Queen's UNIVERSITY

# DEPARTMENT OF ANESTHESIOLOGY

# JOURNAL CLUB
# Via Zoom

**Thursday, 24 March, 2022**
**1630-1800 HOURS**

## PRESENTING ARTICLES:
## Dr. Melanie Jaeger & Dr. Nick Wisdom

**SUGGESTED GUIDELINES FOR CRITICAL APPRAISAL OF PAPERS**
**ANESTHESIOLOGY JOURNAL CLUB**
**QUEEN'S UNIVERSITY**


Two presenters will be assigned to choose and present summaries of their papers. Ideally the two papers will represent similar topics but contrasting research methodologies. The focus remains on critical appraisal of the research and manuscript, more than on the actual contents of the article. Each presenter will then lead an open discussion about the article, based around the guidelines below. The object is to open up the appraisal to wide discussion involving all participants.

**GENERAL**

1. Title of paper: Does it seem like an important problem? Does it reflect the purpose/results?
2. Authors, institution and country of origin

**INTRODUCTION**

1. What is the problem being addressed?
2. What is the current state of knowledge of the problem studied?
3. What is the hypothesis being tested?
4. How does testing the hypothesis help solve the stated problem?

**METHODOLOGY**

1. Study design:
    a) Clinical trial vs. systematic review/meta-analysis
    b) Prospective vs. retrospective
    c) Observational vs. Experimental
    d) Randomized or not
    e) Blinded or not

2. Population studied:
    a) Human, animal, other
    b) Justification
    c) Control groups: experimental vs. historical
    d) Is the sample size/power calculated, and how?
    e) Is the population similar to your own practice?
    f) Single vs. multi-centre

3. Is the study ethically sound?
    a) Clinical equipoise
    b) Does treatment meet standard of care (esp controls)?
    c) Appropriate consent and institutional ethics approval

4. Exclusions: what groups are excluded and why?

5. Experimental protocol
    a) Is it designed to test the hypothesis?

b) Is it detailed enough to be reproducible?
c) Is the methodology validated?
d) Are the drugs/equipment used detailed?
e) How does the randomization take place?

6. What are the primary endpoints?
7. Is power sufficient to justify secondary endpoints?
8. Is the protocol clinically relevant?
9. Data collection and analysis
10. Statistical analysis: Is it appropriate? Are results

**RESULTS**

1. Are the groups comparable?
2. Were any subjects/data eliminated?
3. Analyzed by intent to treat?
4. Are adequate details of results provided? - data, graphs, tables

**DISCUSSION**

1. What is the main conclusion of the study?
2. Do the results support this conclusion?
3. Do the results address the stated purpose/hypothesis of the study?
4. How do the authors explain the results obtained?
5. Are there any alternative interpretations to the data?
6. Are the results clinically as well statistically relevant?
7. How do the results compare with those of previous studies?
8. What do the results add to the existing literature?
9. What are the limitations of the methods or analysis used?
10. What are the unanswered questions for future work?

**APPLICABILITY OF THE PAPER**

1. Have you learned something important from reading this paper?
2. Will the results of this study alter your clinical practice?

# Dabigatran in patients with myocardial injury after non-cardiac surgery (MANAGE): an international, randomised, placebo-controlled trial

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## Summary

**Background** Myocardial injury after non-cardiac surgery (MINS) increases the risk of cardiovascular events and deaths, which anticoagulation therapy could prevent. Dabigatran prevents perioperative venous thromboembolism, but whether this drug can prevent a broader range of vascular complications in patients with MINS is unknown. The MANAGE trial assessed the potential of dabigatran to prevent major vascular complications among such patients.

**Methods** In this international, randomised, placebo-controlled trial, we recruited patients from 84 hospitals in 19 countries. Eligible patients were aged at least 45 years, had undergone non-cardiac surgery, and were within 35 days of MINS. Patients were randomly assigned (1:1) to receive dabigatran 110 mg orally twice daily or matched placebo for a maximum of 2 years or until termination of the trial and, using a partial 2-by-2 factorial design, patients not taking a proton-pump inhibitor were also randomly assigned (1:1) to omeprazole 20 mg once daily, for which results will be reported elsewhere, or matched placebo to measure its effect on major upper gastrointestinal complications. Research personnel randomised patients through a central 24 h computerised randomisation system using block randomisation, stratified by centre. Patients, health-care providers, data collectors, and outcome adjudicators were masked to treatment allocation. The primary efficacy outcome was the occurrence of a major vascular complication, a composite of vascular mortality and non-fatal myocardial infarction, non-haemorrhagic stroke, peripheral arterial thrombosis, amputation, and symptomatic venous thromboembolism. The primary safety outcome was a composite of life-threatening, major, and critical organ bleeding. Analyses were done according to the intention-to-treat principle. This trial is registered with ClinicalTrials.gov, number NCT01661101.

**Findings** Between Jan 10, 2013, and July 17, 2017, we randomly assigned 1754 patients to receive dabigatran (n=877) or placebo (n=877); 556 patients were also randomised in the omeprazole partial factorial component. Study drug was permanently discontinued in 401 (46%) of 877 patients allocated to dabigatran and 380 (43%) of 877 patients allocated to placebo. The composite primary efficacy outcome occurred in fewer patients randomised to dabigatran than placebo (97 [11%] of 877 patients assigned to dabigatran *vs* 133 [15%] of 877 patients assigned to placebo; hazard ratio [HR] 0·72, 95% CI 0·55–0·93; p=0·0115). The primary safety composite outcome occurred in 29 patients (3%) randomised to dabigatran and 31 patients (4%) randomised to placebo (HR 0·92, 95% CI 0·55–1·53; p=0·76).

**Interpretation** Among patients who had MINS, dabigatran 110 mg twice daily lowered the risk of major vascular complications, with no significant increase in major bleeding. Patients with MINS have a poor prognosis; dabigatran 100 mg twice daily has the potential to help many of the 8 million adults globally who have MINS to reduce their risk of a major vascular complication.

**Funding** Boehringer Ingelheim and Canadian Institutes of Health Research.



## Introduction

Myocardial injury after non-cardiac surgery (MINS) includes myocardial infarction and isolated ischaemic troponin elevation occurring within 30 days after surgery,[1] but does not include perioperative myocardial injury due to non-ischaemic causes (eg, sepsis, rapid atrial fibrillation, pulmonary embolism, and chronically elevated troponin measurement).[2] Without routine perioperative troponin measurements, more than 80% of MINS events would go unrecognised, because these patients do not have ischaemic symptoms.[1–3] A proposed explanation for these asymptomatic events is

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See Comment page 2297

*Members are listed in the appendix

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See Online for appendix

## Research in context

### Evidence before this study

Myocardial injury after non-cardiac surgery (MINS) is the most common major perioperative vascular complication, affecting more than 8 million adults worldwide annually. Patients with MINS are at increased risk of thrombotic complications and death during the first 2 years after surgery. We searched MEDLINE, from inception until Jan 20, 2018, using the search terms "myocardial injury", "MINS", "noncardiac", "non-cardiac", "postoperative", and "surgery", restricted to publications in English, to identify studies in human adults 18 years or older evaluating interventions in MINS. Although we did not identify any previous randomised trials, we identified two observational studies. These multivariable analyses, with moderate risk of bias, suggested that aspirin and a statin might prevent death and major cardiac complications in patients who have MINS.

### Added value of this study

Our trial showed that in patients with MINS—90% of whom would not have been identified without troponin screening—dabigatran 110 mg twice daily reduced the risk of a major vascular complication, a composite of vascular mortality and non-fatal myocardial infarction, non-haemorrhagic stroke, peripheral arterial thrombosis, amputation, and symptomatic venous thromboembolism, compared with placebo. Dabigatran did not increase the risk of the primary safety outcome, a composite of life-threatening, major, and critical organ bleeding. MANAGE showed the poor prognosis of patients with MINS; 1 in 7 placebo patients suffered a major vascular complication at a mean of 16 months of follow-up. To our knowledge, MANAGE provides the first randomised trial data in patients with MINS and shows dabigatran 110 mg twice daily can reduce the risk of major vascular complications.

### Implications of all the available evidence

Physicians should routinely measure troponin in at-risk patients undergoing non-cardiac surgery and, in those with MINS, should consider using dabigatran 110 mg twice daily. Our results support the evaluation of interventions in patients with MINS that have established benefit in patients with vascular disease (eg, dual antiplatelet therapy or cholesterol reducing therapies).

that more than 85% of occurrences are within the first 48 h after non-cardiac surgery, when most patients receive analgesic medications that can mask ischaemic symptoms.[1,2] Both symptomatic and asymptomatic perioperative myocardial infarctions are associated with a four times increased risk of 30-day mortality.[4] Moreover, asymptomatic perioperative troponin elevations adjudicated as myocardial injuries due to ischaemia, which do not fulfil the universal definition of myocardial infarction,[5] are also associated with a three-times increased risk of 30-day mortality.[2] On the basis of these findings, MINS diagnostic criteria include myocardial infarction and isolated ischaemic troponin elevation occurring within 30 days after surgery.

MINS, the most common major perioperative vascular complication, is estimated to affect about 8 million adults worldwide annually,[1,2] and is independently associated with an increased risk of cardiovascular complications and death in the first 2 years after surgery.[1–3,6] MINS was only described for the first time 4 years ago and, to our knowledge, no published trial has investigated a potential risk mitigation strategy, therefore management is informed only by observational analyses and indirect evidence from other myocardial ischaemic syndromes.[7]

Patients with MINS are at increased risk of thrombotic complications.[1,2] Anticoagulation therapy is beneficial in non-operative patients at risk of thrombotic events (eg, patients with a myocardial infarction and those with vascular disease).[8–11] Dabigatran, an oral direct thrombin inhibitor, prevents perioperative venous thromboembolism,[12,13] but whether it prevents a broader range of vascular complications in patients with MINS is unknown. The MANAGE trial assessed the potential of dabigatran to prevent major vascular complications among patients with MINS.

## Methods

### Study design and patients

We did this investigator-initiated, international, randomised, placebo-controlled trial at 84 hospitals in 19 countries. We have previously reported details of the trial design and methods.[14] Eligible patients were at least 45 years of age, had undergone non-cardiac surgery, were within 35 days of MINS, and provided written informed consent.[2,5] Patients met the criteria for MINS if, after undergoing non-cardiac surgery, they had either elevated troponin with ischaemic signs or symptoms, ischaemic electrocardiographic changes, or new or presumed new ischaemic abnormality on cardiac imaging (ie, MINS that also met the universal definition of myocardial infarction);[5] or had an isolated elevated troponin measurement without an alternative explanation (eg, sepsis, rapid atrial fibrillation, pulmonary embolism, or chronically elevated troponin measurement) to ischaemic myocardial injury. Preoperative measurement of troponin was not required, as this is not part of routine clinical care. Full inclusion criteria are presented in the appendix.

We excluded patients who had a haemorrhagic disorder or a condition that required therapeutic dose anticoagulation (eg, prosthetic heart valve, venous thromboembolism, or atrial fibrillation). We also excluded patients in whom any of the following criteria persisted beyond 35 days of MINS occurrence:

the attending surgeon believed it was not safe to initiate therapeutic dose anticoagulation therapy; the attending physician believed that the patient required a prophylactic-dose anticoagulant and aspirin, intermittent pneumatic compression, or elastic stockings were not sufficient for venous thromboembolism prophylaxis; or estimated glomerular filtration rate was less than 35 mL/min. Patients were not excluded if they were receiving dual antiplatelet therapy. Full exclusion criteria are presented in the appendix.

Before starting recruitment, all centres obtained ethics committee approval, and the relevant health authorities approved the protocol. Reporting in this publication is consistent with the CONSORT statement.[15]

### Randomisation and masking

Patients were randomly assigned (1:1) to receive dabigatran or placebo and, using a partial 2-by-2 factorial design, patients not taking a proton-pump inhibitor were also randomly assigned (1:1) to omeprazole or placebo to measure its effect on major upper gastrointestinal complications. After obtaining consent, research personnel randomly assigned patients through a central 24 h computerised randomisation system using block randomisation, stratified by centre. Patients, health-care providers, data collectors, and outcome adjudicators were masked to treatment allocation.

### Procedures

Centres were encouraged to obtain troponin measurements for at least the first 2 days after surgery requiring at least overnight hospital admission in patients aged 65 years or older or patients who had a history of coronary artery disease, stroke, or peripheral arterial disease who were aged 45–64 years (as recommended by the Canadian Cardiovascular Society's Perioperative Guidelines).[16] Investigators used the troponin assay that was routinely used at their centre (for thresholds defining a perioperative troponin elevation see appendix).

Study personnel told patients before they gave consent that they would have to take the study drug for a maximum of 2 years, and that in-person follow-up was required at 1, 6, 12, 18, and 24 months.

On the day of randomisation, patients received dabigatran (Boehringer Ingelheim, Ingelheim am Rhein, Germany) 110 mg orally twice daily or matched placebo. Patients enrolled in the partial factorial component of the trial took omeprazole (Laboratorios Liconsa, Barcelona, Spain) 20 mg orally once daily or matched placebo. Patients continued to take study drug and were followed up for a maximum of 2 years, or until the trial was terminated on Nov 30, 2017. Research personnel submitted case report forms and supporting event documentation to the data management system.

Patients were followed up in the hospital and contacted 1 week after randomisation or hospital discharge,

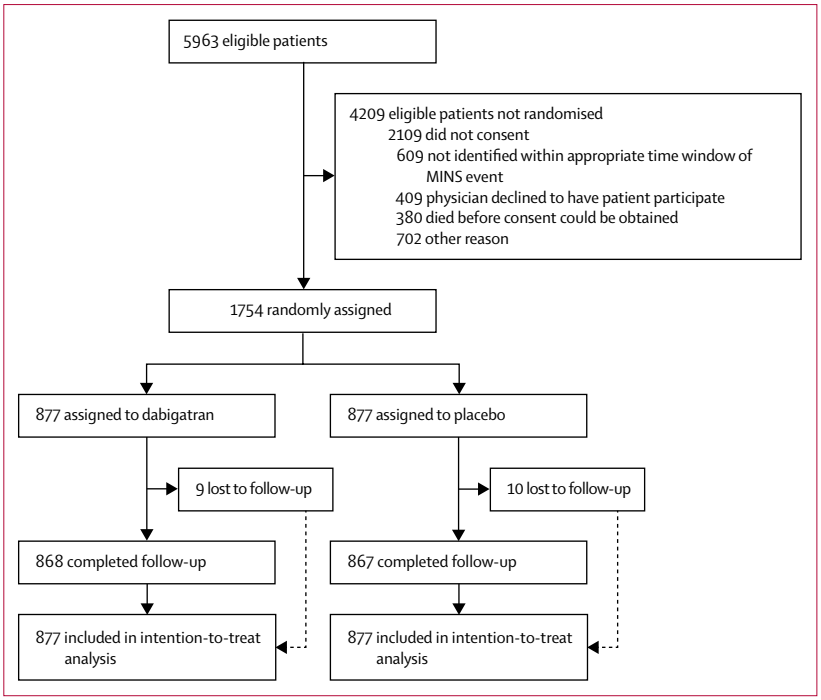


***Figure 1:*** **Trial profile**
MINS=myocardial injury after non-cardiac surgery.

| | Dabigatran group (n=877) | Placebo group (n=877) |
|---|---|---|
| Age (years) | 70 (11) | 70 (11) |
| Sex | | |
| Male | 453 (52%) | 443 (51%) |
| MINS diagnostic criteria | | |
| Myocardial infarction | 172 (20%) | 173 (20%) |
| Isolated ischaemic troponin elevation | 705 (80%) | 704 (80%) |
| Troponin data associated with MINS | | |
| Peak measured troponin value (ng/L) | 82 (45–196) | 82 (45–200) |
| Difference between the highest and lowest troponin values (ng/L)* | 40 (16–160) | 48 (18–154) |
| Difference between the highest and lowest troponin values ≥5 ng/L | 592/625 (95%) | 590/627 (94%) |
| Time from surgery to MINS diagnosis (days) | 1 (1–2) | 1 (1–2) |
| Time from MINS diagnosis to randomisation (days) | 5 (2–14) | 5 (2–14) |
| Medical history | | |
| Previous myocardial infarction | 116 (13%) | 110 (13%) |
| Recent high-risk coronary artery disease† | 17 (2%) | 21 (2%) |
| Previous stroke | 29 (3%) | 42 (5%) |
| Previous peripheral arterial disease | 124 (14%) | 128 (15%) |
| Previous pulmonary embolism | 6 (1%) | 7 (1%) |
| Previous deep venous thrombosis | 16 (2%) | 15 (2%) |
| Diabetes | 222 (25%) | 234 (27%) |
| Hypertension | 585 (67%) | 587 (67%) |
| Laboratory measurements before randomisation | | |
| Haemoglobin (g/L) | 107 (95–119) | 106 (96–120) |
| Calculated creatinine clearance (mL/min) | 79 (58–104) | 75 (57–101) |

(Table 1 continues on next page)

| | Dabigatran group (n=877) | Placebo group (n=877) |
|---|---|---|
| (Continued from previous page) | | |
| Type of surgery preceding MINS | | |
| Orthopaedic | 331 (38%) | 339 (39%) |
| General | 252 (29%) | 241 (27%) |
| Vascular | 119 (14%) | 130 (15%) |
| Urological or gynaecological | 83 (9%) | 77 (9%) |
| Thoracic | 43 (5%) | 41 (5%) |
| Spinal | 31 (4%) | 25 (3%) |
| Low risk surgery | 34 (4%) | 41 (5%) |
| Medications before randomisation | | |
| Aspirin | 511 (58%) | 509 (58%) |
| $P2Y_{12}$ inhibitor | 32 (4%) | 42 (5%) |
| Aspirin or a $P2Y_{12}$ inhibitor | 522 (60%) | 524 (60%) |
| Dual antiplatelet therapy | 22 (3%) | 29 (3%) |
| Angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker | 404 (46%) | 404 (46%) |
| β blocker | 340 (39%) | 326 (37%) |
| Statin | 451 (51%) | 509 (58%) |
| Cardiac testing associated with qualifying MINS | | |
| Coronary angiography | 9 (1%) | 5 (1%) |
| Echocardiography | 194 (22%) | 202 (23%) |
| Radionuclide imaging | 33 (4%) | 34 (4%) |
| Cardiac MRI | 28 (3%) | 41 (5%) |
| Regions | | |
| North America | 381 (43%) | 384 (44%) |
| Europe and Australia | 223 (25%) | 219 (25%) |
| Asia | 134 (15%) | 134 (15%) |
| Africa | 93 (11%) | 94 (11%) |
| South America | 46 (5%) | 46 (5%) |

Data are mean (SD), n (%), or median (IQR). MINS=myocardial injury after non-cardiac surgery. There were 48 patients common to both ASA and $P2Y_{12}$ inhibitors. *1252 patients (71%; 625 allocated to dabigatran and 627 allocated to placebo) had two or more postoperative troponin values recorded on their baseline case report form. The difference between highest and lowest troponin values was established for these patients, as well as the number and percentage of patients with a difference between the highest and lowest troponin values of 5 ng/L or greater. †Defined as a physician diagnosis 6 months or less before non-cardiac surgery of a myocardial infarction, acute coronary syndrome, Canadian Cardiovascular Society (CCSV) class III angina (occurring with level walking of one to two blocks or climbing one or less than one flight of stairs at a normal pace), or CCSV class IV angina (inability to carry on any physical activity without the development of angina).

***Table 1:*** **Baseline characteristics**

whichever was later. Patients were followed up 1 month after randomisation and subsequently every 6 months until they completed the trial. Interim telephone follow-up visits occurred every 3 months between office visits.

## Outcomes

The primary efficacy outcome was a major vascular complication (ie, a composite of vascular mortality, and non-fatal myocardial infarction, non-haemorrhagic stroke, peripheral arterial thrombosis, amputation, and symptomatic venous thromboembolism). The primary safety outcome was a composite of life-threatening, major, and critical organ bleeding. Major bleeding was defined as bleeding that was not specified as life-threatening bleeding, and resulted in one of the following: a drop in haemoglobin of 4·0 g/dL or greater; the patient receiving a transfusion of three or more units of red blood cells within a 24 h period; embolisation, superficial vascular repair, or nasal packing; or intraspinal, intramuscular with compartment syndrome, retroperitoneal, pericardial, or intraocular (confirmed clinically or on imaging) bleeding. Primary outcomes were assessed centrally, with the exception of amputation.

Secondary efficacy outcomes were the following individual outcomes: vascular mortality, all-cause mortality, myocardial infarction, cardiac revascularisation procedure, non-haemorrhagic stroke, peripheral arterial thrombosis, amputation, symptomatic venous thromboembolism, and readmission to hospital for vascular reasons. Secondary individual safety outcomes included life-threatening bleeding, major bleeding, critical organ bleeding, intracranial bleeding, haemorrhagic stroke, any lower gastrointestinal bleeding, minor bleeding, fracture, and dyspepsia (see appendix for outcome definitions).

Physicians with expertise in the trial outcomes, who were masked to treatment allocation, adjudicated the following outcomes: death (vascular *vs* non-vascular), myocardial infarction, non-haemorrhagic stroke, haemorrhagic stroke, peripheral arterial thrombosis, symptomatic pulmonary embolism, symptomatic proximal deep venous thrombosis, life-threatening bleeding, major bleeding, critical organ bleeding, minor bleeding, intracranial bleeding, and clinically significant lower gastrointestinal bleeding. Adjudicated events were used for the analyses.

## Statistical analysis

MANAGE was initially designed to randomly assign 3200 patients followed up for a mean of 1 year with a primary composite outcome of vascular mortality and non-fatal myocardial infarction, stroke, peripheral arterial thrombosis, and symptomatic pulmonary embolism. Patient recruitment was slower than expected, and during the conduct of the trial funding was curtailed. Without knowledge of the trial results, we reduced the sample size to 1750 patients and, based on the COMPASS trial[11] results, broadened the primary outcome by adding amputation and symptomatic proximal deep venous thrombosis to enhance power. A sample size of 1750 patients had 90% power to detect a hazard ratio (HR) of 0·65 (two-sided $\alpha$=0·05) for dabigatran versus placebo, assuming a placebo group survival rate of 20%.

We analysed patients in the groups to which they were randomly assigned, according to the intention-to-treat principle. Missing outcome data occurred as a result of patients being lost to follow-up; therefore, we censored data for such patients on the last day their status was known. For the primary analysis, we used the log-rank test to compare the distributions of the times to the primary efficacy outcome between the dabigatran group and placebo group, and reported the two-tailed p value. We also used a Cox proportional hazard model to estimate

| | Dabigatran (n=877) | Placebo (n=877) | Hazard ratio (95% CI) | p value |
|---|---|---|---|---|
| **Primary efficacy outcome** | | | | |
| Composite of vascular mortality and non-fatal myocardial infarction, non-haemorrhagic stroke, peripheral arterial thrombosis, amputation, and symptomatic venous thromboembolism | 97 (11%) | 133 (15%) | 0·72 (0·55–0·93) | 0·0115 |
| **Secondary efficacy outcomes** | | | | |
| Vascular mortality | 52 (6%) | 64 (7%) | 0·80 (0·56–1·16) | .. |
| All-cause mortality | 100 (11%) | 110 (13%) | 0·90 (0·69–1·18) | .. |
| Myocardial infarction | 35 (4%) | 43 (5%) | 0·80 (0·51–1·26) | .. |
| Cardiac revascularisation procedure | 32 (4%) | 21 (2%) | 1·53 (0·88–2·65) | .. |
| Non-haemorrhagic stroke | 2 (<1%) | 10 (1%) | 0·20 (0·04–0·90) | .. |
| Peripheral arterial thrombosis | 0 | 4 (<1%) | .. | .. |
| Amputation | 18 (2%) | 26 (3%) | 0·70 (0·38–1·27) | .. |
| Symptomatic venous thromboembolism | 8 (1%) | 17 (2%) | 0·47 (0·20–1·08) | .. |
| Readmission to hospital for vascular reasons | 113 (13%) | 130 (15%) | 0·86 (0·67–1·11) | .. |

Data are n (%) unless otherwise indicated.

***Table 2:*** **Efficacy outcomes**

the effect of dabigatran, with stratification according to whether patients were randomised to omeprazole or placebo.[17,18] We assessed the proportional hazards assumption by verifying the non-significance of the log time-by-treatment interaction term in the model. For the primary efficacy composite outcome, we tested for heterogeneous differences in treatment effect between individual components of the primary composite outcome using a composite treatment heterogeneity test.[19] The primary safety outcome and secondary outcomes were analysed using an approach similar to that used for the primary outcome. For the safety outcome, patients were analysed in the groups to which they were randomly assigned, according to the intention-to-treat principle. We also did competing risks analyses for all non-fatal events.[20]

For the primary efficacy outcome, we did four prespecified subgroup analyses based on the timing of randomisation (≤5 days after MINS while still in hospital *vs* >5 days after MINS or after hospital discharge), MINS diagnostic criterion (myocardial infarction *vs* an isolated ischaemic troponin elevation), the presence or absence of peripheral arterial disease, and whether or not the patient received dual antiplatelet therapy at the time of randomisation. The expected direction of the subgroup effects were stated a priori in the statistical analysis plan. We expected larger treatment effects in the following subgroups of patients: patients randomised 5 days or less after MINS while still in hospital; patients who had a myocardial infarction; patients who had peripheral arterial disease, and patients who were not taking dual antiplatelet therapy at the time of randomisation. We used Cox proportional hazards models that incorporated tests of interaction, designated as significant if $p<0·05$.

An independent data monitoring committee reviewed the data when 25, 50, and 75% of the 1-year follow-up data were available. The committee used the modified Haybittle-Peto rule of four SDs for the first and second interim analyses ($\alpha=0·0001$) and three SDs for the third interim analysis ($\alpha=0·00047$). Initiating discussion regarding potential early trial termination required that these predefined boundaries be exceeded in at least two consecutive analyses, 3 or more months apart.

All analyses were done using SAS version 9.4 for UNIX. This trial is registered with ClinicalTrials.gov, number NCT01661101.

### Role of the funding source

Representatives from Boehringer Ingelheim provided input into the study design. The funders of the study had no role in 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.

## Results

Between Jan 10, 2013, and July 17, 2017, we randomly assigned 1754 patients to receive dabigatran (n=877) or placebo (n=877); 556 patients were also randomised in the omeprazole partial factorial component (results not presented here). We followed up patients in both groups for a mean of 16 months (SD 7), and 1735 (99%) of 1754 participants completed follow-up (figure 1).

Baseline characteristics were similar between groups (table 1). 1595 MINS events (91%) occurred without a clinical symptom or sign of cardiac ischaemia (795 MINS events [91%] in the dabigatran group and 800 MINS events [91%] in the placebo group; appendix). Among the 345 patients who fulfilled the universal definition of myocardial infarction,[5] 199 (58%) had an ischaemic electrocardiography change (93 [11%] in the dabigatran group and 106 [12%] in the placebo group; appendix). Various troponin assays were used across centres to diagnose MINS (appendix). 1153 patients (66%;

577 patients [66%] in the dabigatran group and 576 patients [66%] in the placebo group) were diagnosed based on the results of a high sensitivity troponin assay. The median peak measured troponin value associated with the diagnosis of MINS in both treatment groups was 82 ng/L (table 1). Among the patients with two or more postoperative troponin measurements on their baseline case report form, almost all had a difference between the highest and lowest troponin values of 5 ng/L or greater.

Study drug was permanently discontinued in 401 (46%) of 877 patients allocated to dabigatran and 380 (43%) of 877 patients allocated to placebo (appendix). Among patients who permanently discontinued study drug, the median time that patients took the drug was 80 days (IQR 10–212 days) in the dabigatran group and 41 days (6–208) in the placebo group. Among patients who did not permanently discontinue study drug, the median time that patients took the drug was 474 days (237–690) in the dabigatran group and 466 days (261–688) in the placebo group. During follow-up, 1296 patients (74%) were taking aspirin or a $P2Y_{12}$ inhibitor, 1196 (69%) were taking a statin, and 1022 (59%) were taking an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker at one or more follow-up visits (appendix).

The primary efficacy outcome occurred in 97 (11%) of 877 patients allocated to dabigatran and in 133 (15%) of 877 patients allocated to placebo (HR 0·72, 95% CI 0·55–0·93, p=0·0115; table 2, figure 2). The interaction term of log-time by treatment in the model indicated the assumption of proportional hazards was not violated ($p_{interaction}$=0·97). We found no significant heterogeneity in the HRs of the individual components of the primary efficacy composite outcome ($p_{interaction}$=0·66). Omeprazole study drug did not significantly impact the effect of dabigatran on the primary efficacy outcome ($p_{interaction}$=0·93). Of the secondary efficacy outcomes, non-haemorrhagic stroke was significantly reduced with dabigatran treatment (table 2).

We also did post-hoc analyses to investigate consistency of effect for the arterial and venous components of the primary composite outcome (table 2). Dabigatran reduced the arterial and venous components of the primary composite outcome (appendix). To address the potential effect if all patients adhered to study medications, we also did a post-hoc, per-protocol Cox proportional hazard analysis. This analysis, which censored patients 7 days after they permanently discontinued study drug, showed a larger effect of dabigatran on the primary efficacy outcome (appendix).

Dabigatran did not increase the risk of life-threatening, major, or critical organ bleeding (primary safety outcome) compared with placebo (HR 0·92, 95% CI 0·55–1·53, p=0·78; table 3; appendix). Omeprazole had

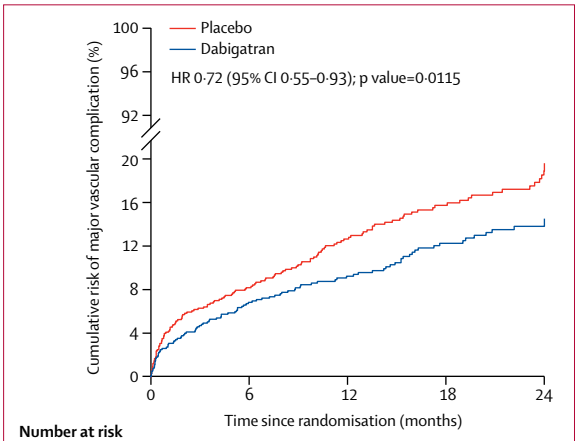


*Figure 2:* **Kaplan-Meier estimates of the primary efficacy outcome**
HR=hazard ratio.

| | Dabigatran (n=877) | Placebo (n=877) | Hazard ratio (95% CI) | p value |
|---|---|---|---|---|
| **Primary safety outcome** | | | | |
| Composite of life-threatening, major, and critical organ bleeding | 29 (3%) | 31 (4%) | 0·92 (0·55–1·53) | 0·78 |
| **Secondary safety outcomes** | | | | |
| Life-threatening bleeding | 9 (1%) | 8 (1%) | 1·11 (0·43–2·88) | .. |
| Major bleeding | 21 (2%) | 25 (3%) | 0·83 (0·46–1·48) | .. |
| Critical organ bleeding | 5 (1%) | 10 (1%) | 0·49 (0·17–1·43) | .. |
| Intracranial bleeding | 4 (<1%) | 3 (<1%) | 1·32 (0·30–5·90) | .. |
| Haemorrhagic stroke | 2 (<1%) | 2 (<1%) | 0·98 (0·14–6·96) | .. |
| Clinically significant lower gastrointestinal bleeding | 15 (2%) | 6 (1%) | 2·50 (0·97–6·44) | .. |
| Clinically non-significant lower gastrointestinal bleeding | 33 (4%) | 7 (1%) | 4·77 (2·11–10·80) | .. |
| Minor bleeding | 134 (15%) | 84 (10%) | 1·64 (1·25–2·15) | .. |
| Fracture | 39 (4%) | 28 (3%) | 1·38 (0·85–2·24) | .. |
| Dyspepsia | 129 (15%) | 98 (11%) | 1·33 (1·02–1·73) | .. |

Data are n (%) unless otherwise indicated.

*Table 3:* **Safety outcomes**

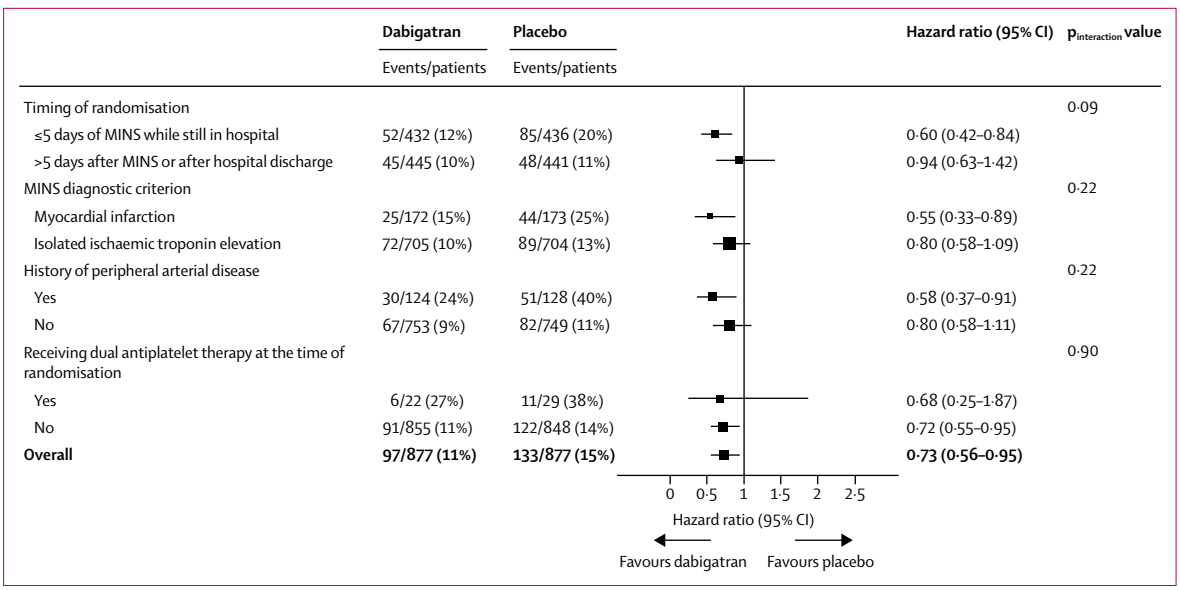


***Figure 3:*** **Subgroup analyses of the primary efficacy outcome**
MINS=myocardial injury after non-cardiac surgery.

no significant effect on the results of the dabigatran primary safety analysis ($p_{interaction}$=0·37). Of the secondary safety outcomes, dabigatran increased the risk of minor bleeding, clinically non-significant lower gastrointestinal bleeding, and dyspepsia.

We did a post-hoc analysis to evaluate the consistency of effect for major bleeding according to the definition of the International Society on Thrombosis and Haemostasis and the Bleeding Academic Research Consortium (ie, ≥type 2 bleeding; appendix).[21–23] Dabigatran did not increase the risk of bleeding according to these definitions. We also did a post-hoc, per-protocol Cox proportional hazard analysis for the primary safety outcome. This analysis—censoring patients 7 days after they permanently discontinued the study drug—showed consistent results for the primary safety outcome.

Competing risks analyses produced similar results to the main secondary analyses (appendix). In subgroup analyses for the primary efficacy outcome, the effect of dabigatran was consistent across subgroups (figure 3).

## Discussion

At a mean of 16 months of follow-up, patients with MINS frequently had major vascular complications (133 [15%] of 877 patients in the placebo group). Dabigatran reduced this risk without significantly increasing the risk of major bleeding.

To our knowledge, no published trial has evaluated an intervention strategy in patients with MINS. Previous multivariable analyses from observational studies[4,24] suggested that aspirin and a statin might prevent death and major cardiac complications in patients who have MINS, but this has not been evaluated in randomised trials. During follow-up, 1296 patients (74%) took aspirin or a $P2Y_{12}$ inhibitor and 1196 (69%) took a statin, highlighting the continued opportunity to improve secondary prophylactic measures in patients with MINS. Our finding of only 118 patients (7%) taking dual antiplatelet therapy during follow-up is consistent with a previous large international study.[4] If most MANAGE patients had taken dual antiplatelet therapy, this might have increased the risk of major bleeding in both the active and control groups, as observed in the ATLAS trial.[10]

The phase 2 RE-DEEM trial[25] randomly assigned patients who were taking dual antiplatelet therapy within 2 weeks of an acute coronary syndrome to placebo (n=371) or one of four different doses of dabigatran, of which one group received dabigatran 110 mg twice daily (n=406). Few major events occurred in the trial,[25] with eight patients (2%) assigned to dabigatran 110 mg twice daily having a major bleed compared with two patients (1%) assigned to placebo. The composite of cardiovascular death, myocardial infarction, and stroke occurred in 12 patients (3%) assigned to dabigatran 110 mg twice daily compared with 14 patients (4%) assigned to placebo.

The results of our trial are consistent with a large body of evidence documenting the ability of anticoagulants to reduce ischaemic events in patients with coronary disease, including acute coronary syndrome.[8–10] The COMPASS trial[11] showed that low-dose rivaroxaban (2·5 mg twice daily) and aspirin (100 mg once daily) compared with aspirin alone lowered the risk of a composite of cardiovascular death, stroke, and myocardial infarction by a quarter and also decreased the risk of venous thromboembolism, acute limb ischaemia, and amputation in patients with stable cardiovascular disease in a non-operative setting. Although COMPASS

evaluated a very low-dose anticoagulant and MANAGE evaluated an intermediate-dose anticoagulant, the magnitude of the relative benefits was similar in COMPASS and MANAGE.[11] However, the absolute risks (and hence absolute differences in event rates) were higher in MANAGE. This result probably occurred because patients in our study were enrolled a short time after their index event (similar to an acute coronary syndrome event), whereas in COMPASS, patients were enrolled about 5 years after an event.[11] Taken together, these trials emphasise the value of initiating treatment with an anticoagulant early and continuing this treatment long term.

Of the 200 million adults worldwide who undergo major non-cardiac surgery annually, about 8 million will have MINS.[7] The MANAGE trial, consistent with a large body of evidence,[1,2] showed that patients who have MINS are at high risk of major vascular complications—one in seven patients in the placebo group had a major vascular complication. MANAGE underestimated the risk associated with MINS, as 380 (9%) of the 5959 eligible patients died before they could be randomly assigned to dabigatran or placebo.

345 patients (20%) fulfilled the universal definition of myocardial infarction, and 1409 patients (80%) had an isolated ischaemic troponin elevation after surgery.[5] Only 159 patients (9%) had a clinical symptom or sign of cardiac ischaemia, suggesting that more than 90% of MINS events would have gone undetected without routine troponin screening.

Although patients with an elevated ischaemic troponin measurement after non-cardiac surgery are at substantial risk of subsequent thrombotic events,[1,2] including vascular death, because the optimal management of such patients was not defined, the clinical use of postoperative troponin measurements to improve outcomes was not established. MANAGE provides evidence that patients with MINS who use dabigatran can reduce their risk of major vascular complications, in relative terms by approximately 25%, thereby establishing treatment with dabigatran as an advance in the management of MINS. Our results reinforce the use of routine troponin measurement in patients after non-cardiac surgery to identify those who would benefit from anticoagulant therapy.

Anticoagulation invariably involves a trade-off between fewer thrombotic events and increased bleeding. MANAGE showed the predictable increase in minor and clinically non-significant lower gastrointestinal bleeding with dabigatran. We found no increase in the composite of life-threatening, major, and critical organ bleeding. Dabigatran showed no significant increase in major bleeding. However, the point estimate of the effect of the International Society on Thrombosis and Haemostasis definition of bleeding suggests the possibility of some increase in bleeding.

Although MANAGE did not find an increase in the composite of life-threatening, major, and critical organ bleeding with dabigatran 110 mg twice daily, anticoagulants would be expected to increase the risk of bleeding based on the dose, setting (eg, increased with invasive procedures), and patient characteristics (eg, increased in patients also taking dual antiplatelet therapy).[10,25] Therefore, dabigatran 110 mg twice daily and other anticoagulants could increase the risk of serious bleeding in specific types of patient.

The MANAGE primary efficacy results are consistent with a number needed to treat of 24 to prevent a major vascular complication. By contrast, the potential for increased major bleeding is substantially lower. Even if we assume for the primary safety outcome that the upper 95% CI of the HR (ie, 1·53) represents the true effect, the number needed to medicate to cause a life-threatening, major, or critical organ bleed (ie, harm) would be 54 patients. Moreover, if we assume the point estimate of effect for the International Society on Thrombosis and Haemostasis definition of major bleeding represents a real effect, this would still result in a number needed to harm of 54 patients.

The one perioperative guideline that makes recommendations regarding management of MINS only recommends initiating aspirin and statin therapy.[16] Despite the benefits of dabigatran therapy, 97 (11%) of 877 patients in the dabigatran group had a major vascular complication at a mean of 16 months follow-up, highlighting the need for further clinical trials to test potential therapies (eg, dual antiplatelet therapy) in patients who have MINS.

During the conduct of MANAGE, we had to decrease our planned sample size from 3200 to 1750 patients. To partially compensate for this, and on the basis of the results of the COMPASS trial,[11] we broadened the primary efficacy outcome to include amputation and symptomatic proximal deep venous thrombosis. We made these changes before unblinding the trial results and without knowledge of any emerging trends. The result of the revised primary outcome was statistically significant, with consistent benefits on both the arterial and venous components of the primary composite outcome. 781 patients (45%) permanently discontinued study drug, and this discontinuation might have led to an underestimation of treatment efficacy effects among compliant patients, as suggested in the per-protocol analyses. Both the intention-to-treat and per-protocol analyses for the primary safety outcome showed no increase in life-threatening, major, or critical organ bleeding with dabigatran.

Although the interaction test did not indicate that the effects of dabigatran varied in different subgroups, this test has limited power.[26] Therefore, we cannot definitively exclude a subgroup effect on the basis of our data. We did not record whether patients had a preoperative troponin measurement. Some troponin elevations could have been due to chronically elevated troponin measurement; however, chronic elevation explained only 7% of the elevated perioperative troponin measurements in a recent

international prospective cohort study[2] that measured preoperative and postoperative troponin measurements in 8831 adults who had non-cardiac surgery. A difference of 5 ng/L or more between the highest and lowest perioperative troponin measurements in the VISION study[2] substantially increased the risk of 30-day mortality after non-cardiac surgery (adjusted HR 4·69, 95% CI 3·52–6·25). In our trial, among the 1252 patients (71%) with two or more postoperative troponin measurements on their baseline case report form, 1182 (94%) had a difference of at least 5 ng/L between the highest and lowest troponin values. At enrolment, we did not record physicians' interpretation of whether patients had a type 1 or 2 myocardial infarction; however, no patient had a type 3, 4, or 5 myocardial infarction.[5]

Patients who have MINS are at substantial risk of major vascular complications. Routine postoperative measurement of troponin is needed to identify these patients. Among patients who had MINS, dabigatran 110 mg twice daily lowered the risk of major vascular complications, with no observed increased risk of major bleeding.

#### Contributors

PJD, SY, GG, RR, JWE, DIS, CK, WS, BMB, DX, and CSM contributed to the study design. PJD, ED, VT, RR, BMB, WS, CSM, MGF, SKS, JE, PM, JN, MR, PVR, NKC, BM, MdN, PPI, JCV, and AH contributed to the collection of data. PR-M did the data analyses. All authors contributed to interpretation of the data. PJD wrote the first draft of the manuscript. All authors provided critical revisions to the manuscript before seeing and approving the final version.

#### Declaration of interests

PJD reports grants from Boehringer Ingelheim and Canadian Health Research Institutes of Canada during the conduct of the study, and grants from Abbott Diagnostics, Boehringer Ingelheim, Covidien, Octopharma, Philips Healthcare, Roche Diagnostics, and Stryker, all outside the submitted work. DX reports grants from Cadila Pharmaceuticals, Boehringer Ingelheim, Sanofi-Aventis, Pfizer, Bristol Myers Squibb, and United Health, all outside the submitted work. CSM reports grants from Ferring Pharmaceuticals and Merck, Sharp and Dohme outside the submitted work. OB reports grants and personal fees from AstraZeneca and Amgen; grants, personal fees, and non-financial support from Bayer; personal fees from Novo Nordisk and Sanofi; and grants from Ethicon, all outside the submitted work. JWE reports honoraria and grant support from AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb/Pfizer, Daiichi Sankyo, Glaxo Smith Kline, Janssen, Sanofi-Aventis, and Eli Lilly; and a personal award from the Heart and Stroke Foundation, all outside the submitted work. CK reports grants from Bayer and personal fees from Bayer and Bristol-Myers Squibb, outside the submitted work. MS reports grants and personal fees from Bayer, Bristol-Myers Squibb, and Daiichi Sankyo, and grants from Boehringer Ingelheim, all outside the submitted work. SJC reports grants and consulting fees from Bayer AG, Boehringer Ingelheim, Bristol-Myers Squibb, Pfizer, Abbott, Portola, Daiichi Sankyo, Medtronic, and Sanofi Aventis, all during the conduct of the study; grants and consulting fees from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Pfizer, Abbott, Portola, Daiichi Sankyo, Medtronic, and Sanofi-Aventis, all outside the submitted work. SY reports grants from Boehringer Ingelheim during the conduct of the study, and grants from Boehringer Ingelheim outside the submitted work. All other authors declare no competing interests.

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The Population Health Research Institute (PHRI) in Hamilton, ON, Canada sponsored the trial. The PHRI obtained a grant from Boehringer Ingelheim to fund MANAGE, and Boehringer Ingelheim provided the dabigatran and placebo study drugs. A Canadian Institutes of Health Research Foundation Grant also supported the trial. The PHRI coordinated MANAGE and was responsible for the randomisation, database, data validation, analyses, and trial coordination. The trial committees and their members, participating centres, and investigators are listed in the appendix. The International Operations Committee designed the trial, and representatives from Boehringer Ingelheim provided input. No MANAGE funding source had a role in the data collection, analyses, or manuscript write-up. The International Operations Committee prespecified the statistical analysis plan before any investigator was unblinded to the trial results. PJD wrote the initial draft of the paper, and the Writing Committee made critical revisions and decided to submit the paper for publication. PJD and SY vouch for the completeness and accuracy of the data.

#### References

1 Botto F, Alonso-Coello P, Chan MT, et al. Myocardial injury after noncardiac surgery: a large, international, prospective cohort study establishing diagnostic criteria, characteristics, predictors, and 30-day outcomes. *Anesthesiology* 2014; **120:** 564–78.

2 Devereaux PJ, Biccard BM, Sigamani A, et al. Association of postoperative high-sensitivity troponin levels with myocardial injury and 30-day mortality among patients undergoing noncardiac surgery. *JAMA* 2017; **317:** 1642–51.

3 Puelacher C, Lurati Buse G, Seeberger D, et al. Perioperative myocardial injury after noncardiac surgery: incidence, mortality, and characterization. *Circulation* 2018; **137:** 1221–32.

4 Devereaux PJ, Xavier D, Pogue J, et al. Characteristics and short-term prognosis of perioperative myocardial infarction in patients undergoing noncardiac surgery: a cohort study. *Ann Intern Med* 2011; **154:** 523–28.

5 Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. *Circulation* 2012; **126:** 2020–35.

6 Levy M, Heels-Ansdell D, Hiralal R, et al. Prognostic value of troponin and creatine kinase muscle and brain isoenzyme measurement after noncardiac surgery: a systematic review and meta-analysis. *Anesthesiology* 2011; **114:** 796–806.

7 Devereaux PJ, Sessler DI. Cardiac complications and major noncardiac surgery. *N Engl J Med* 2016; **374:** 1394–95.

8 Eikelboom JW, Anand SS, Malmberg K, Weitz JI, Ginsberg JS, Yusuf S. Unfractionated heparin and low-molecular-weight heparin in acute coronary syndrome without ST elevation: a meta-analysis. *Lancet* 2000; **355:** 1936–42.

9 Andreotti F, Testa L, Biondi-Zoccai GG, Crea F. Aspirin plus warfarin compared to aspirin alone after acute coronary syndromes: an updated and comprehensive meta-analysis of 25 307 patients. *Eur Heart J* 2006; **27:** 519–26.

10 Mega JL, Braunwald E, Wiviott SD, et al. Rivaroxaban in patients with a recent acute coronary syndrome. *N Engl J Med* 2012; **366:** 9–19.

11 Eikelboom JW, Connolly SJ, Bosch J, et al. Rivaroxaban with or without aspirin in stable cardiovascular disease. *N Engl J Med* 2017; **377:** 1319–30.

12 Eriksson BI, Dahl OE, Rosencher N, et al. Dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total hip replacement: a randomised, double-blind, non-inferiority trial. *Lancet* 2007; **370:** 949–56.

13 Eriksson BI, Dahl OE, Huo MH, et al. Oral dabigatran versus enoxaparin for thromboprophylaxis after primary total hip arthroplasty (RE-NOVATE II*). A randomised, double-blind, non-inferiority trial. *Thromb Haemost* 2011; **105:** 721–29.

14 Duceppe E, Yusuf S, Tandon V, et al. Design of a randomized placebo-controlled trial to assess dabigatran and omeprazole in patients with myocardial injury after noncardiac surgery (MANAGE). *Can J Cardiol* 2018; **34:** 295–302.

15 Moher D, Hopewell S, Schulz KF, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *J Clin Epidemiol* 2010; **63:** e1–37.

16 Duceppe E, Parlow J, MacDonald P, et al. Canadian Cardiovascular Society guidelines on perioperative cardiac risk assessment and management for patients who undergo noncardiac surgery. *Can J Cardiol* 2017; **33:** 17–32.

17 Concato J, Peduzzi P, Holford TR, Feinstein AR. Importance of events per independent variable in proportional hazards analysis. I. Background, goals, and general strategy. *J Clin Epidemiol* 1995; **48:** 1495–501.

18 Peduzzi P, Concato J, Feinstein AR, Holford TR. Importance of events per independent variable in proportional hazards regression analysis. II. Accuracy and precision of regression estimates. *J Clin Epidemiol* 1995; **48:** 1503–10.

19 Pogue J, Devereaux PJ, Thabane L, Yusuf S. Designing and analyzing clinical trials with composite outcomes: consideration of possible treatment differences between the individual outcomes. *PLoS One* 2012; **7:** e34785.

20 Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999; **94:** 496–509.

21 Schulman S, Angerås U, Bergqvist D, Eriksson B, Lassen MR, Fisher W. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in surgical patients. *J Thromb Haemost* 2010; **8:** 202–04.

22 Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost* 2005; **3:** 692–94.

23 Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation* 2011; **123:** 2736–47.

24 Foucrier A, Rodseth R, Aissaoui M, et al. The long-term impact of early cardiovascular therapy intensification for postoperative troponin elevation after major vascular surgery. *Anesth Analg* 2014; **119:** 1053–63.

25 Oldgren J, Budaj A, Granger CB, et al. Dabigatran *vs* placebo in patients with acute coronary syndromes on dual antiplatelet therapy: a randomized, double-blind, phase II trial. *Eur Heart J* 2011; **32:** 2781–89.

26 Altman DG, Bland JM. Interaction revisited: the difference between two estimates. *BMJ* 2003; **326:** 219.

# nejm Spinal anesthesia or general anesthesia for hip surgery in older adults

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# Spinal Anesthesia or General Anesthesia for Hip Surgery in Older Adults

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## ABSTRACT

### BACKGROUND

The effects of spinal anesthesia as compared with general anesthesia on the ability to walk in older adults undergoing surgery for hip fracture have not been well studied.

### METHODS

We conducted a pragmatic, randomized superiority trial to evaluate spinal anesthesia as compared with general anesthesia in previously ambulatory patients 50 years of age or older who were undergoing surgery for hip fracture at 46 U.S. and Canadian hospitals. Patients were randomly assigned in a 1:1 ratio to receive spinal or general anesthesia. The primary outcome was a composite of death or an inability to walk approximately 10 ft (3 m) independently or with a walker or cane at 60 days after randomization. Secondary outcomes included death within 60 days, delirium, time to discharge, and ambulation at 60 days.

### RESULTS

A total of 1600 patients were enrolled; 795 were assigned to receive spinal anesthesia and 805 to receive general anesthesia. The mean age was 78 years, and 67.0% of the patients were women. A total of 666 patients (83.8%) assigned to spinal anesthesia and 769 patients (95.5%) assigned to general anesthesia received their assigned anesthesia. Among patients in the modified intention-to-treat population for whom data were available, the composite primary outcome occurred in 132 of 712 patients (18.5%) in the spinal anesthesia group and 132 of 733 (18.0%) in the general anesthesia group (relative risk, 1.03; 95% confidence interval [CI], 0.84 to 1.27; P=0.83). An inability to walk independently at 60 days was reported in 104 of 684 patients (15.2%) and 101 of 702 patients (14.4%), respectively (relative risk, 1.06; 95% CI, 0.82 to 1.36), and death within 60 days occurred in 30 of 768 (3.9%) and 32 of 784 (4.1%), respectively (relative risk, 0.97; 95% CI, 0.59 to 1.57). Delirium occurred in 130 of 633 patients (20.5%) in the spinal anesthesia group and in 124 of 629 (19.7%) in the general anesthesia group (relative risk, 1.04; 95% CI, 0.84 to 1.30).

### CONCLUSIONS

Spinal anesthesia for hip-fracture surgery in older adults was not superior to general anesthesia with respect to survival and recovery of ambulation at 60 days. The incidence of postoperative delirium was similar with the two types of anesthesia. (Funded by the Patient-Centered Outcomes Research Institute; REGAIN ClinicalTrials.gov number, NCT02507505.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Neuman can be contacted at neumanm@pennmedicine.upenn.edu or at the Department of Anesthesiology and Critical Care, University of Pennsylvania Perelman School of Medicine, 308 Blockley Hall, 423 Guardian Dr., Philadelphia PA, 19106.

*The REGAIN investigators are listed in the Supplementary Appendix, available at NEJM.org.

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Nearly all patients with hip fracture undergo surgery,[1] most commonly with spinal anesthesia or general anesthesia.[2] Observational studies have suggested that spinal anesthesia may be associated with lower risks of death,[3] delirium,[4,5] and major medical complications[6] and with shorter lengths of stay in the hospital than general anesthesia.[7] Randomized trials have shown conflicting results regarding differences in outcomes according to anesthesia type, but most of these trials were conducted more than 30 years ago and do not reflect current practice, had small numbers of participants, or were not designed to assess outcomes beyond the hospital stay.[8] Patients may view recovery of independence in walking after hip fracture as a priority,[9] but studies evaluating the effect of anesthesia technique on this outcome are lacking.[8]

We conducted a trial to evaluate the recovery of walking ability after receipt of spinal as compared with general anesthesia for hip-fracture surgery in older adults who could walk independently before the fracture. We hypothesized that patients assigned to receive spinal anesthesia would be more likely to be alive and walking independently at 60 days than those assigned to receive general anesthesia.

## Methods

### Trial Design and Oversight

We conducted the Regional versus General Anesthesia for Promoting Independence after Hip Fracture (REGAIN) trial, a multicenter, pragmatic, randomized superiority trial funded by the Patient-Centered Outcomes Research Institute. The trial design has been described previously.[10] The trial was investigator-initiated and was planned and conducted with the participation of patients and stakeholder organizations (the Center for Advocacy for the Rights and Interests of the Elderly and the Gerontological Society of America).[11] There was no commercial participation in the trial. The institutional review board of the University of Pennsylvania, the institution that oversaw the conduct of the trial, approved the protocol (available with the full text of this article at NEJM.org) and was the institutional review board of record for 11 sites; approval at other sites was obtained through local institutional review boards.[12] Written informed consent was obtained from the patients or, for patients who could not provide consent, from their health care proxy. The trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

### Trial Population

Trial staff at 46 hospitals in the United States and Canada reviewed emergency department registration lists, hospital admission lists, and surgical case schedules to identify adults who were 50 years of age or older and were scheduled to undergo surgical repair of a clinically or radiographically diagnosed femoral neck, intertrochanteric, or subtrochanteric hip fracture. Inclusion and exclusion criteria were evaluated by means of in-person interview and medical record review. Patients were excluded if they had not been able to walk approximately 10 ft (3 m) or across a room without the assistance of another person before the fracture, as reported by the patient or by a proxy who knew the patient; if a concurrent procedure that was not amenable to spinal anesthesia was planned; if the fracture was periprosthetic; if the patient was at risk for malignant hyperthermia; or if the patient had contraindications to spinal anesthesia (coagulopathy, use of anticoagulant or antiplatelet medications, [13,14] critical or severe aortic stenosis, a high risk of infection at the spinal needle insertion site, or elevated intracranial pressure). Patients were also excluded if they had previously participated in the trial or if they were considered to be unsuitable for randomization by the surgeon or anesthesiologist on the basis of the physician's clinical assessment. Patients who were judged to have delirium before surgery were not excluded if consent would be obtained from a proxy or the patient.

Patients were randomly assigned in a 1:1 ratio, with the use of permuted block randomization with variable block sizes, to receive either spinal anesthesia or general anesthesia.[15,16] Randomization was stratified according to hospital, sex, and fracture location (femoral neck vs. intertrochanteric or subtrochanteric fracture) and was performed centrally through an online data-management system. Site staff obtained each randomization assignment from the data-management system Web portal and communicated it to the treating anesthesia team. Site staff were instructed to obtain and communicate the assignment

on the day of surgery, immediately before the start of anesthesia care. When site personnel could not access the online system, the randomization assignment was communicated by telephone to site staff by the principal investigator or the lead project manager.

### TRIAL TREATMENT

Anesthesia was administered by the usual clinical anesthesia staff at each site. For patients assigned to receive spinal anesthesia, providers received instructions to administer a single-injection spinal anesthetic with sedation as needed for patient comfort; sedation was adjusted to ensure an Observer's Assessment of Alertness/Sedation (OAAS) scale[17] score between 5 ("Responds readily to name spoken in normal tone") and 2 ("Responds only after mild shaking or prodding").[18] Crossover to general anesthesia was permitted on the basis of clinical circumstances or patient request. For patients assigned to general anesthesia, providers were instructed to use an inhaled anesthetic agent for maintenance, with the choice of agent conforming to their usual practice, and to use an endotracheal tube, supraglottic airway, or another device for airway management in accordance with local practice. All other aspects of care were determined by the clinical team. Trial participants and treating clinicians were aware of the treatment assignments.

### OUTCOMES

The primary outcome was a composite of death or an inability to walk 10 feet (3 m) or across a room independently or with a walker or cane but without the assistance of another person at approximately 60 days after randomization. Death was included in the primary outcome to account for potential survivorship bias.[19,20] Data on the primary outcome were obtained through telephone interviews performed by trial staff who were unaware of the treatment assignments; data collection from caregivers or other proxies was permitted when participants were unable to complete the outcome interview. Interviews were recorded and randomly audited. For patients who could not be contacted by telephone for the 60-day interview, we ascertained vital status from subsequent interviews; for U.S. patients for whom vital status could not be ascertained, we searched the National Death Index through 2019, the most recent year available.

Secondary outcomes included the two components of the primary outcome (death by 60 days after randomization and new inability to walk at 60 days among survivors); new-onset delirium, with delirium assessed as present or absent on the basis of the 3-Minute Diagnostic Interview for CAM (Confusion Assessment Method)–defined Delirium (3D-CAM[21]; measurements were conducted before randomization and once daily over each of the first 3 days after surgery by trained site staff); and time from randomization to hospital discharge. Exploratory outcomes included medical complications during hospitalization, ascertained by site trial staff on the basis of medical record review using standardized definitions; time to first ambulation; discharge disposition (i.e., discharge to home or retirement home, nursing home or skilled nursing facility, rehabilitation or acute care hospital, or hospice or other location); residential location at 60 days; and functional status at 60 days, as measured with the 12-item World Health Organization Disability Assessment Schedule 2.0.[22] Data on serious adverse events were reviewed by an internal monitoring committee for severity, expectedness, and relatedness to treatment.

Data were reviewed at prespecified intervals by an independent data and safety monitoring board, the members of which were aware of the treatment assignments. Additional details of the trial monitoring plan are provided in the Supplementary Appendix, available at NEJM.org. The principal investigator, statisticians, coordinating center staff, and coinvestigators remained unaware of the treatment assignments until the database was locked for analysis.

### STATISTICAL ANALYSIS

We estimated that a sample of 1600 patients would provide 80% power to detect a 0.78 relative risk of the primary outcome among patients assigned to spinal anesthesia as compared with those assigned to general anesthesia, at a two-sided significance level of 0.05. The calculation was performed under the assumption that the primary outcome would occur in 34.2% of the patients in the general anesthesia group,[23] loss to follow-up would be 5%, and 5% of the patients assigned to spinal anesthesia would cross over to general anesthesia.[24,25] The primary analysis and analyses of all secondary and exploratory outcomes included patients in the modified intention-to-treat

population for whom complete data were available for the relevant outcomes. The modified intention-to-treat population included all patients who underwent randomization and did not die before receiving treatment. Patients were included in the analysis according to their original treatment assignment. We performed a Mantel–Haenszel test, stratified according to fracture location (femoral neck fracture vs. intertrochanteric or subtrochanteric fracture), sex, and country (United States vs. Canada), to compare the risks of the primary outcome in each group. Although randomization was stratified according to fracture location, sex, and hospital, recruitment at many sites was too low to permit stratification of the analysis according to hospital. Superiority testing was based on a two-sided significance level of 0.05.

Secondary outcomes were analyzed with the use of approaches similar to those used in our primary analysis for binary data. For time-to-event data, we used competing-risk Cox regression and confirmed the proportional hazards assumption with log–log survival plots and Schoenfeld residuals. Patients who were assessed as having delirium before randomization on the basis of 3D-CAM were eligible for enrollment if proxy consent could be obtained, and these patients were excluded from the analysis of incident delirium but were included in analyses of other outcomes. There was no plan for adjustment of the width of confidence intervals for multiple comparisons in analyses of secondary outcomes, and no definite conclusions can be drawn from these results.

To assess the effect of missing data on the findings for the primary outcome, we performed an inverse-probability–weighted analysis[26] that weighted each patient according to the inverse probability of being a "complete case," as estimated on the basis of 10 prerandomization factors (age, sex, enrollment country, fracture location, and status with respect to pulmonary disease, cancer, diabetes, coronary artery disease, cerebrovascular disease, and dementia). We performed an instrumental variable analysis to estimate the per-protocol effect[27] of spinal anesthesia as compared with general anesthesia on the primary outcome (see the Supplementary Appendix).[28] For the primary outcome, we explored prespecified patient characteristics (sex, fracture type, country of enrollment, reliance on assistive devices to ambulate before fracture, age [≥85 years vs. <85 years], location of residence before fracture, and status with respect to dementia, chronic pulmonary disease, and coronary artery disease or heart failure). We conducted exploratory subgroup analyses for interactions with P values of 0.20 or lower. Data are current as of June 17, 2021. Analyses were performed with the use of SAS software, version 9.4 (SAS Institute).

## RESULTS

### PATIENTS AND TREATMENT

Between February 12, 2016, and February 18, 2021, we screened 22,022 patients for eligibility; 1848 provided informed consent, and 248 withdrew consent before randomization. A total of 7.4% of screened patients (1621 of 22,022) were excluded on the basis of physician decision or surgeon nonparticipation. Of the 1600 patients who were randomly assigned to a treatment group, 795 were assigned to receive spinal anesthesia and 805 were assigned to receive general anesthesia (Fig. 1). The characteristics of the patients were similar in the two treatment groups (Table 1). The mean age of the patients was approximately 78 years, 33.0% were men, and 7.6% were Black.

Of the 795 patients who were assigned to the spinal anesthesia group, 119 (15.0%) instead received general anesthesia. Reasons for administration of general anesthesia were an inability to place a spinal block (52 patients), clinician selection of general anesthesia (29 patients), patient or proxy request (18 patients), crossover to general anesthesia after spinal block placement (e.g., due to block failure or intraoperative events; 12 patients), and communication issues (e.g., due to case rescheduling or shift changes; 7 patients); no reason was provided in 1 instance. Ten patients who had been assigned to receive spinal anesthesia (1.3%) withdrew consent before surgery; data collection for these patients stopped at withdrawal. Of the 502 patients with available data on the maximum depth of sedation during spinal anesthesia, 431 (85.9%) had an OAAS score between 5 (lighter sedation) and 2 (deeper sedation), and 71 (14.1%) had a deeper level of sedation.

Of the 805 patients assigned to receive general anesthesia, 28 (3.5%) instead received spinal anesthesia; reasons for administration of spinal anesthesia were clinician selection of spinal anesthesia (15 patients), patient or proxy request

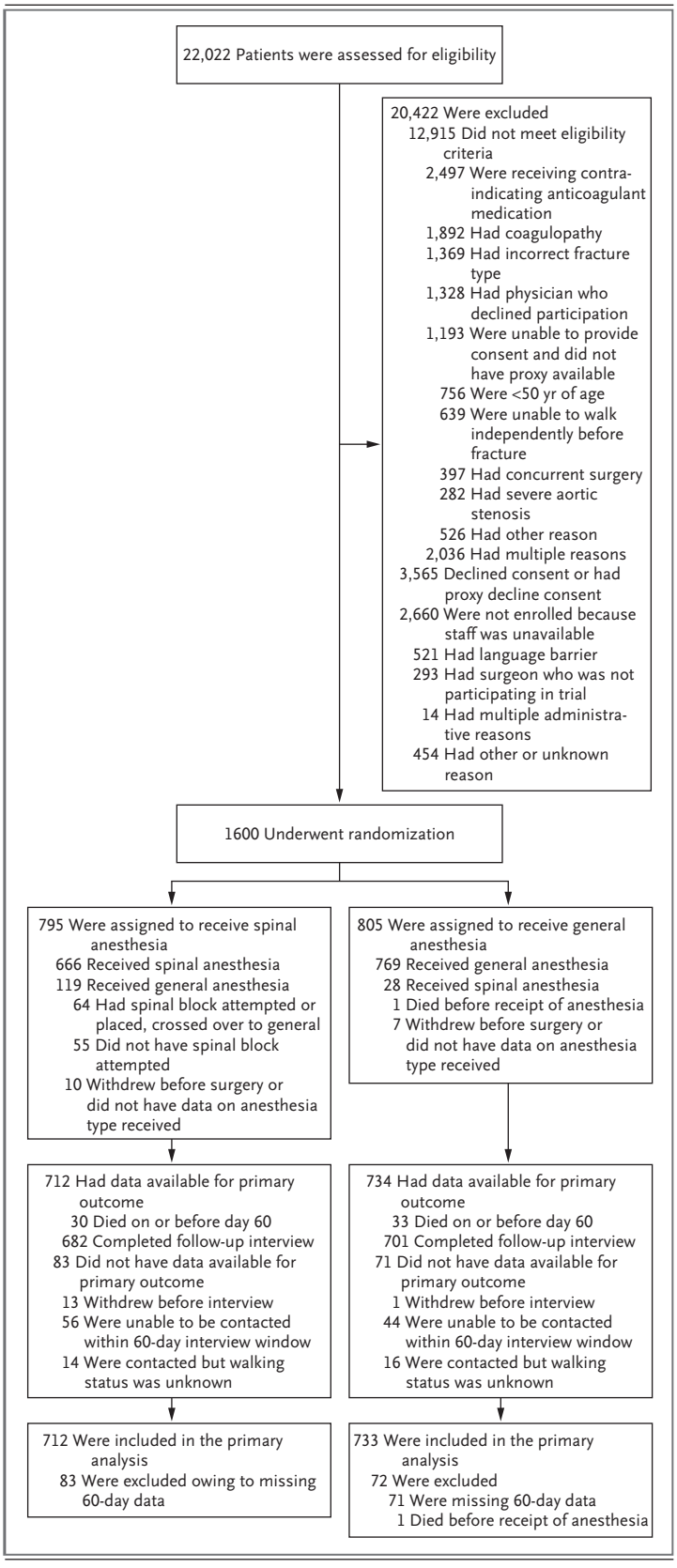


**Figure 1. Screening, Enrollment, Randomization, and Follow-up.**

The other reasons for patients not meeting the eligibility criteria included no surgery planned, history of malignant hyperthermia, previous participation in the trial, elevated intracranial pressure, active skin infection at the needle insertion site, and incarceration. In addition to the 1600 randomization codes generated for enrolled patients, 7 codes were unintentionally generated because of technical errors in operating the screening log for patients who had been excluded from participation at screening; these patients had no data collected and were not included in the trial sample.

(7 patients), and communication issues (i.e., as a result of case rescheduling or shift changes; 4 patients); in 2 cases, no reason was provided. Seven patients who had been assigned to general anesthesia (0.9%) withdrew consent before surgery; no outcome data were collected for these 7 patients after withdrawal. The median total anesthesia time was 132 minutes (interquartile range, 102 to 165) in the spinal anesthesia group and 131 minutes (interquartile range, 103 to 165) in the general anesthesia group (Table S1 in the Supplementary Appendix).

One patient in the general anesthesia group died after randomization but before the start of anesthesia; data from this patient were not included in the outcome analyses. Data on the primary outcome were available for 1445 of the 1599 remaining patients (90.4%) in the modified intention-to-treat analysis (Tables 2 and S2). For patients assigned to spinal anesthesia, the median time from randomization to the primary outcome interview was 59 days (interquartile range, 55 to 65); for patients assigned to general anesthesia, it was 60 days (interquartile range, 54 to 66).

### OUTCOMES

The composite primary outcome of death or a new inability to walk independently occurred in 132 of 712 patients (18.5%) who received spinal anesthesia and in 132 of 733 patients (18.0%) who received general anesthesia (complete case analysis: relative risk, 1.03; 95% confidence interval [CI], 0.83 to 1.28; inverse-probability–weighted analysis: relative risk, 1.03; 95% CI, 0.84 to 1.27; P=0.83) (Table 2). We obtained similar findings in sensitivity analyses that accounted for nonadherence to the anesthesia as-

**Table 1. Characteristics of the Patients Who Underwent Randomization.***

| Characteristic | Spinal Anesthesia (N=795) | General Anesthesia (N=805) |
|---|---|---|
| Age at randomization — yr† | 77.7±10.7 | 78.4±10.6 |
| Male sex — no. (%) | 258 (32.5) | 270 (33.5) |
| Race — no./total no. (%)‡ | | |
| White | 683/762 (89.6) | 691/774 (89.3) |
| Black | 55/762 (7.2) | 67/774 (8.7) |
| Other or more than one race | 24/762 (3.1) | 16/774 (2.1) |
| Hispanic ethnic group — no./total no. (%)‡ | 15/750 (2.0) | 12/763 (1.6) |
| Enrolled at a non-U.S. site — no. (%) | 210 (26.4) | 212 (26.3) |
| Coexisting conditions — no./total no. (%) | | |
| Chronic pulmonary disease | 124/795 (15.6) | 100/804 (12.4) |
| Diabetes mellitus | 155/795 (19.5) | 142/804 (17.7) |
| Disseminated cancer | 60/795 (7.5) | 50/804 (6.2) |
| Coronary artery disease | 118/795 (14.8) | 119/804 (14.8) |
| Cerebrovascular disease | 80/795 (10.1) | 66/804 (8.2) |
| Dementia | 109/795 (13.7) | 94/804 (11.7) |
| Creatinine level >2 mg/dl or current dialysis | 47/790 (5.9) | 41/797 (5.1) |
| American Society of Anesthesiologists Physical Status Classification — no./total no. (%) | | |
| I, no systemic disease | 22/782 (2.8) | 18/793 (2.3) |
| II, mild systemic disease | 229/782 (29.3) | 270/793 (34.0) |
| III, severe systemic disease | 486/782 (62.1) | 463/793 (58.4) |
| IV, severe systemic disease that is a constant threat to life | 45/782 (5.8) | 42/793 (5.3) |
| Final confirmed fracture type — no./total no. (%)§ | | |
| Femoral neck | 406/795 (51.1) | 409/804 (50.9) |
| Intertrochanteric | 355/795 (44.7) | 350/804 (43.5) |
| Subtrochanteric or multiple locations | 34/795 (4.3) | 45/804 (5.6) |
| 3D-CAM assessment positive for delirium before randomization — no./total no. (%) | 96/746 (12.9) | 104/753 (13.8) |
| Used assistive device to ambulate before fracture — no./total no. (%) | 249/779 (32.0) | 248/793 (31.3) |
| Preadmission residence — no./total no. (%) | | |
| Home or retirement home | 688/748 (92.0) | 690/763 (90.4) |
| Nursing home or other location | 60/748 (8.0) | 73/763 (9.6) |

* Plus–minus values are means ±SD. To convert the values for creatinine to micromoles per liter, multiply by 88.4. 3D-CAM denotes 3-Minute Diagnostic Interview for CAM (Confusion Assessment Method)–Defined Delirium.
† Data on age were missing for 1 patient in the general anesthesia group.
‡ Race and ethnic group were reported by the patients or their proxies.
§ Randomization was stratified on the basis of provisional fracture-type data that were subsequently confirmed by medical record review; final confirmed fracture-type data were not available for 1 patient who had been assigned to the femoral neck fracture stratification group for randomization.

signment (Table S3). The percentages of patients with each component of the primary outcome at 60 days were also similar in the two treatment groups. The percentages of patients with the primary outcome in each treatment group were similar across participating sites (Table S4).

New-onset postoperative delirium occurred in 130 of 633 patients (20.5%) assigned to spinal

**Table 2. Primary Outcome and Prespecified Secondary Outcomes (Modified Intention-to-Treat Population).***

| Outcome | Spinal Anesthesia (N=795) | General Anesthesia (N=804) | Relative Risk (95% CI)† | P Value† |
|---|---|---|---|---|
| Primary outcome | | | | |
| Death or inability to walk without human assistance at 60 days — no./total no. (%) | 132/712 (18.5) | 132/733 (18.0) | 1.03 (0.84–1.27) | 0.83 |
| Secondary outcomes‡ | | | | |
| Death by 60 days — no./total no. (%)§ | 30/768 (3.9) | 32/784 (4.1) | 0.97 (0.59–1.57) | |
| Inability to walk without human assistance at 60 days among survivors — no./total no. (%) | 104/684 (15.2) | 101/702 (14.4) | 1.06 (0.82–1.36) | |
| 3D-CAM assessment positive for new-onset delirium — no./total no. (%)¶ | 130/633 (20.5) | 124/629 (19.7) | 1.04 (0.84–1.30) | |
| | | | **Hazard Ratio (95% CI)‖** | |
| Median time from randomization to discharge, according to enrollment location (IQR) — days** | | | | |
| Canada | 6 (4–9) | 6 (5–10) | 0.92 (0.76–1.10) | |
| United States | 3 (2–5) | 3 (3–5) | 1.06 (0.96–1.16) | |

* The modified intention-to-treat population included all patients who underwent randomization with the exception of 1 patient who died before receiving treatment. Patients were included in the analysis according to their original treatment assignment. Results shown for the primary outcome comparison reflect inverse-probability weighting to account for missing outcome data; the variables included in the inverse-probability–weighting model were age, sex, country, fracture type, pulmonary disease, cancer, diabetes, coronary artery disease, cerebrovascular disease, and dementia. All other comparisons were performed by complete case analysis. IQR denotes interquartile range.

† Relative risks and P values were calculated with a Mantel–Haenszel test with adjustment for sex, fracture type, and country of enrollment.

‡ The widths of confidence intervals for secondary outcomes have not been adjusted for multiple comparisons.

§ For patients who could not be contacted for the 60-day interview, vital status at 60 days was ascertained from subsequent planned trial interviews and from the U.S. National Death Index.

¶ This outcome was assessed only among patients who had a negative 3D-CAM assessment for delirium before randomization.

‖ Hazard ratios were calculated with a Cox proportional hazards model with adjustment for sex and fracture type.

** For patients enrolled in Canada, data were available for 210 patients in the spinal anesthesia group and 211 in the general anesthesia group; for patients enrolled in the United States, the corresponding numbers were 585 and 593.

anesthesia and in 124 of 629 patients (19.7%) assigned to general anesthesia (relative risk, 1.04; 95% CI, 0.84 to 1.30); other secondary outcomes were also similar in the two treatment groups (Table 2). The primary outcome was similar across subgroups as judged by visual inspection of descriptive numerical data (Table 3). Death during hospitalization occurred in 5 of 782 patients assigned to spinal anesthesia (0.6%) and in 13 of 790 patients assigned to general anesthesia (1.6%). Acute kidney injury occurred in 32 of 709 patients (4.5%) assigned to spinal anesthesia, and admission to a critical care unit occurred in 18 of 783 (2.3%); the corresponding numbers among the patients assigned to general anesthesia were 55 of 726 (7.6%) and 29 of 793 (3.7%) (Table 4). Table S5 lists the serious adverse events according to treatment group; the incidence of adverse events was similar in the two groups.

## DISCUSSION

In this pragmatic randomized trial involving 1600 older adults undergoing hip-fracture surgery, the incidence of death or a new inability to walk 60 days after randomization did not differ significantly between patients assigned to receive spinal anesthesia and those assigned to receive general anesthesia. Secondary outcomes, including death within 60 days, new inability to walk at 60 days among survivors, incident delirium,

**Table 3. Subgroup Analyses for the Primary Outcome (Modified Intention-to-Treat Population).**

| Subgroup* | Spinal Anesthesia (N=795) | General Anesthesia (N=804) | Relative Risk (95% CI)† |
|---|---|---|---|
| | *no. of patients (%)* | | |
| Age | | | |
| <85 yr | 63/509 (12.4) | 67/499 (13.4) | 0.93 (0.67–1.27) |
| ≥85 yr | 69/203 (34.0) | 65/234 (27.8) | 1.25 (0.94–1.66) |
| History of chronic pulmonary disease | | | |
| Present | 17/109 (15.6) | 22/88 (25.0) | 0.64 (0.35–1.17) |
| Absent | 115/603 (19.1) | 110/645 (17.1) | 1.11 (0.88–1.41) |
| History of congestive heart failure or coronary artery disease | | | |
| Present | 21/103 (20.4) | 31/110 (28.2) | 0.76 (0.47–1.23) |
| Absent | 111/609 (18.2) | 101/623 (16.2) | 1.12 (0.88–1.44) |

* Selected subgroups of interest are shown.
† Relative risks were calculated with a Mantel–Haenszel test with adjustment for sex, fracture type, and country.

and time from randomization to discharge, did not differ substantially according to anesthesia type. The incidences of death during hospitalization, acute kidney injury, and postoperative critical care admission were low but differed between the treatment groups.

Trials evaluating spinal anesthesia as compared with general anesthesia for hip-fracture surgery have primarily assessed differences in intraoperative events[29,30] and in-hospital complications[31-33] and have not been powered to test for differences in outcomes beyond hospital discharge. We evaluated recovery of the ability to walk 10 ft or across a room without the assistance of another person, an outcome that is of importance to patients and families,[9] and delirium, an outcome that our patient partners identified as a priority.[11] We recruited patients from diverse academic and community hospitals. Fewer than 4% of all patients with hip fractures in the United States are Black,[34] and Black patients made up approximately 8% of our trial population.

Limitations of our trial include a considerable amount of missing outcome data; however, the results of sensitivity analyses that accounted for missing data were similar to those in the primary analysis. The primary outcome occurred in a lower percentage of patients than had been anticipated when the trial was planned. This reduced power and may have occurred as a result of enrollment of patients into the trial who were healthier than anticipated. Although approximately 15% of the patients who had been randomly assigned to receive spinal anesthesia crossed over to general anesthesia, our main findings persisted in an instrumental variable analysis that accounted for nonadherence to the assigned treatment. Nevertheless, the rate of nonadherence may have reduced the power to detect differences between the groups. An inability to place a spinal block was the most common reason for nonadherence, followed by clinician selection of the anesthesia type and patient or proxy request for one anesthesia type. Since we aimed to compare anesthetic regimens as they are used in typical practice,[18] we allowed sedation regimens to be given to patients receiving spinal anesthesia in order to follow usual practices, and therefore these practices varied across sites. This heterogeneity may have limited our ability to detect differences in outcomes between the groups. A previous trial showed similar clinical outcomes with deeper as compared with lighter sedation regimens during spinal anesthesia.[35,36] Finally, one component of the composite primary outcome (walking independently) was conditional on the other component (vital status), but we did not conduct a joint modeling analysis because these separate secondary outcomes did not differ between the groups.

In the United States, the use of spinal anesthesia for hip-fracture surgery increased by 50%

**Table 4. Exploratory Outcomes (Modified Intention-to-Treat Population).**

| Outcome | Spinal Anesthesia (N=795) | General Anesthesia (N=804) |
|---|---|---|
| Outcomes in the hospital | | |
| Complications — no./total no. (%) | | |
| Death | 5/782 (0.6) | 13/790 (1.6) |
| Myocardial infarction* | 6/783 (0.8) | 9/793 (1.1) |
| Nonfatal cardiac arrest | 2/780 (0.3) | 0/784 |
| Stroke* | 5/783 (0.6) | 7/793 (0.9) |
| Pneumonia* | 8/783 (1.0) | 16/793 (2.0) |
| Pulmonary edema* | 9/783 (1.1) | 8/793 (1.0) |
| Pulmonary embolism* | 4/783 (0.5) | 5/793 (0.6) |
| Unplanned postoperative intubation | 4/783 (0.5) | 7/793 (0.9) |
| Acute kidney injury* | 32/709 (4.5) | 55/726 (7.6) |
| Surgical-site infection† | 2/783 (0.3) | 0/793 |
| Urinary tract infection* | 35/783 (4.5) | 28/793 (3.5) |
| Postoperative transfusion | 130/782 (16.6) | 146/793 (18.4) |
| Any return to the operating room | 10/783 (1.3) | 14/793 (1.8) |
| Critical care admission | 18/783 (2.3) | 29/793 (3.7) |
| Fall within 12 hr after administration of anesthesia | 1/783 (0.1) | 1/793 (0.1) |
| Median time to first ambulation after surgery (IQR) — days‡ | 1.0 (1.0–2.0) | 1.0 (1.0–2.0) |
| Discharge disposition — no./total no. (%) | | |
| Home or retirement home | 201/777 (25.9) | 191/777 (24.6) |
| Nursing home or skilled nursing facility | 347/777 (44.7) | 349/777 (44.9) |
| Rehabilitation or acute care hospital | 221/777 (28.4) | 229/777 (29.5) |
| Hospice or other location | 8/777 (1.0) | 8/777 (1.0) |
| Outcomes within 60 days after randomization | | |
| Median time to death up to day 60 (IQR) — days§ | 32.5 (16.0–53.0) | 20.0 (7.0–37.0) |
| Median 12-item WHODAS 2.0 score (IQR)¶ | 22.7 (8.3–43.2) | 18.2 (6.3–31.8) |
| Worsened walking ability — no./total no. (%)‖ | 403/672 (60.0) | 397/694 (57.2) |
| Death or transition to new institutional residence — no./total no. (%)** | 108/613 (17.6) | 114/625 (18.2) |

* Events were classified by site staff as mild, moderate, or severe on the basis of standardized definitions in the manual of procedures for the trial; data shown indicate all events reported across severity categories.

† Surgical-site infections were classified by site staff as superficial, deep, or joint-space infections on the basis of standardized definitions in the manual of procedures for the trial; data shown indicate all events reported across infection types.

‡ Data were available for 731 patients in the spinal anesthesia group and 729 patients in the general anesthesia group.

§ Data on time to death were available for 30 patients in the spinal anesthesia group and 31 patients in the general anesthesia group.

¶ The 12-item World Health Organization Disability Schedule 2.0 (WHODAS 2.0) measures disability in six functional domains (cognition, mobility, self-care, social interaction, life activities, and community participation). Scores range from 0 to 100, with lower scores indicating lower degrees of disability. Data were available for 225 patients in the spinal anesthesia group and 242 patients in the general anesthesia group.

‖ Worsened walking ability was defined as death, inability to walk without human assistance, or new use of an assistive device (e.g., cane or walker) at 60 days. Data were available for 672 patients in the spinal anesthesia group and 694 patients in the general anesthesia group.

** This outcome was assessed among patients who were not admitted from a nursing home, rehabilitation facility, or acute care hospital (613 in the spinal anesthesia group and 625 in the general anesthesia group). Institutional residence at 60 days was defined as the reported location of residence (nursing home, acute rehabilitation facility, acute care hospital, hospice, or other location).

between 2007 and 2017,[2] potentially reflecting a belief that spinal anesthesia is superior to general anesthesia. Our finding of similar outcomes at 60 days with either technique suggests that anesthesia choices for hip-fracture surgery may be based on patient preference rather than on anticipated differences in clinical outcomes.

In this pragmatic randomized trial involving older patients undergoing hip-fracture surgery, spinal anesthesia was not superior to general anesthesia with respect to the risk of death or new inability to walk independently at 60 days. The incidence of new-onset delirium and hospital lengths of stay were similar with the two types of anesthesia.

The authors, who make up the REGAIN Investigators Writing Committee, assume responsibility for the content of this article. The views presented in this article are solely the responsibility of the authors and do not necessarily represent the views of the Patient-Centered Outcomes Research Institute, its board of governors, or its methodology committee.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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## APPENDIX

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## REFERENCES


1. Neuman MD, Fleisher LA, Even-Shoshan O, Mi L, Silber JH. Nonoperative care for hip fracture in the elderly: the influence of race, income, and comorbidities. Med Care 2010;48:314-20.
2. Maxwell BG, Spitz W, Porter J. Association of increasing use of spinal anesthesia in hip fracture repair with treating an aging patient population. JAMA Surg 2020;155:167-8.
3. Neuman MD, Silber JH, Elkassabany NM, Ludwig JM, Fleisher LA. Comparative effectiveness of regional versus general anesthesia for hip fracture surgery in adults. Anesthesiology 2012;117:72-92.
4. Ahn EJ, Kim HJ, Kim KW, Choi HR, Kang H, Bang SR. Comparison of general anaesthesia and regional anaesthesia in terms of mortality and complications in elderly patients with hip fracture: a nationwide population-based study. BMJ Open 2019;9(9):e029245.
5. Ravi B, Pincus D, Choi S, Jenkinson R, Wasserstein DN, Redelmeier DA. Association of duration of surgery with postoperative delirium among patients receiving hip fracture repair. JAMA Netw Open 2019;2(2):e190111.
6. Chu C-C, Weng S-F, Chen K-T, et al. Propensity score-matched comparison of postoperative adverse outcomes between geriatric patients given a general or a neuraxial anesthetic for hip surgery: a population-based study. Anesthesiology 2015; 123:136-47.
7. Neuman MD, Rosenbaum PR, Ludwig JM, Zubizarreta JR, Silber JH. Anesthesia technique, mortality, and length of stay after hip fracture surgery. JAMA 2014; 311:2508-17.
8. Guay J, Parker MJ, Gajendragadkar PR, Kopp S. Anaesthesia for hip fracture surgery in adults. Cochrane Database Syst Rev 2016;2:CD000521.
9. Salkeld G, Cameron ID, Cumming RG, et al. Quality of life related to fear of falling and hip fracture in older women: a time trade off study. BMJ 2000;320:341-6.
10. Neuman MD, Ellenberg SS, Sieber FE, Magaziner JS, Feng R, Carson JL. Regional versus General Anesthesia for Promoting Independence after Hip Fracture (REGAIN): protocol for a pragmatic, international multicentre trial. BMJ Open 2016;6(11):e013473.
11. Hruslinski J, Menio DA, Hymes RA, et al. Engaging patients as partners in a multicentre trial of spinal versus general anaesthesia for older adults. Br J Anaesth 2021;126:395-403.
12. Neuman MD, Gaskins LJ, Ziolek T. Time to institutional review board approval with local versus central review in a multicenter pragmatic trial. Clin Trials 2018;15:107-11.
13. Horlocker TT, Vandermeuelen E, Kopp SL, Gogarten W, Leffert LR, Benzon HT. Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines (fourth edition). Reg Anesth Pain Med 2018;43:263-309.
14. Horlocker TT, Wedel DJ, Rowlingson JC, et al. Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines (Third Edition). Reg Anesth Pain Med 2010;35:64-101.
15. Matts JP, Lachin JM. Properties of permuted-block randomization in clinical trials. Control Clin Trials 1988;9:327-44.
16. Lachin JM, Matts JP, Wei LJ. Randomization in clinical trials: conclusions and recommendations. Control Clin Trials 1988;9:365-74.
17. Chernik DA, Gillings D, Laine H, et al. Validity and reliability of the Observer's Assessment of Alertness/Sedation Scale: study with intravenous midazolam. J Clin Psychopharmacol 1990;10:244-51.
18. Neuman MD, Kappelman MD, Israel E, et al. Real-world experiences with generating real-world evidence: case studies from PCORI's pragmatic clinical studies program. Contemp Clin Trials 2020;98: 106171.
19. Diehr P, Patrick DL. Trajectories of health for older adults over time: accounting fully for death. Ann Intern Med 2003; 139:416-20.
20. Diehr P, Johnson LL, Patrick DL, Psaty B. Methods for incorporating death into health-related variables in longitudinal studies. J Clin Epidemiol 2005;58:1115-24.
21. Marcantonio ER, Ngo LH, O'Connor M, et al. 3D-CAM: derivation and validation of a 3-minute diagnostic interview for CAM-defined delirium: a cross-sectional diagnostic test study. Ann Intern Med 2014;161:554-61.
22. Ustun T, Kostanjsek N, Chatterji S. Measuring health and disability: manual for WHO Disability Assessment Schedule (WHODAS 2.0). Geneva: World Health Organization, 2010.
23. Carson JL, Terrin ML, Noveck H, et al. Liberal or restrictive transfusion in high-risk patients after hip surgery. N Engl J Med 2011;365:2453-62.
24. Munhall RJ, Sukhani R, Winnie AP. Incidence and etiology of failed spinal anesthetics in a university hospital: a prospective study. Anesth Analg 1988;67: 843-8.
25. Fuzier R, Bataille B, Fuzier V, et al. Spinal anesthesia failure after local anesthetic injection into cerebrospinal fluid: a multicenter prospective analysis of its incidence and related risk factors in 1214 patients. Reg Anesth Pain Med 2011;36: 322-6.
26. Hogan JW, Lancaster T. Instrumental variables and inverse probability weighting for causal inference from longitudinal observational studies. Stat Methods Med Res 2004;13:17-48.
27. Hernán MA, Robins JM. Per-protocol analyses of pragmatic trials. N Engl J Med 2017;377:1391-8.
28. Matsui S. Stratified analysis in randomized trials with noncompliance. Biometrics 2005;61:816-23.
29. Biboulet P, Jourdan A, Van Haevre V, et al. Hemodynamic profile of target-controlled spinal anesthesia compared with 2 target-controlled general anesthesia techniques in elderly patients with cardiac comorbidities. Reg Anesth Pain Med 2012;37:433-40.
30. Haghighi M, Sedighinejad A, Nabi BN, et al. Is spinal anesthesia with low dose lidocaine better than sevoflorane anesthesia in patients undergoing hip fracture surgery. Arch Bone Jt Surg 2017; 5:226-30.
31. Juelsgaard P, Sand NP, Felsby S, et al. Perioperative myocardial ischaemia in patients undergoing surgery for fractured hip randomized to incremental spinal, single-dose spinal or general anaesthesia. Eur J Anaesthesiol 1998;15:656-63.
32. Tzimas P, Samara E, Petrou A, Korompilias A, Chalkias A, Papadopoulos G. The influence of anesthetic techniques on postoperative cognitive function in elderly patients undergoing hip fracture surgery: general vs spinal anesthesia. Injury 2018;49:2221-6.
33. Parker MJ, Griffiths R. General versus regional anaesthesia for hip fractures: a pilot randomised controlled trial of 322 patients. Injury 2015;46:1562-6.
34. Tajeu GS, Delzell E, Smith W, et al. Death, debility, and destitution following hip fracture. J Gerontol A Biol Sci Med Sci 2014;69:346-53.
35. Sieber FE, Neufeld KJ, Gottschalk A, et al. Effect of depth of sedation in older patients undergoing hip fracture repair on postoperative delirium: the STRIDE randomized clinical trial. JAMA Surg 2018; 153:987-95.
36. Sieber F, Neufeld KJ, Gottschalk A, et al. Depth of sedation as an interventional target to reduce postoperative delirium: mortality and functional outcomes of the Strategy to Reduce the Incidence of Postoperative Delirium in Elderly Patients randomised clinical trial. Br J Anaesth 2019; 122:480-9.