**Expert Opinion:**

**Anti-platelet Drugs : End of the Road or Beginning of the Era**

**Expert:** Dr. Satya Gupta  
MD, DM (CMC Vellore)  
FIC (France)

**Interviewer:** Dr. Jayesh Bhanushali  
MD

**Dr. Jayesh:** I'm with Dr. Satya Gupta, young, dynamic and growing cardiologist of Ahmedabad. Dr. Gupta, what is the aim of this issue?

**Dr. Satya Gupta:** In this issue, I have highlighted common information about anti-platelet drugs. Also, to clarify the difference between anti-platelet, anti-thrombotic and anti-coagulant drugs. What are the indication of these drugs and how long to continue and when to stop these drugs? First of all, we will discuss the mechanism of thrombus formation and then discuss what the roles of various drugs? We must be familiar with the term anti-platelet, anti-coagulant, anti-thrombotic and fibrinolytic. (Table-1) These are not synonymous, but each is different and have different indications.

**Message from Editor**

Platelets have been shown to play a central role in the pathogenesis of atherosclerosis and its fatal consequences. Various platelet receptors have been identified and drugs are available to block every possible mechanism of platelet adhesion and activation. Apart from Aspirin and Clopidogrel, various new anti-platelet agents (Prasugrel, AZD6140, Cangrelor) are in clinical trial which will change our pattern of practice in the near future and would leads to better outcome. This issue highlights very common issues and guidelines which are vitals for use of these drugs in clinical practice.

**Dr. Satya Gupta**
Dr. Jayesh: Sir, in a normal individual, why blood remains in fluid state and when does it turn into a clot (thrombus)?

Dr. Satya Gupta: Normal blood in the circulatory system remains in liquid state in healthy individual. A monolayer of endothelial cells lines the intimal surface of the entire circulatory tree, thereby representing the only stationary cell type that component of blood ever come in contact with under normal circumstances. Normal, quiescent endothelium constitutively displays potent antithrombotic and prothrombotic surfaces which are in balance state in healthy individual. It expresses anticoagulant, pro-fibrinolytic, and platelet inhibitory properties. Whenever endothelium is activated or perturbed (fissure, rupture or ulceration of preformed atheromatous plaque) due to sheer stress or any other factors, it rapidly transforms to a pro-thrombotic surface that actually promotes coagulation, inhibit fibrinolysis, and activates platelets.

Dr. Jayesh: Once the endothelium become active, what happens next?

Dr. Satya Gupta: Plasma coagulation protein (clotting factors) normally circulates in blood in fluid and inactive form. When the thrombo-resistant nature of vascular system is altered, two main systems get activated; firstly release of various platelet activators (epinephrine, collagen, ADP, arachidonic acid and thrombin) from active endothelium leads to activation of inactive platelets with many adhesion receptors on it. Secondly, normal plasma coagulant proteins (soluble form) get converted into active form (insoluble fibrin thread) by activation of clotting cascade. This leads to formation of hemostatic thrombi composed of platelets and fibrin thread which ultimately leads to either partial or complete occlusion of vessel presenting as acute coronary syndrome.

Dr. Jayesh: So, if we can stop any of this mechanism, the formation of clot can be prevented?

Dr. Satya Gupta: Yes, you are right, Dr. Jayesh. If by any mechanism, we can stop activation of platelets and plasma clotting protein, ultimately we can prevent thrombus formation.
**Dr. Jayesh:** Can you explain me mechanism, site of action and doses of all commonly used drugs?

<table>
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<tr>
<th>Drug</th>
<th>Action</th>
<th>Mechanism</th>
<th>Dose</th>
<th>Indications</th>
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<tbody>
<tr>
<td>Aspirin</td>
<td>Anti-platelet</td>
<td>Inhibit TxA2 mediated platelet activation</td>
<td>162-325 mg stat followed by 75-162mg daily as maintenance</td>
<td>All patients with proven CAD unless contraindication or intolerant to Aspirin</td>
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<tr>
<td>Clopidogrel</td>
<td>Anti-platelet</td>
<td>Inhibit ADP mediated platelet activation</td>
<td>300mg bolus followed by 75-150 mg daily</td>
<td>All patients with ACS</td>
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<td>Abciximab</td>
<td>Anti-platelet</td>
<td>Inhibit final pathway of platelet-fibrin aggregation by blocking GP2b3a receptors</td>
<td>0.25mg/kg bolus, then 0.125mg/kg/min up to max of 10µg over 12 h. 180µg/kg bolus, then 3µg/kg/min up to 72-96 h 0.4µg/kg/min IV for 30 min followed by 0.10µg/kg/min for 48-96 h (See product leaflet for dosing in different situations)</td>
<td>Patients with ACS for PCI, Patients with proven Aspirin resistance</td>
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<td>Eptifibatide</td>
<td>Anti-platelet</td>
<td>Inhibit thrombin mediated activation of fibrinogen &amp; ultimately fibrin-platelet clot formation</td>
<td>LMWH: 1mg/kg SC every 12 h</td>
<td>High risk UA patients</td>
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<tr>
<td>Tirofiban</td>
<td>Anti-platelet</td>
<td>Inhibit thrombin mediated activation of fibrinogen &amp; ultimately fibrin-platelet clot formation</td>
<td>UFH: 60-70 IU/kg (Max 5000IU) followed by infusion of 12-15IU/kg/h (max 1000IU/h).</td>
<td>All patients with ACS for at least 5-7 days</td>
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<tr>
<td>Heparin (UFH or LMWH)</td>
<td>Anti-thrombin</td>
<td>Inhibit Thrombin mediated activation of fibrinogen &amp; ultimately fibrin-platelet clot formation</td>
<td>UFH: 60-70 IU/kg (Max 5000IU) followed by infusion of 12-15IU/kg/h (max 1000IU/h).</td>
<td>All patients with ACS for at least 5-7 days</td>
</tr>
<tr>
<td>Bivalirudin</td>
<td>Anti-thrombotic</td>
<td>Direct thrombin inhibition, prevent activation of fibrinogen &amp; ultimately fibrin-platelet clot formation</td>
<td>0.1mg/kg bolus followed by 0.25mg/kg/h IV infusion</td>
<td>Alternative to Heparin, Patients with HIT</td>
</tr>
<tr>
<td>Warfarin Coumadin</td>
<td>Anti-coagulant</td>
<td>Inhibit coagulation pathway by inhibiting Vit-K dependent factors</td>
<td>Start with 2.5-5mg/day, titrate dose according to PT/INR report</td>
<td>AMI with document mural thrombus, AMI with Aftlb</td>
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</table>

**Dr. Jayesh:** What are the advantages of LMWH over standard Heparin?

**Dr. Satya Gupta:** (1) Unlike UFH, it can inhibit platelet bound factor Xa and therefore more effective anticoagulant. (2) LMWH binds less readily to plasma proteins and vascular and blood cells and is more resistant to neutralizations by platelet factor-4; this produces longer plasma half life, more predictable bio-availability. (3) It has less pronounced effect on platelet function and vascular integrity, which contribute to its lower risk of bleeding. (4) It can be administered as a fixed dose, once-daily or twice-daily subcutaneous injection, without need for laboratory monitoring.

**Dr. Jayesh:** Why do we give anti-thrombotic? (viz heparin) for a short period of time and anti-platelets for a life long in a patient of CAD?

**Dr. Satya Gupta:** As I explained, acute coronary syndrome is a result of plaque rupture and thrombus formation; hence we want to inhibit thrombus formation as well as platelet inhibition. While in the chronic maintenance therapy, plaque rupture is not an issue, therefore patient can be only on oral anti-platelet drug.

**Dr. Jayesh:** What is Dual Anti-platelet Therapy (DAPT)?

**Dr. Satya Gupta:** It is very frequently used term today. All post PCI patients should be on two anti-platelet drugs (Aspirin and Clopidogrel ). Continuation of both drugs depends on type of stent used and patient’s clinical risk of thrombosis.

**Dr. Jayesh:** What is drawback of premature stopping of DAPT after Angioplasty?

**Dr. Satya Gupta:** All patients who undergo PCI with stenting should be on strict dual anti-platelet drugs. Premature stopping of either or both drugs lead to acute stent thrombosis. Meta-analysis has shown that premature discontinuation of DAPT is the main factor for acute stent thrombosis.
Dr. Jayesh: What are current recommendations of Aspirin and Clopidogrel in various scenarios?

<table>
<thead>
<tr>
<th>Medical Treatment</th>
<th>PCI with Bare Metal Stent (non-medicated)</th>
<th>PCI with Drug Eluting Stent (Medicated)</th>
<th>Post CABG</th>
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<tr>
<td>Aspirin 75 to 162 mg/d indefinitely (Class-I LOE: A) &amp; Clopidogrel 75 mg/d at least 1 mo (Class-I LOE: A) and up to 1 yr (Class-I LOE: B)</td>
<td>Aspirin 162 to 325 mg/d for at least 1 month, then 75 to 162 mg/d indefinitely (Class-I LOE: A) &amp; Clopidogrel 75 mg/d for at least 1 month and up to 1 yr (Class-I LOE: B)</td>
<td>Aspirin 162 to 325 mg/d for at least 3 to 6 months, then 75 to 162 mg/d indefinitely (Class-I LOE: A) &amp; Clopidogrel 75 mg/d for at least 1 yr or lifelong in high risk patients (Class-I LOE: B)</td>
<td>Aspirin for life long. Clopidogrel to be added if Aspirin allergy or intolerance</td>
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Dr. Satya Gupta: At the end, I would suggest readers not to stop Aspirin and Clopidogrel in patient who received drug eluting stent. Still there is no clear guideline about when to stop these drugs. I wish good luck to all the readers of Healthy Heart.

Patients with bileaflet valve in aortic position without additional risk factor for thromboembolism

- **Warfarin with a target INR of 2.5 (range 2.0-3.0)**
- **Patients with bileaflet or tilting disc valve in the aortic position with Afib or with bileaflet or tilting disc valve in mitral position.**
  - **Warfarin alone with a target INR of 3.0 (range 2.5-3.5)**
  - Or
  - **Warfarin with a target INR of 2.5 (range 2.0-3.0) plus Aspirin (80-100 mg/d)**

Patients with caged valve (“Starr Edwards”) or caged disc valve or those with any mechanical valves and other associated risk factors for thromboembolism.

Combined therapy with Warfarin with a target INR of 3.0 (range 2.5-3.0) and Aspirin (80-100 mg/d)

Dr. Jayesh: What is recommendation for anti-coagulant prophylaxis in women with mechanical prosthetic valve during pregnancy?

Patients with bioprosthetic heart valve

- **Warfarin with a target INR of 2.5 (range 2.0-3.0) for 3 months. After this period, those not at risk of systemic embolism from other factors (Afib) can be treated with Aspirin.**

Dr. Satya Gupta: When blood clotting factors come in contact with artificial prosthetic valve, there is activation of intrinsic coagulation pathway by virtue of contact factors. It is very important to keep coagulation pathway under control. Heparin as an anti-coagulant can be given instead of oral in case of pregnant lady. When we combine anti-platelets drug with oral anti-coagulant, INR can be little less.

Dr. Jayesh: What is the current recommendation of anti-coagulant and anti-platelet drugs in patients with prosthetic valves?

**Dr Satya Gupta:** All patients with mechanical prosthetic valve should receive oral anti-coagulants.

Dr. Satya Gupta: I wish good luck to all the readers of Healthy Heart.
Quiz of the Month

1) Which of the following is not anti-platelet drug:
   A. Aspirin
   B. Warfarin
   C. Heparin
   D. Tirofiban

2) How many GP2b3a receptors are found on one activated platelet:
   A. 3,800
   B. 40,000
   C. 80,000
   D. 1,20,000

3) Patient with unstable angina should receive all of the following drugs except:
   A. Heparin (Either UFH or LMWH)
   B. Aspirin and clopidogrel
   C. Streptokinase or Urokinase
   D. Simvastatin or Atorvastatin

4) Following are the disadvantages of treating a patient of acute STEMI with thrombolytic agent rather than primary angioplasty:
   A. 10% risk of re-infarction
   B. Reperfusion failure in 50-70% of patients
   C. Intra cranial bleeding
   D. All of the above

5) Final common pathway of platelet aggregation and platelet-fibrin interaction is via:
   A. GP2b3a receptors
   B. Thrombin mediated
   C. ADP mediated
   D. Von Willebrand factor

6) Antidote of streptokinase is:
   A. Protamine
   B. Methylene blue
   C. Epsilon amino caproic acid (EACA)
   D. Anti-trypsine

7) Overall mortality reduction with Aspirin in patient with acute MI is:
   A. 17%
   B. 23%
   C. 33%
   D. 42%

8) All of the following are direct thrombin inhibitor except:
   A. Hirudin
   B. Heparin
   C. Bivalirudin
   D. Ximelagatran

9) All of the following can be probable mechanism of Aspirin resistant except:
   A. Concomitant use of other antiplatelets drugs & NSAID
   B. Genetic polymorphism of enzymes
   C. Alternate pathway of thromboxane synthase
   D. Poor patient compliance

10) Current recommendation of Dual anti-platelet drugs (Aspirin & Clopidogrel) for patient with Angioplasty with DES is:
    A. 3 months
    B. 6 months
    C. 9 months
    D. 1 Year or even longer in high risk patients

Echo Fellowship Batch : February 2009

Next Issue : Focus on Arrhythmia & HF Management

Editor : Dr. Ajay Naik
Question and Answer of Previous Issue


1) True about ACE Inhibitors is all except:
   A. Increase renin
   B. Increase angiotensin-1
   C. Decrease renal blood flow
   D. Increase bradykinin

2) Digoxin level is increased in all except:
   A. Phenytoin
   B. Amiodarone
   C. Erythromycin
   D. Verapamil

3) The most densely vascularized area of the heart is:
   A. Apex
   B. Diaphragmatic surface
   C. Interventricular septum
   D. Anterolateral wall

4) RV impulse is prominent in:
   A. MS with severe PAH
   B. Ebstein's anomaly
   C. Tricuspid atresia
   D. TOF with pulmonary atresia

5) Down's syndrome: most commonly associated with:
   A. Endocardial Cushion Defect
   B. TOF
   C. Pulmonary stenosis
   D. VSD

6) Eplerenone is:
   A. Aldosterone antagonist
   B. Endothelin antagonist
   C. Cholesterol absorption inhibitor
   D. Phosphodiesterase 3 inhibitor

7) Regression of atherosclerosis is by all except:
   A. Statins
   B. Nitrates
   C. Calcium channel blockers
   D. ACE-inhibitors

8) Severity of MR is assessed by all except:
   A. Cardiomegaly
   B. Loudness of murmur
   C. Wide splitting of S2
   D. MDM

9) Non synchronized DC shock is used for:
   A. VF
   B. A flutter
   C. AF
   D. VT

10) Kussmaul sign is not found in:
    A. Chronic Constrictive Pericarditis
    B. Cardiac tamponade
    C. RVMI
    D. Pulmonary embolism

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Feed Back Form

Please send your feedback and answers to the Quiz for this issue and drop it in the post box:

Name: _________________________________________________
Degree __________ Name of clinic/hospital: ___________________
Address:________________________________________________
City: ________________ State: _____________ Pin : ___________
Contact No. (O) _______________  (Mobile) __________________
Email ID: _______________________________________________

- Did you like this issue?  Yes □ No □
- Did you like the Topic of the issue? Yes □ No □
- Do you think this issue updated your academic knowledge? Yes □ No □

Answer Sheet of the Quiz of Healthy Heart
Volume 1 Issue-6 (January-February 2009)

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<th>Question No.</th>
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Dear Colleague,

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   (b) HIV or
   (c) Other disease

Patients who are on conventional treatment for Pulmonary Hypertension and either not responding or worsening will be provided the following services free of cost:

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All the patients will be appropriately sent back to you for further management. Newer modalities of treatment and supportive care will be offered to the patient & family.

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At The Heart Care Clinic we are also starting a “Heart Failure Clinic” exclusively for Patients with moderate to severe LV Dysfunction with EF < 35%.

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(a) Dilated Cardiomyopathy
(b) Hypertensive Heart Failure
(c) Non Ischemic severe Heart Failure
(d) Ischemic severe Heart Failure
(e) All severe Heart Failure Patients

Patients will be provided the following services free of cost:

a. Free consultation
b. Free Echocardiography with CD
c. Newer modalities of care will be offered

All the patients will be appropriately sent back to you for further management.

For further details call at The Heart Care Clinic or any of the Cardiologists