Clopidogrel Preloading Prior to PCI

Should this be the standard of care?

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ACC/AHA 2011 Guidelines
Preloading of Anti-Platelet Therapy prior to PCI

A loading dose of a $P2Y_{12}$ receptor inhibitor should be given to patients undergoing PCI with stenting.

Options include:

a. Clopidogrel 600 mg (ACS and non-ACS patients).

b. Prasugrel 60 mg (ACS patients).

c. Ticagrelor 180 mg (ACS patients).

Levine GN et al. JACC 2011; 58: e44-122

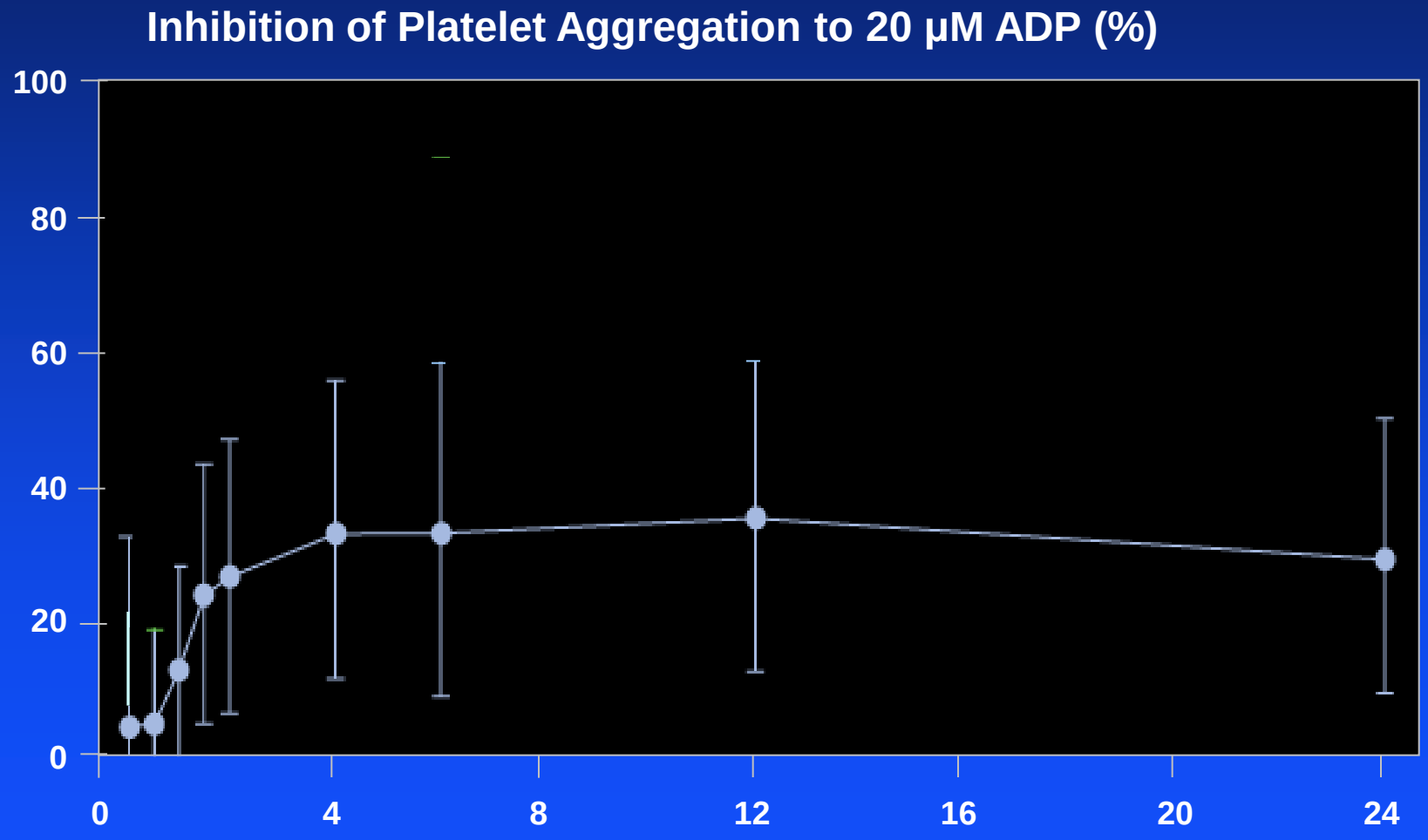
ESC 2010 Guidelines
Preloading of Anti-Platelet Therapy prior to PCI

Elective PCI				
Antiplatelet therapy		Class[a]	Level[b]	Ref.[c]
	ASA	I	B	55
	Clopidogrel	I	A	55
	Clopidogrel - pretreatment with 300 mg loading dose >6 h before PCI (or 600 mg >2 h before)	I	C	—
NSTE-ACS				
Antiplatelet therapy				
	ASA	I	C	—
	Clopidogrel (with 600 mg loading dose as soon as possible)	I	C	—
	Clopidogrel (for 9–12 months after PCI)	I	B	55
STEMI				
Antiplatelet therapy				
	ASA	I	B	55, 94
	Clopidogrel[f] (with 600 mg loading dose as soon as possible)	I	C	—

Wijns W et al. Eur Heart J 2010; 31: 2501-55

Where do the guidelines come from?

Where do the guidelines come from?
Clopidogrel pharmacodynamics



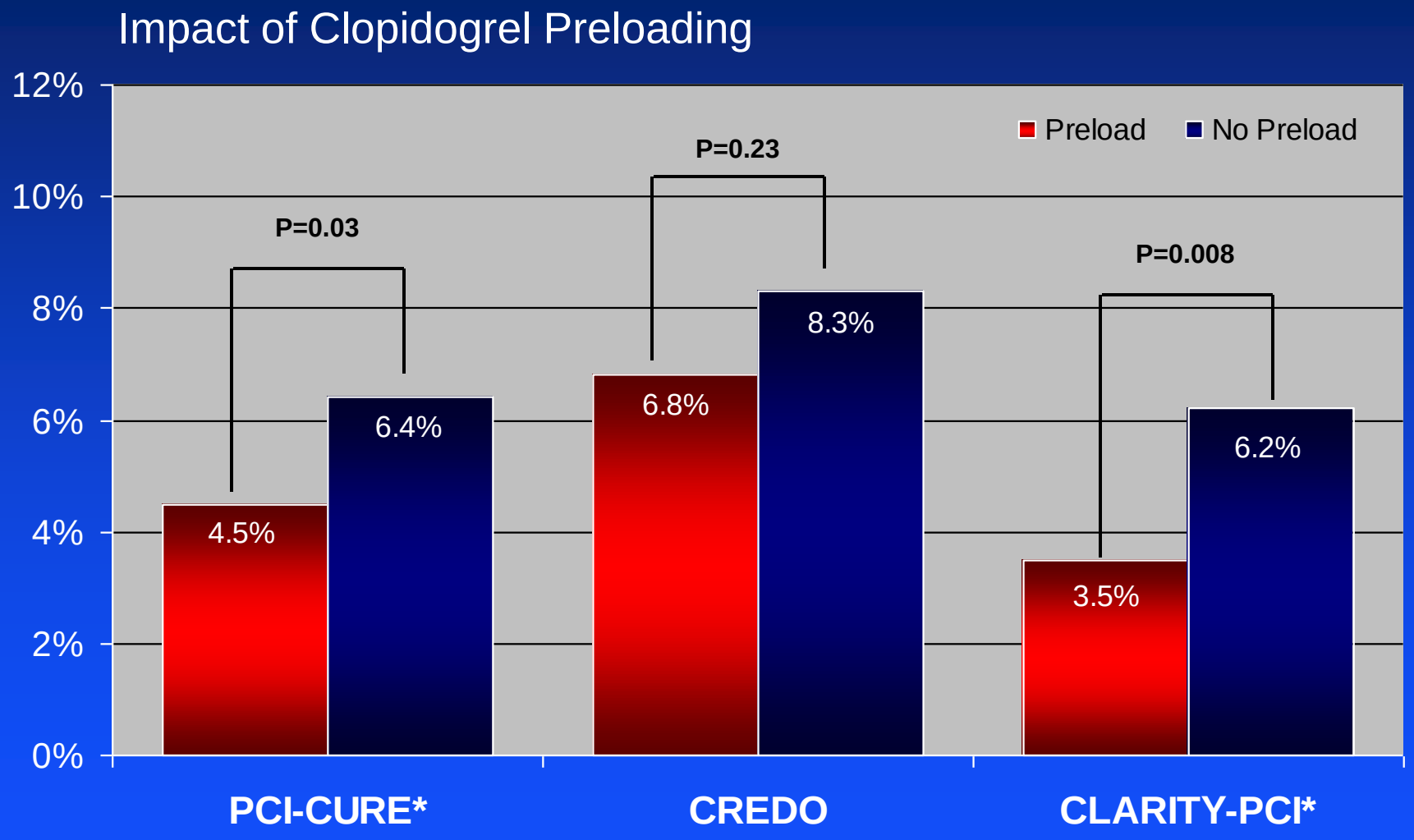
Brandt JT et al. Am Heart J 2007;153:66.e9-16

Why not just preload everyone?

- Increased bleeding risk among patients who do not need revascularization
- Increased bleeding risk among patients who need to go to early CABG
- Treatment delay in patients with surgical anatomy→ increased cost

Since there is potential harm from preloading with clopidogrel (or other P2Y12 inhibitors), we need evidence of benefit to justify this practice

Where do the guidelines come from?
Early clinical trials

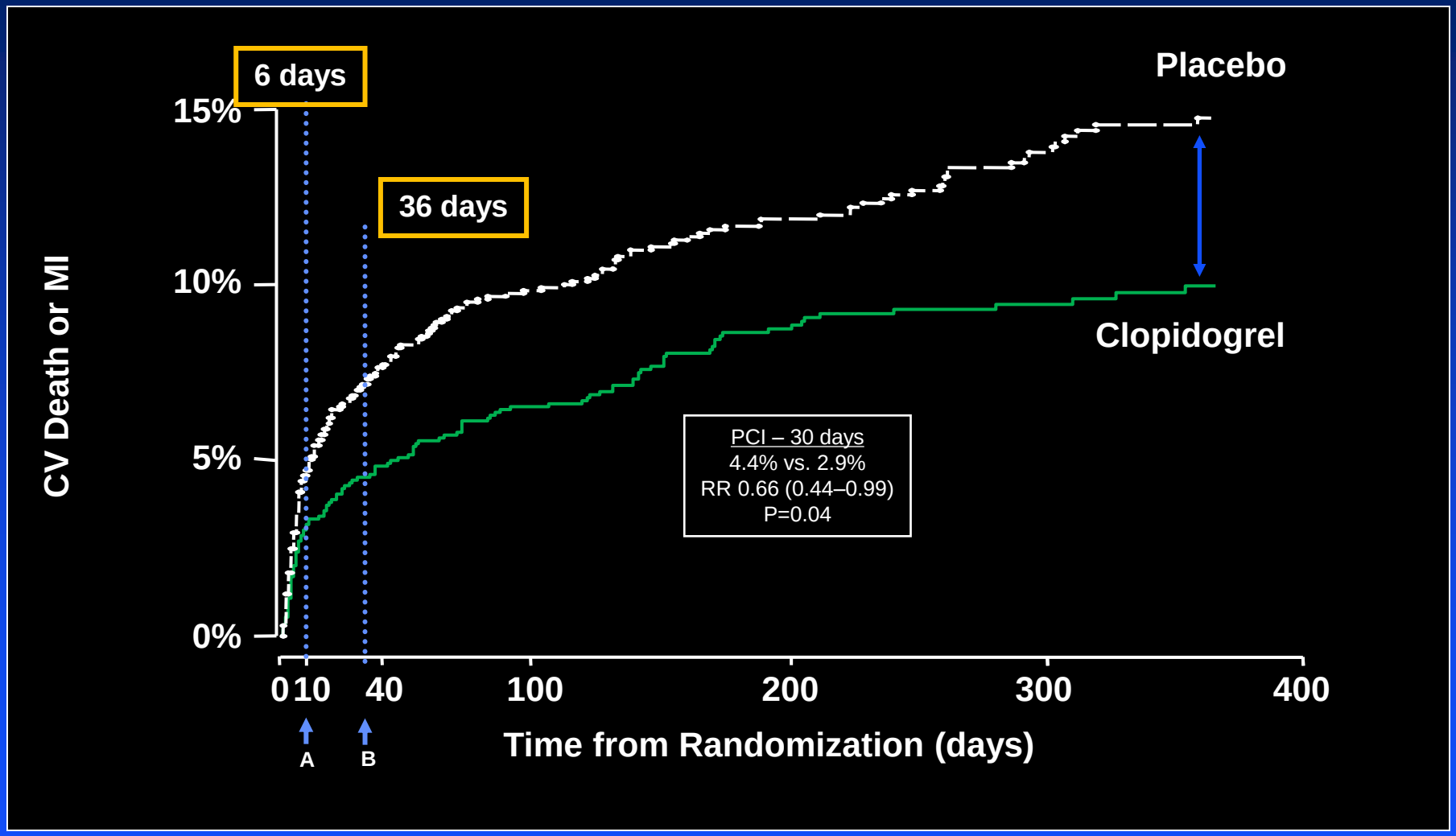


Are these studies relevant in 2014?

	PCI-CURE	CREDO	PCI-Clarity
Population	NSTEMI	Elective PCI	STEMI post-fibrinolytic tx
Patients (n)	2058	2116	1863
Loading dose	300mg	300mg	300mg
Primary Endpoint	CV death or MI	CV death, MI, U-TVR	CV death, MI, stroke
Time from Preload to PCI	**6 days (median)**	**3-24 hours**	**2-8 days**
Follow-Up	30 days	28 days	30 days

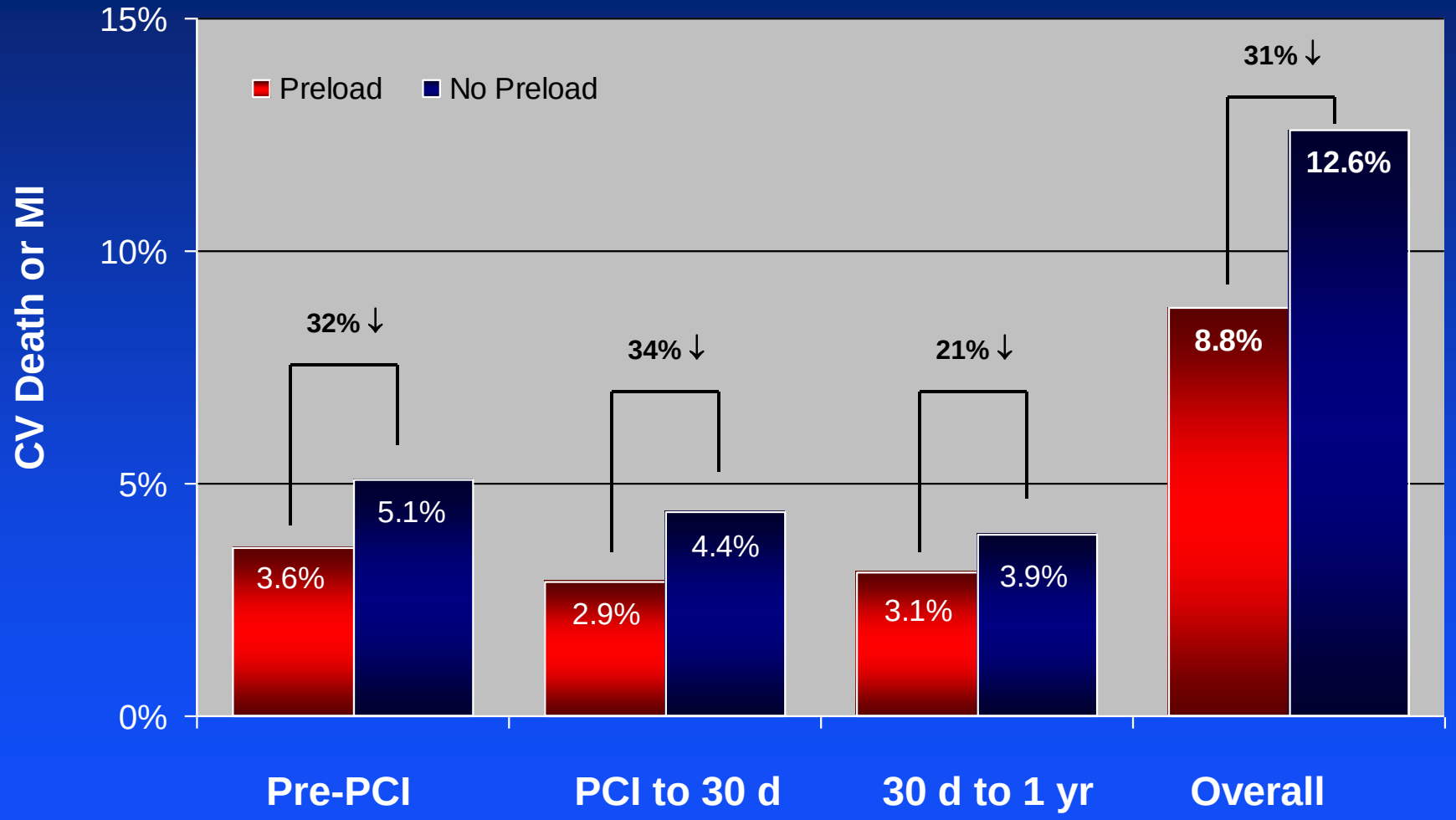
1. Mehta SR et al. Lancet 2001l 358: 527-33.
2. Steinhubl SR et al. JAMA 2002; 288: 2411-20
3. Sabatine MS et al. JAMA 2005; 294: 1224-32

PCI-CURE: 1-Year Outcomes



Mehta SR et al. *Lancet* 2001;21:2033–41

PCI-CURE: Timing of Benefit

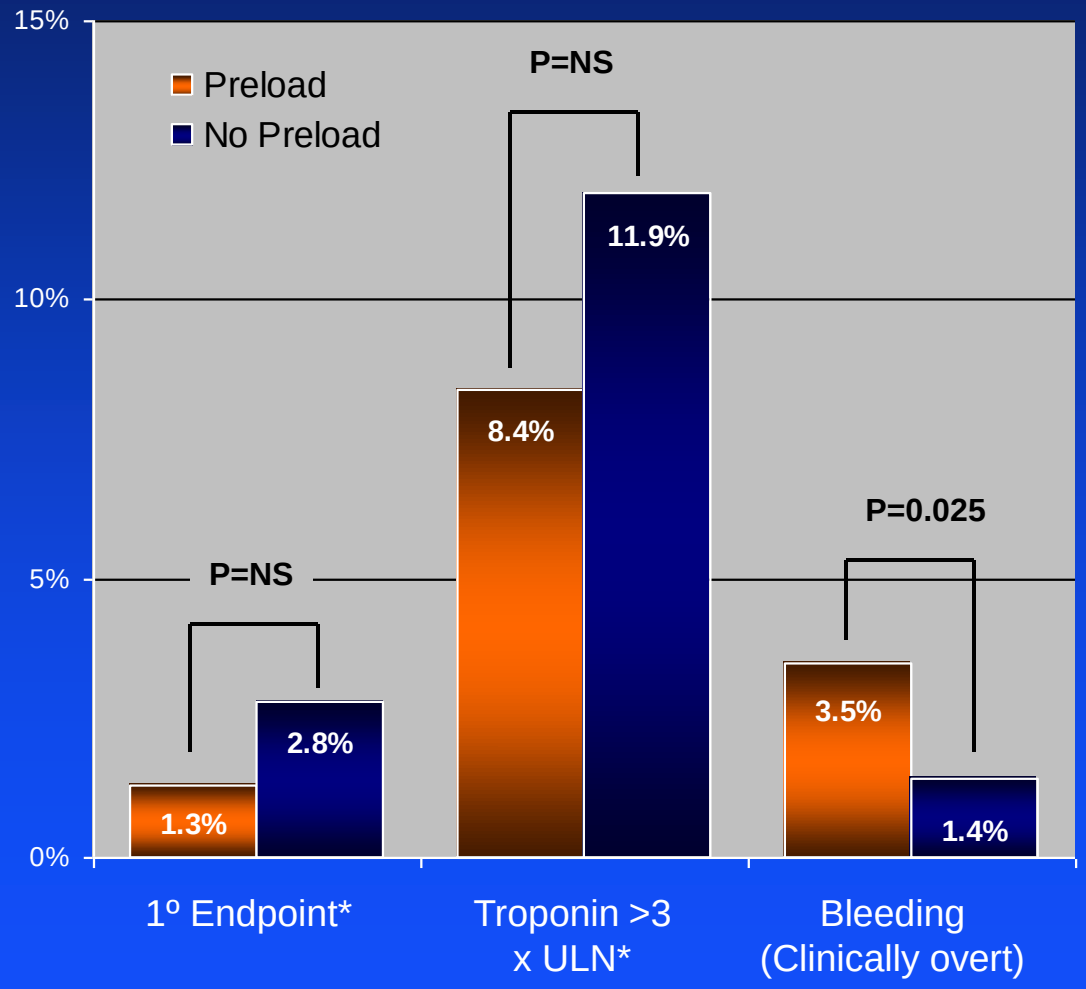


Mehta SR et al. *Lancet* 2001;21:2033–41

Limitations of Early Studies

- Most studies are not true randomized trials but rather post-randomization subgroup analyses of RCTs
- Variable use of loading doses in control groups→ may have exaggerated benefit
- Prolonged delay to PCI not consistent with current practice patterns

PRAGUE-8

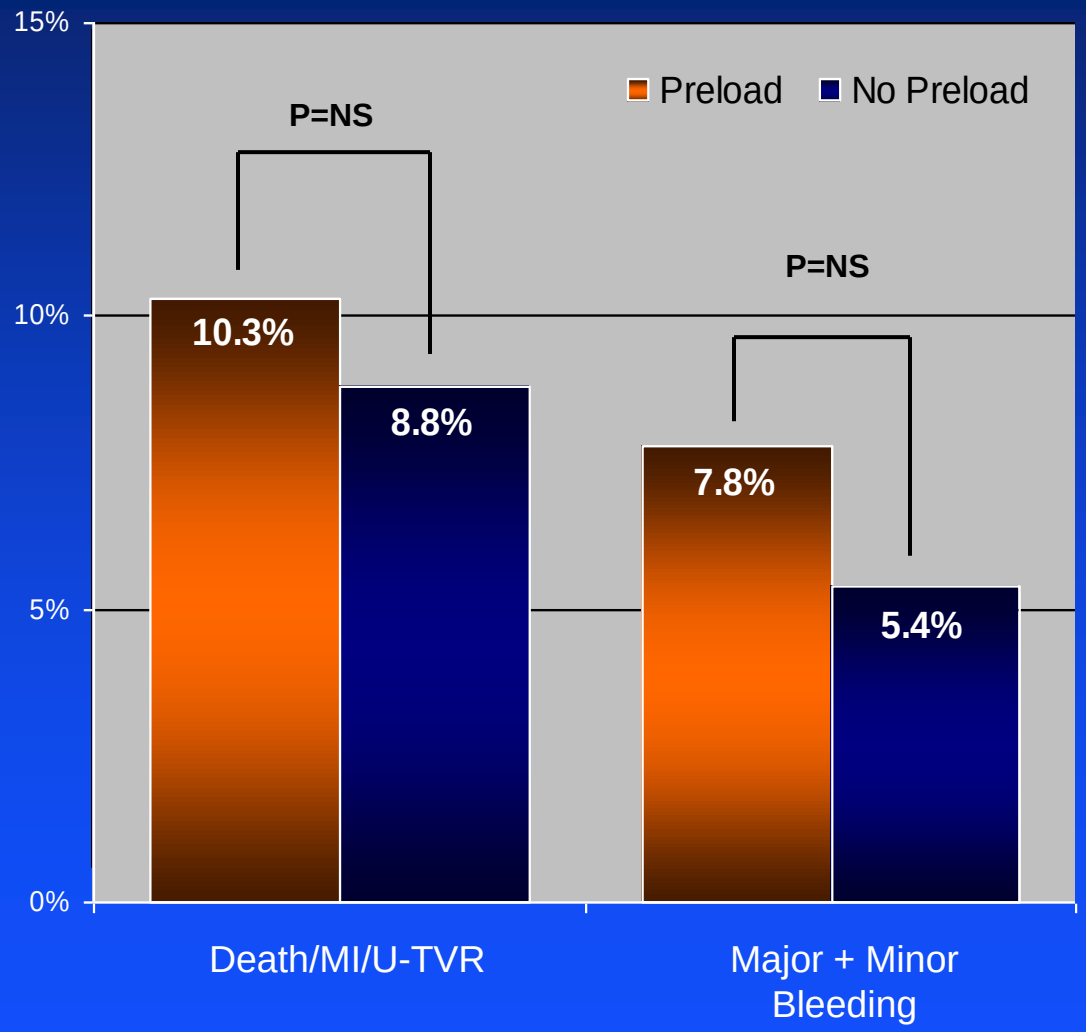


- 1028 patients with stable CAD undergoing cath
- Randomized to:
  - *Preloading: clopidogrel 600 mg 6 hrs prior to cath*
  - *Cath lab loading: 600 mg in lab immediately prior to PCI*
- 1º endpoint: Death, MI, stroke, or U-TVR at 7 days

* Among 293 pts who underwent PCI

Widimsky P et al. Eur Heart J 2008; 29: 1495-1503

ARMYDA-5 Preload



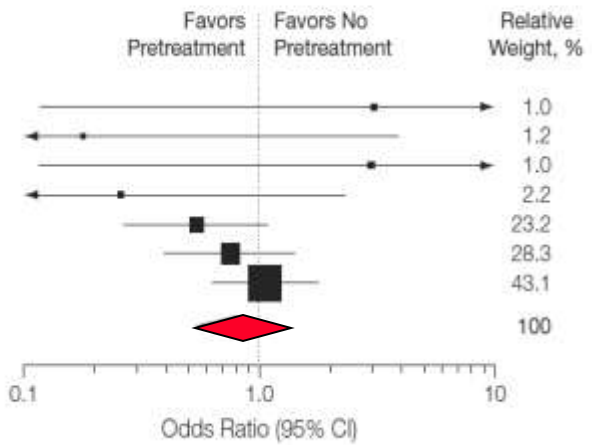
- 409 patients undergoing PCI (36% ACS)
- Randomized to:
  - *Clopidogrel 600 mg given 4-8 hours prior to cath*
  - *Clopidogrel 600 mg in lab immediately prior to PCI*
- 1º endpoint: 30 day death, MI, or U-TVR

Di Sciascio G et al. JACC 2010; 56: 550-7

So does clopidogrel pre-loading do anything?

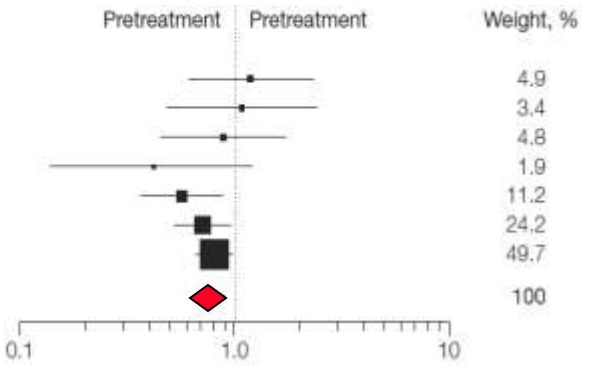
All-Cause Mortality

Source	No. of Events: Pretreatment	No. of Events: No Pretreatment	No. of Patients: Pretreatment	No. of Patients: No Pretreatment	OR (95% CI)
RCTs					
ARMYDA-5 PRELOAD,[17] 2010	1	0	204	205	3.03 (0.12-74.80)
Davlouros et al,[16] 2009	0	2	103	96	0.18 (0.01-3.85)
PRAGUE 8,[18] 2008	1	0	513	515	3.02 (0.12-74.25)
CIPAMI,[7] 2007	1	4	164	171	0.26 (0.03-2.32)
CLARITY PCI,[6] 2005	13	24	933	930	0.53 (0.27-1.05)
CREDO,[3] 2002	18	24	1053	1063	0.75 (0.41-1.40)
PCI CURE,[5] 2001	32	31	1313	1345	1.06 (0.64-1.75)
Overall	66	85	4283	4325	0.80 (0.57-1.11)
					P = .17



MACE

Source	Pretreatment	Pretreatment	Pretreatment	Pretreatment	(95% CI)
RCTs					
ARMYDA-5 PRELOAD,[17] 2010	21	18	204	205	1.19 (0.62-2.31)
Davlouros et al,[16] 2009	15	13	103	96	1.09 (0.49-2.42)
PRAGUE 8,[18] 2008	17	19	513	515	0.89 (0.46-1.74)
CIPAMI,[7] 2007	5	12	164	171	0.42 (0.14-1.21)
CLARITY PCI,[6] 2005	34	58	933	930	0.57 (0.37-0.88)
CREDO,[3] 2002	89	122	1053	1063	0.71 (0.53-0.95)
PCI CURE,[5] 2001	240	292	1313	1345	0.81 (0.67-0.98)
Overall	421	534	4283	4325	0.77 (0.66-0.89)
					P <.001



7 RCTs (n=8608)

Bellemain-Appaix A et al. JAMA 2012; 308: 2507-17

Subgroup Analyses- Clinical Presentation

All-Cause Mortality

	No. of Events		No. of Patients					
	Pretreatment	No Pretreatment	Pretreatment	No Pretreatment	OR (95% CI)	Favors Pretreatment	Favors No Pretreatment	Heterogenity	*P* for Trend χ^2
Presenting feature									
Elective PCI	2	2	820	816	1.12 (0.17-7.27)				
NSTE ACS	50	55	2366	2408	0.93 (0.63-1.36)			2.66	.02
STEMI	14	28	1097	1101	0.50 (0.26-0.96)				

Major Cardiovascualr Events

	No. of Events		No. of Patients					
	Pretreatment	No Pretreatment	Pretreatment	No Pretreatment	OR (95% CI)	Favors Pretreatment	Favors No Pretreatment	Heterogenity	*P* for Trend χ^2
Presenting feature									
Elective PCI	53	50	820	816	1.05 (0.70-1.57)				
NSTE ACS	329	414	2366	2408	0.78 (0.66-0.91)			5.1	.08
STEMI	39	70	1097	1101	0.54 (0.36-0.81)				
Loading dose									

Bellemain-Appaix A et al. JAMA 2012; 308: 2507-17

Conclusions

- Despite Class I guideline recommendations, data supporting clopidogrel pre-loading prior to PCI are uncertain at best
- Most of the data demonstrating benefit are derived from older trials using conservative management strategies with prolonged treatment delays→ substantial proportion of benefit occurs pre-PCI
- Benefits seems to occur mainly in highest risk patients (STEMI, NSTEMI)
- Whether these benefits are still obtained with newer, more rapidly acting agents and under contemporary treatment patterns is unknown