Cardiovascular protection of dabigatran in a high-risk patient population

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In RE-LY, both doses of dabigatran were associated with significant benefits vs warfarin.

**Safety endpoints**

- **Major bleeding**: D150 vs D110, D110 vs warfarin, D150 vs warfarin.
  - P values: 0.41, 0.003, <0.001, <0.001, <0.001.

- **ICH**: D150 vs D110, D110 vs warfarin, D150 vs warfarin.
  - P values: 0.04, <0.001, <0.001.

- **Life-threatening bleeding**: D150 vs D110, D110 vs warfarin, D150 vs warfarin.
  - P values: <0.001, <0.001, <0.001.

**Efficacy endpoints**

- **Stroke/SE**: D150 vs D110, D110 vs warfarin, D150 vs warfarin.
  - P values: <0.001, 0.27.

- **MI**: D150 vs D110, D110 vs warfarin, D150 vs warfarin.
  - P values: 0.12, 0.09.

- **CV mortality**: D150 vs D110, D110 vs warfarin, D150 vs warfarin.
  - P values: <0.001, 0.21.

There was no significant difference in the rate of MI between either dabigatran dose vs warfarin, but questions were raised about a potential imbalance in MI rates.

What additional data are available to demonstrate that dabigatran has at least a similar cardiac safety profile vs warfarin in patients with AF?
# Cardiac safety profile of dabigatran

## Additional RE-LY analyses
- Myocardial ischaemic events analysis
- EU label analysis

## Real-world studies
- Healthcare database analyses
- GLORIA-AF prospective registry

## RCTs of dabigatran in patients at increased CV risk
- RE-DUAL PCI
  - Patients with AF following PCI with stenting
- MANAGE
  - Patients with myocardial injury after non-cardiac surgery

PCI, percutaneous coronary intervention; RCT, randomized controlled trial
In RE-LY, the MI event rates were low and there was no significant difference between dabigatran and warfarin arms.

Myocardial ischaemic events subanalysis

- **Total MI**
  - D150: 0.81
  - D110: 0.82
  - W: 0.64
  - P value: 0.12 vs W, 0.09 vs W

- **Clinical MI**
  - D150: 0.74
  - D110: 0.73
  - W: 0.56
  - P value: 0.09 vs W, 0.10 vs W

- **Silent MI**
  - D150: 0.07
  - D110: 0.09
  - W: 0.08
  - P value: 0.72 vs W, 0.66 vs W

- **Fatal MI**
  - D150: 0.11
  - D110: 0.13
  - W: 0.10
  - P value: 0.88 vs W, 0.46 vs W

- **Composite (MI, UA, CABG, PCI, cardiac arrest, cardiac death)**
  - D150: 3.53
  - D110: 3.38
  - W: 3.60
  - P value: 0.82 vs W, 0.36 vs W

CABG, coronary artery bypass grafting; UA, unstable angina; W, warfarin; Hohnloser et al. Circulation 2012
In RE-LY patients with an MI event were older, with more coronary risk factors, and a higher risk of stroke, vs rest of study population.

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>MI event</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (n=270)</td>
<td>No (n=17,843)</td>
</tr>
<tr>
<td>Mean age, yrs</td>
<td>73.0</td>
<td>71.5</td>
</tr>
<tr>
<td>Prior MI, %</td>
<td>37</td>
<td>16</td>
</tr>
<tr>
<td>Other CAD, %</td>
<td>52</td>
<td>27</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>35</td>
<td>23</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>85</td>
<td>79</td>
</tr>
<tr>
<td>Prior heart failure, %</td>
<td>39</td>
<td>32</td>
</tr>
<tr>
<td>Prior stroke/TIA, %</td>
<td>22</td>
<td>20</td>
</tr>
<tr>
<td>CHADS&lt;sub&gt;2&lt;/sub&gt; score, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td>22</td>
<td>32</td>
</tr>
<tr>
<td>2</td>
<td>35</td>
<td>36</td>
</tr>
<tr>
<td>3–6</td>
<td>43</td>
<td>32</td>
</tr>
</tbody>
</table>

CAD, coronary artery disease; TIA, transient ischaemic attack
Hohnloser et al. Circulation 2012
Asian population analysis: efficacy outcomes (Asia vs non-Asia)

<table>
<thead>
<tr>
<th></th>
<th>Rate (%/year)</th>
<th>Dabigatran 150 mg BID vs warfarin</th>
<th>Dabigatran 110 mg BID vs warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dabigatran</td>
<td>Warfarin</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td></td>
<td>150 mg BID</td>
<td>110 mg BID</td>
<td></td>
</tr>
<tr>
<td>Stroke or SE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asia</td>
<td>1.39</td>
<td>2.50</td>
<td>3.06</td>
</tr>
<tr>
<td>Non-Asia</td>
<td>1.06</td>
<td>1.37</td>
<td>1.48</td>
</tr>
<tr>
<td>Ischaemic stroke</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asia</td>
<td>1.12</td>
<td>2.05</td>
<td>2.02</td>
</tr>
<tr>
<td>Non-Asia</td>
<td>0.81</td>
<td>1.14</td>
<td>0.98</td>
</tr>
<tr>
<td>Haemorrhagic stroke</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asia</td>
<td>0.17</td>
<td>0.11</td>
<td>0.75</td>
</tr>
<tr>
<td>Non-Asia</td>
<td>0.09</td>
<td>0.12</td>
<td>0.32</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asia</td>
<td>0.50</td>
<td>0.51</td>
<td>0.58</td>
</tr>
<tr>
<td>Non-Asia</td>
<td>0.86</td>
<td>0.88</td>
<td>0.65</td>
</tr>
<tr>
<td>Death from any cause</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asia</td>
<td>4.01</td>
<td>5.01</td>
<td>5.09</td>
</tr>
<tr>
<td>Non-Asia</td>
<td>3.57</td>
<td>3.53</td>
<td>3.96</td>
</tr>
</tbody>
</table>

Disclaimer: Dabigatran etexilate is now approved for clinical use in stroke prevention in atrial fibrillation in certain countries. Please check local prescribing information for further details.
What does real-world evidence tell us about the cardiac safety profile of dabigatran vs warfarin?

RE-LY showed there was no significant difference in the rate of MI between either dabigatran dose vs warfarin.

Real-world evidence can add to data from RCTs.

Post-approval, use in clinical practice provides an opportunity to study:
- Broader patient populations
- Different settings

What does real-world evidence tell us about the cardiac safety profile of dabigatran vs warfarin?

Numerous real-world analyses consistently demonstrate that dabigatran has similar or better cardiac safety vs warfarin.

Methodology criteria for analyses included are: new-user design; adjusted comparisons available, e.g. propensity score matching; hazard ratio for major bleeding available; adequate sample size of ≥3000 patients; and analyses published from 2014 to 2017. Other limitations may apply. *VKA-naïve stratum, D150; †US licensed doses dabigatran 150 mg/75 mg BID; ‡OAC-naïve stratum CMS, Centres for Medicare and Medicaid Services. References are provided in slide notes.

Risk of MI with dabigatran vs warfarin

Analyses including >290,000 patients investigating risk of MI with dabigatran vs warfarin

- Larsen 2014, n=12,951*
- Graham 2015, n=134,414†
- Lauffenburger 2015, n=64,935†
- Seeger 2015, n=38,378†
- Villines 2015, n=25,586†
- Chan 2016, n=14,315‡
Findings from GLORIA-AF show low rates of MI in patients taking dabigatran

GLORIA-AF is an ongoing, prospective, global registry program in patients with newly diagnosed AF at risk for stroke

GLORIA-AF\textsuperscript{1} Phase II interim
N=2937

RE-LY EU label analysis\textsuperscript{2}
N=6004 (ITT), N=5981 (safety)

\begin{align*}
\text{MI} & : 0.47 \\
\text{Stroke} & : 0.63 \\
\text{Major bleeding} & : 1.12 \\
\text{All-cause death} & : 2.69 \\
\end{align*}

- In GLORIA-AF, where dabigatran is prescribed by physician choice, MI rates were low when compared with the RE-LY EU label post hoc analysis
- GLORIA-AF confirms the sustained safety and effectiveness of dabigatran over 2 years of follow-up

*Stroke = ischaemic + haemorrhagic stroke in GLORIA-AF, ischaemic stroke in RE-LY

Dabigatran for management of myocardial injury after non-cardiac surgery (MINS)

Randomized, placebo-controlled trial (MANAGE)
What is MINS, and what is the potential role for dabigatran?
What is the difference between MINS and MI?¹

**Myocardial necrosis**

- Increasing severity of ischaemia

**Reversible myocardial injury**

MINS

- A broad spectrum of myocardial damage from reversible myocardial injury to myocardial necrosis³
- **Diagnosis:** cardiac troponin levels⁴

MI

- Includes only one manifestation of acute myocardial ischaemia: myocardial necrosis
- **Diagnosis:** cardiac troponin levels²
- PLUS ischaemic symptoms
- OR ECG changes

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Perioperative cardiovascular events are the leading cause of mortality and morbidity in non-cardiac surgery\textsuperscript{1–4}

**Myocardial injury after non-cardiac surgery (MINS):**
myocardial injury caused by ischaemia that occurs during or within 30 days after surgery\textsuperscript{5}

Worldwide, **200 million** adults undergo major non-cardiac surgery per year\textsuperscript{6}

**100 million** of these surgeries involve adults aged >45 years and at risk for myocardial infarction or injury\textsuperscript{7}

\begin{itemize}
\item \textasciitilde8% (or 8 million) of these patients suffer myocardial infarction or injury\textsuperscript{7}
\end{itemize}

Myocardial injury is the leading cause of mortality after major non-cardiac surgery\textsuperscript{5,8} – accounting for \textasciitilde750 000 deaths annually\textsuperscript{7}

Perioperative myocardial infarction is associated with substantial long-term mortality

Cumulative all-cause mortality within 30 days (P<0.001)

Cumulative all-cause mortality up to 1 year (P<0.001)

MI, myocardial infarction
Puelacher et al. Circulation 2017
Only a minority of patients suffering MINS experience an ischaemic symptom\(^1\)

Study involving 15 065 patients with non-cardiac surgery aged >45 years, of whom 1200 patients were diagnosed with MINS\(^*\)

Ischaemic features (ECG findings\(^†\) or symptoms\(^‡\)) present

- 41.8%
- 58.2%

Most MINS cases are likely to go undetected without routine troponin surveillance and, therefore, are undertreated\(^2\)

\(^*\)Any peak troponin T (TnT) of \(\geq 0.03\) ng/mL that was judged as resulting from myocardial ischemia; \(^†\)Q waves, ST elevation, left bundle branch block, ST depression, T-wave inversion; \(^‡\)Chest discomfort, neck/jaw/arm discomfort, dyspnoea, or pulmonary oedema; 1. Botto et al. Anesthesiology 2014; 2. Biccard et al. Ann Surg 2017
MINS carries a poor prognosis and is an independent predictor of short- (30-day) and long-term mortality

Observational studies showing prognostic importance of MINS

**Devereaux 2017, N=21 842, 30-day F/U**
- aHR (95% CI): 3.69 (2.80–4.85)

**Puelacher 2017, N=2018, 12-month F/U**
- (30-day mortality)
- aHR (95% CI): 2.7 (1.5–4.8)
- aOR (95% CI): 1.6 (1.2–2.2)

**Puelacher 2017, N=2018, 12-month F/U**
- (12-month mortality)
- aHR (95% CI): 1.57 (1.07–2.31)

**Reed 2017, N=12 882, 5-year F/U**
- aHR (95% CI): 
- aOR (95% CI): 

**Botto 2014, N=15 065, 30-day F/U**
- aHR (95% CI): 3.90 (2.90–5.27)

**Redfern 2011, N=1873, 30-day F/U**
- aHR (95% CI): 5.03 (2.88–8.79)

**Levy 2011, N=3318, 12-month F/U**
- aHR (95% CI): 6.7 (4.1–10.9)

Some patients undergoing non-cardiac surgery will fail to obtain the benefits of surgery because MINS ultimately causes fatality.

aHR, adjusted hazard ratio; aOR, adjusted odds ratio; F/U follow-up; Devereaux PJ et al. JAMA 2017;317:1642–51 (VISION investigators); Puelacher et al. Circulation 2017; Reed et al. J Am Heart Assoc 2017; Botto et al. Anaesthesiology 2014; Redfern et al. Anaesthesia 2011; Levy et al. Anaesthesiology 2011; ClinicalTrials.gov: NCT01661101
Observational data showed some CV benefits of perioperative statin use but data on ASA and beta blockers are inconclusive.

**Statins:** may decrease MACE and mortality\(^1,2\)

**ESC/ESA and ACC/AHA guidelines:**
continuation of statins (class I, level C) or initiation of statins (class IIa, level B) in patients undergoing vascular surgery\(^3,4\)

**ASA:** perioperative benefits not proven\(^5\)

**ACC/AHA guidelines:**
continuation of [ASA] for non-urgent, non-cardiac surgery may be reasonable in patients without prior coronary stenting, if the increased risk of cardiac events outweighs the increased risk of bleeding (class IIb, level B)\(^4\)

**Beta blockers:**
perioperative benefits of *de novo* treatment are debated\(^6\)

**ESC/ESA and ACC/AHA guidelines:**
continuation of beta blockers in patients already receiving them (class I, level B). Initiation for high-risk surgery in patients with clinical risk factors or myocardial ischaemia may be considered (class IIb, level B), however not without preoperative titrations (ESC/ESA class III, level B), and not on the day of surgery (ACC/AHA class III, level B)\(^3,4\)

ACC, American College of Cardiology; AHA, American Heart Association; ESC, European Society of Cardiology; MACE, major adverse cardiac events
There is a lack of evidence-based management strategies to prevent and treat MINS

Management of MINS is informed by observational studies only\(^1,2\)
Therefore, the risk–benefit ratios are unknown

<table>
<thead>
<tr>
<th>Preoperative</th>
<th>Intraoperative</th>
<th>Postoperative*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identifying risk factors using cardiac risk indices and biomarkers</td>
<td>No intraoperative measures known to reduce the incidence of MINS(^3)</td>
<td>No postoperative measures known to reduce the incidence of MINS but the following are proposed to help prevent it:(^3,5)</td>
</tr>
<tr>
<td>May be beneficial if patients seen weeks in advance of surgery; however, most patients seen the day before surgery(^3)</td>
<td>Blood pressure optimization may be beneficial(^3,4)</td>
<td>More frequent/continuous vital sign monitoring</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypoxaemia avoidance</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Correction of potentially contributing factors</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intravascular volume optimization</td>
</tr>
</tbody>
</table>

There is an urgent need for clinical trials to identify effective therapies to improve the outcomes of patients suffering MINS

*The majority of MINS occurs within 2 postoperative days
Dabigatran has the potential to prevent a broader range of vascular complications in patients with MINS

- Antithrombotic agents, such as NOACs, might prevent major vascular complications in patients with MINS

- Laboratory, autopsy, imaging, operative, and non-operative data suggest coronary artery thrombosis plays a role in pathogenesis, meaning there is potential benefit with anticoagulant therapy

Timely and appropriate treatment of MINS has the potential to circumvent these events

What are the objectives and design of the MANAGE trial?
MANAGE is the first RCT to evaluate a potential treatment for patients with MINS

Management of Myocardial Injury After Non-cardiac Surgery Trial (MANAGE)

Main objective
MANAGE is a large, international, Phase III, double-blind RCT designed to determine the impact of dabigatran on the risk of major vascular complications in patients who have suffered MINS

Additional objective
MANAGE will also determine the impact of omeprazole on the risk of major upper GI complications*

*Data for this analysis not yet available
Funding was provided by Boehringer Ingelheim and the Canadian Institute of Health
Devereaux et al. ACC 2018; Duceppe et al. Can J Cardiol 2018
MANAGE investigated the effect of dabigatran vs placebo in patients who have had MINS

Patients aged ≥45 years who have undergone non-cardiac surgery ≤35 days after having MINS
MINS diagnostic criteria: universal definition of MI or isolated ischaemic troponin elevation

Dabigatran 110 mg BID
Matching placebo

Mean treatment duration and follow-up: 16 months

Primary endpoint: major vascular complications
(vascular mortality and non-fatal MI, non-haemorrhagic stroke, peripheral arterial thrombosis, amputation, and symptomatic VTE)

The study also assessed the impact of omeprazole on the risk of a major upper GI complications using a partial factorial design (patients not receiving PPIs were randomized to omeprazole 20 mg OD vs placebo

VTE, venous thromboembolism
Devereaux et al. ACC 2018; Duceppe et al. Can J Cardiol 2018
Rationale for dose selection: in RE-LY, dabigatran 110 mg BID had a lower risk of major bleeding vs warfarin.

RE-LY trial: dabigatran 110 mg BID$^{1-3}$

- **Major bleeding**
  - HR (95% CI): 0.80 (0.70–0.93)
  - P value: 0.003

- **Life-threatening bleeding**
  - HR (95% CI): 0.67 (0.55–0.83)
  - P value: <0.001

- **ICH**
  - HR (95% CI): 0.30 (0.19–0.45)
  - P value: <0.001

ICH, intracranial haemorrhage
MANAGE trial design modifications

**Initial trial design**
- Randomize 3200 patients
- Primary composite endpoint: vascular mortality and non-fatal MI, stroke, peripheral arterial thrombosis, and symptomatic PE

But…
- Recruitment was slower than expected
- Funding was reduced

**Updated trial protocol**

*Without knowledge of trial results:*
- **Sample size reduced to 1750 patients** (90% power to detect HR of 0.65 assuming placebo Kaplan–Meier rate of 20%)
- Based on COMPASS and to enhance power, amputation and symptomatic proximal DVT added to primary composite endpoint

DVT, deep vein thrombosis; PE, pulmonary embolism
Devereaux et al. ACC 2018
MANAGE exclusion criteria

- History of bleeding diathesis or prior intracranial, intraocular, or spinal bleeding
- Condition that required treatment with an anticoagulant
- CrCl <35 mL/min

CrCl, creatinine clearance
Devereaux et al. ACC 2018; Duceppe et al. Can J Cardiol 2018
## MANAGE study endpoints

<table>
<thead>
<tr>
<th>Primary efficacy endpoint</th>
<th>Secondary efficacy endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major vascular complication</strong>&lt;br&gt;Composite of vascular mortality and non-fatal MI, non-haemorrhagic stroke, peripheral arterial thrombosis, amputation, and symptomatic VTE</td>
<td>All-cause or vascular mortality&lt;br&gt;Mi&lt;br&gt;Non-haemorrhagic stroke&lt;br&gt;Cardiac revascularization&lt;br&gt;Symptomatic VTE&lt;br&gt;Amputation&lt;br&gt;Peripheral arterial thrombosis&lt;br&gt;Rehospitalization for vascular reasons</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Primary safety endpoint</th>
<th>Additional safety endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Composite of life-threatening bleeding, major bleeding, and critical organ bleeding</strong></td>
<td>Intracranial haemorrhage&lt;br&gt;Haemorrhagic stroke&lt;br&gt;Fracture&lt;br&gt;Lower GI bleeding&lt;br&gt;Minor bleeding&lt;br&gt;Dyspepsia</td>
</tr>
</tbody>
</table>

Devereaux et al. ACC 2018; Ducepte et al. Can J Cardiol 2018
MANAGE is an international study involving 84 centres in 19 countries; 1754 patients were recruited.

Devereaux et al. ACC 2018

MANAGE is an investigator-led study, conducted and overseen by the Population Health Research Institute, Hamilton, Canada.
Patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Dabigatran (n=877)</th>
<th>Placebo (n=877)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years</td>
<td>70</td>
<td>70</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>52</td>
<td>51</td>
</tr>
<tr>
<td>MINS criteria, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Isolated troponin elevation</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>Time from MINS diagnosis to randomization, days (IQR)</td>
<td>5 (2–14)</td>
<td>5 (2–14)</td>
</tr>
</tbody>
</table>

- Follow-up was complete for 99% of patients
- 91% of patients did not experience an ischaemic symptom with MINS
## Concomitant medications

<table>
<thead>
<tr>
<th>Medications, %</th>
<th>Dabigatran (n=877)</th>
<th>Placebo (n=877)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA</td>
<td>74</td>
<td>73</td>
</tr>
<tr>
<td>P2Y12 inhibitor</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>ASA or P2Y12 inhibitor</td>
<td>75</td>
<td>75</td>
</tr>
<tr>
<td>Dual antiplatelet therapy</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>ACE inhibitor or ARB</td>
<td>59</td>
<td>59</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>47</td>
<td>45</td>
</tr>
<tr>
<td>Statin</td>
<td>69</td>
<td>69</td>
</tr>
</tbody>
</table>

ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; ASA, acetylsalicylic acid
Devereaux et al. ACC 2018
Similar rates of permanent study drug discontinuation in the dabigatran and placebo groups

Permanent study drug discontinuation

Dabigatran group

Placebo group

46%

43%

Devereaux et al. ACC 2018
Primary efficacy outcome: significant reduction in risk of major vascular complications with dabigatran vs placebo

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Dabigatran (n=877) n (%)</th>
<th>Placebo (n=877) n (%)</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major vascular complication</td>
<td>97 (11)</td>
<td>133 (15)</td>
<td>0.72 (0.55–0.93)</td>
<td>0.012</td>
</tr>
</tbody>
</table>

**Cumulative risk of major vascular complication**

- **Placebo**
  - 0 months: 0.02
  - 6 months: 0.05
  - 12 months: 0.11
  - 18 months: 0.14
  - 24 months: 0.18
- **Dabigatran**
  - 0 months: 0.01
  - 6 months: 0.03
  - 12 months: 0.07
  - 18 months: 0.10
  - 24 months: 0.13

**No. at risk**

- **Dabigatran**
  - 877
  - 751
  - 550
  - 386
  - 225
- **Placebo**
  - 877
  - 754
  - 559
  - 400
  - 244

HR: 0.72; 95% CI: 0.55–0.93; P=0.012

Devereaux et al. ACC 2018
Secondary efficacy outcomes were similar with dabigatran vs placebo

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Dabigatran (n=877) n (%)</th>
<th>Placebo (n=877) n (%)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular mortality</td>
<td>52 (6)</td>
<td>64 (7)</td>
<td>0.80 (0.56–1.16)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>100 (11)</td>
<td>110 (13)</td>
<td>0.90 (0.69–1.18)</td>
</tr>
<tr>
<td>MI</td>
<td>35 (4)</td>
<td>43 (5)</td>
<td>0.80 (0.51–1.26)</td>
</tr>
<tr>
<td>Cardiac revascularization</td>
<td>32 (4)</td>
<td>21 (2)</td>
<td>1.53 (0.88–2.65)</td>
</tr>
<tr>
<td>Peripheral arterial thrombosis</td>
<td>0 (0)</td>
<td>4 (1)</td>
<td>–</td>
</tr>
<tr>
<td>Amputation</td>
<td>18 (2)</td>
<td>26 (3)</td>
<td>0.70 (0.38–1.27)</td>
</tr>
<tr>
<td>Symptomatic VTE</td>
<td>8 (1)</td>
<td>17 (2)</td>
<td>0.47 (0.20–1.08)</td>
</tr>
<tr>
<td>Vascular readmission</td>
<td>113 (13)</td>
<td>130 (15)</td>
<td>0.86 (0.67–1.11)</td>
</tr>
<tr>
<td>Non-haemorrhagic stroke</td>
<td>2 (&lt;1)</td>
<td>10 (1)</td>
<td>0.20 (0.04–0.90)</td>
</tr>
</tbody>
</table>

Significant reduction in non-haemorrhagic stroke with dabigatran vs placebo
Primary safety outcome: similar rates of the composite primary safety endpoint with dabigatran vs placebo

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Dabigatran (n=877) n (%)</th>
<th>Placebo (n=877) n (%)</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite of life-threatening, major, and critical organ bleeding</td>
<td>29 (3)</td>
<td>31 (4)</td>
<td>0.92 (0.55–1.53)</td>
<td>0.79</td>
</tr>
</tbody>
</table>

No significant effect of omeprazole study drug on dabigatran primary efficacy results (P for interaction, 0.37)
## Secondary safety outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Dabigatran (n=877) n (%)</th>
<th>Placebo (n=877) n (%)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Life-threatening bleeding</td>
<td>9 (1)</td>
<td>8 (1)</td>
<td>1.11 (0.43–2.88)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>21 (2)</td>
<td>25 (3)</td>
<td>0.83 (0.46–1.48)</td>
</tr>
<tr>
<td>Critical organ bleeding</td>
<td>5 (1)</td>
<td>10 (1)</td>
<td>0.49 (0.17–1.43)</td>
</tr>
<tr>
<td>ICH</td>
<td>4 (1)</td>
<td>3 (&lt;1)</td>
<td>1.32 (0.30–5.90)</td>
</tr>
<tr>
<td>Haemorrhagic stroke</td>
<td>2 (&lt;1)</td>
<td>2 (&lt;1)</td>
<td>0.98 (0.14–6.96)</td>
</tr>
<tr>
<td>Fracture</td>
<td>39 (4)</td>
<td>28 (3)</td>
<td>1.38 (0.85–2.24)</td>
</tr>
<tr>
<td>Significant lower GI bleed</td>
<td>15 (2)</td>
<td>6 (1)</td>
<td>2.50 (0.97–6.44)</td>
</tr>
<tr>
<td>Non-significant lower GI bleed</td>
<td>33 (4)</td>
<td>7 (1)</td>
<td>4.77 (2.11–10.80)</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>134 (15)</td>
<td>84 (10)</td>
<td>1.64 (1.25–2.15)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>129 (15)</td>
<td>98 (11)</td>
<td>1.33 (1.02–1.73)</td>
</tr>
</tbody>
</table>

- Low rates of all bleeding outcomes with dabigatran
- Differences seen only for non-significant lower GI bleeds, minor bleeds, and dyspepsia vs placebo

Significant and non-significant refer to GI bleeding severity; Devereaux et al. ACC 2018
Among patients with MINS, dabigatran 110 mg BID:

- Decreased risk of major vascular complications
- With no observed increased risk of major bleeding
Patients with MINS are at high risk: myocardial injury is the leading cause of mortality after major non-cardiac surgery, accounting for \( \sim 750,000 \) deaths annually.

In MANAGE, 91% of MINS were only detected through troponin screening; clinicians will not recognize most MINS without routine perioperative troponin measurements.

MANAGE demonstrates cardiovascular protection with dabigatran (110 mg BID) in a high-risk patient population.

Devereaux et al. ACC 2018
Key points

1. Analyses of RE-LY data demonstrated no significant difference in rates of myocardial ischaemic events between dabigatran and warfarin

2. Numerous real-world data analyses have consistently confirmed that dabigatran has similar or better cardiac safety vs VKAs in clinical practice

3. Results of the placebo-controlled MANAGE trials provide further evidence for the safety of dabigatran in patients at increased CV risk