ANTITHROMBOTIC THERAPY IN DIFFICULT CLINICAL CONDITIONS

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INTRODUCTION
With the development of newer and more potent antithrombotic agents cardiovascular mortality and ischemic complications in patients with acute coronary syndromes has dramatically reduced. But antithrombotic therapy at the same time can be a double edged sword in certain critical situations when there is a high risk of bleeding or thrombosis or both. Attempts to reduce ischemic events, is associated with increased risk of bleeding. Conversely, reducing bleeding complications may increase coronary thrombotic (ischemic) events. Balancing both ends of the spectrum is essential, and an individualized approach to therapy is advocated in these situations. This article will discuss antithrombotic therapy in such critical conditions (Table 1).

ANTITHROMBOTIC THERAPY IN PATIENTS WITH HIGH ISCHEMIC BURDEN
In patients with high ischemic risk such as diabetics, post PCI, small vessel disease, recent ACS (Table 2) etc, we need a more rapid and a greater inhibition of platelets to reduce the ischemic burden. Clopidogrel which has a slow onset of action, inhibits only 50% of platelets and has approximately 25 % incidence of clopidogrel resistance, may not be an appropriate choice. There are two new antiplatelet agents (prasugrel and ticagrelor) which are found to be better than clopidogrel in such situations.

Prasugrel is a new thienopyridine that inhibits adenosine diphosphate-induced platelet aggregation more rapidly, more consistently and to a greater extent than clopidogrel in patients with CAD. In the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction (TRITON–TIMI 38), patients who underwent PCI had a significant 19% risk reduction in cardiovascular death, non-fatal MI or non-fatal stroke when treated with prasugrel as compared with clopidogrel, regardless of the type of coronary stent used (9.7% vs. 11.9%, respectively; p = 0.0001). Prasugrel was also associated with a 52% risk reduction in stent thrombosis irrespective of stent type (1.13% vs. 2.35%, respectively; p < 0.0001). This benefit is somewhat negated, however, by a 39% increased risk of major bleeding with prasugrel compared to clopidogrel (1.71% vs. 1.23%, respectively; p = 0.036).

Ticagrelor is a novel, reversible adenosine diphosphate receptor inhibitor that has a more rapid onset

Table 1: Difficult situations for giving antithrombotic therapy
| Antithrombotic therapy in patients with high ischemic burden |
| Antithrombotic therapy in patients with high bleeding risk |
| Antithrombotic therapy in patients undergoing non-cardiac surgery post angioplasty and stenting |
| Antithrombotic therapy in patients with poor drug compliance |
| Anticoagulant therapy in the presence of antiplatelet therapy |
| Anticoagulant therapy in the presence of renal dysfunction |
| Anticoagulant therapy in pregnancy with prosthetic heart valve |
| Anticoagulant therapy in patients with high INR levels |
| Anticoagulant therapy in patients who sustains embolic stroke while on anticoagulant therapy |
and more pronounced platelet inhibition than clopidogrel. The Platelet Inhibition and Patient Outcomes (PLATO) trial compared ticagrelor and clopidogrel for the prevention of cardiovascular events in patients with ACS. At 1 year, cardiovascular death, MI or stroke had occurred in 9.8% of patients receiving ticagrelor as compared with 11.7% of those receiving clopidogrel with a significant 16% relative risk reduction; p < 0.001. Among patients who underwent PCI, the rate of stent thrombosis was significantly lower with ticagrelor than clopidogrel (1.3% vs. 1.9%, respectively; p = 0.009). Although there was no significant difference in the overall rate of major bleeding in this study, ticagrelor was associated with significantly higher rates of fatal intracranial hemorrhage (0.1% vs. 0.01%, respectively; p = 0.02) and major bleeding unrelated to coronary artery bypass grafting (4.5% vs. 3.8%, respectively; p = 0.03).

Therefore, in patients with high ischemic risk, prasugrel or ticagrelor should be preferred over clopidogrel. However, their use should be discouraged in patients with high bleeding risk.

**ANTITHROMBOTIC THERAPY IN PATIENTS WITH HIGH BLEEDING RISK**

There are patients whose bleeding risks outweigh the potential rewards of an aggressive antithrombotic strategy. Major bleeding related to PCI is associated with a 3-fold increase in mortality. Predictors of major bleeding in PCI and ACS include older age, female gender, hypertension, chronic kidney disease, anemia, bleeding history, history of stroke etc (Table 3a and 3b). Such patients warrant a more conservative approach to antithrombotic therapy and careful selection of antiplatelet and anticoagulant agents that are associated with less bleeding tendencies is advocated. Prasugrel should be avoided. Aspirin should be used in low doses. Loading dose of aspirin should be avoided.

### Table 2: Assessment of ischemic and bleeding risk

<table>
<thead>
<tr>
<th>Increase Ischemic risk</th>
<th>Shared risk factors</th>
<th>Increase Bleeding risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recent ACS</td>
<td>Elderly</td>
<td>Prior history of bleeding</td>
</tr>
<tr>
<td>Recent PCI</td>
<td>Female gender</td>
<td>Recurrent hemorrhagic peptic ulcer</td>
</tr>
<tr>
<td>Recurrent ACS with dual antplatelet therapy</td>
<td>Obesity</td>
<td>Intracranial surgery</td>
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<tr>
<td>LVEF &lt; 30%</td>
<td>Heart failure</td>
<td>Transurethral prostatectomy</td>
</tr>
<tr>
<td>Triple vessel disease</td>
<td>Renal failure</td>
<td>Surgery with extensive detachment</td>
</tr>
<tr>
<td>Diabetes and small vessels</td>
<td>Co-morbidities</td>
<td></td>
</tr>
<tr>
<td>Stent length &gt; 25 mm</td>
<td>Vessel diameter &lt; 2.5 mm</td>
<td></td>
</tr>
<tr>
<td>Incomplete revascularization</td>
<td></td>
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<tr>
<td>Stent thrombosis</td>
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</table>

### Table 3a: Therapeutic strategies in PCI that may enhance antithrombotic efficacy in patients at higher risk of recurrent ischemic events

- Use high-dose aspirin (e.g., 325 mg daily) for the longest recommended duration after PCI (1 month for BMS, 3 mos for SES, 6 months for PES)
- Use higher-dose maintenance aspirin (e.g., 162 mg daily) after PCI
- Use higher leading doses of clopidogrel (e.g., 600 mg; consider 900 mg) during PCI
- Extend duration of post-PCI clopidogrel therapy to at least 15 mos after stenting (consider indefinite thienopyridine therapy)
- Consider prasugrel instead of clopidogrel for both peri-PCI leading and post-PCI maintenance thienopyridine therapy
- Consider starting GP IIb/IIIa inhibitors as early as possible prior to PCI (upstream administration); continue GP IIb/IIIa inhibition after PCI using standard infusion times
- Use periprocedural heparin at higher target activated clotting times (> 300 seconds)
- Do not use fondaparinux as the sole anticoagulant during PCI (always use with heparin)
- If LMWH is used, given higher periprocedural bolus dose (e.g. enoxaparin 0.75 mg/kg); ensure that a periprocedural intravenous bolus dose (e.g., enoxaparin 0.3 mg/kg) is given if more than 8 hours has elapsed since the last pre-PCI subcutaneous dose

### Table 3b: Therapeutic strategies that may reduce hemorrhagic complications of PCI in patients at higher risk of bleeding events.

- Use lower-dose aspirin (e.g., 75-81 mg daily) after PCI
- Consider low-dose aspirin (e.g., 75-81 mg daily) during the immediate post-PCI period
- Use a lower leading dose of clopidogrel (300 mg instead of 600 mg) during PCI
- Shorten the duration of post-PCI thienopyridine therapy to the minimum recommended length (2 weeks for angioplasty, 4 weeks for BMS, 12 months for DES); discontinue at any time if bleeding events occur
- Avoid prasugrel; if used, however, use lower maintenance dose (5 mg daily)
- Avoid upstream administration of GP IIb/IIIa inhibition, consider bolus-only or abbreviated-infusion strategies of GP IIb/IIIa inhibition during PCI
- Avoid prasugrel; if used, however, use lower maintenance dose (5 mg daily)
- Consider lower-dose periprocedural anticoagulation e.g., target activated clotting times < 200 seconds, as long as dual- or triple-antiplatelet therapy is given
- Use periprocedural bivalirudin instead of heparin
- If LMWH is used, give lower periprocedural bolus dose (e.g. enoxaparin 0.3 mg/kg) only if 8-12 hours have elapsed since the last subcutaneous dose; avoid crossover from pre-PCI heparin to procedural LMWH, and vice-versa.

BMS = bare-metal stem; DES = drug-eluting stent; LMWH = low-molecular-weight-heparin; mos = months; PCI = percutaneous coronary intervention; PES = paclitaxel-eluting stems; SES = sirolimus-eluting stent
clopidogrel should be 300 mg and not 600 mg. Avoid upstream use of GP IIb/IIIa inhibitors.

Bivalirudin is a synthetic, short-acting, direct antithrombin agent that binds specifically to thrombin at its active catalytic site. With the promise of reduced bleeding complications, bivalirudin is increasingly becoming a popular alternative anticoagulant to UFH in ACS undergoing PCI. Large randomized trials have consistently shown that the use of bivalirudin in PCI significantly reduced bleeding complications, without a significant increase in ischemic events compared to UFH. 

Fondaparinux is another synthetic, pure factor Xa inhibitor that selectively binds to antithrombin, causing rapid and predictable inhibition of factor Xa. Unlike enoxaparin, fondaparinux has linear pharmacokinetics with low inter-individual and intra-individual variability, obviating the need for laboratory monitoring. Like bivalirudin, the potential for lower bleeding complications has made fondaparinux a viable alternative to heparin in ACS treatment. However during PCI if fondaparinux is used alone it can lead to an increased incidence of catheter thrombosis and hence it should always be used with heparin.

ANTITHROMBOTIC THERAPY IN PATIENTS UNDERGOING NON-CARDIAC SURGERY POST ANGIOPLASTY AND STENTING

Whenever a patient who has earlier undergone a coronary angioplasty and stenting goes for a non cardiac surgery, there is always a dilemma whether to stop antiplatelet agents or continue them in the peri-operative period. Since cessation of antiplatelet therapy in the peri-operative period can lead to rebound thrombotic phenomenon which can result in stent thrombosis that can be fatal. At the same time continuing anti platelet therapy in the peri-operative period may pose a threat of increased risk of bleeding. American College of Cardiology recommends that you delay any NCS for at least 12 months in case of DES and 1 month in case of a bare metal stent. However if you cannot postpone a surgery then there are basically three possible scenarios of temporarily withdrawal of oral anti platelet therapy for planned NCS according to bleeding risk of surgery.

1. **Surgery with low bleeding risk e.g. cataract surgery, oral dental surgery etc:** Interruption of oral antiplatelet therapy is not necessary, irrespective of the ischemic risk profile. Continue both aspirin and clopidogrel.

2. **Surgery with Intermediate bleeding risk e.g. GI surgeries, cholecystectomy, appendicectomy, etc:** Continue aspirin during peri-operative period. Stop clopidogrel 5 days prior to surgery with reintroduction as soon as possible.

3. **Surgeries with high bleeding risk e.g. intracranial surgeries, prostate surgery, aortic surgery, ENT surgeries, and surgery in posterior segment of eye:** Stop aspirin and clopidogrel 5 days before planned surgery, and substitute with alternative antithrombotic therapies which may include low-weight heparin (s.c. dose of 85–100 μg/kg for 12 h). Regular treatment should be resumed as soon as possible after surgery. Ticagrelor and cangrelor which have a very short half life can be very useful in such situations.

ANTITHROMBOTIC THERAPY IN PATIENTS WITH POOR DRUG COMPLIANCE

Warfarin is cumbersome to use, because of their multiple interactions with food and drugs, and they require frequent laboratory monitoring. So in a patient who is not well educated and is living in a remote area where facilities for INR monitoring is not available, any deviation from the narrow therapeutic level of warfarin can either lead to fatal thrombotic episode or a fatal bleeding incident.

Several novel oral anticoagulants (Dabigatran, Rivaroxaban, and Apixaban) have now been developed that act by directly inhibiting thrombin or factor Xa. These drugs have a more predictable pharmacokinetic profile than the vitamin K antagonists, so there is less variation in action between subjects. In addition, interactions with diet and other drugs are uncommon. Dabigatran in the RE-LY study, Rivaroxaban in the ROCKET-AF study and Apixaban in the ARISTOTLE study have shown that these drugs not only have an edge over warfarin in terms of reducing thrombotic events but at the same time bleeding events were less with these drugs. So when regular monitoring for INR is a problem or when multiple drug interactions are expected, Dabigatran, Rivaroxaban and Apixaban are a good alternative to warfarin.

ANTICOAGULANT THERAPY IN THE PRESENCE OF ANTIPLATELET THERAPY

We know that patients who had undergone a PTCA with a DES require a long term dual antiplatelet drugs. Now if these patients develop either an atrial fibrillation or left ventricular thrombus then they require an additional warfarin therapy. Unfortunately, there is very limited information regarding patients treated with triple therapy, who present significant clinical challenges because of the imperative to balance bleeding risks against risks entailed in stopping one of the 3 therapies. Discontinuation of warfarin might increase the potential for stroke, whereas discontinuation of clopidogrel might result in increased risk for stent thrombosis; both events are associated with significant morbidity and mortality. In such situations when the triple therapy is unavoidable there are certain points which should be kept in mind to keep a balance between bleeding and thrombosis. The dose of ASA should be kept as low as possible (i.e., 75 to 81 mg). Clopidogrel should be given at its standard dose of 75 mg/day, and warfarin should...
be administered under tight control to achieve a slightly lower target INR of 1.5 to 2.0. The prophylactic administration of proton-pump inhibitors should be considered. In patients who require long-term oral anticoagulation, serious consideration should be given to the use of BMS prostheses for which dual antiplatelet treatment is recommended for a shorter time after deployment. Newer anticoagulants such as Dabigatran, Rivaroxaban, and Apixaban should be given preference since they have a better predictable pharmacodynamics and pharmacokinetics. The next generation DES which uses a bio-absorbable polymer that physiologically degrades over a period of months after drug elution can be a good option since the requisite duration of dual antiplatelet therapy might be shorter when such bio-absorbable devices are used.17

**ANTICOAGULANT THERAPY IN THE PRESENCE OF RENAL DYSFUNCTION**

Patients with renal failure have an increased risk of both thrombotic and bleeding complications. A number of antithrombotic drugs undergo renal clearance (Table 4). Therefore, estimation of renal function is necessary when prescribing these drugs to patients with renal dysfunction. Unfractionated heparin and vitamin K antagonists generally do not require dose adjustment with renal dysfunction since they have a very minimal renal clearance and hence these should be the preferred anticoagulant in renal dysfunction patients. Low-molecular weight heparins, danaparoid sodium, bivalirudin, fondaparinux sodium and dabigatran all undergo renal clearance and should be avoided in such patients. Among GpIIb/IIIa inhibitors, eptifibatide which has high renal excretion should be avoided in renal dysfunction cases.18

**ANTICOAGULANT THERAPY IN PREGNANCY WITH PROSTHETIC HEART VALVE**

The management of women with prosthetic heart valves during pregnancy poses a particular challenge as there are no available controlled clinical trials to provide guidelines for effective antithrombotic therapy. Oral anticoagulants such as warfarin cause fetal embryopathy while replacing warfarin with subcutaneous administration of heparin sodium has been reported to be ineffective in preventing thromboembolic complications. Thus the anticoagulant approach for the woman with mechanical valve needs to be individualized. For the woman with an older generation or tilting disc mitral prosthesis which has a higher chance of thrombosis, the safer approach may to treat her with warfarin for the first 34 weeks of pregnancy particularly if her dose is less than 5 mg/day. For those patients at lesser risk (aortic prosthesis or bileaflet valves), heparin therapy may be selected as soon as pregnancy is diagnosed, warfarin substituted at 13 to 14 weeks and heparin restarted at approximately 34 weeks in anticipation of delivery.19

**ANTICOAGULANT THERAPY IN PATIENTS WITH HIGH INR LEVELS**

Life-threatening bleeding caused by warfarin requires immediate treatment with enough cryoprecipitate or fresh frozen plasma to normalize the INR and achieve immediate hemostasis. Recombinant human factor VIIa concentrate provides safe and rapid reversal of warfarin induced excessive anticoagulation.20

Minor bleeding with a prolonged INR may merely require interruption of warfarin therapy, without administration of FFP, until the INR has returned to the therapeutic range. If the INR is above 9 but without major bleeding than just giving an oral 2.5 mg of Vitamin K is a reliable and safe method for rapidly correcting an elevated INR. Injectable vitamin K should be avoided since it makes patient refractory to warfarin for up to 2 weeks. Prior to reversing an elevated INR it is useful to ensure that the abnormal laboratory value is a real and not artifactual. If bleeding occurs when the INR is within the therapeutic range, occult malignant disease should be suspected and ruled out.

If the INR is varying too much then first of all make sure that the abnormal laboratory value is a real and not artifactual. Patient drug compliance is adequate or not. Evaluate for the common drug interactions. Take proper history of all the food patient is eating. After doing all this exercise, if INR still is varying too much than consideration should be given to newer anticoagulant with predictable pharmacokinetic like Dabigatran, Rivaroxaban and Apixaban.

**ANTICOAGULANT THERAPY IN PATIENTS WHO SUSTAIN EMBOLIC STROKE WHILE TAKING ANTICOAGULANT**

For patients who sustain cardio-embolic events, while on warfarin, the anticoagulant intensity should be increased to a maximum target INR of 3-3.5 rather than routinely adding antiplatelet agents.21 Consideration should be given to the newer agents like Dabigatran, Rivaroxaban, and Apixaban which have shown superior efficacy to warfarin in preventing thrombo-embolic events.

**CONCLUSION**

Antithrombotic therapy can be tricky in certain critical situations. Balancing both ends of the spectrum with the proper antithrombotic strategy is essential, and an individualized approach to therapy is essential. Novel antithrombotic agents are promising in such situations.

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**Table 4: Renal clearance of Anticoagulants**

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<tr>
<th></th>
<th>Heparin</th>
<th>LMWH</th>
<th>Fondaparinux</th>
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<tr>
<td>Renal clearance</td>
<td>Minimal</td>
<td>100%</td>
<td>100%</td>
<td>20%</td>
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REFERENCES


