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IIb/IIIa Inhibitors: Real Talent, or Just Another Pretty Face?

In the never-ending search for better ways to treat ischemic heart disease, a new set of agents has been developed: the IIb/IIIa inhibitors. Although clearly useful in the acute management of patients undergoing percutaneous transluminal coronary angioplasty, these unpronounceable "super-aspirins" are being investigated as a potential improvement over standard aspirin in the treatment of acute coronary syndrome. This lecturer will discuss these agents and attempt to clarify their current role in treatment regimens.

- Correctly pronounce each member of this drug class.
- Describe the mechanism of action of the glycoprotein IIb/IIIa receptor antagonists.
- Review the current data illustrating the strengths and weaknesses of these agents.
- Discuss their potential usefulness in the treatment of coronary artery disease.

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FACULTY

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Outline:

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Section III: Aspirin: The Gold Standard
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Introduction

Platelets are central to the pathophysiology of acute coronary syndromes (ACS). A new class of drugs has hit the market in the last few years and the marketing has been prolific. Before we jump on the wagon of another expensive class of drugs for ACS we need to be sure that the drugs are safe, effective and cost effective. We must be clear in which patient subgroups and under which clinical scenarios these drugs really have been proven to be beneficial! This lecture will critically review the role of the glycoprotein platelet inhibitors in emergency care from an unbiased, non-manufacture supported perspective.

Section I: Pathophysiology

Platelet aggregation following plaque rupture is now considered central to thrombus formation and propagation in acute coronary syndromes **(ACS)**. Culprit lesions usually has a large lipid core containing tissue factor, and is covered by a thin fibrous cap and infiltrated by macrophages. The acute event is due usually to disruption of the plaque. This sets up a potent environment for thrombus formation and platelet aggregation.

Platelet aggregation is mediated by a numerous mediators. Aspirin blocks platelet aggregation by inhibition of the cyclooxygenase pathway but does so in completely. Ticlopidine and clopidogrel block ADP dependent pathways of platelet aggregation (but takes 10 days to have a significant effect).

The final common pathway of platelet aggregation involves activation of the glycoprotein IIb/IIIa receptor on the surface of platelets (other GP receptors are present but the IIb/IIIa form is the most common).

25 years ago it was noted that patients without GP receptors have recurrent mucocutaneous bleeding and **absent** platelet aggregation. The potential for blockage of the GP receptors, and therefore very potent platelet aggregation, has been studied in over 40,000 patients in the last 10 years.

Types of GP IIb/IIIa inhibitors

Currently there are three basic forms of GP inhibitor on the US market: FAB fragment monoclonal antibodies, peptide and non-peptide receptor blockers. Currently only parental forms are available, but trials of oral forms are in phase II and III clinical trials - though safety of the oral forms appears to be a big question.

Glycoprotein IIb/IIIa Blockers: Modified from Topol et al. LANCET vol 353 Jan 16 1999

Name (manufacture name)	***Manufacturer***	***Route***	***Status***	***Cost (for usual 3 days therapy)*** (Medical Letter 40(1035) Sept. 11 1998)
Monoclonal Antibodies				
Abciximab (REOPRO)	Centocor/Lilly	IV	FDA approved PCI, ACS	**$2160** (24 hour cost0
YM337	Yamanouchi	IV	Phase II	
Peptide				
Eptifibatide (Integrilin)	COR	IV	FDA approved PCI, ACS	**$1625**
Small Molecule				
Tirofiban (Aggrastat)	Merck and Co	IV	FDA approved ACS	**$1260**
Lamifiban	Hoffman LaRoche	IV	Phase III, ACS	
Fradafiban	Boehringer Ingelheim	IV	Phase II, ACS	
Xemilofiban	Searle	Oral	Phase III, PCI	
Orofiban	Searle	Oral	Phase III, ACS	
Sibrafiban (Xubix)	Hoffman La Roche	Oral	Phase III, ACS	
Roxifiban	DuPont-Merck	Oral	Phase II, ACS	
Lotrafiban	SmithKline Beecham	Oral	Phase II, ACS, CBVD	
Lefradifiban	Boehringer Ingelheim	Oral	Phase II, ACS	
SR 121787	Sanofi	Oral	Phase II, ACS	

PCI = percutaneous intervention, ACS = acute coronary syndrome, CBVD = cerebrovascular disease

Section II: Evaluating Trials - What matters

The evaluation of clinical trials of ACS requires that a number of important questions be asked of the trial:

1) Who are the patients in the trial - do they have a high aquity bias - are they the same as the patients I treat?

ACS is spectrum of disease from acute anterior MI with hypotension to worsening of stable angina. Where a person lies on the spectrum will determine short term prognosis and , usually response to aggressive therapy. Patients at lower risk generally derive less benefit from interventions and therapies than high risk patients.

Most studies of ACS enroll high risk patients. Patients with known coronary artery disease, great stories, and ECG changes. Since many patients given the diagnosis of ACS in the ED are not high risk it can be extrapolated that trials showing benefit in high risk patients will NOT be beneficial in the majority of patients in the average ED. Many of who ultimately are proven NOT to even have the disease.

The GP studies generally enroll high acuity patients, many of whom have ECG changes and undergo PTCA. Therefore the efficacy of these agents is NOT PROVEN in usual ED patients with ACS.

2) What are the important "endpoints" and what endpoints are smoke and mirrors

Endpoints

It is very controversial in cardiology circles as to what are the endpoints that really matter in cardiology studies. **The single best endpoint is death.** Death is hard to bias and obviously very clinically important. **Recurrent MI** is also probably a good endpoint as it predicts other important endpoints like later death, CHF etc. Other common endpoints used are things like **"recurrent ischemia"** and need for PTCA or CABG. Recurrent ischemia is defined using a variety of criteria and should be considered a soft endpoint. The need for **PTCA and CABG** or at least the amount of PTCA and CABG is very dependant on institution and cardiologist, so it is very difficult to interpret this endpoint in a randomized trial. Other indicators like readmission to hospital are also very region, physician and health care environment dependant and also open to bias.

Since death and MI are less common than recurrent ischemia many of the GP studies use a surrogate endpoint of death or MI or recurrent ischemia. This allows a smaller study to find a "significant" difference in the patients studied. Beware then, and look for, death and MI as the best outcome measures and pay significantly less attention to the other markers of outcome.

Time Endpoints Measured

It is also important to **consider the time at which the endpoint was measured.** Most studies use a 30 day cutoff, some use 7 days and a few 6 months.

Saving lives or preventing MI early may be important, but only if these lives saved or MI's prevented are sustained for a reasonable duration of time, at least 6 months.

Many interventions can reduce death or MI early but the effects are lost over time. This is probably true of the GP inhibitors that are short acting and the positive effects begin to be attenuated soon after the therapy ends. In the PURSUIT trial death and MI where statistically reduced at 30 days but at 6 months the effect was not longer statistically significant.

Measurement of a combination endpoint that includes recurrent ischemia or need for intervention and a time frame of 30 days is common in GP studies. These endpoints are not robust and falsely elevate the apparent efficacy of these agents.

Section III -Aspirin The Gold Standard

Before commencing any specific discussion on GP platelet receptor blockers one must review the effectiveness and cost effectiveness of aspirin. Aspirin in one the most effective and cost effective drugs in all of medicine and especially cardiology.

Aspirin in Acute MI

ISIS-2 published in 1988 noted a relative reduction in mortality in MI patients with ST segment elevation of 23% in patients randomized to receive aspirin. The number needed to treat (NNT) to save one life was approximately 40 (at 5 weeks). The NNT to prevent one death or MI or stroke is 25!! The cost of this drug approaches zero! These effects are sustained for the duration of therapy.

Aspirin in USA

In the Canadian Cooperative studies and VA cooperative studies aspirin reduced the progression to MI by up to 50% (NNT 20). This was in a high risk population with ECG changes so in lower risk patients this effect may not be as profound.

Aspirin increases bleeding to a small degree, perhaps one significant bleed for ever two to three hundred patients treated.

The cost of aspirin to prevent one death or MI in ACS approaches zero since the cost of the drug approaches zero!!

Section IV: Superaspirins in PTCA and STENT Placement

In patients undergoing PTCA the GPIIa/IIIb inhibitors have been *definitively shown* to reduce death and recurrent MI. This effect is particularly prominent in patients undergoing stent placement with use of the drug abciximab (REOPRO). The non-FAB fragments forms do not appear to have as significant or sustained effect. The studies have included patients at high risk with ACS and patients with lower acuity having more elective PTCA. The relatively low NNT to save a life or prevent one MI probably makes these drugs cost effective in this specific scenario.

Drug Therapy IN ACS patients undergoing PTCA: Death and MI as Endpoint

Study	Standard Therapy	Drug Therapy	NNT
EPILOG NEJM June 1997 N=2792	87/939 (9.4%)	37/935(4.0%) abciximab REOPRO	NNT = 20 (p<0.5)
EPIC NEJM April 1994 N=2099	72/696 (10.3%)	49/708 (6.9%) abciximab REOPRO	NNT = 30 (p<0.5)
CAPTURE Lancet May 1997 N=1265	57/635 (9.0%)	30/630 (4.8%) abciximab REOPRO	NNT = 25 (p<0.5)
EPISTENT Lancet 1998 n=2399	10.2%	5.2% abciximab REOPRO	NNT = 20 (p<0.5)
IMPACT II Lancet 1997 N=4010	8.4%	7.1% Eptifibatide	NNT = 77(p no sig)
Restore Circulation N=2139	6.3%	5.1% Tirofiban	NNT = 80 (p no sig)

Section V: Superaspirins in Non-ST Segment Elevation ACS

In patients with ACS without ST segment elevation (unstable angina by older nomenclature), the effect of the superaspirins depends on which patient subgroup one is considering. ACS without ST segment elevation is a very broad term encompassing patients with widely different short term morbidity and mortality.

In the only two studies of GP inhibitors in ACS have the data been presented in such a way as it is possible to divide PTCA from non-PTCA patients. From these two papers ***there is no good evidence that in patients not undergoing PTCA that these agents results in statistically significant reductions in MI or death.***

It has been stated best by Calvin when he recently noted.... "...of course clinical design is primarily motivated by carving out a wide market, not finding the small subgroups that benefit most..." Calvin JE, Klein LW. Defining risk in unstable angina: Current trial design does not tell us who should be treated with what therapy. AM Heart J 137(2):199-202 1999

Study	**Overall Effect on MI or Death Absolute % Reduction at 30 days**	**Effect in Non-PTCA**
PURSUIT NEJM 1988 N = 19,948 Eptifibatide	1.5% (p=0.04)	1.1% (p=0.23) NOT SIGNIFICANT
PRISM Plus NEJM 1998 N = 1915 Tirofiban	4.5% (p<0.05)	2.3% p NOT SIGNIFICANT NB: RR 0.75;95% CI 0.46 to 1.23)

It may be that there are select patients with ACS not undergoing PTCA that will derive significant and sustained benefit from GP inhibitors. Current study design does not allow us to make this determination at this time. Until studies specially focus on which subgroups benefit the cost and potential side effects of these drugs should prevent the use of the agents in non-PTCA patients except under rare circumstances (e.g. patient has failed all other therapy and has dynamic ECG changes).

Superaspirins in ST-Segment Elevation ACS

Recently a number of relatively small trials have asked the question if GP inhibitors are useful in patients with ST segment elevation ACS (MI).

As an Adjunct to PTCA

RAPPORT TRIAL

The first randomized trial to compare GP inhibition in patients with acute **MI undergoing PTCA.** The agent used in this trial was abciximab. The study enrolled 483 patients with MI within 12 hours of symptom onset. The results are best summarized in the authors own conclusion:

"Aggressive platelet inhibition with abciximab during primary PTCA for acute MI yielded a substantial reduction in the acute (30-day) phase for death, reinfarction, and urgent target vessel revascularization. However, the bleeding rates were excessive, and the 6-month primary end point, which included elective revascularization, was not favorably affected."

As an Adjunct to Fibrinolysis

To date there are no large randomized trial of GP inhibitors in MI patients with ST segment elevation being concurrently treated with thrombolytic therapy. Small trials using the surrogate marker of reperfusion have suggested improved reperfusion with GP's. Only a large well designed trial will determine if this translates into improved survival and at what cost.

STUDY SUMMARIES
TAMI-8
60 patients with acute MI given M73E3 antibody, given 3, 6 or 15 hours after TPA infusion. TIMI-3 flow was 34/37 verus 5/9 in controls.

PARADIGM
353 patients with acute MI where given lamifiban in addition to STK or TPA. Again reperfusion at 90 minutes was improved in the GP group.

IMPACT-AMI
180 patients with acute MI treated with TPA where randomized to receive integrelin or placebo within 6 hours of pain onset. The high dose group had better TIMI grade 3 than the untreated patients.

TIMI-14
A small and ongoing trial of abciximab in acute MI patients again suggests improvement in TIMI- grade 2 and 3 with GP inhibition.

Section VII: The Oral GP inhibitors

Part of the reason for a lack of sustained effect of the Gp inhibitors in ACS not undergoing PTCA is the relatively short half life of the agents. If this agents could be given in oral form for the long term then perhaps better long term results would be found. Currently a number of agents are being trial but early results suggest a very high bleeding rate compared to aspirin alone. This made be correct by dosing adjustments or alternative agents or it may represent a fatal flaw in low term platelet inhibition over and above aspirin alone.

Section VIII: Safety

In all studies to date the safety profile of the GP inhibitors has been good. there has been no increase in intracranial bleeding. In some studies, generally with full does heparin, there has been an increase in bleeding, though generally at the grain site in PTCA patients. Reduction of adjunctive heparin appears to improve this situation. Platelet transfusions are required in abciximab treated patients about 2% of the time. This is significantly less in patients treated with non-FAB fragments but them so is the overall efficacy.

A small though real increase in thrombocytopenia has been noted, and occurs in about 1-2% of patients. It is suggested that platelet counts be check 2-4 hours after commencing infusion and levels less than 20×10^9 should be treated even if there is no life threatening bleeding.

Section IX: Conclusions

GP inhibitors (abciximab in particular) represent an advance in patients undergoing PTCA with significant sustained reduction in real endpoints at 6 moths and beyond. In patients not undergoing PTCA there is little evidence for the efficacy of these drugs. These agents may be definitively shown to be useful in ACS without PTCA but improved study design with particular emphasis on specific subgroups will be required.

In patients with ST segment MI trial to date has been large enough to determine if death or recurrent MI will be improved in patients undergoing thrombolytic therapy. The GUSTO IV trial, which is currently underway, should give some useful information on this topic.

In patients undergoing PTCA for ST segment MI, the one good study to date (using abciximab) failed to show a significant advantage to the addition of the drug at 6 month follow-up.

Oral forms may prove useful in the future, but current studies note an extremely high bleeding rate and the promise may never be realized.

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