
Minneapolis
Heart Institute
Foundation
GRAND ROUNDS

1


Intravenous Antiplatelets Agents
Maen Assali, MD
Cardiology Fellow, PGY-6

2

Things to discuss

- The role of (GP) IIb/IIIa inhibitors + dosing
- Limitations of the early GP IIb/IIIa trials data (dosing, adjunctive therapies, outcomes).
- role in ACS
- Cangrelor

3

- 61-year-old female, no PMH, SOB/EMS arrived
- Low BP + AMS
- Intubated + transcutaenous pacing
- EKG -->

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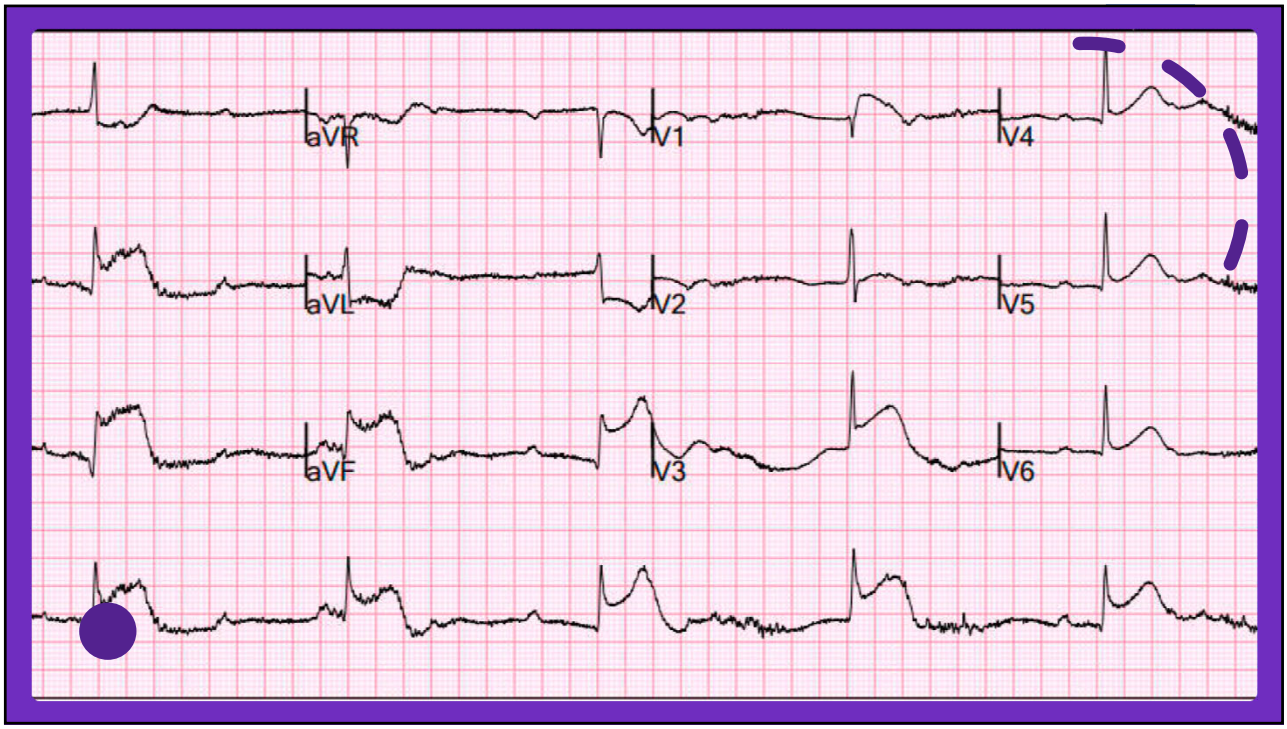

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- cath lab: transvenous pacing (removed after revascularization).
- 100% occlusion of proximal RCA. Successful PCI 1 DES.
- DAPT initiated: Ticagrelor and ASA (loading dose).
- Platelets on presentation was 224 k.
- Bivalirudin bolus and drip was used in the cath lab.

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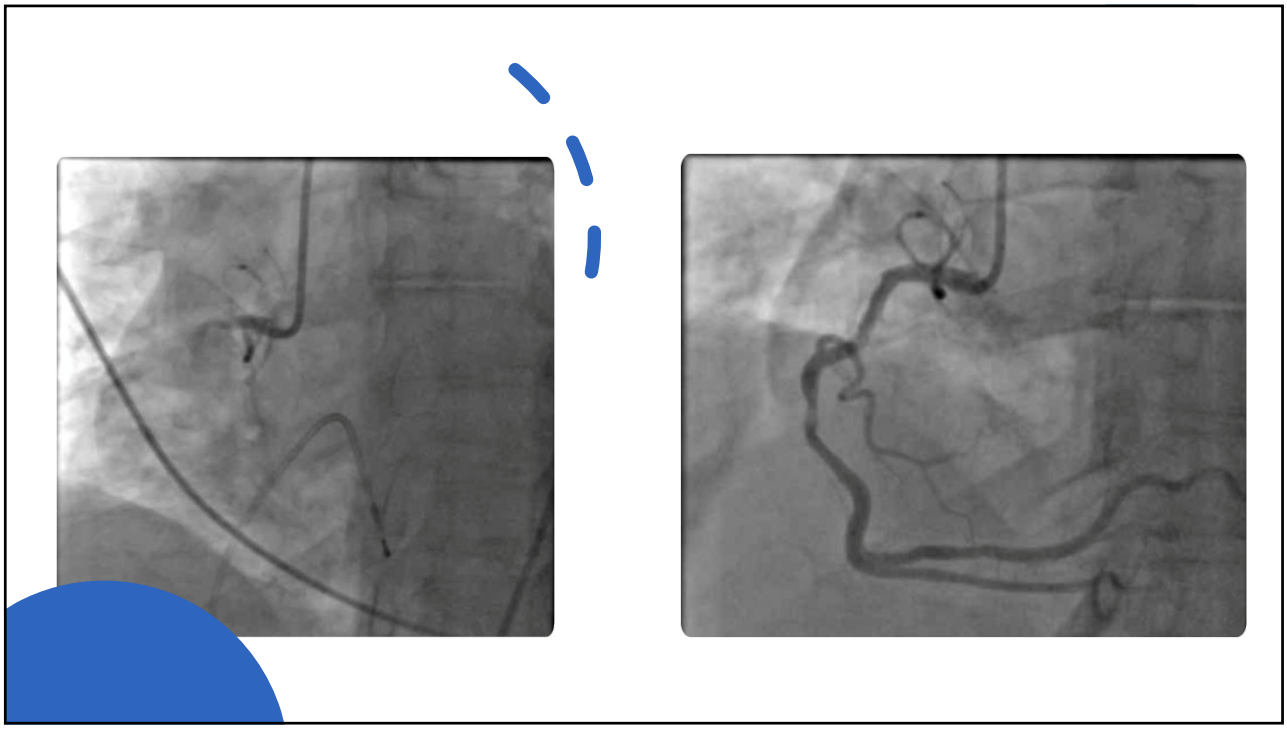

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- 40 min later --> complete heart block
- Angiogram--> acute closure. RCA thrombus aspirated. 2 DES proximal/distal. proper opposition confirmed with IVUS.
- Bailout eptifibatide used 180/2/180 with heparin. And subsequently eptifibatide drip.

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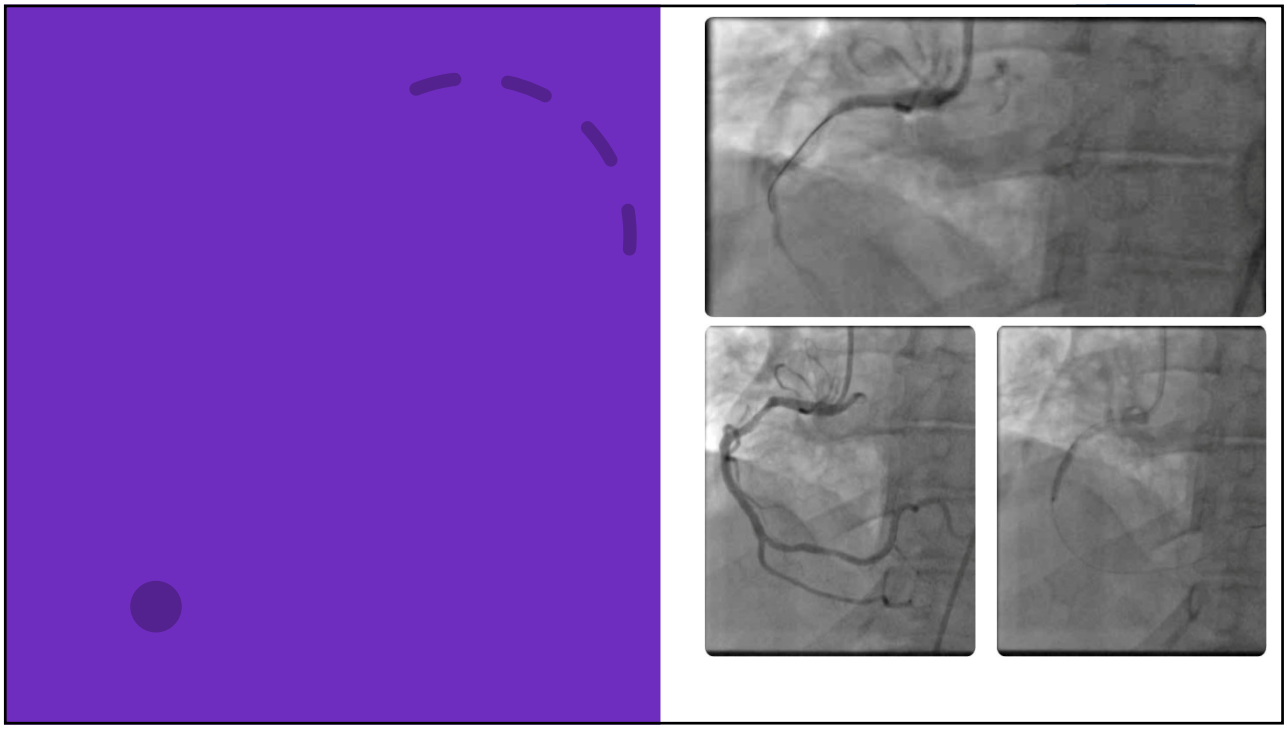

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- She was placed on eptifibatide (integrillin) for a planned 18-hour course and taken to the ICU. She was sent to the ICU on DAPT (Ticagrelor/ASA)
- CBC checked --> platelets = 36 K.
- citrated tube --> true thrombocytopenia.
- Eptifibatide was stopped. 30 min later, bradycardia and ST elevation noted.

10

- Angiogram: TIMI 2 flow in RCA (layered clot extending from proximal RCA to rPDA)
- Thrombectomy.
- Theraputic heparin was continued for 48 hours. No GP IIa/IIIb.

11

Intravenous Antiplatelets agents

12

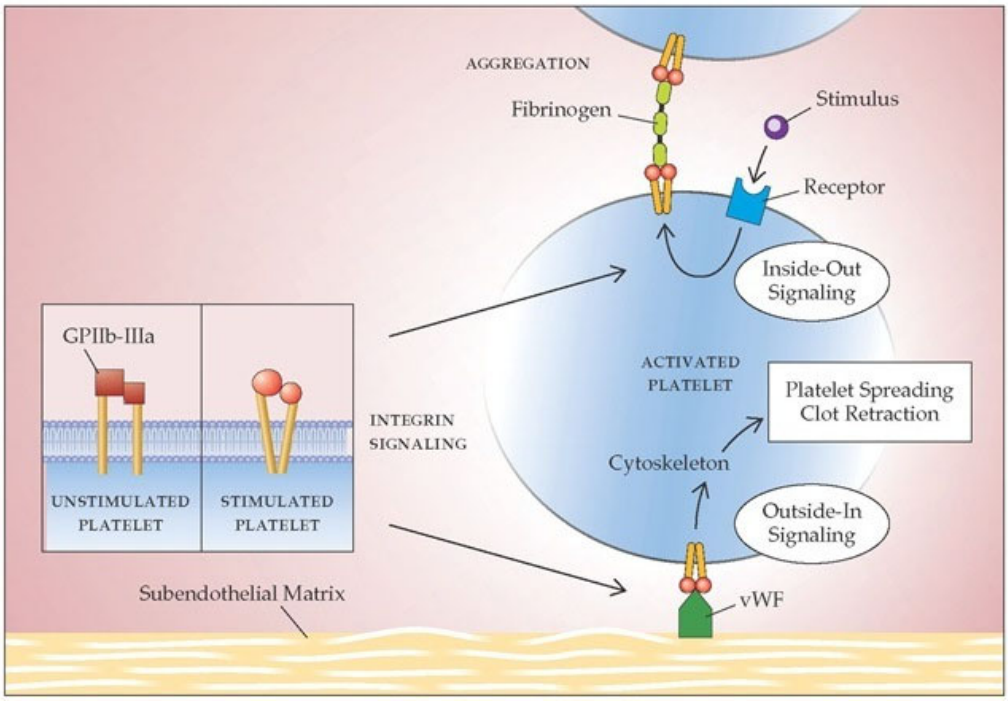
Biology of Platelets function

- plaque rupture ➡ Platelet activation (during PCI or with an ACS
- platelet plug:

Intimal injury ➡ exposure of collagen/subendothelial molecules ➡ adhesion of the platelets to the matrix

- interactions between (vWF) and the platelet surface molecule, GP Ib.

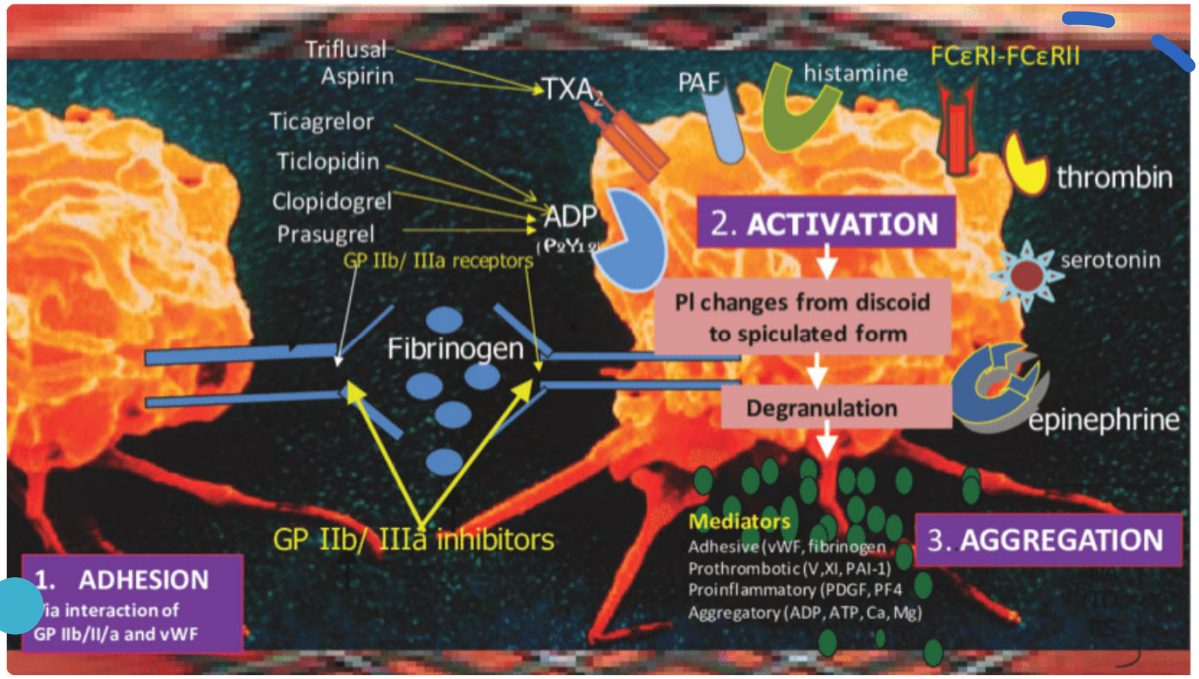
13



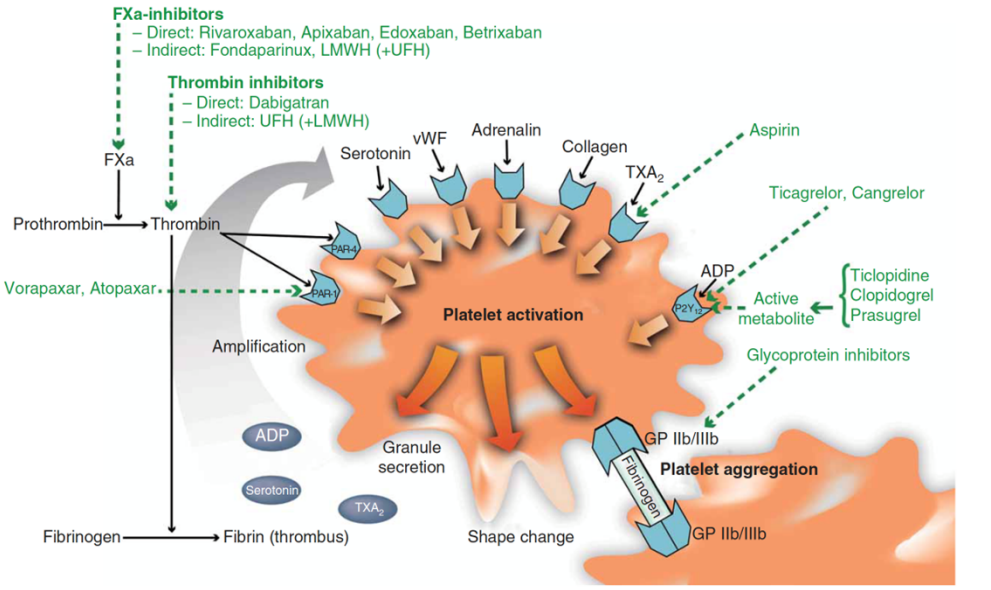
14

- platelet activators : epinephrine, serotonin, (ADP). The most potent activator of platelets is thrombin (factor IIa).
- Thrombin, thromboxane A_2, and ADP directly activate the platelet
- **ADP receptors on the platelet are P2Y1 and P2Y12**

15



16



- Grove, Erik & Würtz, Morten & Thomas, Mark & Kristensen, Steen. (2015). Antiplatelet therapy in acute coronary syndromes. Expert opinion on pharmacotherapy. 16. 1-15. 10.1517/14656566.2015.1079619.

17

- That's why GP IIb/IIIa inhibitors many times more effective than "upstream" platelet inhibitors.

- Intravenous (IV) GP IIb/IIIa inhibitors inhibit ADP-induced platelet aggregation *in vitro* by approximately **80-90%**, *compared* with approximately **10% for aspirin and 30-50% for P2Y12 inhibitors**.

18

The three GP IIb/IIIa inhibitors developed for clinical use are:

1. abciximab (an antibody; no longer available in the US)
2. Eptifibatide (Integrillin).
3. Tirofiban (Aggrestat).

19

Agent	FDA-approved Indication	Dose and Duration	Trials
Abciximab (no longer marketed in the United States as of June 2019)	PCI	Bolus: 0.25 mg/kg Infusion: 0.125 ug/kg/min (maximum of 10 ug/min) for 12 h	EPIC EPISTENT
	UA not responding to medical therapy with PCI planned <24 h	Bolus: 0.25 mg/kg Infusion: 10 ug/min for 18-24 h until 1 h after PCI	CAPTURE
	STEMI (off-label use)	Bolus: 0.25 mg/kg Infusion: 0.125 ug/kg/min (maximum of 10 ug/min) for 12 h	ADMIRAL CADILLAC
		Intracoronary (off-label use): 0.25 mg/kg directly to infarct lesion	AIDA-STEMI INFUSE-AMI
Tirofiban	ACS including medical management and PCI	Bolus: 25 ug/kg over 5 minutes Infusion: 0.15 ug/kg/min for up to 18 hours*	PRISM-PLUS RESTORE
	Elective PCI (off-label use)	Bolus: 25 ug/kg over 5 minutes Infusion: 0.15 ug/kg/min for up to 18 hours*	TARGET TENACITY
	STEMI PCI (off-label use)	Bolus: 25 ug/kg over 5 minutes Infusion: 0.15 ug/kg/min for up to 18 hours*	
		Renal Dysfunction (Cr Cl <60ml/min) Bolus: 25 ug/kg over 5 minutes Infusion: 0.075 ug/kg/min for up to 18 hours*	
Eptifibatide	ACS including medical management and PCI	Bolus: 180 ug/kg bolus Infusion: 2 ug/kg/min 18-24 hr	PURSUIT
	PCI	Bolus: 180 ug/kg bolus x 2, (2nd bolus after 10 min), Infusion: 2 ug/kg/min 18-24 hr**	ESPIRIT

20

Eptifibatide (Integrilin)

- Eptifibatide - **highly specific for the GP IIb/IIIa receptor. Low affinity--> hence rapidly dissociates from it.**
- low molecular weight; **nonimmunogenic.**
- Eptifibatide - half-life of 1.2 hours. Renal clearance ~ 50%.
- Dosing needs to be adjusted for renal insufficiency.

21

- complete inhibition of ADP-induced platelet aggregation within **10-15 min of bolus infusion.**
- Effect **reversed within 2-4 hours** after stopping infusion.
- Thrombocytopenia rates are low **(<1%)**.
- unique dosing during PCI.
  bolus- infusion,- 10 min later 2nd bolus.

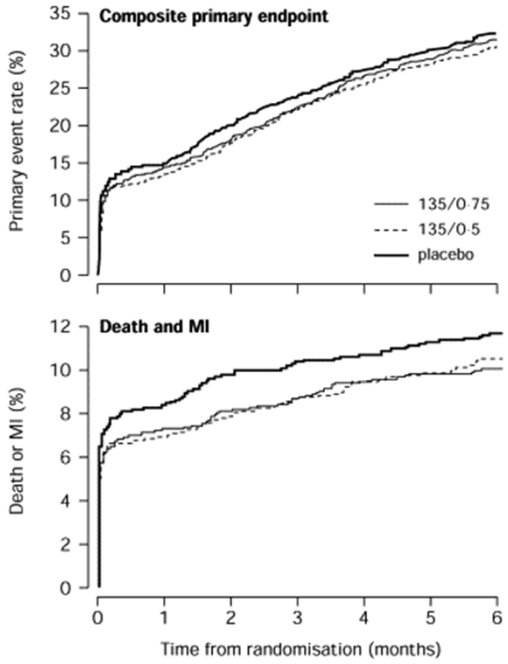
22

Eptifibatide dose development

- less than expected efficacy in **IMPACT II** (Integrilin to Minimize Platelet Aggregation and Coronary Thrombus–II) trial.
- Patients scheduled for elective/urgent/emergency PCI
- Treatment arms:

  Eptifibatide (135/0.5)
  Eptifibatide (135/0.75), or placebo
  Everyone received Aspirin, heparin

23



Treatment arms

- Eptifibatide, 135 mcg/kg bolus followed by 0.5 mcg/kg/min x 24 hours. **9.2%**
- Eptifibatide, 135 mcg/kg bolus followed by 0.75 mcg/kg/min x 24 hours. **9.9%**
- Placebo **11.4%**

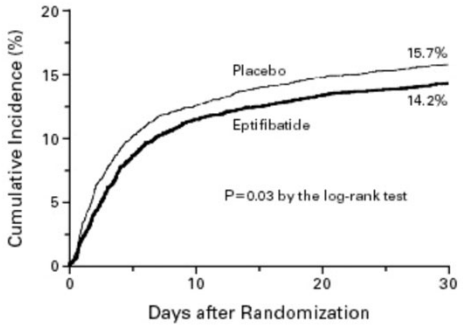
24

PURSUIT (Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy)

- Eptifibatide use in acute coronary syndromes. (did not include STEMI patients)
- Primary endpoints: Composite of death from any cause or nonfatal myocardial infarction at 30 days.
- -Eptifibatide (180/1.3);
  -Eptifibatide (180 mcg/ 2.0 mcg)
  -placebo

25

PURSUIT trial



The 1.5 percent absolute reduction in the frequency of the composite end point was reached by 4 days and maintained for 30 days

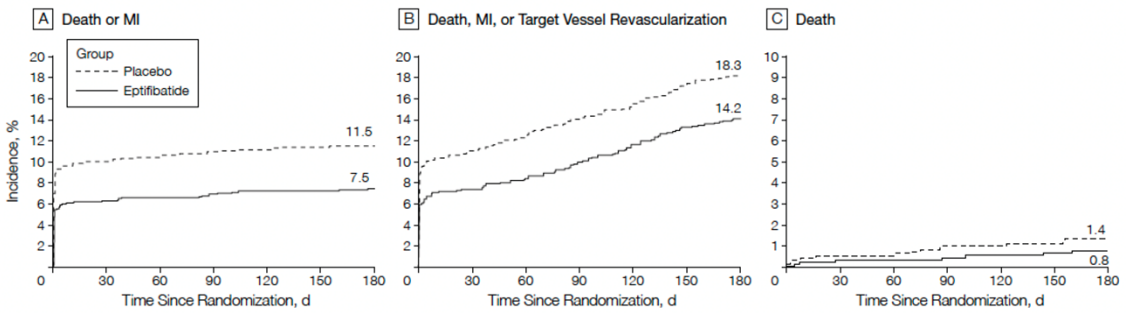
Frequency of the composite end point at 96 hours, 7 days, and 30 days

26

ESPRIT trial (Novel Dosing Regimen of Eptifibatide in Planned Coronary Stent Implantation: A Randomized, Placebo-Controlled Trial)

- Evaluated the new dosing regimen, terminated early given efficacy.
- Two 180 mcg/kg boluses 10 min apart followed by an infusion of 2 mcg/kg/min for 18–24 hours
- Death or MI, a composite of death, MI or (TVR) or the combined end points at 6 months.
- Primary outcome:
  7.5% eptifibatide-treated patients
  11.5% placebo-treated patients

27



28

- ESPRIT and EPISTENT (abciximab vs placebo) trials confirmed better outcomes with gp IIb/IIIa receptor blockers for patients undergoing PCI.
- **pre** PY12 inhibitors era.
- highlighted the importance of platelet inhibition during PCI

29

Tirofiban (Aggrastat)

- Tirofiban is highly specific for the GP IIb/IIIa receptor, unlikely to induce an immune response.
- **short half-life** of only approximately 2 hours.
- After 5 min of a high-dose bolus (HDB), **>80% inhibition of ADP-induced platelet aggregation**.
- bolus followed by an infusion.

30

- Inhibition decreases to **<50% 4 hours after** infusion cessation.
- Renal clearance is around **40%**. Reduced dose in CKD.
- Thrombocytopenia slightly higher compared to heparin alone.

31

Percutaneous Coronary Intervention

- Early trials of GP IIb/IIIa antagonists during PCI - era of **balloon angioplasty and bare-metal stents**, and did **not consistently contain P2Y12 inhibitors** as background therapy.
- They showed ~ 35% reduction in the primary endpoint (composite: 30-day death, MI and TVR)

32

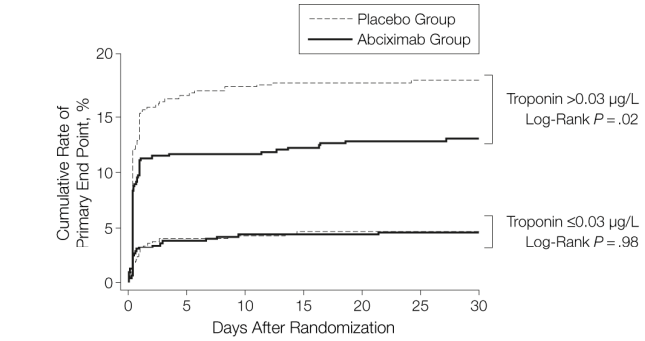
- Considering a triple-component primary endpoint (30-day death, MI, and TVR), the overwhelming majority of event rate reduction was from the prevention of periprocedural MI.
- Although no large-scale prospective study about use of GP IIb/IIIa antagonists in s**aphenous vein graft interventions**, pooled analyses revealed little to **no** benefit.

33

- The ISAR-REACT and ISAR-REACT 2 trials studied abciximab in low-risk and moderate-to-high-risk PCI patients, respectively.

ISAR-REACT (2004)	Abciximab	Low or intermediate risk PCI	Yes	2,159	(a) 0.25 mg/kg bolus, 0.125 μg/kg/min 12 h (b) placebo	Death/MI/TVR 30 d	4.2% (a) 4.0% (b) (p = 0.82)	All pretreated with clopidogrel
ISAR-REACT 2 (2006)	Abciximab	High-risk PCI	Yes	2,022	(a) 0.25 mg/kg bolus, 0.125 μg/kg/min 12 h (b) placebo	Death/MI/TVR 30 d	8.9% (a) 11.9% (b) (p = 0.03)	All pretreated with clopidogrel

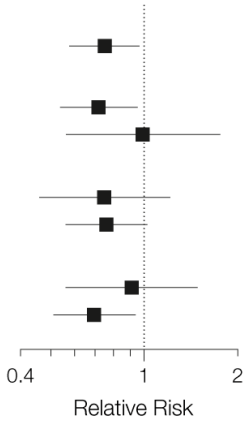
34



No. at Risk							
Troponin >0.03 µg/L							
Placebo	536	445	441	439	439	438	438
Abciximab	513	453	453	450	447	447	446
Troponin ≤0.03 µg/L							
Placebo	474	455	454	452	452	452	452
Abciximab	499	480	477	477	477	476	476

35

	Primary End Point, No. of Events/Total No. (%)	
	Abciximab	Placebo
All Participants	90/1012 (8.9)	120/1010 (11.9)
Troponin Level		
>0.03 µg/L	67/513 (13.1)	98/536 (18.3)
≤0.03 µg/L	23/499 (4.6)	22/474 (4.6)
Clopidogrel Pretreatment Duration		
>3 h	27/475 (5.7)	35/461 (7.6)
≤3 h	63/537 (11.7)	85/549 (15.5)
Diabetes		
Yes	26/252 (10.3)	32/284 (11.3)
No	64/760 (8.4)	88/726 (12.1)



36

- No benefit observed among low-risk patients.
- higher-risk patients, abciximab resulted in a 25% risk reduction in the 30-day composite of primary outcome.
- **This benefit primarily occurred among patients who were troponin positive.**
- **No** differences in terms of major and minor bleeding.

37

- Given observed benefit of GP IIb/IIIa inhibitors with ACS patients undergoing early invasive strategy, question rose re timing of therapy: upstream versus downstream.

- **EARLY ACS** (Early Glycoprotein IIb/IIIa Inhibition in Non-ST Segment Elevation Acute Coronary Syndromes)

9,492 patients with ACS with planned early PCI, randomized to:

A. Eptifibatide **early** (≥12 hours before)

B. During coronary angiography (**delayed** group).

38

- 30-day occurrence of death or MI was not different (OR, 0.89; **p = 0.08**). More bleeding in early treatment.
- Given the trend toward a benefit, a meta-analysis of small-molecule upstream therapy was performed: 12 studies / 45,000 patients.
- 11% reduction in 30-day death/MI with upstream therapy , **but** a 23% higher risk of major bleeding.

39

- based on EARLY ACS, the meta-analysis, and ACUITY –All showed **modest reduction in ischemic** events/ **marked increase in bleeding** - predominantly femoral access approach PCI, hence upstream (early) was not preferred.

40

Can GP IIb/IIIa inhibitors be used as a bridge?

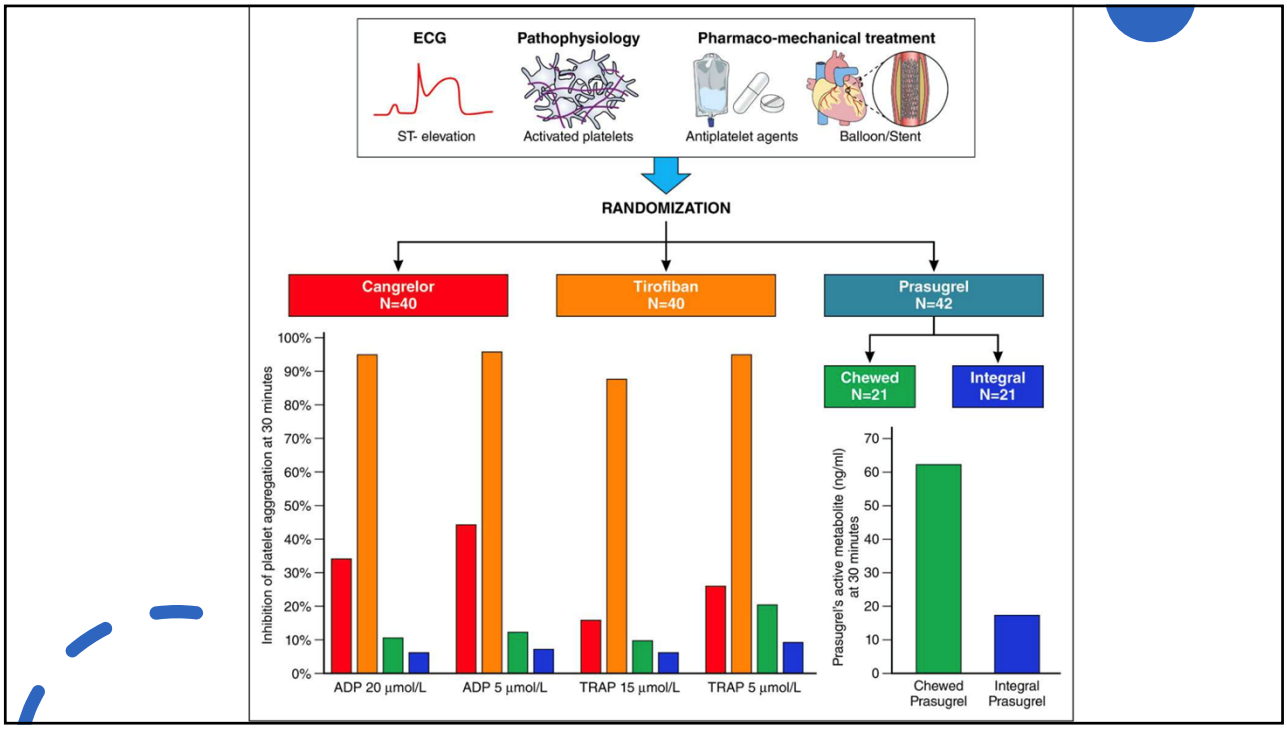
- several small studies have focused on clarifying a potential role for GP IIb/IIIa inhibitors in bridging the therapeutic gap in patients with high-risk ACS between oral P2Y12 inhibitor administration and their onset of action.
- FABOLUS-FASTER trial studies this question (Facilitation Through Aggrastat or Cangrelor Bolus and Infusion Over Prasugrel)

41

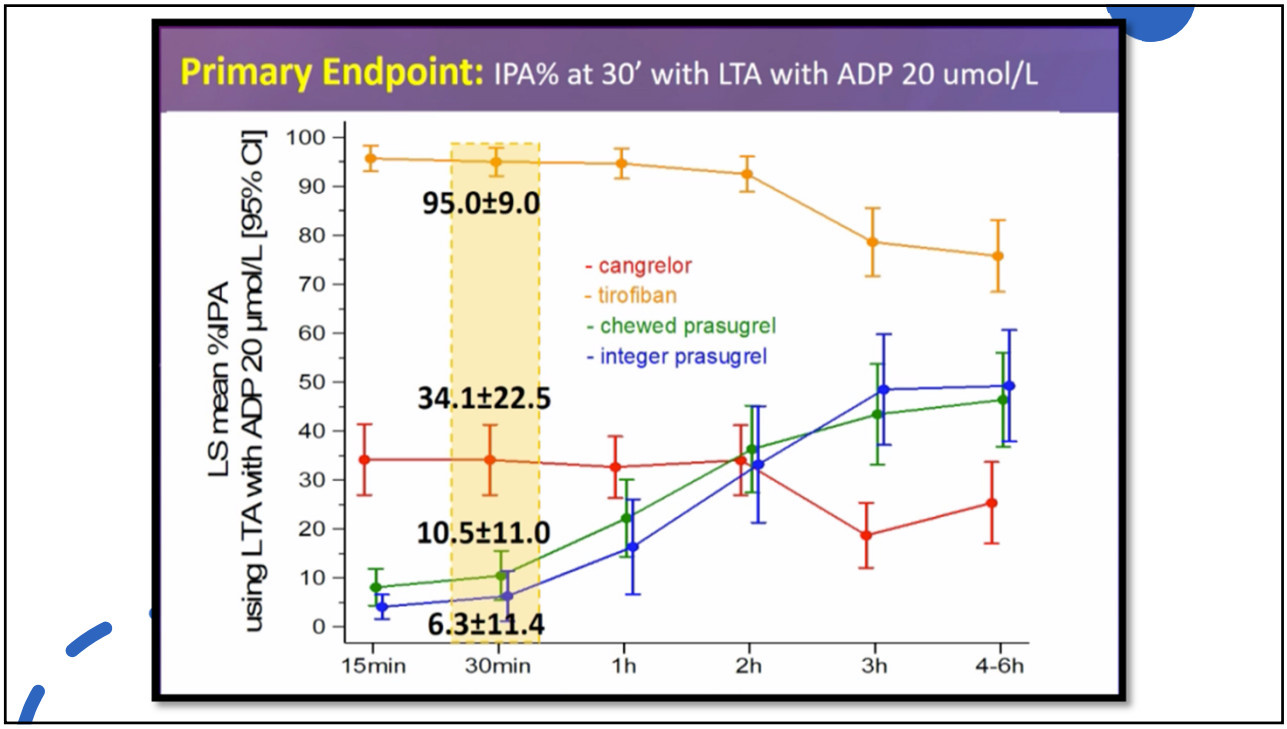
FABOLUS-FASTER

- $P2Y_{12}$-naive STEMI patients were randomly allocated (1:1:1) to cangrelor (n=40), tirofiban (n=40), both administered as bolus and 2h infusion followed by 60 mg of prasugrel, or 60 mg loading dose of prasugrel (n=42).
- Primary outcome- **platelet inhibition** assessed with light transmission aggregometry (LTA) **at 30 minutes**

42


ECG
Pathophysiology
Pharmaco-mechanical treatment
ST- elevation
Activated platelets
Antiplatelet agents
Balloon/Stent
RANDOMIZATION
Cangrelor N=40
Tirofiban N=40
Prasugrel N=42
Chewed N=21
Integral N=21
Inhibition of platelet aggregation at 30 minutes
ADP 20 µmol/L
ADP 5 µmol/L
TRAP 15 µmol/L
TRAP 5 µmol/L
Prasugrel's active metabolite (ng/ml) at 30 minutes
Chewed Prasugrel
Integral Prasugrel

43


Primary Endpoint: IPA% at 30' with LTA with ADP 20 umol/L
LS mean %IPA using LTA with ADP 20 µmol/L [95% CI]
95.0±9.0
34.1±22.5
10.5±11.0
6.3±11.4
- cangrelor
- tirofiban
- chewed prasugrel
- integer prasugrel
15min
30min
1h
2h
3h
4-6h

44

- Tirofiban was superior in Inhibition of platelet aggregation compared with cangrelor.
- Cangrelor and tirofiban were both superior to chewed or whole prasugrel.

45

STEMI (Primary PCI)

- Early studies before the introduction of the P2Y12 inhibitor showed the benefit of using abciximab in the 30-day rate of ischemic events. (less robust benefit at 6 months)
- After introduction of P2y12 inhibitor, several trials showed no benefit and increased risk of bleeding. Those trials include **BRAVE-3** and the **FINESSE**.

46

FINESSE (Facilitated Intervention With Enhanced Reperfusion Speed to Stop Events)

- Patients with STEMI were randomized

1. abciximab + half-dose of the thrombolytic reteplase (n =828)*
2. abciximab alone (n = 818)*
3. or placebo (n = 806).

Patients then underwent PCI

primary endpoint: Composite of all-cause mortality or complications of MI by 90 days

*First two arms- Facilitated

47

- **No difference** in the frequency of death or complications of MI by 90 days when comparing the treatment arms.
- Both facilitated PCI strategies were associated with an increased risk of bleeding.

48

BRAVE-3 (Value of Abciximab in Patients With AMI Undergoing PCI After High Loading Dose of Clopidogrel Pretreatment)

- Upstream abciximab against placebo (800 patients) + preloading with 600 mg of clopidogrel.
- The study failed to show a reduction in infarct size (by technetium-99m sestamibi imaging) with abciximab

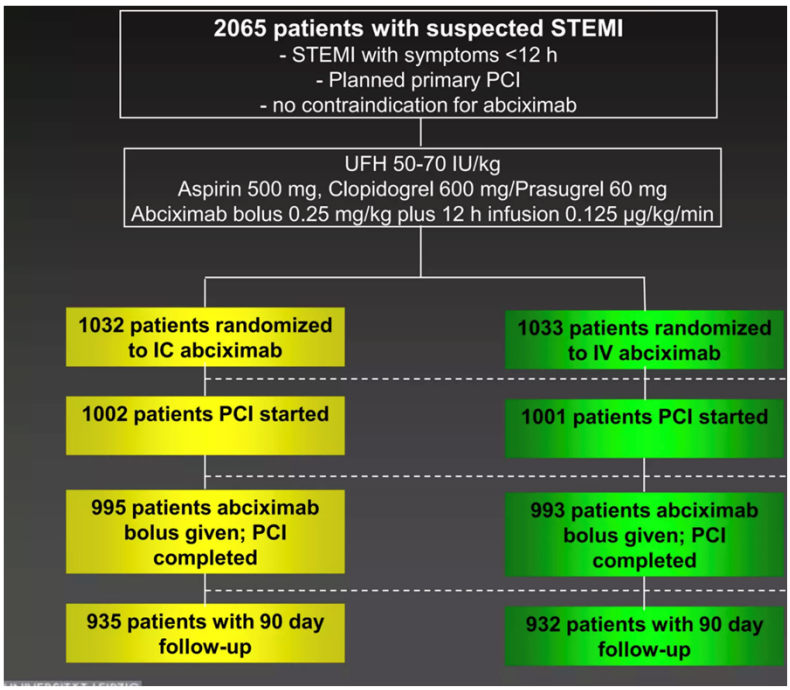
49

AIDA STEMI -Abciximab Intracoronary vs IV in STEMI -

- Evaluate treatment with intracoronary bolus of abciximab vs intravenous bolus among patients with (STEMI) undergoing (PCI).
- **no difference** between IC and IV abciximab in combined all-cause mortality, recurrent infarction, or new congestive heart failure within 90 days (**7% vs. 7.6%; OR, 0.91**; 95% CI, **0.64-1.28; p = 0.58**)

50

AIDA STEMI STRUCTURE

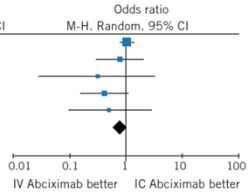


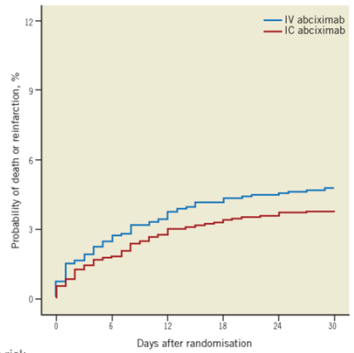
51

Pooled analysis from five randomized controlled trials R. Piccolo Et al.

Study or subgroup	IC Abciximab Events	IC Abciximab Total	IV Abciximab Events	IV Abciximab Total	Weight	Odds ratio M-H, Random, 95% CI
AIDA STEMI	42	1032	43	1033	56.6%	0.98 (0.63, 1.51)
CICERO	8	271	10	263	13.5%	0.77 (0.30, 1.98)
Dominguez-Rodriguez	1	25	3	25	4.0%	0.31 (0.03, 3.16)
Iversen	7	185	15	170	20.6%	0.41 (0.16, 1.02)
Thiele	2	77	4	77	5.3%	0.49 (0.09, 2.74)
Total (95% CI)		1,590		1,568	100.0%	0.78 (0.55, 1.10)
Total events	60		75			

Heterogeneity: Chi²=3.86, df=4 (p=0.43); I²=0%
Test for overall effect: Z=1.42 (p=0.16)





Patients at risk

IC Abciximab	1,568	1,529	1,514	1,503	1,498	1,493
IV Abciximab	1,590	1,562	1,546	1,538	1,533	1,530

- Piccolo, Raffaele et al. "Intracoronary versus intravenous bolus abciximab administration in patients undergoing primary percutaneous coronary intervention with acute ST-elevation myocardial infarction: a pooled analysis of individual patient data from five randomised controlled trials." *EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology* 9 9 (2014): 1110-20 .

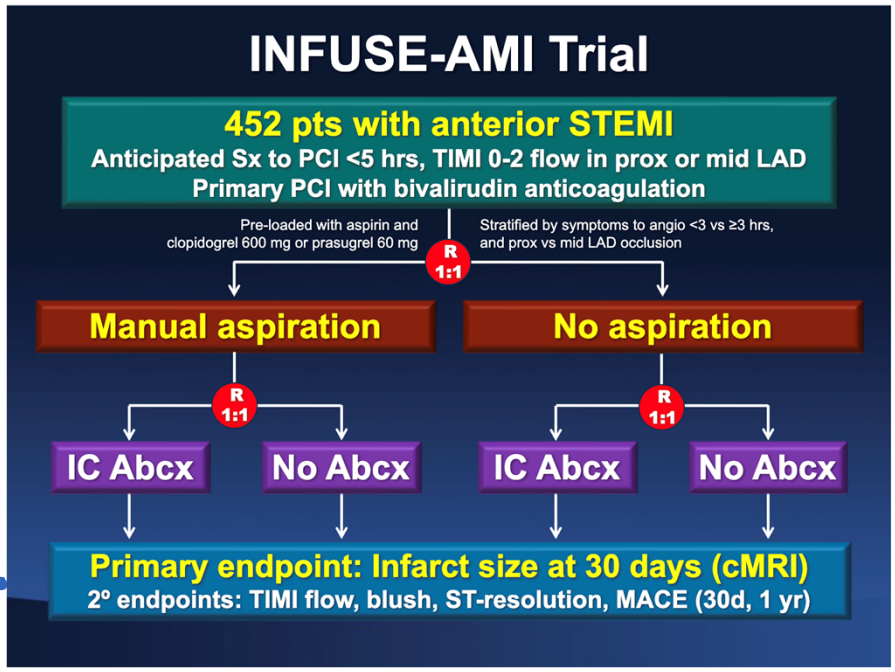
52

Infuse AMI

- Would IC abciximab and manual aspiration thrombectomy provide superior outcomes in patients with anterior (STEMI) who underwent primary (PCI) with bivalirudin?

- Primary endpoint (powered):
  - Infarct size (% total LV mass by cMRI) at 30 days in pts assigned to IC abciximab vs. no abciximab (pooled across the aspiration randomization)
- Major secondary endpoint:
  - Infarct size (% total LV mass by cMRI) at 30 days in pts assigned to aspiration vs. no aspiration (pooled across the abciximab randomization)

53



54

Table 3. Thirty-Day Cardiac Magnetic Resonance Imaging Results for the Pooled Randomized Groups

	Intracoronary Abciximab[a] (n = 188)	No Intracoronary Abciximab[a] (n = 184)	*P* Value	Aspiration Thrombectomy[b] (n = 186)	No Aspiration Thrombectomy[b] (n = 186)	*P* Value
Infarct size, median [IQR], % of total LV mass[c]	15.1 [6.8-22.7] (n = 181)	17.9 [10.3-25.4] (n = 172)	.03	17.0 [9.0-22.8] (n = 174)	17.3 [7.1-25.5] (n = 179)	.51
Total LV myocardial mass, median [IQR], g	128.6 [106.6-152.4] (n = 181)	130.4 [109.9-155.9] (n = 172)	.55	128.3 [108.9-149.8] (n = 174)	132.0 [107.6-156.1] (n = 179)	.50
Infarct mass, median [IQR], g	18.7 [7.4-31.3] (n = 184)	24.0 [12.1-34.2] (n = 175)	.03	20.3 [9.7-31.7] (n = 178)	21.0 [9.1-34.1] (n = 181)	.36
Total abnormal wall motion score, median [IQR]	7.0 [2.0-10.0] (n = 188)	8.0 [3.0-10.0] (n = 184)	.08	7.5 [2.0-10.0] (n = 186)	7.5 [2.0-10.0] (n = 186)	.89
Left ventricular ejection fraction, median [IQR], %	50.2 [44.2-57.9] (n = 182)	48.9 [42.3-56.7] (n = 179)	.22	49.6 [43.3-56.8] (n = 181)	49.5 [41.8-57.6] (n = 180)	.66

Abbreviations: cMRI, cardiac magnetic resonance imaging; LV, left ventricular.
[a]Pooled, either with or without aspiration thrombectomy
[b]Pooled, either with or without intracoronary abciximab.
[c]Primary end point.

55

Different results with INFUSE-AMI

- **TAPAS trial** demonstrated an unequivocal mortality benefit at 1 year with manual aspiration thrombectomy in patients with STEMI undergoing PPCI.

Unclear how many patients underwent direct stenting after mechanical thrombectomy in INFUSE trial.

56

- **AIDA-STEMI** trial demonstrated no clinical benefit with intracoronary abciximab (vs. intravenous abciximab) in these patients.

Distal delivery of abciximab with a microcatheter (as done in INFUSE but not in AIDA-STEMI) could have achieved better local glycoprotein IIb/IIIa inhibition, thereby improving infarct size.

57

- Given the above, guideline states it **may be reasonable** (**Class IIb**) to administer an IV GP IIb/IIIa receptor antagonist in the pre-catheterization laboratory setting (e.g., ambulance, emergency department) to patients with STEMI for whom primary PCI is intended

58

Bleeding Events

- Primary drawback of GP IIB/IIIa inhibitors is bleeding.
- Several trials showed increased risk of major and minor bleeding, especially when activated clotting time or heparin dose is high.
- Whether the bleeding risks of GP IIb/IIIa inhibition can be mitigated by other strategies (e.g., transradial access, shortened infusions) is an area of active interest and study.

59

Brief PCI

- Patients who underwent successful nonemergent PCI with IV eptifibatide during PCI, **2-hour infusion** of eptifibatide was **noninferior** with regard to periprocedural ischemic MI when compared with the standard, **18-hour infusion** of eptifibatide.
- Major bleeding occurred less frequently in the brief group (1.0% vs. 4.2%, p = 0.02)

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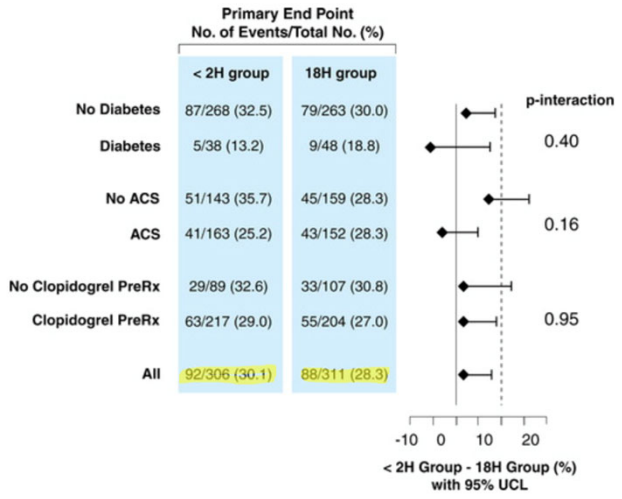

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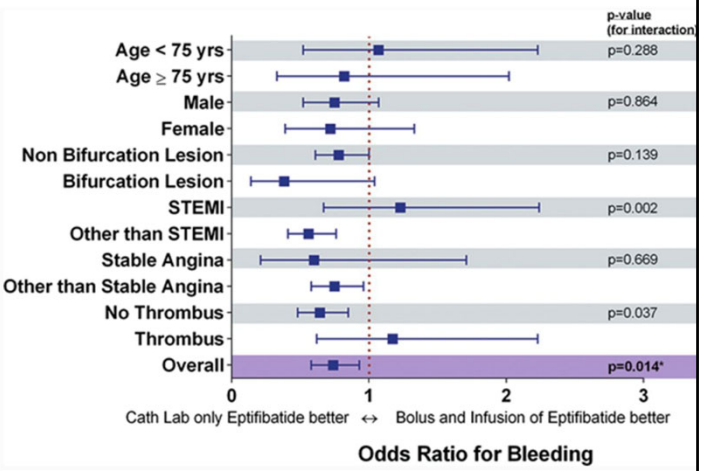
- Gurm et al. evaluated the in-hospital outcomes of >21,000 patients treated with eptifibatide as an adjunct to PCI.
- **Bolus-only** patients had significantly **lower rates of bleeding** (OR = 0.74; p = 0.014) with no statistically significant differences in ischemic endpoints.



62

Major safety points

- Based on GP IIb/IIIa inhibitor trials, risk of **major bleeding is approximately 1%.**
- No increase in ICH/solid organ bleeding. It is characteristically **hollow organs** (GI, GU, and vasculature, and rarely pulmonary).
- **severe thrombocytopenia** with abciximab is roughly **2%**, and is **≤1%** with tirofiban and eptifibatide.
- Excess dosing(specially in CKD patient) -increased rates of bleeding complications.

63

2021 AHA/ACC/SCAI Revascularization Guidelines

Recommendations for Intravenous Glycoprotein IIb/IIIa Inhibitors in Patients Undergoing PCI
Referenced studies that support the recommendations are summarized in Online Data Supplement 34.

COR	LOE	RECOMMENDATIONS
2a	C-LD	1. In patients with ACS undergoing PCI with large thrombus burden, no-reflow, or slow flow, intravenous glycoprotein IIb/IIIa inhibitor agents are reasonable to improve procedural success (1,2).
3: No Benefit	B-R	2. In patients with SIHD undergoing PCI, the routine use of an intravenous glycoprotein IIb/IIIa inhibitor agent is not recommended (3-5).

64

Cangrelor

- IV nonthienopyridine P2Y12 antagonist. Blocks ADP-induced platelet activation.
- Selectively/reversibly bind to P2Y12 receptor. **Onset of action within 2 min.**
- **Reversible Within 1 hour of discontinuation**
- There is **no dose adjustment** for renal insufficiency.

65

- Thienopyridines (clopidogrel and prasugrel), active metabolites are prevented from accessing the P2Y12 receptor by cangrelor. (diminish their antiplatelet effect)
- Not a concern with the nonthienopyridine ticagrelor, which does not require metabolic activation and binds reversibly to P2Y12 receptor.

66

Switching P2Y12 agents

- Transitioning from IV Cangrelor to oral P2Y12 inhibitors varies depending on whether the oral agent is a thienopyridine.
- clopidogrel/prasugrel, a loading dose administered immediately after discontinuing Cangrelor.
- Ticagrelor - any time during Cangrelor infusion or immediately after.

67

FDA-Approved and -Unapproved Indications and Dosing of Cangrelor

Agent	FDA-Approved and -Unapproved Indication	Dose and Duration	Trials
Cangrelor	PCI	Bolus: 30 mcg/kg bolus, Infusion: 4 mcg/kg/min for ≥2 hours or PCI duration, whichever is longer	**CHAMPION PCI/ CHAMPION PLATFORM/ CHAMPION PHOENIX**
	Bridging prior to cardiac surgery (off-label usage)	Infusion: 0.75 mcg/kg/min (without bolus) after P2Y12 discontinuation for up to 7 days Discontinue 1-6 hours prior to surgery Renal dysfunction: No dosing adjustment	**BRIDGE**

68

2021 ACC/AHA/SCAI Coronary Revascularization Guideline

Recommendation for Intravenous P2Y12 Inhibitors in Patients Undergoing PCI
Referenced studies that support the recommendation are summarized in Online Data Supplement 33.

COR	LOE	RECOMMENDATION
2b	B-R	1. In patients undergoing PCI who are P2Y12 inhibitor naïve, intravenous cangrelor may be reasonable to reduce periprocedural ischemic events (1-3).

69

Clinical trials about Cangrelor

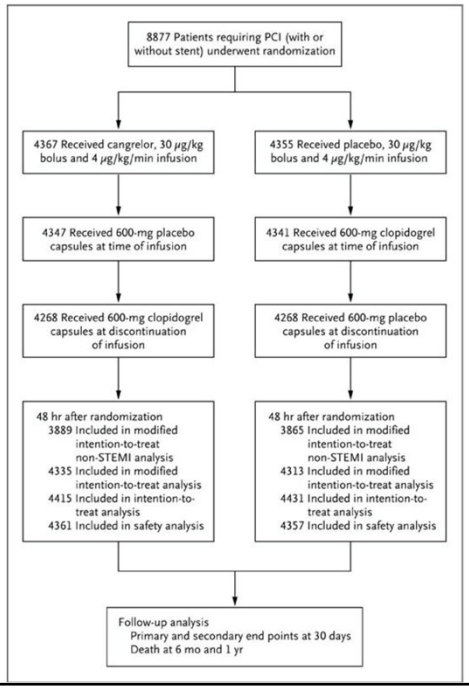
Three large randomized trials, included both patients undergoing **elective** coronary intervention and patients with **ACS**.

- CHAMPION PCI (Cangrelor Versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition–PCI)
- CHAMPION PLATFORM
- CHAMPION PHOENIX

70

CHAMPION PCI

Cangrelor was compared with 600 mg of clopidogrel administered *before* PCI in 8,716 patients with ACS.



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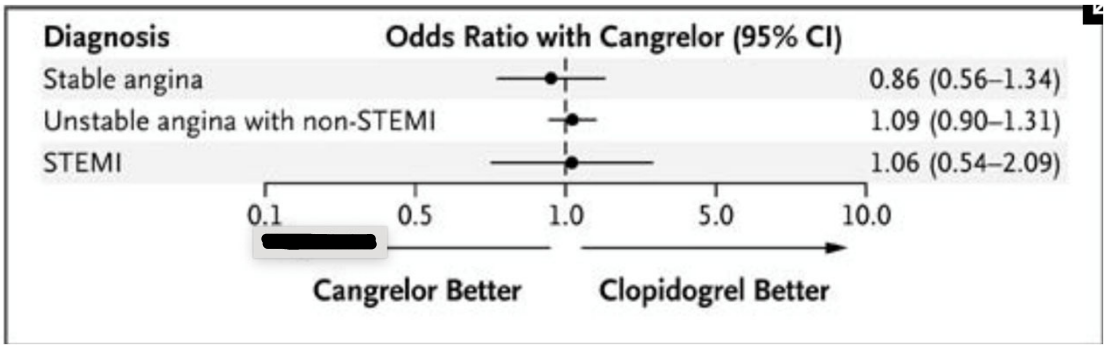

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72

- The primary efficacy endpoint was a composite of death from any cause, MI, or ischemia-driven revascularization at 48 hours
- Cangrelor was not superior to clopidogrel at 48 hours/30 days. (7.5% vs. 7.1%; OR, 1.05)

73

CHAMPION PLATFORM

- Enrolled 5,362 patients (~95% unstable angina or [NSTEMI]) who had not been treated with clopidogrel to receive either cangrelor or placebo *at* PCI, followed by 600 mg of clopidogrel.
- The primary endpoint was not met. Enrollment was stopped. (analysis concluded that the trial would be unlikely to show superiority for this primary endpoint.)

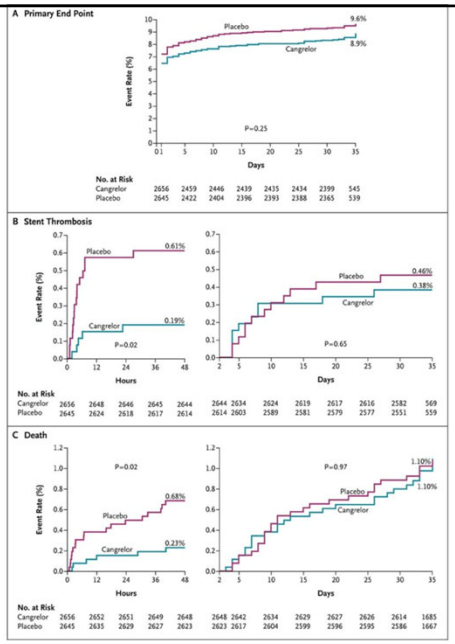
74

- secondary endpoints demonstrated **notable findings at 48 hours:**

  Stent thrombosis at 48 hours was lower in patients receiving cangrelor (0.6% vs. 0.2%; OR, 0.31; 95% CI, 0.11-0.85; p = 0.02)

- The rate of death from any cause (0.7% vs. 0.2%; OR, 0.33;) was also lower.

- The above **likely supports the importance of pre-procedural dual-anti-platelet therapy.**



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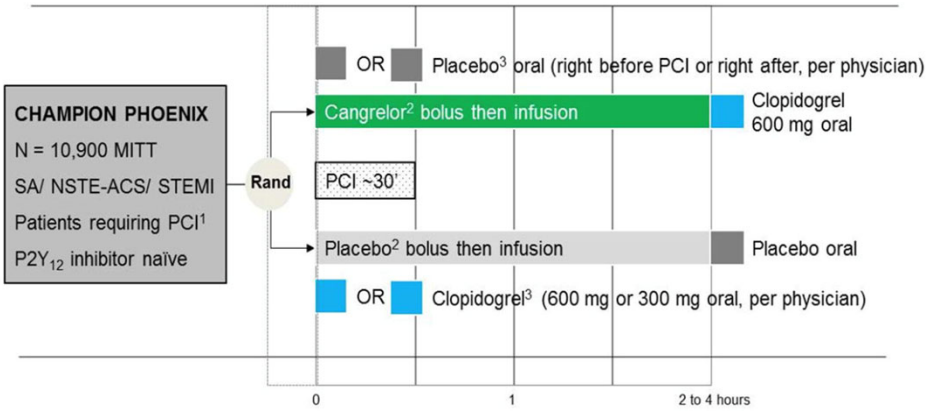
75

CHAMPION PHOENIX



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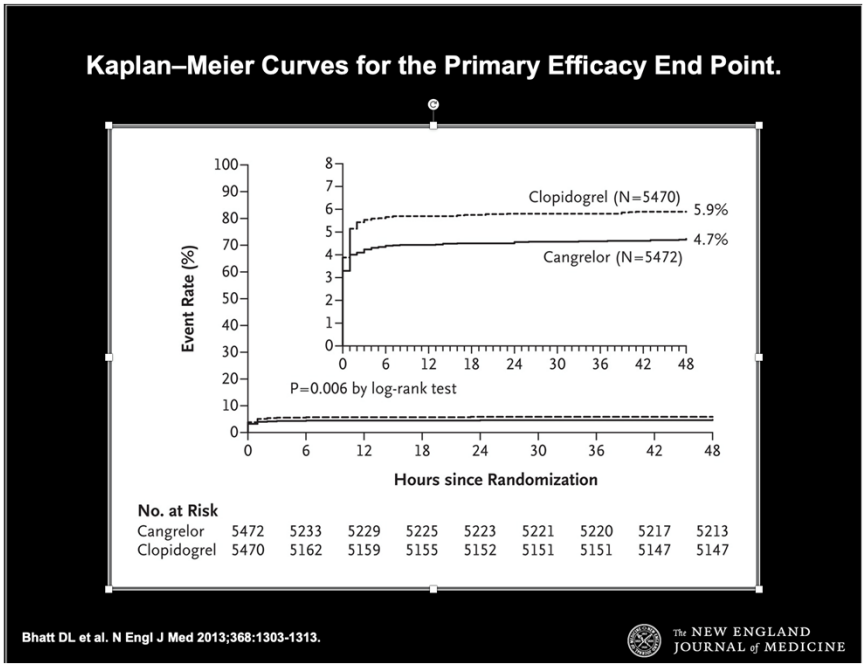
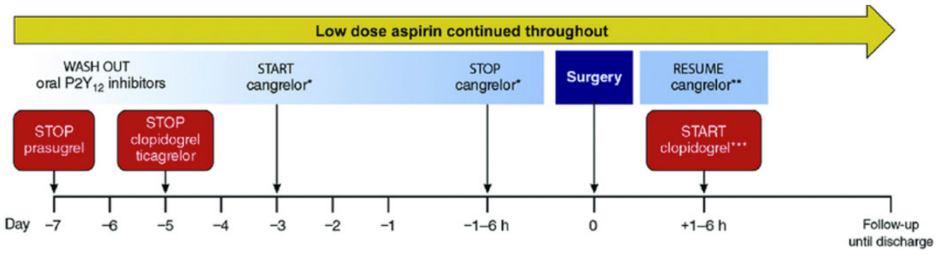


77

BRIDGE (Maintenance of Platelet Inhibition With Cangrelor After Discontinuation of Thienopyridines in Patients Undergoing Surgery)

- Cangrelor has been studied and used off-label to bridge patients on P2Y12 inhibitors who are awaiting cardiac surgery.
- 210 patients with an ACS or treated with a coronary stent and receiving a thienopyridine awaiting coronary artery bypass grafting (CABG) surgery were randomized to either cangrelor or placebo.

78



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- P2Y12 reactivity units <240 was achieved in 98.8% of patients receiving cangrelor versus 19% of patients receiving placebo.
- No difference in excessive CABG surgery–related bleeding in the cangrelor and placebo groups.

- Limitation:

The study was not powered to detect a difference in ischemic events

80

GP IIb/IIIa inhibitors pearls

- 1. What to do if patient pretreated with clopidogrel and aspirin? **do not routinely give GP IIb/IIIa inhibitor**
- 2. GP IIb/IIIa have immediate strong antiplatelets effect.

81

GP IIb/IIIa inhibitors pearls

3. When to use in Elective PCI?
only high thrombotic risk or suboptimal angiographic result. This is just based on clinical experience.

4. The optimal duration of therapy ? **BRIEF PCI**

5. The risk of a major bleeding is mildly increased. specifically **older adults**, **women**, or patients with **renal insufficiency**.

82

GP IIb/IIIa inhibitors pearls

6. Thrombocytopenia — Abciximab and Eptifibatide, more rarely tirofiban

7. In NSTEACS, GP IIb/IIIa inhibitor may be considered for high-risk patients (weak evidence)

evidence of ongoing ischemia
large thrombus burden
no or slow reflow
intraprocedural bailout for distal embolization
coronary artery dissection
hemodynamic instability

83

GP IIb/IIIa inhibitors pearls

- 8. Timing of administration?
  ACUITY, EARLY ACS trials--> no benefit from early initiation (and overall risk outweigh any potential small benefit)

84

Cangrelor Pearls

- CHAMPION PLATFORM, CHAMPION PCI, both failed to show superiority to clopidogrel.
  CHAMPION PHOENIX, showed benefit
- Pooled analysis **of the three trials** (12% STEMI, 57% NSTEMI, 31% stable IHD): **lowered rate of primary** composite efficacy end point (3.8 versus 4.7 %).

85

Cangrelor Pearls

- approved for use as an adjunct to PCI in patients not treated with P2Y12 platelet inhibitor **and not** given GP IIb/IIIa inhibitor.
- Sometimes in STEMI patients with cardiogenic shock, or oral administration of a $P2Y_{12}$ inhibitor is difficult

86

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88