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Management of Antiplatelet and Anticoagulant Therapies Peri-operatively

Clinicians are often faced with the question of how to handle antiplatelet and anticoagulant therapy before a surgical procedure. Despite the frequency of these situations there is a paucity of data in the literature about the best way to manage these therapies peri-operatively. This ***Heartbeat*** will suggest a management plan based on current guidelines and expert consensus.

Antiplatelet Therapy

Discussion of antiplatelet therapy will focus primarily on the management of post percutaneous coronary intervention (PCI) patients with drug eluting stents (DES). The Cypher and Taxus DES were introduced into the market in March, 2003 and April, 2004 respectively. By 2005, 85% of all stents placed were DES because they minimized early thrombotic reocclusion and the need for repeat procedures compared to its bare metal stent (BMS) predecessor. The manufacturer's recommendation discussed dual antiplatelet therapy with 325mg of Aspirin (ASA) and a thienopyradine—usually 75mg of clopidogrel (Plavix) for 3 months after the Cypher (sirolimus-eluting) stent and 6 months after the Taxus (paclitaxel-eluting) stent, after which 81 mg of ASA was deemed sufficient antiplatelet therapy.

However, a small percentage of DES patients were coming in with late stent thrombosis (LST), precipitating catastrophic events at a much higher rate than with BMS. DES's are associated with incomplete healing, fibrin deposition, and inflammatory cells at 6 months compared to BMS's, which have near complete endotheliazation at 28 days after implantation. Sirolimus (the main anti proliferative component of the Cypher Stent) can actually activate platelets and induce aggregation. Premature discontinuation of antiplatelet therapy is the greatest predictor of stent thrombosis. The Premier Registry Study looked at 500 patients with myocardial infarction (MI) with DES and found that there was a 7.5% mortality rate if patients presented with acute MI after discontinuing dual antiplatelet therapy early, compared to a 0.7% mortality rate in the patient subset compliant with dual antiplatelet therapy.[1]

Clinical Perspective: Although DES represents a major advance in the PCI field, their use mandates prolonged dual antiplatelet therapy (ASA and a thienopyradine—clopidogrel).

Risk factors for LST include: suboptimal angiographic result, high risk (small/bifurcated or long) lesions, overlapping DES, diabetes (DM), and chronic kidney disease (CKD)—and obviously early discontinuation of dual antiplatelet therapy. Low risk patients include those with an excellent angiographic response and patients who were compliant with dual antiplatelet therapy. The overall risk of stent thrombosis with DES is relatively low—0.5% to 3.5%. But when it does occur, the statistics

show an MI rate of 25-65% and a staggering fatality rate of 45%-75%.[2]

The Basket Late Trial, presented initially in 2006 at the ACC meeting, compared major adverse cardiac events (MACE)—non-fatal MI or late cardiac death—at six months after dual antiplatelet therapy was discontinued between those with BMS and DES. LST was 2-3 times higher in patients with DES compared to BMS and portended a 4 times higher risk of MACE. Additional risk factors include prior MI, need for IIbIIIa inhibitors, and presence of a preexisting DES.[3]

The 2007 the American College of Cardiology/ American Heart Association (ACC/AHA) focused update of the 2005 Guidelines was more rigorous and recommended 12 months of dual antiplatelet therapy for DES. Full dose ASA 325mg was recommended with the Cypher stent for 3 months and 6 months with the Taxus stent, which should then be decreased to 81mg along with continuing clopidogrel 75mg for at least the first year. The current recommendation for BMS is dual therapy for three months with ASA 325mg/clopidogrel 75mg, and then 81mg/day of ASA indefinitely.[4]

Clinical Perspective: Follow the guidelines above for the first year. Because of the persistent LST catastrophic risk, expert consensus recommends keeping patients with DES on lifelong dual antiplatelet therapy (clopidogrel 75mg and ASA 81mg), especially those with acute coronary syndrome, a long stent, multiple stents, overlapping stents, DM, or CKD. Exceptions would be when cost is prohibitive or if gastrointestinal bleed risk is high.

The perioperative period is risky for the patients post DES. Cessation of antiplatelet therapy is the dominant risk factor for LST. The peri-operative cessation of antiplatelet therapy can result in a rebound pro-thrombotic state. Additionally this period is a hypercoaguable state of decreased fibrinolytic activity, increased procoagulant factors, and inherent hemodynamic fluctuations. The reflexive response for surgeons is to minimize the risk of bleeding and discontinue antiplatelet therapy, irrespective of the presence of cardiac stents. However, this can lead to catastrophic stent thrombosis in 8-30% of DES patients with an incidence of MI/death 64.4%, doubling the rate.[5] A recent review of multiple studies concluded that if ASA therapy is maintained, short-term discontinuation of a thienopyridine may be relatively safe in patients with drug-eluting stents.[6] The caveat here is that the interruption of therapy was not examined in patients undergoing surgery.

Another option when having to discontinue dual antiplatelet therapy is to consider "bridging" with shorter-acting intravenous glycoprotein IIbIIIa inhibitor during the perioperative period. But evidence supporting safety and/or efficacy of this approach is only anecdotal.

Recommendations:

1) Patients should be thoroughly educated about the reasons for taking dual antiplatelet therapy and the risk of discontinuing it early.

2) Patients must be clearly told to contact their cardiologist before stopping any antiplatelet therapy for a procedure, even if instructed to do so by another healthcare professional.

3) Delay elective procedures for a minimum of 12 months in DES patients and 1 month in BMS (optimally 3 months).

4) Surgeon and cardiologist ***must discuss together*** the relative risks of bleeding during the procedure versus LST risk and find an appropriate balance.

5) A DES patient past 12 months may discontinue Plavix after speaking with a cardiologist, but continue with aspirin periprocedurally, and re load with 300mg-600mg of Plavix ASAP post procedure.

Clinical Perspective: Whenever possible dual antiplatelet therapy should be continued throughout the perioperative period, and if

stopped, it should be stopped for as short a period as possible before surgery and restarted as soon as possible after surgery. Maintaining at least aspirin 81mg-162mg monotherapy whenever possible for DES/BMS could minimize the LST risk.

Anticoagulant/ Antithrombotic Tx

All patients with prosthetic heart valves, either mechanical or bioprosthetic should be maintained on ASA 81 mg regardless of valve type unless contraindicated. All patients with mechanical valve prosthesis require anticoagulation with warfarin.[7] The targets for the INR are as follows:

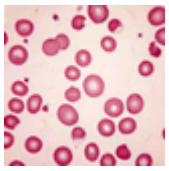
- 2-3 for aortic valve replacement (AVR) (Bileaflet & Medtronic Hall) and no risks and a bioprosthetic mitral valve replacement (MVR) with risk factors
- 2.5-3.5 for AVR (other than bileaflet & Medtronic Hall) and all mitral valve prosthesis or AVR with risk factors

Risk factors are:

- Atrial fibrillation
- Left ventricular systolic dysfunction (LVEF < 35%)
- Prior thromboembolism (previous event off warfarin)
- More than one mechanical valve
- Mitral stenosis
- Hypercoaguable state.

If a patient has any of these features and has an AVR then he/she would be deemed high risk and antithrombotic therapy entails ASA 81mg and warfarin to a goal INR 2.5-3.5.

To Bridge or not to Bridge



Many of these patients at some point will require invasive procedures which may necessitate cessation of anticoagulant therapy. Management options for "bridging" are based upon each individual's risk—valve type, position of the prosthesis, the nature of the procedure, risk of bleeding, and expected duration of the interruption of anticoagulant therapy.

Bridging Therapy: Initiate therapeutic doses of unfractionated heparin when the INR falls below 2.0 (typically 48 hours before surgery), stop 4-6 hours before the procedure, restart as early after surgery as bleeding stability allows, and continue until the INR is again therapeutic with warfarin therapy. Low-molecular weight heparin (LMWH) is a newer bridging option not mentioned in the guidelines.

Bridging is not necessary in those with newer bileaflet AVR and bioprosthetic valves with no risk factors.

Bridging is recommended in patients with high-risk of thrombosis which includes those with any MVR or a mechanical AVR with any risk factor.

In atrial fibrillation (AF) patients, bridging anticoagulation with subcutaneous LMWH or intravenous unfractionated heparin can avoid dreaded complications of arterial thromboembolism (TE), but this strategy also raises risk for bleeding, raises costs, and presents logistic challenges. Retrospective cohort studies provide limited evidence to guide recommendations, and no randomized controlled trials have been performed. All clinicians face uncertainty when deciding whether *'to bridge or not to bridge.'* Such uncertainty can be addressed only through well-designed randomized trials. The Bridging Anticoagulation in Patients who Require Temporary Interruption of Warfarin for an Elective Procedure or Surgery (BRIDGE) trial, a study sponsored by the National Institutes of Health and involving patients with chronic AF who require temporary interruption of warfarin treatment, will attempt to do just that.

Pending that study, the current clinical practice at the Mayo Clinic Thrombophilia Center is to provide LMWH bridging therapy only for those

patients at the highest risk of TE (prior stroke or TE and a CHADS 2 score ≥ 4), taking into account the procedure-associated risk of bleeding. Their strategy is based on a recent study in which the authors concluded that the 3-month cumulative incidence of TE and bleeding among patients with AF in whom anticoagulation was temporarily interrupted for an invasive procedure was low and was not significantly influenced by bridging therapy.[8] Neither bleeding nor thromboembolic events differed by anticoagulant management strategy.

Clinical Perspective: Consensus opinion would recommend bridging therapy with unfractionated heparin or LMWH in AF patients with, prior history of TE, CHAD 2 score ≥ 4, and many would add multiple risk factors and rheumatic mitral stenosis to the list.

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