

The logo for the PLATO CABG trial. It features the word "PLATO" in a large, bold, white sans-serif font. To the right of "PLATO" is a decorative graphic consisting of a cluster of approximately 15 orange dots of varying sizes, arranged in a pattern that suggests movement or a trail. To the right of this graphic is the word "CABG" in a smaller, bold, white sans-serif font.

PLATO CABG

Ticagrelor versus clopidogrel in patients with acute coronary syndromes undergoing coronary artery bypass surgery: results from the PLATO trial

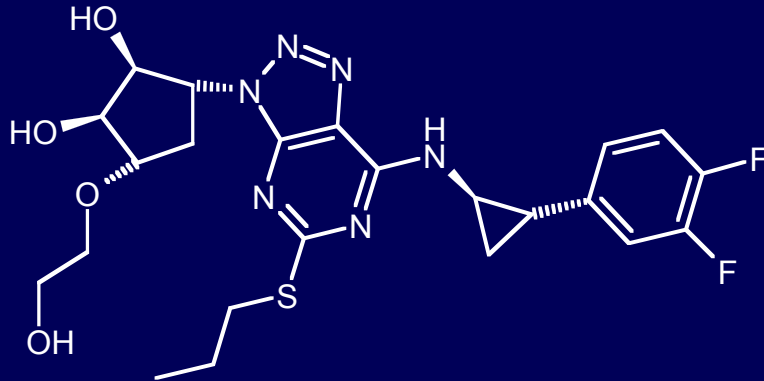
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Disclosures

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Ticagrelor (AZD 6140): an oral reversibly binding P2Y₁₂ antagonist



Ticagrelor is a cyclo-pentyl-triazolo-pyrimidine (CPTP)

- **Direct acting**
 - Not a pro-drug; does not require metabolic activation
 - Rapid onset of inhibitory effect on the P2Y₁₂ receptor
 - Greater inhibition of platelet aggregation than clopidogrel
- **Reversibly bound**
 - Degree of inhibition reflects plasma concentration
 - Faster offset of effect than clopidogrel
 - Functional recovery of circulating platelets within ~48 hours

Background

- In NSTEMI and STEMI ACS, guidelines recommend 12 months' treatment with aspirin and clopidogrel
- Clopidogrel is currently the standard of care but is hampered by
 - slow and variable transformation to the active metabolite
 - modest and variable platelet inhibition
 - risk of stent thrombosis and MI in poor responders
 - irreversible effect – increased risk of bleeding at urgent CABG
- Clopidogrel is recommended to be withdrawn 5 days prior to CABG but clinical reality often requires surgery earlier

Objectives

The objective of this pre-defined analysis was
to evaluate the efficacy and safety
of ticagrelor vs clopidogrel
in patients undergoing CABG
within 7 days of last intake of study drug

PLATO study design

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

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)

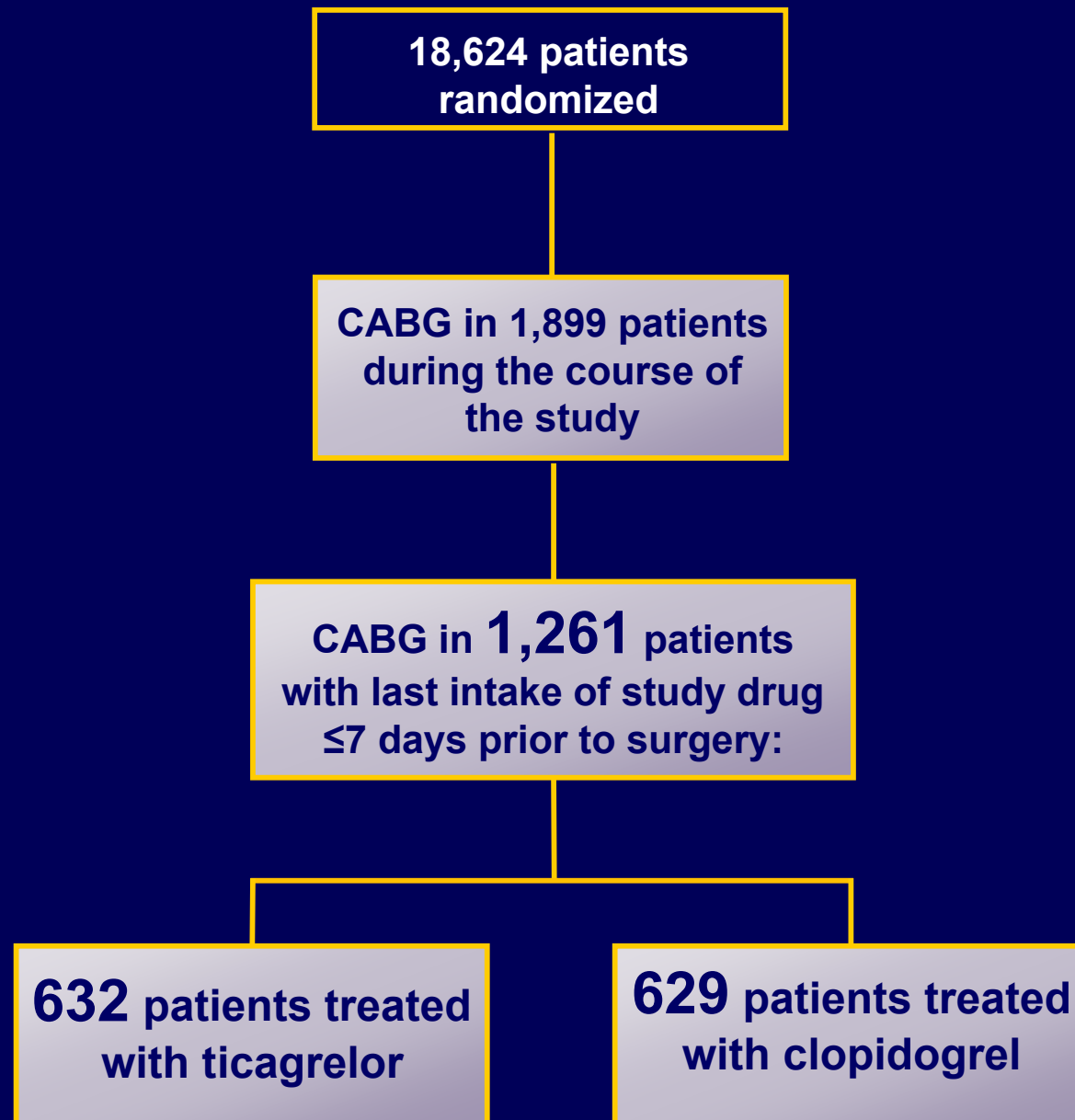
6–12 months treatment

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

Recommendations for patients undergoing CABG:

**Study drugs withheld prior to surgery: 5 d for clopidogrel and 24–72 h for ticagrelor.
Study drug be restarted as soon as possible after surgery and prior to discharge**

Patient disposition



Baseline CV risk and history

Characteristic	Ticagrelor (n=632)	Clopidogrel (n=629)
CV risk factors, %		
Smoker	32.9	29.4
Hypertension	68.5	67.1
Dyslipidemia	56.3	52.1
Diabetes	30.5	32.9
CV history, %		
Angina pectoris	54.4	52.0
MI	19.6	20.8
Congestive heart failure	4.7	3.5
PCI	9.2	11.6
CABG	0.8	2.2
Transient ischemic attack	3.3	2.9
Non-hemorrhagic stroke	3.8	4.0
Peripheral artery disease	6.8	8.4
Chronic renal disease	5.2	4.3

Evaluations and invasive procedures at study entry

Characteristic	Ticagrelor (n=632)	Clopidogrel (n=629)
Median age, %	64	64
Males, %	80.9	76.9
Age >75 years, %	13.6	15.7
Evaluations, %		
Killip class >2	1.4	1.8
ST-segment elevation >1mm/ LBBB	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
<i>CABG pre-discharge</i>	55.7	58.5

LBBB = left bundle branch block; TIMI = thrombolysis in myocardial infarction

Study medication at study entry

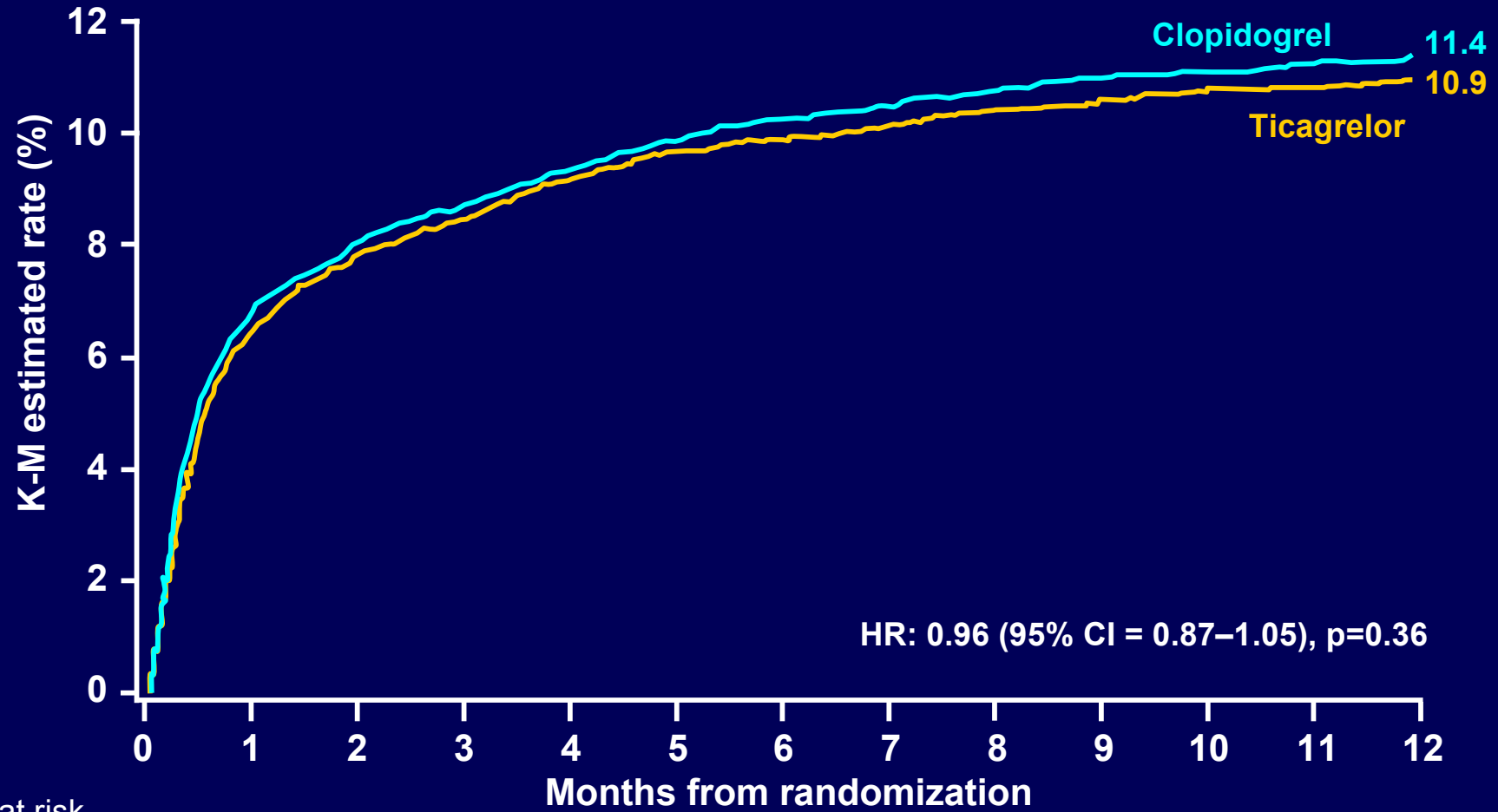
Medication	Ticagrelor (n=632)	Clopidogrel (n=629)
Median treatment duration, days (range)	226 (26–364)	223 (28–353)
Median delay from hospital admission, h	9.0	6.8
Total clopidogrel (OL + IP) pre-randomization to 24 h, %		
300 mg	83.4	81.2
600 mg	16.6	18.8
Open-label clopidogrel pre-randomization, %		
Any dose	46.5	44.2
75 mg (50–150 mg)	14.9	10.5
300 mg (151–449 mg)	22.5	21.5
600 mg (≥450 mg)	9.2	12.2

OL = open-label; IP = investigational product

Study medication pre- and post-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

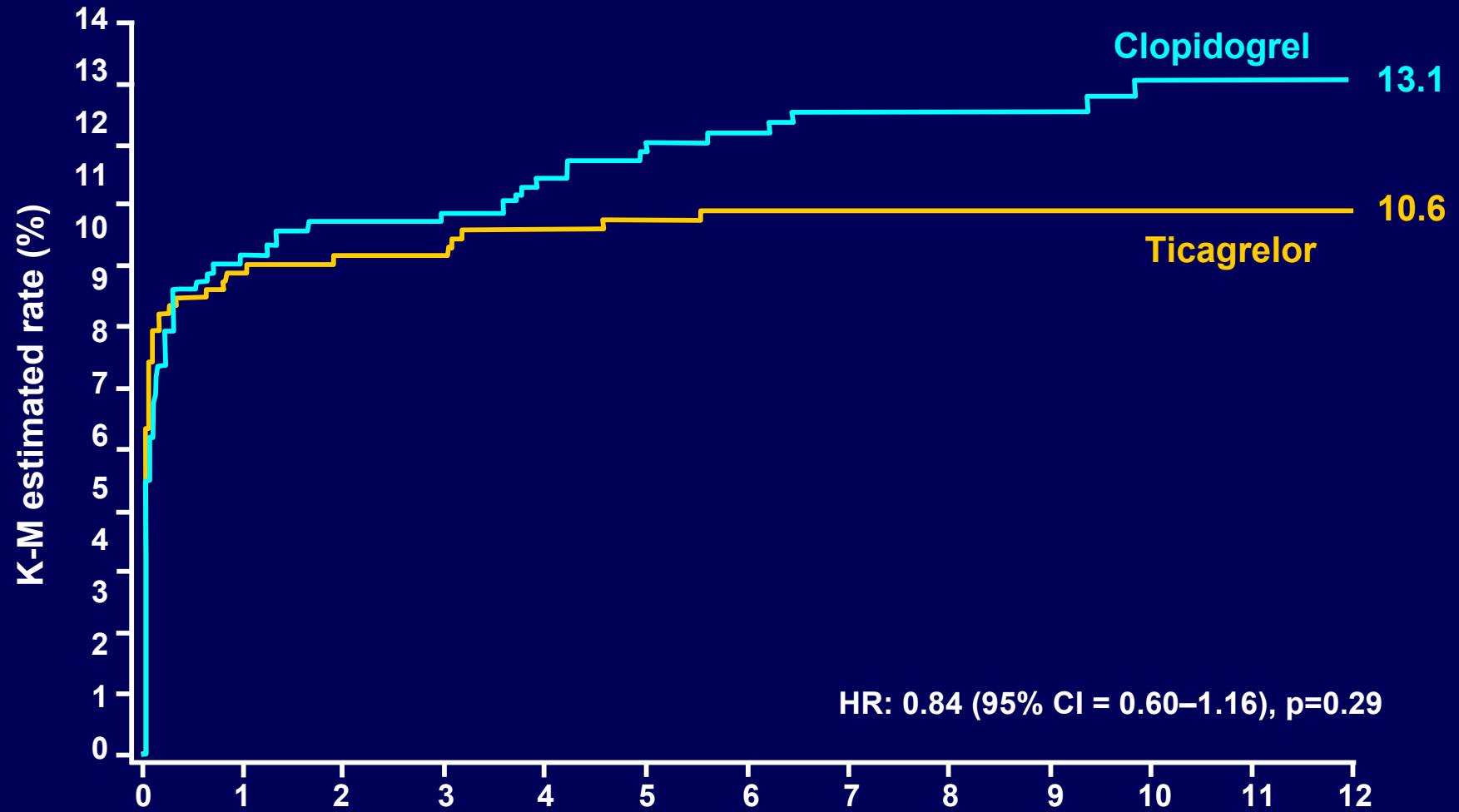
Time from study entry to first CABG surgery (total PLATO population)



No. at risk

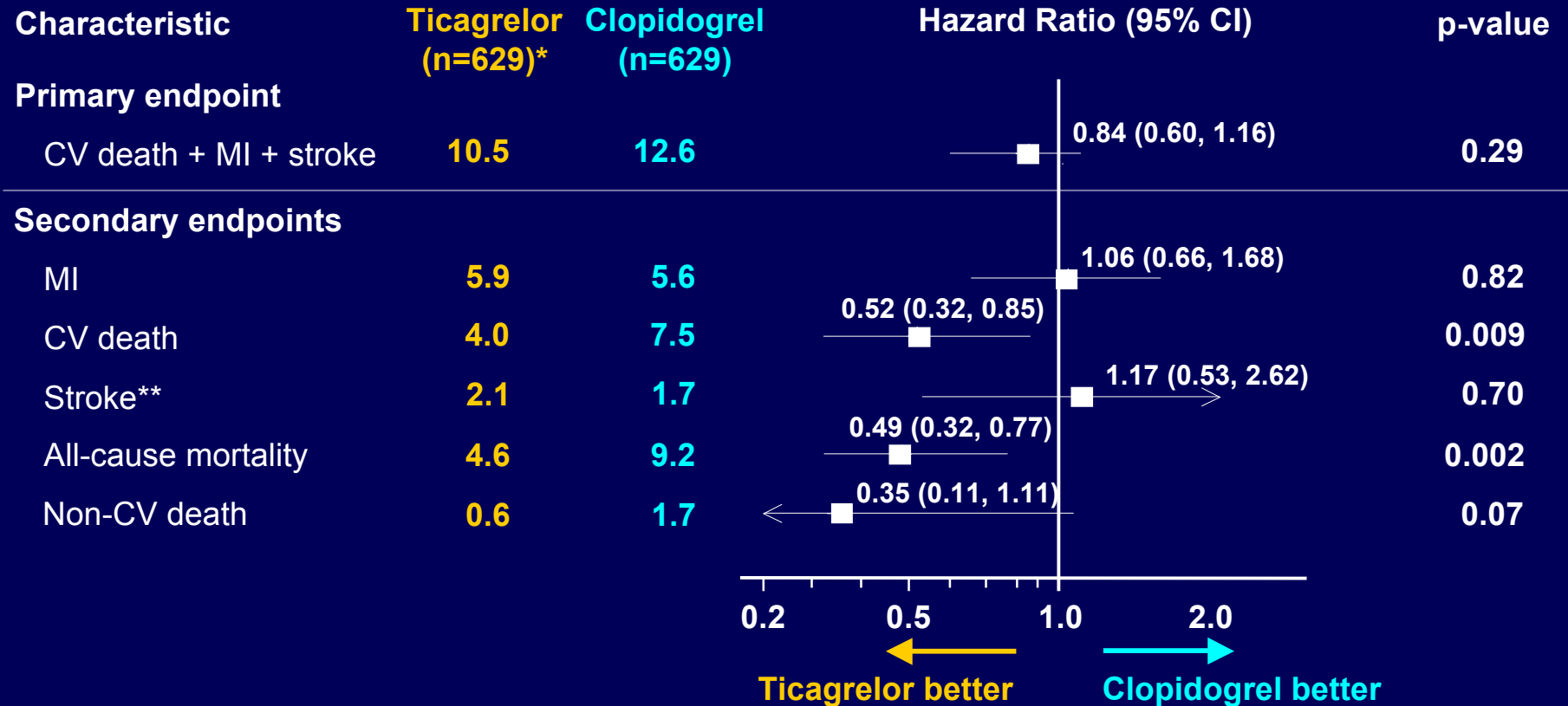
Ticagrelor	9,235	7,289	6,862	6,570	5,144	3,775	3,414
Clopidogrel	9,186	7,320	6,936	6,657	5,209	3,843	3,470

Time from CABG to primary endpoint: CV death, MI or stroke (CABG population)



No. at risk		Months from CABG procedure											
	0	1	2	3	4	5	6	7	8	9	10	11	12
Ticagrelor	629	543	519	458	386	268	108						
Clopidogrel	629	541	516	448	386	255	125						

Primary and secondary efficacy endpoints from time of CABG

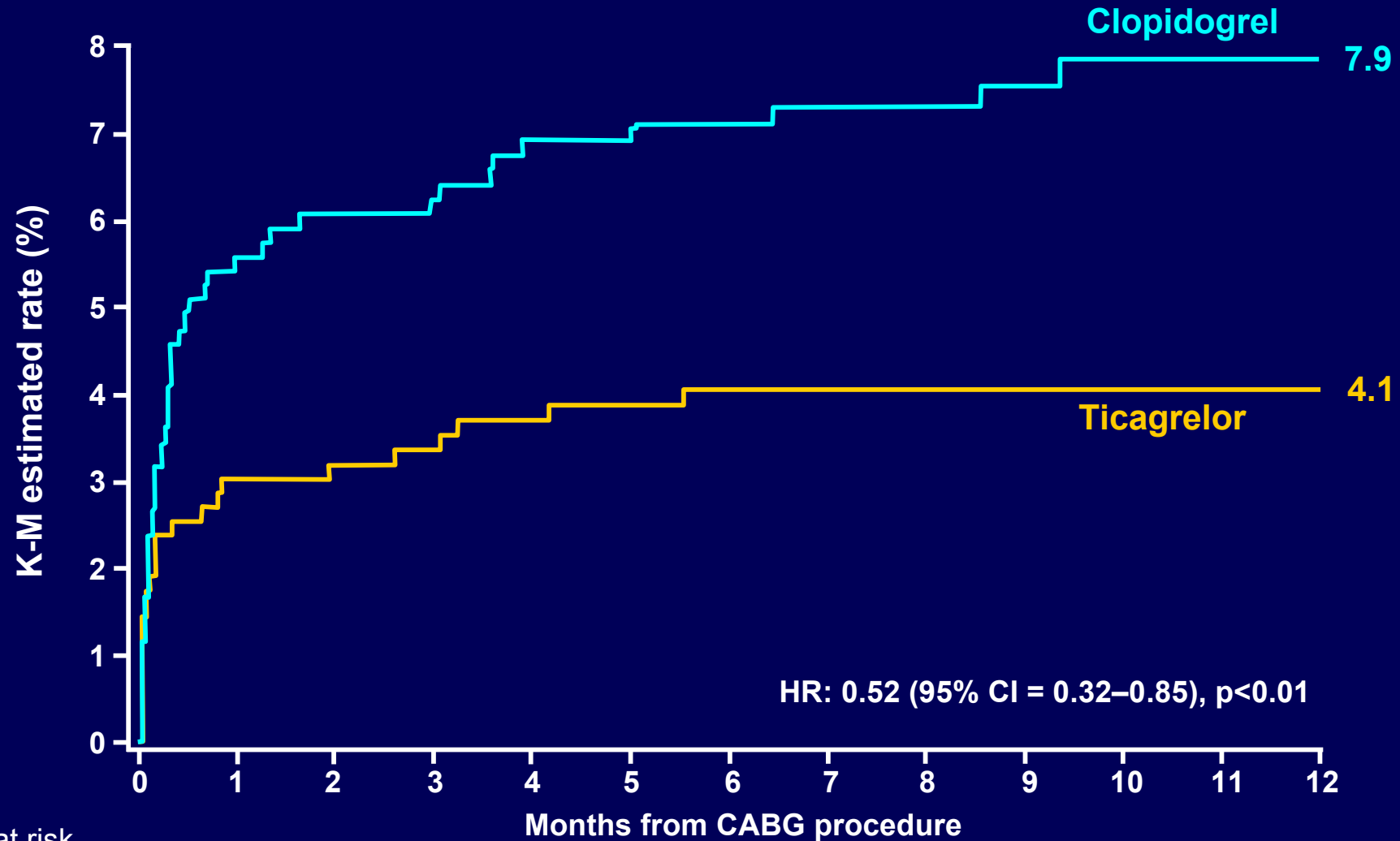


Patients could have had more than one type of endpoint. Values are incidences = number of events divided by n, not rates.

*Three patients had missing values for the efficacy endpoints due to CABG after the censoring date at 12 months

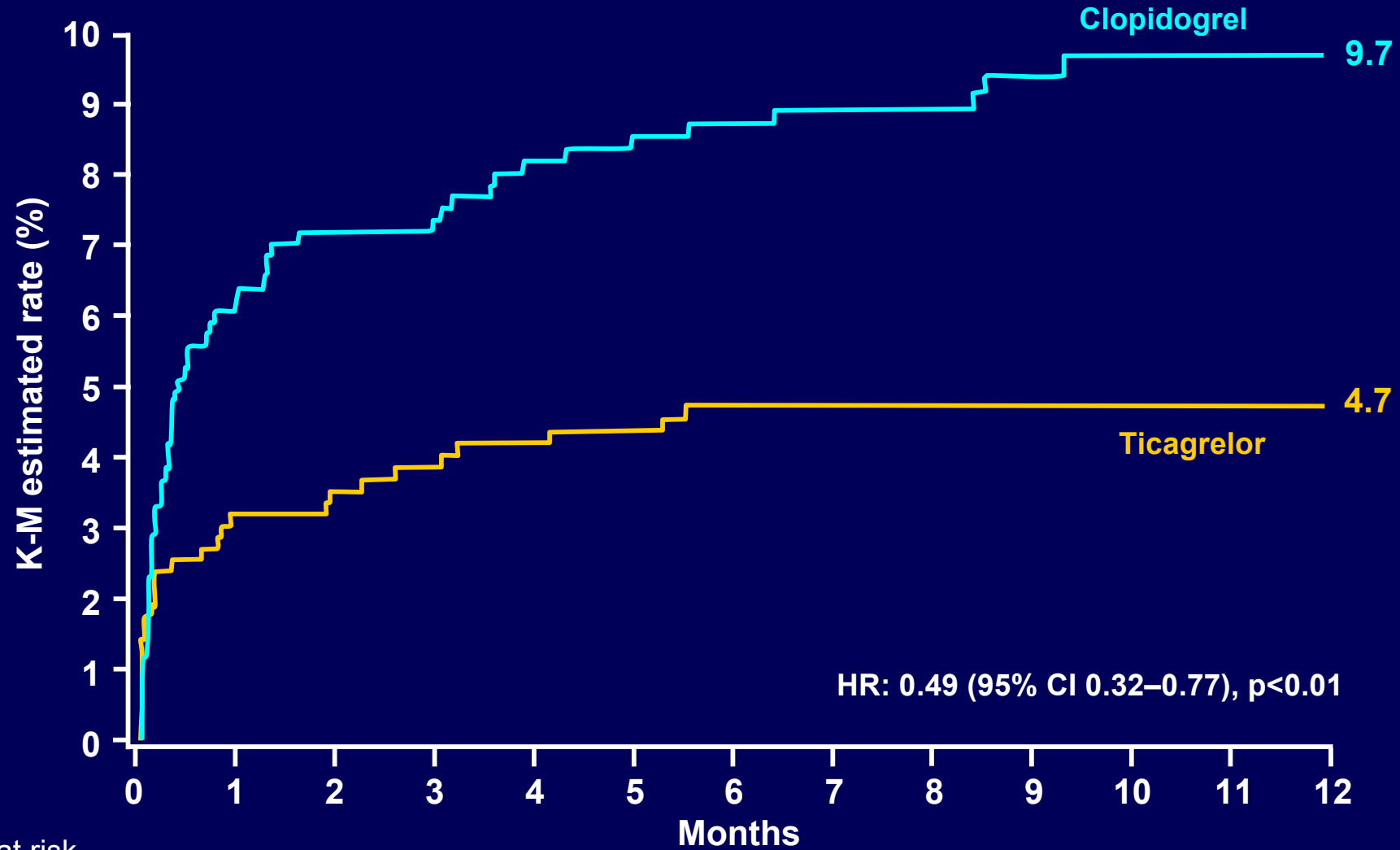
**Results for hemorrhagic stroke: 0.0% (ticagrelor) and 0.2% (clopidogrel); non-hemorrhagic stroke: 2.1% and 1.6%

Time from CABG to CV death (CABG population)



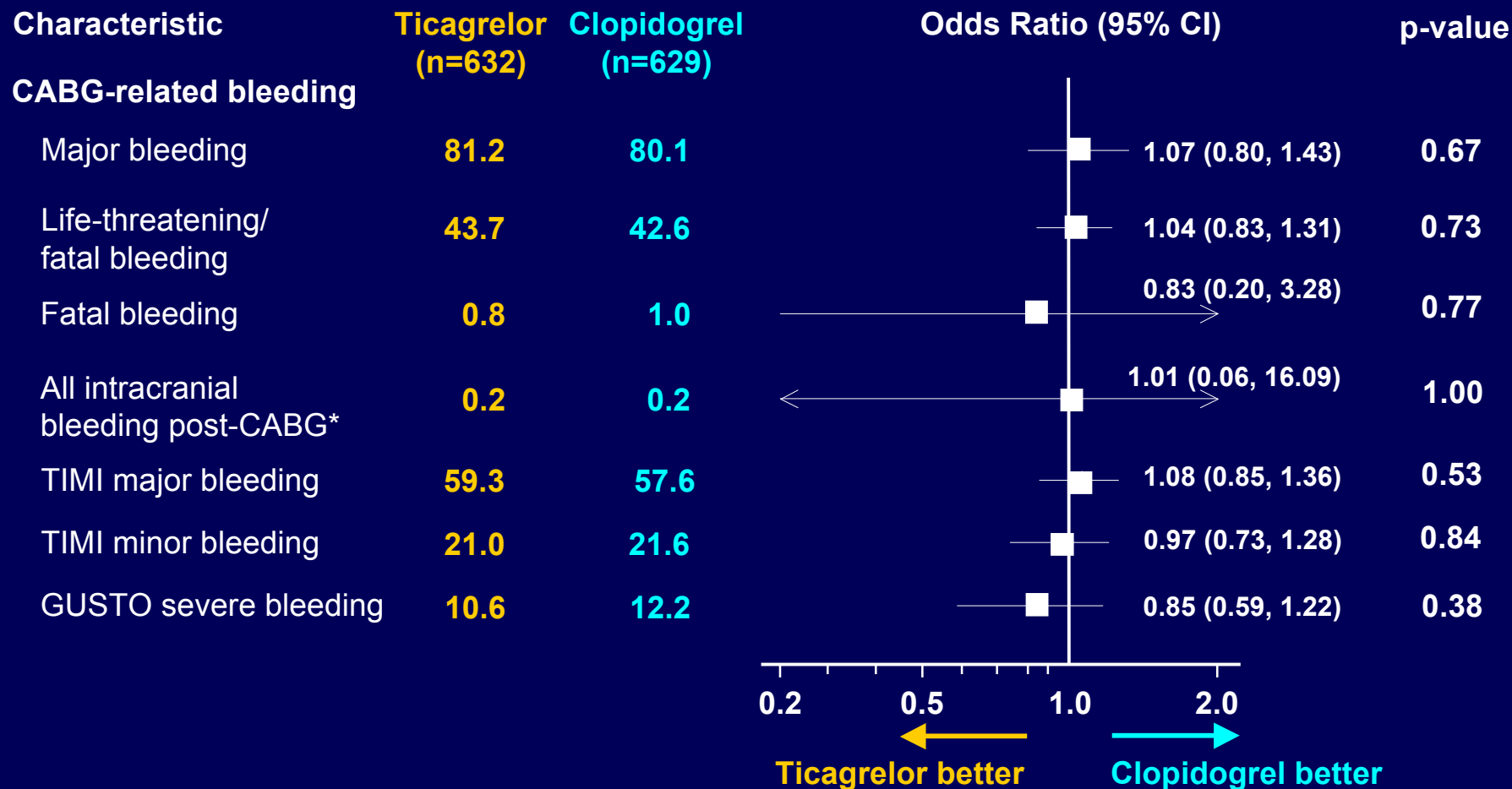
	Months from CABG procedure												
No. at risk	0	1	2	3	4	5	6	7	8	9	10	11	12
Ticagrelor	629	583	557	491	415	291	119						
Clopidogrel	629	565	539	472	404	269	130						

Time from CABG to any death (CABG population)



No. at risk	0	1	2	3	4	5	6	7	8	9	10	11	12
Ticagrelor	629	583	557	491	415	291	119						
Clopidogrel	629	565	539	472	404	269	130						

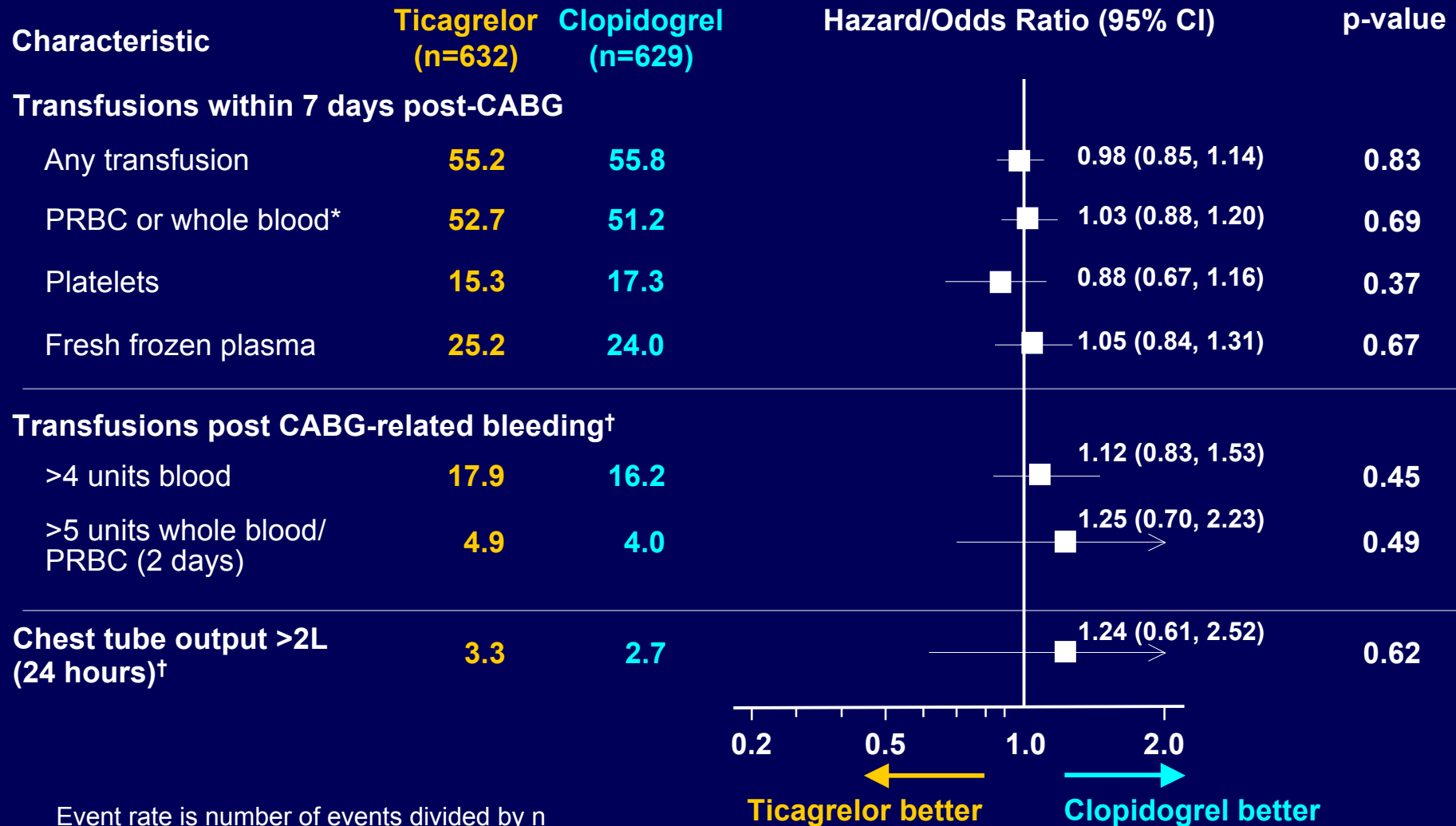
Bleeding from time of CABG



Values are incidences = number of events divided by n, not rates.

*Hazard ratio. Both CABG-related and non-related

Transfusions from time of CABG



Event rate is number of events divided by n

*Median (range) units transfused within 7 days post-CABG: tic 3.0 (2.0–4.0) vs. clop 3.0 (2.0–4.0); p=0.86

†Odds ratio and p-value from Fisher's exact test

Limitations

- **Retrospective analysis of a non-randomized subgroup of patients requiring CABG**
 - selection bias, survivor bias or other confounders
- **The formal adjudication of causes of deaths in the main trial separated death from vascular and non-vascular cause, but a further subcategorization was not performed**
 - a retrospective central review of the causes of post-CABG death is currently ongoing

Conclusions

- In ACS patients undergoing CABG within 7 days after stopping P2Y₁₂-inhibitor treatment, patients previously treated with ticagrelor as compared with clopidogrel have
 - **lower mortality after CABG – both total and CV**
 - **similar rate of CABG-related bleeding**
- The results are consistent with the main study outcomes

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