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# Platelet Glycoprotein 2b / 3a receptor inhibitors (GP 2b / 3a)

*M. Ayman Saleh M.D*

*Prof of Cardiology Ain Shams University*



# Types

All oral forms showed complete clinical failure.

# Types

## IV:

- Abciximab (Reopro)
- Eptifibatide (integriline)
- Tirofiban (Aggrastat)

# Pharmacokinetics properties of GP 2b / 3a receptor inhibitors

Properties	Abciximab (ReoPro®)	Eptifibatide (Integrilin®)	Tirofiban (Aggrastat®)
Type of agent	Monoclonal antibody (MoAb)	Peptide	Non-peptide
Mechanism of 2b/3a receptor inhibition	MoAb binds to receptor causing steric hindrance and conformational changes	Mimics native protein sequence in receptor	Mimics native protein sequence in receptor
Binding to receptors	Long-acting, high-affinity receptor blocker	Short-acting, dose-dependent binding	Short-acting, dose-dependent binding
Reversible with platelet infusions?*	Yes	No. (Platelet function returns to normal in 4 hours)	No. (Platelet function returns to normal in 4 hours)
Speed of reversibility	Slow (> 48 hours; due to prolonged binding to platelets)	Fast (2-4 hours)	Fast (2-4 hours)
Half-life	30 minutes	2.5 hrs	2 hrs
Elimination	Protease degradation	Renal	Renal

\*Note: Reversibility of the effects of eptifibatide and tirofiban with platelet transfusions has not been specifically studied in humans

## Indications:

### a) Coronary circulation

- Adjunctive therapy during percutaneous coronary intervention (PCI)
- Treatment of acute coronary syndrome (ACS)
- In STEMI

### b) Non coronary circulation

# 1- GP 2b/ 3a receptor inhibitors as adjunctive therapy during PCI

- 6 randomized trials including 15,000 patients.
- All three types of GP 2b/ 3a receptor inhibitors .
- The primary end point in these trials was the incidence of a “composite endpoints” at 30 days following treatment.
- This “composite endpoints” included: death, MI and need for urgent revascularization.

# *Abciximab*

- 4.5-6.5% absolute reduction in this endpoint (35-56% RRR)
- Benefit was seen regardless the method of PCI.
- Benefit maintained for up to 3 years in the EPIC trial.
- The high risk patients had the maximum benefit.
- The major impact was on the reduction of nonfatal MI and the need for urgent revascularization.
- Only the EPIstent trial showed a reduction of mortality.

# *Eptifibatide (integriline)*

- Two trial - IMPACT II  
- ESPIRIT

Significant reduction of end point at 48 hrs, 30 days, 6 months & up to 1 year due to reduction of MI.

# *Tirofiban*

- RESTORE
- Only showed benefit at 2<sup>nd</sup> & 7<sup>th</sup> days.
- Did not show benefit at 30 days.

# *Tirofiban*

- TACTICS
- Showed benefit at 30 days for intermediate to high risk group of patients who undergone early stenting in the presence of Tirofiban.

# *Comparative Trial*

- TARGET
- Abciximab vs Tirofiban for planned PCI
- Patients who received Abciximab had a lower 30 days composite end points.

# Indications

- 2- Treatment of ACS
- The three GP 2b / 3a receptor inhibitors were investigated in over 16,000 patients with ACS
- The studies differed in
  - a- Type of patients
  - b- Use of revascularization
  - c- Use of heparin

# Abciximab

- CAPTURE trial showed benefit in high risk patients within 48 hrs. however, all underwent PCI.
- GUSTO IV ACS failed to show benefit in patients with ACS managed without revascularization.

# Eptifibatide

## The PURSUTT

Patients had diminished endpoints than placebo & at 30 days regardless whether they underwent revascularization or not, CABG or PCI.

# Tirofiban

- In PRISM

Benefit over placebo in the first 24 hrs  
( no revascularization )

- PRISM PLUS

PCI not allowed for 48hrs but encouraged at  
48 – 96 hrs & showed statistically significant benefit.

### *3. Use in ST elevation MI (STEMI)*

- Principle goal is to achieve TIMI III flow very early. For every 20% increase in TIMI, there is 1% decrease in mortality.
- Thrombolytics are the main stay in treatment. However, they increase thrombin activity and platelet aggregation.
- GP 2b 3a blockers enhance lysis and prevent reocclusion.

# *FDA approved indications for GP 2b / 3a receptor inhibitor*

Indication	Abciximab	Eptifibatide	Tirofiban
Adjuvant to PCI	yes	yes	No
ACS	Yes if PCI will follow within 24 hrs.	yes	yes
STEMI	Not yet	Not yet	Not yet

# *Adverse Reactions*

- Bleeding
- Others

# *Adverse Reactions*

## Bleeding

- It is the primary safety concern with GP 2b / 3a receptor inhibitors.

Over all ,the incidence of bleeding is  $< 0.2\%$ .

- EPIC trial resulted in a change in the regimens of GP 2b / 3a receptor inhibitors.

# Adverse Reactions

- Thrombocytopenia ( $< 100,000/\text{mm}^3$ ) occurred in approximately 5 % of patients across all trials.
- Severe Thrombocytopenia ( $< 50,000/\text{mm}^3$ ) occurred in 2 % of patients with abciximab as compared to 1 % in other small molecules .

# Adverse Reactions

- Severe acute thrombocytopenia ( 24 hours) occurred in 0.7 % of patients with abciximab ( immune mediated ).

Abciximab induces the formation of antibodies in 6 – 7% of patients so reuse of abciximab results in 3 -4 fold higher incidence of severe acute thrombocytopenia.

# Adverse Reactions

## Others

Incidence of adverse effects	Abciximab	Eptifibatide	Tirofiban
> 10% of patients	Hypotension Back pain Chest pain Nausea	Major bleeding (10.8%) Minor bleeding (13.1%) Hypotension Back pain Injection site reaction	Minor bleeding
1-10% of patients	Major bleeding* Minor bleeding Bradycardia Thrombocytopenia Abdominal pain Headache Puncture site pain Dyspepsia Dizziness	Hypotension Thrombocytopenia	Major bleeding Bradycardia Thrombocytopenia Edema Pelvic pain Leg pain Vasovagal reaction Coronary artery dissection Sweating Dizziness

\*excluding EPIC trial, as all subsequent studies with heparin dosed based on patient weight and early removal of catheter sheath have shown significantly lower incidence of bleeding.

# *Contraindications*

- Contraindications, warnings & precautions are similar for the three agents.
- In general the following contraindications apply to each GP 2b/3a receptor inhibitor.

# *Contraindications*

- Hypersensitivity to any agent component.
- Active internal bleeding or recent ( within 6 months) clinically significant gastrointestinal or genitourinary bleeding.
- History of bleeding diathesis within 30 days.
- Severe uncontrolled hypertension.
- Major surgery or trauma within previous 4 weeks (tirofiban) or 6 weeks (abciximab or eptifibatide ).

# *Contraindications*

- Thrombocytopenia defined as platelet count  $< 100,000/\text{mm}^3$  (abciximab, eptifibatide ).
- History of cerebrovascular accidents (CVA) within previous two years, or CVA with neurological deficit at any time (abciximab).
- History of stroke within 30 days or hemorrhagic stroke at any time (eptifibatide or tirofiban).

# *Contraindications*

- History of intracranial hemorrhage, intracranial neoplasm, arteriovenous malformation or aneurysm.
- History of vasculitis (abciximab)
- History of symptoms suggestive of aortic dissection (tirofiban)
- Concomitant use of another GP2b/3a inhibitor

# Contraindications

- Acute pericarditis (tirofiban).
- Renal dialysis or serum creatinine  $\geq 4.0$ mg/dl or requiring hemodialysis (eptifibatid).
- Use of IV dextran before procedure or intend to use during procedure (abciximab). Administration of oral anticoagulant within previous seven days unless prothrombin time  $\leq 1.2$  times the control (abciximab).

# Dosing & Administration

Drug	Abciximab (ReoPro®)	Eptifibatide (Integrilin®)	Tirofiban (Aggrastat®)
Dose	<p><u>PCI</u>: 0.25mg/kg IV bolus pre-PCI, then 0.125mcg/kg /min (max. 10mcg/min) IV infusion x 12 hrs post-PCI</p> <p><u>ACS with planned PCI</u>: 0.25mg/kg IV bolus, then 10mcg/min IV infusion x 18-24 hrs pre-PCI and x 1 hr post-PCI*</p>	<p><u>PCI</u>: 180mcg/kg IV bolus pre-PCI, then 2.0mcg/kg/min IV infusion, with a second 180mcg/kg bolus 10 minutes after the first bolus. Infusion continues until hospital discharge or for 18-24 hours post PCI (whichever comes first), (ESPRIT dose)**</p> <p><u>ACS</u>: 180mcg/kg IV bolus, then 2mcg/kg/min (max. 15mg/hr) x 72-96 hours</p>	<p>---</p> <p><u>ACS</u>: 0.4mcg/kg/min IV infusion x 30 min, then 0.1mcg/kg/min x 48-108 hrs</p>
Dosage adjustments	N/A	<p>SCr &gt; 2.0 mg/dl- decrease infusion to 1.0mcg/kg/min</p> <p>SCr &gt; 4.0 mg/dl or requires hemodialysis -CI</p>	<p>CrCl &lt; 30 ml/min- decrease bolus rate and infusion rate by 50%</p>

CI = contraindicated

\*FDA approved dose- for PCI, a 12 hour duration post-PCI is recommended.

\*\*The initial FDA approved dose was according to IMPACT II, which has since been found to be a suboptimal dose. Therefore, the ESPRIT dosing

# *Cost - effectiveness*

- In the setting of PCI they are cost effective but it is controversial which of the three are most cost effective.
- In the setting of ACS they are less cost effective & this is one of the reasons to limit its indication in high risk patients.



# Summary

## I. Percutaneous coronary intervention :

- Patients undergoing PCI benefit from treatment with GP 2b/3a receptor inhibitors abciximab & eptifibatide during and after the procedure.

Tirofiban ,at the doses studied , has not showed any benefit in the setting of PCI.

- Non of the agents has proved clinically superior.

# Summary

## I. Percutaneous coronary intervention :

- Results of the only comparative trial (TARGET) show superior results for abciximab compared to tirofiban.
- Abciximab should be given for 12 hours and eptifibatide for 18- 24 hours.
- Heparin should be discontinued after PCI when a patient is receiving any GP 2b/3a receptor inhibitor.

# Summary

## II. Acute Coronary Syndrome:

1- GP 2b/3a receptor inhibitors have modest effects in the medical management of ACS. Due to their lack of proven cost-effectiveness in this setting ,these agents should be restricted to patients at high risk for complications.

# Summary

## II. Acute Coronary Syndrome:

2. The ACC/AHA guidelines for management of patients with unstable angina or non-ST elevation MI recommended the use of eptifibatide or tirofiban in combination with ASA & heparin in patients with continuing ischemia or other high risk features, such as:

- Accelerated tempo of ischemic symptoms.
- Prolonged ongoing (>20 min) rest pain.
- pulmonary oedema, new/worsening murmur, S3 or new/worsening rales.
- hypotension, bradycardia, tachycardia
- age > 75 years
- angina at rest with transient ST changes, new BBB, sustained VT.
- markedly elevated cardiac troponins.
- patients planned for PCI

# Summary

## II. Acute Coronary Syndrome:

3. Based on the GUSTO IV ACS trial, abciximab should not be used for the routine medical management of ACS unless revascularization procedures are planned.

# Summary

## III. Acute ST- Segment Elevation Myocardial Infarction (STEMI)

There is evidence that patients with acute STEMI benefit from abciximab when used in combination with thrombolytics (ADMIRAL study). Yet, it is not FDA approved.