Dear Friends,
Hello!

Winter, the season of conference, has just ended. Hope all of you have gathered some additional knowledge which can help your practice and patient care.

You all have been coming across prescriptions bearing ‘prasugrel’ and ‘ticagrelor’ medicines. Though, so far, these two drugs have been mostly used by interventional cardiologists, soon they would be entering your practice too.

I hope this volume of ‘Healthy Heart’ would provide you with all necessary knowledge and data to use these two drugs in suitable patients.

Best Regards,
- Dr. Anish Chandarana

Acute Coronary Syndrome: Newer Antiplatelet Agents

Acute Coronary syndrome (ACS) includes variety of clinical presentations bearing similar underlying pathophysiologic mechanisms—a disruptive plaque resulting in platelet aggregation and thrombosis, which in turn produces a high-grade stenosis or occlusion of a coronary artery with or without associated emboli entering the microcirculation downstream.

This includes three major groups of patients:
1. Patient with unstable angina at risk of myocardial infarction
2. Patients with non-ST segment elevation (ECG changes other than ST elevation, may include ST depression, T inversion or no significant ECG Changes) myocardial infarction
3. Patients with ST segment elevation myocardial infarction

Early pharmacological treatment in such patients presenting to emergency room is crucial, lessening the impact on both morbidity and mortality, with the centre of management being antiplatelet agents.

Obviously, for nearly a decade or more, aspirin and clopidogrel have been the drugs of choice. An array of newer, more potent and effective antiplatelet agents are now available and few will become available in near future. Definite data has been emerging suggesting these agents have superior antiischemic properties leading to improved short and intermediate-term outcomes. At the same time, some agents do have higher bleeding risks making it mandatory to adopt proper patient selection and continuous vigilance to drive net clinical benefit.

Till almost end of 2011, aspirin+ clopidogrel combination was the standard of care, unless contraindication, for all patients with ACS, irrespective of the management strategy—either only medical care or percutaneous intervention or coronary artery bypass surgery. This combination was superior to aspirin alone in reducing composite end point of death, myocardial infarction or stroke.

Many limitations of clopidogrel got surfaced leading to important clinical consequences like recurrence of ischemic events and stent thrombosis.
1. It’s a pro-drug requiring CYP2C19 dependent two-step metabolic conversion to active form in liver. Upto 15% individuals have impaired metabolism making them ‘non-responders’. And this makes them at upto 3 times increased risk of major cardiovascular events.

2. There are many drug-drug interactions.

3. It has quite slow onset and slow offset of action, raising some serious issues when a patient needs urgent PCI or when a preloaded patient has to have early surgical revascularization.

Various attempts have been made to overcome short falls of clopidogrel. Giving double loading and double maintenance dose of clopidogrel for first 7 days, studying platelet responsiveness and giving higher maintenance dose to selected patients etc. efforts have not resulted into real practical advantages.

This makes it very evident that there is a need of novel antiplatelet agent that could overcome few of these limitations of clopidogrel in the management of ACS. The ideal oral antiplatelet agent would be rapidly and completely absorbed, would achieve fast and thorough antiplatelet effects within few minutes, would show no inter-individual variation of effects, no drug-drug interaction and would have rapid reversibility of its antiplatelet effects. And in addition to being more effective and safer, it should be proven through large protective randomized clinical trials.

Following five agents have been tested and due to good results of RCTs, first two have been into clinical practice for last 1-2 years.

1. Prasugrel
2. Ticagrelor
3. Cangrelor
4. Elinogrel
5. Verapaxer

We will review first two agents in details.

**PRASUGREL:**

**Key Points:**
- Thienopyridine derivative which competitively binds to ADP receptor-P2Y12.
- Orally active prodrug requiring one step hepatic metabolism to get converted to active drug.
- Selective and irreversible inhibition of P2Y12 receptors.
- Potent inhibitor with no inter individual variability, effective in clopidogrel non-responders also.
- Rapid onset but very slow offset of action.

When loaded with 60 mg dose, desired platelet inhibition is achieved in 20-30 minutes and maintenance dose is 10 mg/day for people less than 70 years of age and weighing more than 60 kg. To have complete offset of action, we need to stop this drug for 7 days.
Indication:
1. In ACS patients, after coronary angiography when PCI is planned. It is not an emergency room drug as if patient turns out to be a CABG candidate after CAG, he will require to wait for 7 days if loaded with prasugrel.

In TRITON-TIMI 38 Trial combination of aspirin+ prasugrel was tried in more than 13000 patients with median duration of follow up of 12 months. Composite of death from cardiovascular causes, MI or stroke was less with P+A than with C+A, but at the cost of increased risk of bleeding-TIMI major, life threatening and fatal. Bleeding risk was very high in patients who were aging > 75 years or whose body weight was < 60 kg or who had past history of any stroke/IA.

So these three groups of patients are strong contraindications to use of prasugrel. Benefit was much higher without any increase of bleeding in two subgroups of patients-those with diabetes or those with STEMI. That’s why all patients of diabetes with ACS undergoing PCI or all patients with STEMI undergoing PPCI should be loaded with 60 mg of prasugrel in cath lab after CAG is done if they are already not on clopidogrel or any other antiplatelet other than aspirin. Patient already loaded with clopidogrel should not be switched over to prasugrel–there is no documented safe way to do that.

2. It is not indicated for medically managed patients of ACS as TRILOGY ACS trail which compared prasugrel vs clopidogrel, both in combination of aspirin, failed to show any extra benefit of former over later.

TICAGRELOR:
Key Points:
◆ Direct binding to P2Y12 receptor and it’s reversible
◆ Not a prodrug and does not require any metabolic conversion, so onset of action is fast. With loading dose & 180 mg, adequate antiplatelet effect is achieved in 30 minutes
◆ Greater and more consistent inhibition of platelet with less inter individual variability
◆ Since it binds reversibly, recovery of platelet function does not depend on generation of new platelets. So offset of action is fast, We need to stop 90 mg BD maintenance dose for 3-5 days

Indication:
1. Moderate to high risk patients of NSTEMI-ACS irrespective of management strategy-conservative or invasive
2. STEMI patient, not thrombolyzed undergoing primary PCI

This drug can be given in emergency room, even when management strategy is not decided. And all patients, including those already receiving clopidogrel can

Properties of P2Y12 Antagonists

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Clopidogrel</th>
<th>Prasugrel</th>
<th>Ticagrelor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct acting</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Receptor binding</td>
<td>Irreversible</td>
<td>Irreversible</td>
<td>Reversible</td>
</tr>
<tr>
<td>PD onset</td>
<td>Slow 2-4 hr</td>
<td>Rapid 30 min</td>
<td>Rapid 30 min</td>
</tr>
<tr>
<td>IPA (%)</td>
<td>40-60</td>
<td>&gt; 80</td>
<td>&gt; 80</td>
</tr>
<tr>
<td>PD offset</td>
<td>Slow 5 days</td>
<td>Slow 7 days</td>
<td>Fast 3-5 days</td>
</tr>
<tr>
<td>Non-responders</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>
also be switched over to ticagrelor with safety.

IN PLATO study, ticagrelor with aspirin was compared against clopidogrel with aspirin in more than 18000 patients treated for 6-12 months. Ticagrelor was better than clopidogrel in reducing primary composite endpoints of cardiovascular death, MI or stroke. This was achieved without increase in TIMI major bleeding rates. Even there was reduction in total death rate with ticagrelor. Like prasugrel it showed reduced risk of stent thrombosis as compared to clopidogrel. Unlike prasugrel, ticagrelor showed more consistent benefits over clopidogrel in subgroups of elders, patients with low body weight, patients with past history of stroke/TIA or patients with abnormal renal function.

There are few issues with ticagrelor: It failed to show benefits over clopidogrel in US and Canada, likely reasons were higher doses of aspirin used or selection of low risk patients. Approximately 13% patients on ticagrelor have dyspnea, obviously without any objective evidence of abnormal lung or heart function. One percent has to discontinue medicine. More bradyarrhythmias with > 3 second pauses are seen on ticagrelor, but is not associated with increased need of pacemaker implantation. There is increase in serum creatinine and uric acid levels with ticagrelor.

### 3. CANGRELOR:

It’s a directly acting intravenous antiplatelet agent with very rapid onset (15 minutes) and very rapid offset (60 minutes) of action. Its uses are during PCI in ACS patients and those patients of ACS waiting for CABG. In later subgroup, use of cangrelor can provide good safety till patient sails to CABG after stabilization.

### 4. ELINOGREL:

It’s a directly acting, available in both oral as well as intravenous forms, antiplatelet agent. It’s still under clinical evaluation.

### 5. VORAPAXAR:

It’s a PAR4 receptor blocker.
ECMO ECLS
(Extracorporeal Membrane Oxygenation-Extracorporeal Life Support System)
First in Gujarat, Rajasthan, Madhya Pradesh

ECMO is a ray of hope for patient’s with:
- Multi organ failure
- ARDS & respiratory failure
- Complex congenital heart disease
- Newborns with complex respiratory disease (I.E. PPHN, MAS)
- Post cardiac surgeries and others

ONE OF THE LARGEST ECMO TEAM OF INDIA

ECMO Chief Co-ordinators
Dr. Dhaval Naik +91-90991 11133
Dr. Keyur Parikh +91-98250 66664

ECMO Critical Care/ Respiratory Team
Dr. Vishal Thakkar +91-98250 88220
Dr. Bhagyesh Shah +91-90990 68938
Dr. Harshil Thaker +91-99099 19963
Dr. Dharnshri Ate Singh +91-82380 01977
Dr. Amit H. Patel +91-98243 10150
Dr. Nitesh K. Shah +91-98250 27487

ECMO Neonatology & Pediatric Cardiac Team
Dr. Kishayap Sheth +91-99246 12288
Dr. Shaunak Shah +91-98250 44502
Dr. Amit Chitaliya +91-90999 87400

ECMO Cardiac Team
Dr. Ajay Naik +91-98250 82666
Dr. Satya Gupta +91-99250 45780
Dr. Vineet Sankhla +91-99250 15056
Dr. Gunvant T Patel +91-98240 61266
Dr. Milan Chag +91-98250 66664
Dr. Urmil Shah +91-98250 66939
Dr. Hemang Baxi +91-98250 30111
Dr. Anish Chandarana +91-98250 96922

ECMO Cardiac Surgery Team
Dr. Dhiren Shah +91-98255 75933
Dr. Dhavalk Naik +91-90991 11133
Dr. Saurabh Jaisingh +91-95867 25827

ECMO Cardiac Anaesthetist Team
Dr. Niren Bhavsar +91-98795 71917
Dr. Hiren Dhokalia +91-98593 75818
Dr. Chintan Sheth +91-91732 04454
Dr. Deepak Desai +91-93270 15673

ECMO Trauma Team
Dr. Sanjay Shah +91-98980 00265

ECMO Thoracic Team
Dr. Pranav Modi +91-99240 84700

ECMO Infectious Disease Team
Dr. Surabhi Madan +91-97129 71863

ECMO Perfusionist Team
Mr. Ulihas Padiyak +91-98983 57772
Mrs. Dhanyata Dhokalia +91-95864 49430

ECMO Nursing Team

ECMO Packages (8 days)*

<table>
<thead>
<tr>
<th>Particulars</th>
<th>CIMS Rate</th>
<th>Subsidised from RKP Trust for less affording patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECMO (General Ward)</td>
<td>₹ 4,70,000</td>
<td>₹ 3,95,000**</td>
</tr>
<tr>
<td>ECMO (Single Class)</td>
<td>₹ 6,70,000</td>
<td>---</td>
</tr>
<tr>
<td>ECMO (Suite Class)</td>
<td>₹ 9,00,000</td>
<td>---</td>
</tr>
</tbody>
</table>

*Conditions apply
**The subsidy shall be provided to patients who fulfil the criteria of under privileged as per the Trust's screening process
Calcific aortic stenosis is the most common indication for surgical valve replacement. Currently, surgical valve replacement is the only treatment for this disease process. For years, this disease has been described as a passive process that develops secondary to serum calcium attaching to the valve leaflet surface to cause nodule formation. Therefore, surgical replacement of the valve is the obvious approach toward relieving outflow obstruction in these patients. Recent studies demonstrate an association between atherosclerosis and its risk factors in the mechanism of vascular and aortic valve disease is emerging; progress in studying the cell biology of this disease has been limited in the past paucity of experimental models available.

In 2006, a number of epidemiologic and experimental studies provided evidence that this disease process is not a passive phenomenon. Moreover, the histologic and experimental models indicate that there is an active cellular biology that develops within the valve leaflet and causes a regulated bone formation to occur. A similar paradigm shift occurred in the last part of the twentieth century in the field of vascular disease. Vascular atherosclerosis, once thought to be a “degenerative process,” is now an active biologic process that can be targeted with medical therapy. A similar phenomenon has occurred with aortic valve disease and with the growing number of clinical and experimental studies over the past decade. The growing evidence for the etiology of degenerative calcific aortic valve disease points toward a “response to injury” mechanism similar to what has been described for vascular atherosclerosis.

If the atherosclerosis hypothesis is present in the development of aortic stenosis, then treatment used in slowing the progression of vascular atherosclerosis may be effective in patients who have aortic valve disease. Current management of calcific aortic valve disease focuses on defining patients who have valvular disease and the development of symptoms to determine the timing of surgical valve replacement. This article reviews the pathogenesis and the potential for medical therapy in the management of the patients who have calcific aortic stenosis but the growing number of retrospective and prospective clinical studies evaluating the use of statins as a potential for cholesterol lowering treatment to prevent progression of aortic valve calcification.

Respective studies evaluating statins in aortic valve disease
Currently, there are six retrospective studies in echocardiographic and electron beam CT databases that demonstrate the efficacy of statin and angiotenin-converting enzyme (ACE) inhibitor therapy in the treatment of aortic valve stenosis. These studies demonstrate that the progression of aortic stenosis is slowed in patients who have aortic valve disease and are already on statin therapy and ACE inhibitors as shown by echocardiographic parameters and electron beam CT. The patients who had aortic stenosis in these databases were already taking medications targeting LDL and hypertension. Furthermore, these studies demonstrate the potential effect of slowing the progression of their aortic stenosis with these medications.

Prospective studies for statins and aortic valve disease
The first randomized prospective study testing the effects of statins in aortic valve disease was published in 2005. In this double-blind placebo-controlled trial, patients who had calcific aortic stenosis were randomly assigned to receive 80 mg of atorvastatin daily or a matched placebo. Aortic valve stenosis and calcification were assessed with the use of Doppler echocardiography and helical CT, respectively. The primary end points were changes in aortic-jet velocity and aortic-valve calcium score. Seventy-seven patients were assigned to atorvastatin and 78 to placebo, with a median follow-up of 25 months. Serum LDL cholesterol concentration remained at 130 ± 30mg/dL in the placebo group and fell to 63 ± 23 mg/dL in the atorvastatin group. Increases in aortic-jet velocity were 0.199 ± 0.210 m/sec per year in the atorvastatin group and 0.203 ± 0.208 m/sec per year in the placebo group. Progress in valvular calcification was 22.3 ± 21.0% per year in the atorvastatin group and 21.7 ± 19.8% per year in the placebo group.

The Scottish aortic stenosis and lipid lowering therapy, impact on regression(SALTIRE) investigators concluded that intensive
l lipid-lowering therapy does not halt the progression of calcific aortic stenosis or induce its regression. The major difficulty with the study design is that the patient treated with atorvastatins received the therapy too late in the course of the disease process. In view of the experimental data, the earlier in the disease process the statin therapy I initiated, the better the potential for slowing the progression of this disease.

Currently, there are three other prospective clinical trials testing the effects of statins in aortic valve disease: Aortic Stenosis Progression Observation Measuring Effect of Rosuvastatin (Canada); Simvastatin and the Ezetimide in Aortic Stenosis (Europe); and Stop Aortic Stenosis(Cleveland Clinic, Cleveland, Ohio). The Rosuvastatin Affecting Aortic Valve Endothelium (RAAVE) trial suggested that earlier treatment with statin is more efficacious in the prevention of progression of aortic valve stenosis than late treatment, similar to the effects of statins in the regression of vascular atherosclerosis.

Summary: Our understanding of aortic valve disease has evolved in the past decade from a degenerative process to an active biologic disease. Results of the SALTIRE trial demonstrate that future clinical trials for this disease process are important and that timing of the initiation of therapy is critical in the potential treatment of this disease. The results of this trial have provided important guidelines for enrollment criteria and baseline characteristics for initiation of future aortic valve trials. Aortic valve disease, although it has a similar atherosclerotic pathogenesis, is a different disease in terms of bone calcification. The timing of statin therapy to slow the progression of bone formation in these lesions will dictate the future of medical therapy for these patients. The SALTIRE trial has clearly proved this important effect with the late initiation of treatment in this clinical trial. Understanding of the biology of the valve lesion will play an important role in the understanding of this disease and the future treatment option for these patients.
Healthy Heart Registered under RNI No. GUJENG/2008/28043
Published on 5th of every month
Permitted to post at PSO, Ahmedabad-380002 on the 12th to 17th of every month under
Postal Registration No. GAMC-1725/2012-2014 issued by SSP Ahmedabad valid upto 31st December, 2014
Licence to Post Without Prepayment No. CPMG/GJ/97/2012 valid upto 30th June, 2014

If undelivered Please Return to:
CIMS Hospital, Nr. Shukan Mall,
Off Science City Road, Sola, Ahmedabad-380060.
Ph. : +91-79-2771 2771-75 (5 lines)
Fax: +91-79-2771 2770
Mobile : +91-98250 66664, 98250 66668

Subscribe “Healthy Heart” : Get your “Healthy Heart”, the information of the latest medical updates only ₹ 60/- for one year. To subscribe pay ₹ 60/- in cash or cheque/DD at CIMS Hospital Pvt. Ltd. Nr. Shukan Mall, Off Science City Road, Sola, Ahmedabad-380060. Phone : +91-79-3010 1059 / 3010 1060. Cheque/DD should be in the name of : “CIMS Hospital Pvt. Ltd.”
Please provide your complete postal address with pincode, phone, mobile and email id along with your subscription.

American College of Cardiology (ACC) certifies CIMS Hospital as a Center of Excellence among the FIRST center in the world and India and only one in Gujarat

CIMS Cardiology
Proud to follow ACC/AHA guidelines in cardiac care to match with best care and treatment available in the world

CIMS Hospital : Nr. Shukan Mall, Off Science City Road, Sola, Ahmedabad-380060.
For appointment call : +91-79-3010 1200, 3010 1008 Mobile : +91-98250 66661
email : info@cims.me web : www.cims.me

Care Institute of Medical Sciences
At CIMS... we care

www.indianheart.com