

BMJ Open Effects of accelerated versus standard care surgery on the risk of acute kidney injury in patients with a hip fracture: a substudy protocol of the hip fracture Accelerated surgical Treatment And Care track (HIP ATTACK) international randomised controlled trial

Flavia K Borges,^{1,2} P J Devereaux,^{2,3} Meaghan Cuerden,⁴ Mohit Bhandari,⁵ Ernesto Guerra-Farfán,⁶ Ameen Patel,¹ Alben Sigamani,⁷ Masood Umer,⁸ John Neary,¹ Maria Tiboni,¹ Vikas Tandon,¹ Mmampapatla Thomas Ramokgopa,^{9,10} Parag Sancheti,¹¹ Bobby John,¹² AbdelRahman Lawendy,¹³ Mariano Balaguer-Castro,¹⁴ Richard Jenkinson,^{15,16} Paweł Ślęczka,¹⁷ Aamer Nabi Nur,¹⁸ Gavin C A Wood,¹⁹ Robert Feibel,²⁰ John Stephen McMahon,²¹ Alen Sigamani,²² Bruce M Biccard,²³ Giovanni Landoni,^{24,25} Wojciech Szczeklik,²⁶ Chew Yin Wang,²⁷ Jordi Tomas-Hernandez,⁶ Valsa Abraham,¹² Jessica Vincent,² Valerie Harvey,² Shirley Pettit,² Jessica Sontrop,²⁸ Amit X Garg,^{3,4,28} On behalf of HIP ATTACK investigators

To cite: Borges FK, Devereaux PJ, Cuerden M, *et al.* Effects of accelerated versus standard care surgery on the risk of acute kidney injury in patients with a hip fracture: a substudy protocol of the hip fracture Accelerated surgical Treatment And Care track (HIP ATTACK) international randomised controlled trial. *BMJ Open* 2019;**9**:e033150. doi:10.1136/bmjopen-2019-033150

► Prepublication history and additional material for this paper are available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2019-033150>).

Received 22 July 2019
Revised 28 August 2019
Accepted 29 August 2019



© Author(s) (or their employer(s)) 2019. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

For numbered affiliations see end of article.

Correspondence to
Dr Amit X Garg;
amit.garg@lhsc.on.ca

ABSTRACT

Introduction Inflammation, dehydration, hypotension and bleeding may all contribute to the development of acute kidney injury (AKI). Accelerated surgery after a hip fracture can decrease the exposure time to such contributors and may reduce the risk of AKI.

Methods and analysis Hip fracture Accelerated surgical Treatment And Care track (HIP ATTACK) is a multicentre, international, parallel-group randomised controlled trial (RCT). Patients who suffer a hip fracture are randomly allocated to either accelerated medical assessment and surgical repair with a goal of surgery within 6 hours of diagnosis or standard care where a repair typically occurs 24 to 48 hours after diagnosis. The primary outcome of this substudy is the development of AKI within 7 days of randomisation. We anticipate at least 1998 patients will participate in this substudy.

Ethics and dissemination We obtained ethics approval for additional serum creatinine recordings in consecutive patients enrolled at 70 participating centres. All patients provide consent before randomisation. We anticipate reporting substudy results by 2021.

Trial registration number NCT02027896; Pre-results.

INTRODUCTION

Each year, millions of adults worldwide sustain a hip fracture and require surgical repair.^{1,2} Complications are common, and the

Strengths and limitations of this study

- Hip fracture accelerated surgical treatment and care track is a large international trial designed to address whether early surgery can improve outcomes in patients with a hip fracture.
- This substudy will provide robust estimates on the effects of early versus later surgery on the risk of acute kidney injury.
- Patients and providers are not blinded to the intervention; however, objective measures are used to assess outcomes and outcome assessors are blinded to the intervention assignment.

90-day risk of mortality is 10%–20%. Shortening the time to surgery shows promise for reducing patient morbidity and mortality,^{3–5} and this strategy is currently being tested in comparison with usual care in a multinational randomised controlled trial: the Hip fracture Accelerated surgical Treatment And Care track (HIP ATTACK) trial.⁶ HIP ATTACK has two coprimary outcomes: the 90-day risk of (1) all-cause mortality and (2) major perioperative complications.

One lesser known complication of hip fracture is acute kidney injury (AKI). The

development of AKI associates with a longer hospital stay, increased healthcare costs and a higher risk of death.^{7–9} Approximately 15%–20% of patients who undergo surgery for a hip fracture will experience AKI, with 0.5%–1.8% receiving dialysis as a result.^{10–12} A hip fracture exposes patients to trauma, pain, bleeding, hypotension and dehydration, which can lead to decreased renal perfusion and a heightened inflammatory state, all of which can contribute to the development of AKI.^{13 14} A shorter time to surgery after a hip fracture can decrease the exposure time to such contributors and therefore may reduce the risk of AKI.

This protocol describes a planned kidney substudy of the HIP ATTACK trial to determine if a strategy of accelerated medical assessment and surgical repair, compared with usual care, reduces the risk of AKI in patients who suffer a hip fracture. To do this, we worked with the investigators of the main trial during its planning stages and arranged to provide substudy funding to trial centres to collect additional follow-up measures of serum creatinine. A subgroup analysis by baseline chronic kidney disease (CKD), the most prominent risk factor for AKI, will also be conducted.¹⁵

METHODS AND ANALYSIS

Overview of the main HIP ATTACK trial

The HIP ATTACK trial is a multinational, parallel-group superiority randomised controlled trial of patients who present to the emergency department with a hip fracture requiring surgical repair. The main trial protocol is described elsewhere.⁶ Briefly, patients who sustained a hip fracture were randomly allocated (1:1) to receive accelerated medical assessment and surgical repair (with the goal of having the surgery performed within 6 hours after the orthopaedic diagnosis) or usual care (where a repair typically occurs 24–48 hours after diagnosis). Enrolment occurred between March 2014 and May 2019, and 3001 patients from 70 centres in 18 countries were randomised. Follow-up assessments will continue until August 2019 for the primary analysis. All participating centres obtained ethics board approval to conduct the trial, and all patients provided informed consent to trial participation before enrolling.

Patient recruitment, eligibility and informed consent

Patients were recruited from the emergency department. Eligibility criteria for the main HIP ATTACK trial are fully detailed in the published protocol.⁶ Eligible patients included those aged 45 years or older diagnosed with a hip fracture with a low-energy mechanism (eg, a fracture sustained from a fall not beyond standing height) requiring surgery. To align with the ability to deliver the trial intervention, the diagnosis had to be made during working hours. Exclusion criteria were as follows: (1) patients requiring emergent surgery or emergent interventions for another reason; (2) open hip fracture; (3) bilateral hip fractures; (4) periprosthetic fracture; (5) therapeutic anticoagulation for

which there is no reversing agent available; (6) patients on therapeutic vitamin K antagonist with a history of heparin induced thrombocytopenia (7) patients refusing participation and (8) patients previously enrolled in the trial.

All patients enrolled in HIP ATTACK after the centre of enrolment initiated kidney data collection will be included in the final substudy analysis with the exception of the following:

- i. Patients with prerandomisation end-stage kidney disease defined as prerandomisation estimated glomerular filtration rate (eGFR) <15 mL/min per 1.73 m², receipt of chronic dialysis or a kidney transplant. These patients will be excluded because the prevention of AKI is no longer relevant. We expect less than 2% of randomised patients to be excluded for this reason.
- ii. Patients with no prerandomisation serum creatinine measurement since this measure is needed to identify AKI, which is defined by an acute increase in serum creatinine from the prerandomisation value. We expect approximately 24% of patients to be excluded for this reason.

Randomisation

Randomisation was performed at the time of consent via an interactive web randomisation system maintained by the trial coordinating centre at the Population Health Research Institute, part of McMaster University in Hamilton, Ontario, Canada. This method ensures that the randomisation sequence is concealed from participating centres and patients. Patients were randomly allocated (1:1) to receive the intervention of accelerated medical clearance and surgery or usual care. The randomisation was performed using random permuted blocks of varying sizes that were unknown to research personnel and investigators. Stratification occurred by centre and planned surgery type (open reduction and internal fixation or arthroplasty). Due to the nature of the trial intervention, it was not possible to blind research personnel, health-care providers or participants to the randomised allocation; however, data collectors and outcome adjudicators were unaware of the patient's randomised allocation.

Trial intervention

The trial intervention was an accelerated medical assessment and surgical repair, with the goal of performing the surgery within 6 hours of the orthopaedic diagnosis. Patients underwent medical clearance by an on-call medical specialist (ie, an internist, geriatrician, cardiologist or anaesthesiologist) who was able to quickly come to the emergency department and perform the assessment. Specialists used their own clinical judgement and weighed the potential risks and benefits of rapidly clearing patients for surgery.^{3 6} The patient's orthopaedic surgeon and anaesthesiologist also had to agree that the patient was an appropriate surgical candidate. Following medical clearance, research personnel informed all relevant parties (ie, the surgical booking clerk, orthopaedic surgeon and anaesthesiologist), and patients were moved

to the next available orthopaedic trauma room or elective operating room such that their surgeries were prioritised over scheduled elective cases. All other perioperative care was at the discretion of the attending team. Further logistical details are provided in the pilot report and the main trial protocol.^{3 6}

Patients randomly allocated to the usual-care group were placed on the wait list for surgery according to local standard practices.

Substudy data collection

The prerandomisation (baseline) serum creatinine concentration was obtained from a review of medical records in the 30-day period before hip fracture surgery (as part of routine care, most patients have their serum creatinine tested at the time of emergency room presentation). The most recent test result before randomisation will serve as the baseline value. To accurately capture postrandomisation AKI, all study centres were given substudy funds to measure and record daily serum creatinine values for 7 days after randomisation or until hospital discharge, whichever came first. The highest serum creatinine value recorded between randomisation and hospital discharge was also recorded. Research personnel followed all patients daily during their time in hospital to improve adherence to the scheduled creatinine measurements. Receipt of new dialysis for kidney failure was recorded at hospital discharge and at 30 days after randomisation.

Substudy outcomes

The primary outcome of the kidney substudy is AKI, defined as an increase in the serum creatinine concentration from the prerandomisation value of ≥ 26.5 $\mu\text{mol/L}$ (≥ 0.3 mg/dL) within 48 hours after randomisation or an increase of $\geq 50\%$ within 7 days after randomisation.¹⁶

Secondary definitions of AKI

Six secondary assessments of AKI will be examined to assess whether the primary results are robust:

1. A composite of AKI (primary outcome definition) or death within 48 hours after randomisation which will serve to account for the potential impact of early deaths on outcome ascertainment.
2. Stage 2 AKI (or higher), defined as a postrandomisation increase in serum creatinine of 100% or more from the prerandomisation value within 7 days after randomisation or an increase to an absolute value of 353.6 $\mu\text{mol/L}$ or more (≥ 4.0 mg/dL) within 7 days after randomisation (when the primary outcome definition of AKI is met) or receipt of dialysis within 30 days after randomisation.
3. Stage 3 AKI, defined as a postrandomisation increase in serum creatinine of 200% or more from the prerandomisation value within 7 days after randomisation or an increase to an absolute value of 353.6 $\mu\text{mol/L}$ or more (≥ 4.0 mg/dL) within 7 days after randomisation or receipt of dialysis within 30 days after randomisation.
4. Receipt of dialysis within 30 days after randomisation.
5. Percentage change in serum creatinine in the first 7 days after randomisation, defined as follows: ((peak

postrandomisation serum creatinine—prerandomisation serum creatinine)/prerandomisation serum creatinine) times 100.

6. Absolute change in serum creatinine in the first 7 days after randomisation, defined as follows: peak postrandomisation serum creatinine—prerandomisation serum creatinine.

Statistical considerations

Sample size

The main HIP ATTACK trial enrolled 3001 patients, and more than 90% of these patients were enrolled after the initiation of the renal substudy protocol. We expect that approximately 74% of these patients will be eligible for inclusion in the kidney substudy. A sample of 1998 patients will provide over 80% power to detect a relative risk (RR) reduction of 30% for the primary outcome of AKI (two-sided $\alpha=0.05$), comparing the accelerated approach to usual care, assuming the incidence of AKI is 14% in the usual-care group, after accounting for 4% missing AKI status. Approximately 10%–12% of patients develop postoperative AKI.^{17 18} In hip fracture patients, AKI incidence is even higher, around 15%–20%.^{10–12} With these data in mind, we used a conservative 14% AKI incidence for the usual care group to perform the sample size calculation to ensure we would have adequate statistical power to detect a 30% RR reduction in the primary outcome, if it in truth exists.

Statistical analysis plan

In the primary analysis (intention to treat), a modified Poisson regression model which accounts for the treating centre will be used to estimate the RR and 95% CI for AKI comparing the intervention group to the usual-care group.^{19 20} For patients enrolled in the substudy without a postrandomisation serum creatinine value (expected for $\leq 4\%$ of patients), for the primary analysis model-based multiple imputation methods, using all available data, will be used to impute AKI status.^{18 21 22} Parameters will be estimated using standard methods while allowing for extra imputation variability.²³ A two-tailed p value <0.05 will be considered statistically significant. In our experience, with previous AKI perioperative substudies of large clinical trials, the unadjusted and adjusted results were virtually identical,^{18 24 25} and therefore we have not prespecified any adjusted analyses for this substudy.

Prespecified supporting analyses

Several supporting analyses will be conducted to examine whether there is concordance with the primary analysis. These will include a complete case analysis, an examination of six secondary assessments of AKI and a subgroup analysis of patients with prerandomisation CKD.

Complete case analysis

We will perform a complete case analysis restricted to patients with at least one postrandomisation serum creatinine measurement which is expected to involve greater than 96% of patients in the primary analysis.

Alternative secondary assessments of AKI

We will examine six secondary assessments of AKI (four categorical and two continuous, as described above). RR estimates will be estimated using modified Poisson regression models and continuous outcomes using linear regression models. We will visually inspect the point estimates and 95% CIs and assess concordance with the primary analysis. Given our sample size, analyses of severe AKI will have limited statistical power for small effects.

Subgroup analysis

The risk of AKI will be examined in patients with and without CKD as defined by a prerandomisation eGFR <60 mL/min per 1.73 m² as assessed with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.²⁶ We hypothesise a greater absolute risk reduction of AKI with accelerated versus routine surgery in patients with CKD compared with patients without CKD. The p value for the interaction (CKD × intervention group) will be assessed in a regression model for binary outcome data.

Patient and public involvement statement

There was no direct patient involvement in designing this substudy. Previously, we reported the patient involvement in the main trial in the HIP ATTACK protocol paper.⁶

ETHICS AND DISSEMINATION

We obtained ethics approval in all centres, and all patients provided informed consent before randomisation (see online supplementary material). The dissemination policy will include publication in a peer-reviewed journal and presentations at relevant conferences. The clinical results of this substudy will be incorporated in the HIP ATTACK dissemination plan, including reporting the results in the HIP ATTACK open website (<http://www.hipattacktrial.com>), the HIP ATTACK Twitter account (@HIPATTACKTrial), LinkedIn Profile, the Facebook page and the Reducing Global Perioperative Risk Multimedia Resource Center. This is an online media linked to Elsevier's entire international readership, through which we will disseminate the full-text articles, links to abstracts and data summaries. We expect the substudy results to be reported by 2021.

DISCUSSION

HIP ATTACK is a multinational randomised controlled trial that will determine if a strategy of accelerated medical clearance and surgery compared with usual care improves outcomes for patients with a hip fracture. The present protocol describes a prespecified kidney substudy of HIP ATTACK that will examine the effect of this strategy on the risk of AKI.

AKI is a known consequence of surgery. By adding additional serum creatinine measurements to HIP ATTACK, we will efficiently and reliably determine whether a strategy of accelerated medical clearance and hip surgery reduces

the risk of AKI compared with a usual care. The strengths of this substudy include its randomised trial methodology with concealed allocation, patient recruitment from 70 centres across 18 countries and standardised collection of postrandomisation serum creatinine. The primary outcome and statistical analysis plan are prespecified, and multiple sensitivity analyses are planned to examine the robustness of the primary results.

This substudy has some limitations. First, given the trial's design, we expect that approximately 76% of patients' baseline (prerandomisation) serum creatinine will be obtained at the time of emergency room presentation for hip fracture, and depending on the circumstances of the fracture, some of these patients' serum creatinine concentrations may be unstable or elevated. Instability in baseline serum creatinine may make it difficult to detect an acute rise in postrandomisation serum creatinine, which is needed for the identification of AKI. To examine this issue, we will compare the mean baseline serum creatinine concentration in a subset of patients with serum creatinine measurements before and after hip fracture. Second, similar to other perioperative studies,^{18 24 25} urine output data are not collected in HIP ATTACK given the difficulties with accurate measurement in the setting of international data collection. Third, the most clinically relevant renal outcome would be new kidney failure treated with dialysis. Although we are measuring this outcome, we anticipate that it will occur infrequently (<1%), and therefore the analysis of this outcome will have limited statistical power. Finally, we have over 80% power to detect a 30% or more relative risk reduction in our primary outcome of AKI. As previously described, we will examine changes in the perioperative concentration of serum creatinine as a continuous measure, which might be of particular relevance if the primary outcome is not significant and there are concerns that this is due to a lack of statistical power.

In summary, this prespecified substudy of HIP ATTACK, a large multinational trial, will address the question whether a strategy of accelerated medical clearance and surgery for hip fracture improves renal outcomes.

Author affiliations

¹Department of Medicine, McMaster University, Hamilton, Ontario, Canada

²Department of Perioperative Medicine, Population Health Research Institute, Hamilton, Ontario, Canada

³Departments of Health Research Methods, Evidence, and Impact (HEI), McMaster University, Hamilton, Ontario, Canada

⁴Division of Nephrology, Department of Medicine, Western University, London, Ontario, Canada

⁵Department of Surgery, McMaster University, Hamilton, Ontario, Canada

⁶Department of Orthopaedic Surgery and Traumatology, University Hospital Vall d'Hebron, Barcelona, Spain

⁷Clinical Research, Narayana Hrudayalaya Limited, Bangalore, India

⁸Department of Orthopaedic Surgery, Aga Khan University, Karachi, Pakistan

⁹Department of Orthopaedic Surgery, Chris Hani Baragwanath Academic Hospital, Johannesburg, South Africa

¹⁰Department of Orthopaedic Surgery, University of the Witwatersrand, Johannesburg, South Africa

¹¹Department of Orthopaedic Surgery, Sancheti Institute for Orthopaedics & Rehabilitation, Pune, India

- ¹²Department of Orthopaedic Surgery, Christian Medical College and Hospital Ludhiana, Ludhiana, India
- ¹³Department of Surgery, Western University, London, Ontario, Canada
- ¹⁴Department of Orthopaedic Surgery and Traumatology, Parc Taulí Hospital Universitari, Institut d'Investigació i Innovació Parc Taulí I3PT, Universitat Autònoma de Barcelona, Sabadell, Spain
- ¹⁵Department of Surgery and Institute of Health Policy Management and Evaluation, University of Toronto, Toronto, Ontario, Canada
- ¹⁶Department of Surgery, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada
- ¹⁷Orthopaedic Department, SPZOZ, Myslenice, Poland
- ¹⁸Department of Orthopaedic Surgery, Shifa International Hospital, Islamabad, Pakistan
- ¹⁹Department of Surgery, Queen's University, Kingston, Ontario, Canada
- ²⁰Division of Orthopaedic Surgery, Department of Surgery, University of Ottawa, Ottawa, Ontario, Canada
- ²¹Department of Surgery, Markham Stouffville Hospital, Markham, Ontario, Canada
- ²²Department of Orthopaedic, Government TD Medical College, Allapuzha, India
- ²³Department of Anaesthesia and Perioperative Medicine, University of Cape Town, Rondebosch, South Africa
- ²⁴Department of Anaesthesia and Intensive Care, IRCCS San Raffaele Scientific Institute, Milan, Italy
- ²⁵Department of Anaesthesia and Intensive Care, Vita-Salute San Raffaele University, Milan, Italy
- ²⁶Department of Intensive Care and Perioperative Medicine, Jagiellonian University Medical College, Krakow, Poland
- ²⁷Department of Anaesthesiology, University Malaya, Kuala Lumpur, Malaysia
- ²⁸Department of Epidemiology and Biostatistics, Western University, London, Ontario, Canada

Collaborators Population Health Research Institute Coordinating Centre: V. Harvey (Trial Coordinator), J. Vincent, S. Dragic-Taylor, S. Molnar, S. Pettit, J.R. Wells Trial Monitoring Committee: R. Roberts, Chairperson (McMaster University), F. McAlister (University of Alberta), D. Sackett (McMaster University), J. Wright (University of Oxford) Participating Countries, Centres, and Investigators (recruitment in brackets): Belgium (47) – *Cliniques Universitaires Saint-Luc* (32): L. Veevaete, B. le Polain de Waroux, A. Dekleermaker; *UZ Brussel* (15): P. Forget, M. Reul; Canada (983) – *Juravinski Hospital and Cancer Centre* (293): D. Cowan, A. Worster, G. Guyatt, C. Kearon, D. Simpson, K. Gregus, K. Lawrence; *St. Joseph's Healthcare* (134): A. Adili, V. Khanna, D. Conen, J. Farrell; *Sunnybrook Health Sciences Centre* (81): H.J. Kreder, S. Choi, S. Shadowitz, J.S. Lee; *Thunder Bay Regional Health Sciences Centre* (37): D. Puskas, C. Cullinan, K. Droll; *St. Michael's Hospital* (44): A. Nauth, T. Daniels, M.R. Vicente; *William Osler Health System, Etobicoke General Hospital* (13): A. Sharma; *Vancouver General Hospital* (5): P. Guy; *Kingston Health Sciences Centre* (75): M. Sivilotti, M. Jaeger; S. Mann, F. Howells; *Markham Stouffville Hospital* (58): L.M. McLean, H. Shirali; *London Health Sciences Centre, Victoria Hospital* (92): G.K. Dresser, D.W. Sanders, E.H. Schemitsch, W. Kishta; *The Ottawa Hospital, General Campus* (60): C. Gallant, S. Halman, K.M. McClquham, V. Thiruganasambandamoorthy; *QE II Health Sciences Centre* (25): C.P. Coles, K. Trask; *Humber River Hospital* (2): A.W. Duncan; *University of Alberta* (30): M.J. Jacka, M. Menon; *Concordia Hospital* (12): T.R. Turgeon; *University of Calgary* (13): N.J. White; *Grand River Hospital* (8): S. Gillick; *Royal Victoria Hospital* (1): G. Crawford; China (28) – *Beijing Chaoyang Hospital* (28): J. Zhou; Colombia (1) – *Fundación Cardioinfantil* (1): J.M. Muñoz McCausland; France (46) – *Centre Hospitalier Lyon Sud* (43): P. Chaudier, M. Douplat; *Nîmes University Hospital* (3): P. Landais; Hong Kong (12) – *The University of Hong Kong, Queen Mary Hospital* (12): C.X. Fang; India (471) – *PGIMER* (23): M.S. Dhillon; *Rabindranath Tagore International Institute of Cardiac Sciences, Kolkata* (9): S.U. Singh; *JIPMER* (45): S. Adinarayanan, D. Sharma; *Government TD Medical College Alappuzha* (50): M. Stephen, M. Ashraf; *Sancheti Institute for Orthopaedics & Rehabilitation* (102): C.V. Pradhan, M.P. Borate, A. Shyam; *Bangalore Baptist Hospital* (44): Niranjana M.; S.A. Hiremath, Z.K. Varghese; *SPARSH Hospital* (16): S. Patil; *All India Institute of Medical Sciences* (40): V. Sharma, K. Farooque, R. Malhotra; Christian Medical College & Hospital Ludhiana (100): R.A. Pandey, A.R. Kumar, P. George; *Government Medical College, Trivandrum* (35): P.M. Menon; *Seven Star Hospital* (7): R.P. Dashputra; Italy (93) – *IRCCS San Raffaele Scientific Institute* (25): G. Gioia, E. Colnaghi; *ASST Settelaghi, Varese* (14): M. Binda; *IRCCS Galeazzi Orthopedic Institute* (46): M. Turiet; *Humanitas Research Hospital* (8): M. Cecconi; Malaysia (67) – *University Malaya Medical Centre* (49): C.S. Kumar, P.S. Loh, K.H. Chee; *Hospital Pulau Pinang* (18): M.L. Lee; Netherlands (35) – *Deventer Hospital* (35): Y.V. Kleinlugtenbelt, E.B.M. Landman; Pakistan (244) – *Shifa International Hospital* (78): K.A. Janjua, A.S. Khan, S.H. Orakzai, M.

Ashraf; *Aga Khan University* (166) P.M. Hashmi, R.H. Lakdawala, M.J. Khattak, H. Rashid, D. Begum; Poland (86) – *SPZOZ Myslenice* (81): J.W. Rycombel, W. Satora, W. Ambroży, A. Grzelak; *Medical University in Lodz* (1): W. Machala; *SPZOZ Szpital Powiatowy w Bochni im M. Wieckiej* (4): J. Gucwa; South Africa (131) – *University of Witwatersrand* (114): G. Firth, A. Grisillo-Biscardi, G. Karera, M. Fourtounas; *Groote Schuur Hospital* (12): M. Nejtardt; *Tygerberg Hospital, Stellenbosch University* (5): S. Chetty; Spain (534) – *Vall d'Hebron University Hospital* (300): Jordi Teixidor-Serra, V. Molero-García, J. Minguell-Monyart, Y. García-Sánchez, J.A. Porcel-Vázquez, J. Selga-Marsà, M. Villar-Casares, J. Mestre-Torres; *Hospital Universitario Costa del Sol* (17): E. Guerado, E. Cruz; *Hospital de la Santa Creu I Sant Pau* (26): E. Popova, J.D. Caso, J.L. Higa-Sansone, R. Anaya; *Hospital Universitari Mútua Terrassa* (41): P. Castillón, M. Bernaus, S. Quintas; *Parc Taulí Hospital Universitari* (87): P. Torner, F.A. Marcano-Fernández, M. Jornet-Gibert, J. Càmarra-Cabrera; *Consorci Sanitari del Garraf* (37): A. D. Andrés, O.M. Pérez, L.A. Ivanov; *Hospital Clínico Universitario de Valladolid* (26): H.J. Aguado; Thailand (36) – *Ramathibodi Hospital* (36): P. Sangasongsong; United Kingdom (82) – *Chelsea and Westminster Hospital* (17): M.P. Vizcaychipi; *Peterborough City Hospital* (6): M.J. Parker; *West Middlesex University Hospital* (32): M.A. Kadry, S. Thayaparan; *Sherwood Forest Hospitals* (11): J. John; *Calderdale & Huddersfield NHS Foundation Trust* (16): A.S.E. Mayor; United States (76) – *Tufts Medical Center* (15): S.P. Ryan; *The Ohio State University* (13): S.D. Bergese; *Lahey Hospital & Medical Center* (3): A.J. Marcantonio; *University of Maryland* (18): G.P. Slobogean; *University of California San Francisco* (27): M.T. Marmor; Venezuela (29) – *Hospital Universitario de Caracas* (29): I.A. Escalante Elguezabal, C.G. Sanchez Valenciano

Contributors FKB, PJD, MC, JMS and AXG: wrote the first draft of the protocol manuscript. FKB, PJD, MC, MB, EGF, AP, AS, MU, JN, MT, VT, MTR, Psa, BJ, ARL, MBC, RJ, PSI, ANN, GCAW, RF, JSM, AS, BMB, GL, WS, CYW, JTH, VA, JV, VH, SP, JMS, AXG planned the conceptualisation and the design of the study and the protocol. All authors contributed to critical revisions of the current manuscript.

Funding This work was supported by the following grants: Canadian Institute of Health and Research (CIHR) Foundation Award, CIHR's Strategy for Patient Oriented Research (SPOR), through the Ontario SPOR Support Unit, which is supported by the CIHR and the Province of Ontario, as well as the Ontario Ministry of Health and Long-Term Care, and a grant from Smith & Nephew to recruit 300 patients in Spain. Grants to support this substudy were provided by the Department of Medicine at Western University. Dr Devereaux was supported by a Tier 1 Canada Research Chair in Perioperative Medicine. Dr Amit Garg was supported by the Dr Adam Linton Chair in Kidney Health Analytics and a CIHR Clinician Investigator Award.

Disclaimer The conduct, trial analyses, the composing of this manuscript and its final contents are solely the author's incumbency.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval Hamilton Integrated Research Ethics Board. number 14-058. All other Ethics board are listed on the Supplementary File, Ethics Committees – pages 4 to 6.

Provenance and peer review Not commissioned; externally peer reviewed.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

REFERENCES

1. Leslie WD. Trends in hip fracture rates in Canada. *JAMA* 2009;302.
2. Woolf AD, Pflieger B. Burden of major musculoskeletal conditions. *Bull World Health Organ* 2003;81:646–56.
3. The Hip Fracture Accelerated Surgical Treatment and Care Track (HIP ATTACK) Investigators. Accelerated care versus standard care among patients with hip fracture: the hip attack pilot trial. *Can Med Assoc J* 2014;186:E52–60.
4. Simunovic N, Devereaux PJ, Sprague S, et al. Effect of early surgery after hip fracture on mortality and complications: systematic review and meta-analysis. *Can Med Assoc J* 2010;182:1609–16.
5. Klestil T, Röder C, Stotter C, et al. Impact of timing of surgery in elderly hip fracture patients: a systematic review and meta-analysis. *Sci Rep* 2018;8:13933.
6. Borges FK, Bhandari M, Patel A, et al. Rationale and design of the hip fracture accelerated surgical treatment and care track (hip

- attack) trial: a protocol for an international randomised controlled trial evaluating early surgery for hip fracture patients. *BMJ Open* 2019;9:e028537.
7. Coca SG, Yusuf B, Shlipak MG, et al. Long-Term risk of mortality and other adverse outcomes after acute kidney injury: a systematic review and meta-analysis. *Am J Kidney Dis* 2009;53:961–73.
 8. Ricci Z, Cruz D, Ronco C. The rifle criteria and mortality in acute kidney injury: a systematic review. *Kidney Int* 2008;73:538–46.
 9. Chertow GM, Burdick E, Honour M, et al. Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. *JASN* 2005;16:3365–70.
 10. Bennet SJ, Berry OMB, Goddard J, et al. Acute renal dysfunction following hip fracture. *Injury* 2010;41:335–8.
 11. Ulucay C, Eren Z, Kaspar EC, et al. Risk factors for acute kidney injury after hip fracture surgery in the elderly individuals. *Geriatr Orthop Surg Rehabil* 2012;3:150–6.
 12. Hong SE, Kim T-Y, Yoo J-H, et al. Acute kidney injury can predict in-hospital and long-term mortality in elderly patients undergoing hip fracture surgery. *PLoS One* 2017;12:e0176259.
 13. Sharfuddin AA, Molitoris BA. Pathophysiology of ischemic acute kidney injury. *Nat Rev Nephrol* 2011;7:189–200.
 14. Kinsey GR, Li L, Okusa MD. Inflammation in acute kidney injury. *Nephron Exp Nephrol* 2008;109:e102–7.
 15. Chawla LS, Eggers PW, Star RA, et al. Acute kidney injury and chronic kidney disease as interconnected syndromes. *N Engl J Med* 2014;371:58–66.
 16. Kidney disease: improving global outcomes (KDIGO) acute kidney injury work group. KDIGO clinical practice guideline for acute kidney injury. *Kidney Int Suppl* 2012;2:1–138.
 17. Abelha F, Botelho M, Fernandes V, et al. Determinants of postoperative acute kidney injury. *Crit Care* 2009;13.
 18. Garg AX, Kurz A, Sessler DI, et al. Perioperative aspirin and clonidine and risk of acute kidney injury: a randomized clinical trial. *JAMA* 2014;312:2254–64.
 19. Zou GY, Donner A. Extension of the modified poisson regression model to prospective studies with correlated binary data. *Stat Methods Med Res* 2013;22:661–70.
 20. Zou G. A modified poisson regression approach to prospective studies with binary data. *Am J Epidemiol* 2004;159:702–6.
 21. Little RJ, D'Agostino R, Cohen ML, et al. The prevention and treatment of missing data in clinical trials. *N Engl J Med* 2012;367:1355–60.
 22. Carpenter JR, Kenward MG. Missing data in randomised controlled trials: a practical guide. Available: <https://pdfs.semanticscholar.org/e9c4/6359114e7eb6fd17d3ff93fec7ce54479ef5.pdf> [Accessed 7 Feb 2017].
 23. Van Buuren S, Brand JPL, Groothuis-Oudshoorn CGM, et al. Fully conditional specification in multivariate imputation. *J Stat Comput Simul* 2006;76:1049–64.
 24. Garg AX, Devereaux PJ, Yusuf S, et al. Kidney function after off-pump or on-pump coronary artery bypass graft surgery: a randomized clinical trial. *JAMA* 2014;311:2191–8.
 25. Garg AX, Chan MTV, Cuerden MS, et al. Effect of methylprednisolone on acute kidney injury in patients undergoing cardiac surgery with a cardiopulmonary bypass pump: a randomized controlled trial. *Can Med Assoc J* 2019;191:E247–56.
 26. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009;150:604–12.