Arterial and venous thromboses are major causes of morbidity and mortality. In 1977, Macfarlane proposed that ‘thrombosis is hemostasis in the wrong place’, and since then pathological studies, clinical studies, and meta-analyses of randomized trials of antiplatelet, anticoagulant and thrombolytic drugs have supported this hypothesis by showing that platelet-fibrin hemostatic plugs are the pathophysiological basis for both arterial and venous thrombosis.

Antithrombotic drugs are used for prevention and treatment of thrombosis. These agents target the components of thrombi, and their examples include -

1. Antiplatelet drugs
   - Aspirin
   - ADP receptor antagonist -
     i) Irreversible - clopidogrel, prasugrel
     ii) Reversible - cangrelor, ticagrelor
   - Phosphodiesterase inhibitors - dipyridamole, cilostazole
   - GPIIb/IIIa receptor antagonist -
     i) IV- abciximab, eptifibatide, tirofiban
     ii) oral - xemilofiban, orbofiban, ibrafiban

2. Anticoagulant drugs
   - Parenteral
     i) Heparin, low molecular weight heparin (LMWH), fondaparinux
     ii) Direct thrombin inhibitors - lepirudin, argatroban, bivalirudin
     iii) Direct Xa inhibitors - apixaban, rivaroxaban
   - Oral vitamin K antagonists (VKAs) - warfarin

3. Fibrinolytic drugs
   - streptokinase, alteplase, reteplase, tenecteplase.

The prescription of these life saving drugs should be done keeping in mind their contraindications and adverse effects. The present article underlines the current understanding and recommendations of prescribing antithrombotics in select difficult clinical scenarios.

A. Antithrombotics and renal dysfunction
   - In patients with severe renal insufficiency (creatinine clearance [CrCl] < 30 mL/min) who require therapeutic anticoagulation, the use of unfractionated heparin (UFH) instead of LMWH is suggested. If LMWH is used, a 50% reduction of the total dose is suggested.
   - Dose reduction of lepirudin and desirudin are required in moderate renal insufficiency (CrCl 30-60 ml/min) with monitoring of APTT levels. In patients with a CrCl < 30mL/min, the use of lepirudin or desirudin is not recommended.
   - Both tirofiban (PRISM-PLUS trial) and eptifibatide (ESPRIT trial) have shown increased bleeding rates in moderate to severe renal dysfunction. Although the manufacturer recommends reducing both the bolus and infusion doses of tirofiban by 50% in CrCl < 30mL/min, the proper dose of tirofiban and eptifibatide in such patients is uncertain.

B. Initiation of Anticoagulation in some specific populations including elderly
   - VKAs should be initiated with doses between 5 and 10 mg for the first 1 or 2 days for most individuals, with subsequent dosing based on INR response. In elderly patients or those debilitated, have congestive heart failure or liver disease, have had recent major surgery,
or on drugs that increase the sensitivity to warfarin (eg, amiodarone), the use of a starting dose of < 5 mg is recommended.10

C. Management of nontherapeutic INR with Vitamin K antagonists (VKAs)

- **INRs above the therapeutic range, but < 5.0 and with no significant bleeding** - recommended actions include, lowering the dose or omitting a dose, monitoring more frequently, and resuming therapy at an appropriately adjusted dose when the INR is at a therapeutic level.11

- **For patients with INRs > 5.0 but < 9.0 and no significant bleeding** - recommended actions include, omitting the next one or two doses, and monitoring more frequently or alternatively, omitting a dose and administering vitamin K (1 to 2.5 mg) orally.11,12 If more rapid reversal is required because the patient requires urgent surgery, vitamin K (< 5 mg) orally is suggested, with the reduction of INR expected in 24 h.14

- **For patients with INRs of > 9.0 and no significant bleeding** - recommended actions include, holding warfarin therapy and administering a higher dose of vitamin K (2.5 to 5 mg) orally, with more frequent INR monitoring and additional vitamin K administered if necessary.15

- **Serious bleeding and elevated INR** - regardless of the magnitude of the elevation, recommended actions include, holding warfarin therapy and giving vitamin K (10 mg) by slow IV infusion supplemented with fresh frozen plasma, prothrombin complex concentrate, or recombinant factor VIIa, depending on the urgency of the situation. (Grade 1C).

- **Life-threatening bleeding (eg intracranial hemorrhage) and elevated INR** - regardless of the magnitude of the elevation, recommended actions include, holding warfarin therapy and administering fresh frozen plasma, prothrombin complex concentrate, or recombinant factor VIIa supplemented with vitamin K, 10 mg by slow IV infusion, repeated, if necessary, depending on the INR.14,16,17

- **Patients on long-term warfarin with a variable INR response** - suggested actions include, a trial of daily low-dose oral vitamin K (100-200 µg) with close monitoring of INR and warfarin dose adjustment.18

- **INR in antiphospholipid syndrome** - ordinarily, a therapeutic target INR of 2.5 (INR range, 2.0 to 3.0) is recommended.19 Those who have recurrent thromboembolic events with a therapeutic INR or other additional risk factors for thromboembolic events, a target INR of 3.0 (INR range, 2.5 to 3.5) is suggested.20

D. Perioperative management of patients who are on anticoagulant drugs

- **VKAs before surgery** - In patients who require temporary interruption, VKAs should be stopped approximately 5 days before surgery to allow adequate time for the INR to normalize.21 It is recommended to resume VKAs approximately 12 to 24 h (the evening of or the next morning) after surgery.22

- **VKA interrupted before surgery but with INR still elevated (> 1.5)** - suggested action is to administer low-dose (1 to 2 mg) oral vitamin K to normalize the INR.23

- **In patients with a mechanical heart valve or atrial fibrillation (AF) or venous thromboembolism (VTE) at high or moderate risk for embolism** - recommended actions include, bridging anticoagulation with therapeutic-dose LMWH (preferred) or IV UFH.24,25

- **Patients with a mechanical heart valve or AF or VTE at low risk for thromboembolism** - low-dose SC LMWH is recommended, over bridging with therapeutic-dose SC LMWH or IV UFH.24

- **Stoppage of bridging anticoagulation during surgery** - last preoperative dose of LMWH, is recommended to be administered 24 hrs before surgery and approximately half the total daily dose is given instead of 100% of the total daily dose.26 Bridging anticoagulation with UFH should be stopped approximately 4 h before surgery.27

- **In patients undergoing major surgery or with high bleeding risk** - recommended actions include, delaying the initiation of therapeutic-dose LMWH/UFH for 48 to 72 h after surgery when hemostasis is secured.28

E. Perioperative management of patients who are on antiplatelet drugs

- **Aspirin or clopidogrel before surgery** - If interruption is required, it should be done 7-10 days before surgery.29,30 It is recommended to resume aspirin or clopidogrel approximately 24 h (or the next morning) after surgery when there is adequate hemostasis.31

- **Patients at high risk of cardiac events (exclusive of coronary stents)** - recommended actions include, continuing aspirin up to and beyond the time of surgery;32 if patients are receiving clopidogrel, it should be interrupted at least 5 days and, preferably, within 10 days prior to surgery.33

- **In patients scheduled for elective CABG** - recommended actions include, continuing aspirin up to and beyond the time of CABG;34 if aspirin is interrupted, it should be reinitiated between 6 h and 48 h after CABG.35 If patients are receiving clopidogrel, it should be interrupted at
least 5 days and, preferably, within 10 days prior to CABG.36

- **In patients scheduled for percutaneous coronary intervention (PCI)** - suggested actions include, continuing aspirin up to and beyond the time of the PCI; if clopidogrel is interrupted prior to PCI, it should be resumed after PCI with a loading dose of 300 to 600 mg.37,38

- **In patients with a coronary stent (to prevent stent thrombosis)** - It is recommended to continue aspirin and clopidogrel in the perioperative period in those with bare metal coronary stent who require surgery within 6 weeks of stent placement, and in those with a drug-eluting coronary stent who require surgery within 12 months of stent placement.39,40 In patients with a coronary stent who have interruption of antiplatelet therapy before surgery, the routine use of bridging therapy with UFH, LMWH, direct thrombin inhibitors, or glycoprotein (GP) IIb/IIIa inhibitors is not suggested.41

- **Perioperative management in patients who require minor dental, dermatologic or ophthalmologic (cataract excision) procedures** - For those on VKAs or aspirin, it is recommended to continue them around the time of the procedure. If patients are receiving clopidogrel, it should be interrupted at least 5 days prior to surgery (except for the above recommendations on those with coronary stent).42

- **Patients who are receiving VKAs and require urgent surgery** - For urgent reversal of the anticoagulant effect, recommended actions include, treatment with low-dose (2.5 to 5.0 mg) IV or oral vitamin K.43 For more immediate reversal of the anticoagulant effect, treatment with fresh-frozen plasma or another prothrombin concentrate in addition to low-dose IV or oral vitamin K is suggested.44

- **For patients receiving aspirin, clopidogrel, or both, having excessive or life-threatening perioperative bleeding** - suggested actions include, transfusion of platelets or administration of other prohemostatic agents.45,46

**F. Antithrombotic therapy and pregnancy**

- **For women receiving anticoagulation for VTE who become pregnant** - it is recommended that VKAs be substituted with UFH or LMWH.47

- **Women with mechanical valves who become pregnant** - it is suggested to use either adjusted dose LMWH or UFH throughout pregnancy, or adjusted-dose LMWH or UFH (doses adjusted to keep APTT at least twice control or attain an anti-Xa level of 0.35 to 0.70 U/mL) until the thirteenth week with substitution by VKAs until LMWH or UFH are resumed close to delivery.48 The use of warfarin throughout pregnancy until the 36 weeks has also been recommended when warfarin dose is below 5 mg per day during the first trimester.49

- **In pregnant women with high-risk mechanical valves (eg, older-generation valve in the mitral position or history of thromboembolism)** - it is suggested to use oral anticoagulants over heparin.50,51 This recommendation gives equal importance to prevention of maternal VTE to that of avoiding fetal risks. The addition of low-dose aspirin, 75 to 100 mg/d is also suggested.52

- **For women with antiphospholipid antibodies and recurrent (three or more) pregnancy loss or late pregnancy loss and no history of venous or arterial thrombosis** - recommended actions include, antepartum administration of prophylactic or intermediate-dose UFH or prophylactic LMWH combined with aspirin.53

- **Lactating woman on antithrombotics** - For lactating women using warfarin or UFH, it is recommended to continue these medications.54,55 Also, lactating women using LMWH, danaparoid, or r-hirudin who wish to breastfeed, it is suggested to continue these medications.56 For those women who are on pentasaccharides (eg, fondaparinux), alternative anticoagulants are suggested.47

**G. Cerebrovascular accident (CVA) in a patient on antithrombotics**

- **Initial response** - It is recommended that both Warfarin and heparin be stopped immediately when CVA occurs (heparin shown to have a 15-25% chance of converting a non hemorrhagic into a hemorrhagic stroke).57

- **CT scan reveals no hemorrhage** - Heparin should be administered to maintain an aPTT at the lower end of therapeutic level until Warfarin started.57

- **CT scan reveals hemorrhage** - antithrombotic therapy should be withheld until the bleed is stabilized (7 to 14 days).57

- **Embolic event occurring in a patient on adequate antithrombotic therapy** - the therapy should be altered as follows 57

  - If on warfarin and INR 2 to 3: increase dose to achieve INR 2.5-3.5.
  - If on warfarin and INR 2.5 to 3.5: add aspirin 50 to 100 mg/d
  - If on warfarin and INR 2.5 to 3.5, plus aspirin 80 to 100 mg/d: aspirin dose may be increased to 325 mg/d
  - If on aspirin 325 mg/d: switch to warfarin (INR 2 to 3).


