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

*P J Devereaux, Emmanuelle Duceppe, Gordon Guyatt, Vikas Tandon, Reitze Rodseth, Bruce M Biccard, Denis Xavier, Wojciech Szczeklik, Christian S Meyhoff, Jessica Vincent, Maria Grazia Franzosi, Sadeesh K Srinathan, Jason Erb, Patrick Magloire, John Neary, Mangala Rao, Prashant V Rahate, Navneet K Chaudhry, Bongani Mayosi, Miriam de Nadal, Pilar Paniagua Iglesias, Otavio Berwanger, Juan Carlos Villar, Fernando Botto, John W Eikelboom, Daniel I Sessler, Clive Kearon, Shirley Pettit, Mukul Sharma, Stuart J Connolly, Shrikant I Bangdiwala, Purnima Rao-Melacini, Andreas Hoeft, Salim Yusuf, on behalf of the MANAGE Investigators**

## 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.



*Lancet* 2018; 391: 2325–34

See **Comment** page 2297

*Members are listed in the appendix

**Department of Health Research Methods, Evidence, and Impact** (Prof P J Devereaux MD, E Duceppe MD, Prof G Guyatt MD, Prof C Kearon MD, Prof S I Bangdiwala PhD, Prof S Yusuf MBBS) **and Department of Medicine** (Prof P J Devereaux, Prof G Guyatt, V Tandon MD, P Magloire MD, J Neary MD, J W Eikelboom MD, Prof C Kearon, M Sharma MD, Prof S J Connolly MD, Prof S Yusuf), **McMaster University, Hamilton, ON, Canada; Population Health Research Institute, Hamilton, ON, Canada** (Prof P J Devereaux, J Vincent MSc, S Pettit RN, M Sharma, Prof S J Connolly, Prof S I Bangdiwala, P Rao-Melacini MSc, Prof S Yusuf); **Department of Medicine, University of Montreal, Montreal, QC, Canada** (E Duceppe); **Department of Anaesthesia, University of KwaZulu-Natal, Pietermaritzburg, South Africa** (R Rodseth MBChB); **Department of Anaesthesia and Perioperative Medicine** (Prof B M Biccard MBChB) **and Department of Medicine** (Prof B Mayosi MBChB), **Groote Schuur Hospital and University of Cape Town, Cape Town, South Africa; Department of Pharmacology, St John's Medical College and Research Institute, Bangalore, India** (Prof D Xavier MD, M Rao MD); **Department of Intensive Care and Perioperative Medicine, Jagiellonian University Medical College, Krakow, Poland** (Prof W Szczeklik MD); **Department of Anaesthesia**

## 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

and Intensive Care, Bispebjerg and Frederiksberg Hospital, University of Copenhagen, Copenhagen, Denmark (C S Meyhoff MD); Department of Cardiovascular Research, IRCCS Istituto di Ricerche Farmacologiche Mario Negri, Milan, Italy (M G Franzosi PhD); Department of Surgery, University of Manitoba, Winnipeg, MB, Canada (S K Srinathan MD); Department of Anesthesiology and Perioperative Medicine, Queen's University, Kingston, ON, Canada (J Erb MD); Department of Surgery, Rahate Surgical Hospital, Nagpur, India (P V Rahate MBBS); Department of Surgery, Christian Medical College Hospital, Ludhiana, India (Prof N K Chaudhry MBBS); Department of Anesthesiology, Hospital Universitari Vall d'Hebron, Barcelona, Spain (M de Nadal MD); Department of Anesthesiology, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain (P P Iglesias MD); Instituto de Ensino e Pesquisa do Hospital do Coração (IEP-HCor), São Paulo, Brazil (O Berwanger MD); Departamento de Investigaciones, Fundación Cardioinfantil—Instituto de Cardiología (Bogotá) and Facultad de Ciencias de la Salud, Universidad Autónoma de Bucaramanga, Colombia (Prof J C Villar MD); Estudios Clínicos Latinoamérica (ECLA), Rosario and Hospital Austral, Pilar, Argentina (F Botto MD); Department of Outcomes Research, Cleveland Clinic, Anesthesiology Institute, Cleveland, OH, United States (Prof D I Sessler MD); and Department of Anesthesiology and Intensive Care Medicine, University Hospital Bonn, Bonn, Germany (Prof A Hoeft MD)

Correspondence to:
Prof P J Devereaux, David Braley Research Building, Hamilton General Hospital, Hamilton, ON L8L 2X2, Canada
philipj@mcmaster.ca

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,

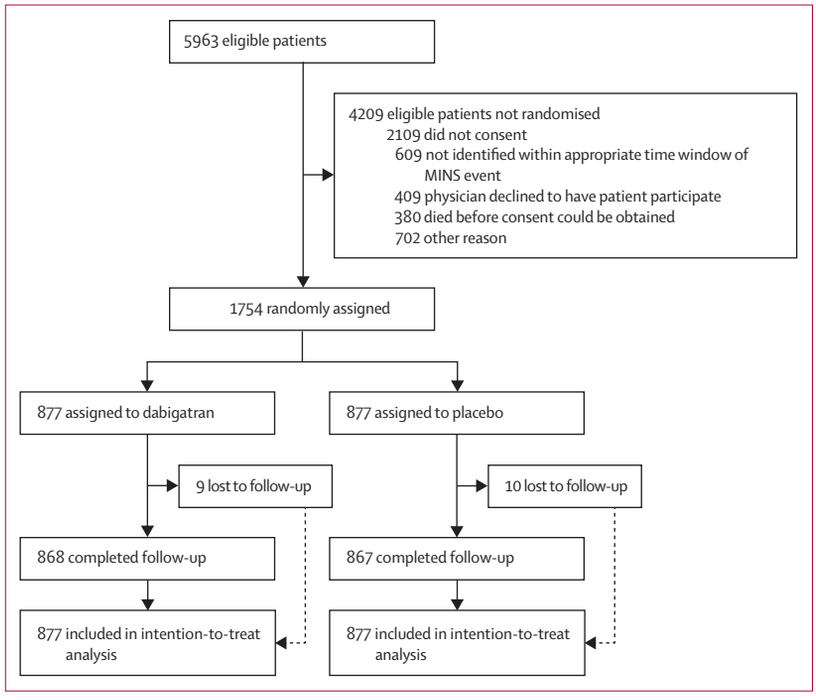


***Figure 1:*** **Trial profile**
MINS=myocardial injury after non-cardiac surgery.

| | 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).

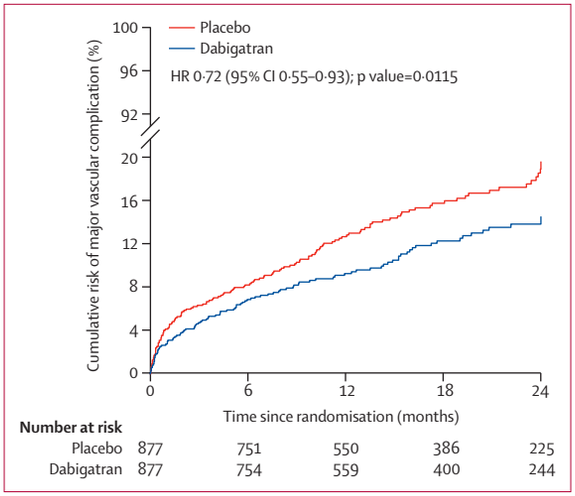


*Figure 2:* **Kaplan-Meier estimates of the primary efficacy outcome**
HR=hazard ratio.

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

| | 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**

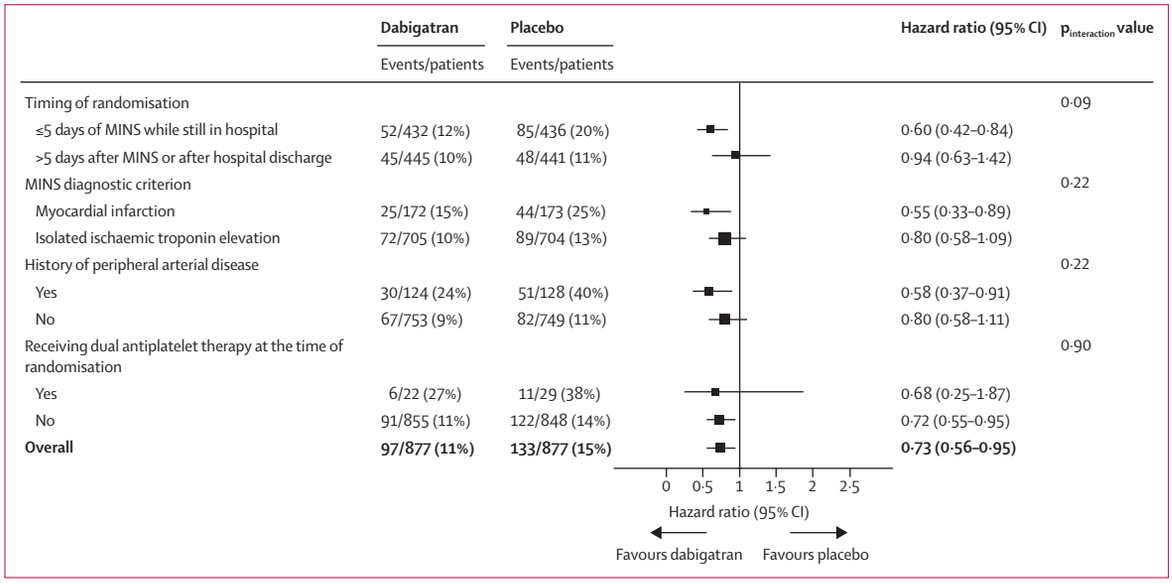


***Figure 3:*** **Subgroup analyses of the primary efficacy outcome**
MINS=myocardial injury after non-cardiac surgery.

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.

#### Acknowledgments

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.