The Perioperative Management of Antiplatelet Medication

Dr Tom Collyer
Declaration of Interest
Aims

- Scale perioperative myocardial injury
- Indications for antiplatelet therapy – arrival of new antiplatelet agents
- The perioperative clinical dilemma and management
Clinical Scenario

- 84 ♂ - Acute admission following fall
- PC
  - # right hip and elbow
- PMH
  - 12/52 post ACS with PCI
  - x2 DES
  - Hypertensive
  - Thin fail lady
Clinical Scenario

- DH
  - Aspirin 75mg od
  - Ticagrelor 90mg bd
  - Antihypertensive, statin

- SH
  - Well-to-do: son barrister
  - Keen for private treatment
Clinical Scenario

- Seen by orthogeriatrician
  - Stopped Aspirin on the day of surgery
  - Continued Ticagrelor
Clinical Scenario

- Would any of the audience be happy to proceed with surgery?

- Would you be happy to perform regional anaesthesia?
If surgery delayed, how long?

- 1 day
- 2 days
- 5 days
- 7 days
Do any of the audience work in centres where surgeons routinely stop aspirin 7 days preoperatively?

Are the indications for antiplatelet treatment assessed and risks/benefits of stopping discussed?
What’s the Scale of the Problem?

“Infected joint / wound can be devastating but I hardly ever see problems of post operative myocardial ischaemia in my patients”
What’s the Scale of the Problem?

- 200 million adults have major non-cardiac surgery annually worldwide (1)
- Estimated that between 1 to 4 million people will die within 30 days of surgery

What’s the Scale of the Problem?

- 47,000 adult patients having inpatient, non-cardiac surgery
- In hospital mortality of 4%
- 8 million deaths per annum
What’s the Scale of the Problem?

Association Between Postoperative Troponin Levels and 30-Day Mortality Among Patients Undergoing Noncardiac Surgery

- Prospective, international cohort study
- Patients over 45 yrs age having non-cardiac surgery with at least an overnight admission
- Post-operative troponins measured
What’s the Scale of the Problem?

- 15,133 patients
- 30 day mortality: 1.9%
- Clinically significant Trop rise in 11.6% (>0.02)
What’s the Scale of the Problem?

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

<table>
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<tr>
<th>Peak troponin T, ng/mL</th>
<th>Days After Surgery</th>
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<tr>
<td>≤0.01</td>
<td>13376 13348 13300</td>
</tr>
<tr>
<td>0.02</td>
<td>13271 13250 13230</td>
</tr>
<tr>
<td>0.03-0.29</td>
<td>12968 12948 12920</td>
</tr>
<tr>
<td>≥0.30</td>
<td>12658 12638 12618</td>
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What’s the Scale of the Problem?

- **Mortality rates:**
  - TnT < 0.01ng/ml: 1.0%
  - TnT > 0.02ng/ml: 4.0%
  - TnT 0.03 to 0.29ng/ml: 9.3%
  - TnT > 0.30ng/ml: 16.9%

- The majority of events are silent: 60 – 70%
- The majority occur early: 75% within 1 day
What’s the Scale of the Problem?

- 8351 patients included in POISE
- 5.0% MI (11.6% mortality – HR 5.2)
- 75% < 48 hrs
- 65.3% were silent
The Nature of Perioperative Myocardial Ischaemia

Figure 2. Differentiation between myocardial infarction (MI) types 1 and 2 according to the condition of the coronary arteries.

- **Plaque rupture with thrombus**
  - MI Type 1

- **Vasospasm or endothelial dysfunction**
  - MI Type 2

- **Fixed atherosclerosis and supply-demand imbalance**
  - MI Type 2

- **Supply-demand imbalance alone**
  - MI Type 2
Clinical Relevance

“Infected joint / wound can be devastating but I hardly ever see problems of post operative myocardial ischaemia in my patients”
Clinical Relevance

- Higher prevalence than thought
- Atypical presentation
- Often undiagnosed and may precede other postoperative complications:
  - Pneumonia / anastamotic leak etc.
- Antiplatelet management clearly has an important role
POISE 2 is a large, international, placebo-controlled, factorial trial to assess the effect of clonidine and acetylsalicylic acid (ASA) in patients undergoing noncardiac surgery who are at risk of a peri-operative cardiovascular event.
Coronary Artery Disease
Coronary Artery Disease

- Leading cause of death in the Western World

UK:

- 2 million have angina
- 160,000 MI /year
- 1 in 5 deaths men / 1 in 6 deaths women
- £19 billion
PCI Rates in the UK

- 87,676 in 2010
- Rate of increase 7.6%
- Interesting we lag considerably behind Europe and North America
PCI Rates in the UK

Figure 3
Absolute number of PCIs and rates (pmp) for 2010 in the UK.
PCI Rates in the UK

Relevance:

- Increasing number with coronary stents presenting for preoperative assessment
- 5% of patients require urgent non-cardiac surgery within 1 year of PCI
- Decisions about antiplatelet management
Antiplatelets

- Cyclo-oxygenase inhibitors:
  - Aspirin
  - NSAIDS

- Thienopyridine derivatives:
  - Clopidogrel, prasugrel, ticlopidine

- Non-thienopyridine derivatives:
  - Cangrelor, Ticagrelor

- GP IIb/IIIa receptor antagonists:
  - Abciximab, tirofiban, eptifibatide

- Others:
  - Dipyridamole, Statins, Dextrans, PgI2
Antiplatelets

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Antiplatelets preoperatively

**Indication for treatment:**
- Primary prevention cardiovascular events
- Secondary prevention of further cardiovascular events
- PCI - Coronary stenting
Aspirin for primary prevention
Antiplatelets for secondary Prevention

- Aspirin or Clopidogrel
  - Patients who survive a occlusive cardiovascular event, significant reduction in subsequent vascular events (22%)
    - Myocardial infarction
    - Stroke
    - Vascular death
  - Modest but significant improvement Clopidogrel cf. Aspirin

- Antithrombotic Trialists’ Collaboration: BMJ 2002
Dual Antiplatelet Therapy (DAPT) and Coronary Stenting
Stent re-stenosis

- **BMS (1986):**
  - Usually due to neointimal hyperplasia
  - Metallic stent only exposed for short period

- **DES (2003):**
  - Hyperplasia inhibited exposing bare metal for much longer periods

- **Bare metal and damaged endothelium is highly thrombogenic**
  - If occurs: 50% chance MI, 20% chance mortality
Dual Antiplatelet Therapy

- **BMS:**
  - Clopidogrel: 6 - 12 weeks
  - Aspirin: Life long

- **DES:**
  - Clopidogrel: 1 year
  - Aspirin: Life long
Dual Antiplatelet Therapy

- **BMS:**
  - Clopidogrel: 3 months
  - Aspirin: Life long

- **DES:**
  - Clopidogrel: 1 year
  - Aspirin: Life long
Despite DAPT, 15% of patients re-hospitalised in one year due to cardiovascular complication. Term: ‘treatment failure’

What degree is this failure related to inadequate platelet inhibition?
Clopidogrel Resistance
Clopidogrel Resistance

- Genetic polymorphism CYP2C19
  - Up to 14% are poor metabolisers
  - x3.5 increased risk of major adverse events

- Number of other issues:
  - Poor compliance – up to 15%
  - Poor absorption
  - Drug interactions
    - PPI
  - DM/obese/smokers
Clopidogrel Resistance – FDA black box warning

FDA NEWS RELEASE
For Immediate Release: March 12, 2010

Media Inquiries: Sandy Walsh, 301-795-4659, sandw.walsh@fda.hhs.gov
Consumer Inquiries: 888-INFO-FDA.

FDA Announces New Boxed Warning on Plavix.
Alerts patients, health care professionals to potential for reduced effectiveness

The U.S. Food and Drug Administration today added a boxed warning to the anti-blood clotting drug Plavix (clopidogrel), alerting patients and health care professionals that the drug can be less effective in people who cannot metabolize the drug to convert it to its active form.

Plavix reduces the risk of heart attack, unstable angina, stroke, and cardiovascular death in patients with cardiovascular disease by making platelets less likely to form blood clots. Plavix does not have its anti-platelet effects until it is metabolized into its active form by the liver enzyme, CYP2C19.
Newer Agents

Prasugrel (Efient)

Ticagrelor (Brilinta)
Prasugrel

- Novel 3rd generation thienopyridine
- Prodrug
Prasugrel

- Novel 3rd generation thienopyridine
  - Prodrug
- More consistent and potent blocker of the platelet P2Y12 receptor
- Action irreversible
Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON-TIMI 38): double-blind, randomised controlled trial

Gilles Montalescot, Stephen D Wiviott, Eugene Braunwald, Sabine A Murphy, C Michael Gibson, Carolyn H McCabe, Elliott M Antman, for the TRITON-TIMI 38 Investigators

Summary

Background Mechanical reperfusion with stenting for ST-elevation myocardial infarction (STEMI) is supported by dual antiplatelet treatment with aspirin and clopidogrel. Prasugrel, a potent and rapid-acting thienopyridine, is a potential alternative to clopidogrel. We aimed to assess prasugrel versus clopidogrel in patients undergoing percutaneous coronary intervention (PCI) for STEMI.
Prasugrel

- 13,608 patients
  - Prasugrel 60mg then 10mg daily + Aspirin
  - Clopidogrel 300mg then 75mg daily + Aspirin
- 2.2% absolute reduction (19% RR)
  - Primary endpoint: CVS death, non fatal MI, nonfatal stroke
  - Largely related to reduction in non fatal MI
- Increase risk of bleeding
Prasugrel

- 3 groups with NO net clinical benefit:
  - History of stroke or TIA – harm
  - > 75 yrs age
  - < 60 kg

- Approved in July 2009
  - With FDA warning
9,300 patients

No significant benefit for Prasugrel versus Clopidogrel in over 75yr or under 75yr
Ticagrelor

- Novel non-thienopyridine
  - Direct acting antagonist

- Produces fast, more consistent and potent blockade of the platelet P2Y12 receptor

- Action reversible
  - Risks v Benefits
Ticagrelor

The NEW ENGLAND JOURNAL of MEDICINE

Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes

Lars Wallentin, M.D., Ph.D., Richard C. Becker, M.D., Andrzej Budaj, M.D., Ph.D., Christopher P. Cannon, M.D., Håkan Emanuelsson, M.D., Ph.D., Claes Held, M.D., Ph.D., Jay Horrow, M.D., Steen Husted, M.D., D.Sc., Stefan James, M.D., Ph.D., Hugo Katus, M.D., Kenneth W. Mahaffey, M.D., Benjamin M. Scirica, M.D., M.P.H., Allan Skene, Ph.D., Philippe Gabriel Steg, M.D., Robert F. Storey, M.D., D.M., and Robert A. Harrington, M.D., for the PLATO Investigators.
Ticagrelor

- 18,624 patients admitted with ACS
  - 11,598 NSTEMI/UA
  - 7026 STEMI
- 64.3% underwent PCI
- DAPT: Clopidogrel versus Ticagrelor
- Primary end point, composite:
  - Death from vascular causes
  - MI
  - Stroke
Ticagrelor

- Primary end point for Ticagrelor:
  - 1.9% absolute reduction
  - 16% relative reduction

- Benefits in both NSTEMI and STEMI

- Benefits in PCI
  - Reduced stent thrombosis

- No difference in the rates of overall major bleeding
  - Increase in non-procedure related bleeding
Ticagrelor

- North American patients (1800):
  - No significant differences between Ticagrelor and Clopidogrel for primary end point

- Aspirin dosing?
  - >300mg

- Approved in July 2011
Antiplatelet Management in ACS

Circulation


Circulation. 2012;126:875-910; originally published online July 16, 2012;
Duration of DAPT

- **UA/NSTEMI without PCI**
  - Aspirin: Life long
  - ADP antagonist: Up to 1 year
Duration of DAPT

- **UA/NSTEMI with PCI – DES**
  - Aspirin: Life long
  - ADP antagonist: 1 year

- **UA/NSTEMI with PCI – BMS**
  - Aspirin: Life long
  - ADP antagonist: up to 1 year
Duration of DAPT

- STEMI with PCI – DES and BMS
  - Aspirin: Life long
  - ADP antagonist: 1 year

- DAPT beyond 1 year?
All Clear So far!
Perioperative Management
Perioperative Management

- Aspirin for Primary and Secondary Prevention:
  - Advice – discontinue 7 days pre-op
  - Why?
Perioperative Management

- **Bleeding risk - Aspirin:**
  - x1.5 increased rate of bleeding
  - No increased severity of bleeding or morbidity.
    (meta-analysis 474 trials)

- **Special consideration:**
  - Intracranial surgery and TURP
  - Ophthalmology: posterior chamber eye surgery
To continue or discontinue aspirin in the perioperative period: a randomized, controlled clinical trial


Impact of preoperative maintenance or interruption of aspirin on thrombotic and bleeding events after elective non-cardiac surgery: the multicentre, randomized, blinded, placebo-controlled, STRATAGEM trial
Perioperative Management

- Aspirin withdrawal
To continue or discontinue aspirin in the perioperative period: a randomized, controlled clinical trial


Impact of preoperative maintenance or interruption of aspirin on thrombotic and bleeding events after elective non-cardiac surgery: the multicentre, randomized, blinded, placebo-controlled, STRATAGEM trial
POISE 2 Study - Peri-operative ischemic evaluation study

POISE 2 is a large, international, placebo-controlled, factorial trial to assess the effect of clonidine and acetylsalicylic acid (ASA) in patients undergoing noncardiac surgery who are at risk of a peri-operative cardiovascular event.

The study is led by the Population Health Research Institute (PHRI) McMaster University, Hamilton Ontario, Canada. The National Coordinator for Australia and New Zealand is Professor Kate Leslie.

There are currently 16 active sites across Australia and New Zealand, as well another 6 sites to come online by the end of 2012. Internationally there are over 6000 patients recruited, with a target of 10,000. The study is expected to finish at the end of 2013.

For further information contact trialsgroup@anzca.edu.au
Perioperative Management

- **Bleeding risk – Clopidrogrel**
  - **Guidance:** stop 7 days preoperatively

- Studies mainly in cardiac surgery
- Little evidence to inform non-cardiac surgery
Perioperative Management

- Bleeding risk – Clopidrogrel
  - J Vasc Surg 2011
  - 10,406 patients:
    - CEA
    - LEB
    - EVAR
    - Open AAA
  - Bleeding requiring reoperation
  - Incidence and volume of blood transfusions
Perioperative Management

- **Bleeding risk – Clopidogrel**
  - No antiplatelet: 19%
  - Aspirin: 69%
  - Clopidogrel: 2.2%
  - DAPT: 9.7

- No difference in reoperation rates, incidence of transfusion and number of units transfused
Perioperative Management

- Clopidogrel – withdrawal
Perioperative Management

- Regional anaesthesia

Guidelines

Regional anaesthesia and patients with abnormalities of coagulation

The Association of Anaesthetists of Great Britain & Ireland
The Obstetric Anaesthetists’ Association
Regional Anaesthesia UK

# Perioperative Management

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<td>Prasugrel</td>
<td>15–30 min</td>
<td>7 days</td>
<td>Not recommended</td>
<td>Not recommended</td>
<td>6 h</td>
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<td>Ticagrelor</td>
<td>2 h</td>
<td>5 days</td>
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Regional anaesthesia:
Coronary Stents:

- 5% patients require surgery < 12 months PCI
  - 6,500 patients in the UK per annum

- Premature disruption of DAPT associated with very high increase in cardiac risk
**Perioperative Management**

- **Coronary Stents:**

- **Non-cardiac surgery < 30days stent:**
  - Interrupted DAPT: 86% mortality
  - Continued DAPT: 5%

- **Non-cardiac surgery with any interruption of DAPT associated with a 37% MI or CVS death**
Perioperative Management

- **Coronary Stents:**

- **Emergency surgery increases adverse cardiovascular events by x3**
Perioperative Management

- **Non-cardiac surgery after PCI:**
  - **PCI and BMS:** (Risk)
    - Vital Sx: postponed for >6 wks (7%)
    - Elective Sx: postponed for >3 months (2.8%)
  - **PCI and DES:**
    - Vital Sx postponed for >3 months (7%)
    - Elective Sx: postponed for >12 months (2-3%)
  - Aspirin life long therapy
Perioperative Management

- Urgent non-cardiac surgery after PCI:
  - Bridging therapy – GPIIb/IIIa antagonists
  - Protocol for managing major haemorrhage if occurs
  - Anaesthetic technique
  - Location for post-op care and monitoring - HDU
  - Plan for post operative antiplatelet management
  - Plan for cardiovascular complications
100% COTTON

MACHINE WASH WARM, INSIDE OUT, WITH LIKE COLORS. USE ONLY NON-CHLORINE BLEACH. TUMBLE DRY MEDIUM. MEDIUM HOT IRON.

DO NOT IRON PRINT!

OR

GIVE IT TO YOUR WIFE

IT'S HER JOB
Clinical Scenario

- Surgery postponed for 2 days
- Platelets and blood available
- GA
- Admitted to HDU post op
- Uncomplicated recovery
Summary

- Perioperative myocardial injury more common than thought - significant
- Increasing numbers of patients with CVD and having PCI
- Changes in DAPT
- Balance of risks verses benefits of antiplatelet therapy perioperatively
- Multidisciplinary approach / Patient consent