Perioperative Management of Patients Receiving Oral Anticoagulants or Antiplatelet Agents

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Disclosures

• None related to this presentation
Case #1

- 78 yo man with proximal LAD stent (DES) 2 weeks ago, presents with displaced hip fracture. Peri-procedural management?
  - Hold both aspirin and Plavix for 7-10 days, resume post-procedure
  - Hold Plavix only for 7-10 days, then resume post-procedure
  - Inpatient Integrilin bridge
Case #2

• 53yo man with history of an MI and a stent 2 years ago is scheduled for routine screening colonoscopy. Peri-procedural management?

  – Hold both aspirin and Plavix for 7-10 days, resume post-procedure
  – Hold Plavix only for 7-10 days, then resume post-procedure
  – Inpatient Integrilin bridge
Case #3

• 70 yo man with chronic a-fib and admitted for colonoscopy. Coumadin was held prior to the procedure. Post-procedure management?

  – IV UFH until INR > 2.0
  – Outpatient LMWH bridge
  – Resume Coumadin without a bridge
Case #4

- 48 yo woman with bi-leaflet aortic valve is to undergo elective inguinal hernia repair. Post-op management?

  - IV UFH until INR > 2.0
  - Outpatient LMWH bridge
  - Resume Coumadin without a bridge
Case #5

- 70 yo man with a mechanical mitral valve (ball in cage) with a-fib, prior CVA, and undergoes colectomy. Post-op management?

  - IV UFH until INR > 2.0
  - Outpatient LMWH bridge
  - Resume Coumadin without a bridge
Anti-platelet therapy

- Anti-platelet agents
  - Cyclo-oxygenase inhibitor
    - Aspirin
  - Adenosine diphosphate receptor (ADP) inhibitors
    - Clopidogrel (Plavix)
    - Prasugrel (Effient)
    - Ticagrelor (Brilinta)
Anti-platelet therapy

• Anti-platelet agents
  – Other agents
    • Phosphodiesterase inhibitors (Cilostazol (Pletal))
    • Adenosine reuptake inhibitors (Dipyridamole (Persantine))
    • Protease-activated receptor-1 (PAR-1) antagonists (Vorapaxar (Zontivity))
    • Glycoprotein IIB/IIIA inhibitors
      – Abciximab (Reopro)
      – Eptifibatide (Integrilin)
      – Tirofiban (Aggrastat)
Aspirin

- Aspirin is the most widely used drug in medicine.
- In 2007, the Agency for Healthcare Research and Quality (AHRQ) reported that nearly 20% of adults in the United States reported taking aspirin daily or every other day, with this number increasing to nearly 50% in those aged 65 and older.
- Aspirin is also one of the oldest drugs in use, with a history dating back to the period of Hippocrates and Galen, when the bark of the willow tree was famous for its analgesic and anti-inflammatory properties.
- Records show its widespread use by ancient Mesopotamian, Greek, and Chinese civilizations.
Aspirin

• In 1758, in the first recorded clinical trial in history, Reverend Edward Stone of the Royal Society of London demonstrated the efficacy of ground, dried bark from the English willow tree for treating the symptoms of malaria.

• However, aspirin as we know it today was not introduced for public use until 1904, following a series of attempts at extraction and purification of salicylic acid from willow bark and subsequent modification to acetylsalicylic acid to reduce the unpleasant side effects.

• In addition to its anti-inflammatory properties, aspirin was also observed to increase bleeding time, and later studies demonstrated the utility of aspirin as an anti-thrombotic agent.
Aspirin

• It was not until 1971 that aspirin’s exact pharmacological mechanism of action of irreversible cyclo-oxygenase (COX) inhibition and related suppression of prostaglandin production was discovered.

• Later studies demonstrated that the antithrombotic effects of aspirin were the result of acetylation of COX in platelets.

• Low-dose aspirin regimens (≥ 30 mg/day) can effectively suppress platelet aggregation without affecting important endothelial cell functions.
Salix alba: White Willow Tree

- Is commonly used as an ornamental tree due to the splendor of its white leaves.
- Contains a compound called salicylic acid that is used to produce aspirin.
- Has wood that is renown for its use as a cricket bat.
- Has springy branches that are perfect for using to weave world class baskets.
- Is one of the fastest growing trees and can reach heights up to 30 meters tall!
Plavix (clopidogrel)

- Began as a search for a new anti-inflammatory drug related to Tinoridine, a thienopyridine compound.
- This search led to ticlopidine, which was found to have antiplatelet effects and eventually marketed as Ticlid.
- After its release, Ticlid was found to induce severe hematological disorders (leukopenia, thrombocytopenia, agranulocytosis) in a few patients.
- A search for a less toxic antiplatelet agent led to the discovery of clopidogrel.
- When clopidogrel entered into preclinical development, its mode of action (and that of ticlopidine) was not fully elucidated but it was obvious that it differed from that of other platelet inhibitors such as aspirin, sulfinpyrazone and dipyridamole.
- At variance with these drugs, it appeared as a powerful inhibitor of ADP-induced platelet aggregation.
Overview

- Major perioperative CV complications such as nonfatal MI, nonfatal stroke, and CV related death occur in nearly 10 million patients annually.
- This number is expected to rise due to the increase in noncardiac surgery and other procedures performed in an aging population.
- Antiplatelet therapy is a mainstay in the management of patients with CAD.
- The risk of a recurrent ischemic event for patients discontinuing or not adhering to aspirin treatment has been suggested to increase 3-fold.
- Higher risk in patients treated with stents.
Overview

• Currently 900,000 patients receive coronary stents in the United States annually.
• After stent implantation, it is recommended that patients receive 6 weeks to 12 months of dual antiplatelet therapy (DAPT) – typically ASA and Plavix.
• Within 1 year of stent implantation, 4% to 5% (36,000-45,000 patients) of such patients will require surgery, a number that rises to 11% (99,000 patients) within 2 years of stenting.
• A much higher number of stented patients will require nonsurgical procedures (such as colonoscopy).
Overview

• There are no established management strategies for patients with coronary stents who are receiving DAPT and require elective surgery.

• Clinicians balance the perceived risk for major adverse cardiovascular events (MACEs) and stent thrombosis (ST) associated with perioperative antiplatelet drug interruption against the risk of bleeding associated with drug continuation.

• Patients with coronary stents have an 8% to 10% risk of developing MACE and ST after elective noncardiac surgery, which exceeds the 1% to 5% risk for MACE in nonstented patients having noncardiac surgery.
Overview

• Fatality from ST ranges from 40% to 60%
• Patients are at highest risk for ST during the time between stent implantation and re-endothelialization at the stent site.
• Premature withdrawal of DAPT is the strongest predictor of ST, with the majority of drug withdrawals occurring in the perioperative setting.
• The risk for MACE and ST diminishes as the interval between stent implantation and surgery increases, irrespective of the stent type, but remains at 5% to 10% if surgery is done > 2 years after stenting.
Embolic Stroke

CT scan of the brain showing infarction in the left temporal region
Stent Thrombosis

Stent thrombosis of both the LAD and Circumflex arteries
Prosthetic Valve Thrombosis

Two-dimensional transesophageal echocardiography showed a huge thrombus (arrows) on the prosthetic mitral valve (PMV) as the cause of obstruction.
Perioperative Bleeding
Risk Factors for Stent Thrombosis

• **Patient factors:**
  – ACS
  – Reduced left ventricular ejection fraction
  – MACE within 30 days of PCI
  – Diabetes mellitus
  – Renal insufficiency
  – Gene polymorphism
  – Hypercoagulable states (e.g., malignancy, surgery, diabetes)

• **Procedural factors:**
  – Residual dissection
  – Incomplete stent apposition
  – Stent underexpansion
  – “Crush” technique
  – Side branch occlusion

• **Coronary anatomy:**
  – Vessel size
  – Type C lesion
  – Left main coronary artery stent
  – Increased lesion length
  – Thrombus
  – Bifurcation
  – In-stent restenosis

• **Plaque characteristics:**
  – Multivessel disease
  – Total occlusion
  – Bypass graft

• **Stent factors:**
  – Stent surface
  – Hypersensitivity to polymer
Coronary Artery Stents

Scanning Electron Micrographs of 14-Day Comparator DES and BMS Controls
Coronary Artery Stents

Scanning Electron Micrographs of 28-Day Comparator DES and BMS Controls
Coronary Artery Stents

Enlarged images of individual stent struts illustrating classification of stent strut coverage. (A) Well apposed and covered; (B) well apposed and not covered; (C) malapposed and not covered; and (D) malapposed but covered.
Management of Antiplatelet Therapy in Patients Undergoing Noncardiac Surgery

• Rebound platelet reactivity after discontinuation of antithrombotic therapy
  – Has been advocated to lead the increased thrombotic risk
  – Not supported by trials
• More likely due to recovery of platelet reactivity to pretreatment levels ("withdrawal of protection")
• Surgery is inherently associated with an increased prothrombotic and inflammatory environment
  – Increased cytokines
  – Neuroendocrine inflammatory mediator release
  – Increased platelet adhesiveness
  – Persistently high platelet counts
  – Decreased or impaired fibrinolysis.
• In case of early surgery, there is a vulnerable period in which stents are not fully endothelialized
Management of Antiplatelet Therapy in Patients Undergoing Noncardiac Surgery

- The first alarming report of adverse perioperative outcomes in patients with BMS was published in 2000
  - These studies, in general, are inherently biased in that patients who require surgery more rapidly are likely to be sicker
- However, because BMS thrombosis is more frequent in the first 2 weeks after stent placement and rare more than 4 weeks after, when endothelialization of the stent has generally occurred, current guidelines recommend delaying surgery 4 to 6 weeks after BMS placement to allow proper thienopyridine use to reduce the risk of coronary stent thrombosis.
- This recommendation is presently given a IIa class with level of evidence B, reflecting the limited and sometimes conflicting evidence mostly coming from nonrandomized studies.
- In a recent large-cohort registry from Wijeysundera et al, the incidence of 30-day ischemic events in patients with BMSs was 2.6% when the interval between stent insertion and major elective cardiac surgery was 45 to 180 days and 6.7% when the interval was <45 days.
Management of Antiplatelet Therapy in Patients Undergoing Noncardiac Surgery

- DES thrombosis may occur late and has been reported up to 5.5 years after implantation, but particularly in the context of discontinuation of antiplatelet agents before noncardiac surgery
  - Although the risk of death, myocardial infarction, or stent thrombosis decreases significantly for the increasing interval between PCI and surgery, the intermediate-term risk extending at least 2 to 3 years remains ≈1%.
  - In the Evaluation of Drug-Eluting Stents and Ischemic Events (EVENT) registry, among 206 patients who received ≥1 DESs and underwent major noncardiac surgery at a median of 6 months after PCI, the risk of cardiac death, myocardial infarction, or stent thrombosis was increased 27-fold in the week following noncardiac surgery in comparison with any other week after stent implantation.
  - Wijeysundera et al\textsuperscript{29} reported a high (20%) 30-day incidence of adverse ischemic events in 905 patients with DESs when the interval between stent insertion and surgery was <45 days, whereas the event rate was only 1.2% once the interval exceeded 180 days.
Management of Antiplatelet Therapy in Patients Undergoing Noncardiac Surgery

• In aggregate, these findings support the understanding that early surgery and antiplatelet therapy discontinuation are risk factors for cardiac events at the time of noncardiac surgery after DES placement, although some relative risk persists at longer term.

• Consistently, current guidelines recommend withholding elective noncardiac surgery for at least 12 months after DES implantation in patients in whom thienopyridine therapy, or aspirin and thienopyridine therapy, will need to be discontinued perioperatively.
Management of Antiplatelet Therapy in Patients Undergoing Noncardiac Surgery

• When facing the problem of perioperative bleeding, it should be important to distinguish bleedings related to the surgical procedure itself from those that occur in patients on antithrombotic therapy, especially when anticoagulant and antiplatelet drugs are administered in proximity to surgery.
  – In fact, certain procedures are not typically associated with postoperative bleeding in patients not on antithrombotic medications but may be if antithrombotics are given in proximity to the procedure.
  – Interestingly, when surgeons are not aware if aspirin was used or not, they often cannot distinguish, based on the type of bleeding, patients on aspirin from those who have discontinued.

• The American College of Chest Physicians guidelines for the perioperative management of antithrombotic therapy have identified a group of surgeries and procedures that appear to be associated with a high risk for bleeding in the context of perioperative anticoagulant and antiplatelet drug use.

• CABG differs from other major surgeries in that it includes specific risk factors for bleeding, including full heparinization therapy, platelet dysfunction from the pump, and altered fibrinolysis.
Management of Antiplatelet Therapy in Patients Undergoing Noncardiac Surgery

• Interventions at High Bleeding Risk
  – Cardiac surgery: Reintervention, endocarditis, coronary artery bypass grafting after failed percutaneous coronary intervention, aortic dissection
  – General surgery: Hepatic resection, pancreaticoduodenectomy
  – Maxillofacial surgery: Radical and reconstructive surgery for cancer of the head and neck, open reduction of orbital-zygomatic fracture, submandibular sialoadenectomy
  – Thoracic surgery: Esophagectomy, pleuropneumectomy, pulmonary decortication
  – Vascular surgery: Open surgery of the thoracic and thoracoabdominal aorta
  – Digestive endoscopy: Dilation for achalasia, mucosectomy, submucosal resection, fine-needle aspiration biopsy of pancreatic cystic lesions, Vater ampulla ampullectomy
Management of Antiplatelet Therapy in Patients Undergoing Noncardiac Surgery

- Interventions at High Bleeding Risk
  - **Gynecological surgery:** Laparoscopic or laparotomic hysterectomy for large uterus, laparoscopic or laparotomic myomectomy, laparoscopic or laparotomic surgery for severe/deep endometriosis, debulking of ovarian cancer, radical surgery for carcinoma of the cervix and endometrium, pelvic/lombo-aortic lymphadenectomy, pelvic evisceration
  - **Neurosurgery:** Removal of intradural lesions (intracerebral masses, intraparenchymal hemorrhages)
  - **Pulmonology:** Transbronchial and lung biopsies, operative bronchoscopy with a rigid bronchoscope
  - **Dentistry and Ophthalmology:** None
  - **Orthopedic surgery:** Major prosthetic surgery (hip, knee), major traumatology (pelvis, long bones), fractures of the proximal femur in elderly patients
  - **Urology:** Total and partial nephrectomy, percutaneous nephrostomy, percutaneous lithotripsy, radical cystectomy and prostatectomy, prostatic endoscopic resection, endoscopic bladder interventions, penectomy, partial orchiectomy
Managing Perioperative Withdrawal of Antiplatelet Agents

• In patients treated with stents who are to undergo subsequent procedures that mandate discontinuation of P2Y$_{12}$ receptor inhibitors, guidelines recommend that aspirin should be continued if at all possible and the thienopyridine restarted as soon as possible after the procedure
  – A systematic review of 161 cases of late stent thrombosis and very late stent thrombosis suggested that, if aspirin therapy is maintained, short-term discontinuation of a thienopyridine might be relatively safe in patients treated with DES
  – Aspirin should only be discontinued if the known bleeding risks are similar or more severe than the observed cardiovascular risks of aspirin withdrawal

• In patients who require early (<6 months) noncardiac surgery within placement of a DES, the American College of Chest Physicians guidelines suggest continuing DAPT around the time of surgery instead of stopping, depending on the bleeding risk intrinsic to each kind of intervention
Managing Perioperative Withdrawal of Antiplatelet Agents

• Clearly, in the absence of patient- and procedure-specific recommendations from practice guidelines, clinical judgment is key.
• Considerations on perioperative withdrawal of antiplatelet agents should include a precise upfront definition of the individual thrombotic profile of patients referred to surgery.
• In aggregate, the available information seems to identify patients at high risk of perioperative thrombotic events as:
  – Those who have received a BMS within 1 month or a DES within 6 months
  – Those who have received a DES >12 months but remain at risk of stent thrombosis or life-threatening complications for unfavorable anatomic or procedural characteristics (ie, long stented segments, multiple stenting, overlapping stents, small vessels, bifurcation lesions, left main, last remaining vessel)
  – Those with unfavorable clinical characteristics (ie, recent ACS, history of stent thrombosis, left ventricular ejection fraction, chronic kidney disease, diabetes mellitus).
• The need for keeping such high-risk patients on aspirin alone, clopidogrel alone, or both during the surgical period, should be individualized based on the surgical context.
Bridging Therapy

• The trade-off of using oral P2Y_{12} receptor inhibitors (clopidogrel, prasugrel, or ticagrelor) in patients with ACS is the increased risk of bleeding complications in those requiring surgery if they have been exposed to oral P2Y_{12} inhibition within the preceding 5 to 7 days.

• On the other hand, patients may develop recurrent complications during the waiting period of P2Y_{12} inhibitors discontinuation before surgery, underscoring the need for strategies aimed at transient platelet inhibition to safely bridge patients to their surgical procedure with minimum risk of ischemic or bleeding events.

• Therefore, the ideal bridging agent should be effective in achieving platelet inhibition similar to that of the oral P2Y_{12} receptor inhibitor, with a rapid onset of action and also rapid offset (short duration of action).

• Evidence on the efficacy and safety of short-acting antithrombotic drugs such as unfractionated heparin, low-molecular-weight heparin or short-acting glycoprotein IIb/IIIa antagonists (eg, tirofiban, eptifibatide) in the perioperative setting are sparse.
Bridging Therapy

• However, it is important to emphasize that, if bridging is necessary, antiplatelet agents should be preferred over anticoagulants, because platelet accumulation at sites of vascular injury is well known as the primary event in arterial thrombosis.

• Importantly, unfractionated heparin makes platelets more reactive to activation by other agonists such as adenosine diphosphate and binds to the glycoprotein IIb/IIIa receptor on the platelet, resulting in a prothrombotic effect.

• Therefore, bridging with heparin can actually be potentially harmful.

• Although low-molecular-weight heparin does not stimulate platelets like unfractionated heparin, this does not have platelet inhibitory effects, which remain key for bridging.
Bridging Therapy

- On this background, the only approved agents with fast-acting and potent platelet inhibitory effects with relatively short duration of action are the small-molecule intravenous glycoprotein IIb/IIIa antagonists (eg, tirofiban, eptifibatide).
- A bridging strategy with perioperative administration of tirofiban was found to be feasible and reasonably safe in a small study of patients with a recently implanted DES and high-risk characteristics for stent thrombosis undergoing major or eye surgery, and later confirmed in slightly larger studies of patients undergoing major surgery.
- Another pilot study of 67 patients who underwent noncardiac or cardiac surgery after DES implantation suggested that, despite preoperative bridging with a glycoprotein IIb/IIIa inhibitor, postoperative stent thrombosis can still occur in patients requiring antiplatelet medication interruption.
- Notably, in these studies, aspirin was mostly continued throughout the perioperative period.
- In light of these mixed results, more studies are needed to assess the role of bridging therapy with glycoprotein IIb/IIIa inhibitors in patients who require P2Y receptor antagonists.
Bridging Therapy

• Cangrelor is a nonthienopyridine adenosine triphosphate analogue that reversibly binds to the P2Y\textsubscript{12} receptor, and, unlike clopidogrel, prasugrel, and ticagrelor, it is administered intravenously with a rapid onset and offset of effect.

• In comparison with glycoprotein IIb/IIIa inhibitors, cangrelor features more desirable characteristics because of its faster offset and specificity to the P2Y\textsubscript{12} receptor.

• In addition, differently from glycoprotein IIb/IIIa inhibitors, dose-finding studies designed to achieve a “thienopyridine-like” platelet inhibitory effect were specifically conducted for cangrelor to reduce the risk of bleeding with prolonged infusion.

• These pharmacological properties make cangrelor the ideal drug to be considered for bridging patients to surgery.
Bridging Therapy

- BRIDGE Trial
  - This hypothesis has been recently tested in the phase II prospective, randomized, double-blind trial, in which 210 patients with an ACS or treated with a coronary stent and receiving a thienopyridine awaiting CABG surgery were randomly assigned to receive either cangrelor (0.75 μg·kg\(^{-1}\)·min\(^{-1}\)) or placebo for at least 48 hours.\(^{106}\)
    - The study drug was discontinued 1 to 6 hours before CABG surgery.
    - Aspirin therapy was maintained throughout perioperative period.
    - Cangrelor consistently achieved and maintained platelet inhibition assessed by the VerifyNow P2Y\(_{12}\) assay at levels known to be associated with a low risk of thrombotic events in comparison with placebo (platelet reaction units <240; 98.8% versus 19.0%; relative risk, 5.2; 95% CI, 3.3–8.1; \(P<0.001\)).
    - Importantly, bridging with a prolonged infusion of cangrelor did not increase major bleeding before surgery, although minor bleedings, largely attributed to ecchymosis at the site of venous puncture, were more commonly documented with cangrelor.\(^{106}\) The BRIDGE trial therefore supports the hypothesis that bridging with intravenous cangrelor may be a successful strategy to provide adequate platelet P2Y\(_{12}\) inhibition after thienopyridine discontinuation in patients referred to cardiac surgery.
  - Although this approach has the potential to also be valid in noncardiac surgery, this possibility has still to be proven, given that different noncardiac operations have variable bleeding risk. Cangrelor is not still approved for clinical use, but filing with regulatory agencies is pending, also based on the results of a recent large-scale trial, showing the drug to be effective in reducing the rate of ischemic events during PCI, with no significant increase in severe bleeding.
Bridging Therapy

* Key Pharmacokinetic and Pharmacodynamic Characteristics of Cangrelor and Small-Molecule Glycoprotein IIb/IIIa Antagonists

<table>
<thead>
<tr>
<th></th>
<th>Cangrelor</th>
<th>Tirofiban</th>
<th>Eptifibatide</th>
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<tbody>
<tr>
<td>Onset of action</td>
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<td>Immediate</td>
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<tr>
<td>Potent platelet inhibition</td>
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<td>Yes</td>
<td>Yes</td>
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<td>Plasma half-life</td>
<td>3–5 min</td>
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<td>Offset of action</td>
<td>1 h</td>
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<td>4–6 h</td>
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<td>P2Y₁₂-specific</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
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<tr>
<td>Thienopyridine-like</td>
<td>Yes</td>
<td>No</td>
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Bridging Therapy

- Proposed bridging strategies with small-molecule glycoprotein IIb/IIIa antagonists.
  - After discontinuation of the P2Y\textsubscript{12} inhibitor as per guidelines recommendations (7 days before surgery for prasugrel, 5 days before surgery for clopidogrel or ticagrelor), bridging with tirofiban or eptifibatide should be initiated ≈72 hours before surgery and continued up to 4 to 6 hours from surgery.
  - In the absence of studies targeting specific levels of platelet inhibition, the maintenance-dosing regimen (0.1 μg·kg\textsuperscript{-1}·min\textsuperscript{-1} for tirofiban, 2.0 μg·kg\textsuperscript{-1}·min\textsuperscript{-1} for eptifibatide) should be that recommended according to the package insert of each molecule.
  - A loading dose is not warranted given that bridging does not occur in an acute setting requiring immediate effects as in the ACS/PCI setting.
  - In patients with renal impairment (creatinine clearance <50 mL/min), a dose reduction is warranted (0.05 μg·kg\textsuperscript{-1}·min\textsuperscript{-1} for tirofiban, 1.0 μg·kg\textsuperscript{-1}·min\textsuperscript{-1} for eptifibatide) and earlier suspension (8–12 hours) should be considered.

- In addition, the timing of surgery should be carefully defined to avoid extending glycoprotein IIb/IIIa antagonist infusion, given that the drugs are being used at the dosing regimen recommended for ACS/PCI settings that are known to be associated with an increased risk of bleeding that can be enhanced with prolonged infusion.
Platelet Transfusion

- Blood transfusions are required as an emergency therapy in 1.8% to 8.0% of patients who bleed.
- Red blood cell transfusion has been found to increase platelet activation and aggregation in healthy volunteers, a mechanism that may partly explain the risk of recurrent ischemic events or mortality after transfusion in anemic patients with ACS.
- In case of hemorrhage that continues despite the usual hemostatic techniques, however, platelet transfusion may be considered as a strategy to reverse bleeding, even if platelet count is normal.
- In a small study on healthy volunteers, the earliest measured time when supplemented platelets were not inhibited by circulating active metabolite of prasugrel was 6 hours after the administration of a 60-mg loading dose.
- Accordingly, the package insert of prasugrel recommends platelet transfusion, when necessary, within 6 hours from the loading dose or 4 hours from the maintenance dose.
- Less effect on platelet aggregability may be anticipated in patients treated with a reversible P2Y₁₂ inhibitor such as ticagrelor in comparison with those on clopidogrel or prasugrel.
- No data exist with ticagrelor regarding a hemostatic benefit of platelet transfusion, but a study in healthy volunteers is ongoing.
Intracoronary Imaging

- Although stent thrombosis is widely recognized as a multifactorial phenomenon, pathological studies have identified strut uncoverage as the primary substrate responsible for this event.
- A potential role for intracoronary imaging has been postulated as a tool to assess for adequate stent strut coverage by neointimal tissue growth.
- Optical coherence tomography is a high-resolution intravascular imaging modality based on infrared light emission, which, because of its resolution in the range of 10 to 15 μm, has emerged as a sensitive tool to assess the presence of stent strut coverage.
- For this reason, optical coherence tomography has the potential to provide evidence to guide the duration of antiplatelet treatment in stented patients who need to prematurely discontinue DAPT.
- This hypothesis, however, has not yet been prospectively tested.
Proposed bridging protocols for patients on dual-antiplatelet therapy with aspirin plus a P2Y12 receptor inhibitor referred to cardiac or noncardiac surgery.

Platelet Function Measurement

**Recommendation**

- Because of their high negative predictive value, preoperative point-of-care testing to assess bleeding risk may be useful in identifying patients with high residual platelet reactivity after usual doses of antiplatelet drugs, and who can undergo operation without elevated bleeding risk
  - **Class IIb**  
  - **Level of Evidence B**

- Point-of-care testing to assess perioperative platelet function may be useful in limiting blood transfusion
  - **Class IIb**  
  - **Level of Evidence B**

- For patients on dual-antiplatelet therapy, it is reasonable to make decisions about surgical delay based on tests of platelet inhibition rather than arbitrary use of a specified period of surgical delay
  - **Class IIb**  
  - **Level of Evidence B**

- Once postoperative bleeding risk is decreased, testing of response to antiplatelet drugs, either with genetic testing or with point-of-care platelet function testing, early after cardiac procedures might be considered to optimize antiplatelet drug effect and minimize thrombotic risk to vein grafts
  - **Class IIb**  
  - **Level of Evidence B**

- For patients with high platelet reactivity after usual doses of clopidogrel, it may be helpful to switch to another P2Y₁₂ inhibitor (eg, prasugrel or ticagrelor)
  - **Class IIb**  
  - **Level of Evidence B**
Management of Antiplatelet Therapy in Patients Undergoing Noncardiac Surgery

• Despite the magnitude of the problem both in terms of the number of patients affected and the potential clinical implications, few recommendations are available on bridging antiplatelet therapy in ACS/PCI patients requiring surgery.

• Therefore, the importance of a joint effort among all those responsible for the management of patients undergoing cardiac and noncardiac surgery to better define antiplatelet-bridging regimens should be emphasized.

• Sufficient time should be spent to make the patient informed of all positive and negative consequences related to the discontinuation of antiplatelet therapy in the perioperative period.
Coumadin: Bridge anticoagulation therapy

• What is it?
• When is it needed?
• Is it dangerous?
• Can I use LMWH?
• Is there data?
What is bridging?

- After warfarin is stopped, 5 to 6 days before surgery (to allow sufficient time for its anticoagulant effect to wane), bridging anticoagulation is started 3 days before surgery, with the last dose given 24 hours before surgery.

- After surgery, bridging is resumed no earlier than 24 hours after surgery; at the same time, warfarin is restarted. Bridging is continued, typically for 4 to 6 days, until the anticoagulant effect of warfarin has resumed and the blood is sufficiently thinned again.
Management of Coumadin in the Perioperative Period

• 2.5 million on chronic anticoagulation.
• 10%/year require interruption for procedures.
• Thus 250,000 patients/year will have the issue of bridging arise.
Warfarin

• Sweet clover
• *(meliotus* sp.)* introduced into midwest as alternative livestock foodsource in difficult terrain.
• Moister than hay, easily rotting and contaminated with molds.
Father of Warfarin

- Karl Link PhD, at the Wisconsin Alumni Research Foundation
- Isolated dicoumarol, and patented as a blood thinner in 1941.
- 1948 WARFarin patented as rat poison (less bait-shyness).
Gaining the trust of the public.

(“You want me to take rat poison?”)

- 1951- Naval recruit survives OD of
- 567 mg warfarin.
Gaining the trust of the public.

(“You want me to take rat poison?”)

1955- President Eisenhower suffers MI. Treated with Warfarin …

… and 1 month bed rest.
Do we need to stop Coumadin?

- Dermatologic
- Cataract
- Dental procedures

- Comprise 20% of procedures.
- Topical agents (transexamic acid mouthwash)
Should we bridge?

- What is the indication for anticoagulation?
- What is the risk of interrupting anticoagulation?
- How long is the period of interruption?
- What is the risk of bleeding?
- What is the risk of prolonged hospitalization?
- What is the cost to the individual and society?
Risks of holding anticoagulation

• Thrombosis of mechanical heart valve is fatal in 15% of patients.
Risks of holding anticoagulation

- Embolic stroke results in a major neurologic deficit or death in 70% patients.
Risks of holding anticoagulation

- VTE- risk of recurrence
- Fatality from P.E 4-9%
Annual risk of thromboembolism on **no** anticoagulation.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Annual Risk</th>
</tr>
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<tbody>
<tr>
<td>Atrial fibrillation</td>
<td>4-5%</td>
</tr>
<tr>
<td>AVR</td>
<td>4-8%</td>
</tr>
<tr>
<td>MVR</td>
<td>?</td>
</tr>
</tbody>
</table>
CHADS$_2$
Stratified Risk of Thrombosis.

Gage et al JAMA 2001:285;2864-70
VTE risk of Thrombembolism coumadin interruption.

- First 4 weeks- 0.3-1.3% /day
- 4-12 weeks- 0.03-.2% /day
- After 12 weeks- < 0.05% /day

Kearon et al NEJM. 1997;336:1506-11.
Anticoagulant drugs in the treatment of pulmonary Embolism: a controlled trial.

Table 1—Autopsy Findings of the Five Patients Who Died With PE Randomized to No Anticoagulation

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age, yr/sex</th>
<th>Underlying Diagnosis</th>
<th>Anatomic Site of Pulmonary Emboli</th>
<th>Source of Thromboemboli</th>
<th>Coincidental Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>54/female</td>
<td>Extensive breast carcinoma</td>
<td>Left main branch</td>
<td>Right femoral DVT</td>
<td>Mixed organism empyema, bronchopneumonia and abscess</td>
</tr>
<tr>
<td>2</td>
<td>56/male</td>
<td>Post operation for intestinal obstruction (adhesions)</td>
<td>Main trunk</td>
<td>Left femoral DVT, hepatic vein thrombosis</td>
<td>Biliary tree sepsis</td>
</tr>
<tr>
<td>3</td>
<td>78/female</td>
<td>Post fractured ankle</td>
<td>Main trunk</td>
<td>Bilateral popliteal DVT</td>
<td>Bronchopneumonia, fungal lung abscess</td>
</tr>
<tr>
<td>4</td>
<td>57/male</td>
<td>Myocardial infarction</td>
<td>Left lobar</td>
<td>Bilateral femoral DVT, right ventricular mural thrombus</td>
<td>Staphylococcus aureus lung abscess</td>
</tr>
<tr>
<td>5</td>
<td>41/male</td>
<td>Nephrotic syndrome secondary to primary amyloidosis</td>
<td>Both main branches</td>
<td>Left calf DVT, renal vein thrombosis</td>
<td>None</td>
</tr>
</tbody>
</table>

*From the study by Barritt and Jordan. DVT = deep vein thrombosis.


- The only placebo-controlled trial demonstrating mortality benefit.
- 5/19 deaths in untreated group.
- 0/16 in treated.
- Several deaths not clearly due to PE.
Coumadin and Heparin compared with Coumadin Alone in initial Treatment of Proximal-Vein Thrombosis.

- Randomized double-blind.
- 120 patients at termination with DVT.
- Terminated early secondary to excess symptomatic events in OAC alone group
- 20% vs 6.7% in combined treatment. (p=0.058)
- Asymptomatic extension of DVT 39.6% OAC vs. 8.2%. (p=<.001)

Prosthetic valves: Risk of Thromboembolism

Cannegieter et al. Circ.1994;89:635-641

Major embolism = death, residual neuro deficit, peripheral ischemia requiring surgery

<table>
<thead>
<tr>
<th>Anticoagulation</th>
<th>Incidence Rates per 100 Patient-Years (95% Confidence Intervals)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Valve Thrombosis</td>
</tr>
<tr>
<td>None</td>
<td>1.8 (0.9-3.0)</td>
</tr>
<tr>
<td>Antiplatelet</td>
<td>1.6 (1.0-2.5)</td>
</tr>
<tr>
<td>Dipyridamole</td>
<td>4.1 (1.9-7.2)</td>
</tr>
<tr>
<td>Aspirin†</td>
<td>1.0 (0.4-1.7)</td>
</tr>
<tr>
<td>Cumarin</td>
<td>0.2 (0.2-0.2)</td>
</tr>
<tr>
<td>Cumarin and antiplatelet</td>
<td>0.1 (0.0-0.3)</td>
</tr>
</tbody>
</table>

*This category includes all reported incidences (valve thrombosis, major embolism, and minor embolism).
†Aspirin alone or in combination with dipyridamole or pentoxifylline.
Prosthetic valves: Risk of Thromboembolism

Cannegieter et al. Circ. 1994; 89: 635-641

Risk for patients on Coumadin

<table>
<thead>
<tr>
<th>Valve Position</th>
<th>Valve Thrombosis</th>
<th>Major Embolism</th>
<th>Total Embolism*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic</td>
<td>0.1 (0.1-0.2)</td>
<td>0.8 (0.7-0.9)</td>
<td>1.1 (1.0-1.3)</td>
</tr>
<tr>
<td>Mitral</td>
<td>0.5 (0.3-0.7)</td>
<td>1.3 (1.1-1.5)</td>
<td>2.7 (2.3-3.0)</td>
</tr>
<tr>
<td>Both</td>
<td>0.4 (0.2-0.7)</td>
<td>1.4 (1.0-1.9)</td>
<td>2.1 (1.6-2.7)</td>
</tr>
</tbody>
</table>

*This category includes all reported incidences (valve thrombosis, major embolism, and minor embolism).
Evolution of Prosthetic valves.

Newer valves pose less thrombotic risk
Risk Stratification
for perioperative thromboembolism

Low risk (<5%)

• Atrial fibrillation: CHADS2 score 0-2 (no prior CVA)
• Prosthetic valve: Bileaflet aortic valve (w/o risk factors)*
• Venous thromboembolism: VTE > 12 months ago

*Age>75 years, atrial fibrillation, congestive heart failure, HTN, DM, or stroke/TIA
Risk Stratification for perioperative thromboembolism

Moderate risk (5-10%)

- Atrial fibrillation: CHADS2 score 3 or 4
- Prosthetic valve: Bileaflet aortic valve w/ > 1 risk factor(s)*
- Venous thromboembolism: VTE within 3-12 months, VTE with prior DC of anticoagulation

*Age>75 years, atrial fibrillation, congestive heart failure, HTN, DM, or stroke/TIA
Risk Stratification for perioperative thromboembolism

High risk (>10%)

- Atrial fibrillation: CHADS2 score 5 or 6, Recent (within 3 months) CVA/TIA, Rheumatic valvular disease
- Prosthetic valve: Any mechanical mitral valve, Older mechanical aortic valve, Recent (within 3 months) CVA/TIA
- Venous thromboembolism: VTE within 3 months, High risk thrombophilia*

*Deficiency of protein C, protein S, or antithrombin; antiphospholipid syndrome, homozygous factor V Leiden or prothrombin gene mutation
Mathematical model:
Risk of holding anticoagulation.

- Assume anticoagulation is sub-therapeutic for 4 days.
- Risk = (annual risk/365 days) x 4 days.

- Low: $(1\%/365) \times 4 = 0.01\%$ (for 4 days)
- Moderate: $(5\%/365) \times 4 = 0.05\%$
- High: $(10\%/365) \times 4 = 0.11\%$
Mathematical model: Risk of holding anticoagulation.

- Assume anticoagulation decreases risk 75%.

- Low Risk  .01% to .0025%
  - ARR=.01 - .0025 = .0075% (for the 4 days)
  - NNT = 1/ARR = 13,333

- Moderate Risk  .05% to .0125%
  - AAR = .05 - .0125 = .0375%
  - NNT = 2,666

- High Risk  .11% - .0275%
  - AAR = .11 - .0275 = .0825%
  - NNT = 1,212
Risk of holding anticoagulation.

- This does not take into account: Potential rebound effect from stopping coumadin
  - increased. Prothrombin fragments 1 and 2,
  - Thrombin-antithrombin complexes
  - D-dimer,
  - fibrinopeptide A,
  - Factor VIII

- Hypercoagulability from surgical milieu.
  - Plasminogen activator inhibitor 1
Perioperative Management of Patients Receiving Oral Anticoagulants-A Systematic Review.

Review of 31 studies available- none randomized, overall ‘poor quality’. Observed thromboembolic event rate by strategy:

- Continue OAC 0.4% (1/237)
- Hold OAC and no bridge 0.6% (6/996).
- Hold OAC and bridge UFH 0% (0/180).
- Hold OAC and LMWH bridge 0.6% (1/180)
- Hold OAC and LMWH bridge 8% (21/263)
- Unspecified or unclear Overall 1.6% (29/1868)
- Overall stroke 0.4% (7/1868)

Benefit may be hard to prove.

- Prospective cohort study of patients with non-valvular A fib. referred to the Mayo Thrombophilia center.
- Bridging with LMWH was done at discretion of consultant.
- Low rate of TE (3 were ACS in pt.s with CAD).

Thrombosis vs. Bleeding
When should we not bridge?

- Low risk of bleeding
  - Dermatologic
  - Dental
  - Cataract

- Continue Coumadin !!!
When should we not bridge?

• High risk of bleeding
  – CNS, spinal
  – CABG
  – Major orthopedic
  – Recon. Plastic
  – Major cancer surgery
  – PCK pocket
  – Sessile polyps
  – Prostate biopsy
Risk of bleeding from post-operative anticoagulation.

• Data difficult to interpret.
• Increased risk of major bleed over 2 days post-op:
  – Major surgery- 2-4%
  – Invasive procedures- 0-2%

Dunn and Turpie. Arch Int Med 2003;163:901-908
Management of Anticoagulation Before and After Elective Surgery.

- Assumes 3% rate of major bleed,
- Assumes 3% mortality from major bleed.
- Risk of bleed outweighs thrombosis in valves, atrial fib., recurrent VTE.

Kearon and Hirsh, NEJM 1997;336:1506-1511

**Table 2. Adverse Events Caused or Prevented by the Preoperative and Postoperative Administration of Intravenous Heparin, According to the Indication for Anticoagulation.**

<table>
<thead>
<tr>
<th>Indication for Heparin</th>
<th>Thromboembolism</th>
<th>Major Bleeding</th>
<th>Death or Disability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute venous thromboembolism</td>
<td>-7162†</td>
<td>+500</td>
<td>-559</td>
</tr>
<tr>
<td>Month 1</td>
<td>-1328†</td>
<td>+300</td>
<td>-93</td>
</tr>
<tr>
<td>Months 2 and 3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent venous thromboembolism†</td>
<td>-332†</td>
<td>+300</td>
<td>-13</td>
</tr>
<tr>
<td>Nonvalvular atrial fibrillation</td>
<td>-2</td>
<td>+300</td>
<td>+12</td>
</tr>
<tr>
<td>Nonvalvular atrial fibrillation and previous embolism</td>
<td>-4</td>
<td>+300</td>
<td>+11</td>
</tr>
<tr>
<td>Mechanical heart valve</td>
<td>-3</td>
<td>+300</td>
<td>+12</td>
</tr>
<tr>
<td>Arterial embolism</td>
<td>-65</td>
<td>+300</td>
<td>-26</td>
</tr>
<tr>
<td>Month 1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Values shown are estimated numbers of major events caused (+) or prevented (−) if therapy is administered to 10,000 patients undergoing major surgery.

†A 100-fold increase in the postoperative rate of venous thromboembolism has been assumed, to reflect the added risk associated with major surgery.

‡The term refers to patients whose last episode of venous thromboembolism occurred more than three months before evaluation but who require long-term anticoagulation because of a high risk of recurrence.
Am College of Gastroenterology: Management of antithrombotic agents for endoscopic procedures

- **Aspirin/NSAID**
  - **Low Bleeding Risk**
    - Continue
  - **High Bleeding Risk**
    - Continue

- **Thienopyridines (e.g. Clopidogrel)**
  - **Low Bleeding Risk**
    - Continue
  - **High Bleeding Risk**
    - Discontinue
      - In patients with high thromboembolic risk, consider bridge therapy

- **Warfarin**
  - **Low Bleeding Risk**
    - Continue
  - **High Bleeding Risk**
    - Discontinue

---

If unable to delay procedure for 7-10 days, hold as many days as possible up to 7-10 days

In patients on dual antiplatelet therapy or monotherapy with a thienopyridine, consider continuing aspirin (dual therapy patients) or starting aspirin (thienopyridine monotherapy patients) in the periendoscopic period
Case #1

- 78 yo man with proximal LAD stent (DES) 2 weeks ago, presents with displaced hip fracture. Peri-procedural management?

  - Hold both aspirin and Plavix for 7-10 days, resume post-procedure
  - Hold Plavix only for 7-10 days, then resume post-procedure
  - Inpatient Integrilin bridge
Case #2

• 53yo man with history of an MI and a stent 2 years ago is scheduled for routine screening colonoscopy. Peri-procedural management?

  – Hold both aspirin and Plavix for 7-10 days, resume post-procedure
  – Hold Plavix only for 7-10 days, then resume post-procedure
  – Inpatient Integrilin bridge
Case #3

• 70 yo man with chronic a-fib and admitted for colonoscopy. Coumadin was held prior to the procedure. Post-procedure management?

  – IV UFH until INR > 2.0
  – Outpatient LMWH bridge
  – Resume Coumadin without a bridge
Case #4

- 48 yo woman with bi-leaflet aortic valve is to undergo elective inguinal hernia repair. Post-op management?

  - IV UFH until INR > 2.0
  - Outpatient LMWH bridge
  - Resume Coumadin without a bridge
Case #5

- 70 yo man with a mechanical mitral valve (ball in cage) with a-fib, prior CVA, and undergoes colectomy. Post-op management?

  - IV UFH until INR > 2.0
  - Outpatient LMWH bridge
  - Resume Coumadin without a bridge
Questions ???
Helpful References