Temporary interruption of antiplatelet therapy during surgical procedures exposes patients to thrombotic risk.

Continuation of these agents, however, is associated with an increased risk of bleeding. Managing this can be a particular challenge in the Emergency setting.

An emergency procedure: is one in which life is threatened if not in the operating room where there is No or very limited time for clinical evaluation, typically within <6 hours.

An urgent procedure: is one in which there may be time for a limited clinical evaluation, usually when life or limb is threatened if not in the operating room, typically between 6 and 24 hours.

Risk of Mortality & AMI in Patients on DAPT & Emergency Surgery: Depends upon:

- Previous medical conditions
- Perioperative major bleeding events


Major adverse cardiac and cerebrovascular events are mainly related to previous medical conditions and perioperative major bleeding events.
**Surgical Risk: Based on Patient Condition**

**Clinical Predictors of Increased Perioperative Cardiovascular Risk**

<table>
<thead>
<tr>
<th>Major</th>
<th>Intermediate</th>
<th>Minor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unstable coronary syndromes</td>
<td>Mild angina pectoris (Canadian class I or II)</td>
<td>Advanced age (older than 75 years)</td>
</tr>
<tr>
<td>Acute or recent* MI with evidence of important ischemic risk by clinical symptoms or noninvasive study</td>
<td>Previous MI by history or pathologic Q waves</td>
<td>Abnormal electrocardiography results (e.g., left ventricular hypertrophy, left bundle branch block, ST-T abnormalities)</td>
</tr>
<tr>
<td>Unstable or severe angina (Canadian class III or IV)</td>
<td>Compensated or prior heart failure</td>
<td>Rhythm other than sinus (e.g., atrial fibrillation)</td>
</tr>
<tr>
<td>Decompensated heart failure</td>
<td>Diabetes mellitus (particularly insulin-dependent)</td>
<td>Low functional capacity (e.g., inability to climb one flight of stairs with a bag of groceries)</td>
</tr>
<tr>
<td>Significant arrhythmias</td>
<td>Renal insufficiency</td>
<td>History of stroke</td>
</tr>
<tr>
<td>High-grade atioventricular block</td>
<td></td>
<td>Uncontrolled systemic hypertension</td>
</tr>
<tr>
<td>Symptomatic ventricular arrhythmias in the presence of underlying heart disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supraventricular arrhythmias with uncontrolled ventricular rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe valvular disease</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


**Additional risk factors for stent thrombosis (PCI)**

<table>
<thead>
<tr>
<th>Clinical factors:</th>
<th>Anatomic factors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>• Previous stent thrombosis</strong></td>
<td><strong>• Left main stenting</strong></td>
</tr>
<tr>
<td><strong>• Advanced age (&gt;80 years)</strong></td>
<td><strong>• Bifurcation stenting</strong></td>
</tr>
<tr>
<td><strong>• ACS indication for stent</strong></td>
<td><strong>• Ostial stenting</strong></td>
</tr>
<tr>
<td><strong>• Diabetes</strong></td>
<td><strong>• Small (&lt;3mm) stent</strong></td>
</tr>
<tr>
<td><strong>• Renal impairment</strong></td>
<td><strong>• Long (&gt;18mm) stent</strong></td>
</tr>
<tr>
<td><strong>• Low ejection fraction</strong></td>
<td><strong>• Multiple stents</strong></td>
</tr>
</tbody>
</table>

**There is NO sufficient published data to quantify the risk associated with each factor and clinical judgment is required.**

**Each factor contributes independently; the greater the number of risk factors, the greater the perioperative risk of stent thrombosis.**

An increasing number of potent antiplatelet and anticoagulant medications are being used for the longterm management of cardiac, cerebrovascular, and peripheral vascular conditions.

Management of these medications in the perioperative and peri-injury settings can be challenging for surgeons, mandating an understanding of these agents and the risks and benefits of various management strategies.

Clinical Pharmacology of:-
Aspirin, P2Y12 Inhibitors, and Glycoprotein IIb/IIIa Inhibitors

Yeung LYY, et al., Trauma Surg Acute Care, 2016-000022
Emergent or urgent surgery

During the Re-endothelialization period

Consider continuation of dual antiplatelet therapy (default)

- The role of DAPT is even more important during the Re-endothelialization period after PCI, in which thrombotic risk is greatest due to endothelial injury by ballooning or stent coverage.
- Clearly, non-first-generation DES showed better ischemic protection with less thrombogenicity requiring a shorter period for Re-endothelialization ...... Accordingly, the necessary duration of DAPT after DES placement has been shortened in the new guidelines.
Emergent or urgent surgery during the Re-endothelialization period

**Consider continuation of dual antiplatelet therapy (default)**

- In surgeries with serious bleeding risk, if time is allowed, consider continuation of aspirin (or 3–4 days of cessation, if necessary) and discontinuation of oral P2Y12 inhibitors with bridge therapy using cangrelor, tirofiban, or eptifibatide.
- In cases of non-surgical bleeding, platelet function test may be performed to guide platelet transfusion.
- **Restart** dual antiplatelet therapy as soon as possible following surgery for the intended duration after percutaneous coronary intervention.

Surgery after the Re-endothelialization period

- Continue aspirin, whenever possible (except for intracranial surgery, consider discontinuation for 3–4 days).
- **Discontinue** P2Y12 inhibitor, if necessary (Clopidogrel 5–7 days, Prasugrel 7–10 days, ticagrelor 3–5 days).
- **Platelet function test** may be considered to determine the optimal timing of surgery after discontinuation.
Ideally, the consensus among the:

- anesthesiologist,
- cardiologist,
- surgeon,
- and patient

on perioperative DAPT should be individually tailored to minimize both ischemic and bleeding risks.


The Cardiac Society of Australia and New Zealand

Guidelines for the use of antiplatelet therapy in patients with coronary stents undergoing non-cardiac surgery
Approximately 40% of reported Coronary stent thrombosis cases have occurred in the context of non-cardiac surgery (NCS) performed in patients with coronary artery stents, in whom dual antiplatelet therapy OR Clopidogrel alone has been ceased.

Death/MI/stent thrombosis/urgent revascularization are increased if non-cardiac surgery is performed within 6 weeks of BMS (5-30%).

This event rate among DES group with the early surgery (<6 mon.) who stopped DAPT was 30%.


This event rate occurs in at least 5% of DES patients if dual antiplatelet therapy is stopped and non-cardiac surgery performed within 12 months.

Despite the observation that dual antiplatelet therapy increases the likelihood of bleeding for most surgical procedures, the consequences of this bleeding are generally less significant than those of stent thrombosis.

Wherever possible, continuation of antiplatelet therapy is recommended in patients with prior coronary artery stenting undergoing non-cardiac surgery.

In conclusion,

- The incidence of stent thrombosis at 9 months after successful drug-eluting stent implantation (sirolimus-eluting and paclitaxel-eluting stents) in consecutive real-world patients was 1.3%.
- Premature antiplatelet therapy discontinuation, bifurcation lesions, and low ejection fraction were identified as independent predictors of subacute (<30 days), late (>30 days), and cumulative stent thrombosis.
- In addition, stent length, renal failure, and diabetes were predictors of both subacute and cumulative stent thrombosis.
- In these conditions; DAPT discontinuation increases the incidence of stent thrombosis.
- The clinical consequences were ...... death in 45% of patients and nonfatal MI in the majority of the others.

A meta-analysis of cohort studies of patients receiving clopidogrel prior to urgent cardiac surgery reported:

- An increased risk of bleeding if Clopidogrel was continued.
- A bout 1% increase in the risk of a myocardial infarction if Clopidogrel was ceased.
The aim of this project was to study ACS patients undergoing urgent cardiac surgery (CABG) and how DAPT with ASA and ticagrelor influences:

- perioperative bleeding risks,
- how bleeding can be treated,
- and to investigate if survival after CABG is influenced by antiplatelet therapy.

Cardiac surgery and antiplatelet therapy
© Carl Johan Malm 2017
carl.malm@vgregion.se
Platelets Transfusion

- **A**: Administration of (Low or High) platelet concentrate does NOT improve ADP-induced aggregation (bleeding) after discontinuation of Ticagrelor.
- **B**: Platelet concentrate markedly improves ADP-induced aggregation in patients with ongoing ASA treatment.

**Changes from baseline**
in ADP-dependent platelet aggregation

**After addition of low or high dose of:**

**Aprotinin** and **Tranexamic acid**.

**The addition of Aprotinin (Trasylol = anti-fibrinolytic) increased the ADP-induced aggregation compared to baseline levels in whole blood samples from ACS patients with ongoing ASA and ticagrelor treatment. Low dose aprotinin increase aggregation with **20.4 ± 6.0 % (p = 0.004)**, and high dose increase with **22.6 ± 5.4 % (p < 0.001)**.**

**The addition of Tranexamic acid (Cyklokapron = anti-fibrinolytic) did not alter ADP-induced aggregation (low dose +3.2 ± 7.5 %, p = 0.55; high dose −5.3 ± 6.3 %, (p = 0.50)**
CONCLUSIONS

- The use of Platelet Function Tests can predict severe bleeding complications in ticagrelor-treated cardiac surgery patients.
- There is a large degree of inter-individual variability in recovery of ADP-induced platelet aggregation after discontinuation of ticagrelor in ACS patients awaiting CABG.
- Administration of platelet concentrate does NOT improve ADP-induced aggregation (bleeding) after discontinuation of Ticagrelor.
- Platelet concentrate markedly improves ADP-induced aggregation in patients with ongoing ASA treatment.

<table>
<thead>
<tr>
<th></th>
<th>Univariable Cox reg.</th>
<th>Multivariable Cox reg.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unmatched</td>
<td>PS matched</td>
</tr>
<tr>
<td>DAPT vs ASA</td>
<td>0.58 (0.36-0.92)</td>
<td>0.54 (0.33-0.88)</td>
</tr>
<tr>
<td>Tic. + ASA vs ASA</td>
<td>1.02 (0.57-1.81)</td>
<td>0.79 (0.41-1.53)</td>
</tr>
<tr>
<td>Tic. + ASA vs clop. + ASA</td>
<td>0.34 (0.17-0.70)</td>
<td>0.42 (0.20-0.89)</td>
</tr>
</tbody>
</table>

All-cause mortality after discharge in CABG treated ACS patients of propensity score matched groups.
ASA = Acetylsalicylic acid; Tic. = ticagrelor
Hazard ratios for comparisons of different postoperative antiplatelet treatments calculated with univariable and multivariable Cox regression analysis for both unmatched and propensity score matched groups of patients. 95% confidence intervals are given within parenthesis. PS = propensity score; DAPT = dual antiplatelet therapy; ASA = acetylsalicylic acid; Clop. = clopidogrel; Tic. = ticagrelor
CONCLUSIONS

- **Aprotinin** improves the ADP-dependent platelet aggregation in ticagrelor treated ACS patients. Tranexamic acid was not associated with any improvement in platelet function.
- Less than 30% of ACS patients in Sweden currently discharged with DAPT after CABG surgery.
- Postoperative antiplatelet therapy may influence survival after CABG in patients with ACS.
- DAPT with Ticagrelor and ASA is associated with improved one year survival.
Restoring platelet function

- Platelet **counts** alone demonstrates limited correlation with bleeding risk.
- The indications for providing agents to restore platelet function in the setting of bleeding risk are controversial.
- For ASA-induced platelet dysfunction, intravenous Desmopressin has been shown to restore activity, though little clinical outcome data are available.
- Desmopressin (increasing the levels of vWF as well as coagulant factor VIII) 3 to 5-fold in the setting of ASA therapy, although indications have not been well elucidated.


- **Premature Discontinuation** of antiplatelet therapy resulted in a 29% thrombosis rate and a 45% mortality for patients with stent thrombosis. The calculated HR for all stent thrombosis (subacute and late) was 89.78 for premature antiplatelet therapy Discontinuation.


Platelet Function Test

- Currently, to determine if **platelet transfusion** is indicated, an assessment of **platelet function** should be undertaken.
- Assessing platelet function and its contribution to bleeding risk in elective and emergent settings remains challenging, particularly with the use of aspirin or Clopidogrel.
- Platelet activity comprises 80% of overall clot strength and the remaining 20% is determined by fibrin.
- As such, overall clot strength is probably best assessed using a whole blood assay rather than serum-based testing of platelet function alone.

Yeung LYY, et al., Trauma Surg Acute Care, 2016-22
Basic characteristics and interpretation of commonly used assays to assess platelet function
Yeung LYY, et al., Trauma Surg Acute Care, 2016-22

<table>
<thead>
<tr>
<th>Test</th>
<th>Medium</th>
<th>Interpretation</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Light transmission</td>
<td>Plasma</td>
<td>Increased light transmission α increased platelet function</td>
<td>Does not account for effect of blood cells on clotting</td>
</tr>
<tr>
<td>aggregrometry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Impedance aggregrometry</td>
<td>Whole blood</td>
<td>Increased impedance α increased platelet function</td>
<td></td>
</tr>
<tr>
<td>PFA-100</td>
<td>Whole blood</td>
<td>Decreased closure time α increased platelet function</td>
<td>Not approved for detection of clopidogrel</td>
</tr>
<tr>
<td>VerifyNow</td>
<td>Whole blood</td>
<td>Akin to light transmission aggregrometry</td>
<td></td>
</tr>
<tr>
<td>TEG platelet map</td>
<td>Whole blood</td>
<td>Directly reports the percentage of inhibition in maximal platelet function</td>
<td>Variable and high degree of inhibition noted due to illness and injury</td>
</tr>
</tbody>
</table>

TEG, thrombelastography-platelet mapping.

Platelet Transfusion

- The indications for platelet transfusion to restore platelet function remain controversial.
- Antiplatelet therapy has been shown to worsen the outcome of patients with intracranial hemorrhage or traumatic brain injury. Grzegorski T, et al, Neurol Neurochir Pol 2015;49:278–89.
- Some authors and guidelines recommend transfusion of 5–10 units of platelet concentrates in patients with intracranial hemorrhage receiving antiplatelet therapy.

- Patients with:
  1) active bleeding or...
  2) at high risk of bleeding
  3) and those who have platelet counts <50 000/mL undergo platelet transfusion.

The guidelines are limited to the management of patients with coronary stents who are on antiplatelet drugs and require elective surgery.

There is NO universal evidence-based consensus, for the indications, method, timing or endpoints of treatment to reverse the antiplatelet action of Clopidogrel in patients requiring emergency non-cardiac surgery.

Patients on antiplatelet drugs should continue their treatment throughout surgery, except when bleeding might occur in a closed space.


**Proposed algorithm to manage patients on antiplatelet drugs requiring emergency non-cardiac surgery**

(CVA = cerebrovascular accident, MI = myocardial infarction, PCI = percutaneous coronary intervention).

• Antiplatelet Agents: Recommendations
• ACC/AHA 2014

• Class I
• 1. In patients undergoing urgent noncardiac surgery during the first 4 to 6 weeks after BMS or DES implantation, DAPT should be continued unless the relative risk of bleeding outweighs the benefit of the prevention of stent thrombosis. *(Level of Evidence: C)*
• 2. In patients who have received coronary stents and must undergo surgical procedures that mandate the discontinuation of P2Y12 platelet receptor–inhibitor therapy, it is recommended that aspirin be continued if possible and the P2Y12 platelet receptor–inhibitor be restarted as soon as possible after surgery. *(Level of Evidence: C)*

• Antiplatelet Agents: Recommendations
• ACC/AHA 2014

• 3. Management of the perioperative antiplatelet therapy should be determined by a consensus of the surgeon, anesthesiologist, cardiologist, and patient, who should weigh the relative risk of bleeding versus prevention of stent thrombosis. *(Level of Evidence: C)*
Take Home Messages

- The emergency perioperative management of patients receiving DAPT can be problematic.
- It is important that the benefit of surgery is first weighed against the risk of altering the antiplatelet regimen.
- Where doubt exists, there should be a discussion involving the physician, the surgeon, the anesthetist and the patient about the risks and benefits of continuing the antiplatelet agents.

IS there an urgent need for the development of guidelines to manage antiplatelet drugs requiring emergency non-cardiac surgery?

THANK YOU
Risk of Mortality & AMI

Cardiac Risk Stratification Based on the Noncardiac Surgical Procedure