Accelerated surgery versus standard care in hip fracture (HIP ATTACK): an international, randomised, controlled trial

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See Online for appendix

Summary

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

Methods HIP ATTACK was an international, randomised, controlled trial done at 69 hospitals in 17 countries. Patients with a hip fracture that required surgery and were aged 45 years or older were eligible. Research personnel randomly assigned patients (1:1) through a central computerised randomisation system using randomly varying block sizes to either accelerated surgery (goal of surgery within 6 h of diagnosis) or standard care. The coprimary outcomes were mortality and a composite of major complications (ie, mortality and non-fatal myocardial infarction, stroke, venous thromboembolism, sepsis, pneumonia, life-threatening bleeding, and major bleeding) at 90 days after randomisation. Patients, health-care providers, and study staff were aware of treatment assignment, but outcome adjudicators were masked to treatment allocation. Patients were analysed according to the intention-to-treat principle. This study is registered at ClinicalTrials.gov (NCT02027896).

Findings Between March 14, 2014, and May 24, 2019, 27 701 patients were screened, of whom 7780 were eligible. 2970 of these were enrolled and randomly assigned to receive accelerated surgery (n=1487) or standard care (n=1483). The median time from hip fracture diagnosis to surgery was 6 h (IQR 4–9) in the accelerated-surgery group and 24 h (10–42) in the standard-care group (p<0·0001). 140 (9%) patients assigned to accelerated surgery and 154 (10%) assigned to standard care died, with a hazard ratio (HR) of 0·91 (95% CI 0·72 to 1·14) and absolute risk reduction (ARR) of 1% (–1 to 3; p=0·40). Major complications occurred in 321 (22%) patients assigned to accelerated surgery and 331 (22%) assigned to standard care, with an HR of 0·97 (0·83 to 1·13) and an ARR of 1% (–2 to 4; p=0·71).

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

Funding Canadian Institutes of Health Research.

Introduction

Worldwide, more than 1·5 million adults have a hip fracture each year.[1] Non-surgical management of a hip fracture is associated with a low probability of remaining ambulatory and an increased risk of chronic pain and mortality.[2,3] In high-income countries, about 95% of hip fractures are managed surgically.[4,5] Patients undergoing hip fracture surgery have higher risk-adjusted mortality and major complications than patients undergoing elective total hip replacement surgery, suggesting hip fractures, independent of surgery, increase patients' risks.[6]

Patients who have a hip fracture are at substantial risk of major complications (ie, cardiovascular, infectious, bleeding, and neurocognitive) and mortality.[7–9] Observational studies suggest that accelerated surgery for a hip fracture is associated with a lower risk of mortality and major complications.[10,11] Hip fractures result in pain, bleeding, and immobility, and activate inflammatory, hypercoagulable, catabolic, and stress states that can precipitate medical complications.[12–15] Accelerated surgery will reduce the time patients are exposed to these harmful states and therefore might reduce the risk of medical complications and mortality. We did the hip fracture accelerated surgical treatment and care track (HIP ATTACK) trial to establish whether accelerated surgery for hip fracture was superior to standard care in reducing death or other major complications.

Methods

Study design and patients

We did this investigator-initiated, randomised, controlled trial at 69 hospitals in 17 countries (Canada, Spain, India, Pakistan, South Africa, Italy, Poland, the UK, the USA, Malaysia, Belgium, France, Thailand, the Netherlands, China, Hong Kong, and Colombia). We have previously reported details of the trial design and methods.[16,17] Before commencing recruitment, all centres obtained ethics approval, and the relevant health authorities approved the protocol.

Eligible patients were aged 45 years or older and diagnosed during regular working hours with a low-energy mechanism hip fracture that required surgery.

Research in context

Evidence before this study

Hip fracture is common and associated with important patient outcomes. We searched MEDLINE using the keywords "hip fracture", "surgical procedures", "operative", "surgery", "time", "accelerated," or "early" for articles in any language from its inception up to Dec 18, 2019. We identified only two small randomised controlled trials, including our HIP ATTACK pilot trial in 60 hip fracture patients randomly assigned to accelerated surgery or standard care. We identified five systematic reviews and meta-analyses, including one published in 2010 that identified five prospective observational studies that did risk-adjusted analysis. Earlier surgery was associated with a reduction in mortality (relative risk 0·81 [95% CI 0·68–0·96], p=0·01) compared with usual care. The other systematic reviews reported similar results. These observational data are susceptible to residual confounding.

Added value of this study

The HIP ATTACK trial is the first large randomised controlled trial to assess the effects of accelerated surgery (ie, goal of surgery within 6 h of diagnosis) compared with standard care. We showed that accelerated surgery did not reduce 90-day mortality or a composite of major complications (ie, mortality and non-fatal myocardial infarction, stroke, venous thromboembolism, sepsis, pneumonia, life-threatening bleeding, and major bleeding) compared with standard care in patients with a hip fracture. Accelerated surgery was associated with lower risk of delirium, faster mobilisation, and a shorter length of hospital stay.

Implications of all the available evidence

Accelerated surgery for hip fracture is feasible and safe relative to standard care. The multidisciplinary team (eg, anaesthesiologists, medicine physicians, and surgeons) and hospital administrators involved in managing patients with a hip fracture will have to weigh the potential reduction in delirium and length of hospital stay against organising an accelerated surgery pathway. Research should further explore the subgroup of patients with increased troponin before randomisation, who show a significant reduction in mortality with accelerated surgery. Future research should also focus on strategies to optimise postoperative care in patients who have surgery for a hip fracture.

Centres defined their study hours based on the local regular working hours. We excluded patients taking a therapeutic dose of an anticoagulant for which no reversing drug was available, patients with a history of heparin-induced thrombocytopenia if they were taking a therapeutic dose of vitamin K antagonist, those with a peri-prosthetic or open fracture, with bilateral fractures, requiring emergency surgery for another reason (eg, subdural haematoma), refusing consent, or previously enrolled in HIP ATTACK.

Our approach to patient engagement was guided by the Canadian Institutes of Health Research strategy for patient-oriented research patient engagement framework.[17] Patients were involved in trial governance auditing and provided input on the importance of the trial outcomes.

Randomisation and masking

Patients were randomly assigned (1:1) to accelerated surgery (ie, goal of surgery within 6 h of hip fracture diagnosis) or standard care. Our objective with accelerated surgery was to facilitate surgery as quickly as possible. We selected a goal of 6 h because we knew this was a substantial improvement beyond standard care and achieving this target was feasible, based on the HIP ATTACK pilot. After obtaining consent from the patient or substitute decision maker, patients were assigned through a central computerised randomisation system using randomly varying block sizes to accelerated or standard surgery. Study personnel and investigators were unaware of the block sizes. Randomisation was stratified by centre and type of planned surgery (ie, arthroplasty or open reduction and internal fixation). Patients, health-care providers (eg, physicians doing preoperative medical clearance, anaesthesiologists, and surgeons), and study personnel were aware of patients' allocated treatment assignment. Outcome adjudicators were masked to treatment allocation.

Procedures

Patients assigned to accelerated surgery had medical clearance by physicians who were available to rapidly assess these patients. After obtaining medical clearance, these patients moved into the next orthopaedic elective or trauma operating room slot (ie, they were prioritised over elective cases and other non-emergent trauma cases). Any displaced elective cases were moved to the subsequent slot and, to avoid cancellation of any moved elective cases, an extra operating room slot was facilitated at the end of the day if needed. Patients randomised to standard care had medical clearance and were waitlisted for surgery according to local standard practices. The difference between the groups was that a physician was available to do rapid medical assessment of patients in the accelerated-surgery group, whereas patients in the standard-care group were seen and medically cleared by a physician according to standard-care timelines (ie, their medical assessment was not expedited).

All patients received the same structured follow-up for outcomes. For the first 7 days after randomisation, patients had daily troponin measurements and were assessed for delirium with the confusion assessment method.[18] Patients were followed up daily in hospital until hospital discharge to assess for trial outcomes, mobilisation timing, critical care admission, and medication usage. They were contacted at 30 days and 90 days after randomisation to establish trial outcomes.

Outcomes

The coprimary outcomes were mortality and a composite of major complications (ie, mortality and non-fatal myocardial infarction, stroke, venous thromboembolism, sepsis, pneumonia, life-threatening bleeding, and major bleeding) at 90 days after randomisation. Secondary outcomes were vascular mortality, non-vascular mortality, myocardial infarction, myocardial injury not fulfilling the definition of myocardial infarction, congestive heart failure, new clinically important atrial fibrillation, stroke, venous thromboembolism, pulmonary embolism, proximal deep venous thrombosis, infection, sepsis, pneumonia, life-threatening bleeding, major bleeding, new residence in a nursing home, and pressure ulcer at 90 days after randomisation and delirium within 7 days of randomisation. Other outcomes and definitions are in the appendix (pp 5–9).

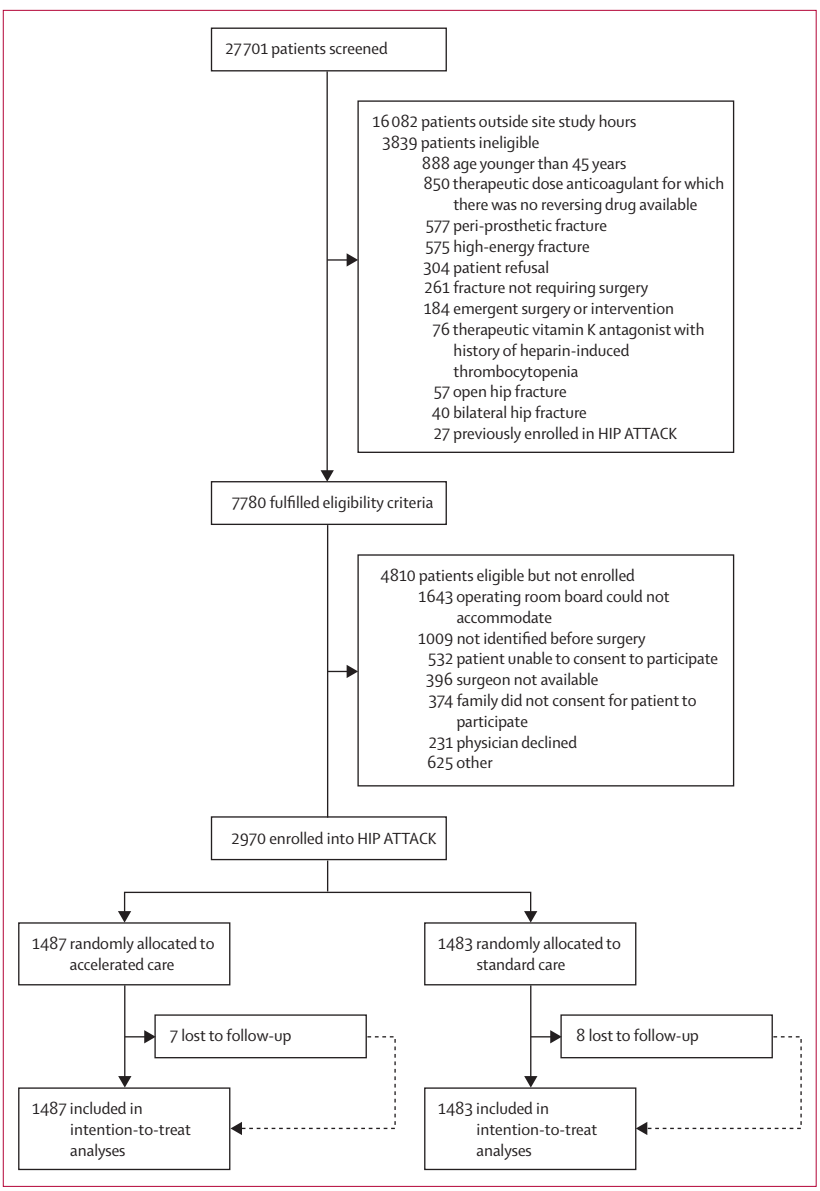

Figure 1: **Patient flow diagram**

Trial monitoring

Monitoring in HIP ATTACK consisted of central data consistency checks, statistical data monitoring, and site monitoring. Site monitoring occurred at hospitals that enrolled at least 40 patients or stood out on central data consistency checks or statistical data monitoring. For site monitoring, the study statistician randomly selected participants with and without primary outcomes, and independent monitors audited their hospital charts and supporting documents. Site monitoring occurred at 26 hospitals that enrolled 76% of the trial patients. Study personnel corrected any data errors identified through central data consistency checks or site monitoring. Central data consistency checks and statistical monitoring raised concerns regarding three centres that had major issues during site monitoring. Data from these sites (65 patients) were removed (appendix p 10).

Statistical analysis

HIP ATTACK was originally designed to enrol 1200 patients and the primary outcome was time to a composite of major complications at 30 days of follow-up. At an investigator meeting in April, 2017, without knowledge of the trial results, a decision was made to increase the sample size to 3000 patients with two co-primary outcomes of mortality and a composite of major complications at 90 days of follow-up. This increase in sample size was needed to provide adequate power for the new co-primary outcome of mortality. For the comparison of accelerated surgery versus standard care, a sample size of 3000 patients provided the following: 88% power to detect a hazard ratio (HR) of 0·70 (two-sided α=0·0400) for mortality, assuming a standard-care group mortality rate of 13%; and 99% power to detect an HR of 0·70 (two-sided α=0·0150) for the composite of major complications, based on a 45% overlap between the two co-primary outcomes and assuming a standard-care group major complications rate of 30%.

The independent trial monitoring committee reviewed the data when 50% of the patients had completed 30 days of follow-up based on the initial sample size of 1200 patients, and when 50% and 75% of the patients had completed 90 days of follow-up based on the final sample size of 3000 patients. The committee used a modified Haybittle-Peto rule of four standard deviations (SDs; α=0·0001) for analyses when 50% of the patients had completed follow-up and three SDs (α=0·00047) for the analysis when 75% of patients had completed follow-up.

The operations committee wrote and finalised the statistical analysis plan before analyses were done or any investigators were unmasked to trial results. Patients were analysed in the groups to which they were randomly

assigned (ie, based on the intention-to-treat principle), regardless of the timing of their surgery. Patients lost to follow-up without having had the outcome of interest were censored on the last day their outcome status was known.

For the co-primary outcomes, we used Cox proportional hazards models to estimate the effect of accelerated surgery versus standard care, with stratification based on the type of planned surgery (ie, arthroplasty *vs* open reduction and internal fixation). For the co-primary outcomes, we also plotted event rates over time using Kaplan-Meier plots and used the log-rank test to establish p values.

The co-primary analyses were based on a fallback procedure such that if the first co-primary outcome (ie, time to death) was significant at $\alpha=0\cdot0400$, then the α would be unused and passed to the second co-primary outcome (ie, time to a major complication), which would then be assessed at $\alpha=0\cdot05$.[19] If the first co-primary outcome was found to be non-significant, the second co-primary outcome would be assessed at $\alpha=0\cdot0150$. With the fallback hierarchical testing procedure, the type I error rate is partitioned among the co-primary outcomes in an order established a priori; if the first hypothesis is rejected, the type I error rate can be accumulated, thus preserving the family-wise type I error rate.[19]

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

For the co-primary outcomes, we performed the following two prespecified subgroup analyses: time from fracture to hospital arrival (<4 h *vs* 4–24 h *vs* >24 h); and acute severe medical condition after hip fracture but before randomisation (yes *vs* no; appendix p 11). We expected a larger relative treatment effect in patients who presented earlier and a smaller treatment effect in patients who had acute severe medical conditions. We used Cox proportional hazards models that incorporated tests of interaction, designated as significant if $p<0\cdot05$. Trained physicians, masked to treatment allocation, adjudicated the following outcomes: myocardial infarction, myocardial injury not fulfilling the definition of myocardial infarction, congestive heart failure, non-fatal cardiac arrest, stroke, pulmonary embolism, deep vein thrombosis, pneumonia, sepsis, and bleeding. Adjudicated events were used for the analyses.

All analyses were performed in SAS, version 9.4. This trial was registered with ClinicalTrials.gov, NCT02027896.

Trial coordination and role of the funding source

The funders of the trial had no role in study design, data collection, data analyses, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

	Accelerated-surgery group (n=1487)	Standard-care group (n=1483)
Age, years	79 (12)	79 (11)
Sex		
Men	456 (31%)	461 (31%)
Women	1031 (69%)	1022 (69%)
History before hip fracture		
Hypertension	902 (61%)	922 (62%)
Needing assistance with activities of daily living	476 (32%)	502 (34%)
Diabetes	333 (22%)	320 (22%)
Residing in nursing home	265 (18%)	269 (18%)
Dementia	256 (17%)	266 (18%)
Osteoporosis	229 (15%)	219 (15%)
Chronic obstructive pulmonary disease	149 (10%)	130 (9%)
Stroke	131 (9%)	123 (8%)
Myocardial infarction	120 (8%)	110 (7%)
Hip fracture	97 (7%)	118 (8%)
Congestive heart failure	101 (7%)	82 (6%)
Coronary revascularisation	92 (6%)	88 (6%)
Chronic atrial fibrillation	80 (5%)	81 (5%)
Active cancer*	70 (5%)	73 (5%)
Transient ischaemic attack	68 (5%)	73 (5%)
Peripheral arterial disease	41 (3%)	56 (4%)
Aortic stenosis	35 (2%)	30 (2%)
Deep venous thrombosis	24 (2%)	29 (2%)
Subarachnoid haemorrhage	17 (1%)	9 (1%)
Pulmonary embolism	14 (1%)	11 (1%)
Renal failure receiving dialysis	11 (1%)	11 (1%)
New diagnoses from time of hip fracture until randomisation		
Infection	27 (2%)	27 (2%)
Atrial fibrillation	8 (1%)	10 (1%)
Significant hyponatraemia or hypernatraemia	8 (1%)	10 (1%)
Significant hypokalaemia or hyperkalaemia	10 (1%)	6 (<1%)
Non-ST-elevation myocardial infarction without mechanical complication†	10 (1%)	5 (<1%)
Myocardial infarction with ST elevation or mechanical complication†	3 (<1%)	2 (<1%)
Congestive heart failure	1 (<1%)	3 (<1%)
Glasgow Coma Scale <12 of unknown origin	3 (<1%)	1 (<1%)
Subarachnoid haemorrhage	1 (<1%)	2 (<1%)
Stroke	0	1 (<1%)
Physiological measurements before randomisation		
Body-mass index, kg/m^2	24 (22 to 27)	24 (21 to 27)
Systolic blood pressure, mm Hg	140 (129 to 160)	140 (126 to 160)
Diastolic blood pressure, mm Hg	78 (70 to 86)	77 (69 to 85)
Heart rate, beats per min	80 (72 to 90)	80 (71 to 90)
Laboratory measurements before randomisation		
Haemoglobin, g/L	123 (110 to 134)	121 (109 to 134)
Estimated glomerular filtration rate, mL/min per 1·73 m^2‡	71 (52 to 84)	69 (51 to 83)

(Table 1 continues on next page)

	Accelerated-surgery group (n=1487)	Standard-care group (n=1483)
(Continued from previous page)		
Medications taken at least once 7 days to 24 h before surgery		
Angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker	485 (33%)	484 (33%)
Antiplatelet agent	418 (28%)	380 (26%)
Statin	363 (24%)	377 (25%)
β blocker	333 (22%)	325 (22%)
Prophylactic antithrombotic	75 (5%)	190 (13%)
Therapeutic dose vitamin K antagonist	47 (3%)	54 (4%)
Therapeutic non-vitamin K antagonist anticoagulant	31 (2%)	36 (2%)
Prothrombin complex concentrate	3 (<1%)	2 (<1%)
Medications taken ≤24 h before surgery		
Angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker	346 (23%)	300 (20%)
Statin	262 (18%)	266 (18%)
β blocker	251 (17%)	257 (17%)
Prophylactic antithrombotic	141 (9%)	396 (27%)
Antiplatelet agent	247 (17%)	163 (11%)
Therapeutic non-vitamin K antagonist anticoagulant	27 (2%)	35 (2%)
Therapeutic dose vitamin K antagonist	22 (1%)	5 (<1%)
Prothrombin complex concentrate	19 (1%)	8 (1%)
Type of fracture§		
Intertrochanteric	773 (52%)	768 (52%)
Femoral neck	648 (44%)	650 (44%)
Subtrochanteric	88 (6%)	76 (5%)
Other	2 (<1%)	2 (<1%)
Intraoperative anaesthetic		
Neuraxial	964 (65%)	967 (65%)
General	464 (31%)	452 (30%)
General and neuraxial	42 (3%)	42 (3%)
Type of hip surgery performed		
Open reduction and internal fixation	947 (64%)	930 (63%)
Arthroplasty	521 (35%)	528 (36%)
Hemiarthroplasty	429 (29%)	437 (29%)
Total hip arthroplasty	87 (6%)	90 (6%)
Other arthroplasty	5 (<1%)	1 (<1%)
Other	3 (<1%)	1 (<1%)

Data are mean (SD), n (%), or median (IQR). Coronary revascularisation=coronary artery bypass graft surgery or percutaneous coronary intervention. *Defined as a patient with a diagnosis of cancer who is receiving, or has received, active treatment for their cancer (eg, chemotherapy, radiation, or surgery) within the previous 6 months. This does not apply to patients with non-melanoma skin cancers or surgery for biopsy. †Mechanical complication included acute papillary muscle rupture or ventricular septal defect. ‡Estimated glomerular filtration rate calculated using the Chronic Kidney Disease Epidemiology Collaboration equation. §Some patients had more than one type of fracture.

Table 1: **Baseline characteristics and surgical details**

Results

Study personnel recruited patients from March 14, 2014, to May 24, 2019. 27701 patients were screened, of whom 7780 were eligible. 2970 patients were enrolled and randomly assigned to receive accelerated surgery (n=1487) or standard care (n=1483). 15 (<1%) of 2970 patients were lost to follow-up after hospital discharge (figure 1). The baseline characteristics and details of surgery were similar between groups (table 1). The mean age of the participants was 79 years (SD 11), 2053 (69%) were women, 978 (33%) needed help with activities of daily living, 653 (22%) had diabetes, 522 (18%) had dementia, and 534 (18%) resided in a nursing home before their hip fracture. The most common types of fractures were intertrochanteric (1541 [52%]) and femoral neck (1298 [44%]). The surgeries done were open reduction and internal fixation in 1877 (63%) participants and arthroplasty in 1049 (35%).

The timelines from hip fracture to randomisation were similar between the two groups (table 2). The median time from hip fracture to hospital arrival was 3 h (IQR 1–15), and the median time from hospital arrival to randomisation was 3 h (2–5). The median time from hip fracture diagnosis to medical clearance was 2 h (1–4) in the accelerated-care group and 4 h (2–13) in the standard-care group, p<0·0001. The median time from hip fracture diagnosis to surgery was 6 h (4–9) in the accelerated-surgery group and 24 h (10–42) in the standard-care group; median absolute difference of 18 h (95% CI 17–19), p<0·0001.

140 (9%) patients assigned to accelerated surgery and 154 (10%) assigned to standard care died, with an HR of 0·91 (95% CI 0·72 to 1·14) and absolute risk reduction (ARR) of 1% (–1 to 3; p=0·40; table 3, figure 2). A major complication occurred in 321 (22%) patients assigned to accelerated surgery and 331 (22%) assigned to standard care, with an HR of 0·97 (0·83 to 1·13) and ARR of 1% (–2 to 4; p=0·71). Post-hoc random-effects Cox models that adjusted for potential site-clustering effects produced similar results to the primary analyses (appendix p 13).

Regarding the secondary outcomes, fewer strokes occurred in patients assigned to accelerated surgery than those assigned to standard care (five [<1%] patients *vs* 14 [1%] patients; HR 0·35 [95% CI 0·13–0·97]; p=0·0470; table 3). Post-hoc Fisher's exact test for stroke resulted in p=0·0405. Delirium was less common in the accelerated-surgery group (132 [9%] patients) than in the standard-care group (175 [12%] patients), with an odds ratio (OR) of 0·72 (95% CI 0·58–0·92) and ARR of 3% (95% CI 1–5). Fewer patients assigned to accelerated surgery (170 [11%] patients) than to standard care had an infection without sepsis (207 [14%] patients), with an HR of 0·80 (0·65–0·98). Fewer patients had a urinary tract infection in the accelerated-surgery group (120 [8%] patients) than in the standard-care group (150 [10%] patients), with an HR of 0·78 (0·61–0·99) and ARR of 2% (<1–4; appendix p 14).

For the tertiary clinical outcomes, including five orthopaedic outcomes (ie, hip re-operation, prosthetic hip dislocation, implant failure, peri-prosthetic fracture, and surgical site infection), the groups were not significantly different (appendix p 15). Patients allocated to accelerated care were faster to mobilise after randomisation than patients allocated to standard care (25 h

[IQR 21–45] for accelerated surgery *vs* 46 h [31–71] for standard care; absolute median difference 21 h [95% CI 20–22], p<0·0001; appendix p 16). The mean time from randomisation to hospital discharge was 10 days (SD 8) in the accelerated-surgery group and 11 days (9) in the standard-care group, with an absolute mean difference of 1 day (95% CI 1–2; p<0·0001).

Patients assigned to accelerated surgery stood up and were able to fully weight bear earlier than patients assigned to standard care (absolute median difference 21 h [95% CI 18–24] for standing; and 26 h [21–30] for full weight bearing; appendix p 17). Post-hoc analyses showed that more patients assigned to accelerated care than standard care were discharged 10 days or sooner after randomisation, whereas more patients assigned to standard care than accelerated care stayed 11–20 days and more than 20 days from randomisation to hospital discharge (appendix p 18).

The effects on mortality did not differ across the prespecified subgroups (figure 3). For the co-primary outcome of major complications, the subgroup analysis based on time from hip fracture to hospital arrival demonstrated a significant interaction (p=0·0198). This subgroup analysis demonstrated that the HR for major complications decreased as the time from hip fracture to hospital arrival increased.

Subgroup analyses for the co-primary outcomes based on an expanded list of acute medical conditions (appendix pp 12, 21), broader than the prespecified subgroup, showed the effects were consistent across the subgroups (appendix p 21). Post-hoc subgroup analyses for the co-primary outcomes on the basis of whether patients had an increased troponin measurement before randomisation showed a statistically significant interaction (p=0·048) for mortality (appendix p 22). These analyses suggested patients with an increased troponin measurement at baseline had a lower risk of mortality with accelerated surgery than standard care (17 deaths [10%] of 163 accelerated-surgery patients *vs* 36 deaths [23%] of 159 standard-care patients; HR 0·43 [95% CI 0·24–0·77]).

Post-hoc subgroup analyses for the co-primary outcomes, based on the type of fracture (ie, intertrochanteric *vs* femoral neck) and separately based on the type of surgery (open reduction and internal fixation *vs* arthroplasty), showed that the effects were consistent across the subgroups (appendix pp 23–24). Post-hoc analyses for the co-primary outcomes on the basis of patients' age group (ie, 45–64, 65–84, and ≥85 years) showed that the effects were consistent across the subgroups (appendix p 25).

The day after randomisation, patients in the accelerated-surgery group had a lower pain score than patients in the standard-care group (appendix p 19), but the difference was not significant on days 2–7. Fewer patients in the accelerated-care group than the standard-care group had moderate-to-severe pain on days 4–7 after randomisation (appendix p 20).

	Accelerated-care group (n=1487)	Standard-care group (n=1483)
Time from hip fracture to randomisation, h		
Hip fracture to arrival at hospital	3 (1 to 14)	3 (1 to 15)
Arrival at hospital to randomisation	3 (2 to 5)	3 (2 to 5)
Arrival at hospital to hip x-ray	1 (<1 to 2)	1 (<1 to 2)
Hip x-ray to hip fracture diagnosis	1 (<1 to 2)	1 (<1 to 2)
Hip fracture diagnosis to consent for HIP ATTACK	1 (<1 to 2)	1 (<1 to 2)
HIP ATTACK consent to randomisation	<1 (<1 to <1)	<1 (<1 to 1)
Time from hip fracture diagnosis to surgery, h		
Hip fracture diagnosis to medical clearance	2 (1 to 4)	4 (2 to 13)
Hip fracture diagnosis to start of surgery	6 (4 to 9)	24 (10 to 42)

Data are median (IQR).

Table 2: **Time from hip fracture to surgery**

	Accelerated-care group (n=1487)	Standard-care group (n=1483)	Hazard ratio (95% CI)	p value
Primary outcomes				
Death	140 (9%)	154 (10%)	0·91 (0·72 to 1·14)	0·40
Composite of major complications*	321 (22%)	331 (22%)	0·97 (0·83 to 1·13)	0·71
Secondary outcomes				
Vascular death	77 (5%)	94 (6%)	0·82 (0·61 to 1·11)	0·19
Non-vascular death	63 (4%)	60 (4%)	1·04 (0·73 to 1·48)	0·81
Myocardial infarction	84 (6%)	80 (5%)	1·05 (0·77 to 1·43)	0·77
Myocardial injury not fulfilling myocardial infarction definition	438 (29%)	463 (31%)	0·95 (0·83 to 1·08)	0·44
Congestive heart failure	32 (2%)	30 (2%)	1·06 (0·64 to 1·74)	0·81
New clinically important atrial fibrillation	22 (1%)	24 (2%)	0·91 (0·51 to 1·62)	0·75
Venous thromboembolism†	14 (1%)	19 (1%)	0·73 (0·37 to 1·46)	0·38
Pulmonary embolism	7 (<1%)	11 (1%)	0·63 (0·24 to 1·63)	0·35
Proximal deep venous thrombosis	8 (1%)	8 (1%)	0·99 (0·37 to 2·64)	0·99
Life-threatening or major bleeding	91 (6%)	75 (5%)	1·22 (0·90 to 1·66)	0·20
Life-threatening bleeding	9 (1%)	7 (<1%)	1·28 (0·48 to 3·44)	0·62
Major bleeding	83 (6%)	68 (5%)	1·23 (0·89 to 1·69)	0·21
Pressure ulcer	48 (3%)	41 (3%)	1·18 (0·76 to 1·80)‡	0·46
Pneumonia	64 (4%)	51 (3%)	1·25 (0·87 to 1·81)	0·23
Infection	225 (15%)	258 (17%)	0·85 (0·71 to 1·02)	0·08
Infection with sepsis	73 (5%)	68 (5%)	1·07 (0·77 to 1·49)	0·69
Infection without sepsis	170 (11%)	207 (14%)	0·80 (0·65 to 0·98)	0·032
New residence in nursing home	217 (15%)	230 (16%)	0·94 (0·76 to 1·14)‡	0·49
Stroke	5 (<1%)	14 (1%)	0·35 (0·13 to 0·97)	0·047
Delirium	132 (9%)	175 (12%)	0·72 (0·58 to 0·92)‡	0·0089

*Death and non-fatal myocardial infarction, stroke, venous thromboembolism, sepsis, pneumonia, life-threatening bleeding, and major bleeding. †Venous thromboembolism is a composite of pulmonary embolism and proximal deep venous thrombosis. ‡Odds ratio.

Table 3: **Primary and secondary outcomes**

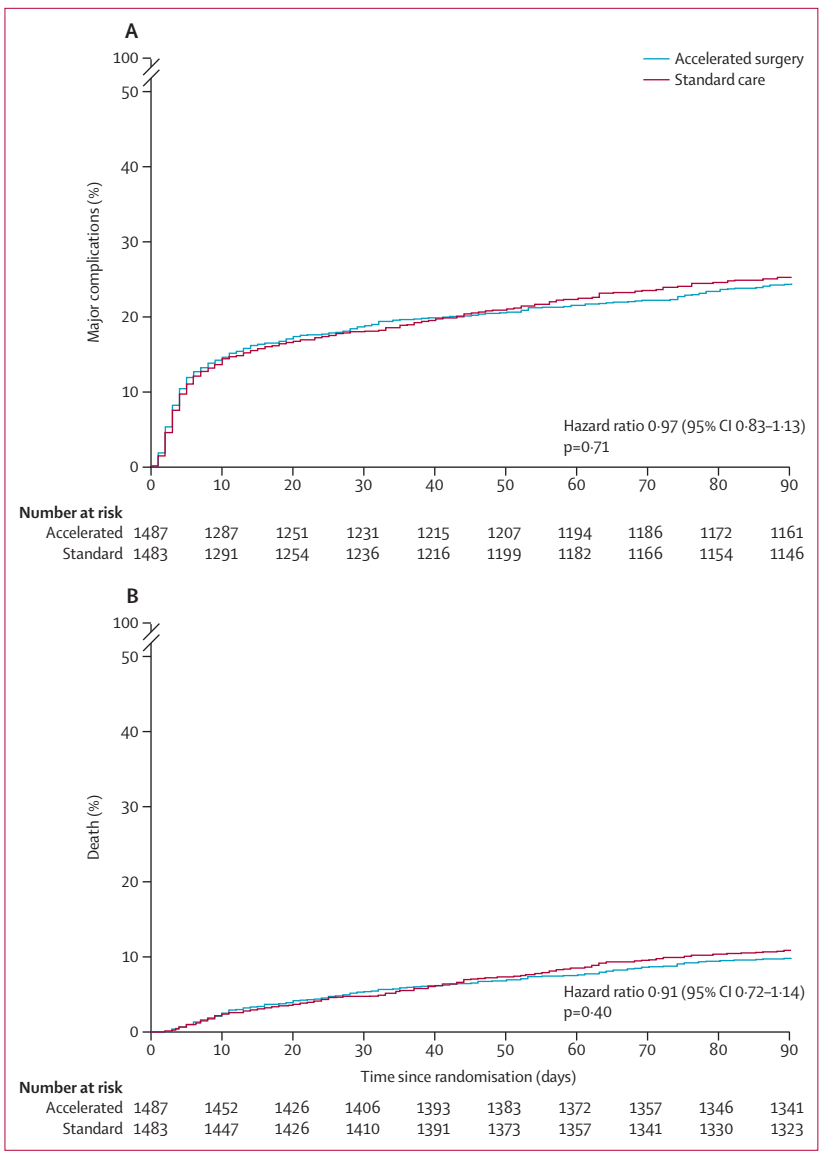

Figure 2: **Kaplan-Meier estimates for the coprimary outcomes**
Composite of major complications (A) and mortality (B).

Discussion

Accelerated surgery did not reduce the risk of the co-primary outcomes of mortality and a composite of major complications compared with standard care. Accelerated surgery compared with standard care resulted in a lower risk of delirium (OR 0·72 [95% CI 0·58–0·92]), urinary tract infection (HR 0·78 [0·61–0·99]), and moderate-to-severe pain on days 4–7 after randomisation. Accelerated surgery also resulted in faster mobilisation after randomisation (absolute median difference 21 h [95% CI 20–22]), and a shorter time from randomisation to hospital discharge (absolute mean difference 1 day [1–2]).

A systematic review and meta-analysis of risk-adjusted observational data showed that, irrespective of the cutoff defining delayed surgery (24, 48, or 72 h), earlier surgery (ie, within the cutoff time) was associated with a significantly lower risk of mortality (4208 patients, 721 deaths; relative risk [RR] 0·81 [95% CI 0·68–0·96]).[10] Risk-adjusted observational studies have shown that surgery within 12 h of a hip fracture diagnosis was associated with a lower risk of mortality.[11,20,21] Although these observational studies did risk-adjusted analyses, observational studies remain at risk of confounding by indication and residual confounding.

Two small trials randomly assigned patients with a hip fracture to accelerated surgery versus standard care. One trial assigned 71 patients with a hip fracture to early surgery or standard care; median time to surgery was 1 day (IQR 1–9) for early surgery versus 2 days (2–15) for standard care.[22] The investigators reported that patients allocated to early surgery had a shorter length of hospital stay than patients allocated to standard care (21 *vs* 33 days; RR 0·48 [95% CI 0·27–0·85]). HIP ATTACK also showed that accelerated surgery had a reduced time from randomisation to hospital discharge. The HIP ATTACK pilot assigned 60 patients to accelerated surgery or standard care with median times from diagnosis to surgery of 6 h for accelerated surgery versus 24 h for standard care.[7] In this pilot, four patients assigned to accelerated surgery and nine patients assigned to standard care developed delirium. These results were consistent with the HIP ATTACK trial.

Despite surgery being done at a median time of 6 h after the hip fracture diagnosis in the accelerated-surgery group versus a median of 24 h in the standard-care group (median absolute difference of 18 h [95% CI 17–19]), accelerated surgery did not have a significant effect on mortality (HR 0·91 [0·72–1·14]) or major complications (HR 0·97 [0·83–1·13]). However, accelerated surgery did demonstrate a reduction in delirium (OR 0·72 [0·58–0·92], ARR 3% [1–5]), urinary tract infection (HR 0·78 [0·61–0·99], ARR 2% [<1–4]), and moderate-to-severe pain on days 4–7 after randomisation. The ARRs for delirium and urinary tract infection are effects that patients are likely to consider important.

Accelerated surgery might have reduced the risk of delirium by reducing urinary tract infection, reducing moderate-to-severe pain, and having patients mobilise, stand, and weight bear more rapidly than patients assigned to standard care. In patients presenting with a hip fracture, to avoid the discomfort associated with using a bedpan to urinate, it is common practice to insert a Foley catheter. These catheters are usually not removed until after surgery, when patients start to mobilise. That patients assigned to accelerated surgery had surgery 18 h earlier and mobilised 21 h earlier than patients assigned to standard care might explain how accelerated surgery reduced the risk of urinary tract infection. Although patients allocated to accelerated surgery had a lower risk of stroke, we offer cautious interpretation of this finding. In contrast to delirium (307 events) and urinary tract infection (270 events),

only 19 strokes occurred and this result has a fragility index of 2 (ie, only two patients in the accelerated-care group would have to change from not having a stroke to having a stroke to reverse statistical significance).[23]

The mean time from randomisation to hospital discharge was 10 days in the accelerated-surgery group and 11 days in the standard-care group; absolute mean difference 1 day (95% CI 1–2; p<0·0001). Given the cost associated with spending an extra day in hospital, this is an important difference. Several points support the credibility of this finding: (1) the coherence of the data across outcomes—patients assigned to accelerated surgery had surgery 18 h earlier, mobilised 21 h earlier, stood 21 h earlier, and achieved full weight bearing 26 h earlier, compared with patients assigned to standard care, and one would anticipate that patients who mobilise, stand, and weight bear more quickly will also be discharged earlier; (2) more patients assigned to accelerated care were discharged within 10 days after randomisation, whereas more patients assigned to standard care stayed for either 11–20 days or more than 20 days from randomisation to hospital discharge (appendix p 18); and (3) previous data from a small trial support this finding.[22]

Of our two a priori subgroup analyses, one demonstrated a statistically significant interaction p value (ie, for the composite outcome based on time from hip fracture to hospital arrival). Although a significant interaction p value suggests that the differences in treatment effects are beyond what would be expected on the basis of chance and supports the credibility of a subgroup effect, the observed direction of effect was the opposite of our stated a priori hypothesis (ie, we expected a larger treatment effect in patients who present within shorter time periods of their hip fracture; whereas we observed the opposite), which substantially lowers the credibility that this result represents a real subgroup effect.[24,25]

Some authors have cautioned that accelerated surgery for a hip fracture may negatively impact patients' outcomes by preventing or limiting the opportunity to optimise patients' medical conditions before surgery;[26,27] however, our subgroup analysis based on acute medical conditions does not support this concern (appendix p 21). Moreover, our post-hoc subgroup analysis suggested patients with an increased troponin measurement at baseline had a lower risk of mortality with accelerated surgery than those who had standard care (HR 0·43 [95% CI 0·24–0·77]). An increased baseline troponin measurement in patients with a hip fracture might identify patients who are not tolerating the physiological stress associated with the hip fracture, and these patients might benefit from accelerated surgery.

Waiting for hip fracture surgery is undesirable. When patients sustain a hip fracture, they are forced to lie flat in a bed and are either in pain or needing analgesic medications, which often have side-effects. Furthermore, patients usually have to fast while waiting for surgery and many will get a urinary catheter, which will only be removed after surgery. That less than 5% of eligible patients declined to participate in the HIP ATTACK trial provides evidence that patients want accelerated surgery.

HIP ATTACK further provides evidence of the safety and benefits (eg, reduced risk of delirium and more rapid mobilisation) of accelerated surgery compared with standard care. Insufficient operating room time and medical clearance are the main barriers to accelerated surgery.[28,29] We demonstrated in HIP ATTACK that it is possible to overcome these barriers. Patients assigned to accelerated surgery went into the next orthopaedic elective or trauma operating room slot and any displaced elective cases were moved to the subsequent slot. To avoid cancelling any elective cases, when needed, an extra operating room slot was facilitated at the end of the day. Adding an extra operating room slot at the end of the day is the main cost to centres to facilitate accelerated surgery. This cost along with the cost savings from discharging a patient home a day earlier will help inform the economics of accelerated surgery. We plan to publish formal economic analyses related to the HIP ATTACK data. Additionally, we will publish the 1-year results, after all patients have completed the 1-year follow-up.

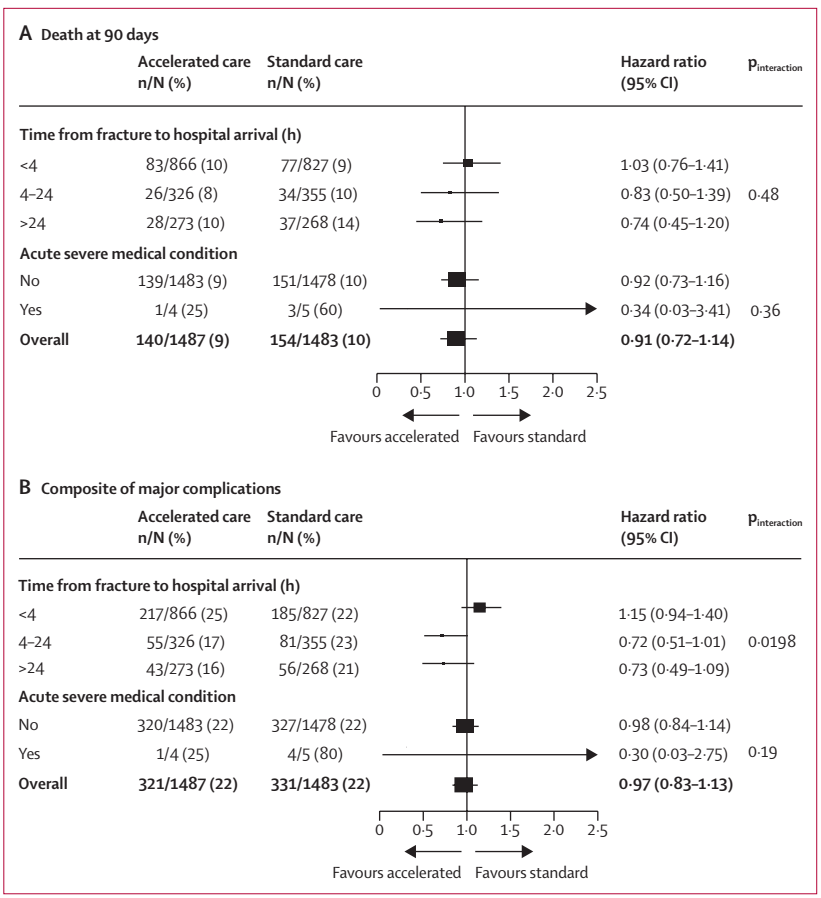

Figure 3: **Results by prespecified subgroups for the two coprimary outcomes**
Mortality at 90 days (A) and composite of major complications (B). n=number of events. N=number of patients.

HIP ATTACK included patients aged 45 years or older, and the trial does not inform the effect of accelerated surgery on younger patients. Patients younger than 45 years are, however, commonly excluded from perioperative trials because of their lower risk of postoperative complications.[30–32] Moreover, it is uncommon for patients younger than 45 years to suffer a low-energy mechanism hip fracture.

HIP ATTACK is the first large randomised trial to inform the effects of accelerated surgery compared with standard care. We obtained follow-up on more than 99% of participants. HIP ATTACK has limitations. Three centres had major data quality issues, and we had to remove these centres and their 65 patients from the trial. Although this resulted in our trial falling just short of our intended sample size (ie, 2970 patients instead of 3000), this did not have a meaningful effect on power. Despite variation in the time from hip fracture diagnosis to surgery in our standard-care group, our results primarily inform the effects for patients who went to surgery a median of 6 h versus 24 h after their hip fracture was diagnosed. Observational data, clinical experience, and biological rationale suggest that the longer a patient is immobile and lying in a bed, the higher the risk of poor outcomes.[2] Therefore, our findings do not preclude different results in centres with standards of care that take substantially longer to get patients into surgery than the standard-care group in HIP ATTACK.

We did not collect data on the orthopaedic outcomes of non-union or malunion; however, accelerated surgery had no effect on the five orthopaedic outcomes we did assess (appendix p 15). We did not collect data on the timing of urinary catheter removal after surgery. We expected a standard-care group mortality rate of 13% but it was 10% and a major complications rate of 30% but it was 22%. Considering the 95% CIs around their associated treatment effects, a 28% relative risk reduction for mortality and a 17% relative risk reduction for major complication are still a possibility. We only included patients diagnosed during regular working hours. Given that after regular working hours, there tend to be fewer health-care providers in hospitals and those providers might be more fatigued, understanding the effects of accelerated surgery outside of regular working hours will require its own trial. We did not collect data on the seniority of surgeons, anaesthesiologists, and physicians. Although physician skill level might vary across sites and might affect outcomes, randomisation was stratified by centre to minimise any such effects between the groups.

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

Contributors

FKB, MB, EG-F, AP, AS, MU, MET, VT, JT-H, JT-S, VRAA, MW, MTR, WS, GL, CYW, JDN, AA, PKS, A-RL, MB-C, PS, RJJ, ANN, GCAW, RJF, EP, BMB, IKM, MHM, JV, VH, SMP, LPG, GHG, and PJD contributed to the design of the study. FKB, MB, EG-F, AP, AS, MU, MET, MdMV-C, VT, JT-H, JT-S, VRAA, MW, MTR, WS, GL, CYW, DB, JDN, AA, PKS, A-RL, MB-C, PS, RJJ, ANN, GCAW, RJF, SJM, AS, EP, BMB, IKM, PF, PL, YG-S, LPG, DC, AXG, EPB-C, MM, AL, RW, and PJD contributed to data collection. KB did the data analyses. All authors contributed to the interpretation of the data. PJD and FKB wrote the first draft of the manuscript. All authors provided critical revisions to the manuscript before seeing and approving the final version.

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Declaration of interests

MB reports grants and personal fees from Sanofi and Pendopharma and grants from Ferring, Aphria, and Acumed, outside the submitted work. MW reports personal fees from Stryker Canada outside the submitted work. EG-F reports grants from Smith and Nephew during the conduct of the study; and personal fees from Biocomposite outside the submitted work. JT-H reports grants from Smith and Nephew during the conduct of the study; personal fees from Stryker, Smith and Nephew, and Depuy outside the submitted work. JT-S reports grants from Smith and Nephew during the conduct of the study; and personal fees from Stryker outside the submitted work. MdMV-C and YG-S report grants from Smith and Nephew during the conduct of the study. EP reports personal fees from Roche Diagnostics outside the submitted work. PJD reports grants from Canadian Institutes of Health Research and from Ontario Strategy for Patient Oriented Research Support Unit/Ministry of Health and Long-Term Care during the conduct of the study; and grants from Abbott Diagnostics, Boehringer Ingelheim, Philips Healthcare, Roche Diagnostics, and Siemens outside the submitted work. All other authors declare no competing interests.

Data sharing

The Population Health Research Institute (PHRI) is the sponsor of this trial. The PHRI believes the dissemination of clinical research results is vital and sharing of data is important. PHRI prioritises access to data analyses to researchers who have worked on the trial for a significant duration, have played substantial roles, and have participated in raising the funds to conduct the trial. PHRI balances the length of the research study and the intellectual and financial investments that made it possible with the need to allow wider access to the data collected. Data will be disclosed only upon request and approval of the proposed use of the data by a review committee. Data are available to *The Lancet* for evaluation of reported analyses. Data requests from other non-HIP ATTACK investigators will not be considered until 5 years after the close of the trial.

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