A patient with NSTE- ACS and "high likelihood for CABG" – A therapeutic Dilemma

Case presentations

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Disclosures

I have the following potential conflicts of interest to report:

- **Consulting and or lecture fees**: Abott, Boston-Scientific, Medtronic, Pfizer, Sanofi-Aventis, MSD, AstraZeneca, Elli-Lilly, Bayer, Boehringer Ingelheim

- 72 Y.O. diabetic man
- Prolonged chest pain 6 hours before arriving the ER
  - First manifestation of CAD
- Currently (Friday afternoon):
  - Asymptomatic
  - ECG: old inf. MI with 2mm ST depression in anterior leads
  - Troponin I – 2.1
- Received (ER)
  - 500mg ASA and 80mg Enoxaparin (1mg/Kg)
- Plan: Invasive strategy
  - Cardiac cath is planned for Sunday (48h)

Options for additional antiplatelet Rx

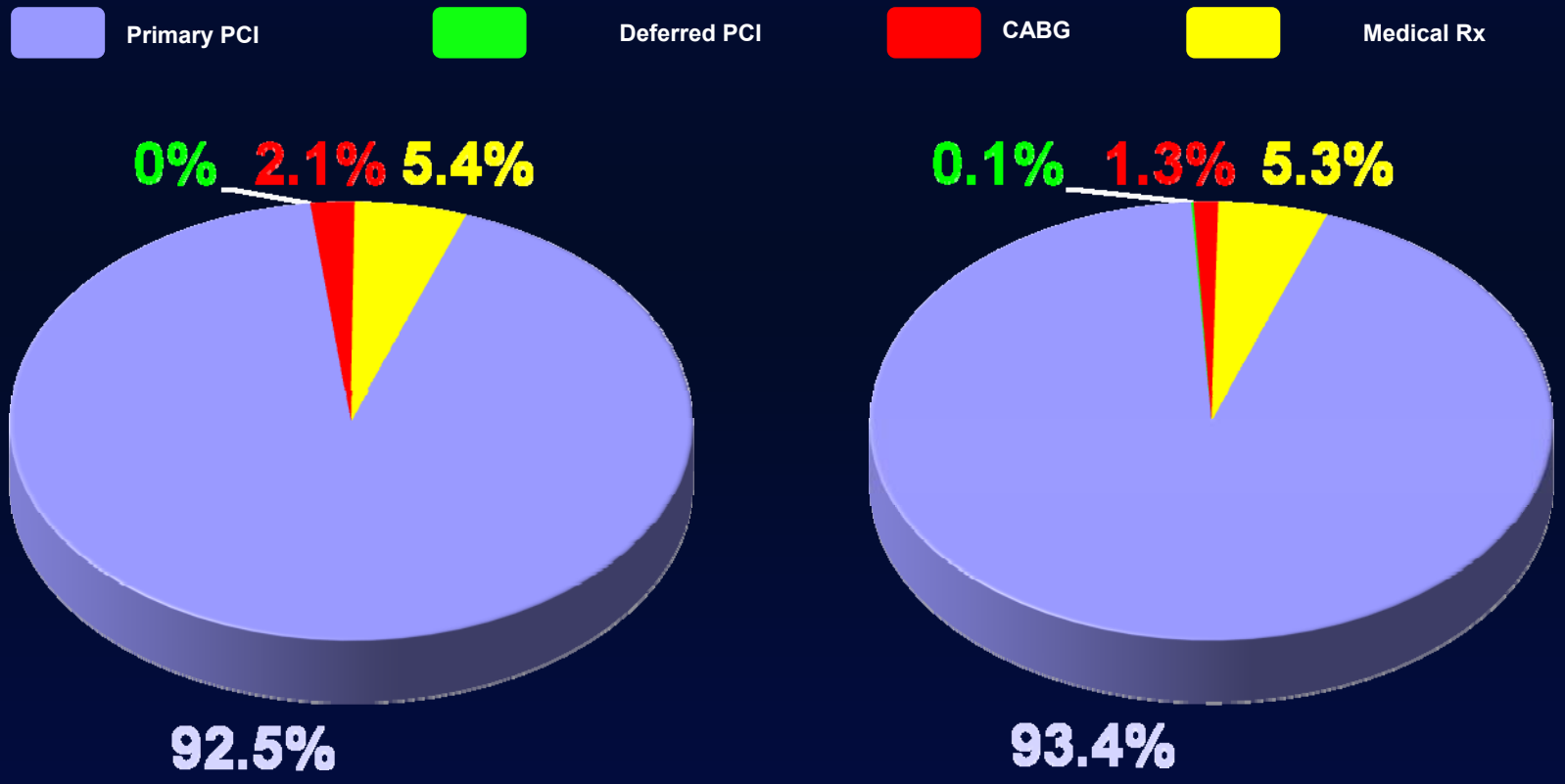
1. No additional oral P2Y12 antagonist (GPIIbIIIa antagonist)
   - Diabetic patient with "high likelihood for CABG"
2. One of the available oral P2Y12 antagonists
   - Clopidogrel
   - Prasugrel
   - Ticagrelor

- Can we reliably predict likelihood for CABG
  - Does it matter?

HORIZONS: STEMI
Primary Management Strategy

UFH + GP IIb/IIIa Inhibitor
N=1802

Bivalirudin Monotherapy
N=1800



1 – 2% of patients with planned primary PCI eventually required CABG

Non STE ACS – Planned Invasive Strategy

ACUITY	UFH/Enox + GPI (N=4,603)	Bivalirudin alone (N=4,612)
Angio.	**99%**	**99%**
Adm. to angio (h)	**20**	**20**
Actual procedure		
PCI	56%	57%
CABG	**12%**	**11%**
Medical	32%	32%

SYNERGY	Enox. (N=4,993)	UFH (N=4,985)
Angio.	**92%**	**92%**
Adm. to angio (h)	**21**	**21**
Actual procedure		
PCI	46%	47%
CABG	**19%**	**18%**
Medical	35%	35%

10-20% of patients with planned invasive approach eventually required CABG

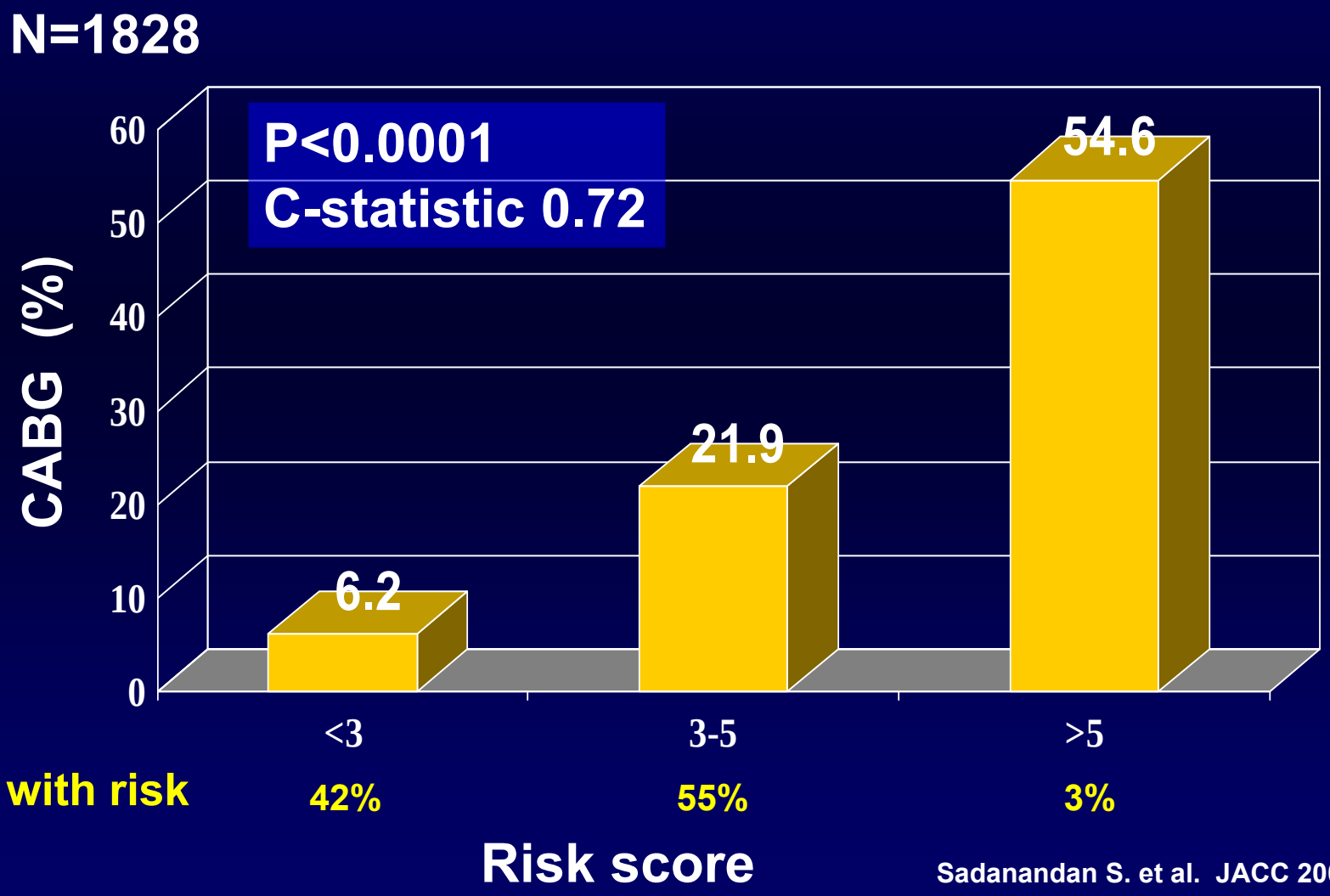
Variables independently associated with CABG – TACTICS TIMI 18

Variable	Odds Ratio	95% CI	P-value	Risk score
Hx prior CABG	0.35	0.2-0.5	<0.0001	-2
(+) Troponins	3.9	2.7 – 5.5	<0.0001	3
Prior Angina	1.8	1.3 – 2.6	0.001	1
ST deviation	1.7	1.3 – 2.2	<0.0001	1
Male Gender	1.6	1.2 – 2.2	0.001	1
Hx PAD	1.6	1.1 – 2.6	0.038	1

- **Rate of CABG during index hospitalization - 16.3%**
- **Median time to CABG – 3.8 days**
- **DM did not have independent contribution to CABG rate**

Sadanandan S. et al. JACC 2004;44:799-803

Rates of in-hospital CABG by Increasing Risk Score: TACTICS TIMI 18



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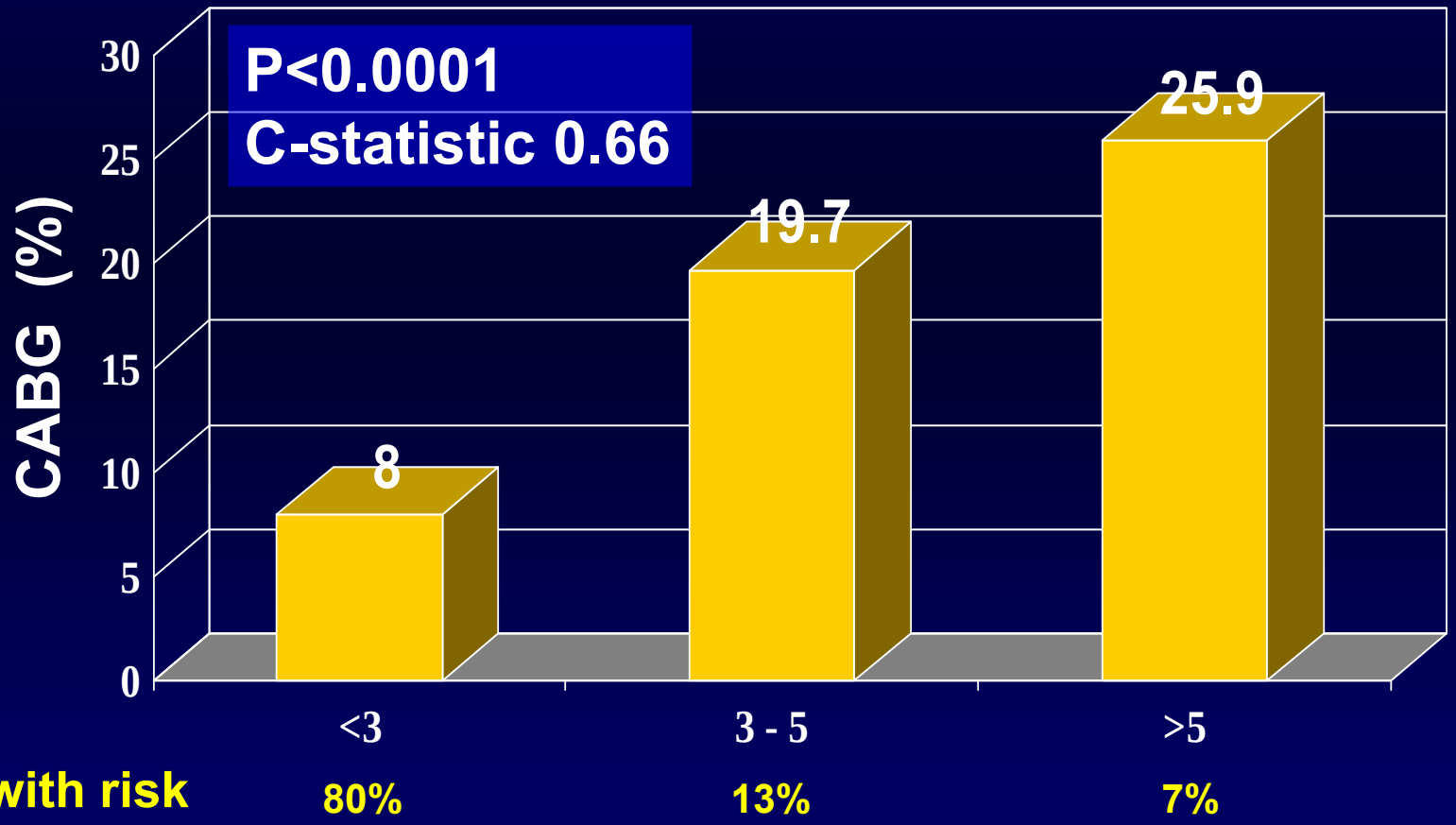
Validation of TACTICS CABG Risk Score in TIMI III Registry

N=1,139



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Conclusion – likelihood for CABG

- Likelihood for CABG can't be reliably predicted for the majority of patients with NSTE-ACS
- Treatment with a P2Y12 antagonist is thus highly recommended as soon as possible in the majority of patients

- Risk score for our patient = 4
- Troponin (3) ST depression (1)

$P2Y_{12}$ Inhibitors

	Clopidogrel	Prasugrel	Ticagrelor
Class	Thienopyridine	Thienopyridine	Triazolopyrimidine
Reversibility	Irreversible	Irreversible	Reversible
Activation	Prodrug, limited by metabolization	Prodrug, not limited by metabolization	Active drug
Onset of effect	2-4 h	30 min	30 min
Duration of effect	3-10 days	5-10 days	3-4 days
Withdrawal before major surgery	5 days	7 days	5 days

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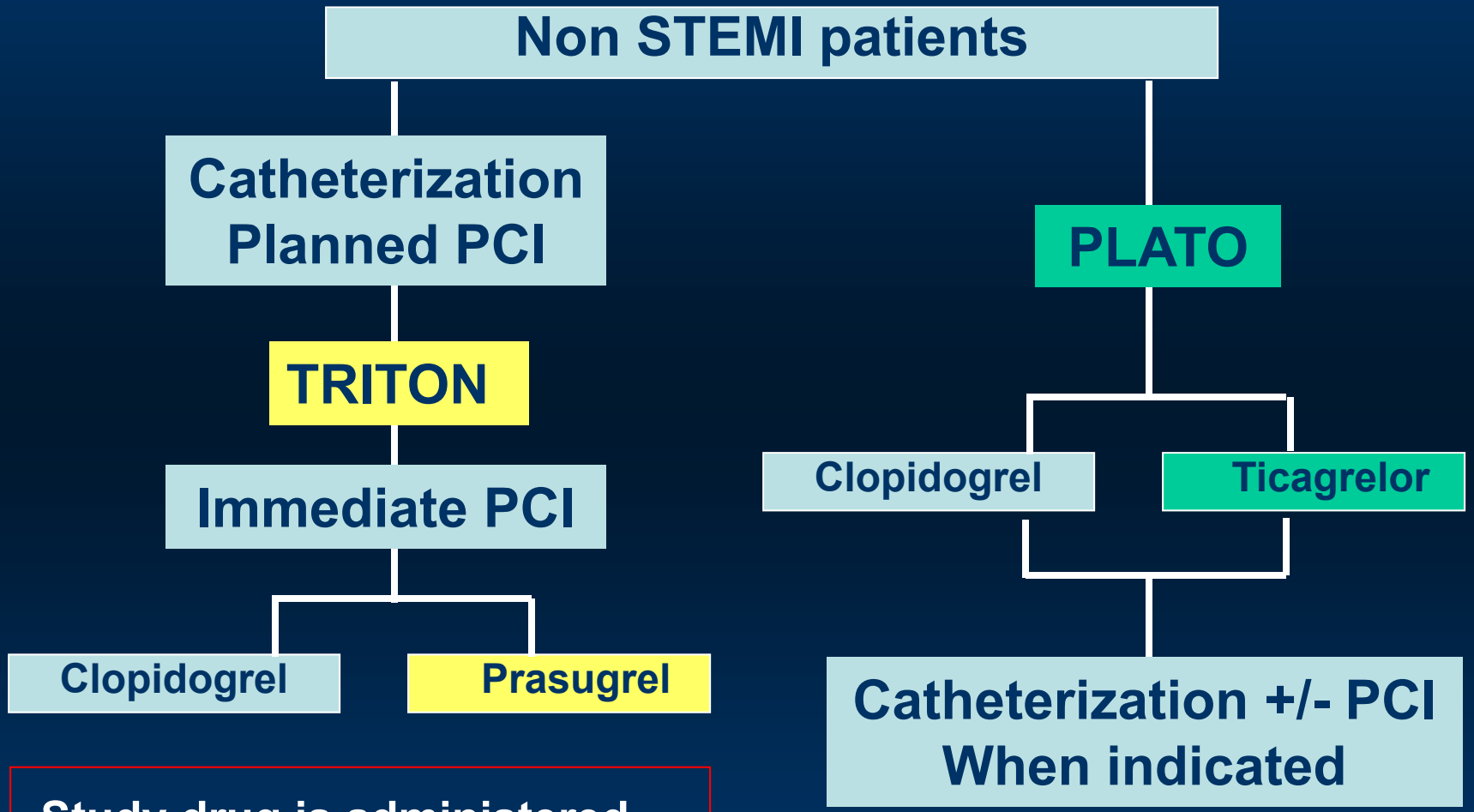
doi:10.1093/eurheartj/ehr236

TRITON / PLATO design: Non STEMI



Study drug is administered only after Cath / PCI to avoid CABG bleeding

Recommendations for oral antiplatelet agents (1)

Recommendations	Class	Level
Aspirin should be given to all patients without contraindications at an initial loading dose of 150-300 mg, and at a maintenance dose of 75-100 mg daily long-term regardless of treatment strategy.	I	A
A $P2Y_{12}$ inhibitor should be added to aspirin as soon as possible and maintained over 12 months, unless there are contraindications such as excessive risk of bleeding.	I	A
A proton pump inhibitor (preferably not omeprazole) in combination with DAPT is recommended in patients with a history of gastrointestinal haemorrhage or peptic ulcer, and appropriate for patients with multiple other risk factors *(H. elicobacter pylori* infection, age ≥ 65 years, concurrent use of anticoagulants or steroids).	I	A
Prolonged or permanent withdrawal of $P2Y_{12}$ inhibitors within 12 months after the index event is discouraged unless clinically indicated.	I	C
Ticagrelor (180 mg loading dose, 90 mg twice daily) is recommended for all patients at moderate-to-high risk of ischaemic events (e.g. elevated troponins), regardless of initial treatment strategy and including those pre-treated with clopidogrel (which should be discontinued when ticagrelor is commenced).	I	B
Prasugrel (60 mg loading dose, 10 mg daily dose) is recommended for $P2Y_{12}$-inhibitor-naïve patients (especially diabetics) in whom coronary anatomy is known and who are proceeding to PCI unless there is a high risk of life-threatening bleeding or other contraindications.	I	B

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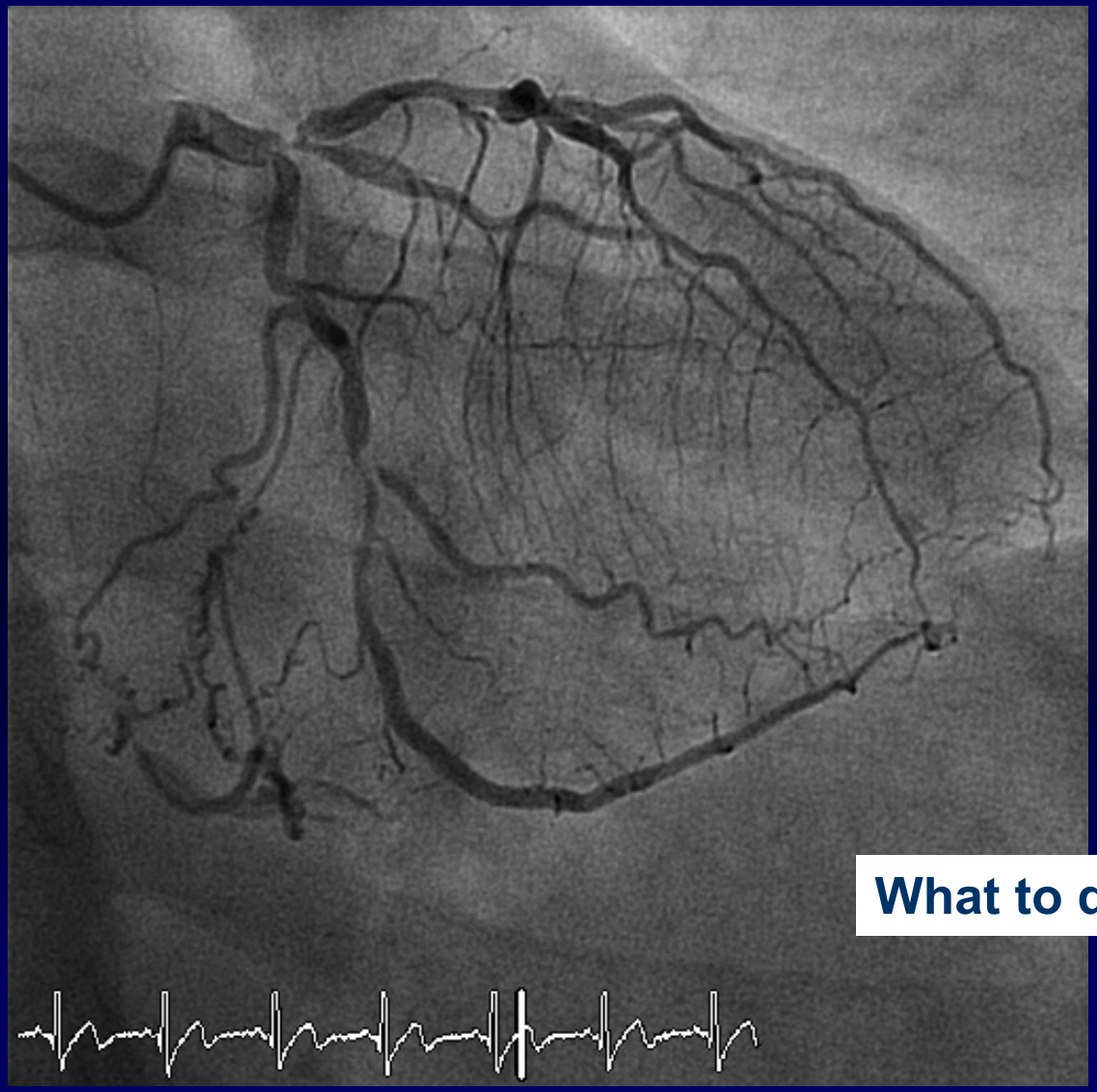
Options for additional antiplatelet Rx

1. No additional oral P2Y12 antagonist (GPIIbIIIa antagonist)
   - Diabetic patient with “high likelihood for CABG”
2. One of the available oral P2Y12 antagonists
   - Clopidogrel
   - Prasugrel
   - Ticagrelor therapy was initiated in the CCU

Uncomplicated hospital course until cath

Cath Result



- Severe TVD
- EF – 45%
- Recommendation:
  - Urgent CABG

What to do with P2Y12 Inhibition?

What would you do?

1. D/C P2Y12 and operate when the effect is over (accept the ischemic risk)
   - 5 days recommended for ticagrelor
2. Operate while the patient receives ticagrelor (accept bleeding risk)
3. D/C ticagrelor and bridge with GPIIb/IIIa
4. Switch to clopidogrel and operate
   - Surgeons are used to operate on clopidogrel

PLATO study design

PLATO
Study drug ≤7 days before CABG

NSTEMI ACS (moderate-to-high risk) STEMI (if primary PCI) (N=18,624)
Clopidogrel-treated or -naive; randomized <24 hours of index event

After randomization, 1,261 patients underwent CABG and were on study drug treatment for ≤7 days prior to surgery

Clopidogrel
If pre-treated, no additional loading dose;
if naive, standard 300 mg loading dose,
then 75 mg qd maintenance;
(additional 300 mg allowed pre-PCI)

Ticagrelor
180 mg loading dose, then
90 mg bid maintenance;
(additional 90 mg pre-PCI)

6–12 months treatment

Primary endpoint: CV death + MI + Stroke
Primary safety endpoint: Total major bleeding

Recommendations for patients undergoing CABG:
Study drugs withheld prior to surgery – 5 days for clopidogrel and 24–72 hours for ticagrelor. Study drug be restarted as soon as possible after surgery and prior to discharge

PCI = percutaneous coronary intervention
CV = cardiovascular

Evaluations and invasive procedures

PLATO
Study drug ≤7 days before CABG

Characteristic	Ticagrelor (n=632)	Clopidogrel (n=629)
Evaluations		
Abnormal physical findings, %	17.1	17.0
Median heart rate, bpm	72	73
Median systolic blood pressure, mmHg	131	132
Median diastolic blood pressure, mmHg	80	80
Killip class >2, %	1.4	1.8
Persistent ST-segment elevation >1mm / LBBB/final diagnosis of STEMI, %	32.6	33.4
TIMI STEMI risk score >2, %	59.2	55.2
Invasive procedures in hospital, %		
Coronary angiography	89.2	90.1
PCI within 24 hours of randomization	17.7	20.0
Any PCI pre-discharge	20.6	21.5
Any CABG pre-discharge	55.7 (n=352)	58.5(n=368)

bpm = beats per minute; LBBB = left bundle branch block; TIMI = thrombolysis in myocardial infarction

Study medication pre- and post-CABG

PLATO
Study drug ≤7 days before CABG

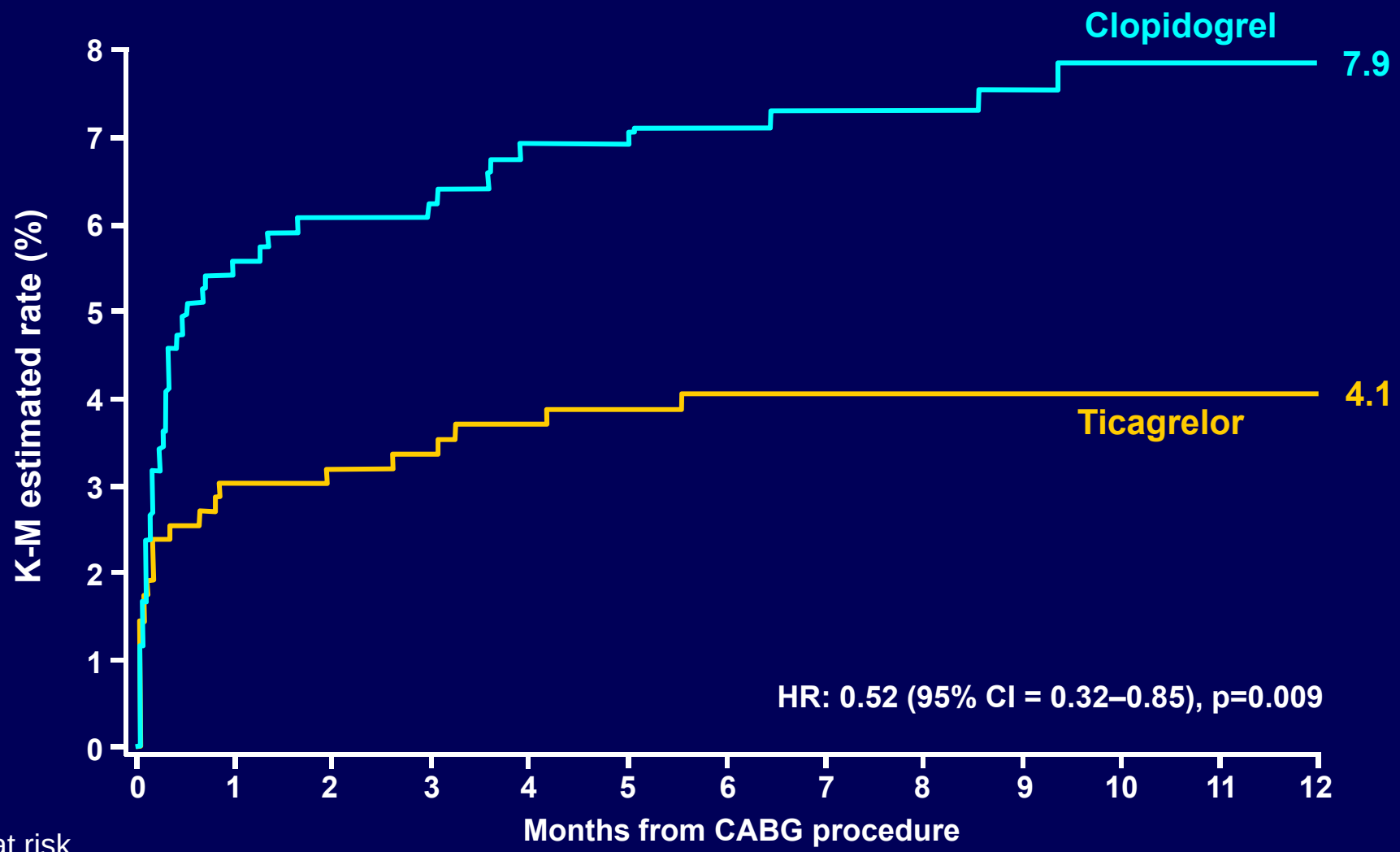
	Ticagrelor (n=632)	Clopidogrel (n=629)
Days study drug stopped before CABG, %		
1 day	13.3	14.0
2 days	16.8	13.7
3 days	18.0	11.6
4 days	13.3	11.0
5 days	12.5	15.3
6 days	14.4	17.5
7 days	11.7	17.0
Patients not restarted on study drug/unknown	n=234	n=238
Time study drug restarted after CABG, %*	(n=398)	(n=391)
<7 days	57.0	57.5
7–14 days	27.9	25.6
>14 days	15.1	16.9

Per protocol ~ 50%

*Percentages calculated based on number of patients with available data

CV death post-CABG

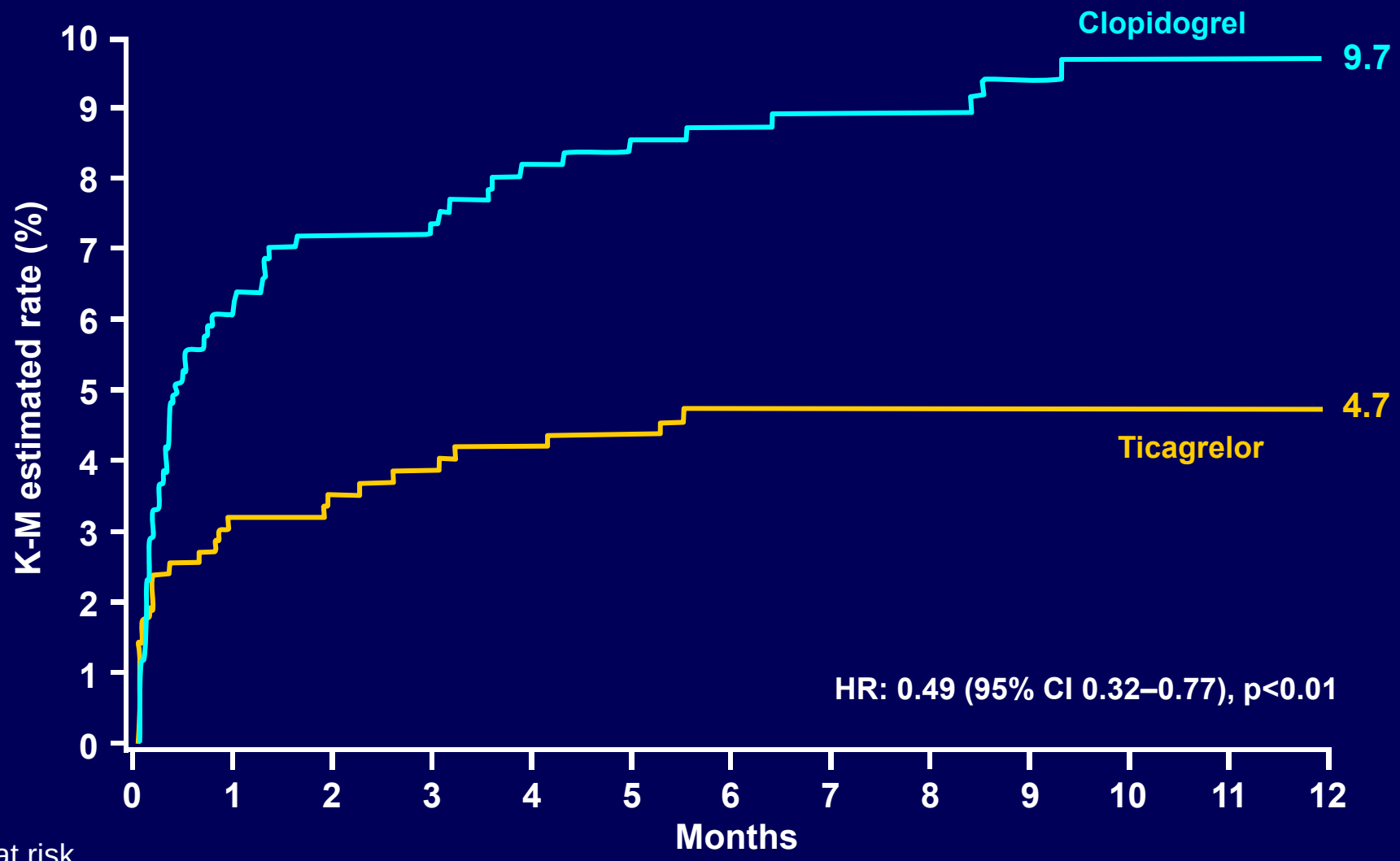
PLATO
Study drug ≤7 days before CABG



No. at risk							
Ticagrelor	629	583	557	491	415	291	119
Clopidogrel	629	565	539	472	404	269	130

All cause mortality post-CABG

PLATO
Study drug ≤7 days before CABG



No. at risk							
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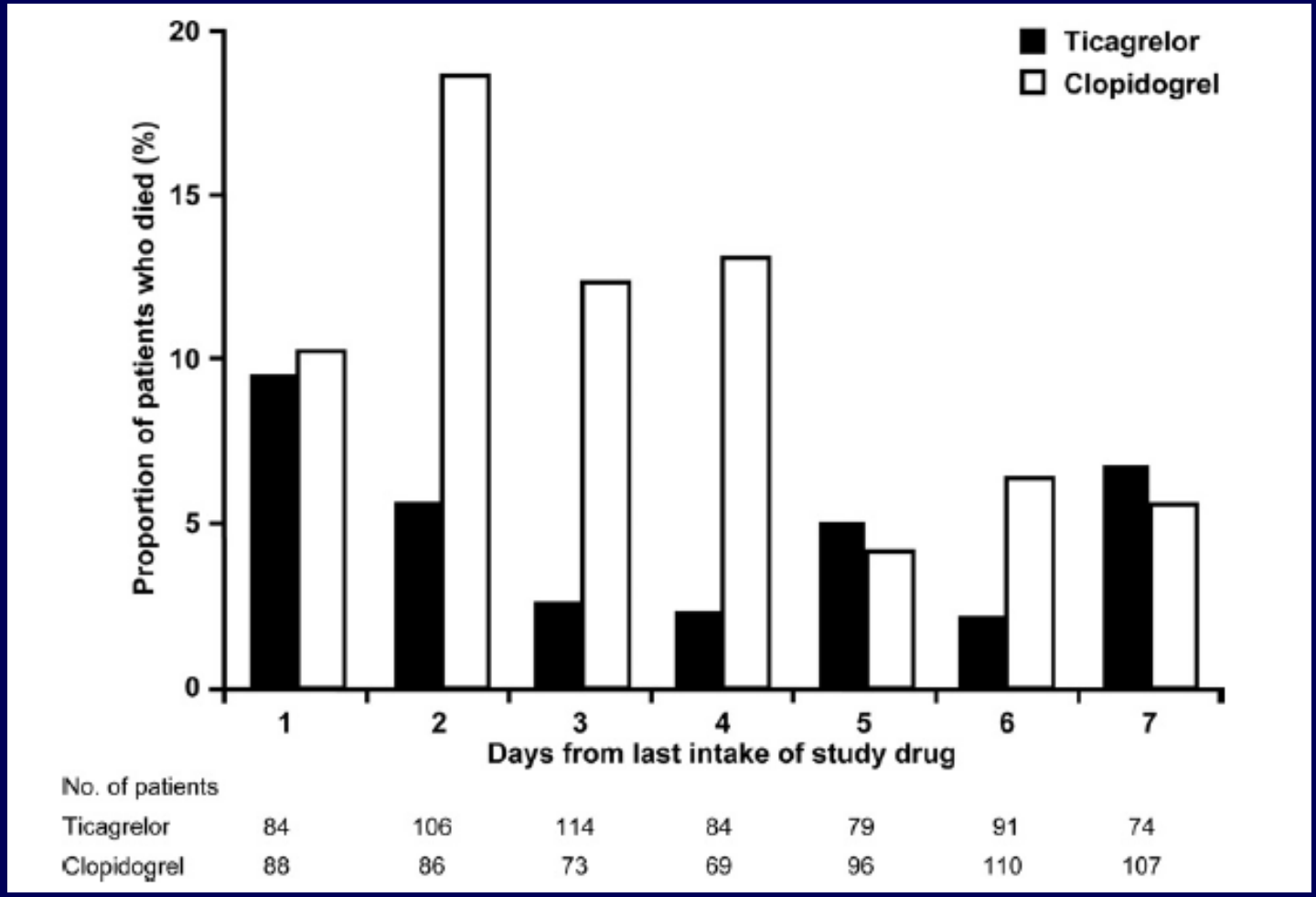
Cumulative Risk of Any Death by Last Intake of Study Drug

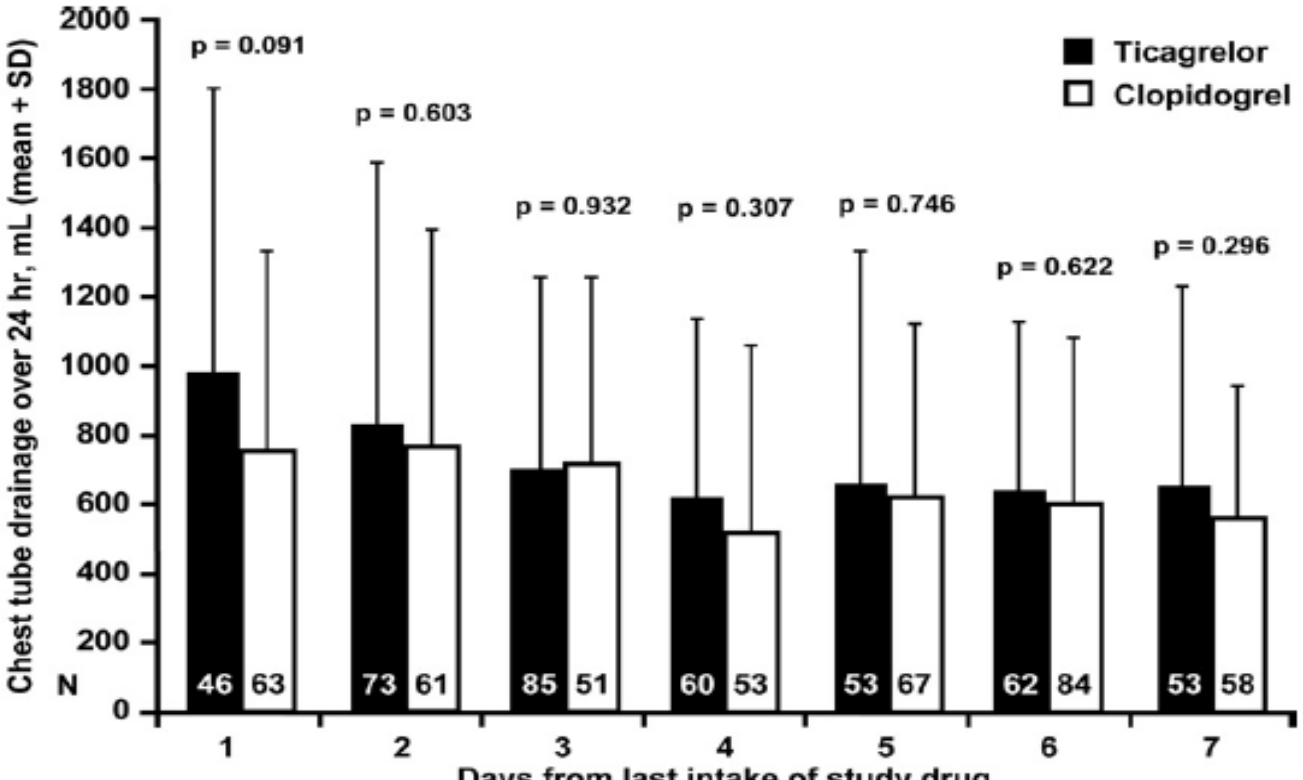
PLATO
Study drug ≤7 days before CABG



No. of patients							
Ticagrelor	84	106	114	84	79	91	74
Clopidogrel	88	86	73	69	96	110	107

24 hours Chest Tube drainage by Last Intake of Study Drug

PLATO
Study drug ≤7 days before CABG



Patients with > 500 mL (%)							
Ticagrelor	72	60	56	52	57	56	51
Clopidogrel	67	64	53	43	52	54	47

$P2Y_{12}$ Inhibitors

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Conclusions

PLATO
Study drug ≤7 days before CABG

- In ACS patients undergoing CABG within 7 days after stopping treatment with ticagrelor – a reversible, more intense $P2Y_{12}$ receptor antagonist – is associated with
  - substantially fewer deaths – both total and CV
  - no change in the overall risk of CABG-related bleeding

In ACS patients undergoing CABG surgery, ticagrelor is a more effective alternative to clopidogrel for the continuous prevention of cardiovascular and total death without an increase in major bleeding

Thank You

Comulative Incidence for CABG PLATO and TRITON