Title: Myocardial injury in hip fractures: a HIP ATTACK-1 randomized trial substudy.

Running title: Myocardial injury in hip fractures

Authors: Flavia K. Borges, MD, PhD[1,2,3], Ernesto Guerra-Farfan, MD[4], Mohit Bhandari, MD, PhD[5], Ameen Patel, MD[2], Gerard Slobogean, MD[6], Robert J. Feibel, MD[7], Parag K Sancheti, FRCS, MS, DNB, MCh, Ph.D[8], Maria E Tiboni, MD[2], Mariano Balaguer-Castro, MD[9, 10], Vikas Tandon, MD[2], Jordi Tomas-Hernandez, MD[11], Alben Sigamani, MD[12], Alen Sigamani, MD[13], Wojciech Szczeklik, MD, PhD[14], Stephen J McMahon, MD[15], Pawel Ślęczka, MD, PhD[16], Mmampapatla T Ramokgopa, MBChB, MSc, FCS (SA)[17], S Adinaryanan, MD[18], Masood Umer, MBBS, FCPS[19], Richard J Jenkinson, MD[20], Abdel Lawendy, MD, PhD[21, 22], Ekaterine Popova, MD[23,24], Aamer Nabi Nur, MD[25], Chew Yin Wang, MBChB[26], Marcela Vizcaychipi, MD, PhD,FRCA, EDICM, FFICM[27], Bruce M Biccard, MBChB, FCA(SA), FFARCSI, MMedSci, PhD[28], Sandra Ofori, MBBS, MSc[2], Jessica Spence, MD, PhD[29], Emmanuelle Duceppe MD PhD[1,30], Maura Marcucci, MD, MSc[1, 2, 3], Valerie Harvey, BSc[1], Kumar Balasubramanian, MsC[31], Jessica Vincent, MSc[32], Ana Claudia Tonelli, MD, PhD[1,33, 34] and P.J. Devereaux, MD, PhD[1, 2, 3]. On behalf of HIP ATTACK Investigators.

1. Population Health Research Institute, Hamilton, Canada;

2. Department of Medicine, McMaster University, Hamilton, Canada;

3. Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Canada;

4. Department of Orthopaedic Surgery and Traumatology, Hospital Universitario Vall d'Hebron, Barcelona, Spain;

5. Department of Surgery, Division of Orthopaedic Surgery, McMaster University, Hamilton, Canada;

6. Department of Orthopaedics, University of Maryland School of Medicine, Baltimore, United States of America;

7. Division of Orthopaedic Surgery, Department of Surgery, University of Ottawa, The Ottawa Hospital - General Campus, Ottawa, Canada;

8. Sancheti Institute For Orthopaedics & Rehabilitation & PG College. Pune, India;

9. Department of Orthopaedic Surgery and Traumatology, Parc Taulí Hospital Universitario, Sabadell, Barcelona, Spain;

10. Department of Orthopaedic Surgery and Traumatology, Hospital Clinic Barcelona, Barcelona, Spain;

11. Orthopaedic and Traumatology Department, Vall d'Hebron Hospital, Barcelona, Spain;

12. Numen Health Bangalore, Bangalore Karnataka, India;

13. Department of orthopedics Government TD medical college Vandanam Alappuzha, India;

14. Center for Intensive Care and Perioperative Medicine, Jagiellonian University Medical College, Krakow, Poland;

15. Department of Surgery, Oak Valley Health, Markham, Canada;

16. Independent Public Health Care Center, SPZOZ Myślenice, Myślenice, Poland;

17. Division of Orthopaedic Surgery, University of the Witwatersrand, Johannesburg, South Africa;

18. Department of Anaesthesiology and Critical Care, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Pondicherry, India;

19. Department of Surgery, Aga Khan University, Karachi City, Pakistan;

20. Department of Surgery and Institute of Health Policy Management and Evaluation. Sunnybrook Health Sciences Center, Toronto, Canada;

21. Department of Surgery University of Western Ontario, London, Canada;

22. Lawson Health Research Institute, London, Canada;

23. IIB SANT PAU, Institut d'Investigació Biomèdica Sant Pau, Barcelona, Spain;

24. Centro Cochrane Iberoamericano, Barcelona, Spain;

25. Department of Orthopaedic Surgery, Shifa International Hospital, Islamabad, Pakistan;

26. Department of Anaesthesiology, Faculty of Medicine, University Malaya, Kuala Lumpur, Malaysia;

27. Section of Anaesthetics, Pain Medicine & Intensive Care, Department of Surgery and Cancer, Imperial College London, Chelsea and Westminster Hospital, London, United Kingdom;

28. Department of Anaesthesia and Perioperative Medicine, Groote Schuur Hospital and the University of Cape Town, Western Cape, South Africa;

29. Department of Anesthesia and Critical Care, McMaster University;

30. Department of Medicine, University of Montreal, Montreal, Canada;

31. Department of statistics, Population Health Research Institute, David Braley Cardiac, Vascular and Stroke Research Institute, Hamilton, Canada;

32. Perioperative Medicine and Surgical Research Unit, Population Health Research Institute, David Braley Cardiac, Vascular and Stroke Research Institute, Hamilton, Canada;

33. Department of Medicine, Unisinos University, São Leopoldo, Brazil;

34. Internal Medicine Service, Hospital de Clinicas de Porto Alegre, Porto Alegre, Brazil.

Corresponding Author: Dr. Flavia Kessler Borges

Address: Population Health Research Institute, Hamilton General Hospital Campus, DBCVSRI. 237 Barton Street East. Room C1-109. Hamilton, Ontario, Canada L8L 2X2

Email: Flavia.borges@phri.ca. Tel: (+1) 905-527-4322 Ext 40455; (+1) 289-253-7686

Fax: (+1) 905-297-3778

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Abstract

Background: Myocardial injury after a hip fracture is common and has a poor prognosis. Patients with hip fracture and myocardial injury may benefit from accelerated surgery to remove the physiological stress associated with the hip fracture. This study aimed to determine if accelerated surgery is superior to standard-care on the 90-day risk of death in hip fractured patients who presented with an elevated cardiac biomarker/enzyme at hospital arrival.

Methods: The HIP ATTACK-1 trial was a randomized controlled trial designed to determine whether accelerated surgery for hip fracture was superior to standard-care in reducing death or major complications. This substudy is a post-hoc analysis of 1392/2970 patients with a cardiac biomarker/enzyme measurement (>99.9% had a troponin measurement) at hospital arrival. The primary outcome was all-cause mortality. The secondary composite outcome included all-cause mortality, myocardial infarction, stroke, and congestive heart failure 90 days after randomization.

Results: 322/1392 (23%) patients had troponin elevation at hospital arrival. Among patients with troponin elevation, median time from hip fracture diagnosis to surgery was 6 h (IQR 5–13) in the accelerated-care group and 29 h (IQR 19–52) in the standard-care group. Patients with increased troponin had lower risk of mortality with accelerated surgery compared to standard-care (17/163 [10%] versus 36/159 [23%]; HR 0.43 [95% CI 0.24–0.77]); and lower risk of the composite outcome (23/163 [14%] versus 47/159 [30%]; HR 0.43 [CI 95% 0.26-0.72]).

Conclusion: One in 5 patients with hip fracture presented myocardial injury. Accelerated surgery demonstrated lower mortality risk than standard-care, however, these findings need to be confirmed. Level of Evidence: Level I

Introduction

Hip fractures are common and associated with high mortality.(1, 2) The fracture initiates inflammatory, hypercoagulable, and stress states, increasing the risk of delirium, infections, bleeding, and vascular events.(3, 4)

The most common perioperative complication associated with hip fracture is myocardial injury, happening in at least 20% of patients at hospital presentation.(5, 6) Myocardial injury is frequently unrecognized, as patients usually do not have typical cardiac ischemic symptoms and routine perioperative troponin screening is not established as standard of care. Myocardial injury in patients with a hip fracture is important because it is associated with poor prognosis and risk for premature death.(5, 6) Due to the complexity of these patients, medical specialists are frequently consulted for preoperative medical assessment/clearance for surgery. Surgical timing is a common dilemma if evidence of myocardial injury. Physicians often perceive medical management and testing as a priority; however, the resulting surgical delay may worsen their prognosis.(5, 7, 8)

The impetus for the HIP fracture Accelerated surgical TreaTment And Care tracK-1 (HIP ATTACK-1) trial arose from a patient who presented with a hip fracture and troponin elevation. The HIP ATTACK-1 trial randomized 2,970 patients with hip fracture to accelerated surgery (median of 6 hours from orthopedic diagnosis) or standard-care (median of 24 hours from orthopedic diagnosis). The HIP ATTACK-1 trial demonstrated that accelerated surgery was feasible and safe, even in the subgroup of patients with acute medical conditions.

During the HIP ATTACK-1 trial, we recognized that several patients presented with an elevated cardiac biomarker/enzyme at hospital arrival before randomization. Therefore, we designed this substudy to determine the impact of accelerated surgery versus standard-care on

130 the 90-day risk of death and vascular outcomes in patients who presented with a hip fracture and
131 with a myocardial injury at hospital arrival.

132 **Methods**

133 The HIP ATTACK-1 trial was an international randomized controlled trial (RCT) of
134 2970 patients aged 45 years or older, with a low energy mechanism hip fracture presenting
135 during working hours who required a surgical intervention. The main exclusion criteria were
136 patients on therapeutic anticoagulants with no reversing drug available, peri-prosthetic and high-
137 energy fracture. The primary objective was to determine the effect of accelerated surgery
138 compared to standard-care on the 90-day risk of all-cause mortality and major perioperative
139 complications. The HIP ATTACK-1 protocol and the main trial results (NCT02027896) were
140 published previously.(6, 9) We followed CONSORT recommendations, patient flow diagram is
141 shown in Figure 1.

142 In brief, eligible patients were randomized stratified by planned surgery type (open
143 reduction and internal fixation or arthroplasty) in a 1:1 fashion through a central computerized
144 randomization system with randomly varying block sizes to accelerated surgery (goal of
145 surgery in 6 hours from orthopedic diagnosis) or standard-care. We recruited patients in 69
146 centres, from 17 countries. All sites obtained local Research Ethics Board approval. All patients
147 provided consent before randomization. Patients, health-care providers, and research staff were
148 aware of the treatment assignment; however, outcome adjudicators were blinded to treatment
149 allocation.

150 All patients had the same structured follow-up for outcome assessment and troponin
151 measurements post-randomization days 1 to 7 using the assay available at each site were
152 performed. Research personnel followed all patients throughout their index hospitalization and
153 contacted patients at 30 and 90 days after randomization noting any outcomes. Baseline cardiac

biomarker/enzymes, from hip fracture to randomization, were measured at the discretion of the physicians involved in the patient's care. Myocardial injury at hospital presentation was defined as a baseline troponin elevation before randomization that was above the upper limit of normal (ULN) for the site specific assay, except for the high sensitivity troponin T assay (hsTnT) where the threshold was defined as ≥20 ng/L, and for the non-high sensitivity troponin T (TnT) where the threshold was defined as ≥0.03 ng/mL, based on perioperative troponin thresholds associated with short term mortality in noncardiac surgery.(10-12)

A committee of independent experts in perioperative medicine, masked to participants' allocation, adjudicated the following events: myocardial infarction, myocardial injury after randomization not meeting the universal definition of myocardial infarction(13), nonfatal cardiac arrest, stroke, pulmonary embolism, proximal deep venous thrombosis, congestive heart failure, infection, sepsis, life-threatening bleeding, and major bleeding. For adjudicated events we used the decision of the adjudicators for all statistical analyses.

For this substudy, we determined a priori that the primary outcome was all-cause mortality 90 days after randomization. Secondary outcomes included a composite of major perioperative vascular complications (i.e., all-cause mortality and non-fatal myocardial infarction, heart failure, and stroke). The individual secondary outcomes were: vascular mortality, non-vascular mortality, myocardial infarction, myocardial injury after randomization not meeting the universal definition of myocardial infarction(13), congestive heart failure, new clinically important atrial fibrillation, and stroke. Duration of hospital stay after index admission for hip fracture, delirium, and moderate to severe pain, and time to first mobilization, standing, and weight bearing after randomization were also analyzed as secondary outcomes. Tertiary outcomes, and outcomes' definitions are described in the supplemental material.

Statistical Analyses

All randomized participants with baseline cardiac biomarker/enzyme measurement before randomization in the HIP ATTACK-1 trial were included in this analysis. As baseline troponins were measured at the discretion of the attending physicians involved in patient's care, there was no specific sample size calculation for this substudy. Patients were analyzed according to the treatment groups to which they were randomized, according to the intention-to-treat principle.

For the primary and secondary binary outcomes with an event date, we performed a Cox proportional hazard model with treatment group as the covariate and adjusted for stratification variable. We assessed for subgroup effects using tests of interaction, designated as significant if p value for interaction was <0.05. The interaction p value informs if the treatment effect across different subgroups is not attributable to chance. For the primary outcome, we performed a sensitivity analysis including centre as a random effect (frailty model). We hypothesized a priori that patients with baseline cardiac biomarker/enzyme elevation would benefit from accelerated surgery compared to standardcare than patients with no baseline cardiac biomarker/enzyme elevation.

We undertook a post-hoc Cox regression analysis to determine the relationship between baseline cardiac biomarker/enzyme measurements and 90-day mortality. Cox proportionality assumption was met (details in the supplemental material). The dependent variable was 90-day mortality, and independent variables were age, sex, Revised Cardiac Risk Index score which includes history of coronary artery disease, congestive heart failure, cerebrovascular disease, diabetes on insulin, creatinine > 177 umol/L and high-risk surgery (reference 0, 1, 2, or ≥3); baseline cardiac biomarker/enzyme elevation (no, yes), history of peripheral vascular disease, history of chronic obstructive pulmonary disease (COPD), and active cancer. For all Cox models,

we determined the hazard ratio (HR) of each predictor and its associated 95% confidence interval (CI). We repeated this analysis including baseline cardiac biomarker/enzyme as an independent variable assessed by terciles (reference being no elevation). Only observed values were used for analysis and no attempt was made to impute missing values. In cases of patients lost to follow-up, the participants were censored on their last day of available contact during the study or the date of death. All outcomes were tested using two-sided tests at the 0.05 significance level. The fragility index was estimated to assess the fragility of our results for the primary outcome. The fragility index indicates how many patients would be required to convert a trial from being statistically significant to not significant: the larger the index the more robust is the data. All analyses were performed in SAS® using version 9.4.

Results

This substudy included 1392 patients (47%) out of the 2970 patients recruited in the HIP ATTACK-1 trial, from 61 sites, that had a cardiac biomarker/enzyme measurement (>99.9% of those had a troponin measurement) at hospital arrival. Appendix Table 1 reports details of baseline characteristics of all the HIP ATTACK-1 trial participants. Among patients with baseline cardiac biomarker/enzyme measurements, 322/1392 patients (23%) had a cardiac biomarker/enzyme elevation at hospital arrival. Patients with a baseline cardiac biomarker/enzyme elevation compared with patients with no baseline cardiac biomarker/enzyme elevation had higher baseline risk of complications. They were more likely to be male [36.0% versus 29.1%], have a history of hypertension [64.6% versus 57.8%], had higher median creatinine [88.4 umol/L versus 74.3 umol/L] and lower median hemoglobin levels [117 g/L versus 122 g/L], respectively. Patients with and without a baseline cardiac biomarker/enzyme elevation had similar history of myocardial infarction (8.7% versus 8.0%), stable angina (2.8%

versus 2.7%), coronary artery revascularization (5.0% versus 5.3%) and aortic valve stenosis (1.6% versus 2.0%). These baseline characteristics were also similar to the overall HIP ATTACK-1 trial population (Appendix Table 1).

Table 1 presents details of baseline characteristics in the subgroup of patients according to cardiac biomarker/enzyme and treatment allocation. Among patients with an elevated cardiac biomarker/enzyme, the median time from hip fracture diagnosis to surgery was 6 hours (interquartile range [IQR] 5–13) in the accelerated surgery group, and 29 hours (IQR 19–52) in the standard-care group (median absolute difference 23 hours). Among patients without an elevated cardiac biomarker/enzyme, the median time from hip fracture diagnosis to surgery was 6 hours (IQR 4–8) in the accelerated surgery group, and 29 hours (IQR 9–36) in the standard-care group (median absolute difference 23 hours).

Patients with an increased baseline cardiac biomarker/enzyme had a lower risk of mortality with accelerated surgery compared to standard-care (17/163 [10%] in accelerated surgery patients compared to 36/159 [23%] in standard-care patients; hazard ratio [HR] 0.43, 95% confidence interval [CI] 0.24–0.77), whereas the patients with no elevated cardiac biomarker/enzyme demonstrated no mortality reduction with accelerated surgery, p value for interaction = 0.048) – Table 2. The fragility index for the primary outcome was 6.

Table 3 presents the cardiovascular secondary composite outcome and its components. Among patients with a baseline elevated cardiac biomarker/enzyme, there was a lower risk of the secondary composite outcome of major perioperative vascular complications in accelerated surgery patients (23/163 patients [14%]) compared to standard-care patients (47/159 [30%]) with a HR of 0.43, CI 95% 0.26-0.72), whereas the patients with no elevated cardiac biomarker/enzyme demonstrated no reduction in vascular complications with accelerated

surgery, p value for interaction = 0.025. Additional secondary and tertiary outcomes are presented in the Supplemental material (Appendix Tables 2, 3, 4 and 5). Patients with cardiac biomarker/enzyme elevation >2.1 times the ULN had lower mortality risk following accelerated surgery compared with standard-care (3/53 [6%] versus 17/56 [30%]; HR 0.17, CI 95% 0.05-0.58) when compared to patients with lower levels of cardiac biomarker elevation, p value for interaction=0.034 (Table 4).

Table 5 presents the Cox model with predictors of 90-day all-cause mortality including all 1392 patients with cardiac biomarker/enzymes measurements available. Elevated baseline cardiac biomarker/enzyme was independently associated with 90-day mortality (adjusted HR 1.80 [95% CI 1.27-2.56], p=0.001) when adjusted for cardiovascular risk factors, other clinically important comorbidities, and for treatment effect. In multivariable analysis, accelerated surgery was associated with lower all-cause mortality as compared to standard of care (adjusted HR 0.66 [95% CI 0.47-0.92]; p= 0.0152).

Discussion

We found that 1 in 5 patients with hip fracture had evidence of a myocardial injury identified by an elevated cardiac biomarker/enzyme measurement when they present to the hospital. In patients with a hip fracture, the presence of myocardial injury before surgery was associated with 3 times higher mortality at 90 days.(6) In a multivariable analyses, a baseline cardiac biomarker/enzyme elevation was an independent predictor of 90-day all-cause mortality (adjusted HR 1.80 [95% CI 1.27-2.56], p=0.001), offering additional information on top of clinical predictors including the RCRI score. Accelerated surgery lowered the risk of mortality compared with standard-care in patients with a baseline elevated cardiac biomarker/enzyme (HR

0.43; 95% CI, 0.24 - 0.77) compared to patients without a baseline elevated cardiac biomarker/enzyme (HR 0.88; 95% CI, 0.58-1.34), p-value for interaction 0.048.

Our results are similar to previous cohort studies demonstrating that preoperative myocardial injury is common in hip fracture patients (15-30%) and carries a poor prognosis.(5, 7, 14, 15) Currently, there are no clinical guidelines on how to manage those patients. Conventional treatment focuses on medically managing the myocardial injury. Usually, physicians only proceed to hip surgery when it is believed that the myocardial injury is stabilized.(7, 16) This typically prevents hip surgery from occurring for at least 24 hours after the hip fracture diagnosis. However, with the current approach, 23% of patients presenting with a hip fracture and myocardial injury die within 90 days.(6) This short-term mortality rate is much worse than outcomes for hip fracture patients without an elevated troponin (9%).(6)

Most likely the myocardial injury is a consequence of the physiologic stress induced by hip fracture and is a marker of patients with poor cardiac reserve. Although troponins are specific for myocardial injury (17), multiple different etiologies, play a role in the perioperative setting. These include dehydration, hypoperfusion, bleeding, inflammation, or ischemia. These are also common causes of type 2 supply-demand mismatch myocardial infarction.(18) Patients are commonly managed accordingly to ACS guidelines (16), despite hip fracture patients being frequently excluded from ACS trials. Indeed, coronary artery thrombosis is uncommon in the perioperative context, and physicians' judgement of thrombosis etiology is frequently inaccurate.(19, 20)

Our results suggest the possibility of a beneficial paradigm shift in perioperative medicine, proposing expedited surgery among patients with a hip fracture and myocardial injury at hospital presentation, as an alternative approach based on a strong biologic rationale and

encouraging preliminary data. Similar to other causes of myocardial injury, where the standard of care is to control the trigger (i.e., upper gastrointestinal bleeding), earlier surgical repair of the hip fracture seems to reduce the risk of further medical complications and all-cause mortality. Hip fractures result in pain, bleeding, inflammation, and hypercoagulation which can precipitate myocardial injury.(21-27) Patients undergoing hip fracture surgery have higher risk-adjusted mortality and major complications than patients undergoing elective hip surgery.(28) This suggests that the hip fracture, independent of surgery, increases patient risk. Typical medical treatments for myocardial injury such as antithrombotics and beta-blockers, may worsen physiological factors resulting from the hip fracture by way of increased bleeding and hypotension.(29, 30) . Additionally, performing multiple preoperative cardiac tests delays surgical access, prolongs the aforementioned stress state, and frequently does not change perioperative clinical management.(31) Thus, accelerated hip surgery has the potential to quickly restore a patient's overall physiologic health, and reduce the risk of death compared to standard-care.

Overall, our results suggest that patients presenting with a myocardial injury are not tolerating the additional cardiac stress associated with hip fracture and could benefit from expedited surgical care. These patients are frequently asymptomatic from a cardiac perspective and will not be identified without routine preoperative troponin screening. Additionally, if only postoperative troponin is monitored, the myocardial injury could be attributed to the surgical stress rather than the hip fracture. A common concern when identifying an elevated troponin is surgical delays and cancellations. It is clear these patients are very high-risk, and they are not being identified. Instead of ignoring this problem, we should identify these patients and propose new strategies to improve their prognosis. HIP ATTACK-1 is the first trial that provides insights

on this topic, suggesting accelerated surgery may be the best approach. Despite the fact that the first participants in HIP ATTACK-1 were enrolled a decade ago, current practice has not changed.(7)

Our study has some limitations. Reasons for cardiac biomarker/enzymes elevation before randomization were not recorded. However, only 19/322 (6%) patients presented with an acute myocardial infarction as per site report (13 in the accelerated-care group and 6 in the standard-care group). These low numbers did not allow any solid comparisons, however, they go in the conservative direction for the accelerated-care group. Indeed, regardless of the etiology of the myocardial injury, its presence identifies the potential benefit of accelerated surgery. Sites used multiple different troponin assays. Therefore, it was not possible to establish specific troponin thresholds independently associated with mortality. We thus performed analysis by terciles. The data presented is based on a post-hoc analysis, being underpowered to be a definitive practice changing trial, to access additional strategies to improve outcomes such as type of anesthesia, or to make positive statements on secondary exploratory outcomes. The ongoing HIP ATTACK-2 trial will include 1100 participants, and is powered to answer this question. (NCT04743765).

In conclusion, 1 in 5 patients with hip fracture present with acute myocardial injury. Mortality is three-fold higher in this population. Accelerated surgery has the potential to improve mortality and major cardiovascular outcomes compared with standard-care. These findings must be confirmed in additional trials.

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Supplement material, pg 2-4.

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Legends

Figure 1. Patient Flow diagram

475 **Table 1. Characteristics of participants in the cardiac biomarker/enzyme substudy**
476

	Participants with NO cardiac biomarker/enzyme elevation		Participants WITH cardiac biomarker/enzyme elevation	
	Accelerated	Standard	Accelerated	Standard
	N (%)	N (%)	N (%)	N (%)
Randomized	516	554	163	159
Age - Mean (SD)	77.7 (11.5)	78.6 (11.1)	81.8 (11.1)	81.5 (11.5)
Male	152 (29.5%)	159 (28.7%)	64 (39.3%)	52 (32.7%)
History before hip fracture				
Assistance with activities of daily living	145 (28.1%)	190 (34.3%)	59 (36.2%)	60 (37.7%)
Current Nursing home residence	107 (20.7%)	131 (23.6%)	29 (17.8%)	32 (20.1%)
Tobacco use	142 (27.5%)	138 (24.9%)	31 (19.0%)	23 (14.5%)
Total Pack Years - Mean (SD)	34.7 (31.0)	33.2 (27.9)	36.6 (30.4)	27.9 (24.1)
Stroke	52 (10.1%)	33 (6.0%)	11 (6.7%)	19 (11.9%)
Subarachnoid hemorrhage	4 (0.8%)	3 (0.5%)	5 (3.1%)	1 (0.6%)
Transient ischemic attack	22 (4.3%)	29 (5.2%)	7 (4.3%)	7 (4.4%)
Myocardial infarction	46 (8.9%)	40 (7.2%)	12 (7.4%)	16 (10.1%)
Unstable Angina	11 (2.1%)	6 (1.1%)	2 (1.2%)	2 (1.3%)
Stable Angina	14 (2.7%)	15 (2.7%)	4 (2.5%)	5 (3.1%)
Pulmonary Embolism	3 (0.6%)	4 (0.7%)	3 (1.8%)	4 (2.5%)
Deep Vein Thrombosis	8 (1.6%)	16 (2.9%)	4 (2.5%)	5 (3.1%)
CABG	17 (3.3%)	14 (2.5%)	4 (2.5%)	2 (1.3%)
PCI	16 (3.1%)	17 (3.1%)	6 (3.7%)	6 (3.8%)
CABG or PCI	29 (5.6%)	28 (5.1%)	9 (5.5%)	7 (4.4%)
Peripheral Vascular Disease	14 (2.7%)	15 (2.7%)	6 (3.7%)	7 (4.4%)
Aortic Stenosis	10 (1.9%)	11 (2.0%)	3 (1.8%)	2 (1.3%)
Paroxysmal Atrial Fibrillation	17 (3.3%)	16 (2.9%)	6 (3.7%)	6 (3.8%)
Chronic Atrial Fibrillation	27 (5.2%)	32 (5.8%)	10 (6.1%)	9 (5.7%)
Congestive Heart Failure	33 (6.4%)	21 (3.8%)	12 (7.4%)	12 (7.5%)
Hypertension	284 (55.0%)	334 (60.3%)	98 (60.1%)	110 (69.2%)
Diabetes	113 (21.9%)	104 (18.8%)	33 (20.2%)	37 (23.3%)
COPD	44 (8.5%)	55 (9.9%)	16 (9.8%)	6 (3.8%)
Active Cancer	24 (4.7%)	24 (4.3%)	5 (3.1%)	7 (4.4%)
Renal Failure requiring Dialysis	1 (0.2%)	2 (0.4%)	3 (1.8%)	2 (1.3%)
Dementia	71 (13.8%)	107 (19.3%)	33 (20.2%)	31 (19.5%)

	Participants with NO cardiac biomarker/enzyme elevation		Participants WITH cardiac biomarker/enzyme elevation	
	Accelerated	Standard	Accelerated	Standard
	N (%)	N (%)	N (%)	N (%)
Osteoporosis prior to Fracture	69 (13.4%)	88 (15.9%)	20 (12.3%)	17 (10.7%)
Previous Hip Fracture	31 (6.0%)	41 (7.4%)	9 (5.5%)	11 (6.9%)
Physiological measurements before randomization				
Systolic Blood Pressure (mmHg)-mean (SD)	142.4 (24.5)	142.5 (26.1)	140.0 (126.0-159.0)	140.0 (126.0-157.0)
Diastolic Blood Pressure (mmHg)-mean (SD)	76.9 (13.0)	76.8 (13.0)	80.0 (70.0- 87.0)	77.0 (70.0- 82.0)
Heart Rate (bpm)	81.0 (13.5)	80.8 (13.6)	80.0 (70.0- 87.0)	81.0 (72.0- 90.0)
Baseline Laboratory Assessments				
Creatinine (umol/L)	82.2 (38.8)	83.5 (40.8)	88.4 (70.7-122.0)	90.5 (69.8-124.6)
Hemoglobin (g/L)	120.9 (18.3)	121.1 (18.4)	118.5 (103.0-131.5)	115.5 (101.0-125.5)

Abbreviations: CABG: cardiac artery by pass; COPD: chronic obstructive pulmonary disease; PCI: percutaneous coronary intervention

Table 2. Subgroup analyses for 90-day all-cause mortality based on whether patients had a baseline elevated cardiac biomarker/enzyme measurement after hip fracture and before randomization

	Accelerated care	Standard care		
All-cause Mortality	**Events/ Patients (%)**	**Events/ Patients (%)**	**HR (95% CI)**	**P Value for Interaction***
Overall	**140 / 1487 (9.4)**	**154 / 1483 (10.4)**	**0.91 (0.72 – 1.14)**	**.**
Non-elevated cardiac biomarker/enzyme	**39 / 516 (7,6)**	**48 / 554 (8.7)**	**0.88 (0.58 – 1.34)**	**0.048**
Elevated cardiac biomarker/enzyme	**17 / 163 (10.4)**	**36 / 159 (22.6)**	**0.43 0.24 – 0.77)**	

***P value for interaction for the subgroup analysis comparing the treatment effect on patients with non-elevated cardiac biomarker/enzyme versus treatment effect on patients presenting with elevated cardiac biomarker/enzyme**

Table 3. Secondary outcomes at 90 days according to allocation groups

		Accelerated care	Standard care			
Outcome	**Baseline Troponin elevation**	**Events/ Patients (%)**	**Events/ Patients (%)**	**HR (95% CI)**	**P Value**	**P Value for Interaction**
Secondary composite outcome*	No	65/516 (12.6)	81/554 (14.6)	0.86 (0.62-1.19)	.3602	.0256
	Yes	23/163 (14.1)	47/159 (29.6)	0.43 (0.26-0.72)	.0011	
Vascular Mortality	No	21/516 (4.1)	32/554 (5.8)	0.71 (0.41-1.23)	.2219	.2509
	Yes	10/163 (6.1)	22/159 (13.8)	0.41 (0.19-0.87)	.0196	
Non-vascular Mortality	No	18/516 (3.5)	16/554 (2.9)	1.22 (0.62-2.39)	.5647	.0844
	Yes	7/163 (4.3)	14/159 (8.8)	0.46 (0.19-1.15)	.0967	
Myocardial Infarction	No	29/516 (5.6)	35/554 (6.3)	0.89 (0.54-1.45)	.6305	.2903
	Yes	9/163 (5.5)	16/159 (10.1)	0.52 (0.23-1.18)	.1189	
Stroke	No	3/516 (0.6)	5/554 (0.9)	0.64 (0.15-2.70)	.5479	.0725
	Yes	0/163 (0)	4/159 (2.5)	-	.9949	
Congestive Heart Failure	No	5/516 (1.0)	8/554 (1.4)	0.67 (0.22-2.05)	.4809	.2647
	Yes	1/163 (0.6)	5/159 (3.1)	0.18 (0.02-1.55)	.1183	
New Clinically important Atrial Fibrillation	No	8/516 (1.6)	9/554 (1.6)	0.96 (0.37-2.49)	.9308	.2488
	Yes	0/163 (0)	1/159 (0.6)	-	.9975	
Recurrent myocardial injury after randomization	No	110/516 (21.3)	146/554 (26.4)	0.80 (0.63-1.03)	.0851	.6033
	Yes	37/163 (22.7)	50/159 (31.4)	0.68 (0.44-1.04)	.0775	

*All-cause mortality, Non fatal myocardial infarction, Non fatal stroke, Non fatal congestive heart failure.

Table 4. 90-day all-cause mortality by troponin terciles at hospital presentation according to the accelerated care group and standard care group

Troponin levels	Accelerated Events/Patients (%)	Standard Events/Patients (%)	HR (95% CI)	*p* Value	*p* Value for Interaction
Not elevated	39/516 (8)	48/554 (9)	0.88 (0.58-1.34)	.552	.0340
Elevated times* (1 - 1.32)	4/54 (7)	7/53 (13)	0.54 (0.16-1.88)	.335	
Elevated times* (1.33 - 2.1)	10/56 (18)	12/50 (24)	0.71 (0.31-1.66)	.431	
Elevated times* (> 2.1)	3/53 (6)	17/56 (30)	0.17 (0.05-0.58)	.054	

*Elevated times of the upper reference limit of the troponin assay at each site. Abbreviations: CI: confidence interval; HR: hazard ratio.

Table 5. Cox model with predictors of 90-day all-cause mortality

Variables	HR (95% CI)	P value
Elevated troponin versus not elevated	1.80 (1.27-2.56)	.0010
RCRI score 1 vs 0	1.39 (0.93-2.07)	.1098
RCRI score 2 vs 0	1.95 (1.15-3.33)	.0140
RCRI score ≥3 vs 0	2.56 (1.20-5.48)	.0151
Age	1.04 (1.02-1.06)	<0.0001
Sex - Male vs Female	1.62 (1.14-2.30)	.0067
History of peripheral vascular disease	1.11 (0.52-2.38)	.7791
History of COPD	1.63 (0.99-2.66)	.0526
Active cancer	1.57 (0.81-3.03)	.1823
Accelerated versus Standard care	0.66 (0.47-0.92)	.0152

Abbreviations: CI: confidence interval; COPD: chronic obstructive pulmonary disease; HR: hazard ratio; RCRI: Revised Cardiac Index Risk.