Prevention of cardiovascular complications after noncardiac surgery: New insights in surveillance and management

Emmanuelle Duceppe, MD
General Internal Medicine / Perioperative Medicine
McMaster University
Population Health Research Institute
Hamilton, Ontario, Canada
Disclosure

• No conflict of interest to disclose
Introduction

Population Health Research Institute,
McMaster University, Hamilton,
Ontario, Canada

CHUM Research Center
University of Montreal, Montreal,
Quebec, Canada
Objectives

- Summarize the evidence for monitoring perioperative troponins
- Define the concept of myocardial injury after noncardiac surgery (MINS)
- Describe the treatment options for MINS
- Learn about first large trial on how to manage MINS
- Address the issue of VTE prophylaxis in the MANAGE Trial
- Summarize data on perioperative bleeding associated with dabigatran
Prognostic Value of Troponin and Creatine Kinase Muscle and Brain Isoenzyme Measurement after Noncardiac Surgery

A Systematic Review and Meta-analysis

Michael Levy, M.D., M.P.H.,* Diane Heels-Ansdell, M.Sc.,† Rajesh Hiralal, M.D.,‡
Deborah Cook, M.D., M.Sc.,** Juan Carlos Villar, M.D., Ph.D., †† Matthew McQueen, M.B., Ch.B., Ph.D., ‡‡
Edward McFalls, M.D., Ph.D., §§ Miodrag Filipovic, M.D., |||| Holger Schünemann, M.D., Ph.D., ##
John Sear, M.B.B.S., Ph.D., *** Pierre Foex, M.D., Ph.D., ††† Wendy Lim, M.D., M.Sc., ††‡
Giora Landesberg, M.D., D.Sc., §§§ Gilles Godet, M.D., |||| Don Poldermans, M.D., Ph.D., ####
Francesca Bursi, M.D., M.Sc., **** Miklos D. Kertai, M.D., Ph.D., †††† Neera Bhatnagar, M.L.I.S., †††‡
P. J. Devereaux, M.D., Ph.D. §§§§

Anesthesiology. 2011 Apr;114(4):796-806.
Included studies in meta-analysis

• Inclusion criteria
  – Patient with at least 1 troponin or CKMB postop
  – at least 1 pt with a major CV outcome or mortality
  – Prognostic significance of trop analyzed by multivariate analysis

• 15 studies included
  – 12 studies in vascular surgery
  – 7 studies in ortho surgery
  – 4 studies in abdo/general surgery
  – 3 studies in urology or gynecology surgery

• 3,318 patients – 459 death
Included studies in meta-analysis

• Included troponin I and troponin T

• 99th percentile used to define troponin elevation in majority of studies

• Troponin on day 1, day 2 and day 3 for most studies
• Troponin elevation associated with all-cause mortality

• All studies have same direction of effect

**Fig. 2.** Adjusted odds ratio for an increased postoperative troponin measurement to predict all-cause mortality.

Anesthesiology. 2011 Apr;114(4):796-806.
Significative association with major cardiovascular complications

Anesthesiology. 2011 Apr;114(4):796-806.

<table>
<thead>
<tr>
<th>Study</th>
<th>Composite Cardiac Outcome</th>
<th>No. of Patients</th>
<th>No. of Events</th>
<th>Adjusted Odds Ratio</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lopez-Jimenez</td>
<td>Cardiac death, nonfatal myocardial infarction, and admission for unstable angina</td>
<td>722</td>
<td>19</td>
<td>4.6</td>
<td>NR</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Bursi, Ausset</td>
<td>Death and myocardial infarction</td>
<td>391</td>
<td>83</td>
<td>4.7*</td>
<td>2.9–7.7</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td></td>
<td>Cardiac death, myocardial infarction, congestive heart failure, need for coronary revascularization, or unstable angina</td>
<td>88</td>
<td>8</td>
<td>17.4*</td>
<td>3.7–82</td>
<td>NR</td>
</tr>
<tr>
<td>Chong</td>
<td>Myocardial infarction, congestive cardiac failure, atrial fibrillation, or major arrhythmia</td>
<td>102</td>
<td>33</td>
<td>3.9</td>
<td>1.4–10.7</td>
<td>0.008</td>
</tr>
<tr>
<td>Bolliger</td>
<td>Hospitalization for myocardial revascularization, acute coronary syndrome, acute congestive heart failure, or death</td>
<td>133</td>
<td>19</td>
<td>13.1</td>
<td>3.8–44.6</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

* Adjusted hazard ratio.
NR = not reported.
Significant association with mortality even after **12 months** postop

**Fig. 4.** Adjusted odds ratio for an increased postoperative troponin measurement to predict all-cause mortality based on duration of follow-up.
Association Between Postoperative Troponin Levels and 30-Day Mortality Among Patients Undergoing Noncardiac Surgery

The Vascular Events In Noncardiac Surgery Patients Cohort Evaluation (VISION) Study Investigators

Context  Of the 200 million adults worldwide who undergo noncardiac surgery each year, more than 1 million will die within 30 days.

Objective  To determine the relationship between the peak fourth-generation troponin T (TnT) measurement in the first 3 days after noncardiac surgery and 30-day mortality.

JAMA. 2012;307(21):2295-2304
VISION design and methods

• Prospective, international, cohort study
• Eligibility criteria
  – >45 yrs undergoing in-hospital noncardiac surgery
• Sampling method
  – representative sample
• Participating countries
  – North and South America, Europe, Asia, Africa, Australia
• Sample size – 40,000 patients
  – after first 15,000 patients
    • event rate was >3 X expected
    • switched from 4th gen Trop T to 5th gen (hs) Trop T
      – report results related to 4th generation Trop T
VISION method and design

• Objective:
  – Determine the relationship between portop troponin T and 30-day mortality
  – Troponin T measured at 6-12 hrs post-op, day 1, day 2, day 3 postop
• Cox regression analysis
  – determine the prognostic signification of postop trop T
  – determine the predictive factors for mortality at 30 days
• Determine the troponin cutoff that carried a change in prognostic
# VISION population

<table>
<thead>
<tr>
<th>Type of surgery</th>
<th>No of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major orthopedic</td>
<td>3094 (20.4%)</td>
</tr>
<tr>
<td>Major general</td>
<td>3076 (20.3%)</td>
</tr>
<tr>
<td>Major urologic or gynecology</td>
<td>1888 (12.5%)</td>
</tr>
<tr>
<td>Major neurosurgery</td>
<td>888 (5.9%)</td>
</tr>
<tr>
<td>Major vascular</td>
<td>504 (3.3%)</td>
</tr>
<tr>
<td>Major thoracic</td>
<td>376 (2.5%)</td>
</tr>
<tr>
<td>Low-risk</td>
<td>5960 (39.4%)</td>
</tr>
</tbody>
</table>
VISION - population

- **Age**

<table>
<thead>
<tr>
<th>Baseline clinical variable</th>
<th>Participants (N=15,133)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>45-64 years old</td>
<td>7697 (50.9%)</td>
</tr>
<tr>
<td>65-74 years old</td>
<td>3779 (25.0%)</td>
</tr>
<tr>
<td>≥75 years old</td>
<td>3657 (24.2%)</td>
</tr>
</tbody>
</table>
Predictive value of postop troponin

Figure 2. Kaplan-Meier Estimates of 30-Day Mortality Based on Peak Troponin T Values

<table>
<thead>
<tr>
<th>Peak troponin T, ng/mL</th>
<th>0.01</th>
<th>0.02</th>
<th>0.03-0.29</th>
<th>0.30</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. at risk</td>
<td>13376</td>
<td>492</td>
<td>1121</td>
<td>142</td>
</tr>
<tr>
<td>Days After Surgery</td>
<td>13348</td>
<td>492</td>
<td>1103</td>
<td>136</td>
</tr>
<tr>
<td>Cumulative Hazard</td>
<td>13300</td>
<td>489</td>
<td>1075</td>
<td>129</td>
</tr>
<tr>
<td>Days After Surgery</td>
<td>13271</td>
<td>485</td>
<td>1058</td>
<td>127</td>
</tr>
<tr>
<td>Cumulative Hazard</td>
<td>13250</td>
<td>480</td>
<td>1036</td>
<td>121</td>
</tr>
<tr>
<td>Days After Surgery</td>
<td>13230</td>
<td>477</td>
<td>1030</td>
<td>118</td>
</tr>
<tr>
<td>Cumulative Hazard</td>
<td>13209</td>
<td>473</td>
<td>1018</td>
<td>117</td>
</tr>
</tbody>
</table>

16.9% 9.3% 4.0% 1.0%
### 30-day mortality prediction model including postop troponin

<table>
<thead>
<tr>
<th>Facteurs de risque potentiels</th>
<th>aHR (95% CI)</th>
<th>P value</th>
<th>Population attributable risk* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 65-75</td>
<td>1.57 (1.11-2.23)</td>
<td>0.01</td>
<td>39.7 % (26.2-52.8)</td>
</tr>
<tr>
<td>Age ≥ 75</td>
<td>2.37 (1.71-3.28)</td>
<td>&lt;.001</td>
<td>-</td>
</tr>
<tr>
<td>High risk CAD (6 months)</td>
<td>2.13 (1.17-3.88)</td>
<td>0.01</td>
<td>2.4 % (0.0-5.4)</td>
</tr>
<tr>
<td>History of PVD</td>
<td>1.83 (1.27-2.66)</td>
<td>0.001</td>
<td>7.9 % (2.8-13.0)</td>
</tr>
<tr>
<td>History of Stroke</td>
<td>1.82 (1.29-2.57)</td>
<td>&lt;.001</td>
<td>7.2 % (2.5-12.1)</td>
</tr>
<tr>
<td>COPD</td>
<td>2.07 (1.54-2.78)</td>
<td>&lt;.001</td>
<td>12.6 % (6.7-18.5)</td>
</tr>
<tr>
<td>Active cancer</td>
<td>2.32 (1.74-3.10)</td>
<td>&lt;.001</td>
<td>20.6 % (12.6-28.6)</td>
</tr>
<tr>
<td>Urgent surgery</td>
<td>3.55 (2.73-4.60)</td>
<td>&lt;.001</td>
<td>32.9 % (25.8-40.1)</td>
</tr>
<tr>
<td>Major general surgery</td>
<td>3.16 (1.59-6.29)</td>
<td>0.001</td>
<td>23.6 % (15.9-31.3)</td>
</tr>
<tr>
<td>Major Neurosurgery</td>
<td>3.44 (1.55-7.62)</td>
<td>0.002</td>
<td>5.6 % (2.3-9.2)</td>
</tr>
<tr>
<td>TnT max 0.02</td>
<td>2.41 (1.33-3.77)</td>
<td>&lt;.001</td>
<td>41.8 % (34.5-49.0)</td>
</tr>
<tr>
<td>TnT max 0.03-0.29</td>
<td>5.00 (3.72-6.76)</td>
<td>&lt;.001</td>
<td>-</td>
</tr>
<tr>
<td>TnT max ≥ 0.30</td>
<td>10.48 (6.25-16.62)</td>
<td>&lt;.001</td>
<td>-</td>
</tr>
</tbody>
</table>

*The Population Attributable Risk (or Population Attributable Fraction) indicates the number (or proportion) of cases that would not occur in a population if the factor were eliminated. The attributable risk in a population depends on the prevalence of the risk factor and the strength of its association (relative risk) with the disease.
## Prognostic value of postop troponin

<table>
<thead>
<tr>
<th>Max troponin T</th>
<th>Incidence</th>
<th>aHR (95% CI) mortalité à 30 jours</th>
</tr>
</thead>
<tbody>
<tr>
<td>TnT max 0.02</td>
<td>3.3%</td>
<td>2.41 (1.33-3.77)</td>
</tr>
<tr>
<td>TnT max 0.03-0.29</td>
<td>7.4%</td>
<td>5.00 (3.72-6.76)</td>
</tr>
<tr>
<td>TnT max ≥ 0.30</td>
<td>0.9%</td>
<td>10.48 (6.25-16.62)</td>
</tr>
</tbody>
</table>
## Timing mortality

<table>
<thead>
<tr>
<th>Peak TnT value</th>
<th>Median days to death (IQR)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.02 µg/L</td>
<td>13.5 (8.5-20)</td>
<td></td>
</tr>
<tr>
<td>0.03-0.29 µg/L</td>
<td>9.0 (3.5-16)</td>
<td>0.013</td>
</tr>
<tr>
<td>≥0.30 µg/L</td>
<td>6.5 (1.5-15)</td>
<td></td>
</tr>
</tbody>
</table>

- 26.6% death after discharge
- median between discharge and mortality is 11.0 days (IQR, 4.0-15.0 d)
Myocardial Injury after Noncardiac Surgery

A Large, International, Prospective Cohort Study Establishing Diagnostic Criteria, Characteristics, Predictors, and 30-day Outcomes

The Vascular events In noncardiac Surgery patients cOhort evaluatioN (VISION) Writing Group, on behalf of The Vascular events In noncardiac Surgery patients cOhort evaluatioN (VISION) Investigators

(Anaesthesiology 2014; 120:564-78)
MINSD diagnostic criteria

- Cox regression analysis
  - dependent variable – 30-day mortality
  - independent variables
    - preop and surgical variables independently associated with death in 1st analyses
    - time dependent post op variables (stroke, PE, DVT, pneumonia, sepsis, infection)
    - proposed MINS variables
      - post-op peak TnT ≥0.04 with clinical feature
      - post-op peak TnT ≥0.04 with no clinical feature,
      - post-op peak TnT = 0.03, post-op peak TnT =0.02
      - post-op peak TnT ≤0.01)
Cox model based on 15,065 patients and 260 deaths

<table>
<thead>
<tr>
<th>Proposed MINS variables</th>
<th>Adjusted HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak TnT ≥0.04 with clinical feature</td>
<td>4.82 (3.40-6.84)</td>
</tr>
<tr>
<td>Peak TnT ≥0.04 with no clinical feature</td>
<td>3.30 (2.26-4.81)</td>
</tr>
<tr>
<td>Peak TnT = 0.03</td>
<td>4.30 (2.68-6.91)</td>
</tr>
<tr>
<td>Peak TnT = 0.02</td>
<td>1.61 (0.91-2.86)</td>
</tr>
</tbody>
</table>

Therefore definition of MINS is
- TnT ≥0.03 due to ischemic etiology
- 100 million adults ≥45 y/o have surgery annually and 8% MINS risk
## Impact des MINS

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Patients sans MINS N=13823</th>
<th>Patients avec MINS N=1189</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Nonfatal c arrest</td>
<td>8 (0.06)</td>
<td>10 (0.8)</td>
</tr>
<tr>
<td>CHF</td>
<td>137 (1.0)</td>
<td>112 (9.4)</td>
</tr>
<tr>
<td>Stroke</td>
<td>58 (0.4)</td>
<td>23 (1.9)</td>
</tr>
<tr>
<td>Mortality</td>
<td>147 (1.1)</td>
<td>117 (9.8)</td>
</tr>
<tr>
<td>Composite of events above</td>
<td>325 (2.4)</td>
<td>224 (18.8)</td>
</tr>
</tbody>
</table>
### Post-op variables predicting death at 30 days after surgery

<table>
<thead>
<tr>
<th>Variable</th>
<th>Incidence (%)</th>
<th>Adjusted HR (95% CI)</th>
<th>PAR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MINS (TnT ≥0.03)</td>
<td>1200 (8.0)</td>
<td>3.87 (2.96-5.08)</td>
<td>34.0% (26.6-41.5)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>812 (5.4)</td>
<td>7.18 (5.17-9.97)</td>
<td>30.5% (23.7-37.2)</td>
</tr>
<tr>
<td>stroke</td>
<td>81 (0.5)</td>
<td>3.50 (2.05-5.97)</td>
<td>4.5% (1.3-7.8)</td>
</tr>
<tr>
<td>PE</td>
<td>95 (0.6)</td>
<td>6.11 (3.18-11.74)</td>
<td>3.5% (0.9-6.2)</td>
</tr>
</tbody>
</table>
MINS timing and presentation

- MINS occur in early postop period
  - 87.1% elevation in first 48 hours postop

- Majority are asymptomatic
  - 84.2% without ischemic symptoms
    - Analgesia
    - Transient ECG changes
Should you monitor periop trops?

- MINS that would probably go undetected without trop monitoring
  - 84.2% asymptomatic – won’t trigger ECG request
  - 9.0% 30-day risk of mortality
  - 3rd Universal Definition of MI and Up To Date now recommend monitoring troponins after Sx
Cost consequence of Trop monitoring

- VISION data
- Estimated incremental cost to detect an additional MINS was <$1,300 CAD in selected populations
  - patients aged ≥65 years, undergoing urgent/emergent surgery, or with a history of cardiovascular disease
- By way of comparison, cost of cancer screening programs
  - US $12,580 per detected breast cancer
  - US $15,885 per detected cervical cancer
  - US $10,086 per detected prostate cancer
Treatment options for MINS

• POISE multivariable regression analysis among patients suffering MINS
  • identified 2 drugs associated with reduced 30-day risk of death
    • Aspirin - adjusted OR, 0.54; 95% CI, 0.29-0.99
    • Statin - adjusted OR, 0.26; 95% CI, 0.13-0.54

Treatment options for MINS

• French propensity matched study of 1 year outcome (survival without MI, coronary revasc, or CHF requiring hospitalization)
  – 66 MINS patients and 132 matched non-MINS patients (controls)
  – among MINS patients
    • 43 received therapeutic intensification of \( \geq 1 \) of 4 cardiac medications (ASA, statin, beta-blocker, ACE-I)
    • 23 patients did not receive therapeutic intensification after MINS
  – MINS patients not receiving therapeutic intensification had
    • HR, 1.77; 95% CI, 1.13-2.42
  – MINS patients receiving therapeutic intensification had
    • HR, 0.63; 95% CI, 0.10-1.19
How are MINS that probably would go undetected managed (VISION data)

<table>
<thead>
<tr>
<th>Medication</th>
<th>Preop usage</th>
<th>During first 3 days after Sx</th>
<th>At discharge from hospital</th>
<th>At 30 days post-op</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA</td>
<td>26%</td>
<td>33%</td>
<td>37%</td>
<td>37%</td>
</tr>
<tr>
<td>Statin</td>
<td>32%</td>
<td>31%</td>
<td>35%</td>
<td>34%</td>
</tr>
<tr>
<td>ACE-I/ARB</td>
<td>45%</td>
<td>39%</td>
<td>44%</td>
<td>44%</td>
</tr>
</tbody>
</table>
First trial on how to treat MINS

MANAGE
Management of myocardial injury After NonCardiac surgery
MANAGE Trial

• Primary efficacy objectives
• In MINS patients, to determine effect of
  – dabigatran versus placebo
    • on risk of major vascular complication
  – omeprazole versus placebo
    • on risk of major upper GI complication
MANAGE Trial design

- RCT of 3200 MINS patients
  - randomized to dabigatran 110 mg BID or placebo
  - within 5 days of suffering MINS **
- Partial 2X2 factorial design
  - patients not already on PPI (n~1900)
    - randomize to omeprazole 20 mg OD or placebo
- Blind investigator initiated trial
- F/U 6-24 months
Rationale for MANAGE Trial

- Growing evidence supporting coronary artery thrombosis
- post-operative environment
  - pro-coagulant, pro-inflammatory, elevated catecholamines
- Cath study - consecutive PACS patients and randomly selected non-operative ACS patients and stable CAD patients

<table>
<thead>
<tr>
<th>Outcome</th>
<th>PACS n=120</th>
<th>Non-op ACS n=120</th>
<th>Stable CAD n=240</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ambrose’s II lesions</td>
<td>45%</td>
<td>57%</td>
<td>16%</td>
</tr>
<tr>
<td>Time to cath</td>
<td>5.5 days</td>
<td>1.3 days</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>15%</td>
<td>4%</td>
<td></td>
</tr>
</tbody>
</table>
Short-term impact of antithrombotic on non-op MI

- Acute NSTEMI
  - RCTs of heparin + ASA vs. ASA alone
    - meta-analysis 2919 patients
      - heparin reduced 7 day risk of death, MI
        » OR 0.53; 95% CI, 0.38-0.73

- Acute STEMI treated with lytic and ASA
  - addition of LMWH vs control
    - meta-analysis 16,943 patients
      - LMWH reduced risk of in hospital
        » MI - OR 0.72; 95% CI, 0.58-0.90)
        » Death - OR, 0.90; 95% CI, 0.80 to 0.99
Long-term impact of antithrombotic on non-op MI

- Warfarin +ASA vs. ASA alone
  - M-A 7836 patients after ACS f/u 3 months to 5 yrs
  - reduction in death, MI, stroke
    - OR, 0.73; 95% CI, 0.63-0.84
  - increased risk of bleeding
    - OR, 2.32; 95% CI, 1.63-3.29
Rational for dabigatran 110 mg BID for MANAGE

- Non-inferior to warfarin in preventing thrombo-embolic events
- No difference to warfarin in preventing MI
- Less unstable angina
- Less bleeding
  - major
  - life-threatening
  - intracranial
- major and GI in comparison to 150 mg dabigatran
Rational for omeprazole in MANAGE

- Major bleeding after MI increases mortality and major vascular complications
- 7.6% of MINS patients suffer GI bleed in first 30 days
- ASA and dabigatran increase risk of gastrointestinal bleeding and dyspepsia
- Omeprazole reduces risk of GI bleeds and dyspepsia and increases drug compliance
Issue of VTE prophylaxis in MANAGE

• Patients can start dabigatran study drug up to 5 days after MINS
  – usually post-op day 7

• Recommended that all patients in MANAGE be treated with aspirin for cardiovascular prevention and VTE prophylaxis
PEP Trial

- 13,356 patients undergoing surgery for hip fracture, and
  4,088 patients undergoing elective hip or knee arthroplasty
- Intervention:
  - Aspirin 160 mg daily aspirin or placebo, started preoperatively and continued for 35 days.
PEP Trial

- Aspirin reduced risk of:
  - PE (HR, 0.57; 95% CI, 0.40-0.82),
  - fatal PE (HR, 0.42, 95% CI, 0.24-0.73), and
  - DVT (HR, 0.71; 95% CI, 0.52-0.97)

- PE Mortality in aspirin group = 0.002%
- Overall PE mortality = 0.004%
Aspirin Versus Low-Molecular-Weight Heparin for Extended Venous Thromboembolism Prophylaxis After Total Hip Arthroplasty

- Multicenter randomized, controlled trial with a noninferiority design
- 778 patients with elective unilateral THA
- Intervention:
  - Initial 10 days of dalteparin prophylaxis after elective THA for all patients followed by
  - dalteparin versus aspirin for 28 days
- Results:
  - ASA non-inferior to LMWH for VTE prophylaxis

ASA

- Grade 1B in major orthopedic surgery
- same as: LMWH, fondaparinux, apixaban, dabigatran, rivaroxaban, LDUH, and adjusted dose VKA
POISE-2 aspirin results

HR (95% CI) 0.89 (0.61-1.28); P=0.52

Only 113 VTE events
### Main Results: POISE-2

<table>
<thead>
<tr>
<th>Event</th>
<th>ASA (n=4998)</th>
<th>Placebo (n=5013)</th>
<th>Hazard ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VTE – no. (%)</td>
<td>53 (1.1)</td>
<td>60 (1.2)</td>
<td>0.89 (0.61-1.28)</td>
<td>0.520</td>
</tr>
<tr>
<td>DVT</td>
<td>25 (0.5)</td>
<td>35 (0.7)</td>
<td>0.73 (0.42-1.20)</td>
<td>0.202</td>
</tr>
<tr>
<td>PE</td>
<td>33 (0.7)</td>
<td>31 (0.6)</td>
<td>1.07 (0.65-1.74)</td>
<td>0.794</td>
</tr>
</tbody>
</table>
## Meta-analysis ASA for DVT prevention

32,108 surgical patients; 1,675 events

<table>
<thead>
<tr>
<th>Studies</th>
<th>Aspirin</th>
<th>Placebo</th>
<th>Odds Ratio</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>General Surgery</td>
<td>278</td>
<td>1434</td>
<td>396</td>
<td>1459</td>
</tr>
<tr>
<td>Elective Orthopedics</td>
<td>160</td>
<td>427</td>
<td>232</td>
<td>436</td>
</tr>
<tr>
<td>Traumatic Orthopedics</td>
<td>163</td>
<td>454</td>
<td>186</td>
<td>444</td>
</tr>
<tr>
<td>PEP</td>
<td>84</td>
<td>8726</td>
<td>116</td>
<td>8718</td>
</tr>
<tr>
<td>POISE-2</td>
<td>25</td>
<td>4998</td>
<td>35</td>
<td>5012</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Studies</th>
<th>Events</th>
<th>Total</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>710/16039</td>
<td>965/16069</td>
<td>0.66 [0.58, 0.75]</td>
</tr>
</tbody>
</table>

Heterogeneity: P = 0.33; I² = 13%

Test for overall effect: Z = 6.46 (P < 0.00001)

OR 0.66; 95% CI 0.58-0.75, heterogeneity p=0.33
Meta-analysis ASA for PE prevention

36,345 surgical patients; 375 events

<table>
<thead>
<tr>
<th>Studies</th>
<th>Events</th>
<th>Total</th>
<th>Events</th>
<th>Total</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Surgery</td>
<td>16</td>
<td>3408</td>
<td>58</td>
<td>3419</td>
<td>0.27 [0.16, 0.48]</td>
<td></td>
</tr>
<tr>
<td>Elective Orthopedics</td>
<td>14</td>
<td>529</td>
<td>29</td>
<td>537</td>
<td>0.48 [0.25, 0.91]</td>
<td></td>
</tr>
<tr>
<td>Traumatic Orthopedics</td>
<td>14</td>
<td>504</td>
<td>34</td>
<td>494</td>
<td>0.39 [0.20, 0.73]</td>
<td></td>
</tr>
<tr>
<td>PEP</td>
<td>55</td>
<td>8726</td>
<td>91</td>
<td>8718</td>
<td>0.60 [0.43, 0.84]</td>
<td></td>
</tr>
<tr>
<td>POISE-2</td>
<td>33</td>
<td>4998</td>
<td>31</td>
<td>5012</td>
<td>1.07 [0.65, 1.75]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>0.52 [0.33, 0.80]</strong></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>132/18165</td>
<td>243/18180</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: P = 0.005; I² = 73%
Test for overall effect: Z = 2.93 (P = 0.003)

OR 0.52; 95% CI 0.33-0.80, heterogeneity p=0.005
**POISE-2 and PEP for VTE: Anticoagulant prophylaxis**

23,588 surgical patients; 376 events

<table>
<thead>
<tr>
<th>Studies</th>
<th>Aspirin Events</th>
<th>Placebo Events</th>
<th>Odds Ratio, M-H, Random, 95% CI</th>
<th>Odds Ratio, M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticoag POISE-2 &amp; PEP</td>
<td>80</td>
<td>112</td>
<td>0.70 [0.52, 0.94]</td>
<td></td>
</tr>
<tr>
<td>No anticoag POISE-2 &amp; PEP</td>
<td>73</td>
<td>111</td>
<td>0.69 [0.51, 0.93]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>153/ 11677</strong></td>
<td><strong>223/ 11911</strong></td>
<td><strong>0.70 [0.57, 0.86]</strong></td>
<td><strong>Favors aspirin</strong></td>
</tr>
</tbody>
</table>

Heterogeneity: \( P = 0.95; I^2 = 0\%

Test for overall effect: \( Z = 3.42 \) (\( P = 0.0006 \))

OR 0.70; 95% CI 0.57-0.86, heterogeneity \( p=0.95 \)
Interpretation

• Updated meta-analysis confirms the efficacy of aspirin for VTE prevention in surgical patients
VTE prophylaxis in MANAGE

- Not changing all surgical VTE prophylactic care
  - just in MINS patients
- When MINS occurs need to shift focus to MINS as high short and intermediate-term mortality
- Alternative effective VTE prophylaxis methods
VTE prophylaxis

Pulmonary Embolism

PEP Trial

- 0.2% mortality

VISION

- 10% mortality

MINS
Concerns about dabigatran and bleeding

• What is rate of bleeding in patients treated with dabigatran?
  – compared with warfarin
  – following major surgery

• What are outcomes after bleeding with dabigatran?
Intracranial Hemorrhage

- Dabigatran 110 mg BID
- Dabigatran 150 mg BID
- Rivaroxaban 20 mg QD
- Apixaban 5 mg BID

<table>
<thead>
<tr>
<th>Comparator</th>
<th>HR (95% CI)</th>
<th>Superiority p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran 110 mg BID</td>
<td>0.50</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dabigatran 150 mg BID</td>
<td>0.75</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Rivaroxaban 20 mg QD</td>
<td>1.25</td>
<td>0.02</td>
</tr>
<tr>
<td>Apixaban 5 mg BID</td>
<td>1.00</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Major Bleeding

- Dabigatran 110 mg BID
- Dabigatran 150 mg BID
- Rivaroxaban 20 mg QD
- Apixaban 5 mg BID

<table>
<thead>
<tr>
<th>Comparator</th>
<th>HR (95% CI)</th>
<th>Superiority p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran 110 mg BID</td>
<td>0.25</td>
<td>0.003</td>
</tr>
<tr>
<td>Dabigatran 150 mg BID</td>
<td>1.00</td>
<td>0.31</td>
</tr>
<tr>
<td>Rivaroxaban 20 mg QD</td>
<td>0.75</td>
<td>0.58</td>
</tr>
<tr>
<td>Apixaban 5 mg BID</td>
<td>0.50</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Major and intracranial bleeding**

### Intracranial Hemorrhage

- **Dabigatran 110 mg BID**
- **Dabigatran 150 mg BID**
- **Rivaroxaban 20 mg QD**
- **Apixaban 5 mg BID**

Superiority p-value:
- Dabigatran 110 mg BID: \(<0.001\)
- Dabigatran 150 mg BID: \(0.02\)
- Rivaroxaban 20 mg QD: \(<0.001\)
- Apixaban 5 mg BID: \(<0.001\)

Intracranial bleeding RR: 0.31 (0.20-0.47)

### Major Bleeding

- **Dabigatran 110 mg BID**
- **Dabigatran 150 mg BID**
- **Rivaroxaban 20 mg QD**
- **Apixaban 5 mg BID**

Superiority p-value:
- Dabigatran 110 mg BID: \(0.003\)
- Dabigatran 150 mg BID: \(0.58\)
- Rivaroxaban 20 mg QD: \(<0.001\)
- Apixaban 5 mg BID: \(<0.001\)

Major bleeding RR: 0.80 (0.69-0.93)

---

RE-LY patients going to surgery bleeding outcomes

- 1 in 4 patients had surgery
  - 1,487 dabigatran 110 mg patients and 1,558 warfarin patients had surgery
- Dabigatran patients had last dose closer to surgery than warfarin patients
  - 49 (IQR, 35-85) hours vs. 114 (87 –144) hours, P<0.001
  - no difference in CV mortality (0.6% vs. 0.5%, p=0.5) up to 30 days after surgery
**Major bleeding in RE-LY patients undergoing surgery**

<table>
<thead>
<tr>
<th>Surgery</th>
<th>Dabigatran 110, %</th>
<th>Warfarin, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Within 24 h</td>
<td>2.8%</td>
<td>15.4%</td>
</tr>
<tr>
<td>Urgent</td>
<td>17.8%</td>
<td>21.6%</td>
</tr>
<tr>
<td>Elective</td>
<td>2.8%</td>
<td>3.3%</td>
</tr>
<tr>
<td>Major</td>
<td>6.1%</td>
<td>7.8%</td>
</tr>
<tr>
<td>Minor</td>
<td>1.9%</td>
<td>1.8%</td>
</tr>
</tbody>
</table>

MANAGE doses of dabigatran in major orthopedic surgery: major bleeding

- 10,240 patients in 4 RCTs
- dabigatran 110 mg versus enoxaparin for VTE prophylaxis
- No difference in bleeding
- dabigatran started 4-6 hours post-op
  - much earlier than in MANAGE
### MANAGE doses of dabigatran in major orthopedic surgery: major bleeding

<table>
<thead>
<tr>
<th>Study / Trial Name</th>
<th>Time anticoagulant started after surgery</th>
<th>Major Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-NOVATE I Trial (Lancet. 2007; 370:949-56)</td>
<td>1-4 hours</td>
<td>Dabigatran 220 mg once daily</td>
</tr>
<tr>
<td>RE-MODEL Trial (Throm Haemost, 2007; 5: 2178-2185)</td>
<td>1-4 hours</td>
<td>Enoxaparin 40 mg once daily</td>
</tr>
<tr>
<td>RE-MOBILIZE Trial (Journal of Arthroplasty, 2009, 24:1-9)</td>
<td>6-12 hours</td>
<td>Dabigatran 220 mg once daily</td>
</tr>
<tr>
<td>RE-NOVATE II Trial (Thromb Haemost, 2011; 105:721-9)</td>
<td>1-4 hours</td>
<td>Enoxaparin 40 mg once daily</td>
</tr>
</tbody>
</table>
MANAGE doses of dabigatran in major orthopedic surgery: major bleeding

Questions

• What is the rate of bleeding in patients treated with dabigatran?
  – Compared with warfarin
  – Following major surgery

• What are outcomes after bleeding with dabigatran?
Dabigatran vs. warfarin is associated with better outcomes after bleeding

The Kaplan–Meier analysis suggest reduced risk for death with dabigatran vs warfarin during 30 days after bleeding (P=0.052)

Conclusions

- MINS is strong independent predictor of 30-day mortality after noncardiac surgery
- Without routine monitoring many MINS would potentially go undetected
- 3rd Universal Definition of MI and Up To Date now recommend monitoring troponins after Sx
Conclusions

- MANAGE Trial will inform treatment and pathophysiology
- Aspirin is reasonable alternative to anticoagulant for VTE prophylaxis in patients suffering MINS
- Dabigatran 110mg BID compared to warfarin has less intracranial and major bleeding and better outcomes when patients bleed or require surgery
- Dabigatran 110 mg BID has no difference in bleeding compared to enoxaparin
- MANAGE is the first trial to address MINS
- We need your help and support to conduct MANAGE Trial
NSTEMI type I vs NSTEMI type II

- NSTEMI Type I = coronary artery thrombosis
- NSTEMI Type II = mismatch supply-demand

Patients with type 2 MIs were 6.9 times more likely to die than those with type 1 MIs ($p < 0.001$)

Type 2 MIs occurring during a severe medical illness did not differ significantly from those type 2 MIs following non-cardiac surgery with respect to mortality (OR 0.75; 95%, CI 0.42 - 1.34)

World Journal of Cardiovascular Diseases, 2012, 2, 237-241
NSTEMI type I vs NSTEMI type II


**Figure 1. In-hospital complications.** In-hospital complications of patients with type-I compared to patients with type-II MI. (** denotes significant difference with p<0.001). Pul. edema - pulmonary edema Re-MI - recurrent myocardial infarction AF - atrial fibrillation TIA - transient ischemic attack ARF - acute renal failure.
NSTEMI type I vs NSTEMI type II

# NSTEMI type I vs NSTEMI type II

**Table 6.** Guideline-directed medications at discharge.

<table>
<thead>
<tr>
<th></th>
<th>Type-I (n = 2691)</th>
<th>Type-II (n = 127)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>97</td>
<td>86</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>86</td>
<td>50</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>83</td>
<td>72</td>
<td>0.001</td>
</tr>
<tr>
<td>ACE-I/ARB</td>
<td>79</td>
<td>69</td>
<td>0.006</td>
</tr>
<tr>
<td>HMG-CoA reductase inhibitors</td>
<td>94</td>
<td>87</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Historical perspective

- VA Hypertension Trial - JAMA 1967;202:116-22
- US veterans with DBPs 115-129 randomized to
  - antihypertensive drugs or PLACEBO – f/u 18 months
- Many “experts” believed HTN was essential for brain perfusion
- Primary outcome - death, dissecting/ruptured aortic aneurysm, cerebral hemorrhage/disabling stroke, MI, CHF, retinal hemorrhage + papilledema, and rapidly progressive renal failure
  - 43% placebo group vs 3% in antihypertensive group
- Antihypertensive drugs RRR 93% (78-98); P=0.000000002
Historical perspective

- 35 years ago most cardiologists did not believe nonvalvular AF was risk factor for stroke
  - rather simply nuisance for some patients causing palpatations
- Historical perspective suggests physicians can overlook important diagnoses
  - evidence suggests MINS is prognostically important and overlooked by most physicians
    - due to lack of periop troponin monitoring
  - fragmented nature of perioperative f/u likely facilitates physicians under-appreciating impact of MINS