S4-S5). The mean between-group difference in the percentage and absolute change in Scr to the peak value was −1.5 (95% CI, −5.2 to 2.2) and −1.9 (95% CI, −5.1 to 1.3), respectively. The time to AKI after randomization in each group is shown in Figure S2. Pre-existing chronic kidney disease (CKD) did not significantly modify the effect of the accelerated surgery intervention versus standard care on AKI (Table S6), nor did prerandomization eGFR considered as a continuous variable ($P = 0.1$ for the interaction between the group allocation and eGFR).

The strengths of this substudy include its randomized concealed allocation, recruitment from 69 hospitals in 17 countries, and standardized collection of postrandomization Scr. Three limitations merit discussion. First, baseline Scr was obtained at the time of hospital admission for 99% of patients. Depending on the circumstances of the fracture, instability in the baseline measurement could complicate detecting an acute rise in postrandomization Scr, which is needed to identify AKI. That said, the average baseline Scr was 0.96 mg/dL, a level considered normal. Second, urine output data were not collected, given challenges with accurate measurement in an international setting. Third, we were underpowered to detect an RR reduction <30% for the primary AKI outcome. Therefore, we conducted prespecified analyses of the percentage change and the absolute change to the peak postrandomization Scr; however, no statistically significant between-group differences were observed.

In summary, the risk of perioperative AKI was not significantly different in patients allocated to accelerated surgery versus standard care for hip fracture. AKI occurred nearly twice as often in patients with versus without CKD (21% vs 11%); however, regardless of CKD status, the risk of AKI was not significantly lower with accelerated surgery versus standard care.

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Table 1. Baseline Characteristics and Surgical Details

	Accelerated Surgery (n = 1,216)	Standard Care (n = 1,229)
Sociodemographic characteristics		
Age, y	79 ± 12	79 ± 11
Female sex	852 (70%)	852 (69%)
Ethnicity		
White	755 (62%)	767 (62%)
Asian	363 (30%)	360 (29%)
Hispanic/Latino	50 (4%)	60 (5%)
Black/African descent	39 (3%)	38 (3%)
Other	9 (1%)	4 (<1%)
Health history before hip fracture		
History of tobacco use in 5 years before randomization	338 (28%)	294 (24%)
Residing in a nursing home	219 (18%)	234 (19%)
Comorbidities		
Hypertension	736 (61%)	750 (61%)
Needing assistance with activities of daily living	392 (32%)	431 (35%)
Diabetes	271 (22%)	250 (20%)
Dementia	210 (17%)	226 (18%)
Osteoporosis	201 (17%)	200 (16%)
Chronic obstructive pulmonary disease	127 (10%)	106 (9%)
Stroke	107 (9%)	95 (8%)
Myocardial infarction	103 (8%)	93 (8%)
Hip fracture	80 (7%)	104 (8%)
Congestive heart failure	86 (7%)	61 (5%)
Coronary revascularization	77 (6%)	72 (6%)
Chronic atrial fibrillation	63 (5%)	65 (5%)
Active cancer[a]	62 (5%)	61 (5%)
Transient ischemic attack	60 (5%)	67 (5%)
Peripheral vascular disease	37 (3%)	44 (4%)
Aortic stenosis	29 (2%)	25 (2%)
Deep venous thrombosis	21 (2%)	26 (2%)
Subarachnoid hemorrhage	15 (1%)	7 (1%)
Pulmonary embolism	13 (1%)	8 (1%)
Kidney failure receiving dialysis	0 (0%)	0 (0%)
Coronary artery bypass graft	42 (3%)	37 (3%)
Percutaneous coronary intervention	47 (4%)	41 (3%)
New diagnoses from time of hip fracture until randomization		
Infection	27 (2%)	27 (2%)
Atrial fibrillation	8 (1%)	9 (1%)
Significant hyponatremia or hypernatremia	8 (1%)	9 (1%)
Significant hypokalemia or hyperkalemia	9 (1%)	4 (<1%)
Non-ST-elevation MI without mechanical complication[b]	10 (1%)	4 (<1%)
MI with ST elevation or mechanical complication[b]	2 (<1%)	2 (<1%)
Congestive heart failure	0 (0%)	2 (<1%)
Glasgow Coma Scale <12 of unknown origin	2 (<1%)	1 (<1%)
Subarachnoid hemorrhage	1 (<1%)	2 (<1%)
Stroke	0 (0%)	1 (<1%)
Expanded acute medical condition[c]	66 (5%)	56 (5%)
Prerandomization physiological measurements		
Body mass index, kg/m^2	24 [21, 27]	24 [21, 27]
Obesity: body mass index ≥30 kg/m^2	129 (11%)	110 (10%)
Systolic blood pressure, mm Hg	141 [130, 160]	141 [126, 160]
Diastolic blood pressure, mm Hg	78 [70, 86]	77 [69, 85]
Heart rate, beats per minute	80 [71, 89]	80 [70, 90]
Prerandomization laboratory measurements		
Hemoglobin, g/L	121 ± 18	121 ± 18
Scr, mg/dL	0.95 ± 0.40	0.96 ± 0.41
eGFR, mL/min/1.73 m^2	69 ± 23	68 ± 22
<30 mL/min/1.73 m^2	59 (5%)	60 (5%)
30-44 mL/min/1.73 m^2	143 (12%)	156 (13%)
45-59 mL/min/1.73 m^2	212 (17%)	248 (20%)
60-89 mL/min/1.73 m^2	596 (49%)	582 (47%)
≥90 mL/min/1.73 m^2	206 (17%)	183 (15%)
Medications taken at least once 7 days to 24h before surgery		
ACEI/ARB	412 (34%)	410 (33%)
Antiplatelet agent	351 (29%)	322 (26%)
Statin	310 (25%)	327 (27%)
β-blocker	286 (24%)	274 (22%)
Prophylactic antithrombotic	59 (5%)	156 (13%)
Therapeutic dose vitamin K antagonist	37 (3%)	43 (4%)
Therapeutic non–vitamin K antagonist anticoagulant	25 (2%)	28 (2%)
Prothrombin complex concentrate	3 (<1%)	2 (<1%)
Medications taken ≤24h before surgery		
ACEI/ARB	288 (24%)	244 (20%)
Antiplatelet agent	201 (17%)	130 (11%)
Statin	223 (18%)	226 (18%)
β-blocker	215 (18%)	216 (18%)
Prophylactic antithrombotic	123 (10%)	325 (26%)
Therapeutic dose vitamin K antagonist	19 (2%)	4 (<1%)
Therapeutic non–vitamin K antagonist anticoagulant	22 (2%)	29 (2%)
Prothrombin complex concentrate	16 (1%)	8 (1%)
Type of fracture[d]		
Intertrochanteric	631 (52%)	638 (52%)
Femoral neck	527 (43%)	528 (43%)
Subtrochanteric	76 (6%)	71 (6%)
Other	2 (<1%)	1 (<1%)
Intraoperative anesthetic		
Neuraxial	766 (63%)	782 (64%)
General	406 (34%)	395 (33%)
General and neuraxial	36 (3%)	36 (3%)
Type of hip surgery performed		
Open reduction and internal fixation	779 (64%)	777 (63%)
Arthroplasty	427 (35%)	434 (35%)
Hemiarthroplasty	351 (29%)	356 (29%)
Total hip arthroplasty	71 (6%)	77 (6%)
Other arthroplasty	5 (<1%)	1 (<1%)
Other	3 (<1%)	1 (<1%)

Data presented as mean ± SD, median [25th, 75th percentile], or number (percentage). Body mass index was missing in 137 participants (6% in accelerated surgery group and 6% in standard care group); missing data on other variables was <2%. Abbreviations: ACEI/ARB, angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker; eGFR, estimated glomerular filtration rate (calculated with CKD-EPI equation[10]); MI, myocardial infarction; Scr, serum creatinine concentration.

[a]A patient with a diagnosis of cancer who is receiving, or has received, active cancer treatment (eg, chemotherapy, radiation, or surgery) in the previous 6 months.

[b]Mechanical complication included acute papillary muscle rupture or ventricular septal defect.

[c]Occurred after the hip fracture but before randomization (eg, cardiac or central nervous system conditions; full details in Item S2).

[d]Some patients had more than 1 type of fracture.

Table 2. Accelerated Hip-Repair Surgery Versus Standard Care and the Risk of AKI

	No. (%) of events[a]			
	Accelerated Surgery Group (n = 1,216)	Standard Care Group (n = 1,229)	RR (95% CI)[b]	*P*[c]
AKI	163/1,204 (13.5%)	179/1,203 (14.9%)	0.91 (0.74-1.13)	0.4
AKI or death[d]	166/1,216 (13.7%)	180/1,229 (14.7%)	0.93 (0.77-1.12)	–
Stage 2 AKI or higher[e]	35/1,215 (2.9%)	38/1,228 (3.1%)	0.93 (0.65-1.33)	–
Stage 3 AKI[f]	5/1,215 (0.4%)	12/1,228 (1.0%)	0.42 (0.20-0.91)	–
Receipt of dialysis[g]	0/1,213 (0.0%)	1/1,226 (0.1%)	–	–

[a]Based on all participants with at least 1 postrandomization Scr in the first 7 days after randomization.
[b]A modified Poisson regression model that accounts for the treating center and planned surgery type (open reduction and internal fixation or arthroplasty) was used to estimate the RR and 95% CI for AKI comparing the randomized groups. A missing outcome variable was imputed using multiple imputation; standard methods were used to combine estimates from each imputed dataset, as detailed in Item S2. For the outcomes of AKI or death, stage 2 AKI or higher, and stage 3 AKI, complete-case analysis was used, since <2 patients had missing outcome status.
[c]Calculated for the primary outcome only; for this analysis, missing data on postrandomization Scr (12 [1.0%] in the accelerated surgery group; 26 [2.1%] in the standard care group) were imputed using fully conditional specification (detailed in Item S2).
[d]A composite of AKI (primary outcome definition) or death within 48 hours after randomization. For patients with at least 48 hours of follow-up postrandomization (to assess the death outcome) who were missing all postrandomization Scr, a value of 0 (no AKI or death within 48 hours) was imputed.
[e]Defined as a postrandomization increase in Scr of ≥100% from the prerandomization value within 7 days after randomization or an increase to an absolute value of ≥4.0 mg/dL (353.6 μmol/L) within 7 days after randomization (when the primary outcome definition of AKI was met) or receipt of dialysis within 30 days after randomization. A patient was considered to have observed outcome data if ≥1 Scr was provided within 7 days after randomization or the patient was followed for ≥30 days after randomization to assess dialysis status.
[f]Defined as a postrandomization increase in Scr of ≥200% from the prerandomization value within 7 days after randomization or an increase to an absolute value of ≥4.0 mg/dL (353.6 μmol/L) within 7 days after randomization or receipt of dialysis within 30 days after randomization. A patient was considered to have observed outcome data if ≥1 Scr was provided within 7 days after randomization or the patient was followed for ≥30 days after randomization to assess dialysis status.
[g]Receipt of dialysis within 30 days after randomization. A patient was considered to have observed outcome data if the patient was followed for ≥30 days after randomization to assess dialysis status.

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Supplementary Material

Supplementary File (PDF)

Figures S1-S2; Items S1-S3; Tables S1-S6.

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