ACC.17
66th Annual Scientific Session & Expo

Core Curriculum: ACS: What Would You Do?

Pharmacologic Options: Update on Antiplatelet Therapies in ACS

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FRI • SAT • SUN
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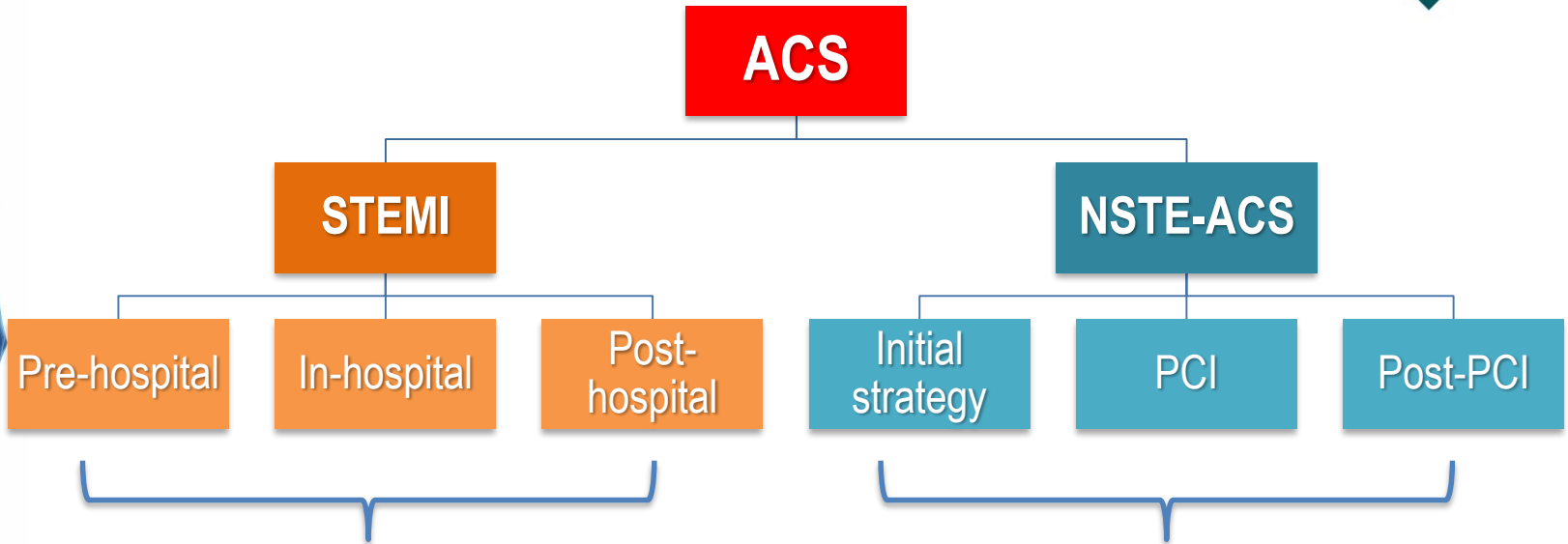
Antiplatelet Therapies in ACS
Outline

- Questions relevant to everyday clinical practice *(relevance)*
- End-user perspective on published evidence & guideline recommendations *(application)*
- APT in ACS *'life-cycle' management*

ACS: acute coronary syndrome; APT: antiplatelet therapy

Antiplatelet Therapies in ACS

'Life-cycle' management: STEMI, NSTE-ACS



STEMI: ST segment elevation myocardial infarction or MI; NSTE-ACS: non-ST segment elevation acute coronary syndrome

What would you do?

A 62 y/o male with no significant past medical history, except for poorly controlled high blood pressure is promptly referred to the cath lab for primary PCI of an inferior STEMI. Which of the following treatment options is not consistent with current guideline recommendations:

A. Loading dose of Ticagrelor or Prasugrel may be preferable to Clopidogrel

B. Pre-hospital loading with Ticagrelor in the ambulance would improve flow in an infarct-related artery

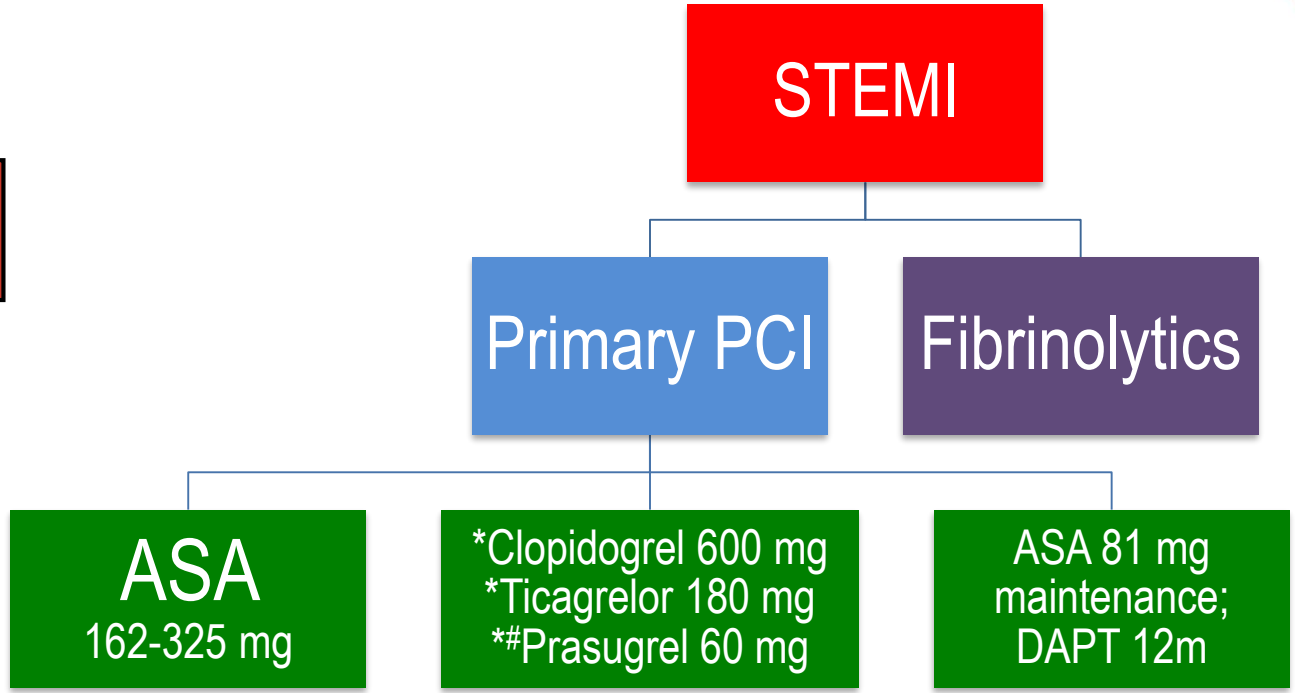
C. Intracoronary GPIIb/IIIa may be used during PCI

D. DAPT after BMS or DES implantation, $P2Y_{12}$ inhibitor therapy (clopidogrel, prasugrel, or ticagrelor) should be given for at least 12 months

E. In patients treated with DAPT after DES implantation who develop a high risk of bleeding discontinuation of P2Y12 inhibitor therapy after 6 months is reasonable

APT Decisions in STEMI

ACC/AHA Guidelines



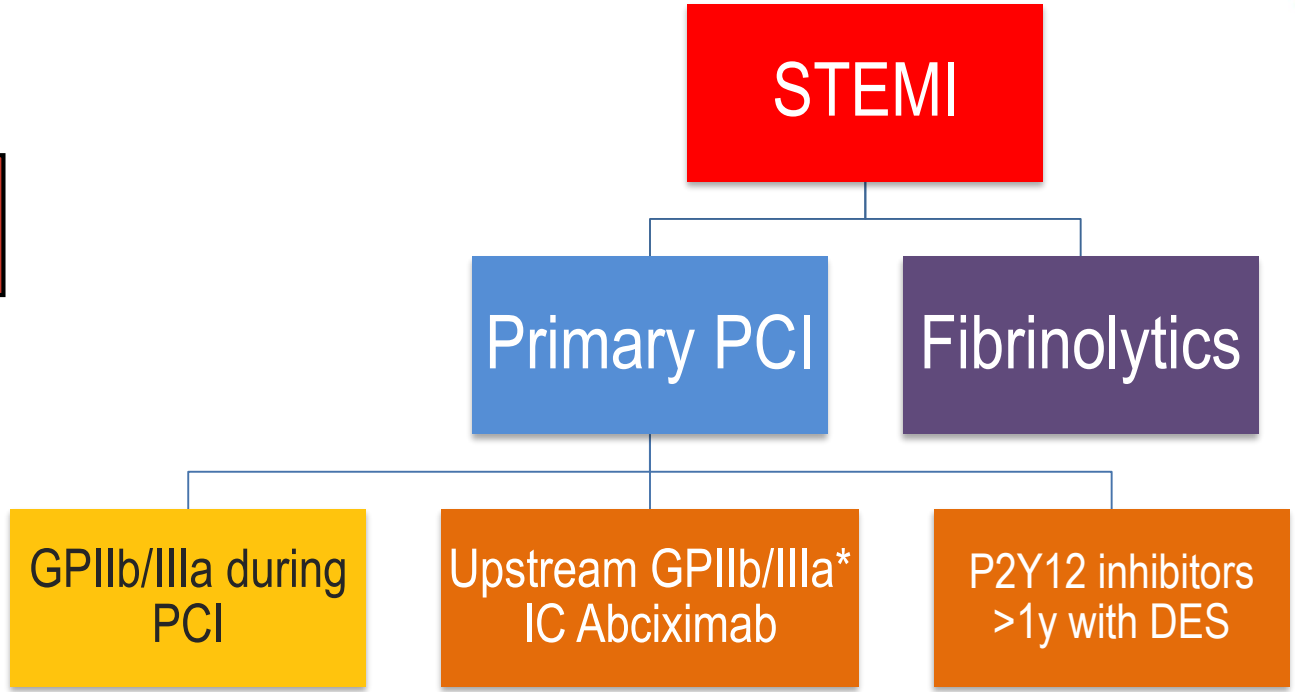
III

Prior stroke, TIA#

*Given as early as possible or at time of primary PCI; ASA 81 mg with Ticagrelor

APT Decisions in STEMI

ACC/AHA Guidelines

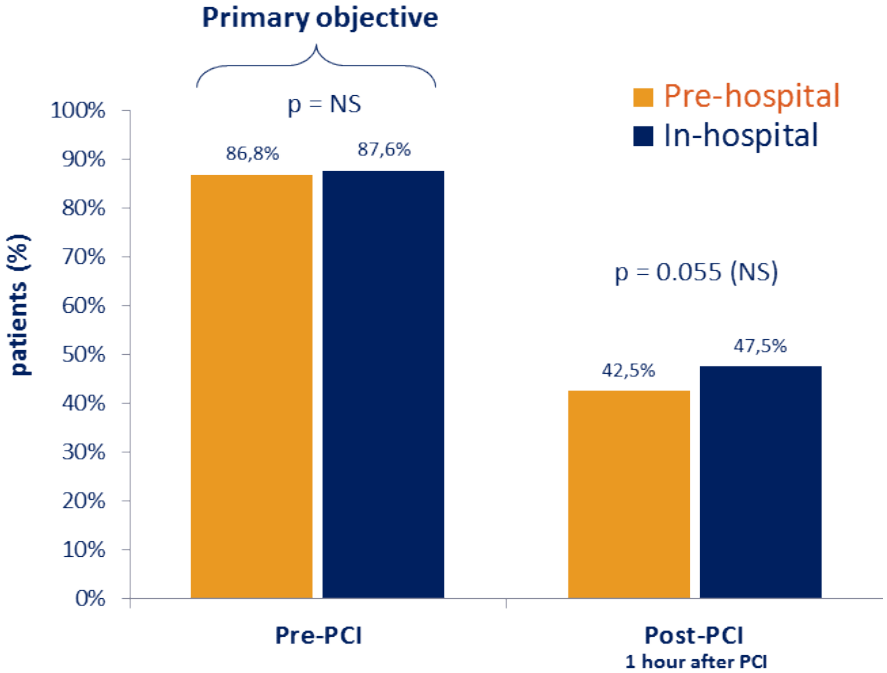


*FINESSE trial: post-hoc analysis in transfer patients for primary PCI (*JACC Cardiovasc. Interv.* 2, 917–924, 2009); concentrated Tirofiban (3.75 mg/15 mL)

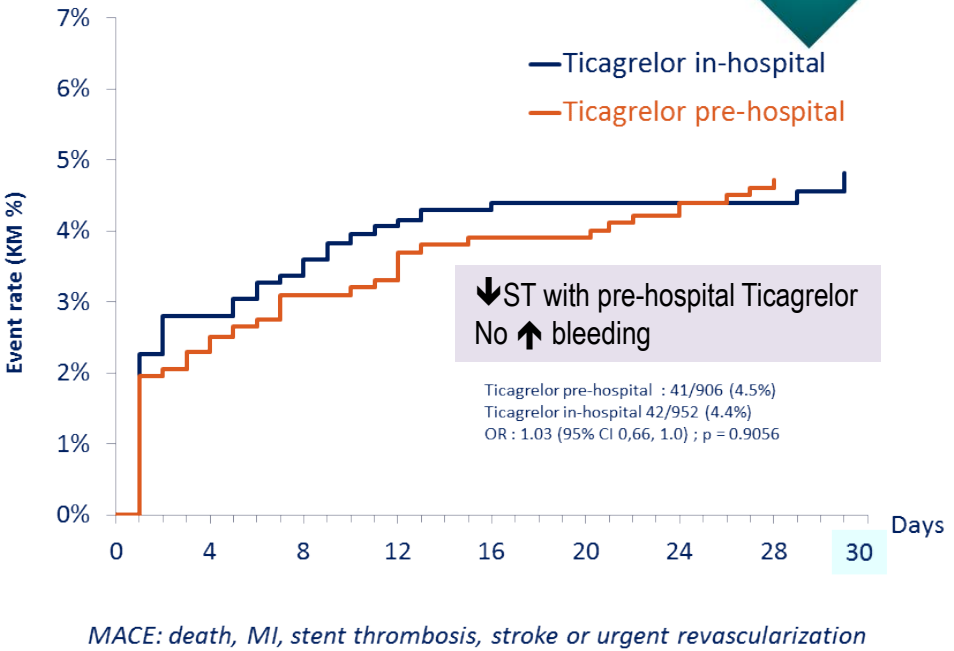
UFH: unfractionated heparin; IC: intracoronary; DES: drug-eluting stents

Ticagrelor Pretreatment in STEMI

Primary PCI: ATLANTIC (n=1,875)



≥70% ST elevation resolution



MACE: death, MI, stent thrombosis, stroke or urgent revascularization

30-day MACE

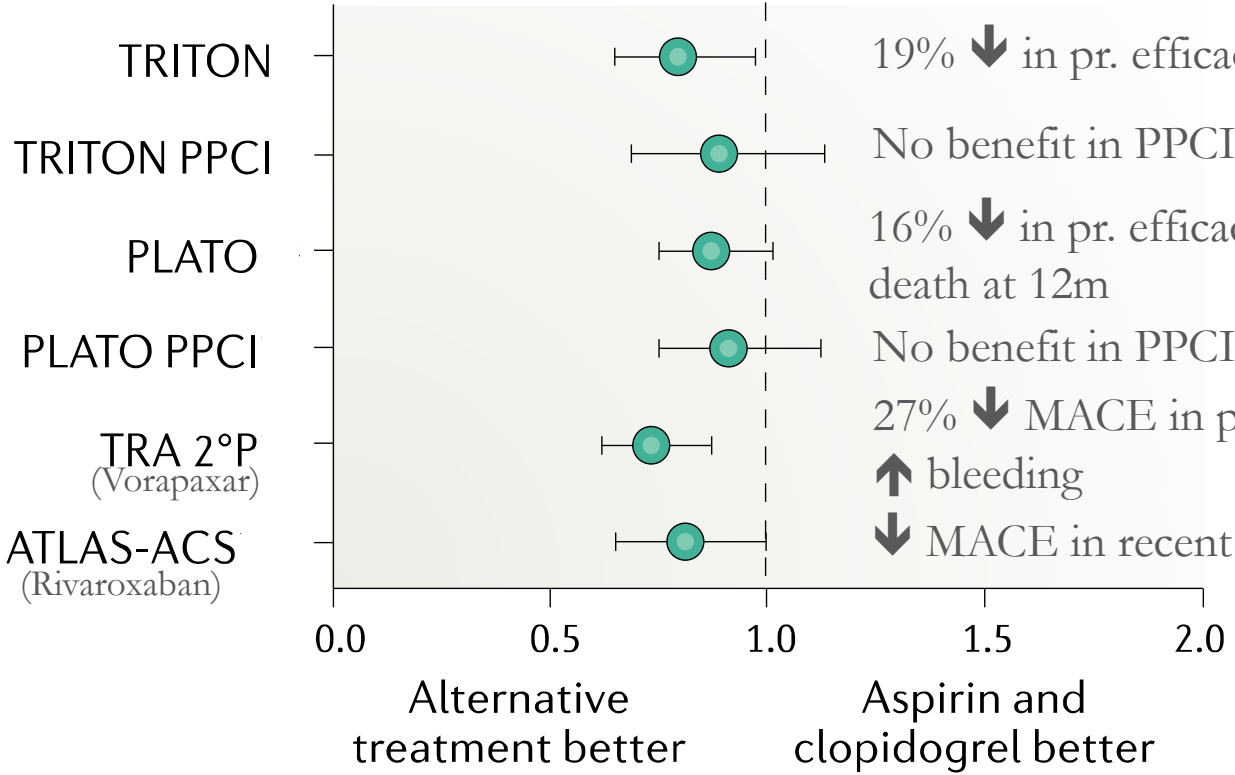
Montalescot et al. N Engl J Med 2014; 371:1016-1027

Specific P2Y12 Inhibitors in STEMI

COR	LOE	Recommendations
IIa	B-R	In patients with STEMI treated with DAPT after coronary stent implantation it is reasonable to use ticagrelor in preference to clopidogrel for maintenance $P2Y_{12}$ inhibitor therapy
IIa	B-R	In patients with STEMI treated with DAPT after coronary stent implantation who are not at high risk for bleeding complications and who do not have a history of stroke or TIA, it is reasonable to choose prasugrel over clopidogrel for maintenance $P2Y_{12}$ inhibitor therapy

Levine et al. Circulation. 2016;134:e123–e155

STEMI subgroups of Major RCTs



19% ↓ in pr. efficacy at 14.5m

No benefit in PPCI enrolled ≤12h symptoms

16% ↓ in pr. efficacy at 12m; 21% ↓ in CV death at 12m

No benefit in PPCI ≤12 c/w overall PPCI

27% ↓ MACE in previous STEMI (2 wk-12m); ↑ bleeding

↓ MACE in recent STEMI (24h-7d); ↑ bleeding

(GEMINI-ACS): Rivaroxaban+ Clop/Ticag

PPCI: primary PCI

Franchi et al. Nat Rev. in Cardiology, 2017

Duration of P2Y12 Inhibitors in STEMI

COR	LOE	Recommendations
I	B-R	In patients with STEMI treated with DAPT after BMS or DES implantation, $P2Y_{12}$ inhibitor therapy (clopidogrel, prasugrel, or ticagrelor) should be given for at least 12 months
IIb	B-R	In patients treated with coronary stent implantation who have tolerated DAPT without a bleeding complication and who are not at high bleeding risk continuation of DAPT for longer than 12 months may be reasonable
IIb	B-R	In patients treated with DAPT after DES implantation who develop a high risk of bleeding, are at high risk of severe bleeding complication, or develop significant overt bleeding, discontinuation of $P2Y_{12}$ inhibitor therapy after 6 months may be reasonable

Levine et al. Circulation. 2016;134:e123–e155

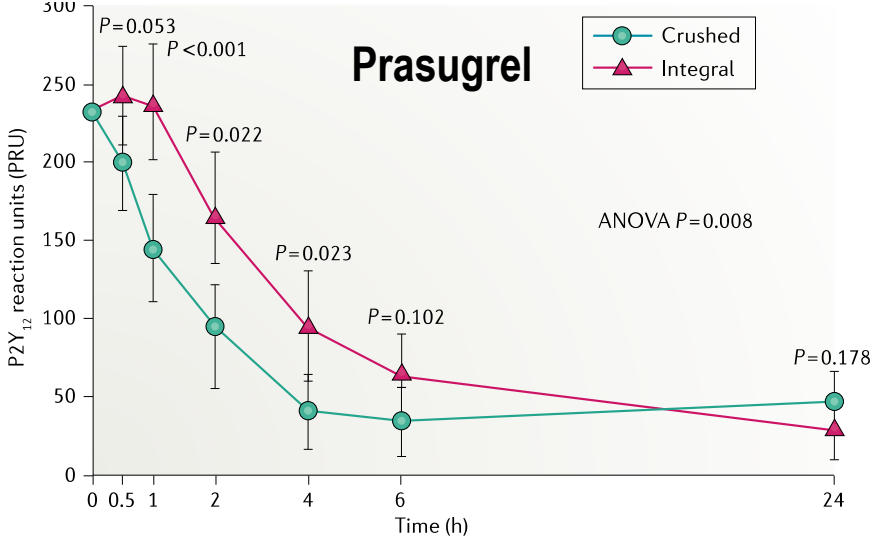
P2Y12 Inhibitors in STEMI FAQs

Question	Evidence	Results
Escalating Ticagrelor dose in STEMI PCI	Franchi et al. JACC Cardiovasc Interv. 2015 Sep;8(11):1457-67; a PK-PD RCT (LDs: 180 mg, 270 mg, 360 mg)	Impaired response to Ticagrelor in STEMI; high-in treatment platelet reactivity not overcome by ↑LDs
Double Ticagrelor vs. standard Prasugrel in STEMI PCI	Parodi et al. Am Heart J. 2014 Jun;167(6):909-14 (Ticagrelor 360 mg vs. Prasugrel 60 mg)	High residual platelet reactivity (HPRR) P2Y12 reaction units (PRU) ≥240 in 43% and 56% of patients (p =0.386) on Ticagrelor & Prasugrel, respectively
Ticagrelor (180 mg) vs. Prasugrel (60 mg) in STEMI PCI	RAPID PCI RCT: Parodi et al. J Am Coll Cardiol. 2013 Apr 16;61(15):1601-6	HRPR (PRU ≥240) in 44% and 60% of patients (p = 0.258) at 2h on Prasugrel & Ticagrelor, respectively; Morphine independent predictor

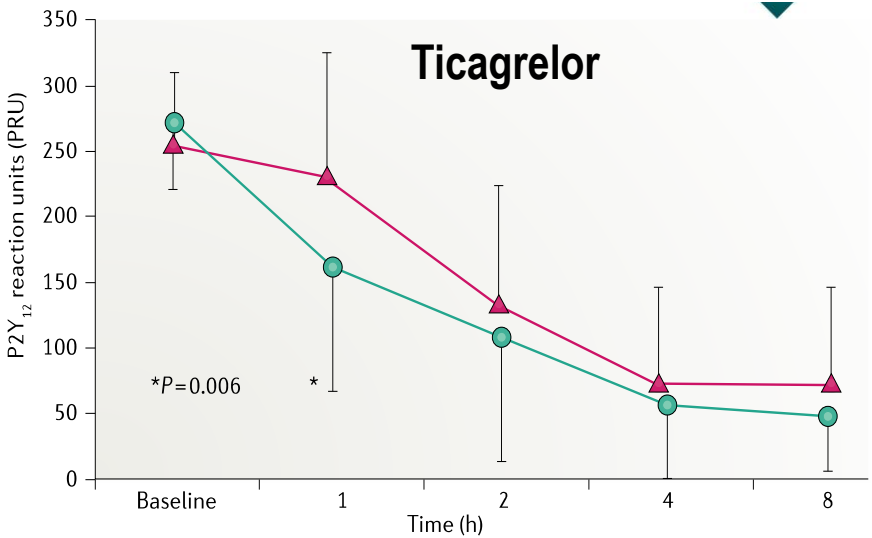
FAQ: frequently asked questions; PK: pharmacokinetic; PD: pharmacodynamic; RCT: randomized clinical trial; LD: loading dose

Crushed vs. Integral P2Y12 in STEMI

CRUSH Study: Rollini et al. JACC. 2016



MOJITO Trial: Parodi et al. Am. Heart J. 2014



Crushed Prasugrel & Ticagrelor were associated with faster drug absorption and more prompt & potent antiplatelet effects compared with whole-tablet ingestion

Cangrelor in STEMI Primary PCI

Primary Endpoint		Cangrelor	Clopidogrel	OR
Overall mITT* (N=24,910)		473/12,459 (3·8%)	579/12,422 (4·7%)	0·81 (0·71–0·91)
STEMI† (n=2884)		41/1407 (2·9%)	51/1477 (3·5%)	0·84 (0·55–1·27)
	0.1 1 10			

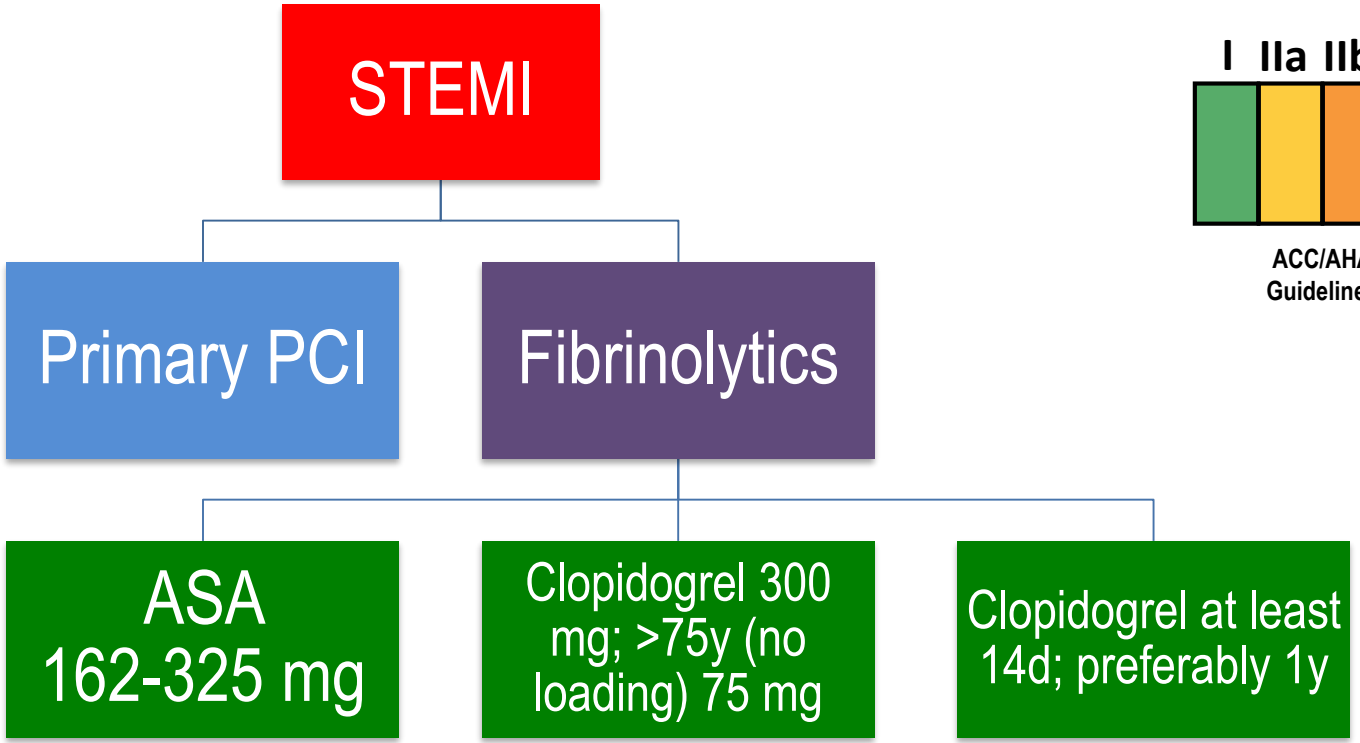
Stent thrombosis				
Overall mITT* (N=24,881)		62/12,459 (0·		
STEMI (n=2,884)		16/1407 (1.1%		
	0.1 1 10			

Not endorsed by U.S. Guidelines
ACS: IIb ESC indication in P2Y12 naïve patients (not specific for STEMI)

GUSTO sev/mod bleeding				
Overall safety* (N=25,107)		103 (0·8%)	79 (0·6%)	1·30 (0·97– 1·75)
STEMI (n=3008)		17/1463(1.2%)	15/1545(1.0%)	1.20(0.60 - 2.41)
	0.1 1 10			

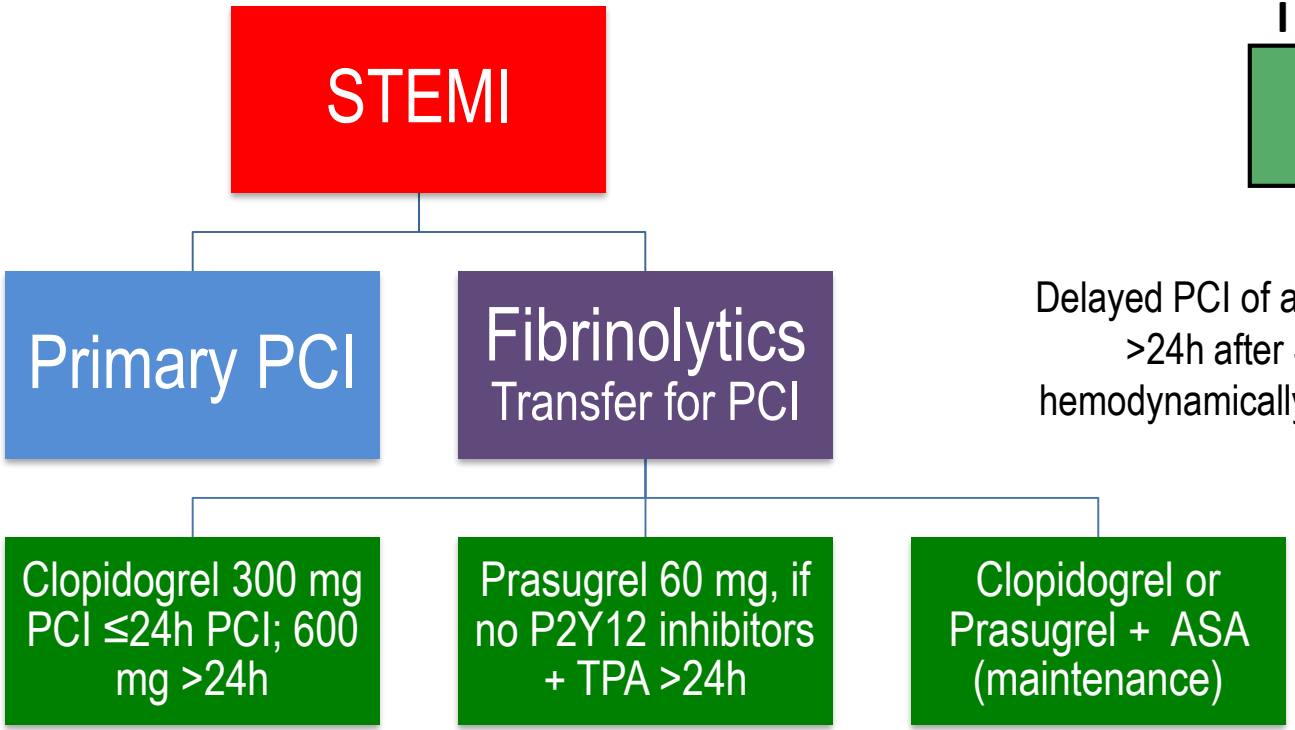
* Overall population includes CHAMPION PHOENIX, PCI and PLATFORM ; †STEMI population from PHOENIX and PCI
* Steg PG, Lancet 2013; 82: 1981–92

APT Decisions in STEMI



ACC/AHA Guidelines

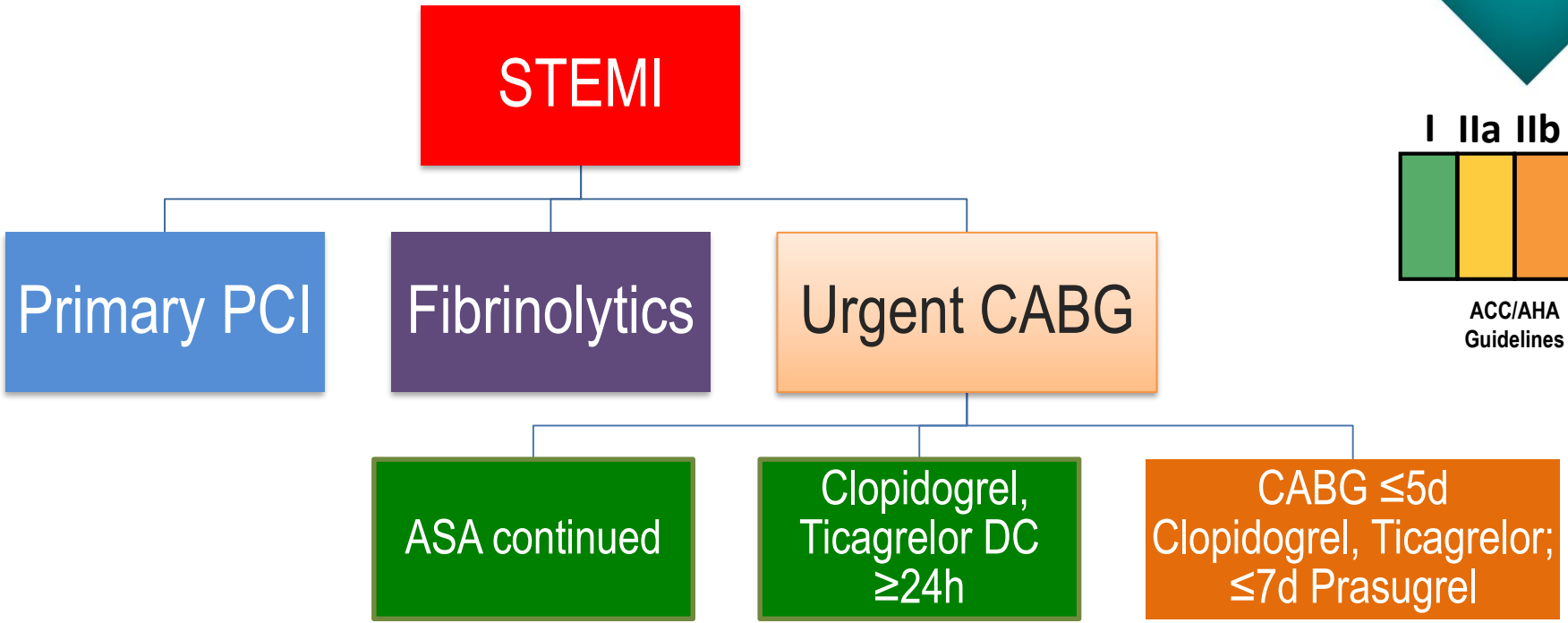
APT Decisions in STEMI



ACC/AHA Guidelines

Delayed PCI of a totally occluded infarct artery >24h after STEMI in asymptomatic hemodynamically & electrically stable patients

APT Decisions in STEMI



I IIa IIb III

ACC/AHA Guidelines

Antiplatelet Therapies in ACS

'Life-cycle' management: STEMI

Pre-hospital APT Decision: PPCI capable hospital; ASA; Fibrinolysis

In-hospital APT: Ticagrelor, Prasugrel > Clopidogrel in PPCI; bail-out GPIIb/IIIa

Post-hospital APT Decisions: DAPT 12m

What would you do?

A 62y male with no significant past medical history, except for poorly controlled high blood pressure is promptly referred to the cath lab for primary PCI of an inferior STEMI. Which of the following treatment options is not consistent with current guideline recommendations:

A. Loading dose of Ticagrelor or Prasugrel may be preferable to Clopidogrel

B. Pre-hospital loading with Ticagrelor in the ambulance would improve flow in the infarct-related artery

C. Intracoronary GPIIb/IIIa may be used during PCI

D. DAPT after BMS or DES implantation, $P2Y_{12}$ inhibitor therapy (clopidogrel, prasugrel, or ticagrelor) should be given for at least 12 months

E. In patients treated with DAPT after DES implantation who develop a high risk of bleeding discontinuation of P2Y12 inhibitor therapy after 6 months may be reasonable

Antiplatelet Therapies in ACS

'Life-cycle' management: NSTE-ACS

Initial Rx Strategy-APT

PCI APT Decisions

Post-PCI APT Decisions

What would you do?

A 82 y woman is admitted for ongoing chest discomfort and dynamic ST changes on her surface EGG. She is initially treated with clopidogrel and ASA. On the following day, she is referred for coronary angiography for ongoing rest pain, and undergoes PCI of a large caliber mid RCA with a 3.5 mm in diameter BMS.

Select the best antiplatelet regimen:

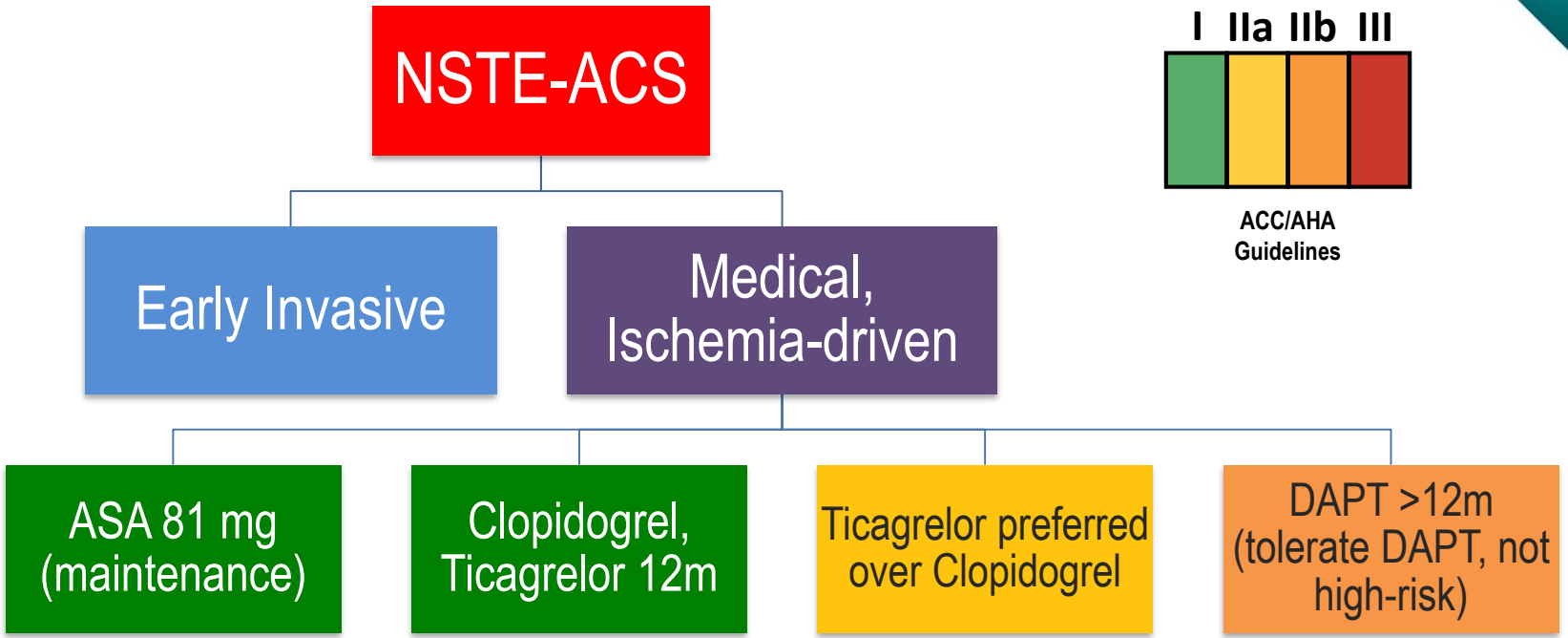
A. Loading dose of Prasugrel in the cath lab, followed by 12 month of DAPT

B. Reload with Clopidogrel post-PCI, followed by 12 month of DAPT

C. Continue DAPT (Clopidogrel + ASA) for 30 days

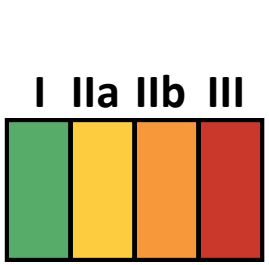
D. Continue DAPT (Clopidogrel + ASA) for 12 months

APT Decisions in NSTE-ACS



Levine et al. Circulation. 2016;134:e123–e155

APT Decisions in NSTE-ACS



ACC/AHA Guidelines

NSTE-ACS

Early Invasive (PCI)

Medical, Ischemia-driven

Ticagrelor, Clopidogrel (initial mgmt.); Prasugrel only pre-PCI with stent

GPIIb/IIIa during PCI (not on P2Y12 inhibitor)

Consider Cangrelor

Clopidogrel, Prasugrel, or Ticagrelor + ASA 81 mg for 12m

Prefer Ticagrelor over clopidogrel

Prefer Prasugrel over clopidogrel*

DAPT >12m≠
Discont. P2Y12 @ 6m±

III

Prior stroke, TIA*

≠DAPT well tolerated, not at high-risk for bleeding; ±significant overt bleeding or at a high-risk of bleeding

Levine et al. Circulation. 2016;134:e123–e155

DAPT Duration Post-PCI

Individual patient & network meta-analysis of six randomized trials and 11 473 patients

- ≤6-month DAPT was associated with non-significantly higher 1-year rates of MI or ST c/w 1-year DAPT (HR: 1.48; 95% CI: 0.98-2.22; p = 0.059)
- In patients with ACS (low-risk), 3-month but not 6-month DAPT was associated with higher rates of MI or ST c/w 1-year DAPT, whereas in stable CAD, no such difference was apparent

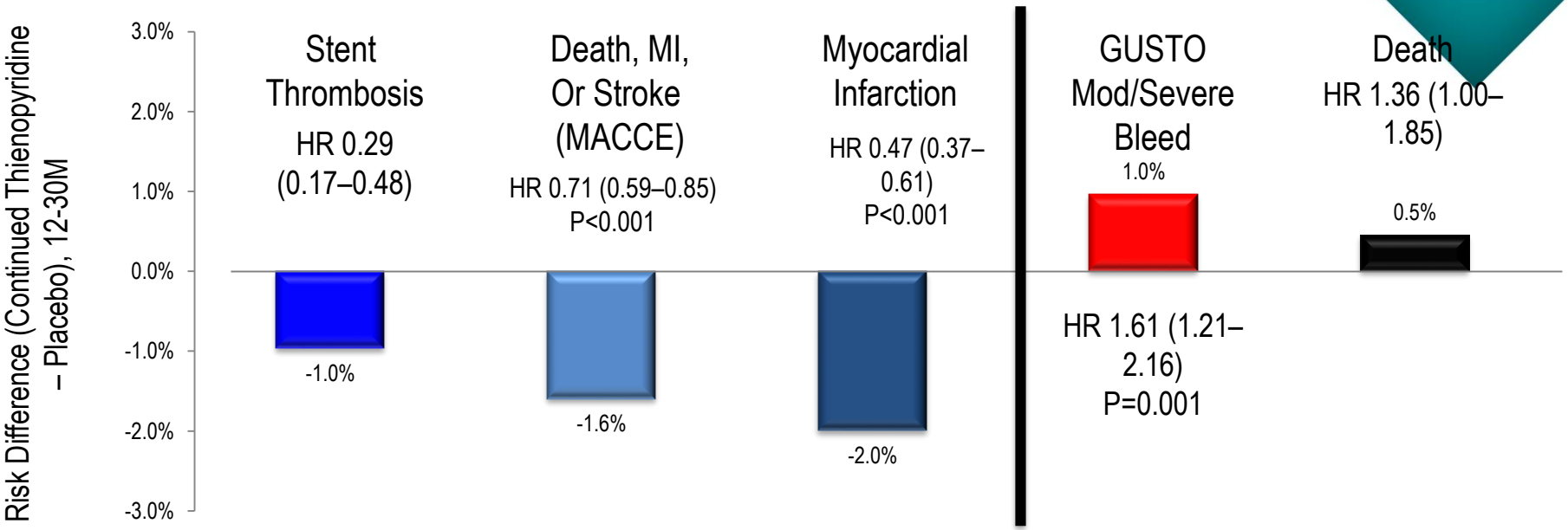
Palmerini et al. EHJ 2017

Duration of P2Y12 in NSTE-ACS CABG

COR	LOE	Recommendations
I	C-EO	In patients treated with DAPT after coronary stent implantation who subsequently undergo CABG, $P2Y_{12}$ inhibitor therapy should be resumed postoperatively so that DAPT continues until the recommended duration of therapy is completed
I	C-LD	In patients with NSTE-ACS being treated with DAPT who undergo CABG, $P2Y_{12}$ inhibitor therapy should be resumed after CABG to complete 12 months of DAPT therapy after ACS
I	B-NR	In patients treated with DAPT, a daily aspirin dose of 81 mg (range, 75 mg to 100 mg) is recommended

Levine et al. Circulation. 2016;134:e123–e155

DAPT Study



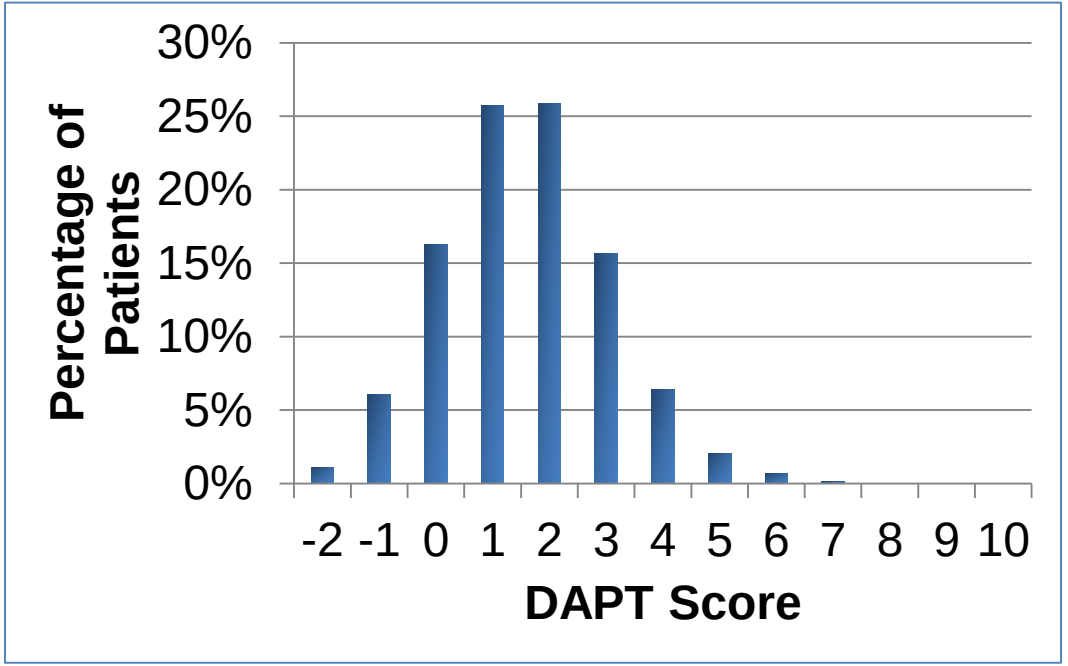
Continuation of DAPT beyond 12 months reduced ischemic complications after coronary stenting compared with aspirin alone, yet increased moderate or severe bleeding

Mauri et al. NEJM. 2014 Dec 4:371:2155-66

The DAPT Score

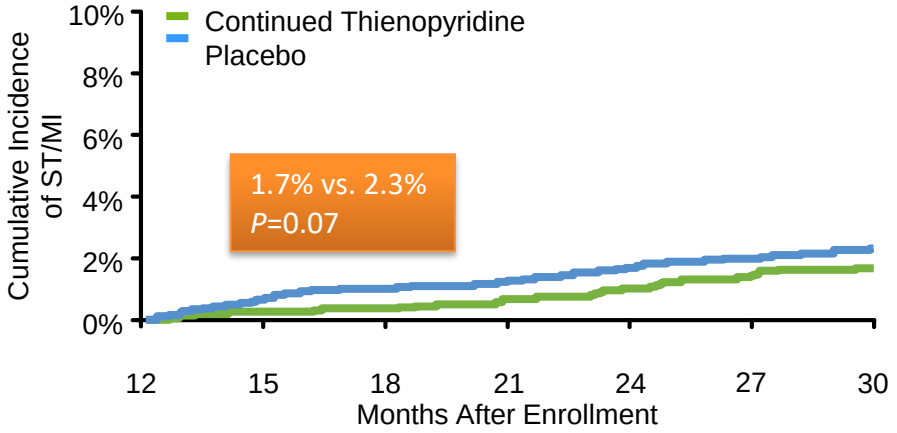
Variable	Points
Patient Characteristic	
Age	
≥ 75	-2
65 - <75	-1
< 65	0
Diabetes Mellitus	1
Current Cigarette Smoker	1
Prior PCI or Prior MI	1
CHF or LVEF < 30%	2
Index Procedure Characteristic	
MI at Presentation	1
Vein Graft PCI	2
Stent Diameter < 3mm	1

Distribution of DAPT Scores among all randomized subjects in the DAPT Study

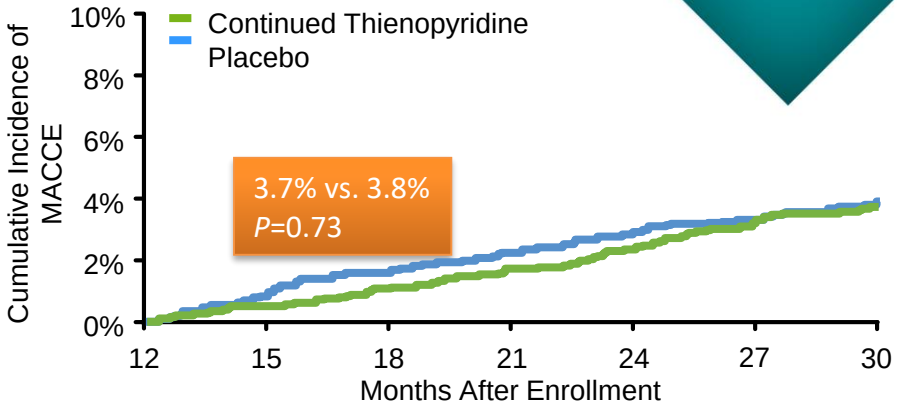


Continued Thienopyridine vs. Placebo DAPT Score <2 (Low); N=5731

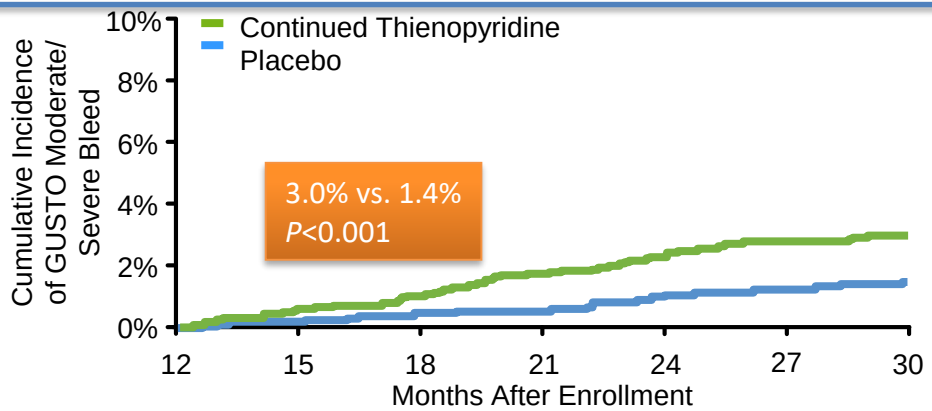
Myocardial Infarction or Stent Thrombosis



Death, MI, or Stroke (MACCE)

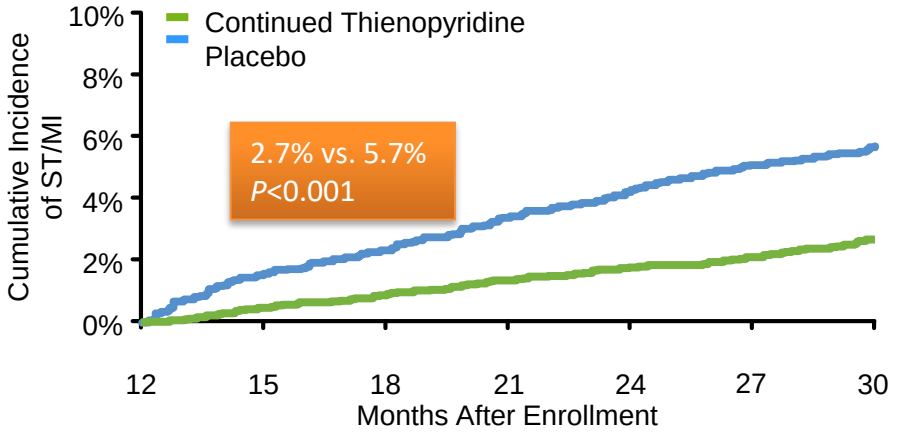


GUSTO Moderate/ Severe Bleeding



Continued Thienopyridine vs. Placebo DAPT Score ≥ 2 (High); N=5917

Myocardial Infarction or Stent Thrombosis



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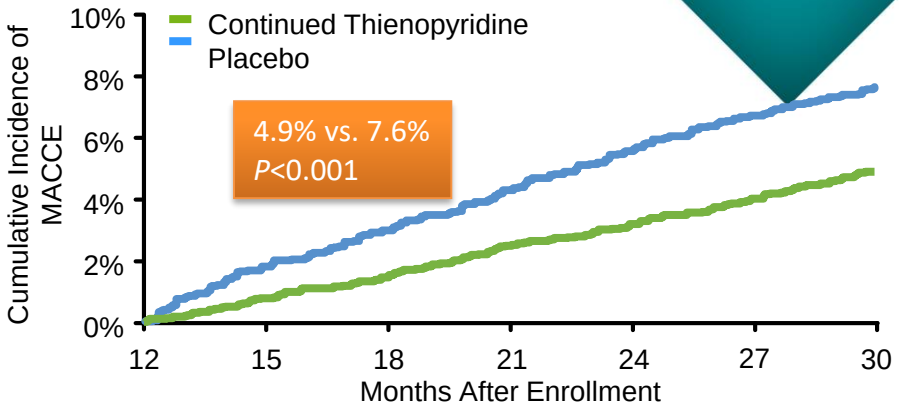
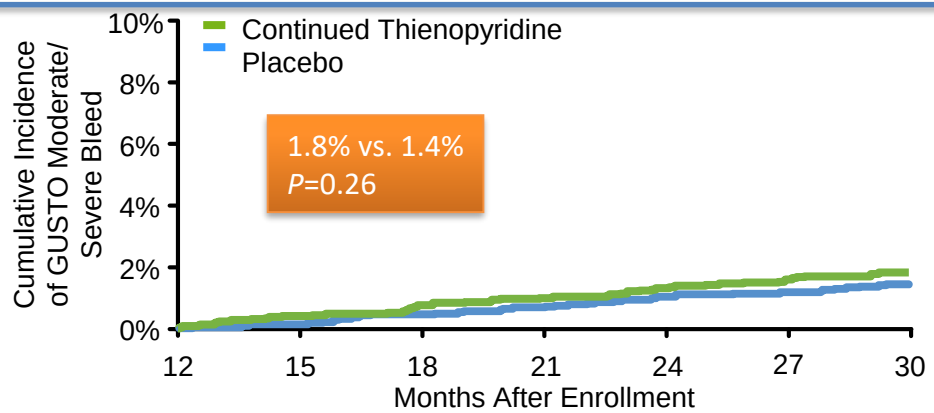


GUSTO Moderate/ Severe Bleeding



The DAPT Score

Among patients who have not had a major ischemic or bleeding event within the first year after PCI:
The DAPT Score identified patients for whom ischemic benefits outweighed bleeding risks, & for whom bleeding risks outweighed ischemic benefits

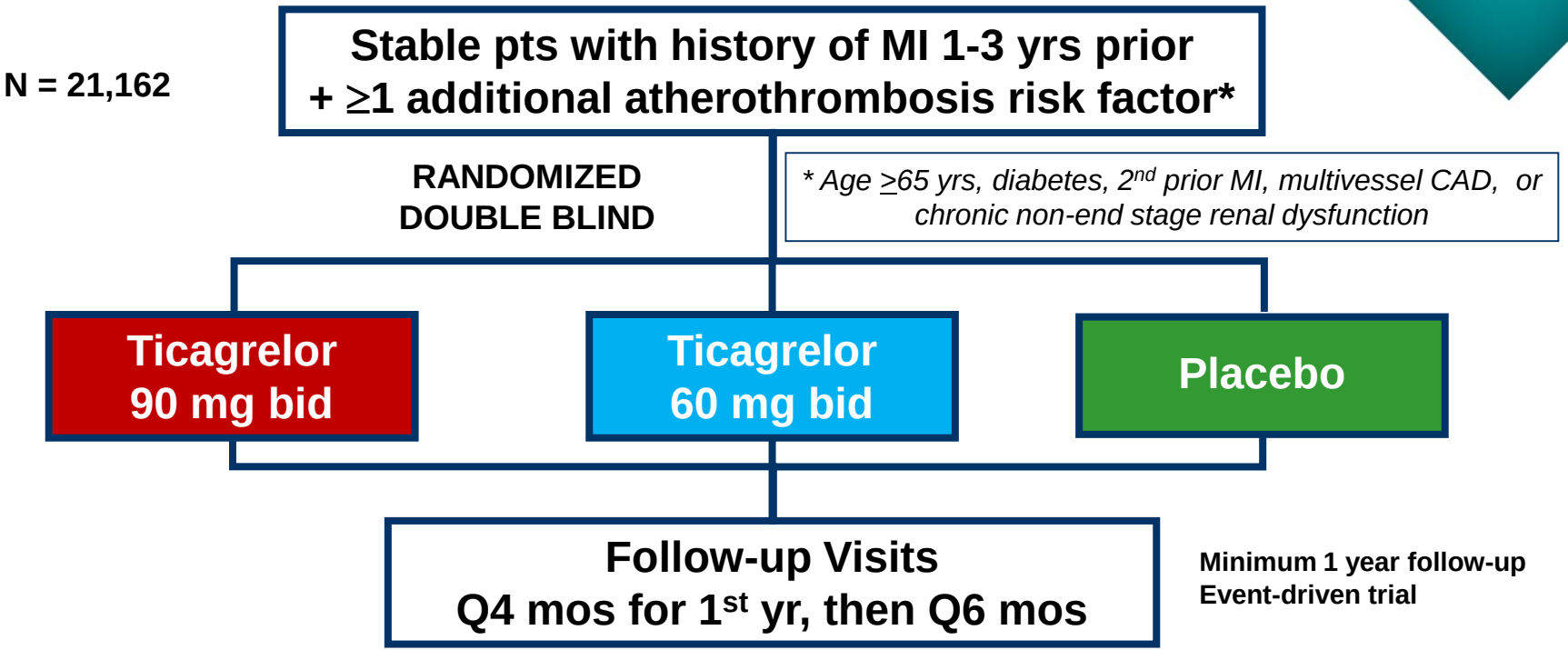
Low DAPT Score (< 2)
NNT to prevent ischemia = 153
NNH to cause bleeding = 64

High DAPT Score ≥ 2
NNT to prevent ischemia = 34
NNH to cause bleeding = 272

DAPT Score may help clinicians decide *who should, and who should not* be treated with extended DAPT

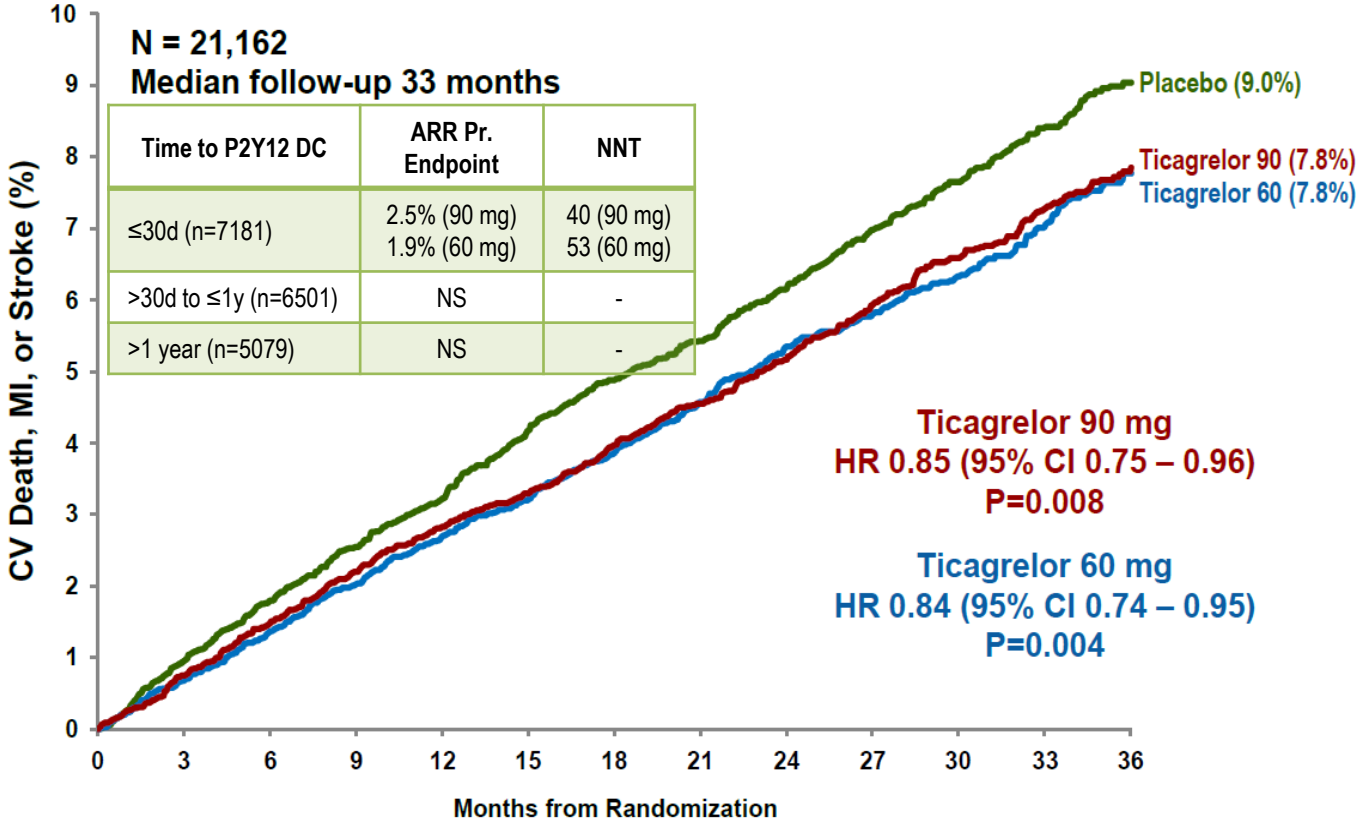
Yeh et al. JAMA. 2016;315(16):1735-1749

PEGASUS-TIMI 54



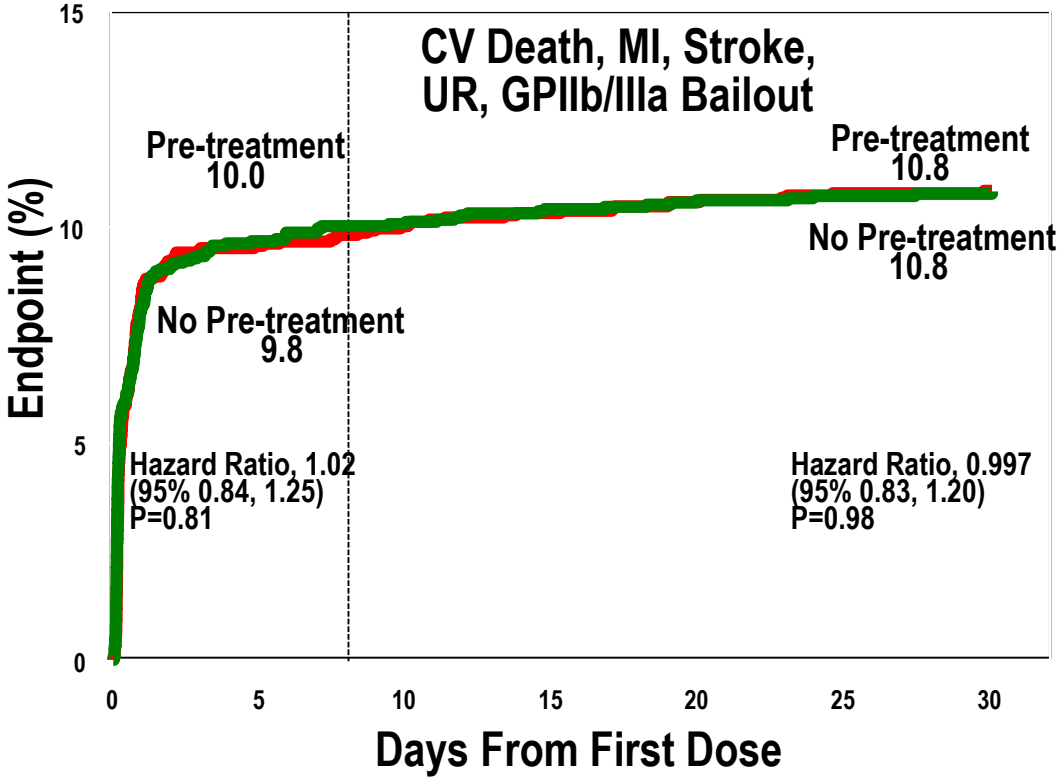
Bonaca MP, Bhatt DL, Braunwald E, et al. Sabatine MS. Am Heart J. 2014

PEGASUS TIMI- 54 Overall Results



Bonaca MP et al. NEJM. 2015

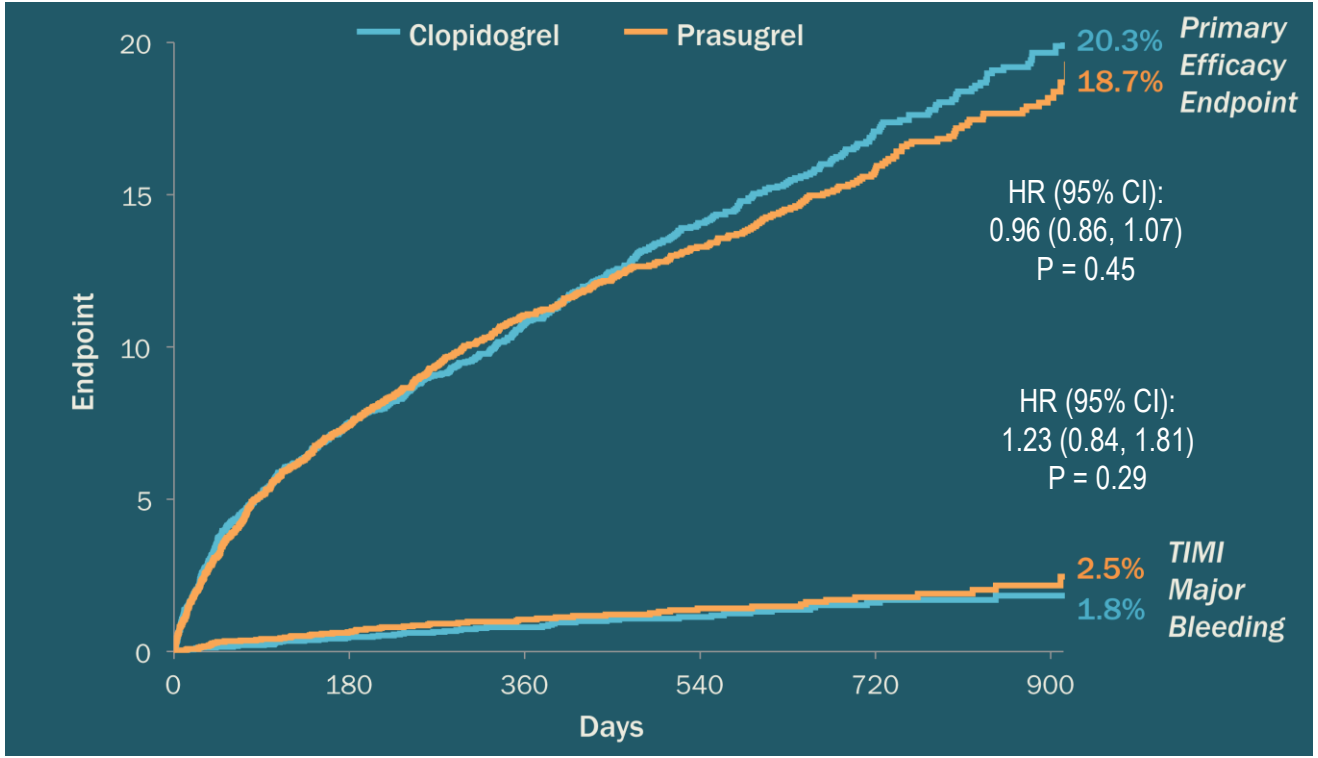
ACCOAST: Prasugrel Pretreatment NSTEMI-PCI



No ischemic benefit and significantly higher bleeding (2.9% vs. 1.4%)

Montalescot et al. N Engl J Med 2013

TRILOGY ACS:
Prasugrel in Medically Managed ACS



- Medically managed NSTE-ACS without revascularization (PCI or CABG) is 40-60%
- Under-represented in contemporary ACS trials

Roe et al. NEJM 2012

P2Y12 Inhibitor Switch

Have you switched P2Y12 inhibitors in your ACS patients either in hospital or during out-patient follow-up?

A. Yes I have in ≤10% of my ACS patients

B. Yes I have in >10% of my ACS patients

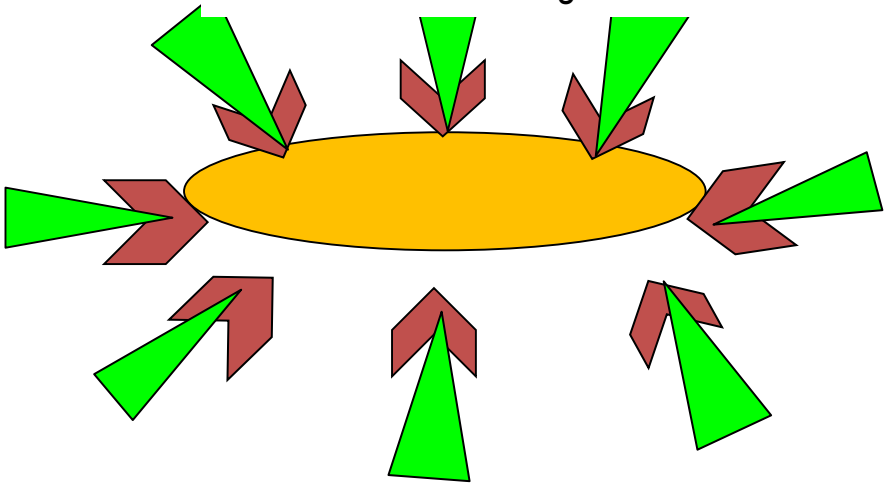
C. Never switched P2Y12 inhibitors in ACS patients

D. Never switched, and do not see the need

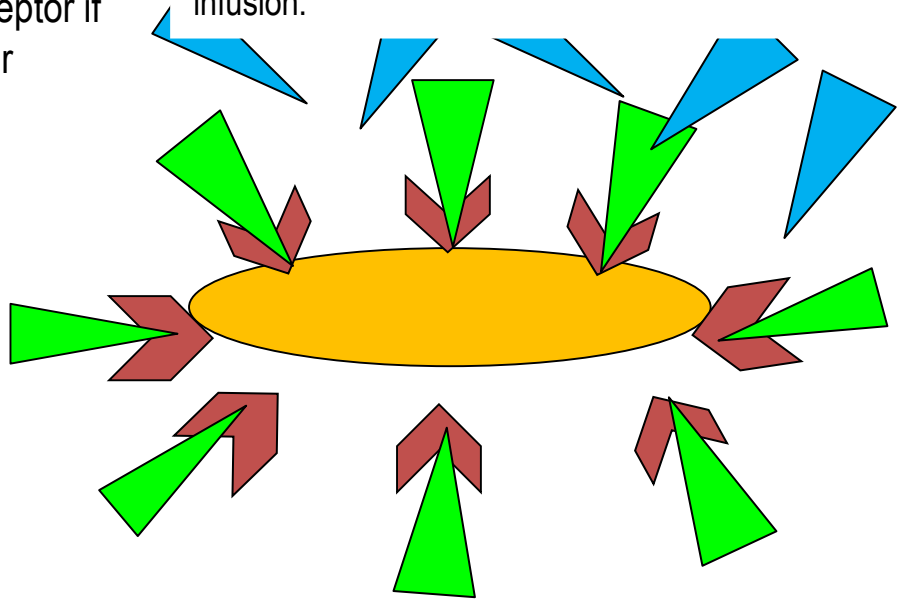
P2Y12 Inhibitor Transition & Switch

Active metabolites of thienopyridines are very unstable with rapid clearance from systemic circulation. They will not bind to the P2Y12 receptor if occupied and thus should be administered after discontinuation of cangrelor infusion.

EMA label: Prasugrel can be administered 30 minutes prior to discontinuation of cangrelor infusion.



CANGRELOR



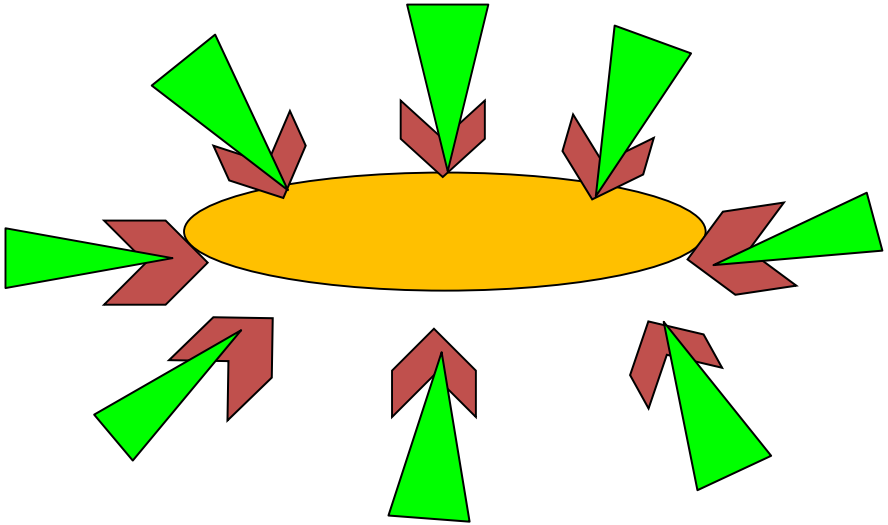
CANGRELOR + THIENOPYRIDINE

Adapted from Rollini F, Franchi F & Angiolillo DJ. Nat. Rev. Cardiol. 2016

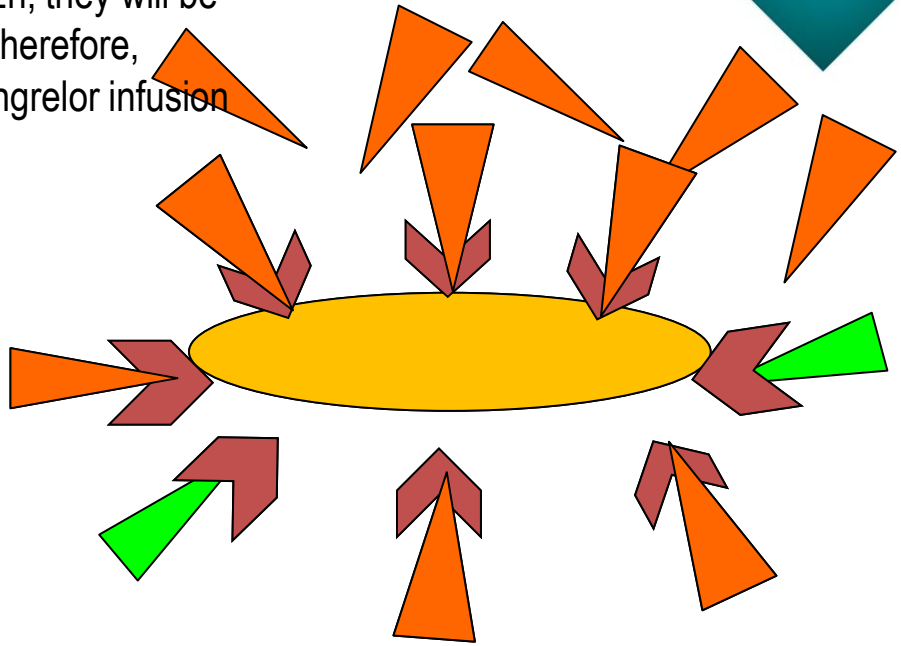
EcelsiorLOAD-2 Trial: JACC 2017

P2Y12 Inhibitor Transition & Switch

Ticagrelor and its major metabolite will not bind to the P2Y12 receptor when occupied. However, given their half-lives of ~10-12h, they will be available for binding once cangrelor has been cleared. Therefore, ticagrelor can be administered before, during or after cangrelor infusion



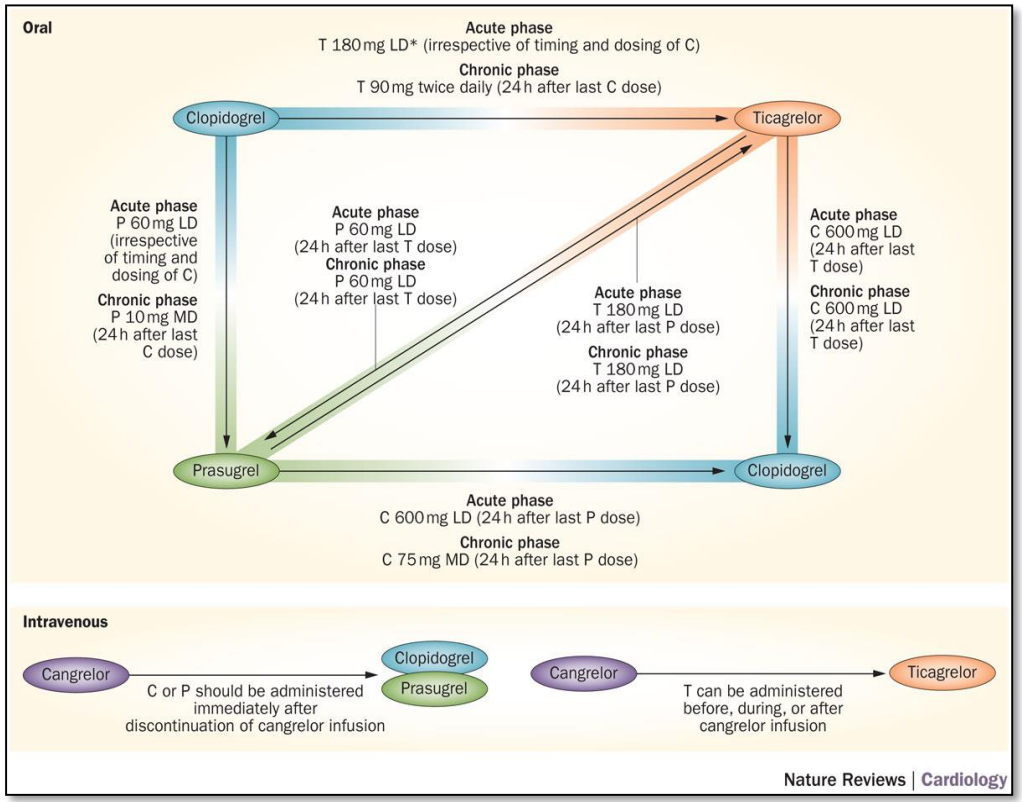
CANGRELOR



CANGRELOR + TICAGRELOR

Adapted from Rollini F, Franchi F & Angiolillo DJ. *Nat. Rev. Cardiol. 2016*

P2Y12 Switch: Practical Suggestions



Key reasons for switching:

1. Clinical failure (ST)
2. Cost
3. Hypersensitivity
4. Unrecognized stroke, TIA
5. Side-effects: dyspnea
6. Bleeding, anticoagulation
7. Non-adherence

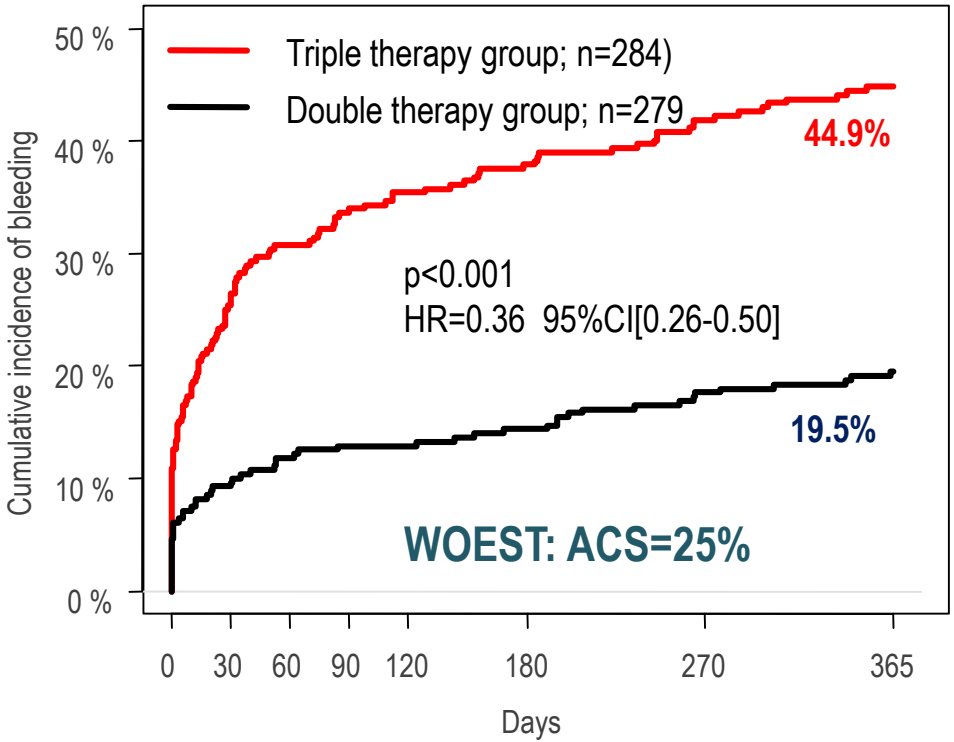
Longitudinal Assessment of Treatment Patterns & Events in ACS Registry:

Switching ~10%

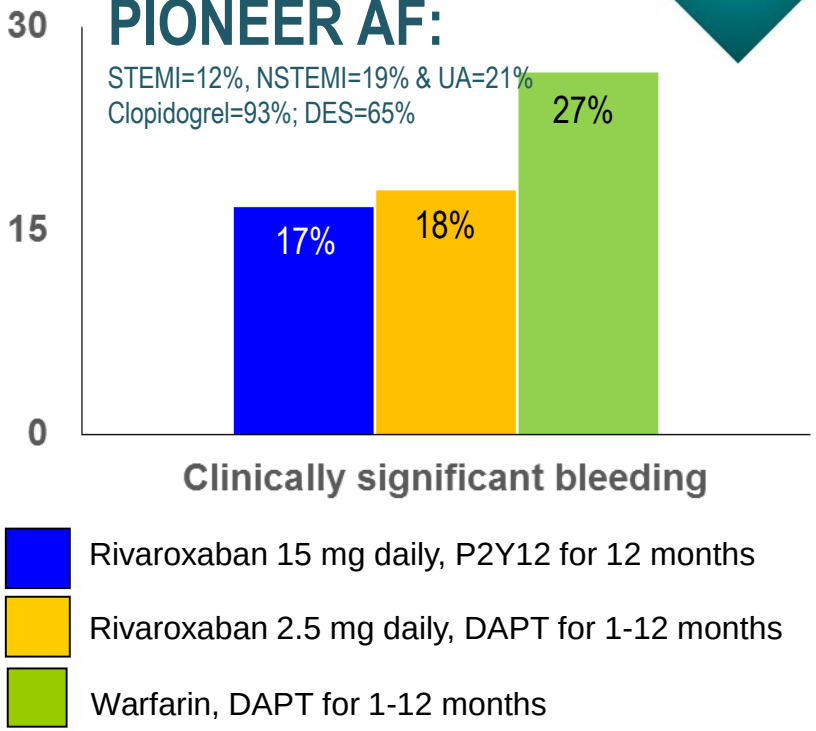
Rollini, Angiolillo et al. *Nat. Rev. Cardiol 2015; Bagai et al. Circulation 2012*

Antiplatelet & Anticoagulant Combination

It may be safe to treat patients with an increased risk for bleeding with anticoagulation



Dewilide et al. Lancet 2013



Gibson et al NEJM 2016

Antiplatelet Therapies in ACS

'Life-cycle' management: NSTE-ACS

Initial APT Decisions: PCI; Med: T >C

PCI APT Decisions: DAPT: P, T >C

Post-PCI APT Decisions: DAPT 12m

P: prasugrel; T: ticagrelor; C: clopidogrel

What would you do?

A 82 y woman is admitted for ongoing chest discomfort and dynamic ST changes on her surface EGG. She is initially treated with clopidogrel and ASA. On the following day, she is referred for coronary angiography for ongoing rest pain, and undergoes PCI of a large caliber mid RCA with a 3.5 mm in diameter BMS.

Select the best antiplatelet regimen:

1. Loading dose of Prasugrel in the cath lab, followed by 12 month of DAPT
2. Reload with Clopidogrel post-PCI, followed by 12 month of DAPT
3. Continue DAPT (Clopidogrel + ASA) for 30 days
4. Continue DAPT (Clopidogrel + ASA) for 12 months

Antiplatelet Therapies in ACS
Conclusions

- Highly relevant issue to everyday clinical practice; APT selection in ACS intimately tied to treatment strategy
- Current guideline recommendations provide important key concepts
- An astute & informed clinician will always need to tailor available evidence to patient needs

Session 772: Interrupting DAPT for Surgery, Afib or Bleeding: Room 201; March 19; 2.00-3.30 pm

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