

1 **Accelerated surgery versus standard care in hip fracture (HIP ATTACK):**

2 **An international, randomised, controlled trial**

3

4 **The HIP ATTACK Investigators**

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6 **Summary word count: 264**

7 **Text word count: 4,471**

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9 **SUMMARY**

10 **Background:** Observational studies have suggested that accelerated surgery is associated with
11 improved outcomes in patients with a hip fracture. The HIP ATTACK trial assessed whether
12 accelerated surgery could reduce mortality and major complications.

13 **Methods:** We randomised 2970 patients from 69 hospitals in 17 countries. Patients with a hip
14 fracture that required surgery and were ≥ 45 years of age were eligible. Patients were randomly
15 assigned to accelerated surgery (goal of surgery within 6 hours of diagnosis; 1487 patients) or
16 standard care (1483 patients). The co-primary outcomes were 1.) mortality, and 2.) a composite
17 of major complications (i.e., mortality and non-fatal myocardial infarction, stroke, venous
18 thromboembolism, sepsis, pneumonia, life-threatening bleeding, and major bleeding) at 90 days
19 after randomisation. Outcome adjudicators were masked to treatment allocation, and patients
20 were analysed according to the intention-to-treat principle; ClinicalTrials.gov, NCT02027896.

21 **Findings:** The median time from hip fracture diagnosis to surgery was 6 hours (interquartile
22 range [IQR] 4-9) in the accelerated-surgery group and 24 hours (IQR 10-42) in the standard-care
23 group, $p < 0.0001$. Death occurred in 140 patients (9%) assigned to accelerated surgery and 154
24 patients (10%) assigned to standard care; hazard ratio (HR) 0.91, 95% CI 0.72-1.14; absolute risk
25 reduction (ARR) 1%, 95% CI -1-3%; $p = 0.40$. The primary composite outcome occurred in 321
26 patients (22%) randomised to accelerated surgery and 331 patients (22%) randomised to standard
27 care; HR 0.97, 95% CI 0.83-1.13; ARR 1%, 95% CI -2-3%; $p = 0.71$.

28 **Interpretation:** Among patients with a hip fracture, accelerated surgery did not significantly
29 lower the risk of mortality or a composite of major complications compared to standard care.

30 **Funding:** Canadian Institutes of Health Research.

31

32 INTRODUCTION

33 Worldwide, >1.5 million adults suffer a hip fracture each year.¹ Non-surgical
34 management of a hip fracture is associated with a low probability of remaining ambulatory and
35 an increased risk of chronic pain and mortality.^{2,3} In high-income countries, approximately 95%
36 of hip fractures are managed surgically.^{4,5} Patients undergoing hip fracture surgery have higher
37 risk-adjusted mortality and major complications than patients undergoing elective total hip
38 replacement surgery, suggesting hip fractures, independent of surgery, increase patients' risks.⁶

39 Patients who suffer a hip fracture are at substantial risk of major complications (i.e.,
40 cardiovascular, infectious, bleeding, and neuro-cognitive) and mortality.⁷⁻⁹ Observational studies
41 suggest that accelerated surgery for a hip fracture is associated with a lower risk of mortality and
42 major complications.^{10,11} Hip fractures result in pain, bleeding, and immobility, and activate
43 inflammatory, hypercoagulable, catabolic, and stress states that can precipitate medical
44 complications.¹²⁻¹⁵ Accelerated surgery will reduce the time patients are exposed to these
45 harmful states and therefore may reduce the risk of medical complications and mortality. We
46 undertook the *HIP* fracture *Accelerated surgical Treatment And Care track* (HIP ATTACK) trial
47 to determine whether accelerated surgery for hip fracture was superior to standard care in
48 reducing death or other major complications.

49

50 METHODS

51 Study design, patients, and patient engagement

52 We undertook this investigator-initiated, randomised, controlled trial at 69 hospitals in 17
53 countries (i.e., Canada, Spain, India, Pakistan, South Africa, Italy, Poland, United Kingdom,
54 United States, Malaysia, Belgium, France, Thailand, Netherlands, China, Hong Kong,
55 Colombia). We have previously reported details of the trial design and methods.^{16,17} Study

56 personnel recruited patients from March 14, 2014 to May 24, 2019. Before commencing
57 recruitment, all centres obtained ethics approval, and the relevant health authorities approved the
58 protocol.

59 Eligible patients were ≥ 45 years of age and diagnosed during regular working hours with
60 a low-energy mechanism hip fracture that required surgery. Centres defined their study hours
61 based on the local regular working hours. We excluded patients taking a therapeutic-dose of an
62 anticoagulant for which no reversing agent was available, with a history of heparin induced
63 thrombocytopenia if they were taking a therapeutic-dose vitamin K antagonist, with a peri-
64 prosthetic or open fracture, with bilateral fractures, requiring an emergency surgery for another
65 reason (e.g., subdural hematoma), refusing consent, or previously enrolled in HIP ATTACK.

66 Our approach to patient engagement was guided by the Canadian Institutes of Health
67 Research (CIHR) Strategy for Patient-Oriented Research Patient Engagement Framework.¹⁷
68 Patients were involved in trial governance auditing and provided input on the importance of the
69 trial outcomes.

70

71 **Randomisation and masking**

72 Patients were randomly assigned (1:1) to accelerated surgery (i.e., goal of surgery within
73 6 hours of hip fracture diagnosis) or standard care. Our objective with accelerated surgery was
74 to facilitate surgery as quickly as possible. We selected a goal of 6 hours because we knew this
75 was a substantial improvement beyond standard care and achieving this target was feasible,
76 based on the HIP ATTACK pilot. After obtaining consent from the patient or substitute decision
77 maker, research personnel randomised patients through a central computerised randomisation
78 system using randomly varying block sizes. Study personnel and investigators were unaware of

79 the block sizes. Randomisation was stratified by centre and type of planned surgery (i.e.,
80 arthroplasty or open reduction and internal fixation). Patients, healthcare providers (e.g.,
81 physicians undertaking preoperative medical clearance, anaesthesiologists, surgeons), and study
82 personnel were aware of patients' allocated treatment assignment. Outcome adjudicators were
83 masked to treatment allocation.

84

85 **Procedures**

86 Patients randomised to accelerated surgery underwent medical clearance by physicians
87 who were available to rapidly evaluate these patients. After obtaining medical clearance, these
88 patients moved into the next orthopaedic elective or trauma operating room slot (i.e., they were
89 prioritised over elective cases and other non-emergent trauma cases). Any displaced elective
90 cases were moved to the subsequent slot and, to avoid cancellation of any moved elective cases,
91 when needed an extra operating room slot was facilitated at the end of the day. Patients
92 randomised to standard care underwent medical clearance and were waitlisted for surgery
93 according to local standard practices. All patients in the accelerated-surgery and standard-care
94 groups underwent medical assessment and clearance before surgery. The difference between the
95 groups was that a physician was available to undertake rapid medical assessment of patients in
96 the accelerated-surgery group, whereas patients in the standard-care group were seen and
97 medically cleared by a physician according to standard-care timelines (i.e., their medical
98 assessment was not expedited).

99 All patients received the same structured follow-up for outcomes. For the first 7 days
100 after randomisation, patients had daily troponin measurements and were assessed for delirium

101 with the confusion assessment method (CAM).¹⁸ Patients were followed in hospital and
102 contacted at 30 and 90 days after randomisation to determine trial outcomes.

103

104 **Outcomes and adjudication**

105 The co-primary outcomes were 1.) mortality and 2.) a composite of major complications
106 (i.e., mortality and non-fatal myocardial infarction, stroke, venous thromboembolism, sepsis,
107 pneumonia, life-threatening bleeding, and major bleeding) at 90 days after randomisation. The
108 Appendix presents secondary and tertiary outcomes and all outcome definitions. Trained
109 physicians, masked to the treatment allocation, adjudicated the following outcomes: myocardial
110 infarction, myocardial injury not fulfilling the definition of myocardial infarction, congestive
111 heart failure, non-fatal cardiac arrest, stroke, pulmonary embolism, deep vein thrombosis,
112 pneumonia, sepsis, and bleeding. Adjudicated events were used for the analyses.

113

114 **Trial Monitoring**

115 Monitoring in HIP ATTACK consisted of central data consistency checks, statistical data
116 monitoring, and site monitoring. Site monitoring occurred at hospitals that randomised ≥ 40
117 patients or stood out on central data consistency checks or statistical data monitoring. For site
118 monitoring, the study statistician randomly selected participants with and without primary
119 outcomes, and independent monitors audited their hospital charts and supporting documents.
120 Site monitoring occurred at 26 hospitals that randomised 76% of the trial patients. Study
121 personnel corrected any data errors identified through central data consistency checks or site
122 monitoring. Central data consistency checks and statistical monitoring raised concerns regarding

123 3 centres that had major issues during site monitoring. Data from these sites (total of 65 patients)
124 were removed and further details are provided in the Appendix.

125

126 **Statistical considerations**

127 HIP ATTACK was originally designed to randomise 1200 patients, and the primary
128 outcome was time to a composite of major complications at 30 days of follow-up. At an
129 Investigator Meeting in April 2017, without knowledge of the trial results, a decision was made
130 to increase the sample size to 3000 patients with 2 co-primary outcomes of mortality and a
131 composite of major complications at 90 days of follow-up. This increase in sample size was
132 needed to provide adequate power for the new co-primary outcome of mortality. For the
133 comparison of accelerated surgery versus standard care, a sample size of 3000 patients provided
134 the following: 88% power to detect a hazard ratio (HR) of 0.70 (2-sided $\alpha=0.0400$) for mortality,
135 assuming a standard-care group mortality rate of 13%; and 99% power to detect a HR of 0.70 (2-
136 sided $\alpha=0.0150$) for the composite of major complications, based on 45% overlap between the
137 two co-primary outcomes and assuming a standard care group major complications rate of 30%.

138 The Independent Trial Monitoring Committee reviewed the data when 50% of the
139 patients had completed 30 days of follow-up based on the initial sample size of 1200 patients,
140 and when 50% and 75% of the patients had completed 90 days of follow-up based on the final
141 sample size of 3000 patients. The committee used a modified Haybittle-Peto rule of 4 standard
142 deviations (SDs) ($\alpha=0.0001$) for analyses when 50% of the patients had completed follow-up and
143 3 SDs ($\alpha=0.00047$) for the analysis when 75% of patients had completed follow-up.

144 The Operations Committee wrote and finalized the statistical analysis plan before
145 analyses were undertaken or any investigators were unmasked to trial results. Patients were

146 analysed in the groups to which they were randomised (i.e., based on the intention-to-treat
147 principle), regardless of the timing of their surgery. Patients lost to follow-up without having
148 had the outcome of interest were censored on the last day their outcome status was known.

149 For the co-primary outcomes, we used Cox proportional hazards models to estimate the
150 effect of accelerated surgery versus standard care, with stratification based on the type of
151 planned surgery (i.e., arthroplasty versus open reduction and internal fixation). For the co-
152 primary outcomes, we also plotted event rates over time using Kaplan-Meier methodology and
153 used the log-rank test to determine p values.

154 The co-primary analyses were based on a fallback procedure such that if the first co-
155 primary outcome (i.e., time to death) was significant at $\alpha=0.0400$, then the alpha would be
156 unused and passed to the second co-primary outcome (i.e., time to a major complication), which
157 would then be evaluated at $\alpha=0.05$.¹⁹ If the first co-primary outcome was found to be non-
158 significant, the second co-primary outcome would be evaluated at $\alpha=0.0150$. With the fallback
159 hierarchical testing procedure, the type I error rate is partitioned among the co-primary outcomes
160 in an order determined *a priori*; if the first hypothesis is rejected, the type I error rate can be
161 accumulated, thus preserving the family-wise type I error rate.¹⁹

162 Secondary and tertiary binary events with an event date were analysed using an approach
163 similar to that of the primary outcomes. For secondary and tertiary outcomes that were binary
164 events but without an event date (e.g., new residence in a nursing home), logistic regression was
165 undertaken to estimate the effect of accelerated surgery versus standard care, and a χ^2 test was
166 used to calculate the p value.

167 For the co-primary outcomes, we performed the following 2 prespecified subgroup
168 analyses: 1.) patients who presented to the hospital <4 hours after their hip fracture, ≥ 4 -24 hours

169 after their hip fracture, versus >24 hours after their hip fracture; and 2.) patients who had, versus
170 did not have, an acute severe medical condition (Appendix) after their hip fracture but before
171 randomisation. We expected a larger relative treatment effect in patients who presented earlier
172 after their fracture and a smaller treatment effect in patients who had acute severe medical
173 conditions after their fracture but before randomisation. We used Cox proportional hazards
174 models that incorporated tests of interaction, designated as significant if $p < 0.05$.

175 All analyses were performed in SAS[®], version 9.4. This trial was registered with
176 ClinicalTrials.gov, number NCT02027896.

177

178 **Trial coordination and role of the funding sources**

179 The study was funded by grants from the CIHR, the Ontario Strategy for Patient Oriented
180 Research Support Unit, the Ontario Ministry of Health and Long-Term Care, the Hamilton
181 Health Sciences Foundation, Physicians' Services Incorporated Foundation, Michael G.
182 DeGroote Institute for Pain Research and Care, Smith & Nephew (to recruit patients in Spain),
183 and Indiegogo Crowdfunding. The Population Health Research Institute was the trial
184 coordinating centre and was responsible for the randomisation system, maintenance of the
185 database, data monitoring, analyses, and study-centre coordination. The funders of the trial had
186 no role in data collection, data analyses, data interpretation, or writing of the manuscript. The
187 corresponding author had full access to all of the data and had final responsibility for the
188 decision to submit for publication.

189

190 **RESULTS**

191 We randomised 2970 patients to receive accelerated surgery (n=1487) or standard care
192 (n=1483). Fifteen patients (<1%) were lost to follow-up after hospital discharge (Figure 1). The
193 baseline characteristics and details of surgery were similar between groups (Table 1). Among
194 participants, the mean age was 79 years, 69% were women, 33% needed help with activities of
195 daily living, 22% had diabetes, 18% had dementia, and 18% resided in a nursing home before
196 their hip fracture. The most common types of fractures were intertrochanteric (52%) and
197 femoral neck (44%). The surgeries performed were open reduction and internal fixation in 63%
198 of participants and arthroplasty in 35%.

199 The timelines from hip fracture to randomisation were similar between the 2 groups
200 (Table 2). The median time from hip fracture to hospital arrival was 3 hours (interquartile range
201 [IQR], 1-15), and the median time from hospital arrival to randomisation was 3 hours (IQR, 2-5).
202 The median time from hip fracture diagnosis to medical clearance was 2 hours (IQR, 1-4) in the
203 accelerated-care group and 4 hours (IQR, 2-13) in the standard-care group, $p<0.0001$. The
204 median time from hip fracture diagnosis to surgery was 6 hours (IQR, 4-9) in the accelerated-
205 surgery group and 24 hours (IQR, 10-42) in the standard-care group; median absolute difference
206 of 18 hours (95% confidence interval [CI] 17-19), $p<0.0001$.

207 Death occurred in 140 patients (9%) assigned to accelerated surgery and 154 patients
208 (10%) assigned to standard care; HR 0.91, 95% CI 0.72-1.14; absolute risk reduction (ARR) 1%,
209 95% CI -1-3%; $p=0.40$, (Table 3, Figure 2). A major complication occurred in 321 patients
210 (22%) randomised to accelerated surgery and 331 patients (22%) randomised to standard care;
211 HR 0.97, 95% CI 0.83-1.13; ARR 1%, 95% CI -2-3%; $p=0.71$. Post-hoc random-effects Cox
212 models that adjusted for potential site-clustering effects produced similar results to the primary
213 analyses (Supplemental Table 1).

214 Among the secondary outcomes, there were fewer strokes in patients randomised to
215 accelerated surgery compared to standard care (5 patients [$<1\%$] versus 14 patients [1%]; HR
216 0.35, 95% CI 0.13-0.97; $p=0.0470$) (Table 3). Post-hoc Fisher's exact test for stroke
217 demonstrated $p=0.0405$. Delirium was less common in the accelerated-surgery group (132
218 patients [9%]) compared to the standard-care group (175 patients [12%]), odds ratio (OR) 0.72,
219 (95% CI 0.58-0.92); ARR 3%, 95% CI 1-5%. Fewer patients randomised to accelerated surgery
220 compared to standard care had an infection without sepsis (170 patients [11%] versus 207
221 patients [14%]; HR 0.80, 95% CI 0.65-0.98). Fewer patients had a urinary tract infection in the
222 accelerated-surgery group compared to the standard-care group (120 patients [8%] versus 150
223 patients [10%]; HR 0.78, 95% CI 0.61-0.99; ARR 2%, 95% CI $<1-4\%$) (Supplemental Table 2).

224 For the tertiary clinical outcomes, including 5 orthopaedic outcomes (i.e., hip re-
225 operation, prosthetic hip dislocation, implant failure, peri-prosthetic fracture, and surgical site
226 infection), there were no significant differences between the randomised groups (Supplemental
227 Table 3). Patients allocated to accelerated care were faster to mobilise after randomisation
228 compared to patients allocated to standard care (25 hours [IQR, 21-45] versus 46 hours [IQR, 31-
229 71]; absolute median difference 21 hours; 95% CI 20-22; $p<0.0001$) (Supplemental Table 4).
230 The mean time from randomisation to hospital discharge was 10 days in the accelerated-surgery
231 group and 11 days in the standard-care group; absolute mean difference 1 day (95% CI 1-2;
232 $p<0.0001$).

233 Patients randomised to accelerated surgery stood up and were able to fully weight bear
234 earlier than patients randomised to standard care (absolute median difference 21 hours, 95% CI
235 18-24; and 26 hours, 95% CI 21-30, respectively) (Supplemental Table 5). Post-hoc analyses
236 demonstrated that more patients randomised to accelerated care were discharged ≤ 10 days after

237 randomisation, whereas more patients randomised to standard care stayed 11-20 days and >20
238 days from randomisation to hospital discharge (Supplemental Table 6).

239 The effects on mortality did not differ across the prespecified subgroups (Figure 3). For
240 the co-primary outcome of major complications, the subgroup analysis based on time from hip
241 fracture to hospital arrival demonstrated a significant interaction ($p=0.0198$). This subgroup
242 analysis demonstrated that the HR for major complications decreased as the time from hip
243 fracture to hospital arrival increased.

244 Subgroup analyses for the co-primary outcomes based on an expanded list of acute
245 medical conditions (Appendix), broader than the pre-specified subgroup, demonstrated the
246 effects were consistent across the subgroups (Supplemental Figure 1). Post-hoc subgroup
247 analyses for the co-primary outcomes based on whether patients had an elevated troponin
248 measurement before randomisation demonstrated a statistically significant interaction ($p=0.0076$)
249 for mortality (Supplemental Figure 2). These analyses suggested patients with an elevated
250 troponin measurement at baseline had a lower risk of mortality with accelerated surgery
251 compared to standard care (17 deaths among 174 accelerated-surgery patients [10%] versus 42
252 deaths among 175 standard-care patients [24%]; HR 0.38, 95% CI 0.21-0.66).

253 Post-hoc subgroup analyses for the co-primary outcomes, based on the type of fracture
254 (i.e., intertrochanteric versus femoral neck) and separately based on the type of surgery (open
255 reduction and internal fixation versus arthroplasty), demonstrated that the effects were consistent
256 across the subgroups (Supplemental Figure 3 and 4, respectively). Post-hoc analyses for the co-
257 primary outcomes based on patients' age (i.e., 45-64, 65-84, and ≥ 85 years) demonstrated the
258 effects were consistent across the subgroups (Supplemental Figure 5).

259 The day after randomisation, patients in the accelerated-surgery group had a lower pain
260 score than patients in the standard-care group (Supplemental Table 7). Fewer patients in the
261 accelerated-care group had moderate to severe pain on days 4-7 after randomisation, compared to
262 patients in the standard-care group (Supplemental Table 8).

263

264 **DISCUSSION**

265 **Statement of principal findings**

266 Accelerated surgery did not reduce the risk of the co-primary outcomes of mortality and a
267 composite of major complications, compared to standard care. Accelerated surgery compared to
268 standard care resulted in a lower risk of delirium (OR 0.72, 95% CI 0.58-0.92), urinary tract
269 infection (HR 0.78, 95% CI 0.61-0.99), and moderate to severe pain on days 4-7 after
270 randomisation. Accelerated surgery also resulted in faster mobilisation after randomisation
271 (absolute median difference, 21 hours; 95% CI 20-22), and a shorter time from randomisation to
272 hospital discharge (absolute mean difference, 1 day; 95% CI 1-2).

273

274 **Our trial in relation to other studies**

275 A systematic review and meta-analysis of risk-adjusted *observational* data demonstrated,
276 irrespective of the cut-off defining delayed surgery (24, 48, or 72 hours), earlier surgery (i.e.,
277 within the cut-off time) was associated with a significantly lower risk of mortality (4208 patients,
278 721 deaths; relative risk 0.81, 95% CI 0.68–0.96).¹⁰ Risk adjusted observational studies have
279 demonstrated that surgery within 12 hours of a hip fracture diagnosis was associated with a
280 lower risk of mortality.^{11,20,21} Although these observational studies undertook risk-adjusted

281 analyses, observational studies remain at risk of confounding by indication and residual
282 confounding.

283 Two small trials randomised patients with a hip fracture to accelerated surgery versus
284 standard care. One trial randomised 71 patients with a hip fracture to early surgery or standard
285 care; median time to surgery was 1 day versus 2 days, respectively.²² The investigators reported
286 that patients allocated to early surgery had a shorter length of hospital stay compared to patients
287 allocated to standard care (21 versus 33 days; relative risk [RR] 0.48, 95% CI 0.27-0.85). HIP
288 ATTACK also showed that accelerated surgery had a reduced time from randomisation to
289 hospital discharge. The HIP ATTACK pilot randomised 60 patients to accelerated surgery or
290 standard care with median times from diagnosis to surgery of 6 versus 24 hours, respectively.⁷
291 In this pilot 4 patients randomised to accelerated surgery and 9 patients randomised to standard
292 care developed delirium. These results were consistent with the HIP ATTACK trial.

293

294 **Interpretation**

295 Despite surgery being performed at a median time of 6 hours after the hip fracture
296 diagnosis in the accelerated-surgery group versus a median of 24 hours in the standard-care
297 group (median absolute difference of 18 hours, 95% CI 17-19), there was no significant effect of
298 accelerated surgery on mortality (HR 0.91, 95% CI 0.72-1.14) or major complications (HR 0.97,
299 95% CI 0.83-1.13). Accelerated surgery did, however, demonstrate a reduction in delirium (OR
300 0.72, 95% CI 0.58-0.92, ARR 3%, 95% CI 1-5%), urinary tract infection (HR 0.78, 95% CI 0.61-
301 0.99, ARR 2%, 95% CI, <1-4%), and moderate to severe pain on days 4-7 after randomisation.
302 The ARR for delirium and urinary tract infection represent effects that patients are likely to
303 consider important.

304 Accelerated surgery may have reduced the risk of delirium by reducing urinary tract
305 infection, reducing moderate to severe pain, and having patients mobilise, stand, and weight bear
306 more rapidly than patients randomised to standard care. In patients presenting with a hip
307 fracture, to avoid the discomfort associated with using a bedpan to urinate, it is common practice
308 to insert a Foley catheter. These catheters are usually not removed until after surgery, when
309 patients start to mobilise. That patients randomised to accelerated surgery underwent surgery 18
310 hours earlier and mobilised 21 hours earlier than patients randomised to standard care may
311 explain how accelerated surgery reduced the risk of urinary tract infection. Although patients
312 allocated to accelerated surgery demonstrated a lower risk of stroke, we offer cautious
313 interpretation of this finding. In contrast to delirium (307 events) and urinary tract infection (270
314 events), there were only 19 strokes and this result has a fragility index of 2 (i.e., only 2 patients
315 in the accelerated-care group would have to change from not having a stroke to having a stroke
316 to reverse statistical significance).²³

317 The mean time from randomisation to hospital discharge was 10 days in the accelerated-
318 surgery group and 11 days in the standard-care group; absolute mean difference 1 day (95% CI
319 1-2; $p < 0.0001$). Given the cost associated with spending an extra day in the hospital, this
320 represents an important difference. Several points support the credibility of this finding: 1.) the
321 coherence of the data across outcomes – patients randomised to accelerated surgery had surgery
322 18 hours earlier, mobilized 21 hours earlier, stood 21 hours earlier, and achieved full weight
323 bearing 26 hours earlier, compared to patients randomised to standard care; one would anticipate
324 that patients who mobilize, stand, and weight bear more quickly will also be discharged earlier;
325 2.) more patients randomised to accelerated care were discharged ≤ 10 days after randomisation,
326 whereas more patients randomised to standard care stayed 11-20 days and > 20 days from

327 randomisation to hospital discharge (Supplemental Table 6); and 3.) prior data from a small trial
328 supports this finding.²² Of our two *a priori* subgroup analyses, one demonstrated a statistically
329 significant interaction p value (i.e., for the composite outcome based on time from hip fracture to
330 hospital arrival) (Figure 3). Although a significant interaction p value suggests the differences in
331 treatment effects are beyond what would be expected based on chance and supports the
332 credibility of a subgroup effect, the observed direction of effect was the opposite of our stated *a*
333 *priori* hypothesis (i.e., we expected a larger treatment effect in patients who present within
334 shorter time periods of their hip fracture, whereas we observed the opposite), which substantially
335 lowers the credibility that this represents a real subgroup effect.^{24,25}

336 Some authors have cautioned that accelerated surgery for a hip fracture may negatively
337 impact patients' outcomes by preventing or limiting the opportunity to optimize patients'
338 medical conditions before surgery;^{26,27} however, our subgroup analysis based on acute medical
339 conditions does not support this concern (Figure 3, Supplemental Figure 4). Moreover, our post-
340 hoc subgroup analysis suggested patients with an elevated troponin measurement at baseline had
341 a lower risk of mortality with accelerated surgery compared to standard care (HR 0.38, 95% CI
342 0.21-0.66). An elevated baseline troponin measurement in patients with a hip fracture may
343 identify patients who are not tolerating the physiological stress associated with the hip fracture,
344 and these patients may benefit from accelerated surgery.

345 Waiting for hip fracture surgery is undesirable. When patients sustain a hip fracture, they
346 are forced to lie flat in a bed and are either in pain or needing analgesic medications, which often
347 have side effects. Moreover, patients usually have to fast while waiting for surgery and many
348 will get a urinary catheter, which will only be removed after surgery. That <5% of eligible

349 patients declined to participate in the HIP ATTACK trial provides evidence that patients want
350 accelerated surgery.

351 HIP ATTACK further provides evidence of the safety and benefits (e.g., reduced risk of
352 delirium and more rapid mobilisation) of accelerated surgery compared to standard care. Lack of
353 operating room time and medical clearance are the main barriers to accelerated surgery.^{28,29} We
354 demonstrated in HIP ATTACK that it is possible to overcome these barriers. Patients
355 randomised to accelerated surgery went into the next orthopaedic elective or trauma operating
356 room slot and any displaced elective cases were moved to the subsequent slot. To avoid
357 cancelling any elective cases, when needed, an extra operating room slot was facilitated at the
358 end of the day. This represents the main cost to centres to facilitate accelerated surgery. This
359 cost along with the cost savings from discharging a patient home a day earlier will help inform
360 the economics of accelerated surgery. We plan to publish formal economic analyses related to
361 the HIP ATTACK data. Moreover, we will publish the 1-year results, after all patients have
362 completed the 1-year follow-up.

363 HIP ATTACK included patients ≥ 45 years of age, and the trial does not inform the effect
364 of accelerated surgery on younger patients. Patients < 45 years of age are, however, commonly
365 excluded from perioperative trials because of their lower risk of postoperative complications.³⁰⁻³²
366 Moreover, it is uncommon for patients < 45 years of age to suffer a low-energy mechanism hip
367 fracture.

368

369 **Strengths and limitations**

370 HIP ATTACK is the first large randomised trial to inform the effects of accelerated
371 surgery compared to standard care. We obtained follow-up on $> 99\%$ of participants. HIP

372 ATTACK has limitations. Three centres had major data quality issues, and we had to remove
373 these centres and their 65 randomised patients from the trial. Although this resulted in our trial
374 falling just short of our intended sample size (i.e., 2970 patients instead of 3000), this did not
375 have a meaningful impact on power. Despite variation in the time from hip fracture diagnosis to
376 surgery in our standard-care group, our results primarily inform the effects for patients who went
377 to surgery a median of 6 versus 24 hours after their hip fracture was diagnosed. Observational
378 data, clinical experience, and biological rationale suggest that the longer a patient is immobile
379 and lying in a bed the higher the risk of poor outcomes.² Therefore, our findings do not preclude
380 different results in centres with standards of care that take substantially longer to get patients into
381 surgery than the standard-care group in HIP ATTACK.

382 We did not collect data on the orthopaedic outcomes of non-union or malunion; however,
383 accelerated surgery had no effect on the 5 orthopaedic outcomes we did evaluate (Supplemental
384 Table 3). We did not collect data on the timing of urinary catheter removal following surgery.
385 We expected a standard-care group mortality rate of 13% but it was 10% and a major
386 complications rate of 30% but it was 22%. Considering the 95% CIs around their associated
387 treatment effects, there is still the possibility of a 28% relative risk reduction (RRR) for mortality
388 and a 17% RRR for major complication. We only included patients diagnosed during regular
389 working hours. Given that after regular working hours, there tend to be fewer healthcare
390 providers in hospitals and those providers may be more fatigued, understanding the effects of
391 accelerated surgery outside of regular working hours will require its own trial. We did not
392 collect data on the seniority of surgeons, anaesthesiologists, and physicians. Although physician
393 skill level may vary across sites and may affect outcomes, randomisation was stratified by centre
394 to minimize any such impact on the effects of the study treatment groups.

395

396 **Conclusions**

397 Among patients with a hip fracture, accelerated surgery did not lower the risk of
398 mortality or a composite of major complications compared to standard care. It did, however,
399 reduce the risk of delirium, urinary tract infection, and moderate to severe pain, and resulted in
400 faster mobilisation, standing, weight bearing, and hospital discharge.

401

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483 **DECLARATION OF INTERESTS**

484 MB reports grants and personal fees from Sanofi, grants and personal fees from Pendopharma,
 485 grants from Ferring, grants from Aphria, grants from Acumed, outside the submitted work.
 486 MW reports personal fees from Stryker Canada, outside the submitted work. EGF reports grants
 487 from Smith & Nephew, during the conduct of the study; personal fees from Biocomposite,
 488 outside the submitted work. JTH reports grants from Smith & Nephew, during the conduct of
 489 the study; personal fees from STRYKER, SMITH-NEPHEW and DEPUY, outside the submitted
 490 work. JTS reports grants from Smith & Nephew, during the conduct of the study; personal fees
 491 from STRYKER, outside the submitted work. MMVC and YGS report grants from Smith &
 492 Nephew, during the conduct of the study. EP reports personal fees from Roche Diagnostics,

493 outside the submitted work. PJD reports grants from Canadian Institutes of Health Research and
494 from Ontario Strategy for Patient Oriented Research Support Unit/Ministry of Health and Long-
495 Term Care, during the conduct of the study; grants from Abbott Diagnostics, Boehringer
496 Ingelheim, Philips Healthcare, Roche Diagnostics and Siemens, outside the submitted work.
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508 **Data Sharing Statement:** The Population Health Research Institute (PHRI) is the sponsor of
509 this trial. The PHRI believes the dissemination of clinical research results is vital and sharing of
510 data is important. PHRI prioritizes access to data analyses to researchers who have worked on
511 the trial for a significant duration, have played substantial roles, and have participated in raising
512 the funds to conduct the trial. PHRI balances the length of the research study, and the
513 intellectual and financial investments that made it possible with the need to allow wider access to
514 the data collected. Data will be disclosed only upon request and approval of the proposed use of
515 the data by a Review Committee. Data are available to the journal for evaluation of reported
516 analyses. Data requests from other non-HIP ATTACK investigators will not be considered until
517 5 years after the close out of the trial.

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519 **REFERENCES**

- 520 1. Johnell O, Kanis JA. An estimate of the worldwide prevalence and disability associated
521 with osteoporotic fractures. *Osteoporos Int* 2006; **17**(12): 1726-33.
- 522 2. Neuman MD, Silber JH, Magaziner JS, Passarella MA, Mehta S, Werner RM. Survival
523 and functional outcomes after hip fracture among nursing home residents. *JAMA Intern Med*
524 2014; **174**(8): 1273-80.
- 525 3. Berry SD, Rothbaum RR, Kiel DP, Lee Y, Mitchell SL. Association of Clinical
526 Outcomes With Surgical Repair of Hip Fracture vs Nonsurgical Management in Nursing Home
527 Residents With Advanced Dementia. *JAMA Intern Med* 2018; **178**(6): 774-80.
- 528 4. Cram P, Yan L, Bohm E, et al. Trends in Operative and Nonoperative Hip Fracture
529 Management 1990-2014: A Longitudinal Analysis of Manitoba Administrative Data. *J Am*
530 *Geriatr Soc* 2017; **65**(1): 27-34.
- 531 5. Royal College of Physicians. National Hip Fracture Database annual report 2018.
532 London: Royal College of Physicians, 2018.
- 533 6. Le Manach Y, Collins G, Bhandari M, et al. Outcomes After Hip Fracture Surgery
534 Compared With Elective Total Hip Replacement. *JAMA* 2015; **314**(11): 1159-66.
- 535 7. Investigators THA. Accelerated care versus standard care among patients with hip
536 fracture: the HIP ATTACK pilot trial. *CMAJ* 2014; **186**: E52-E60.
- 537 8. Prevention of pulmonary embolism and deep vein thrombosis with low dose aspirin:
538 Pulmonary Embolism Prevention (PEP) trial. *Lancet* 2000; **355**(9212): 1295-302.
- 539 9. LeBlanc ES, Hillier TA, Pedula KL, et al. Hip fracture and increased short-term but not
540 long-term mortality in healthy older women. *Arch Intern Med* 2011; **171**(20): 1831-7.

- 541 10. Simunovic N, Devereaux PJ, Sprague S, et al. Effect of early surgery after hip fracture on
542 mortality and complications: systematic review and meta-analysis. *CMAJ* 2010; **182**(15): 1609-
543 16.
- 544 11. Nyholm AM, Gromov K, Palm H, et al. Time to Surgery Is Associated with Thirty-Day
545 and Ninety-Day Mortality After Proximal Femoral Fracture: A Retrospective Observational
546 Study on Prospectively Collected Data from the Danish Fracture Database Collaborators. *J Bone*
547 *Joint Surg Am* 2015; **97**(16): 1333-9.
- 548 12. Beloosesky Y, Hendel D, Weiss A, et al. Cytokines and C-reactive protein production in
549 hip-fracture-operated elderly patients. *J Gerontol A Biol Sci Med Sci* 2007; **62**(4): 420-6.
- 550 13. Chuang D, Power SE, Dunbar PR, Hill AG. Central nervous system interleukin-8
551 production following neck of femur fracture. *ANZ J Surg* 2005; **75**(9): 813-6.
- 552 14. Desborough JP. The stress response to trauma and surgery. *Br J Anaesth* 2000; **85**(1):
553 109-17.
- 554 15. Onuoha GN, Alpar EK. Elevation of plasma CGRP and SP levels in orthopedic patients
555 with fracture neck of femur. *Neuropeptides* 2000; **34**(2): 116-20.
- 556 16. Borges FK, Bhandari M, Patel A, et al. Rationale and design of the HIP fracture
557 Accelerated surgical Treatment And Care track (HIP ATTACK) Trial: a protocol for an
558 international randomised controlled trial evaluating early surgery for hip fracture patients. *BMJ*
559 *Open* 2019; **9**(4): e028537.
- 560 17. McGillion MH, Lin-Rogano L, Borges FK. Patient engagement in research related to
561 accelerated surgical care and treatment for hip fracture. *CMAJ* 2018; **190**(Suppl): S38-S9.

- 562 18. Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying
563 confusion: the confusion assessment method. A new method for detection of delirium. *Ann*
564 *Intern Med* 1990; **113**(12): 941-8.
- 565 19. Wiens BL, Dmitrienko A. The fallback procedure for evaluating a single family of
566 hypotheses. *J Biopharm Stat* 2005; **15**(6): 929-42.
- 567 20. Uzoigwe CE, Burnand HG, Cheesman CL, Aghedo DO, Faizi M, Middleton RG. Early
568 and ultra-early surgery in hip fracture patients improves survival. *Injury* 2013; **44**(6): 726-9.
- 569 21. Bretherton CP, Parker MJ. Early surgery for patients with a fracture of the hip decreases
570 30-day mortality. *Bone Joint J* 2015; **97-B**(1): 104-8.
- 571 22. Swanson CE, Day GA, Yelland CE, et al. The management of elderly patients with
572 femoral fractures. A randomised controlled trial of early intervention versus standard care. *Med J*
573 *Aust* 1998; **169**(10): 515-8.
- 574 23. Walsh M, Srinathan SK, McAuley DF, et al. The statistical significance of randomized
575 controlled trial results is frequently fragile: a case for a Fragility Index. *J Clin Epidemiol* 2014;
576 **67**(6): 622-8.
- 577 24. Yusuf S, Wittes J, Probstfield J, Tyroler HA. Analysis and interpretation of treatment
578 effects in subgroups of patients in randomized clinical trials. *JAMA* 1991; **266**(1): 93-8.
- 579 25. Sun X, Briel M, Walter SD, Guyatt GH. Is a subgroup effect believable? Updating
580 criteria to evaluate the credibility of subgroup analyses. *BMJ* 2010; **340**: c117.
- 581 26. Gandhi R, Perruccio AV. Reducing mortality and morbidity following hip fracture: Is
582 expedited surgery the way to go? *CMAJ* 2016; **188**(12): E277-E8.
- 583 27. Lewis PM, Waddell JP. When is the ideal time to operate on a patient with a fracture of
584 the hip? : a review of the available literature. *Bone Joint J* 2016; **98-B**(12): 1573-81.

- 585 28. Orosz GM, Hannan EL, Magaziner J, et al. Hip fracture in the older patient: reasons for
586 delay in hospitalization and timing of surgical repair. *J Am Geriatr Soc* 2002; **50**(8): 1336-40.
- 587 29. Charalambous CP, Yarwood S, Paschalides C, Siddique I, Hirst P, Paul A. Factors
588 delaying surgical treatment of hip fractures in elderly patients. *Ann R Coll Surg Engl* 2003;
589 **85**(2): 117-9.
- 590 30. Devereaux PJ, Yang H, Yusuf S, et al. Effects of extended-release metoprolol succinate
591 in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. *Lancet*
592 2008; **371**(9627): 1839-47.
- 593 31. Myles PS, Leslie K, Chan MT, et al. The safety of addition of nitrous oxide to general
594 anaesthesia in at-risk patients having major non-cardiac surgery (ENIGMA-II): a randomised,
595 single-blind trial. *Lancet* 2014; **384**(9952): 1446-54.
- 596 32. Devereaux PJ, Mrkobrada M, Sessler DI, et al. Aspirin in patients undergoing noncardiac
597 surgery. *N Engl J Med* 2014; **370**(16): 1494-503.

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