ДРУЖЕСТВО НА КАРДИОЛОЗИТЕ В БЪЛГАРИЯ

Научен симпозиум

НОВОСТИ В АНТИАГРЕГАНТНАТА И АНТИКОАГУЛАНТНА ТЕРАПИЯ
11-12 май 2013 г
Парк —хотел Москва, София

Предимства и ограничения при избора на нови перорални антиагреганти (Prasugrel и Ticagrelor)

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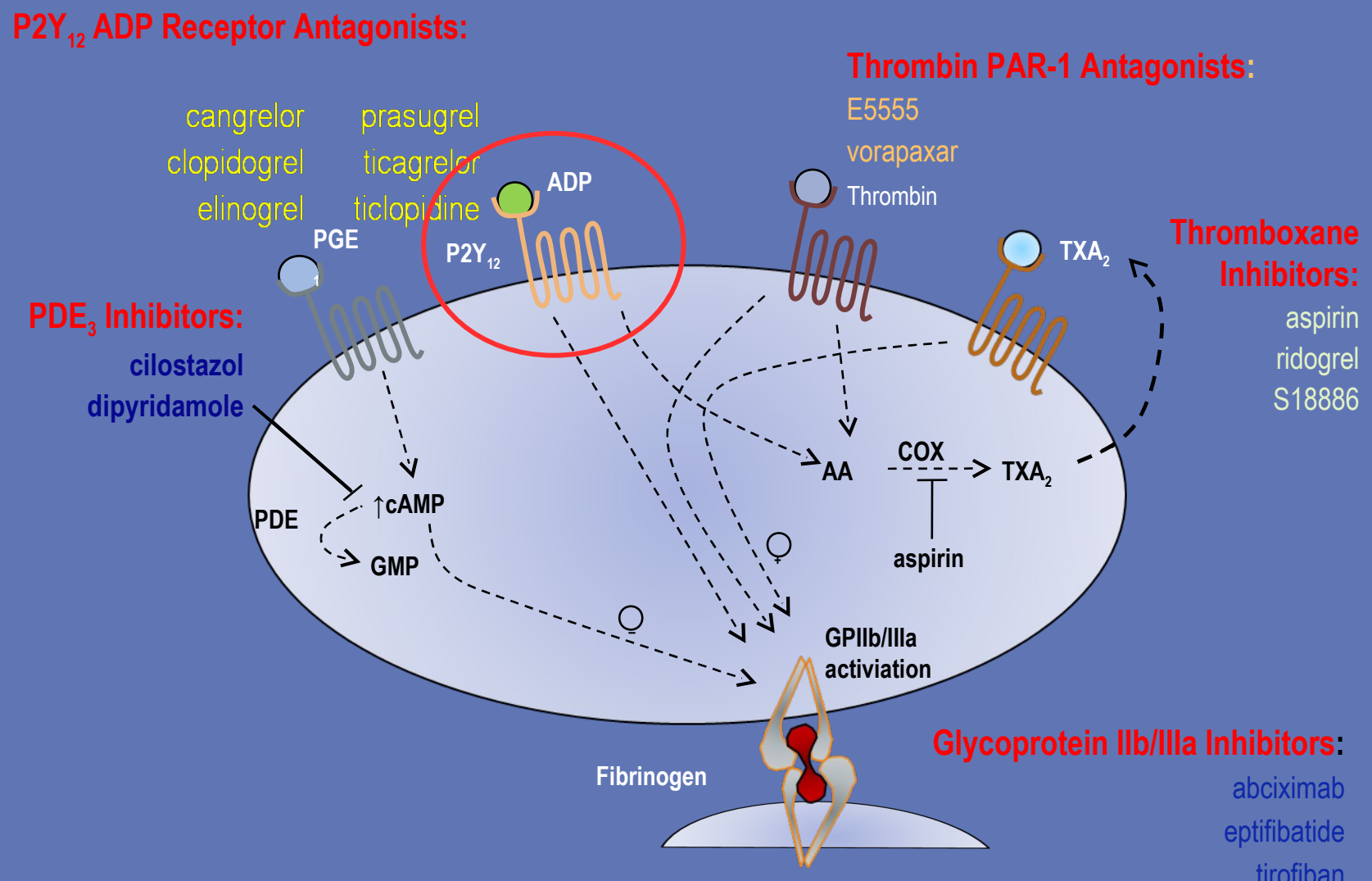
„Идеален“ антитромбоцитен медикамент

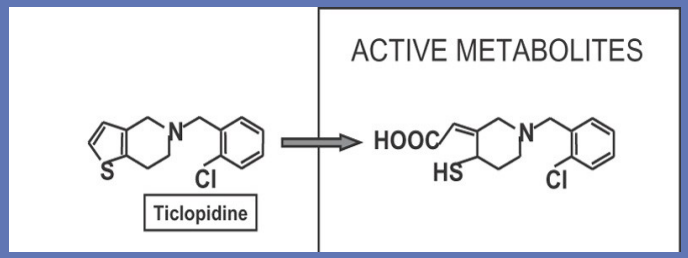
- ✓ Предвидим фармакодинамичен профил, без необходимост от мониториране
- ✓ Бързо начало на ефекта
- ✓ Бързо инактивиране (и/или наличен антидот)
- ✓ Липса на неблагоприятни взаимодействия с други медикаменти
- ✓ Мощен антитромботичен ефект
- ✓ Нисък риск
- ✓ Ниска цена
- ✓ Лесно приложение

Антитромбоцитни медикаменти



Adapted from: Meadows TA, Bhatt DL. *Circ Res.* 2007;100:1261-1275.
Desai NR, Bhatt DL. *JACC Cardiovasc Interv.* 2010;3:571-583.

Тиенопиридини – 1-ва и 2-ра генерация



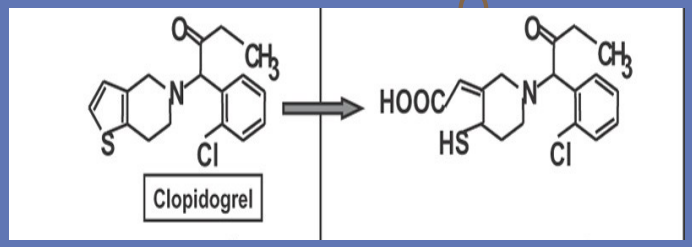
Ticlopidine

(1-ва генерация)

+ ADP рецепторен антагонист, антитромботично лечение на избор при коронарно стентиране

– Странични ефекти: неутропения, тромбоцитопения, обрив, диария и др..

– Много бавно достигане на пълен антитромбоцитен ефект



Clopidogrel

(2-ра генерация)

+ По-добър профил на безопасност- малко странични ефекти
(CLASSICS trial. Bertrand NE et al. *Circulation*. 2000;102:624-629.)

+ По-бързо достигане на ефект след първоначална насищаща доза
(Cadroy Y et al. *Circulation*. 2000;101:2823-2828.)

+ По-добри клинични резултати
(Bhatt DL *et al. J Am Coll Cardiol.* 2002;39:9-14.)

Ограничения в терапията с Клопидогрел

- **Неадекватно подтискане на Тр при 15% to 48% пациентите**
  - Допринася за относително висок риск от усложнения
- **Бавно настъпващ начален антитромбоцитен ефект** (макс.блокиране P2Y12 на 4-5 ден след ежедневен прием по 75мг) – преодолява се с въвеждането на насищащата доза.
  - **Предлекарство, което изисква трансформиране в активен метаболит**
    - Различия в метаболизма, които водят до променлива ефективност върху подтискането на Тр агрегация **- резистентост**
- **Бавно изчерпване на ефекта -** необратимо свързване с Тр P2Y12 –след спиране на медикамента, което се определя от генерирането на нови Тр.

James S, et al. *Am Heart J.* 2009;157:599-605.

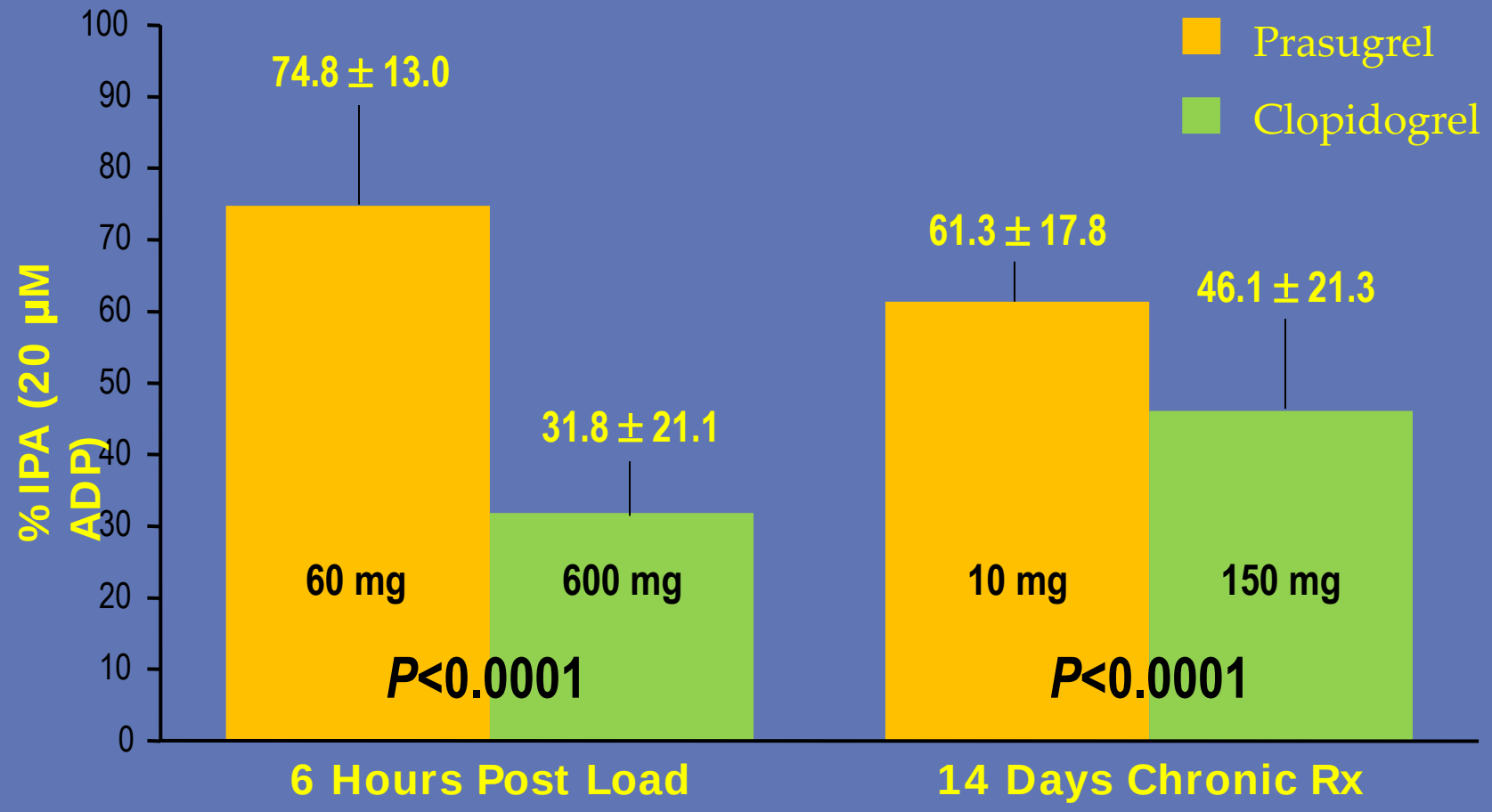
Еволюция на антитромбоцитната терапия

Prasugrel

- Тиенопиридин
- Значително по-бързо начало на ефекта – различна структура, позволяваща бърза конверсия в акт.метаболит - поява в кръвта до 15 мин и достигане на максимална плазмена концентрация към 30 мин.
- По-бързо и по-силно подтискане на Тр активност.
- По-малко влияние на CYP 2C19 генотипа върху фармакокинетиката и фармакодинамиката
- Високо ниво на подтискане на Тр активност при клопидогрел резистентни пациенти
- Необратимо свързване с P2Y12 рецептор

PRINCIPLE-TIMI 44

Prasugrel vs Clopidogrel

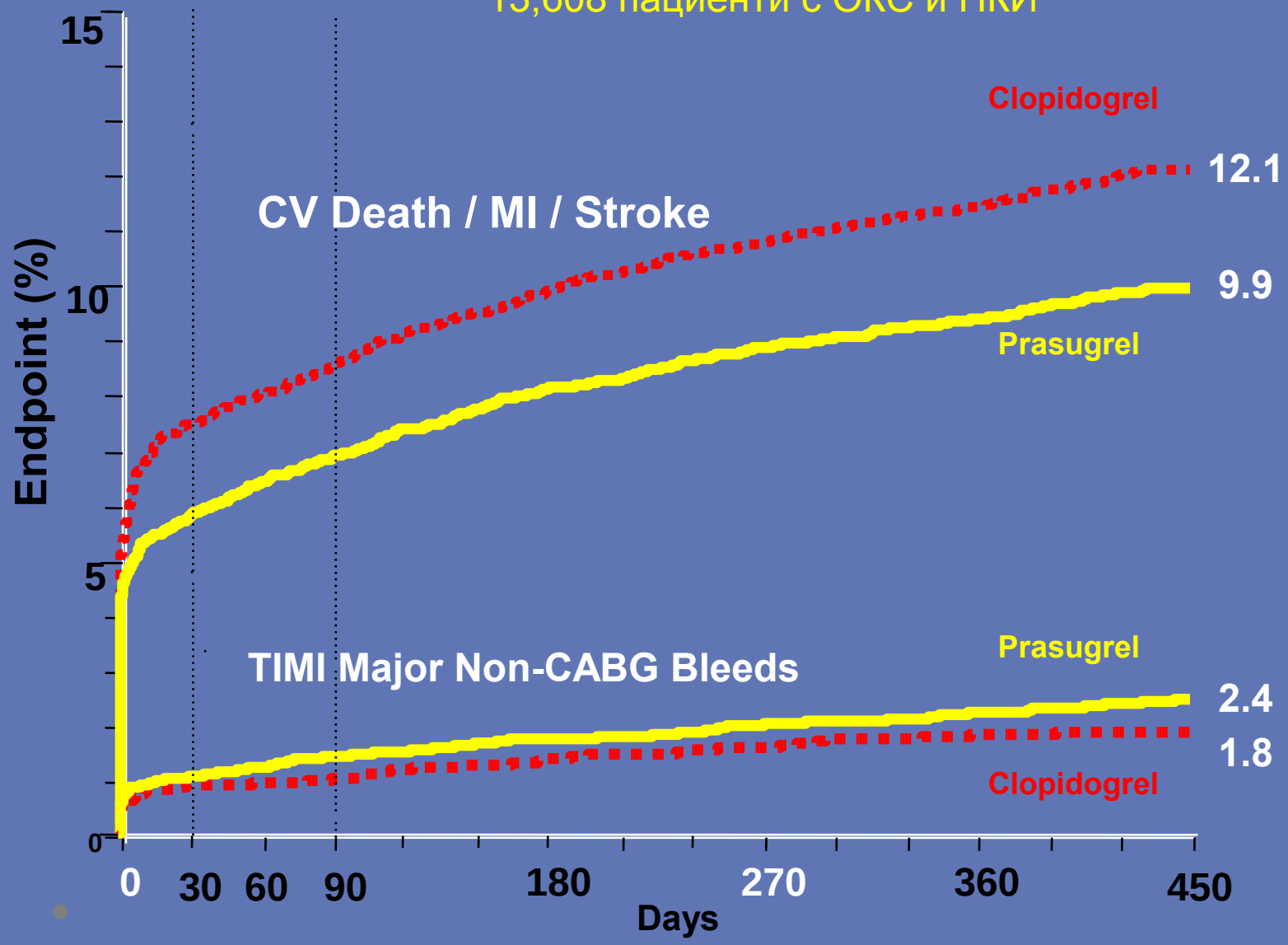


Adapted from Wiviott SD et al. *Circulation*. 2007;116:2923-2932.

TRITON TIMI 38

Prasugrel vs Clopidogrel

13,608 пациенти с ОКС и ПКИ



↓ 138 events

HR 0.81 (0.73-0.90) p=0.0004

NNT = 46

↑ 35 events

HR 1.32 (1.03-1.68) p=0.03

NNT = 167

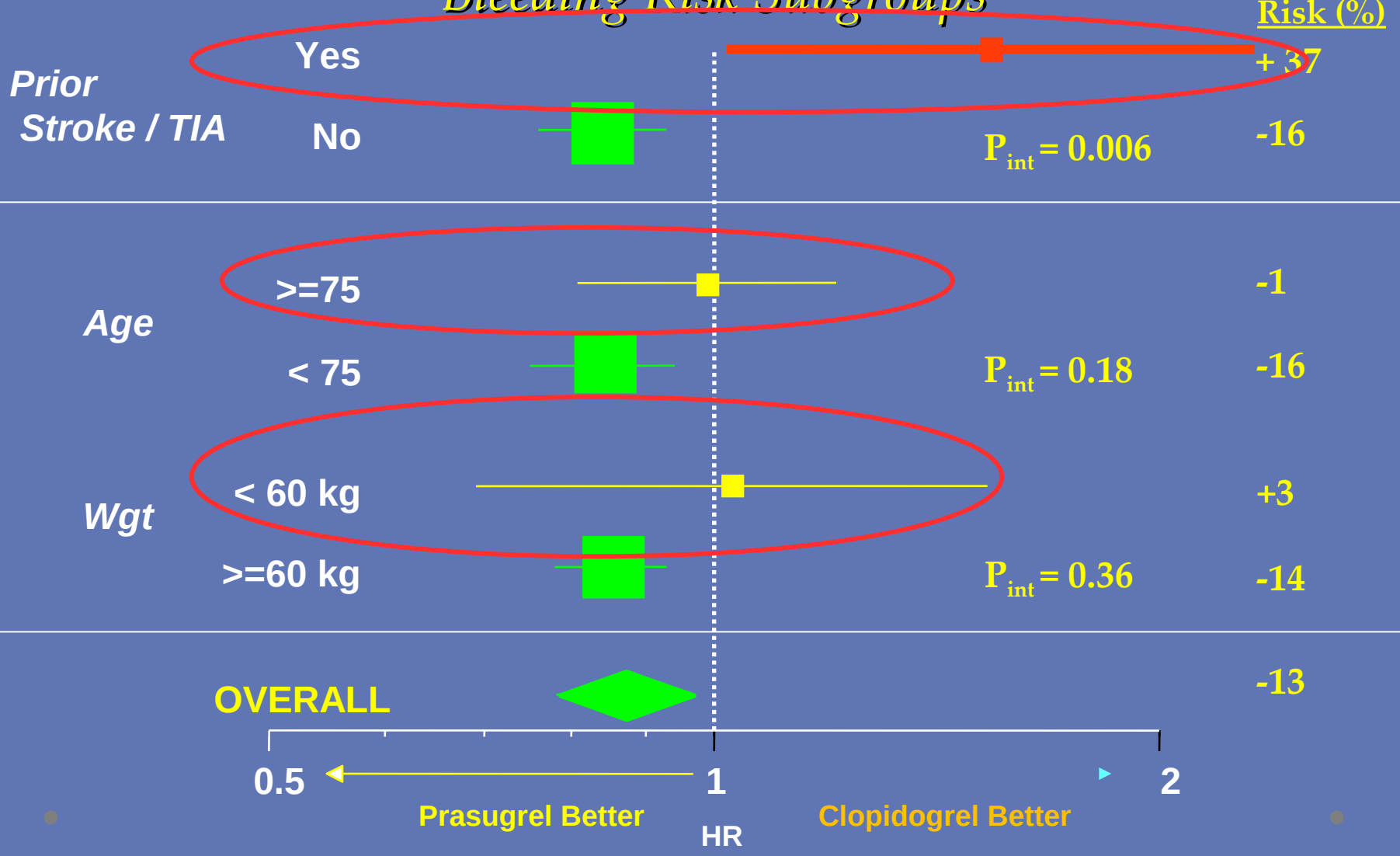
Triton –TIMI Investigators. NEJM; 357: 2001 2015

TRITON TIMI 38

Post-hoc analysis

Prasugrel vs Clopidogrel

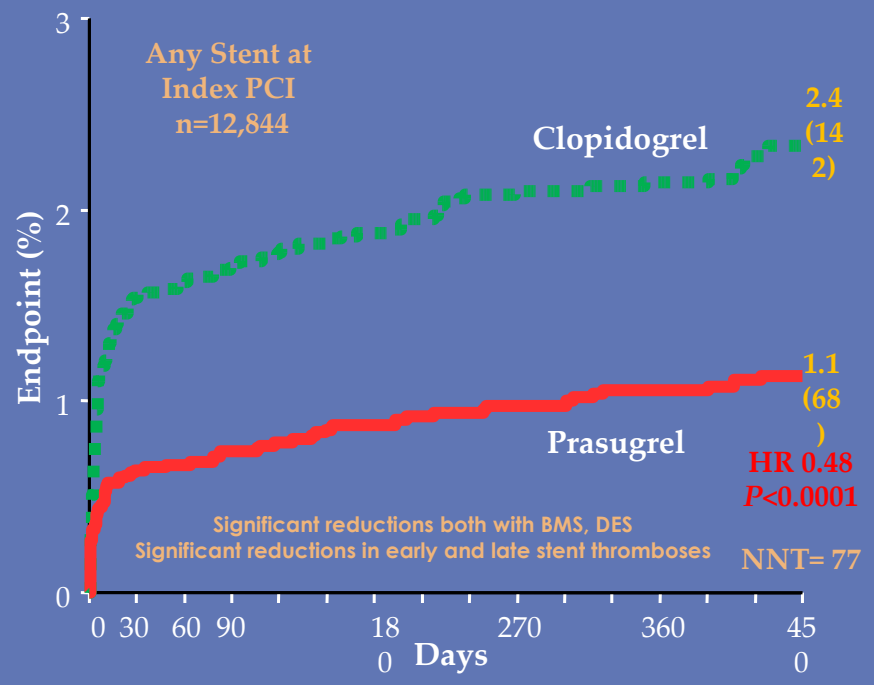
Bleeding Risk Subgroups



TRITON TIMI 38
Post-hoc analysis

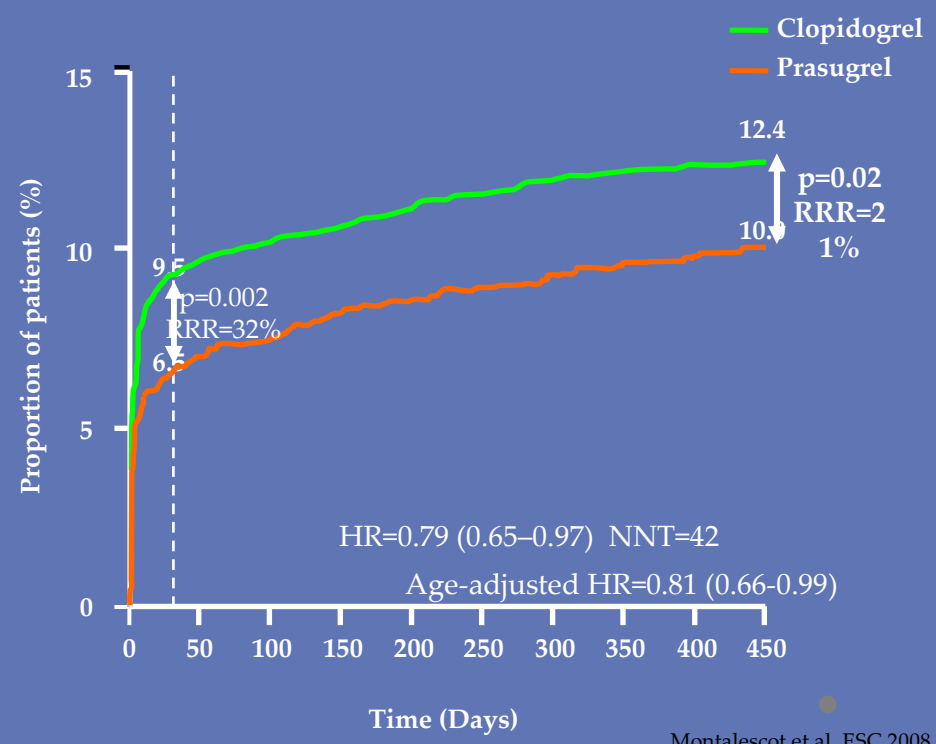
Prasugrel vs Clopidogrel

STENT THROMBOSIS



Adapted from Wiviott SD et al. *Lancet*. 2008;371:1353-1362.

STEMI Cohort



Montalescot et al. ESC 2008

TRITON TIMI 38

Prasugrel vs Clopidogrel

- При пациенти с ОКС, празугрел значително намалява риска от нефатален МИ в сравнение с клопидогрел (p<0,001), без сигнификантна разлика по отношение на честотата на ССС и МСИ

- При пациенти с ОКС и ПКИ, празугрел се свързва със значителна редукция на исхемичните инциденти, вкл.стент тромбоза, но с повишен риск от голямо кървене, вкл.фатално.

- Редукция на дозата при пациенти >75 год. и <60 кг.

- Общата смъртност е без сигнификантна разлика в сравнение с клопидогрел
- Голямо кървене се наблюдава по-често в сравнение с клопидогрел*

-- по-ефективен метаболизъм на празугрел –по-ефективно блокиране на Тр активност, докато при терапия с Клопидогрел това се постига в 30-50% от пациентите, което обяснява по-голяма честота на МАСЕ и по-малко кървене

- Празугрел не решава проблема с бавното изчерпване на ефекта, поради необратимото свързване с P2Y12.

Еволюция на антитромбоцитната терапия

Директни P2Y12 инхибитори

Ticagrelor

- Нов клас cyclo-pentyl-triazolo-pyrimidine (CPTP)
- Директно действие

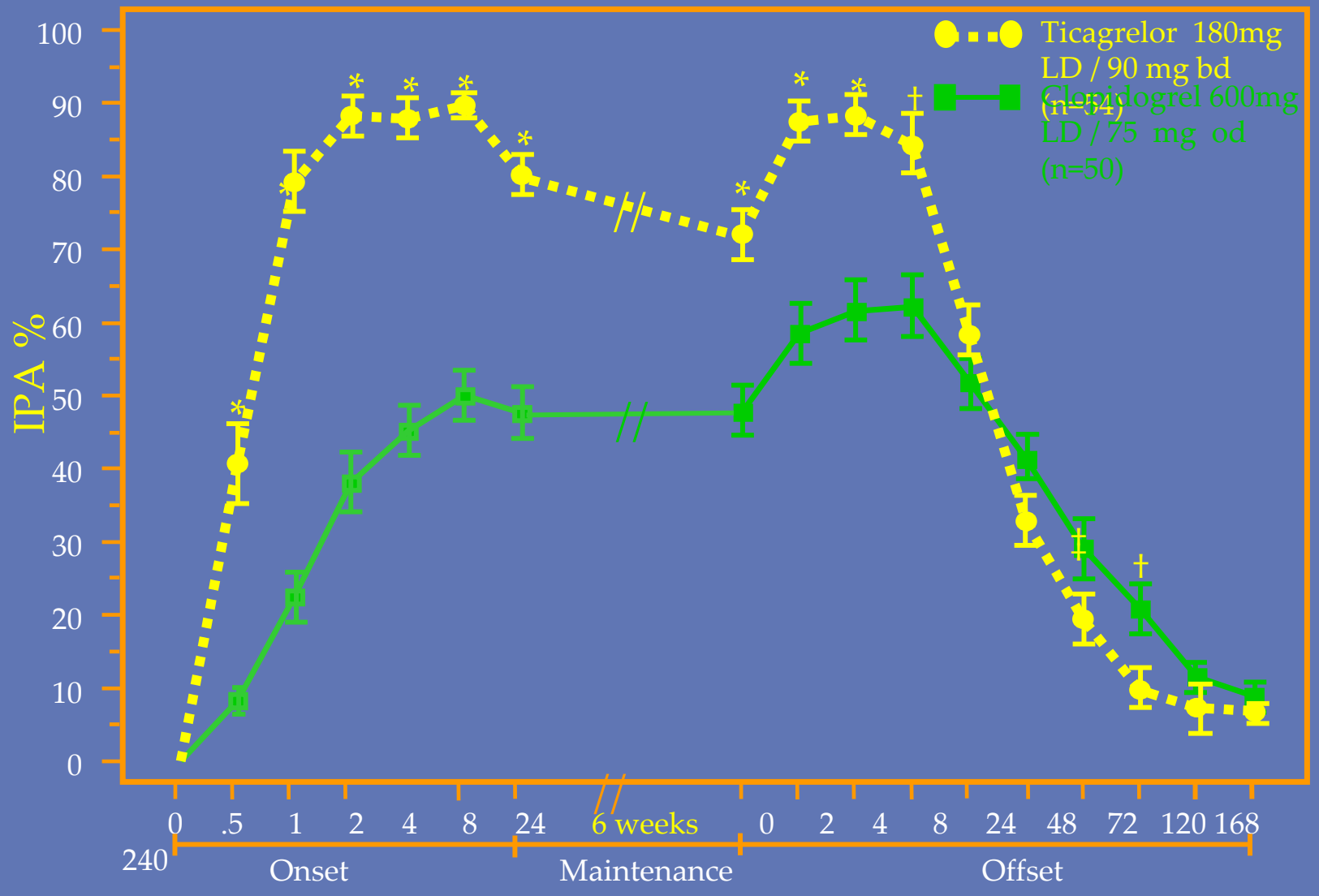
-- не е предлекарство

-- не изисква метаболитна активация

- Значително по-бърз ефект от Клопидогрел
- Обратимо свързване с P2Y12 рецептора.

ONSET/OFFSET Study

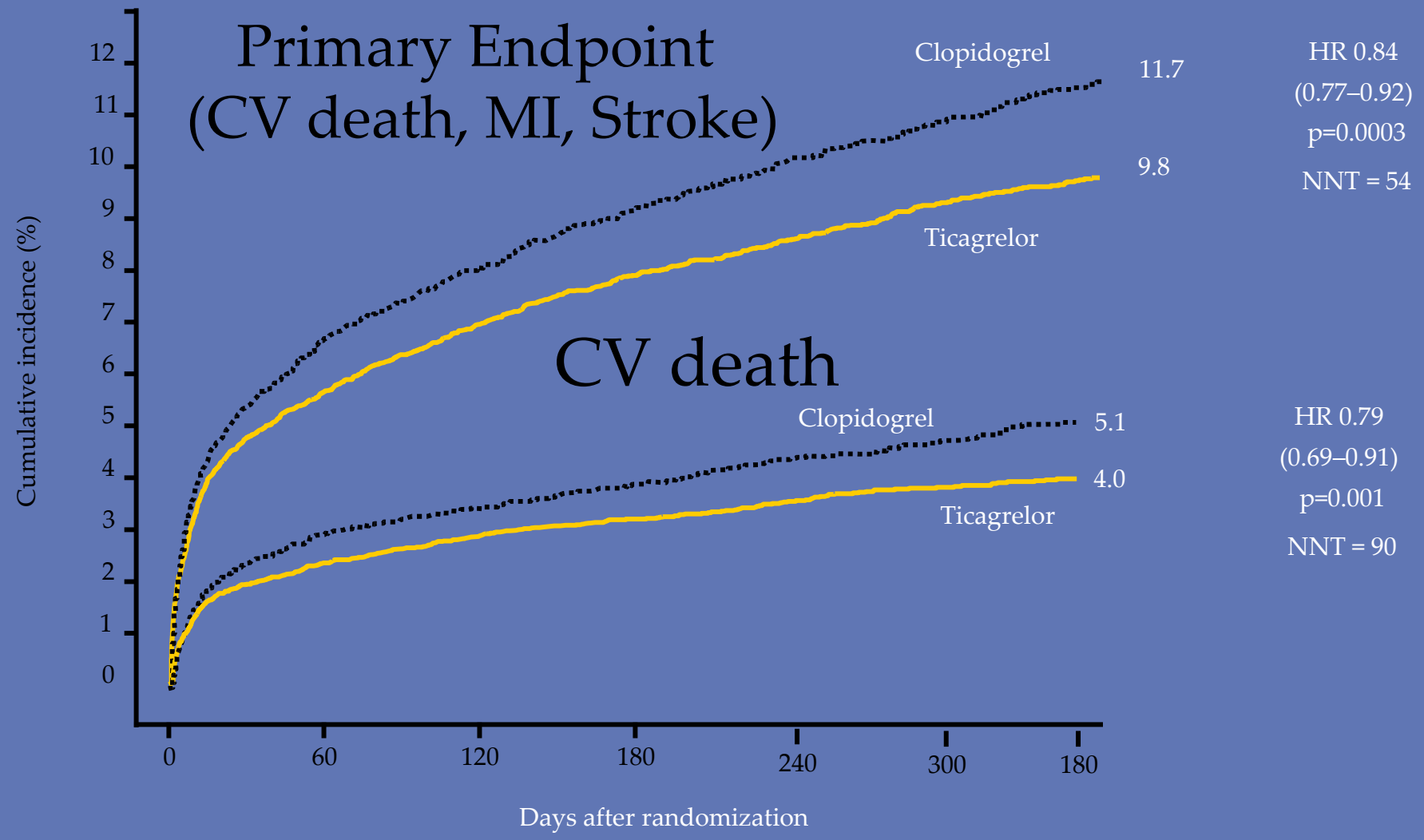
Подтискане на тромбоцитната активност



Gurbel PA et al. Circulation 2009

PLATO

N=18,624

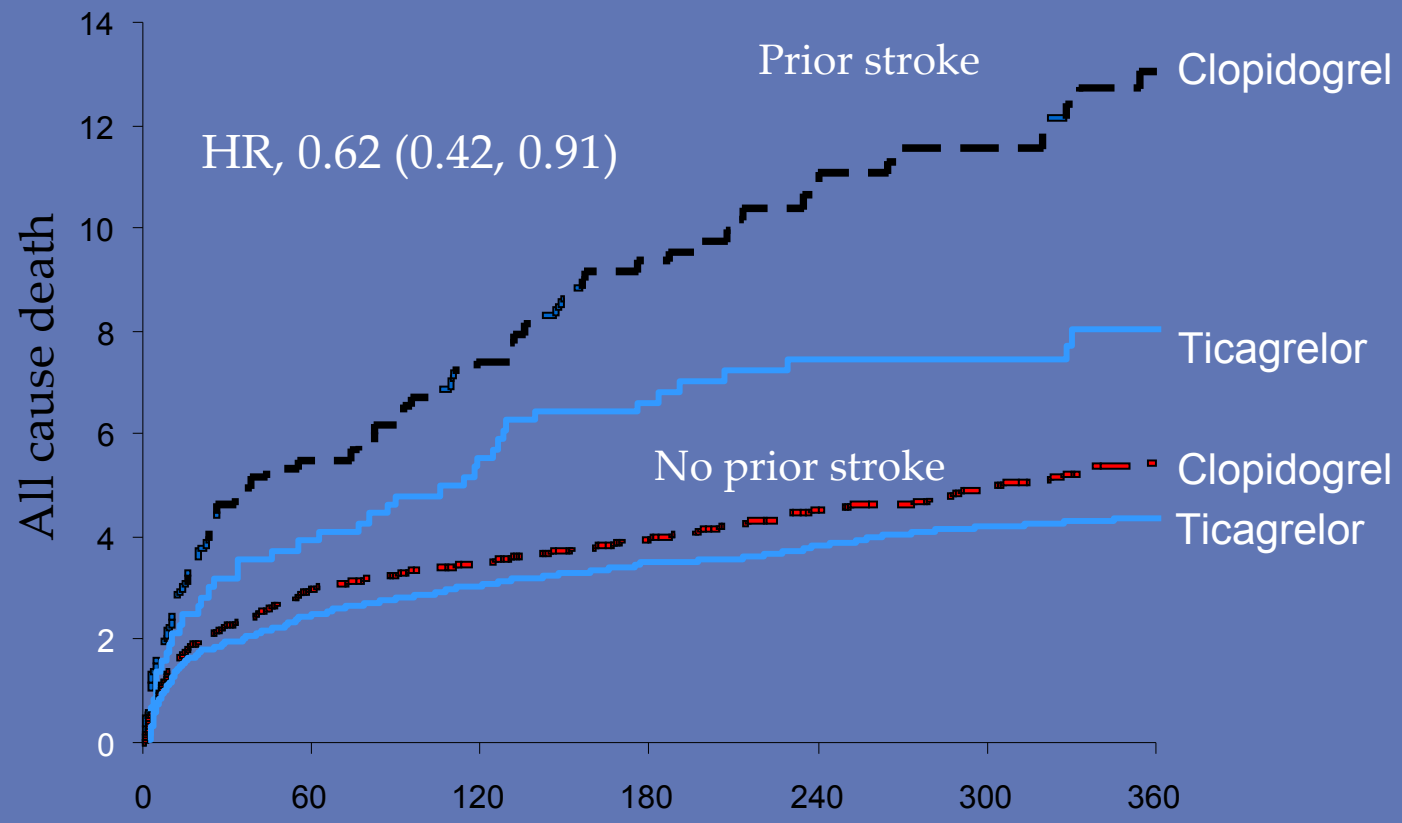


Wallentin L, et al. N Engl J Med. 2009;361:1045-57.

Предшествващ ИМИ/ ТИА

Stroke

N=1052

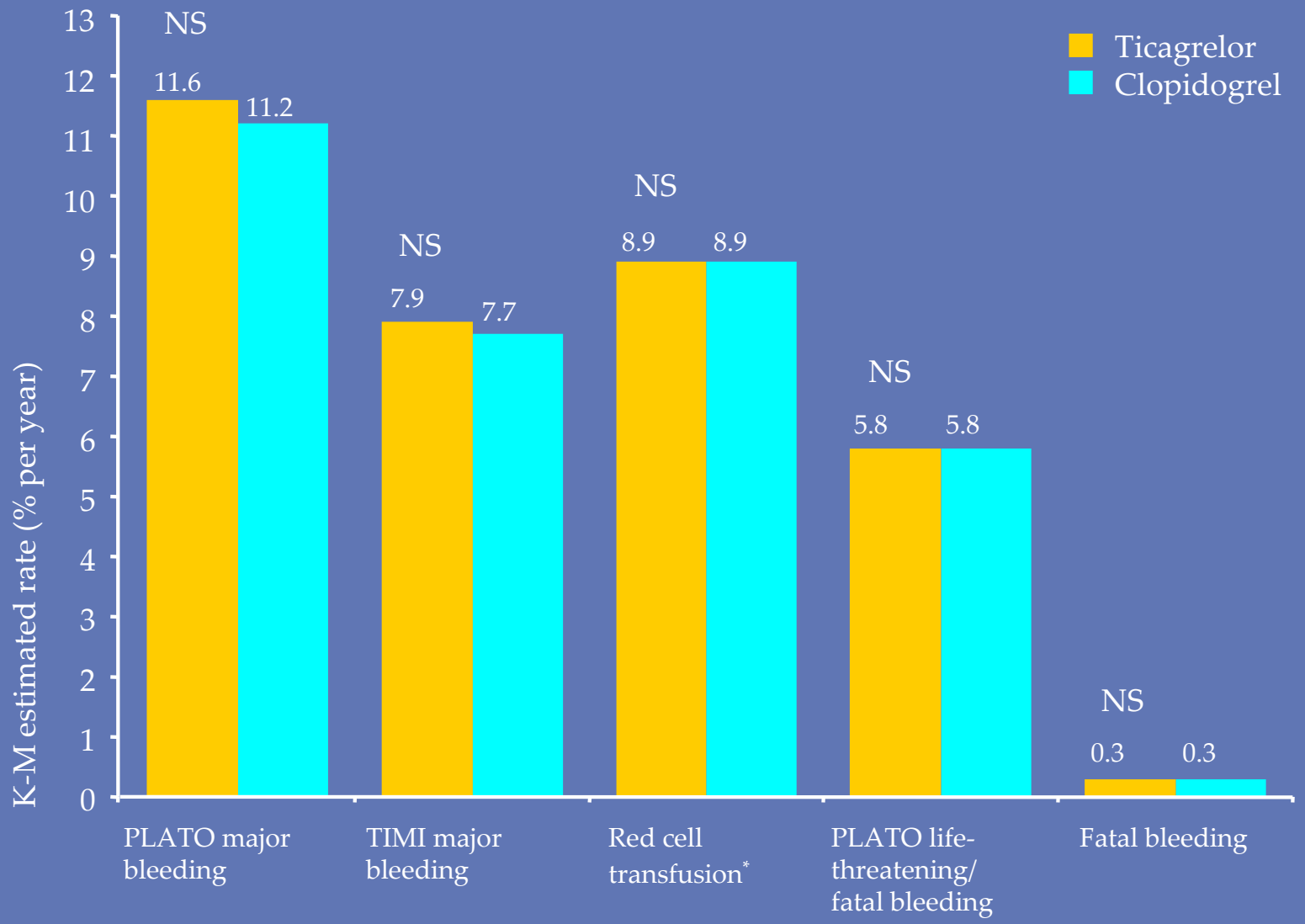


Patient at risk

Prior stroke	Clopidogrel	588	542	530	507	397	314	246
	Ticagrelor	564	534	525	511	411	332	254
No prior stroke	Clopidogrel	8699	8318	8245	8078	6679	5124	4115
	Ticagrelor	8761	8382	8289	8107	6701	5143	4162

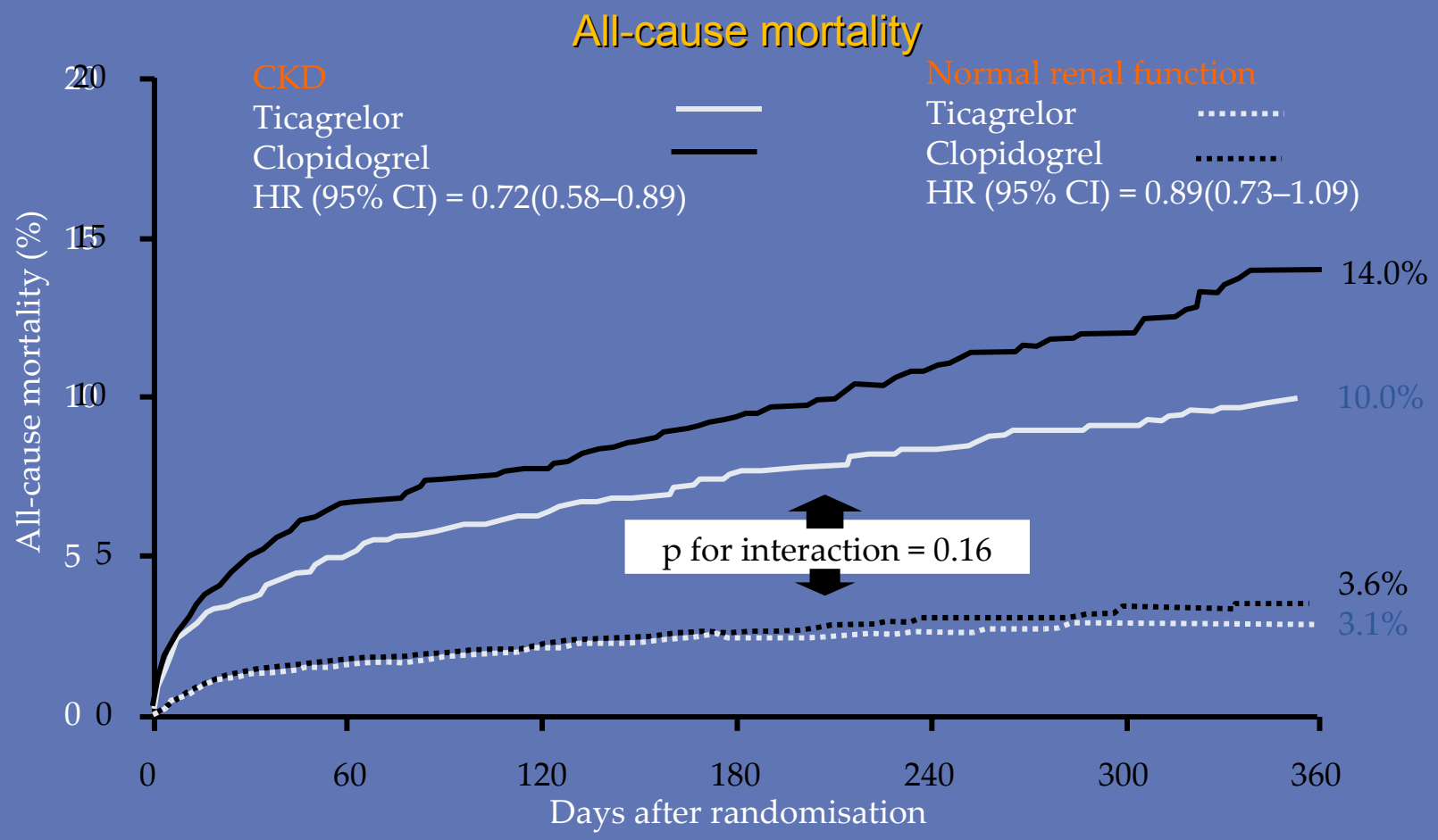
James, S et al, ESC 2011

Кървене



Major bleeding and major or minor bleeding according to TIMI criteria refer to non-adjudicated events analysed with the use of a statistically programmed analysis in accordance with definition described in Wiviott SD et al. NEJM 2007;357:2001–15;
*Proportion of patients (%); NS = not significant

Бъбречна функция



All-cause mortality benefit with ticagrelor was consistent with the overall PLATO trial results

No interaction between treatment and renal function (p=0.16)

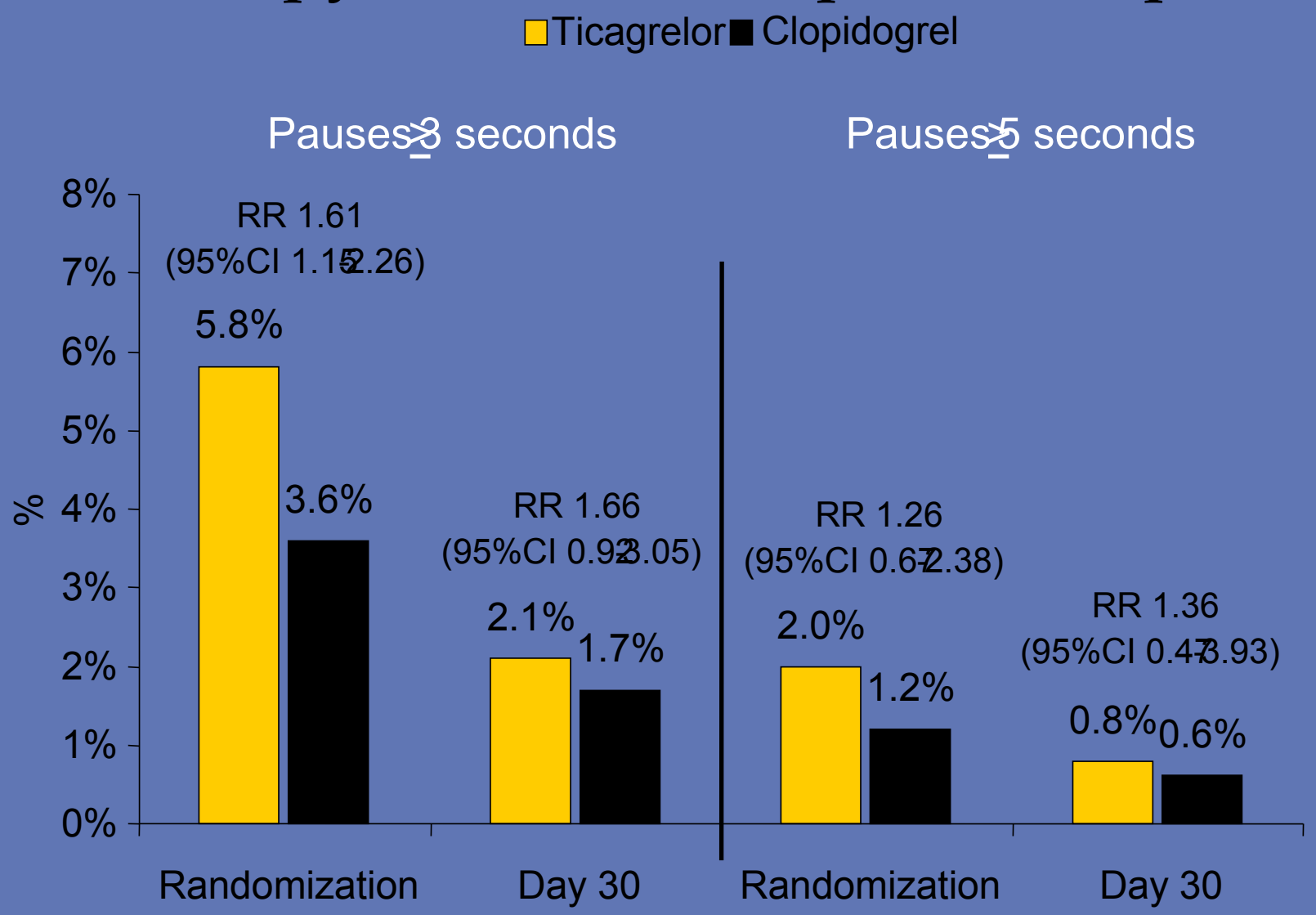
CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio.

James S, et al. Circulation 2010;122:1056–1067;

Wallentin L, et al. N Engl J Med 2009;361:1045–1057.

PLATO Holter

Нарушение на сърдечния ритъм



Sirica B, et al. J Am Coll Cardiol. 2011 May 10;57(19):1908-16

PLATO

Dyspnea

Диспнея

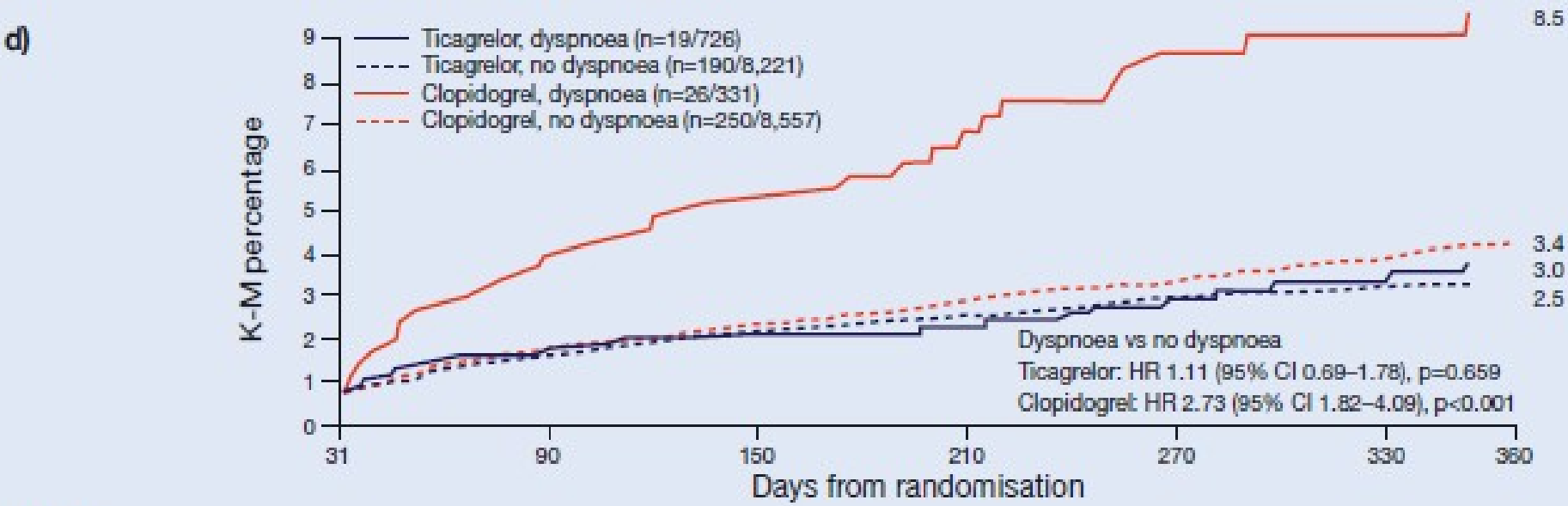
- 13.8% от пациентите, приемащи ticagrelor и 7.8% от тези на clopidogrel са съобщили за диспнея
- Не е наблюдаван неблагоприятен нежелан ефект върху функцията на белите дробеве при пациентите с диспнея
- Ticagrelor-свързаната диспнея не повлиява ефективността

All patients	Ticagrelor (n=9,235)	Clopidogrel (n=9,186)	p value*
Dyspnoea, %			
Any	13.8	7.8	<0.001
With discontinuation of study treatment	0.9	0.1	<0.001

PLATO

Dyspnea

Смъртност при пациентите със диспнея през първите 30 дни



No. at risk						
Ticagrelor (dyspnoea)	726	717	713	628	582	431
Ticagrelor (no dyspnoea)	8,221	8,089	8,004	6,711	6,220	4,666
Clopidogrel (dyspnoea)	331	319	314	264	240	191
Clopidogrel (no dyspnoea)	8,557	8,419	8,344	7,036	6,508	4,853

Storey, R et al Eur Heart J. 2011 Jul 30.

PLATO

Ticagrelor vs Clopidogrel

- Тикагрелор сравнен с клопидогрел намалява исхемичните инциденти и смъртността във всички подгрупил
- Общият показател за кървене не се повишава, но несвързаното с АКБ кървене е повишено.
- Добра поносимост от пациентите с бъбречна недостатъчност
- Тикагрелор може да предизвика диспнея , която често се задържа и дори се усилва
- Тикагрелор може да предизвиква паузи, но без клинични последствия

Indication	Clopidogrel Low dose	Clopidogrel High dose	Prasugrel	Ticagrelor
Elective PCI	++			
ACS conservative strategy	+			++
ACS PCI planned		+	+ (After angio)	++
ACS hs-troponin negative	++			
Non STE ACS			+ (After angio)	++
STEMI, primary PCI		+	++	++
STEMI, fibrinolysis	++			
ACS diabetes			++	++
ACS renal failure			+	++
ACS CABG likely				++
ACS prior stroke	+			++
ACS prior intracerebral bleed	(+)			
ACS frail patients	+			

Заключение

- Празугрел редуцира значително исхемичните СС инциденти в сравнение с клопидогрел, като в най-голяма степен това се определя от намаляване честотата на нефаталнитя МИ.
- Тикагрелор редуцира исхемичните инциденти като намалява СС смърт, както и МИ.
- Рискът от голямо кървене е по висок при пациентите на празугрел в сравнение с клопидогрел.
- Тикагрелор и празугрел не се различават по показателя за общо кървене.
- И двата медикамента имат сходна ефективност и безопасност при пациенти с ОКС и е предпочитана пред клопидогрел

STEMI

Recommendations	Class[a]	Level[b]
Antiplatelet therapy		
Aspirin oral or i.v. (if unable to swallow) is recommended	I	B
An ADP-receptor blocker is recommended in addition to aspirin. Options are:	I	A
• Prasugrel in clopidogrel-naive patients, if no history of prior stroke/TIA, age <75 years.	I	B
• Ticagrelor.	I	B
• Clopidogrel, preferably when prasugrel or ticagrelor are either not available or contraindicated.	I	C

NSTEMI

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

2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction

Antiplatelet Therapy to Support Primary PCI for STEMI

A loading dose of a $P2Y_{12}$ receptor inhibitor should be given as early as possible or at time of primary PCI to patients with STEMI. Options include:

- Clopidogrel 600 mg; or
- Prasugrel 60 mg; or
- Ticagrelor 180 mg

A loading dose of a $P2Y_{12}$ receptor inhibitor should be given as early as possible or at time of primary PCI to patients with STEMI. Options include:

- Clopidogrel 600 mg; or
- Prasugrel 60 mg; or
- Ticagrelor 180 mg

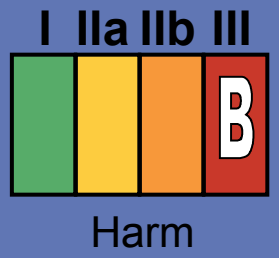
2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction

Antiplatelet Therapy to Support Primary PCI for STEMI

$P2Y_{12}$ inhibitor therapy should be given for 1 year to patients with STEMI who receive a stent (BMS or DES) during primary PCI using the following maintenance doses:

- Clopidogrel 75 mg daily; or
- Prasugrel 10 mg daily; or
- Ticagrelor 90 mg twice a day*

*The recommended maintenance dose of aspirin to be used with ticagrelor is 81 mg daily.



Prasugrel should not be administered to patients with a history of prior stroke or transient ischemic attack.

Благодаря за вниманието

Periprocedural anti thrombotic medication in primary PCI

Recommendations	Class[a]	Level[b]
Antiplatelet therapy		
Aspirin oral or i.v. (if unable to swallow) is recommended	I	B
An ADP-receptor blocker is recommended in addition to aspirin. Options are:	I	A
• Prasugrel in clopidogrel-naive patients, if no history of prior stroke/TIA, age <75 years.	I	B
• Ticagrelor.	I	B
• Clopidogrel, preferably when prasugrel or ticagrelor are either not available or contraindicated.	I	C

ADP = adenosine diphosphate

Anti thrombotic medication for NSTE ACS

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

European Heart Journal (2011) 32:2999–3054
doi:10.1093/eurheartj/ehr236

PLATO: conclusions

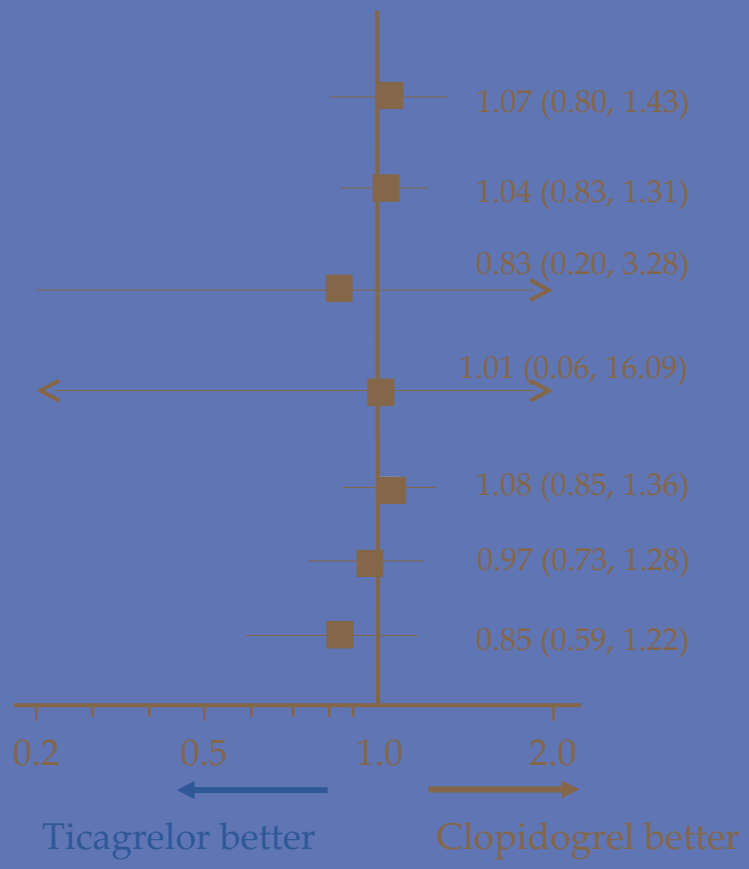
- In a broad population of ACS patients, including patients planned for invasive management, as well as patients intended to be medically managed, treatment with ticagrelor significantly reduced the composite endpoint of CV death, MI, or stroke compared with clopidogrel
  - This result is largely related to a significant reduction in CV death ($P<0.001$) and in MI ($P<0.001$) compared to clopidogrel, with no significant difference between treatments in the rate of stroke
- Total major bleeding events, including fatal bleeding, were not significantly different between ticagrelor and clopidogrel

PLATO: обобщение

- В PLATO е включен пълният спектър от ОКС-пациенти (UA, NSTEMI or STEMI), както на консервативна, така и на инвазивна терапия.
- Ticagrelor постига по-висока ефикасност спрямо клопидогрел без увеличение на честота на общото кървене.
- Резултатите в PLATO сочат, че терапията на 1000 пациенти за 12 месеца с ticagrelor вместо с clopidogrel, води до 14 смъртни случая по-малко, 11 инфаркта по-малко, 6 стент тромбози по-малко.
- При пациентите, които са имали вентрикуларни паузи и диспнея, крайните резултати са в съответствие с резултатите, наблюдавани при останалите пациенти в проучването.

Bleeding from time of CABG

Characteristic	Ticagrelor (n=632)	Clopidogrel (n=629)	Odds Ratio (95% CI)	p-value
CABG-related bleeding				
Major bleeding	81.2	80.1	1.07 (0.80, 1.43)	0.67
Life-threatening/ fatal bleeding	43.7	42.6	1.04 (0.83, 1.31)	0.73
Fatal bleeding	0.8	1.0	0.83 (0.20, 3.28)	0.77
All intracranial bleeding post-CABG*	0.2	0.2	1.01 (0.06, 16.09)	1.00
TIMI major bleeding	59.3	57.6	1.08 (0.85, 1.36)	0.53
TIMI minor bleeding	21.0	21.6	0.97 (0.73, 1.28)	0.84
GUSTO severe bleeding	10.6	12.2	0.85 (0.59, 1.22)	0.38

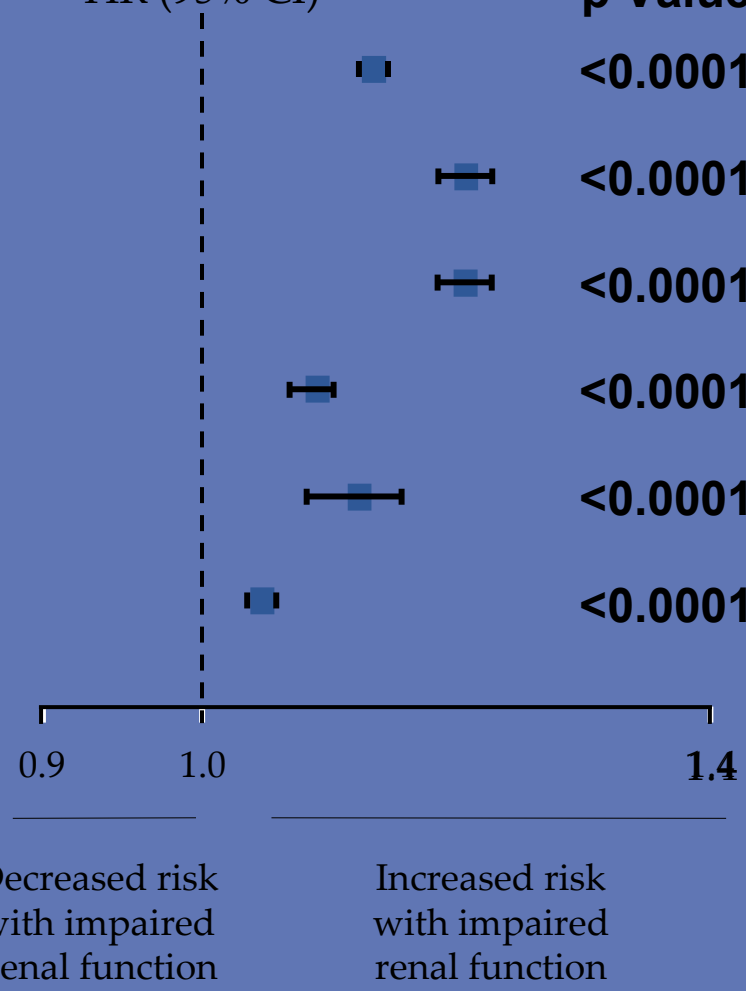


lues are incidences = number of events divided by n, not rates.
azard ratio. Both CABG-related and non-related

Held C et al. JACC 2011;57:672

PLATO: Baseline renal function and outcomes

Event	n*	HR (95% CI)	p Value
CV death, MI or stroke	1538		<0.0001
CV death	643		<0.0001
All-cause death	728		<0.0001
MI	910		<0.0001
Stroke	184		<0.0001
Major bleeding	1518		<0.0001

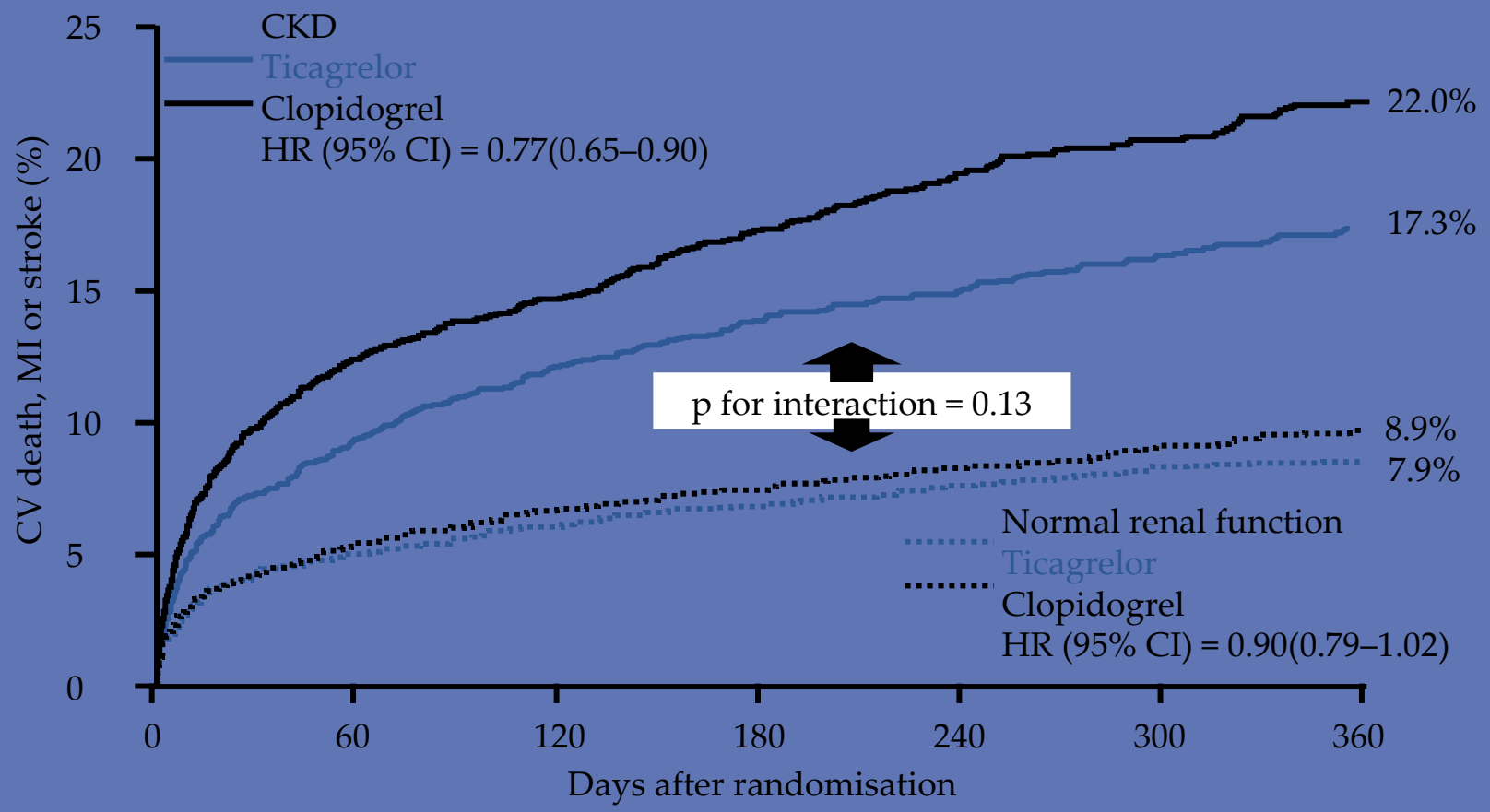


*n=number of patients in both treatment arms combined with 1 or more event.
CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction.

James S, et al. Circulation 2010;122:1056–1067.

Renal function and outcomes in PLATO:

Primary composite endpoint



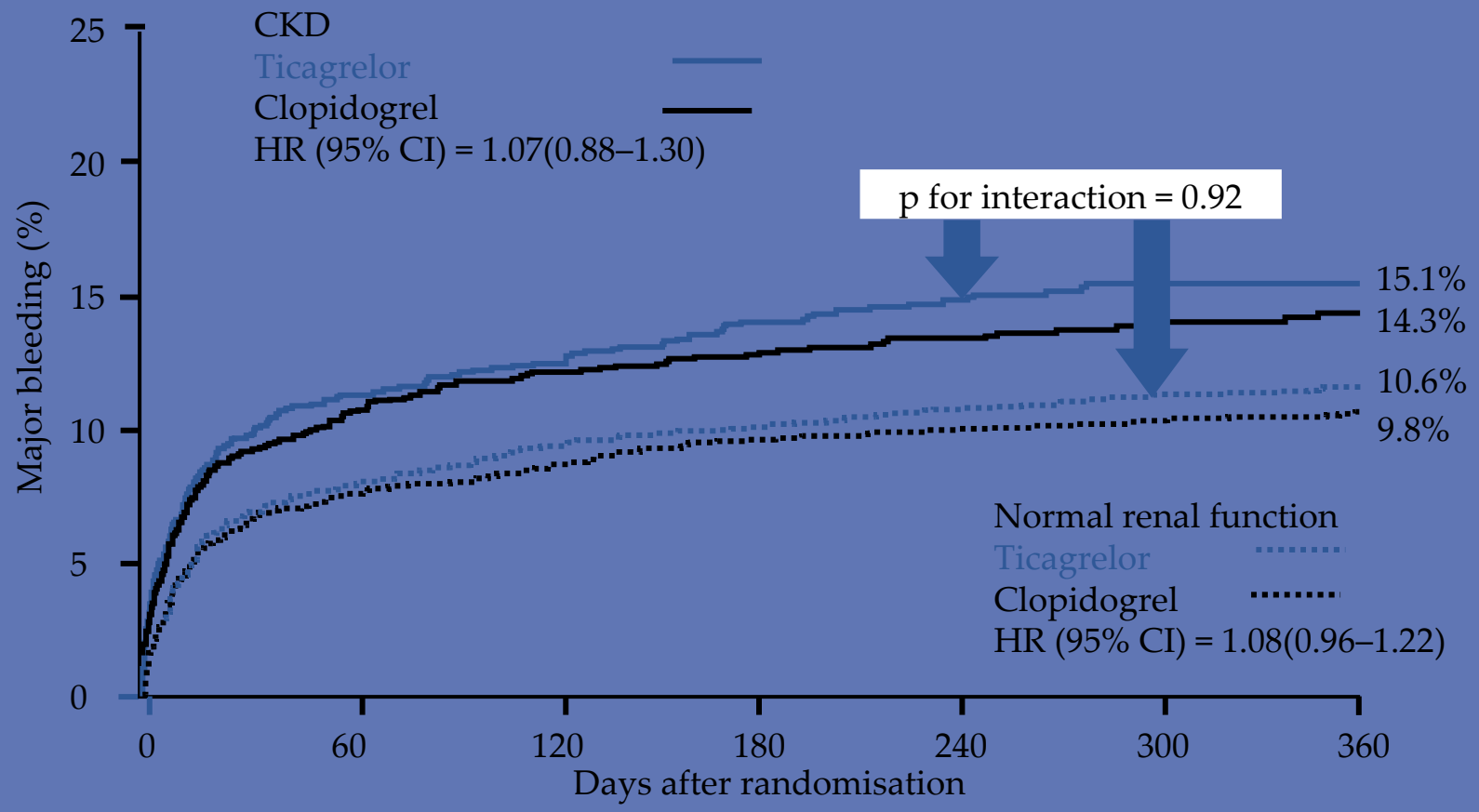
Primary endpoint benefit with ticagrelor was consistent with the overall PLATO trial results

No interaction between treatment and renal function (p=0.13)

CI, confidence interval; CKD, chronic kidney disease; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction.

James S, et al. Circulation 2010;122:1056–1067;
Wallentin L, et al. N Engl J Med 2009;361:1045–1057.

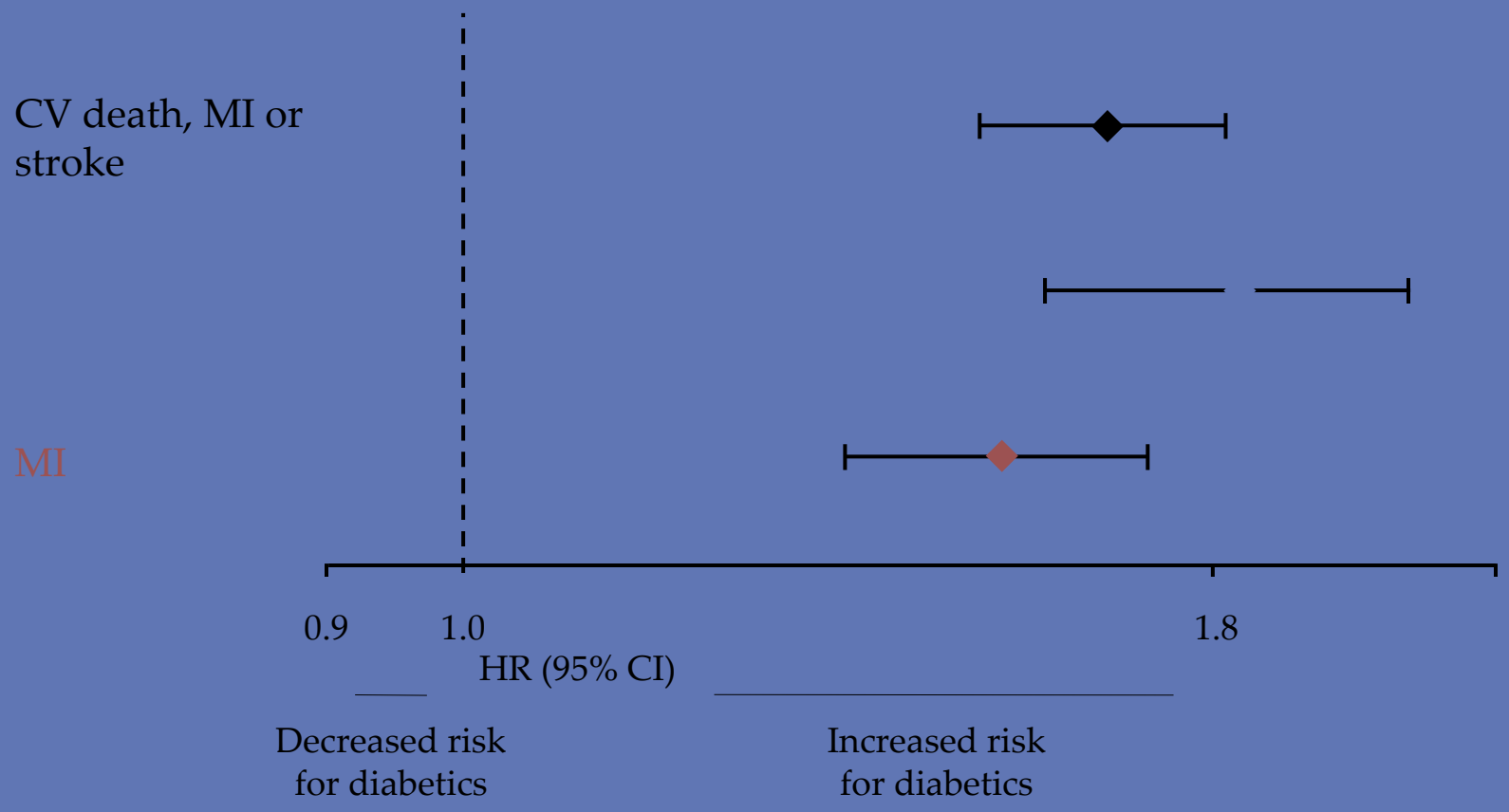
Renal function and outcomes in PLATO: Major bleeding



Bleeding occurred with similar frequency in the ticagrelor and clopidogrel groups[James 2010:J]

NB: Figure labeled 'Non-CABG TIMI bleeding' in manuscript.
CABG, coronary artery bypass graft; CI, confidence interval; CKD, chronic kidney disease HR, hazard ratio; TIMI, Thrombolysis in Myocardial Infarction.
James S, et al. Circulation 2010;122:1056–1067.

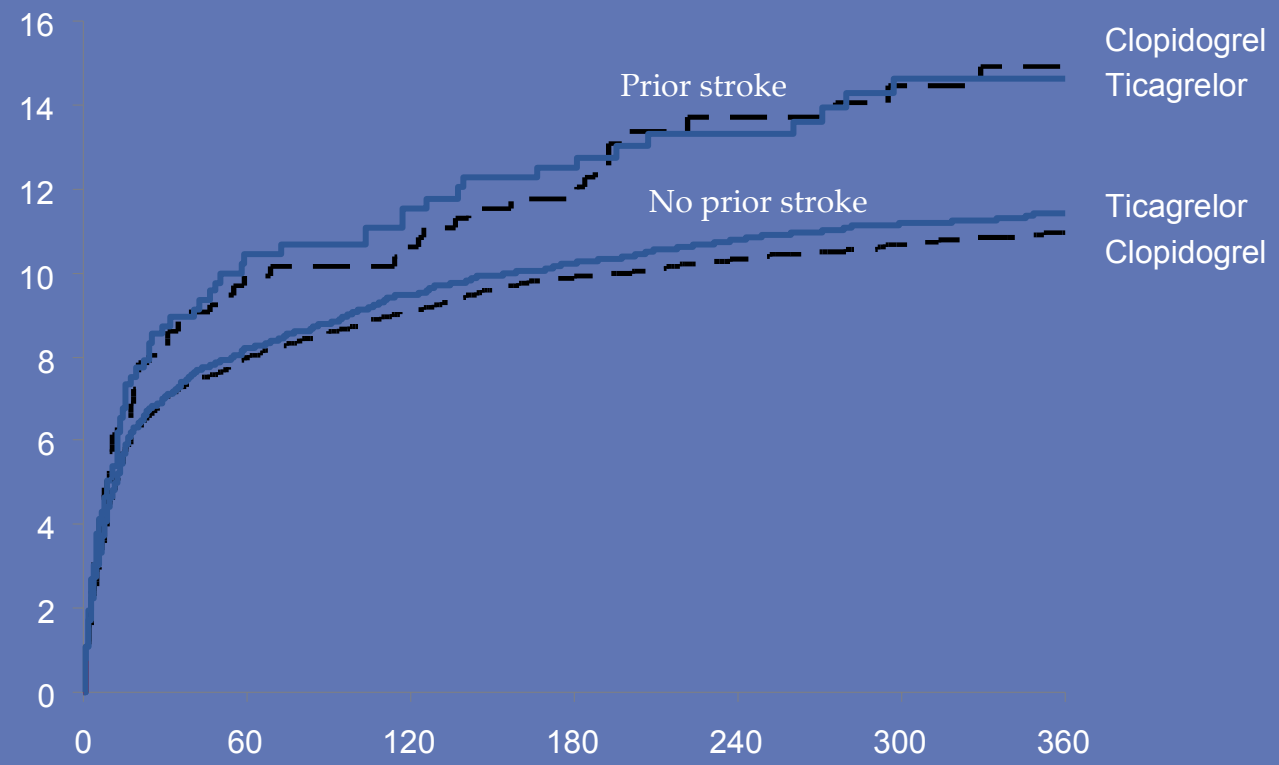
Increased risk of ischaemic events in diabetic patients



CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction.
James S, et al. Eur Heart J 2010;31:3006–3016.

PLATO Stroke

Major bleeding



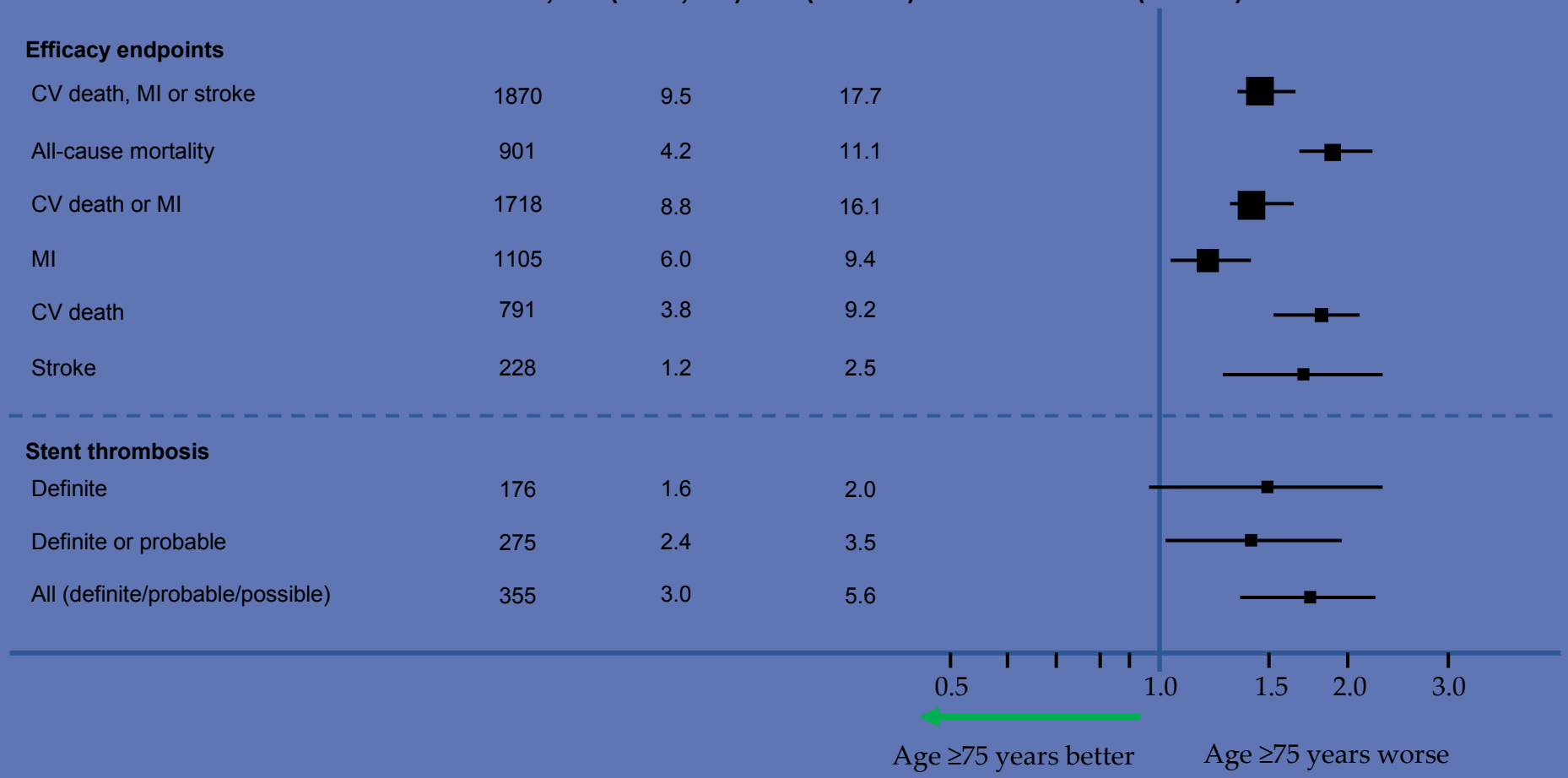
Patient at risk

Prior stroke	Clopidogrel	578	412	387	358	270	198	179
	Ticagrelor	558	415	383	364	282	222	190
No prior stroke	Clopidogrel	8607	6892	6542	6311	4938	3642	3299
	Ticagrelor	8675	6830	6442	6180	4846	3560	3243

PLATO elderly patient subgroup analysis:

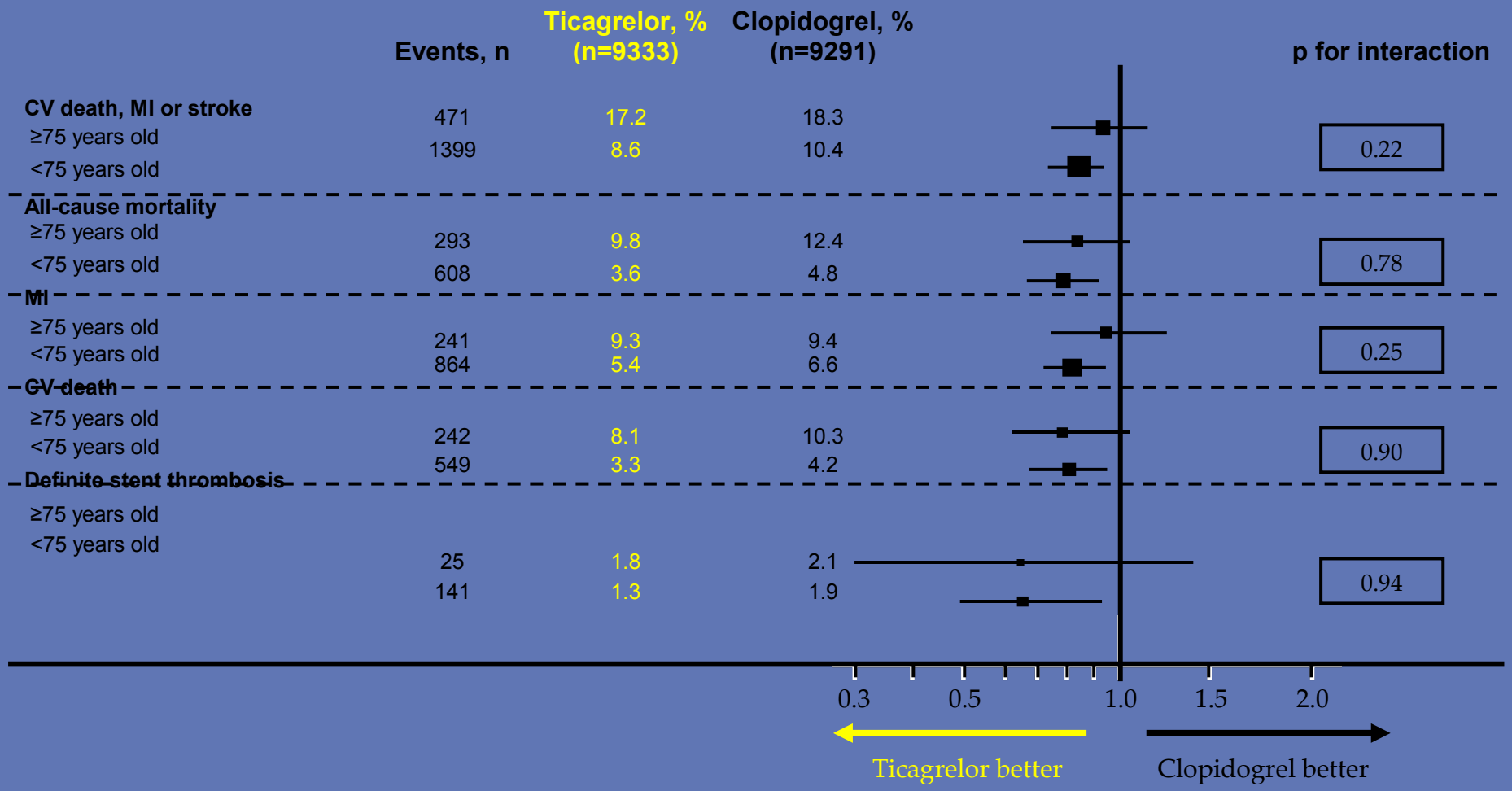
Age and CV thrombotic outcomes

	Events, n	Age <75 years old, % (n=15,744)	Age ≥75 years old, % (n=2878)
Efficacy endpoints			
CV death, MI or stroke	1870	9.5	17.7
All-cause mortality	901	4.2	11.1
CV death or MI	1718	8.8	16.1
MI	1105	6.0	9.4
CV death	791	3.8	9.2
Stroke	228	1.2	2.5
Stent thrombosis			
Definite	176	1.6	2.0
Definite or probable	275	2.4	3.5
All (definite/probable/possible)	355	3.0	5.6



CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction.
Husted S, et al. J Am Coll Cardiol 2011;57:E1099.

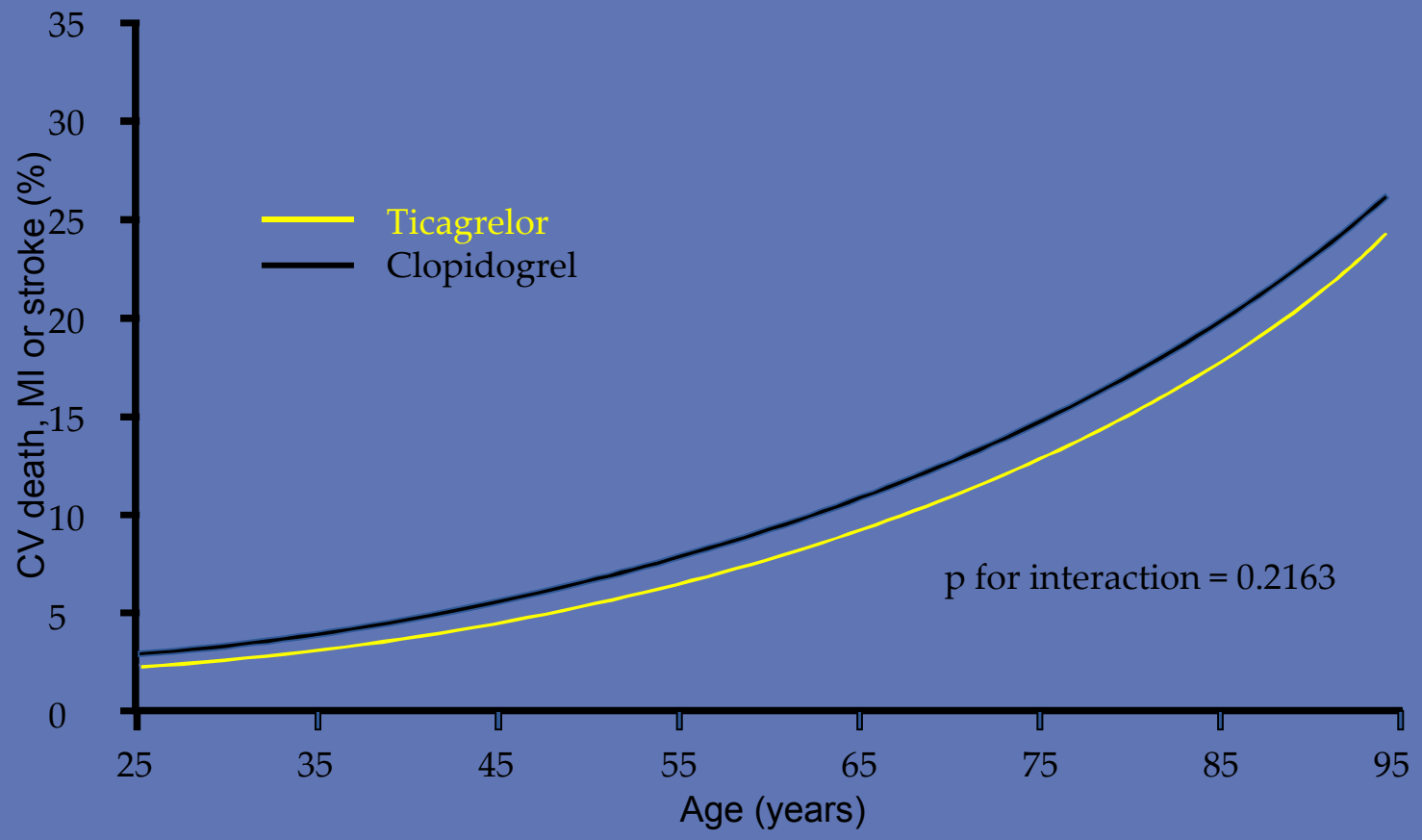
PLATO elderly patient subgroup analysis: Age, treatment and CV thrombotic outcomes



CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction.
Husted S, et al. J Am Coll Cardiol 2011;57:E1099.

PLATO elderly patient subgroup analysis:

Primary composite endpoint according to age

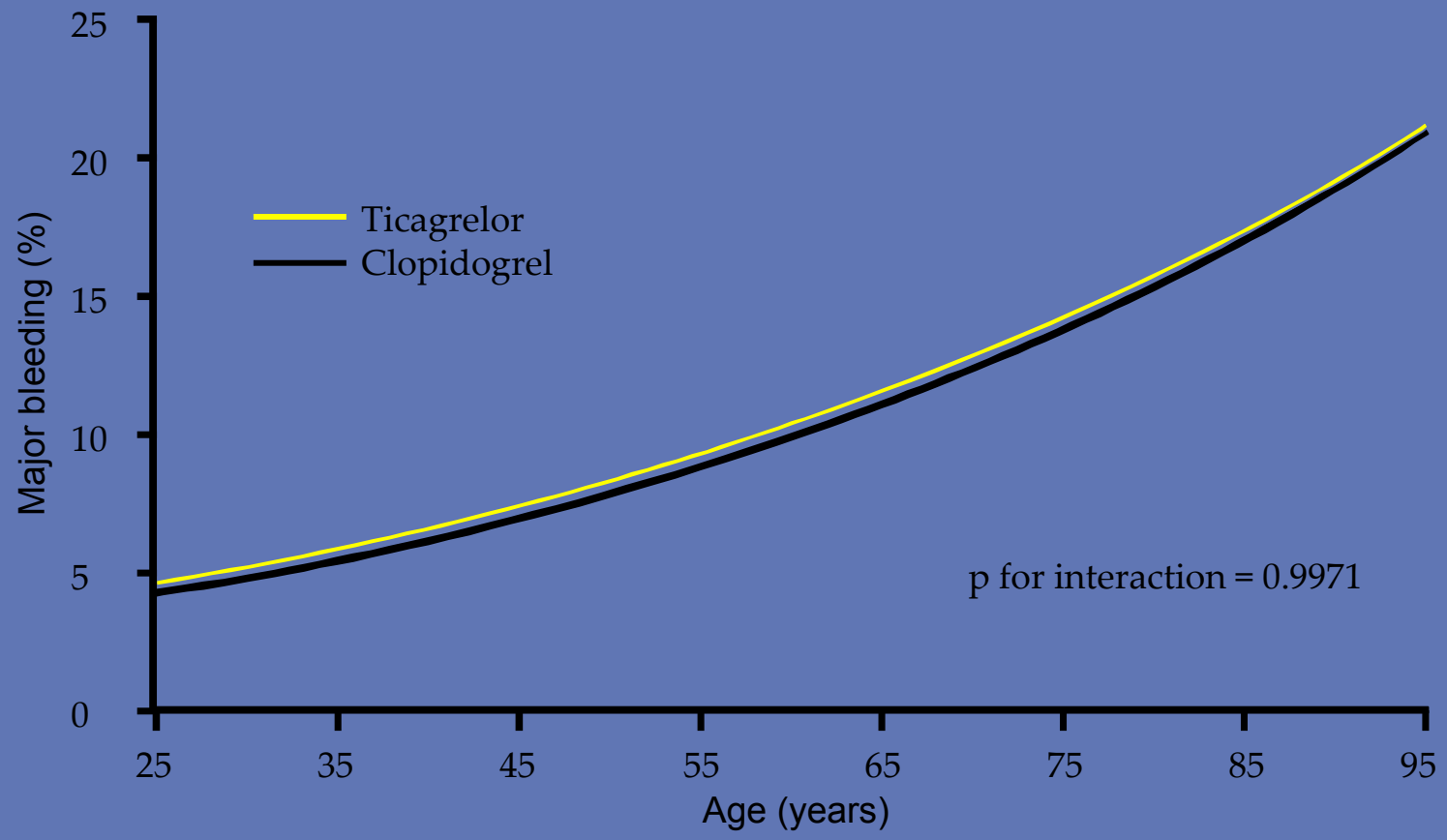


Primary endpoint benefit with ticagrelor was consistent with the overall PLATO trial results
No interaction between age and treatment was observed

CV, cardiovascular; MI, myocardial infarction.
Husted S, et al. J Am Coll Cardiol 2011;57:E1099;
Wallentin L, et al. N Engl J Med 2009;361:1045–1057.

PLATO elderly patient subgroup analysis:

Major bleeding according to age



Major bleeding occurred with similar frequency in the ticagrelor and clopidogrel groups as observed in the overall PLATO population

No interaction between age and treatment was observed

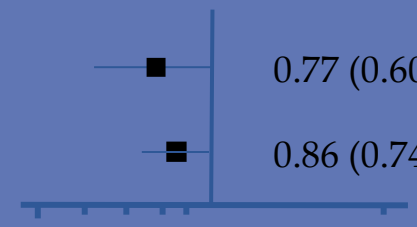
Husted S, et al. J Am Coll Cardiol 2011;57:E1099.

PLATO genetic substudy:

Primary efficacy endpoint – *CYP2C19*

- The primary composite outcome of CV death, MI or stroke up to 12 months was consistently reduced with ticagrelor versus clopidogrel in patients in each genotype group (p for interaction=0.46)
  - This difference was driven by consistent reductions in CV death and MI

	Ticagrelor		Clopidogrel			
	Patients with events, n (%)	K-M event rate, %	Patients with events, n (%)	K-M event rate, %	HR (95% CI)	p value
CV death, MI and stroke						
Any LOF	115 (8.3)	8.6	149 (10.7)	11.2	0.77 (0.60–0.99)	0.038
No LOF	296 (8.3)	8.8	332 (9.4)	10.0	0.86 (0.74–1.01)	0.061



0.46 (interaction)

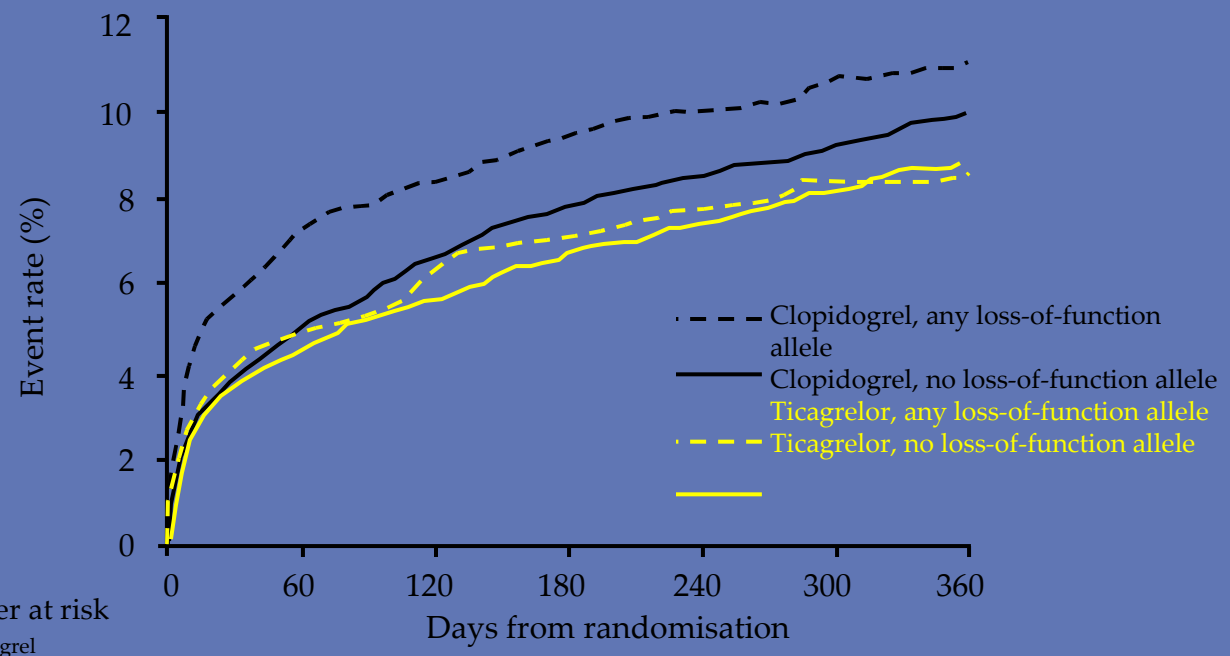
Ticagrelor better ← → Clopidogrel better

CI, confidence interval; CV, cardiovascular; HR, hazard ratio; LOF, loss-of-function; K-M, Kaplan–Meier; MI, myocardial infarction.
Wallentin L, et al. Lancet 2010;376:1320–1328.

PLATO genetic substudy:

Primary efficacy endpoint – CYP2C19 genotype

- The primary composite outcome of CV death, MI or stroke up to 12 months was consistently reduced with ticagrelor vs. clopidogrel in patients in each genotype group



Number at risk

Cloopidogrel							
Any LOF	1388	1275	1259	1226	1027	801	658
No LOF	3516	3321	3256	3186	2691	2123	1757
Ticagrelor							
Any LOF	1384	1305	1274	1250	1053	834	683
No LOF	3354	3352	3301	3222	2718	2127	1761

CV, cardiovascular; MI, myocradial infarction; LOF, loss-of-function.
Wallentin L, et al. Lancet 2010;376:1320–1328.

MODIFIED Recommendation

A loading dose of thienopyridine is recommended for STEMI patients for whom PCI is planned. Regimens should be one of the following:

Clopidogrel at least 300 mg to 600mg† should be given as early as possible before or at the time of primary or non-primary PCI.

Recommendations for the use of Thienopyridines

MODIFIED Recommendation

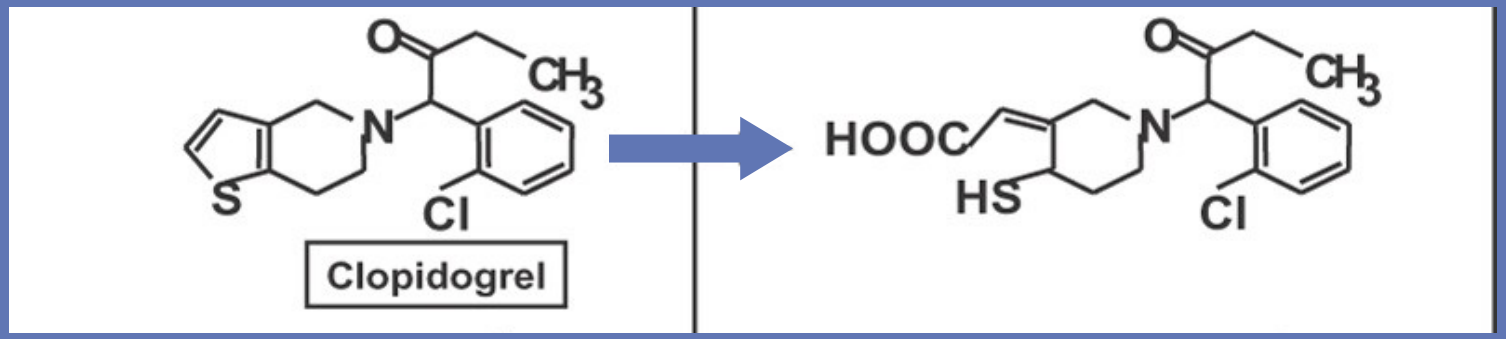
Prasugrel 60 mg should be given as soon as possible for primary PCI.

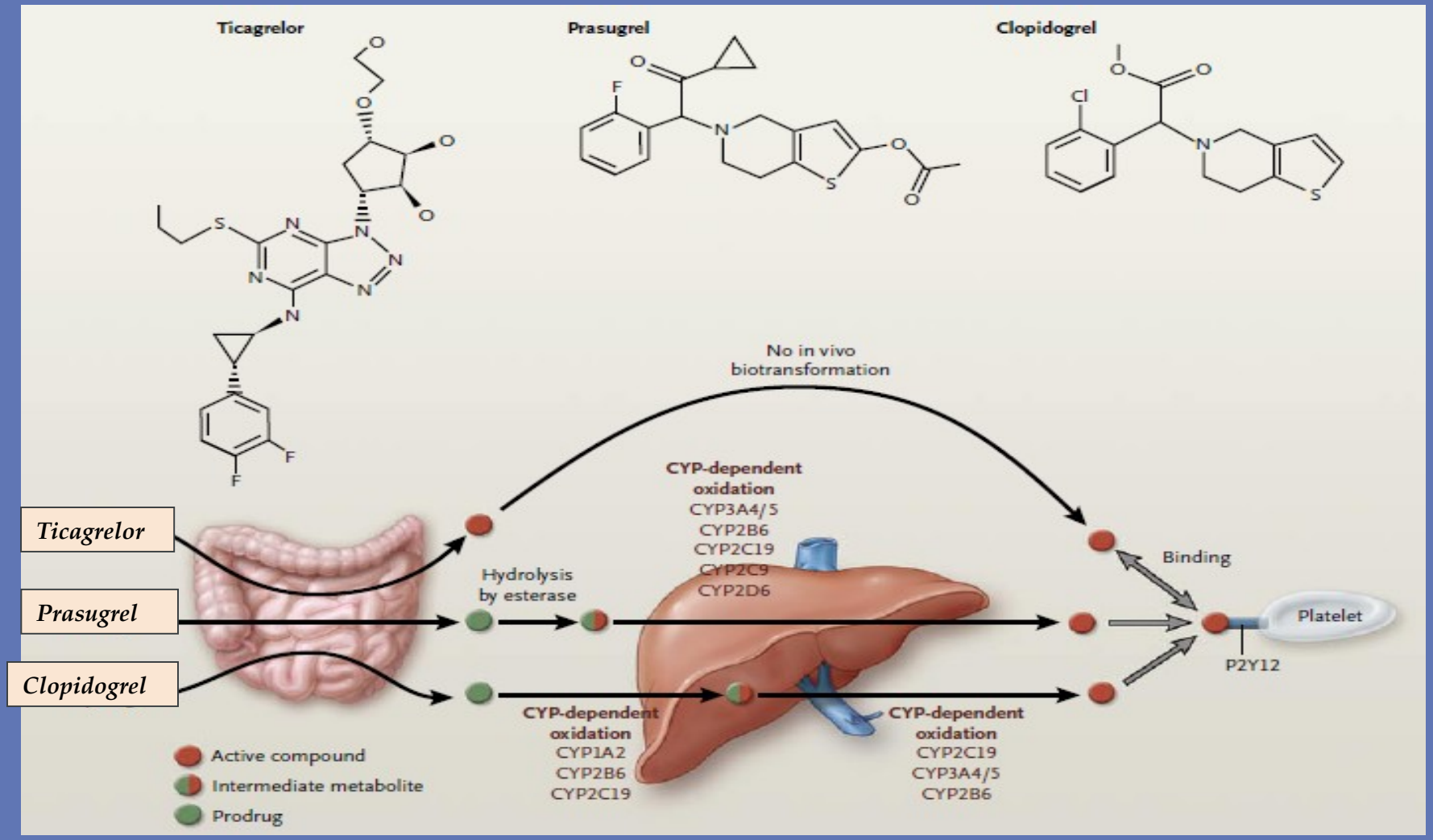
Налични антитромбоцитни медикаменти

DRUG	DRUG CLASS	CLINICAL CHARACTERISTICS
Aspirin	COX-1 inhibitor	PO, Irreversible binding
Ticlopidine	$P2Y_{12}$ (ADP) receptor antagonist	PO, Irreversible binding
Clopidogrel	$P2Y_{12}$ (ADP) receptor antagonist	PO, Irreversible binding
Prasugrel	$P2Y_{12}$ (ADP) receptor antagonist	PO, Irreversible binding
Ticagrelor	$P2Y_{12}$ (ADP) receptor antagonist	PO, Reversible binding
Cilostazol	PDE inhibitor; Increase cAMP	PO, Reversible inhibition
Dipyridamole	PDE inhibitor; Increase cAMP	PO, Reversible inhibition

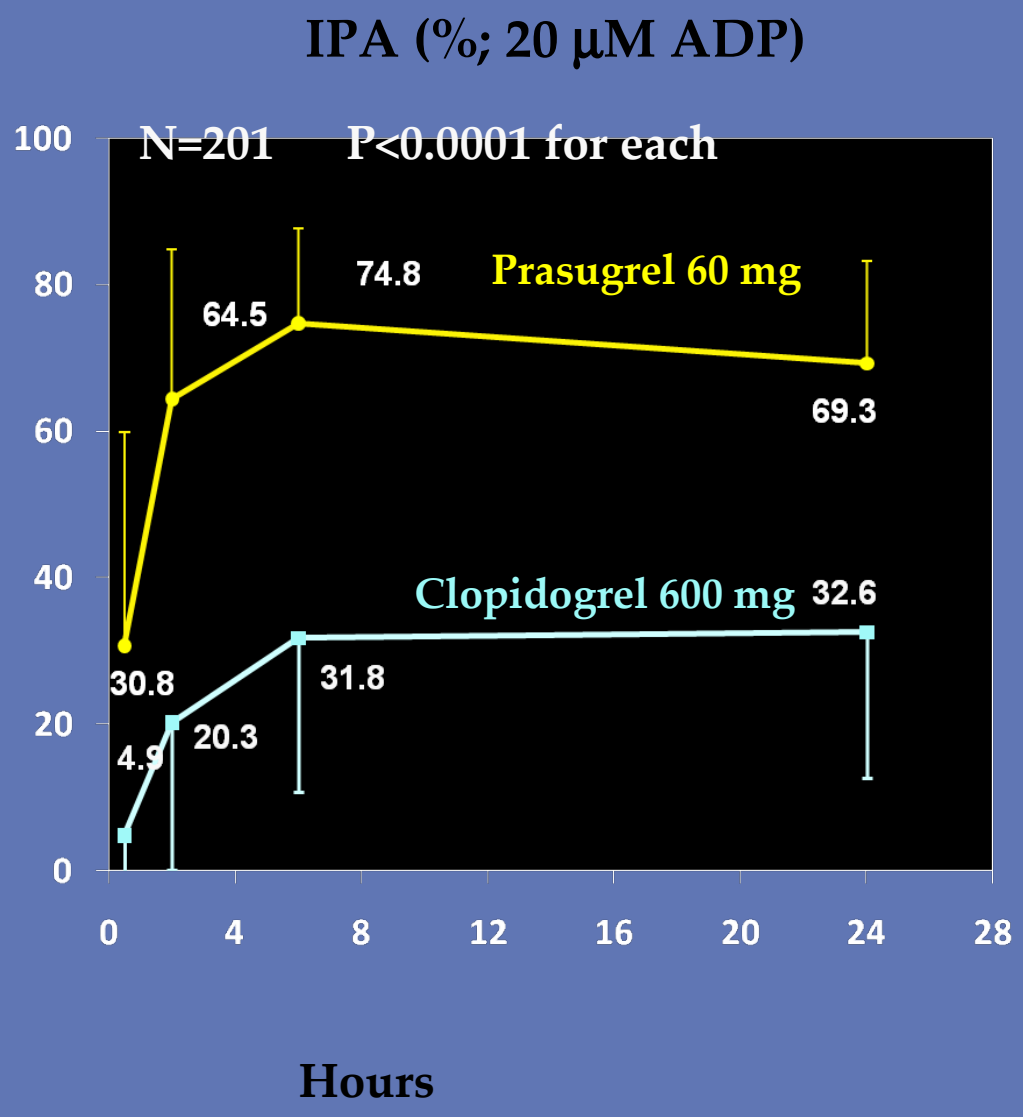
COX = cyclooxygenase; ADP = adenosine diphosphate; PDE = phosphodiesterase

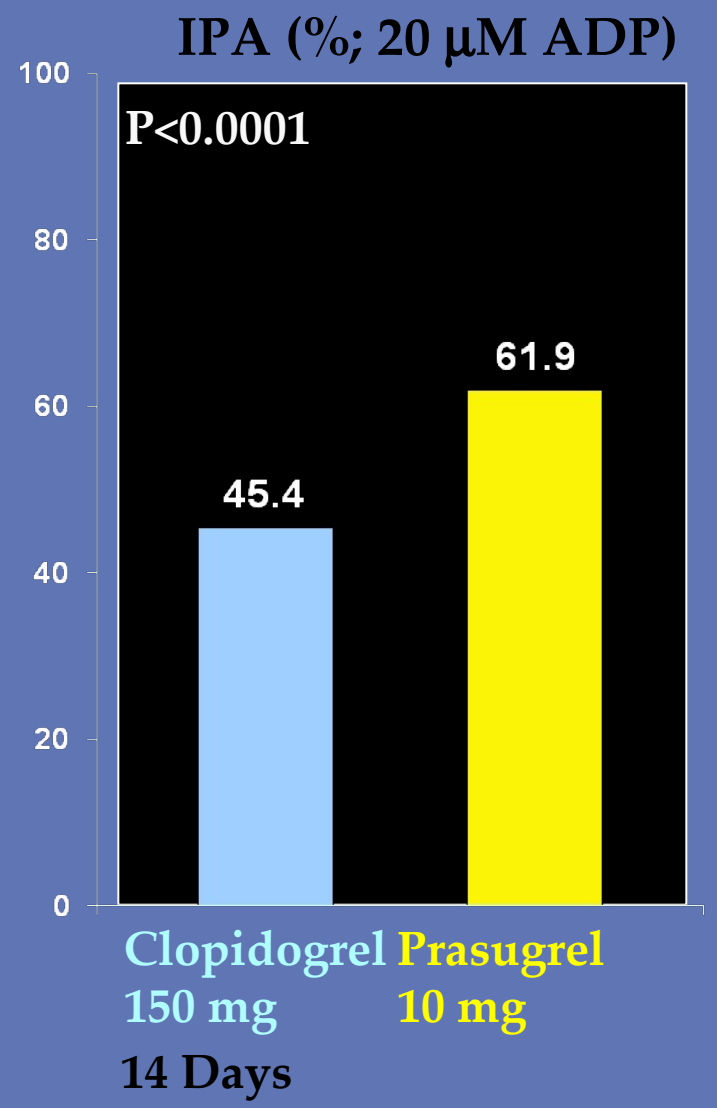
Тиенопиридините са prodrugs




Ticagrelor
Prasugrel
Clopidogrel
No in vivo biotransformation
CYP-dependent oxidation
CYP3A4/5
CYP2B6
CYP2C19
CYP2C9
CYP2D6
Hydrolysis by esterase
Binding
Platelet
P2Y12
CYP-dependent oxidation
CYP1A2
CYP2B6
CYP2C19
CYP-dependent oxidation
CYP2C19
CYP3A4/5
CYP2B6
Active compound
Intermediate metabolite
Prodrug

Comparison of prasugrel with higher dose clopidogrel





Wiviott et al Circ 2007

TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-thrombolysis In Myocardial Infarction (TRITON TIMI-38): study design

Acute coronary syndrome with scheduled PCI
All received aspirin (75-162 mg daily)
randomized within 72 hours (UA/NSTEMI) or 12 hours (STEMI)
of onset of symptoms
(N=13,608)

Prasugrel
Loading dose: 60 mg
Daily maintenance: 10 mg

Clopidogrel
Loading dose: 300 mg
Daily maintenance: 75 mg

6-15 months
Median duration 14.5 months

Primary endpoint:
- Composite of death from CV causes, nonfatal MI or nonfatal stroke

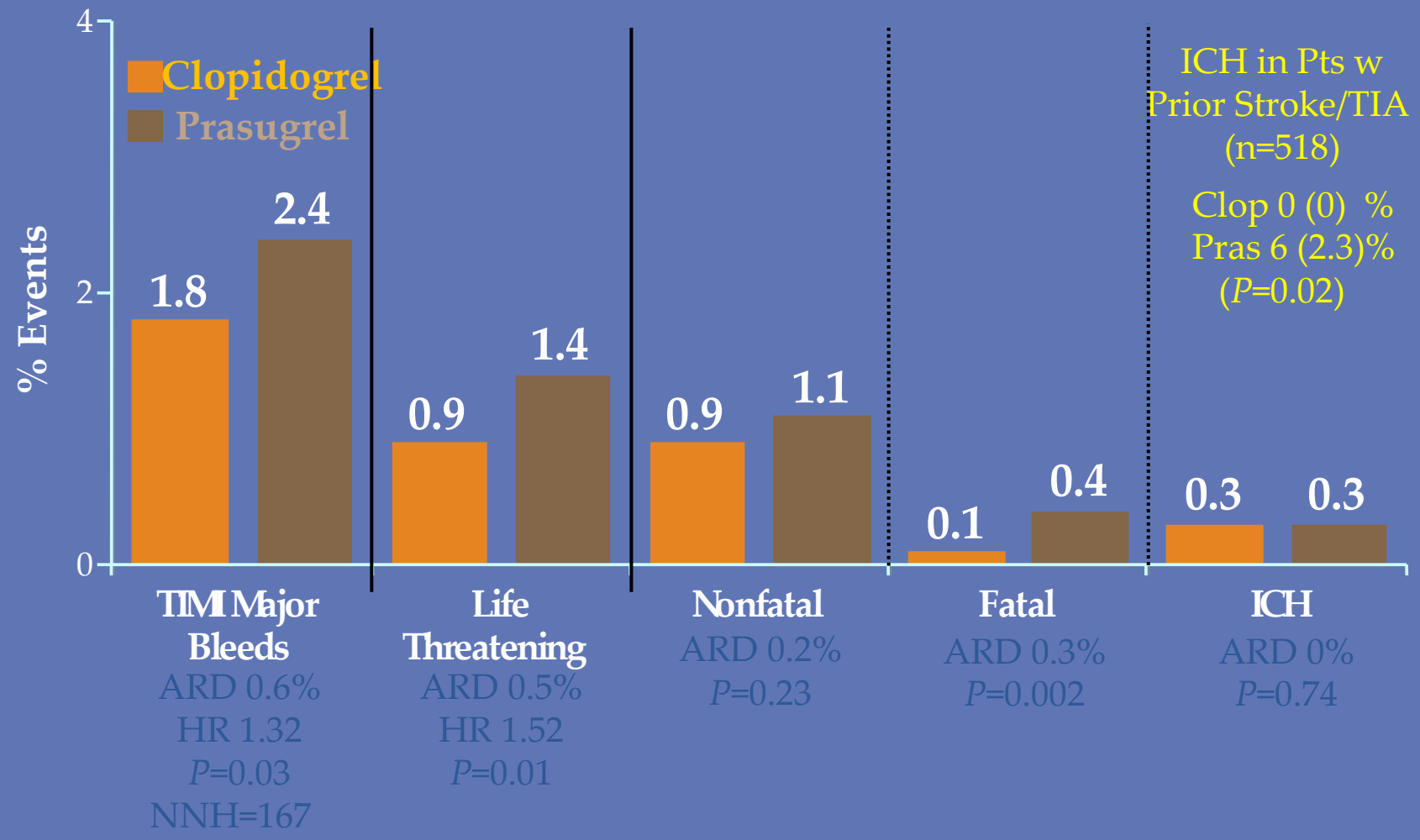
Key secondary endpoints:
- Stent thrombosis
- Composite of death from CV causes, nonfatal MI, nonfatal stroke, or rehospitalization due to a cardiac ischemic event

Key safety endpoints:
- TIMI major bleeding not related to CABG
- NonCABG-related TIMI life-threatening bleeding
- TIMI Major or Minor bleeding

Wiviott SD, et al. *N Engl J Med.* 2007;357:2001-2015.

TRITON TIMI-38

Bleeding Events Safety Cohort (n=13,457)



Wiviott SD et al. *N Engl J Med.* 2007;357:2001-2015.

Study Goals

1. To test the hypothesis that higher and less variable IPA prevents clinical ischemic events.
2. To evaluate the safety of a regimen that produces higher IPA.

These goals were achieved by evaluating the efficacy and safety of prasugrel compared to clopidogrel in mod/high risk patients with ACS undergoing PCI on a background of ASA.

Study Design

ACS (STEMI or UA/NSTEMI) & Planned PCI

ASA ↓ **N= 13,600**

Double-blind

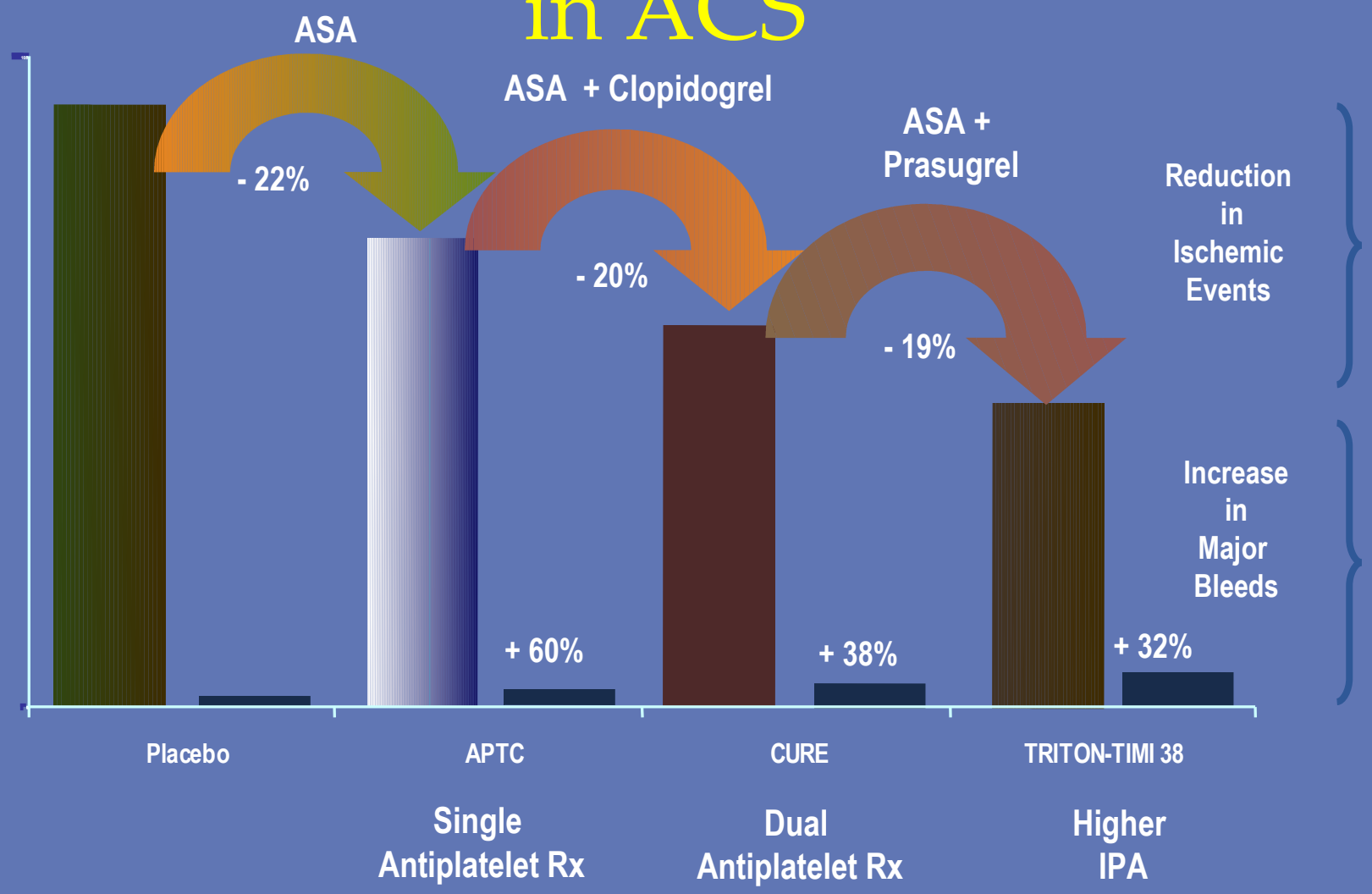
CLOPIDOGREL
300 mg LD/ 75 mg MD

PRASUGREL
60 mg LD/ 10 mg MD

Median duration of therapy - 12 months

1º endpoint: CV death, MI, Stroke
2º endpoints: CV death, MI, Stroke, Rehosp-Rec Isch CV death, MI, UTVR
Stent Thrombosis (ARC definite/prob.)
Safety endpoints: TIMI major bleeds, Life-threatening bleeds
Key Substudies: Pharmacokinetic, Genomic

Evolution of Antiplatelet Therapy in ACS



APTC. *BMJ.* 1994;308:81-106.
Mehta SR et al. *Lancet.* 2001;358:527-533.

Bleeding is a Major Issue of Concern

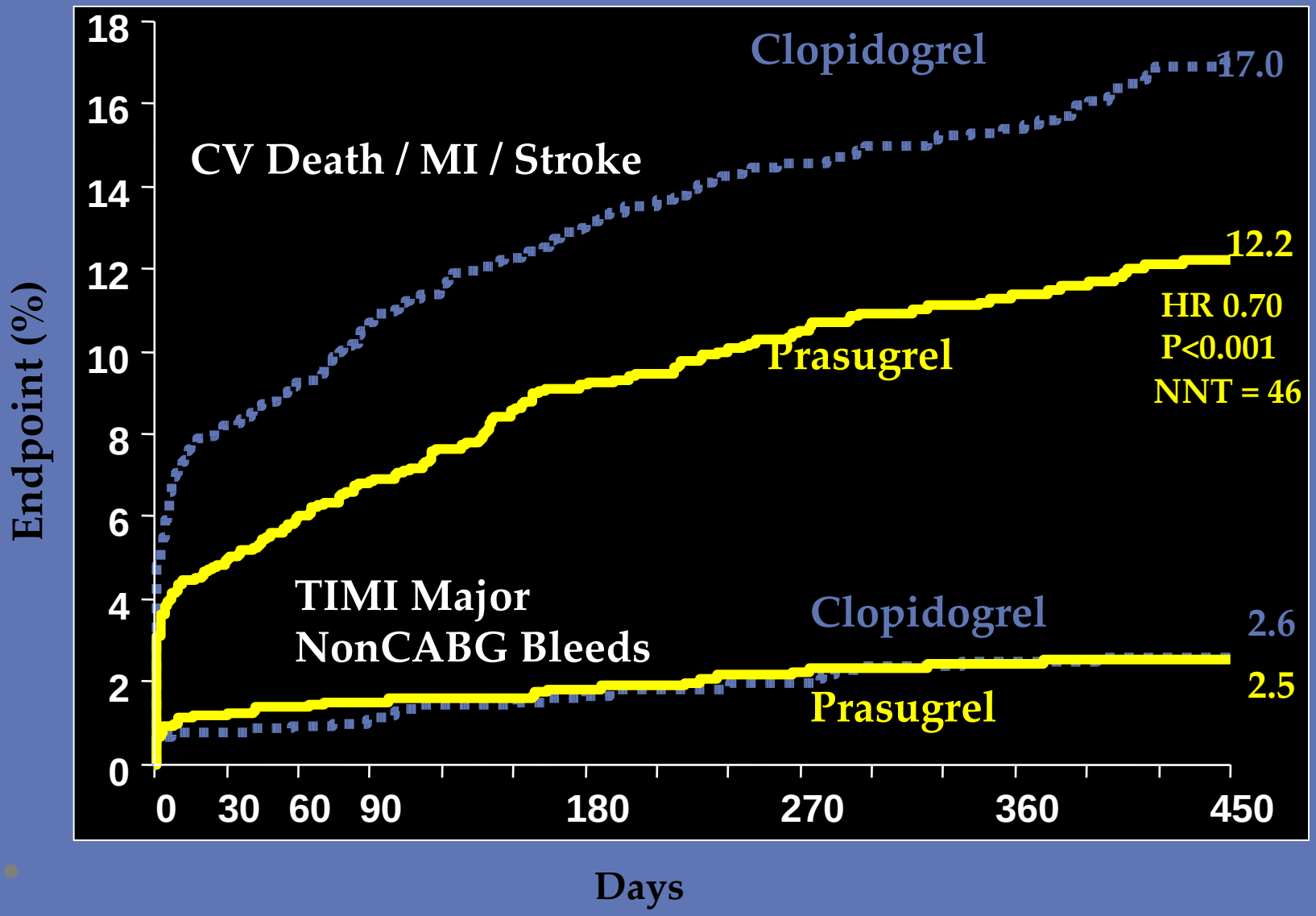
- Bleeding carries a high risk of death, MI, and stroke
- Rate of major bleeding is as high as the rate of death at the acute phase of NSTE-ACS
- Prevention of bleeding is equally as important as prevention of ischemic events and results in a significant risk reduction for death, MI, and stroke
- Risk stratification for bleeding should be part of the decision-making process

Risks for Ischemic and Bleeding Events

- High risk for ischemic events
  - age
  - diabetes
  - ST segment depression in anterior leads
  - elevated troponin
- High risk for bleeding complications
  - age
  - past history of hemorrhagic stroke
  - BMI: 19.2kg/m^2

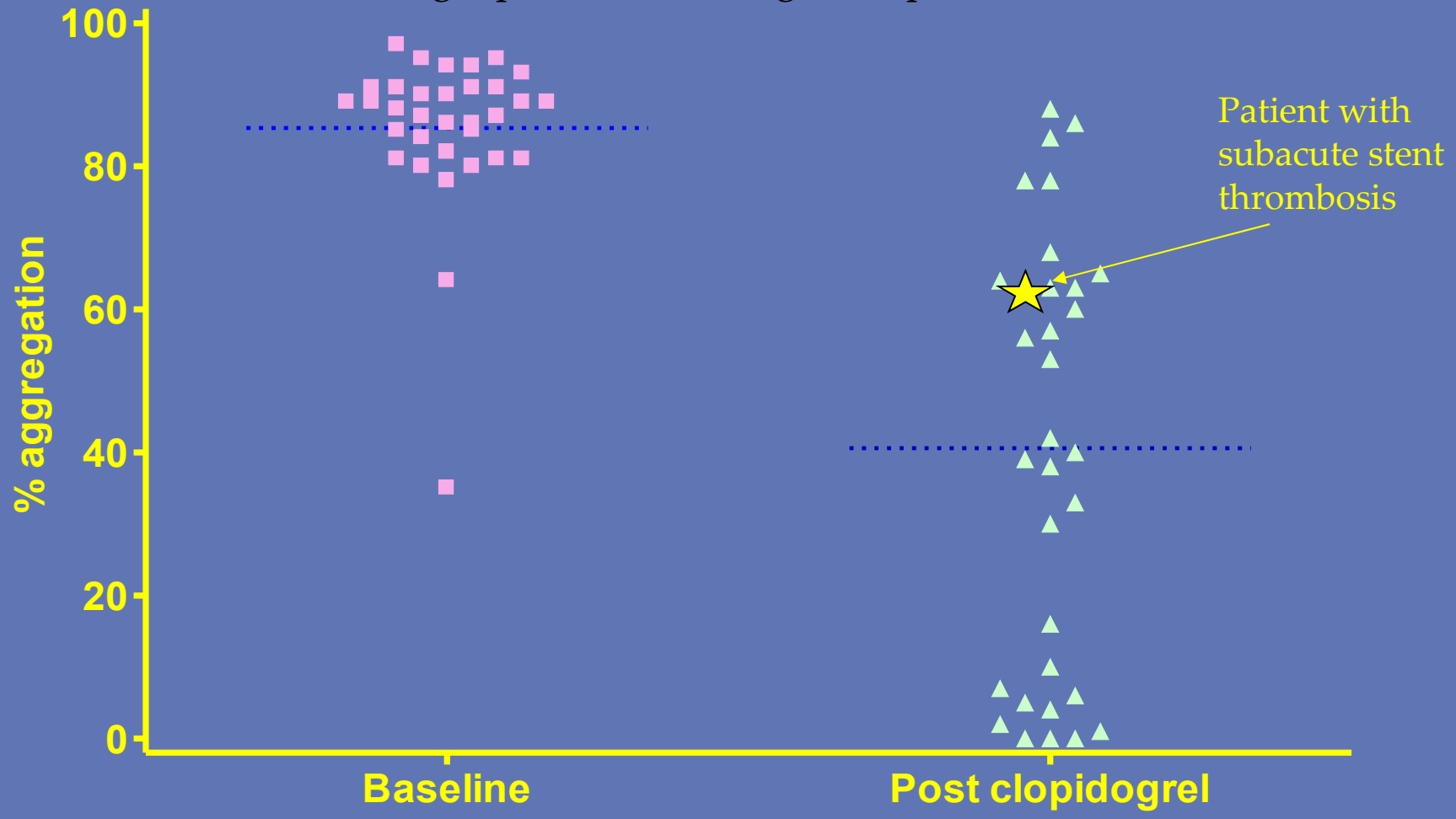
TRITON Diabetic Subgroup

N=3146



Platelet aggregation before and 4 hours after clopidogrel 600 mg in patients undergoing PCI

Whole blood single platelet counting in response to ADP 10 uM



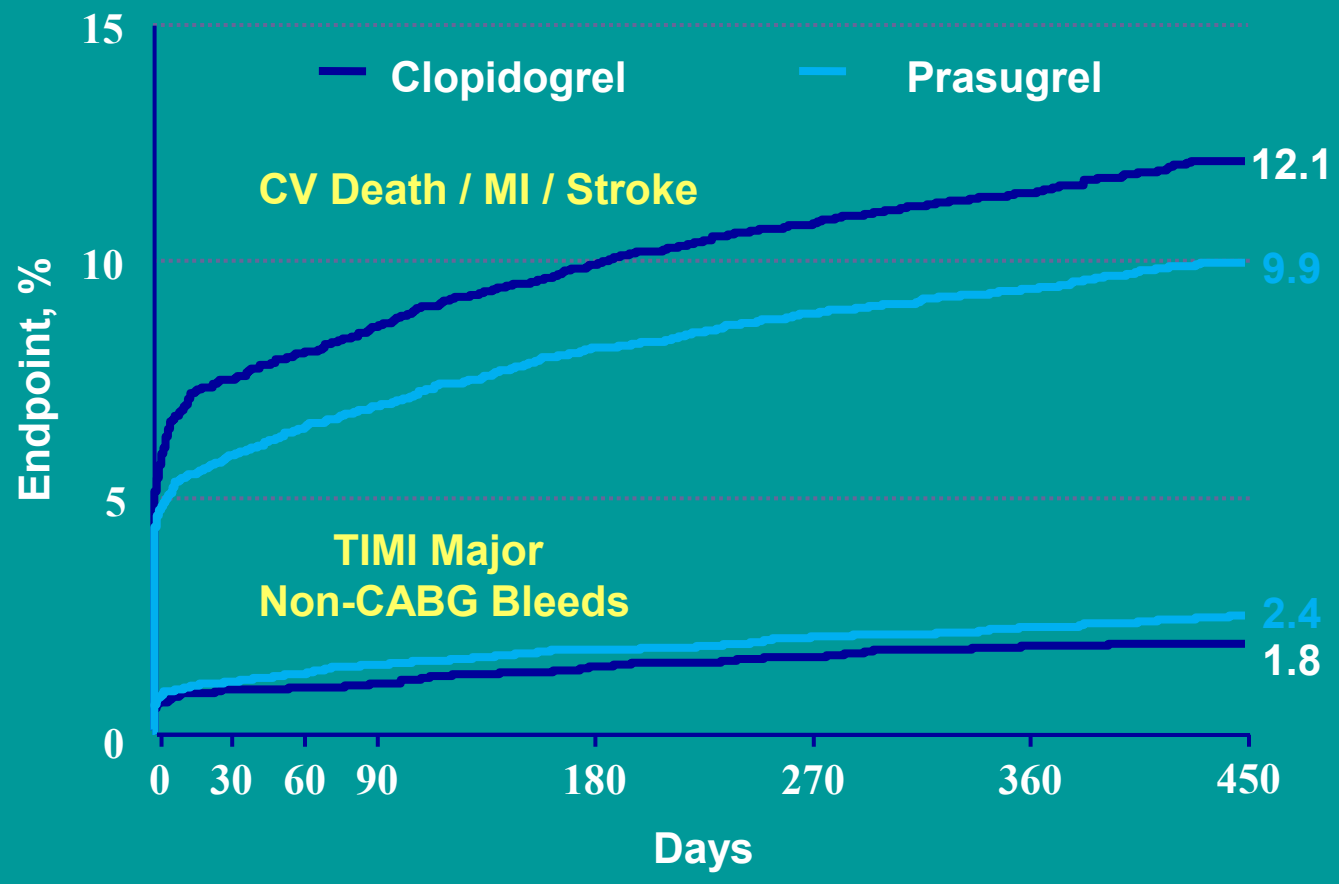
Smith SMG et al. *Platelets* 2006; 17: 250-258

TRITON TIMI-38

Prasugrel vs Clopidogrel

TRITON-TIMI 38:

Primary Endpoint: CV Death / MI / Stroke; TIMI Non-CABG Bleeding



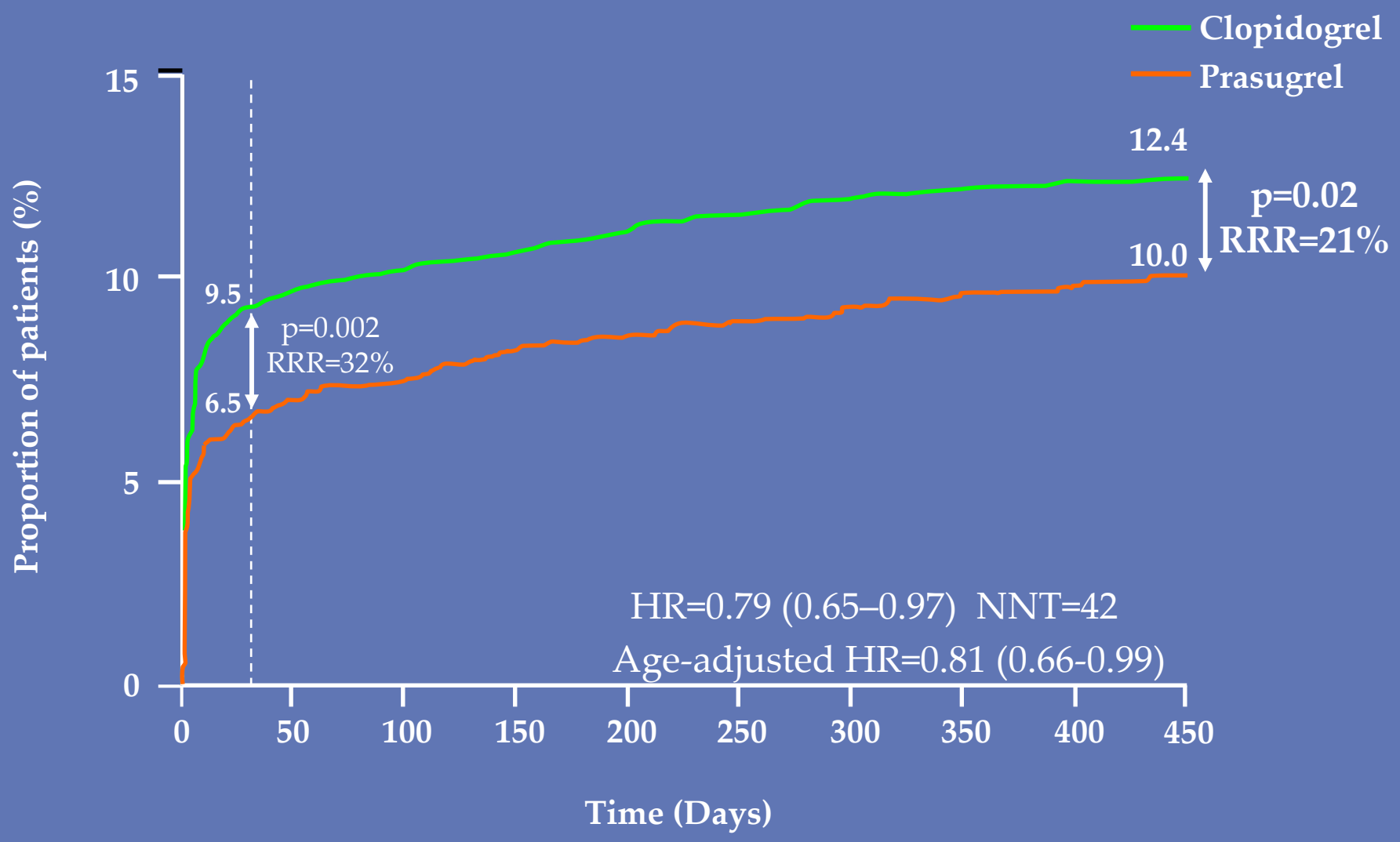
↓138 Events
HR 0.81
(95% CI, 0.73-0.90)
P<0.001
NNT=46

↑35 Events
HR 1.32
(95% CI, 1.03-1.68)
P=0.03
NNH=167

CABG, coronary artery bypass graft; NNH, number needed to harm; NNT, number needed to treat; TRITON-TIMI 38, Trial to Assess Improvement in Therapeutic Outcomes by Optimising Platelet Inhibition with Prasugrel−Thrombolysis in Myocardial Infarction 38.
Wiviott SD, et al. *N Engl J Med*. 2007;357:2001-15.

TRITON STEMI cohort

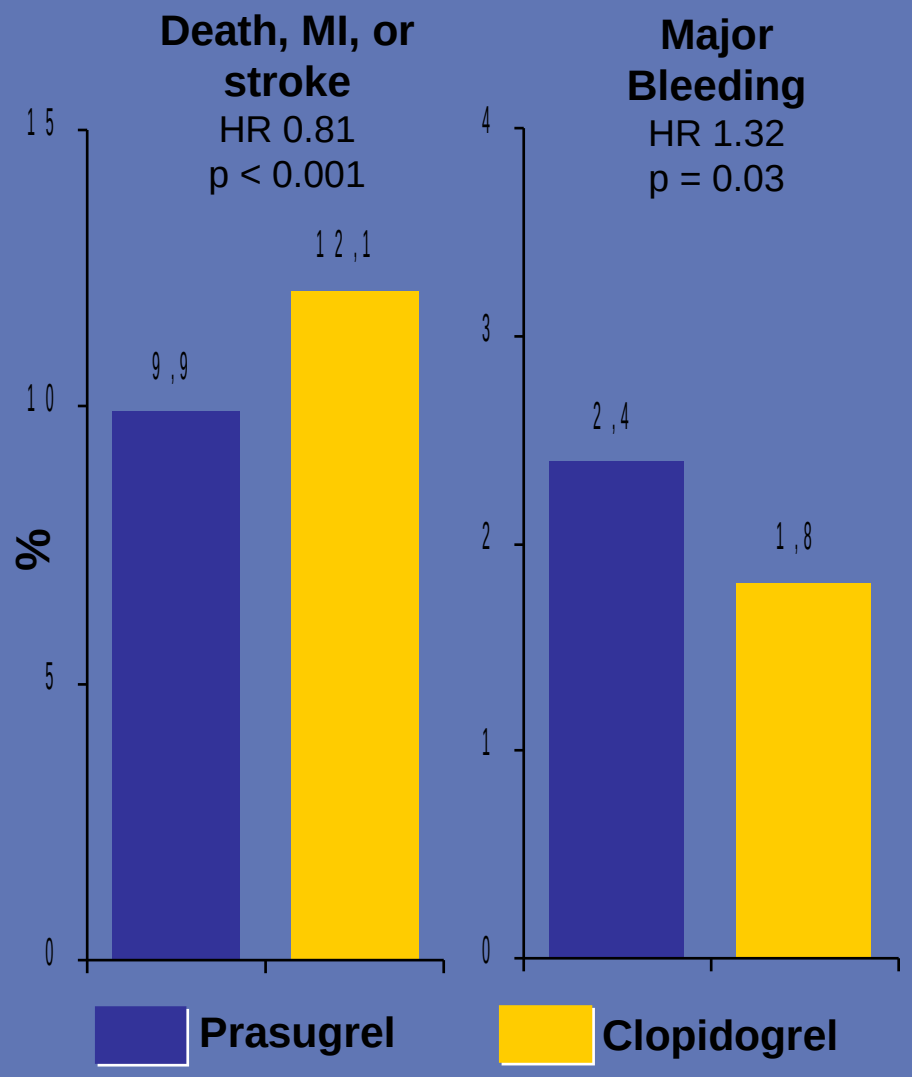
Primary EP (CV death, MI and stroke at 15 months)



Montalescot et al. ESC 2008

TRITON-TIMI 38

Trial Design: TRITON-TIMI 38 was a randomized, double-blind trial of prasugrel (n = 6,813) compared to clopidogrel (n = 6,795) in patients undergoing planned PCI for an acute coronary syndrome (ACS). Primary endpoint was CV death, MI or stroke with a median follow-up of 14.5 months.



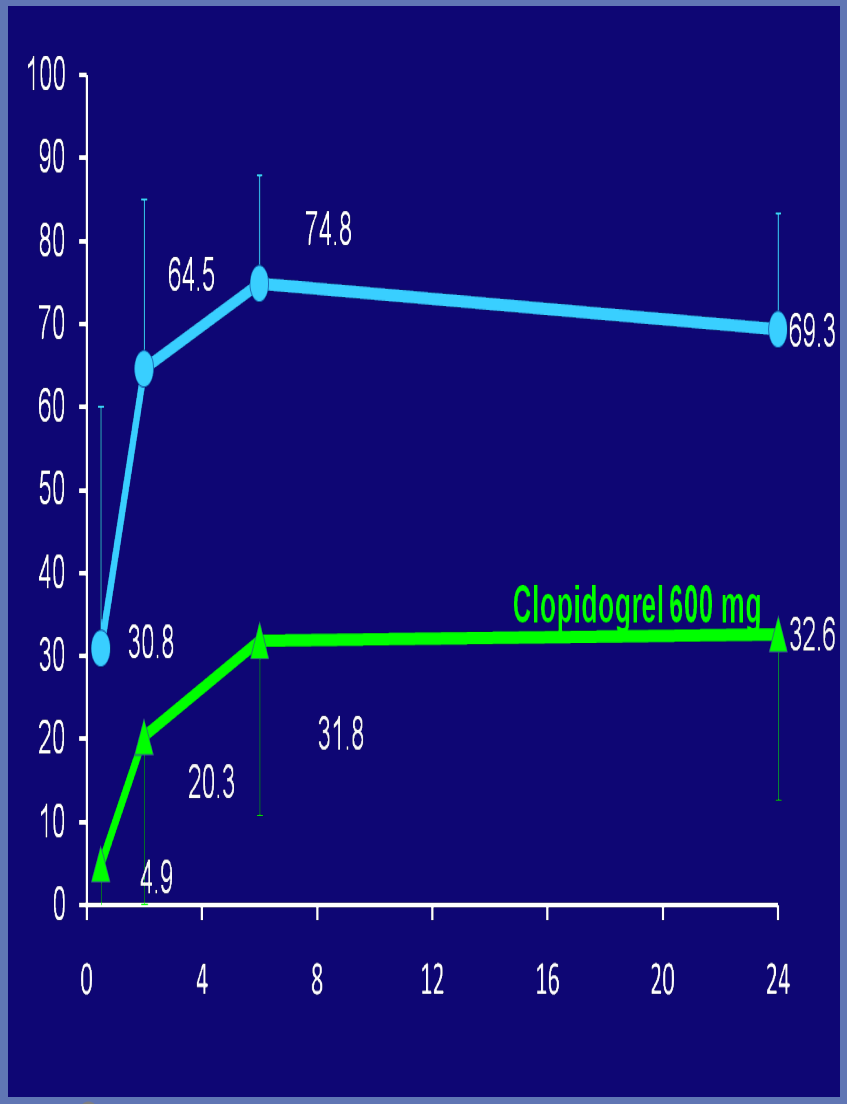
Results

- CV death, MI or stroke ↓with prasugrel vs clopidogrel (Figure)
- Stent thrombosis also ↓with prasugrel (1.1% vs. 2.4%, HR 0.48, p < 0.001)
- TIMI major non-CABG bleeding ↑with prasugrel than clopidogrel (Figure),
- Net clinical benefit endpoint (primary+bleeding) favored prasugrel (12.2% vs. 13.9%, HR 0.87, p = 0.004)

Conclusions

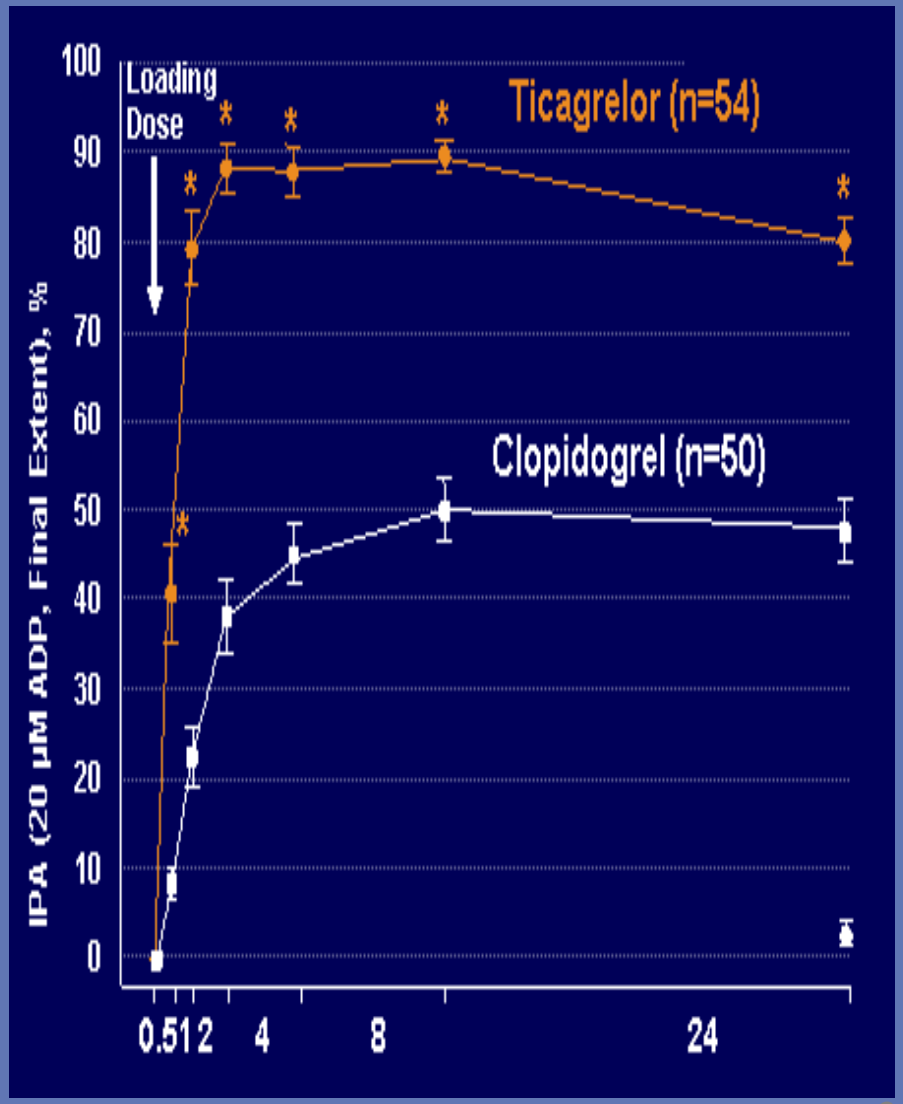
- Among patients undergoing planned PCI for ACS, treatment with novel thienopyridine, prasugrel, was associated with reduction in composite of CV death, MI or stroke compared with clopidogrel
- As would be expected with greater platelet inhibition, bleeding events were significantly higher in prasugrel group, including life-threatening and fatal bleeding
- Despite this increase, net clinical benefit endpoint incorporating mortality, ischemic events, and major bleeding events, favored prasugrel

PRINCIPLE-TIMI44



(Wiviott SD et al. *Circulation* 2007)

ONSET-OFFSET



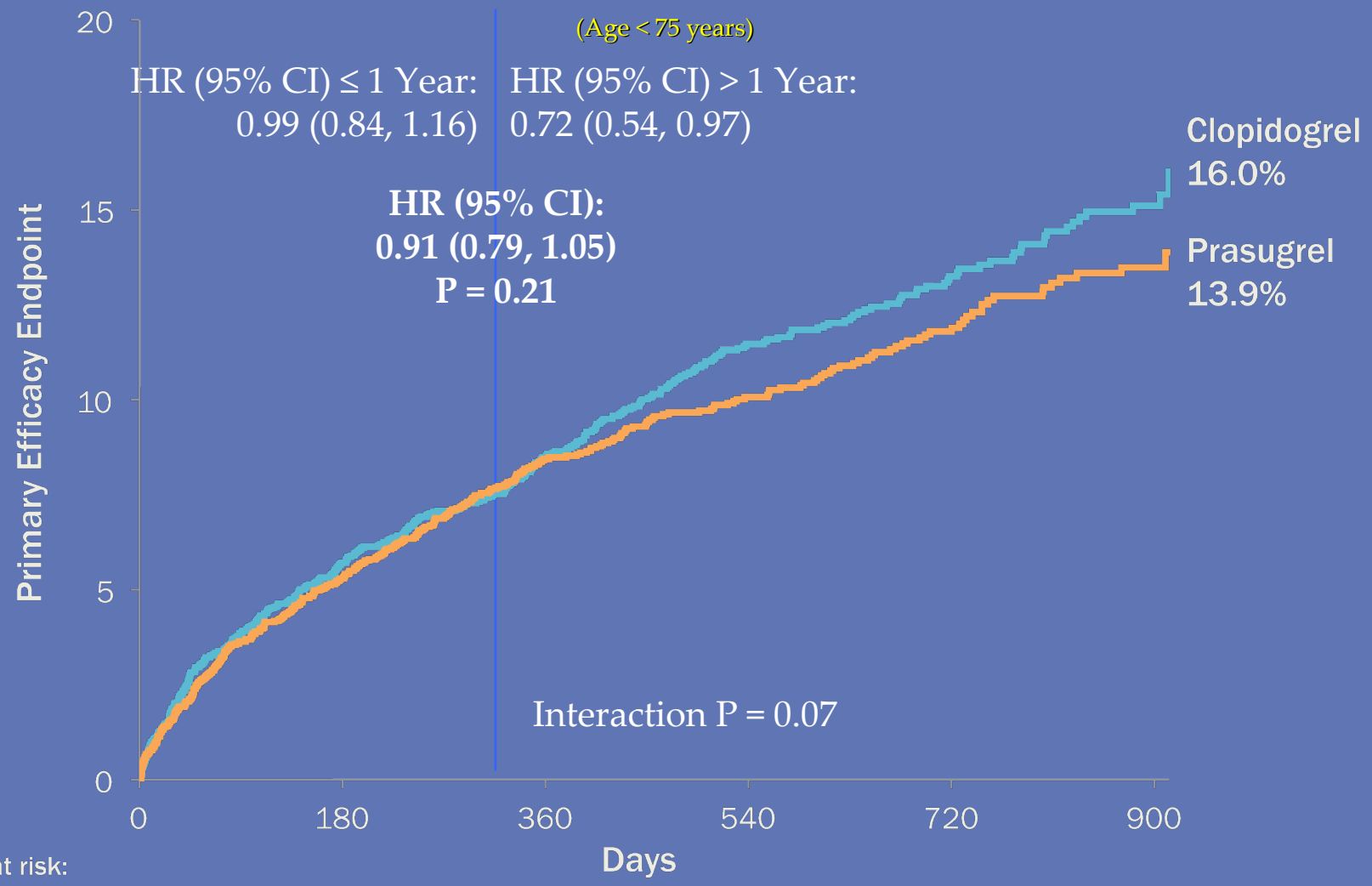
(Gurbel PA et al. *Circulation* 2009)

Ticagrelor mechanism of action

- Ticagrelor is a cyclo-pentyl-triazolo-pyrimidine (CPTP)[Husted 2006:A]
- Ticagrelor is direct acting[Husted 2006:A]
  - Not a prodrug
  - Does not require metabolic activation
- Ticagrelor is the first reversibly binding, oral ADP receptor antagonist[Husted 2006:A]
- Rapid onset of inhibitory effect on the $P2Y_{12}$ receptor[Husted 2006:B]
- Consistent inhibition of platelet aggregation[Gurbel 2009-1:A]

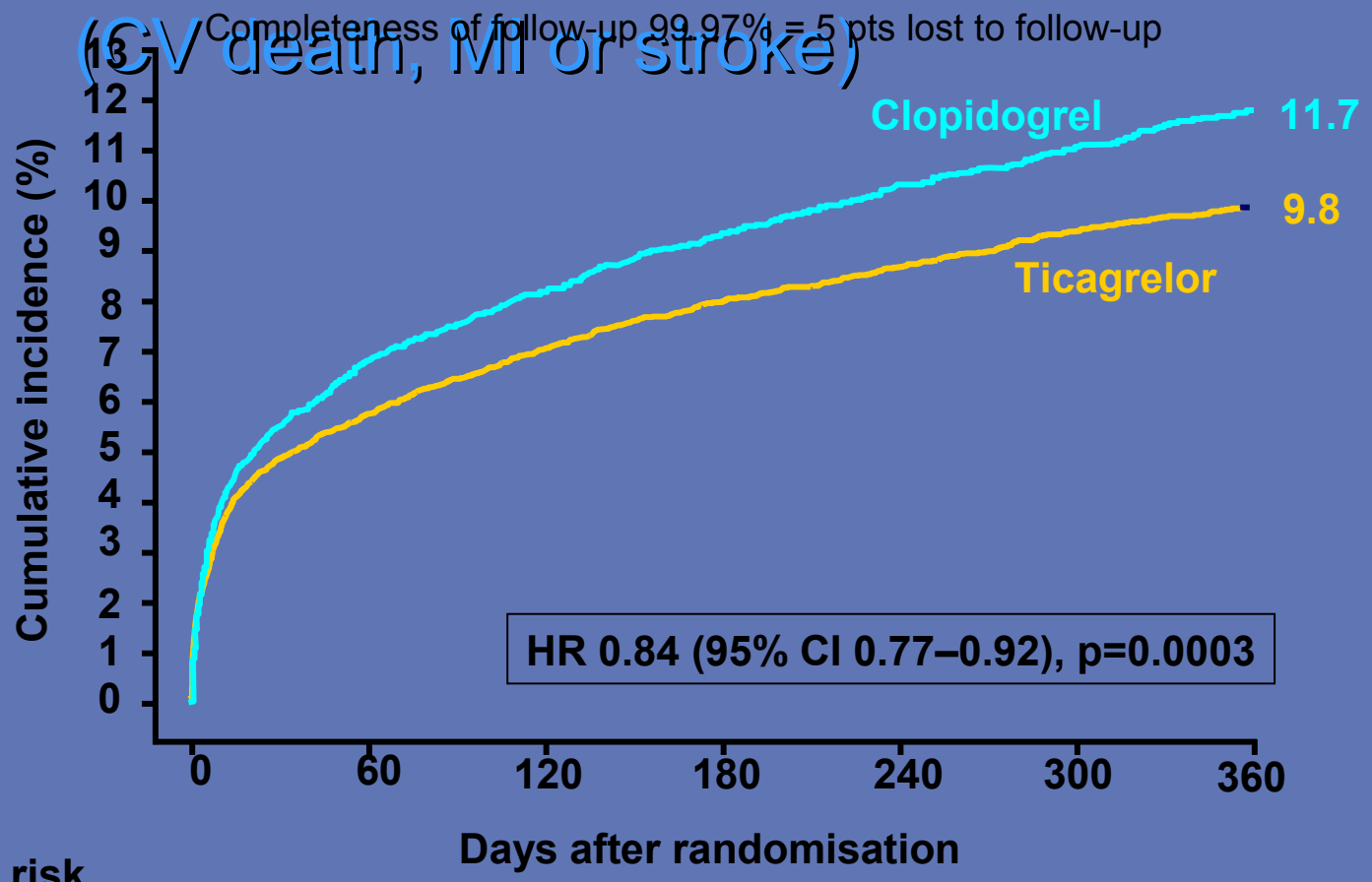
Husted S, et al. *Eur Heart J*. 2006;27:1038-1047; Gurbel PA, et al. *Expert Opin Drug Metab Toxicol*. 2009;5(8):989-1004-1.

Primary Efficacy Endpoint to 30 Months



No. at risk:						
Prasugrel:	3620	3248	2359	1611	953	389
Clopidogrel:	3623	3244	2390	1596	946	399

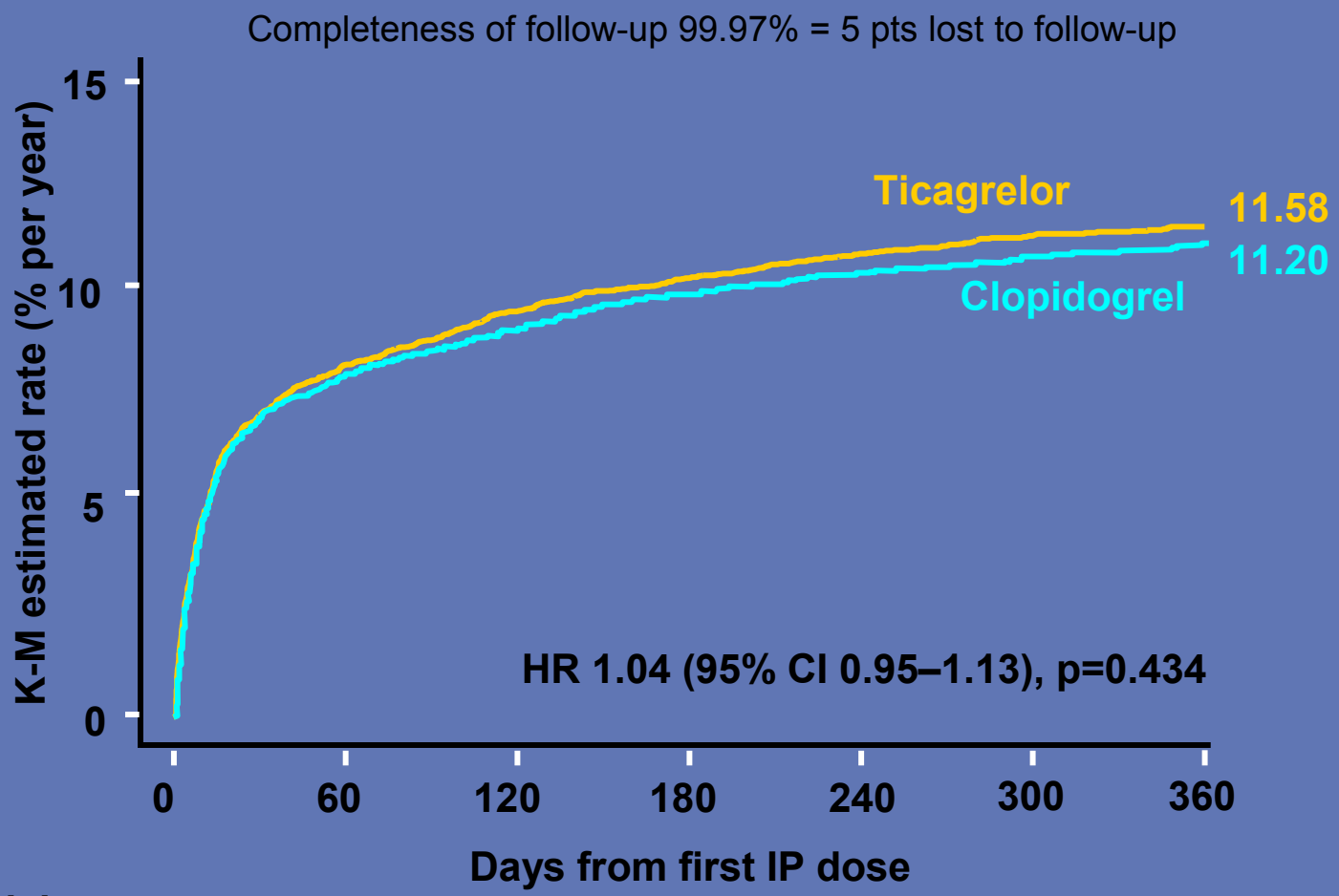
PLATO: Time to first primary efficacy event (CV death, MI or stroke)



No. at risk							
Ticagrelor	9,333	8,628	8,460	8,219	6,743	5,161	4,147
Clopidogrel	9,291	8,521	8,362	8,124	6,743	5,096	4,047

Wallentin, L Presented at ESC Congress 2009 Barcelona Spain

PLATO Time to Major Bleeding - Primary Safety Event



No. at risk							
Ticagrelor	9,235	7,246	6,826	6,545	5,129	3,783	3,433
Clopidogrel	9,186	7,305	6,930	6,670	5,209	3,841	3,479

Wallentin, L Presented at ESC 2009 Barcelona Spain

PLATO – дизайн на проучването

НА/ИМ без ST-E (умерен към висок риск) ИМ със ST-E (при първична ПКИ)
Всички на ASA; лекувани с клопидогрел или не;
Рандомизирани до 24 часа от включващия инцидент
(N=18,624)

Клопидогрел
Без натоварваща доза при предшестващо лечение;
Нелекувани – стандартна натоварваща доза 300 mg, след това поддържаща доза 75 mg веднъж дневно;
(преди ПКИ се допускаха допълнително 300 mg)

Тикагрелор
Натоварваща доза 180 mg, след това поддържаща доза 90 mg два пъти дневно;
(допълнително 90 mg преди ПКИ)

6–12 месеца прием

Първичен проследяван показател:
- **СС смърт + ИМ + инсулт**

Ключови вторични показатели:
- **CV смърт + ИМ + инсулт при планирани за инвазивно лечение пациенти**
- **Обща смъртност + ИМ + инсулт**
- **СС смърт + ИМ + инсулт + рецидивираща исхемия + ПИК + артериална тромбоза**
- **само ИМ / Само СС смърт / Само инсулт / Обща смъртност**

Първичен показател на безопасността:
- **Общо значими кръвоизливи**

СС = сърдечно-съдов; НА = нестабилна ангина; ПКИ = перкутанна коронарна интервенция; ПИК = преходна исхемична криза; ASA = ацетилсалицилова киселина;

James S, et al. *Am Heart J.* 2009;157:599-605.

P2Y21 in ACS: Conclusions

- Thrombosis key mechanism in large variety of cardiovascular diseases
- Multiple choices now available for antithrombotics in management of CAD
- Potent P2Y12 receptor inhibition is a central part of ACS treatment
- Challenges with increasing patient complexity along with understanding nuances of various combinations and interface with care strategies
- Evidence based therapy improves outcomes

Five key features of optimal platelet inhibition

- Short delay to reperfusion in STE- and NSTE-ACS
- Anti-thrombotic agents with fast and predictable action
- Favourable balance between efficacy and bleeding risk
- Positive net clinical benefit across subgroups
- Reliable early benefit that is sustained during long-term treatment

Trial Schema

N ~ 21,000

Stable pts with history of MI 1-3 yrs prior + ≥1 additional atherothrombosis risk factor*

** Age ≥65 yrs, diabetes, 2nd prior MI, multivessel CAD, or chronic non-end stage renal dysfunction*

RANDOMIZE DOUBLE BLIND

Planned treatment with ASA 75 – 150 mg & Standard background care

Ticagrelor 90 mg bid

Ticagrelor 60 mg bid

Placebo

Follow-up Visits Q4 mos for 1st yr, then Q6 mos

Min 12 mos and median 26 mos follow-up
Event-driven trial

Primary Efficacy Endpoint: CV Death, MI, or Stroke
Primary Safety Endpoint: TIMI Major Bleeding

GLOBAL LEADERS

All-Comers PCI Population
ACS and Elective/Stable patients
(n=16,000)

Biolimus-eluting stent (BES)
BioMatrix Flex ™

1:1 Randomization, Open-Label Design

ASA Ticagrelor

Study Treatment Strategy

1-month
ASA + Ticagrelor

23-months monotherapy Ticagrelor

Reference Treatment Strategy

12-months DAPT
ACS pts (ASA + Ticagrelor)
Elective pts (ASA + C

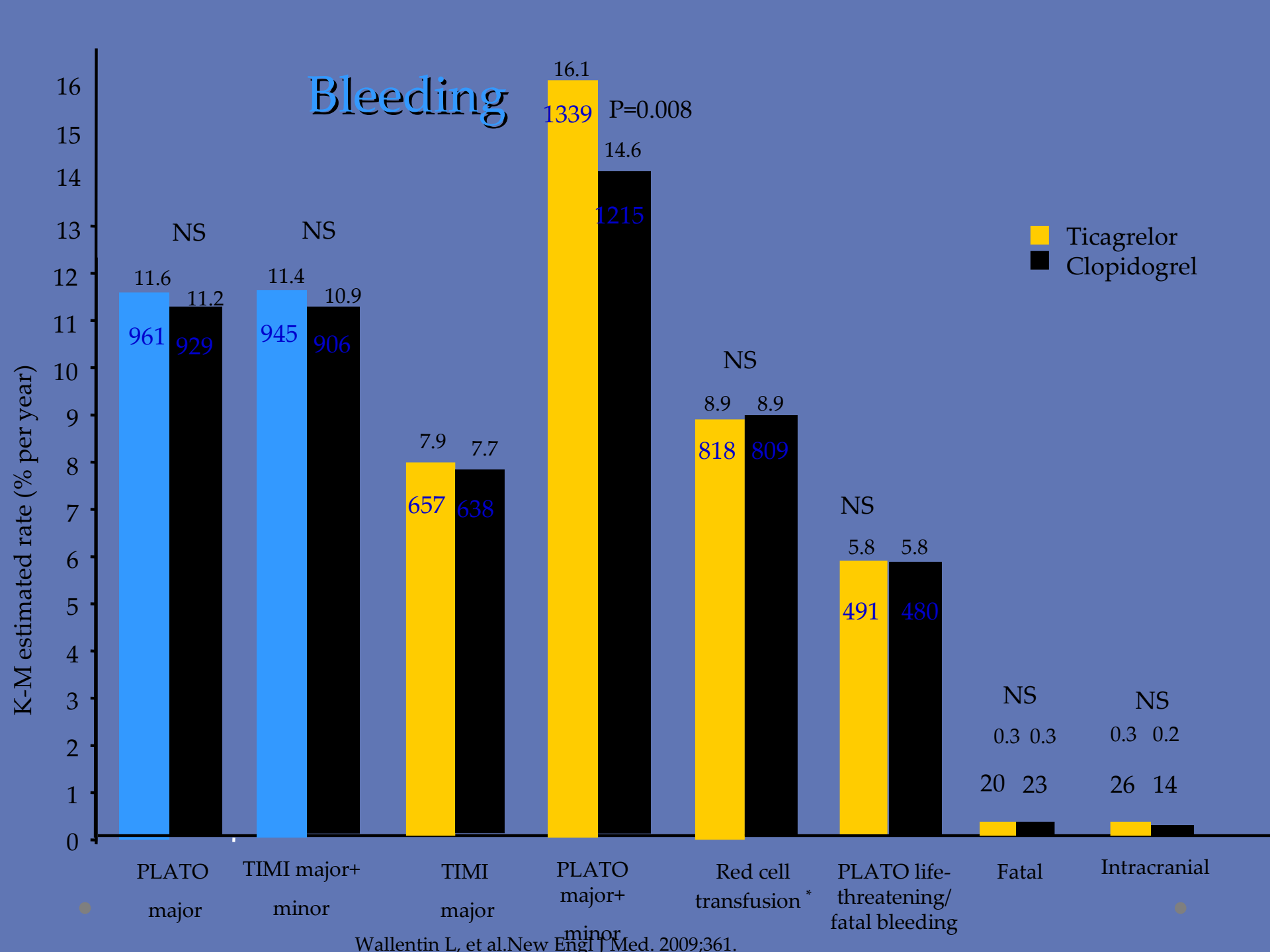
12-months monotherapy ASA

ASA Ticagrelor Clopidogrel

[Not allowed in elective pts]

[Only in elective pts]

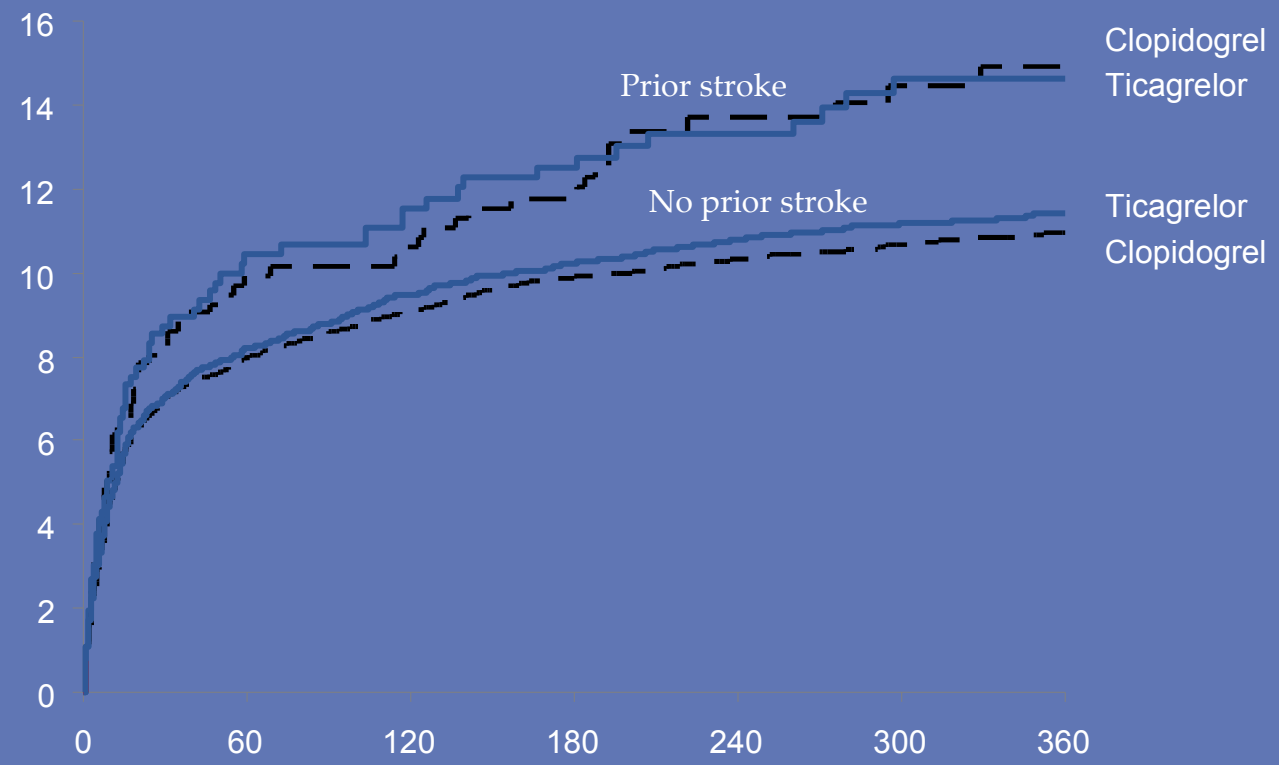
<u>Primary Endpoint</u>
Study treatment strategy <u>superior</u> to reference treatment strategy on cumulative 2 year composite of all cause mortality and new Q-wave MI



Wallentin L, et al.New Engl J Med. 2009;361.

PLATO Stroke

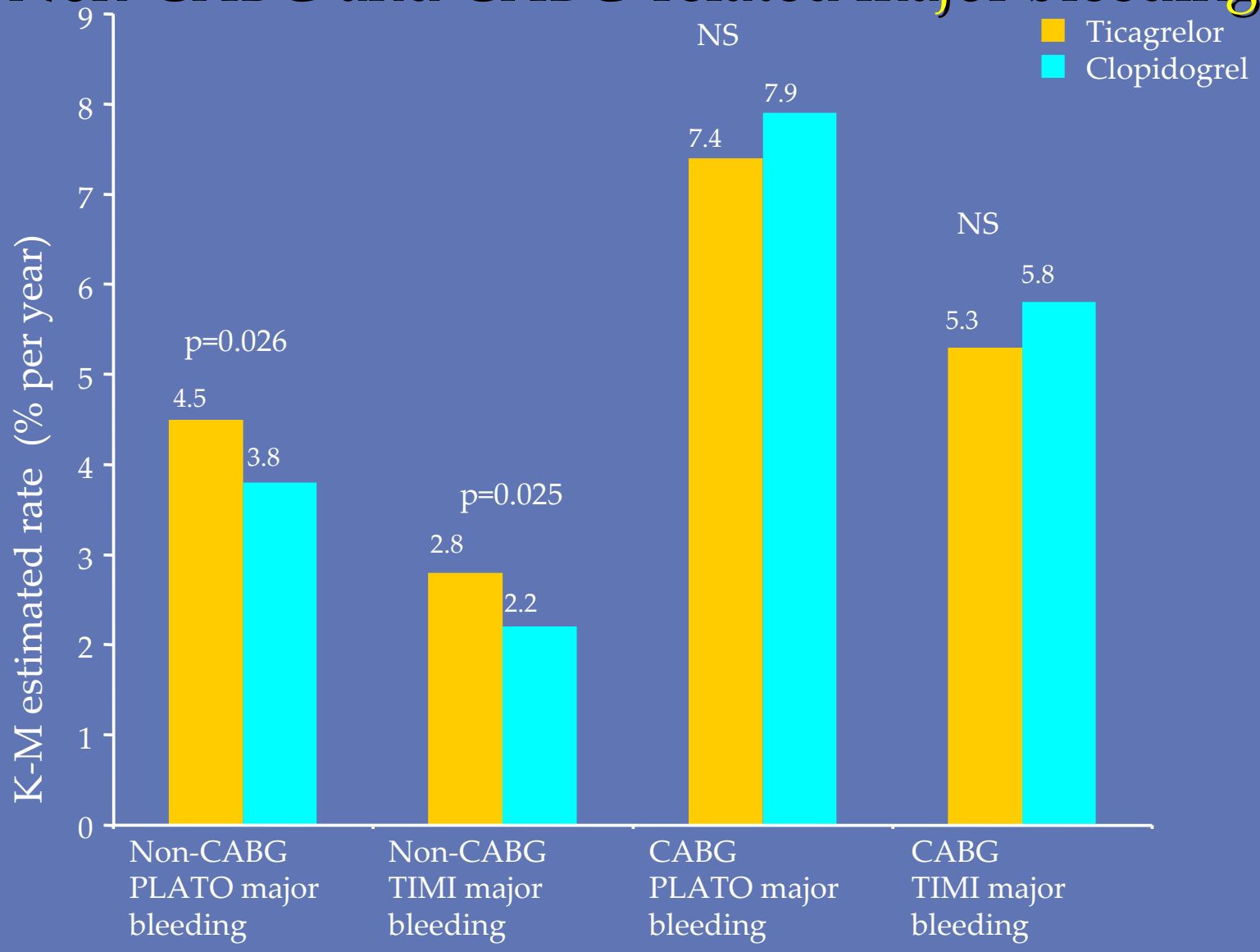
Major bleeding



Patient at risk

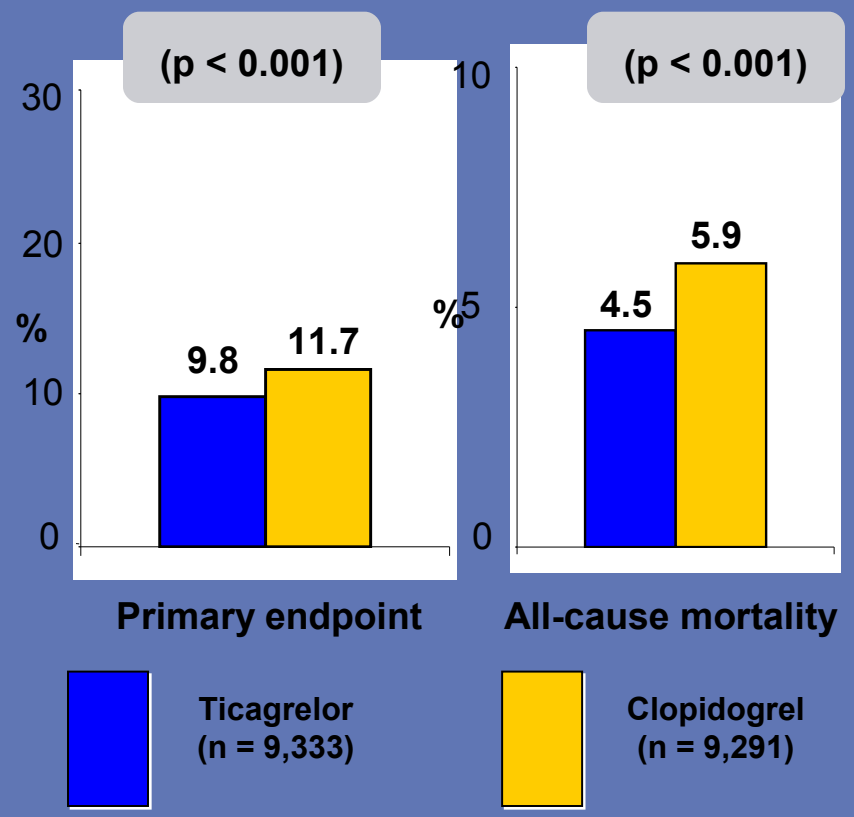
Prior stroke	Clopidogrel	578	412	387	358	270	198	179
	Ticagrelor	558	415	383	364	282	222	190
No prior stroke	Clopidogrel	8607	6892	6542	6311	4938	3642	3299
	Ticagrelor	8675	6830	6442	6180	4846	3560	3243

Non-CABG and CABG-related major bleeding



PLATO

Trial design: Patients with ACS were randomized to ticagrelor (180 mg loading dose, 90 mg bid thereafter) or clopidogrel (300 mg loading dose, 75 mg daily thereafter). Patients were followed for 12 months.



Results

- Death from vascular cause, MI, stroke lower in ticagrelor arm, including in patients undergoing PCI
- Mortality, stent thrombosis (p = 0.02) ↓ with ticagrelor; stroke rate similar (p = 0.22)
- No increase in fatal bleeding or overall major bleeding, but higher rate of non-CABG major bleeding (p = 0.03)

Conclusions

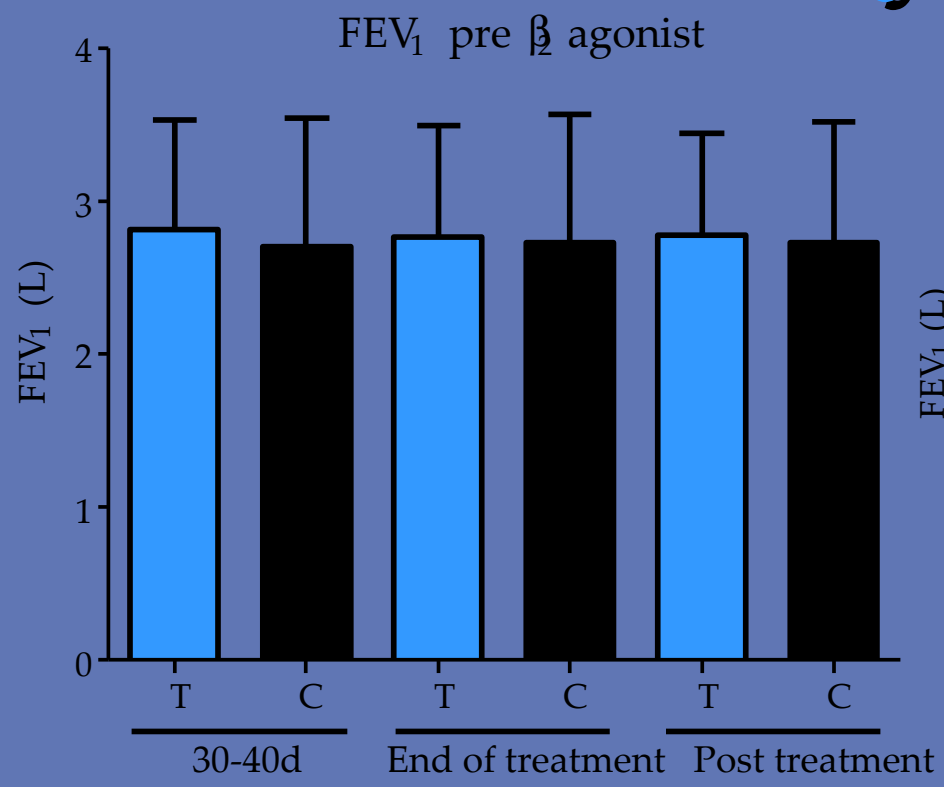
- Ticagrelor superior to clopidogrel for several outcomes including death, MI, and stent thrombosis in patients presenting with ACS
- Very promising results; reduction in CV mortality notable in the modern era of ACS

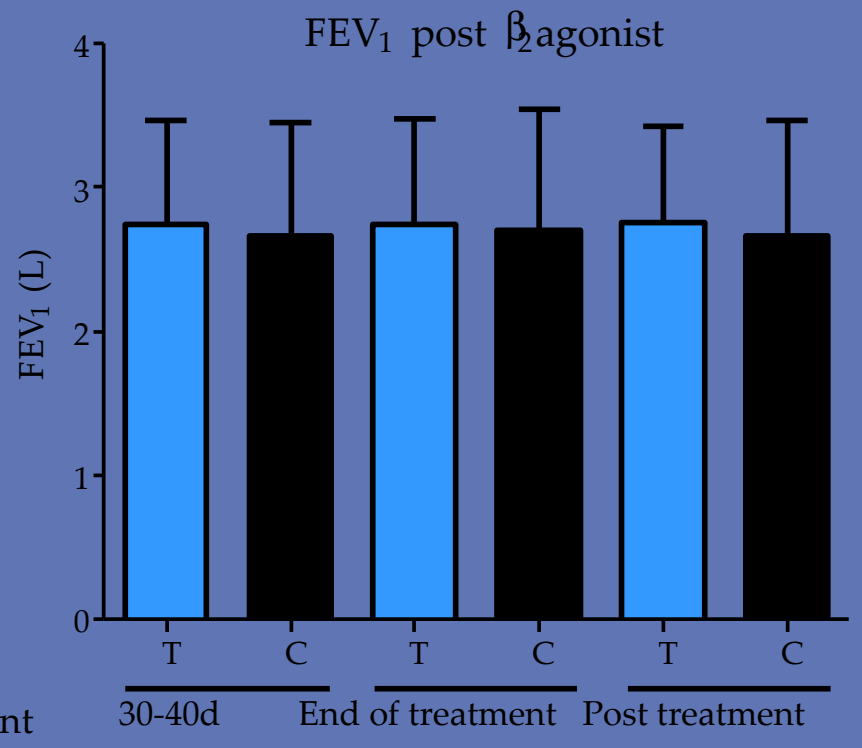
Cannon CP, et al. Lancet 2010;375:283-93

PLATO

Pulmonary

Pulmonary function





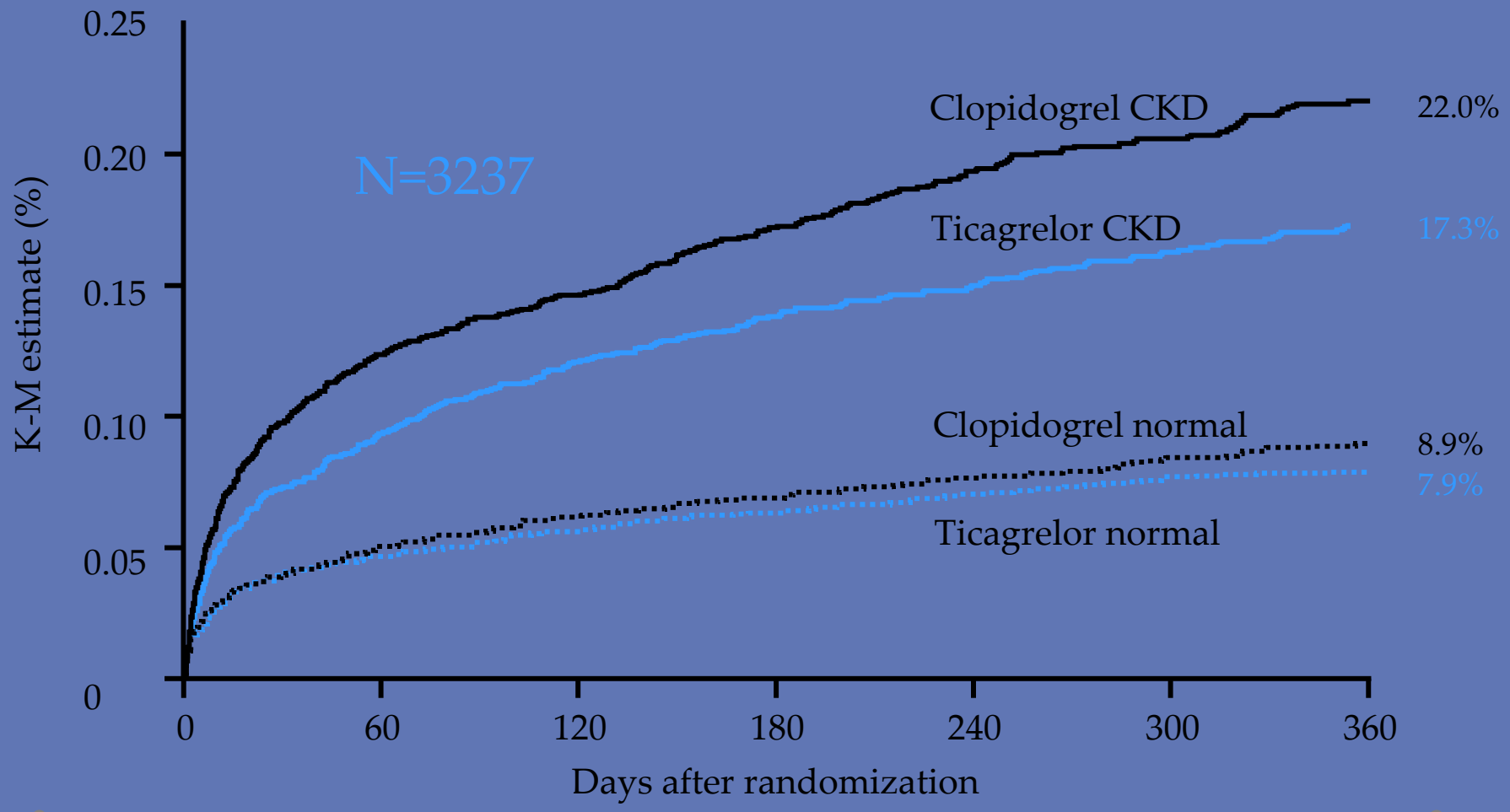
Storey, R et al, Am J Cardiol. 2011 Sep 3. [Epub ahead of print]

PLATO

Renal dysfunction

Renal

(creatinine clearance <60 mL/min),



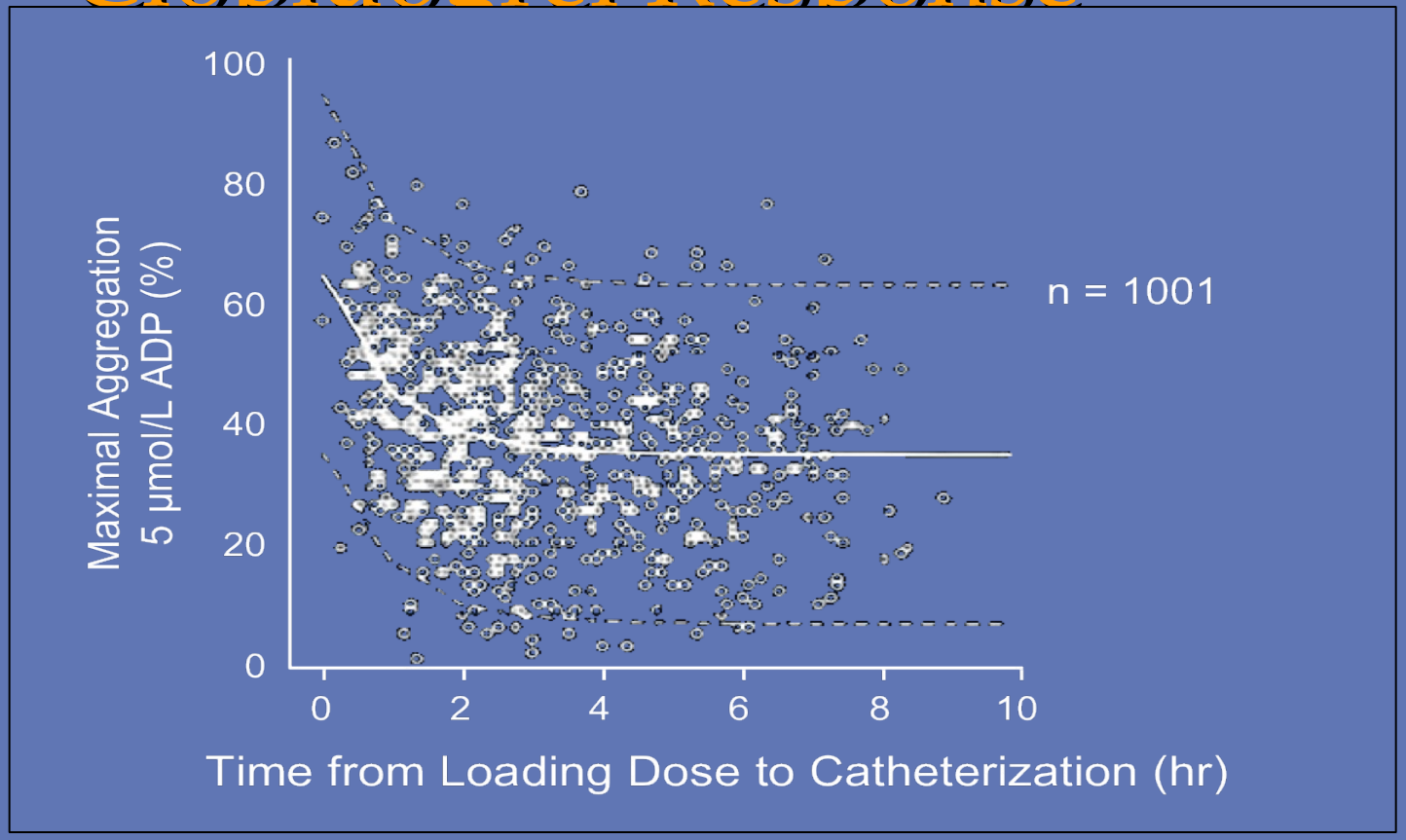
James, S et al, Circulation. 2010;122:1056-1067.)

PLATO: goals of the trial design

- Designed to closely mimic current clinical practice
  - Randomized a broad spectrum of ACS patients based on initial presentation and electrocardiogram (ECG) within 24 hours[James 2009:A,B]
    - UA
    - NSTEMI
    - STEMI
  - Randomized patients for whom both invasive and medical management was planned prior to actual treatment[a][James 2009:C]
  - Permitted inclusion of patients previously treated with clopidogrel and allowed clopidogrel loading doses greater than 300 mg[James 2009:A; Serebruany 2010:A]
- PLATO bleeding categories were designed to be inclusive and clinically relevant measures for assessing bleeding events, whether or not they were associated with surgery or other medical procedures[James 2009:D]

James S, et al. *Am Heart J.* 2009;157:599-605; Serebruany VL.*Thromb Haemost.* 2010;103:259-261.

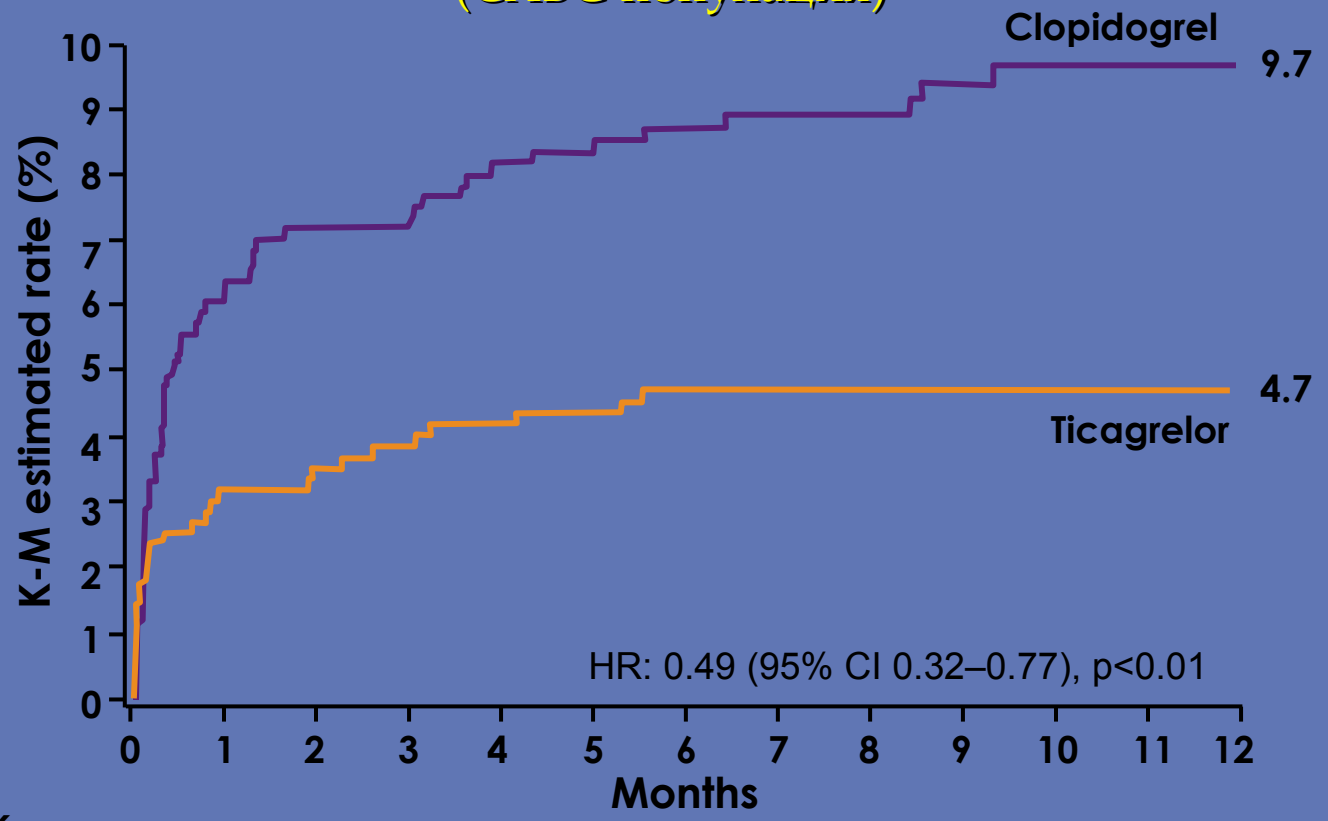
Variability in Inter-Individual Clopidogrel Response



Hochholzer, et al. Circulation. 2005;111:2560-2564.

Намаляване на смъртността след CABG с 51 %

(CABG популация)

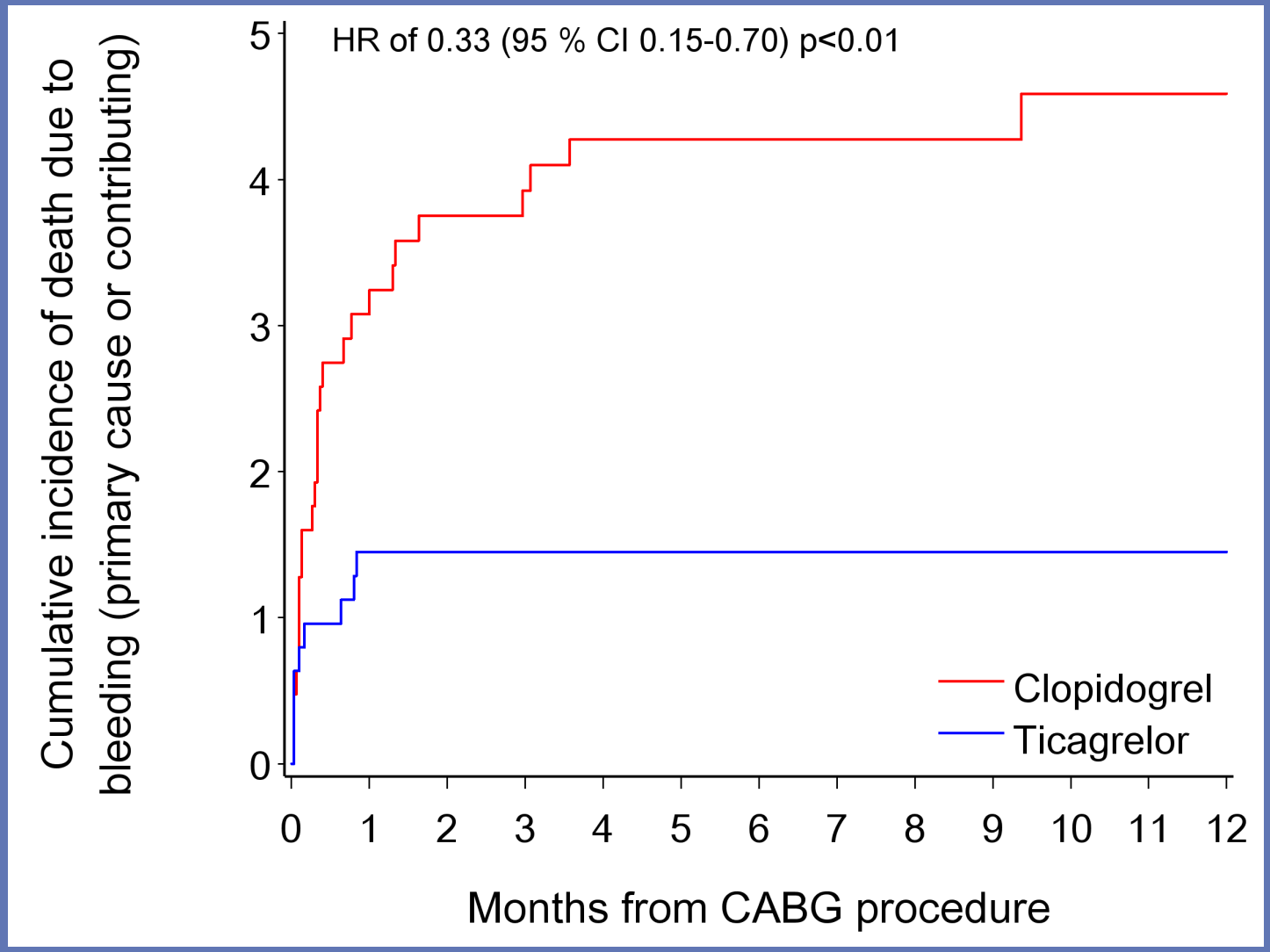


Number at risk

Ticagrelor	629	583	557	491	415	291	119
Clopidogrel	629	565	539	472	404	269	130

C Held ACC 2010

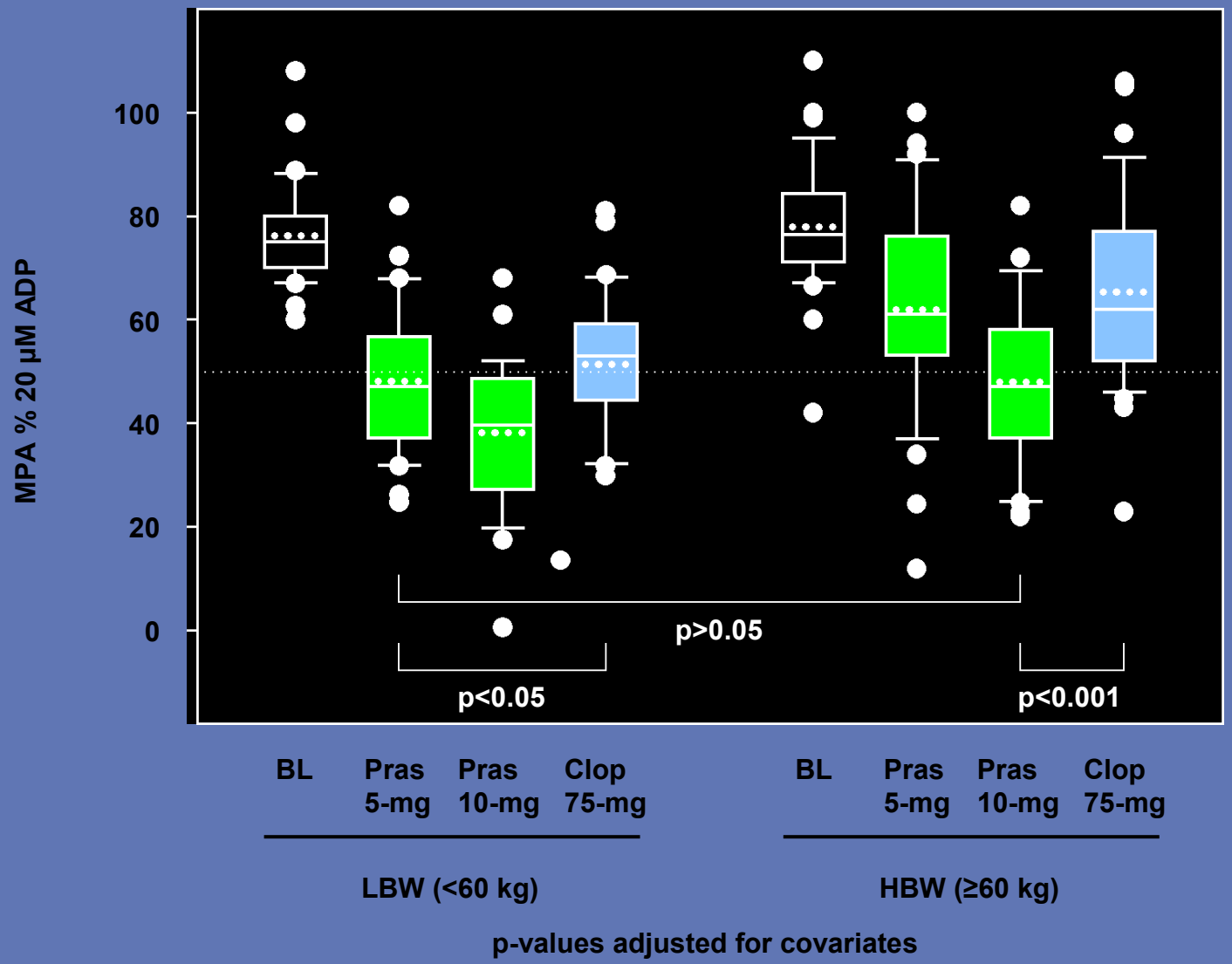
PLATO
CABG



Varenhorst C, et al. *J Am Coll Cardiol* 2012;

FEATHER

Primary Endpoint



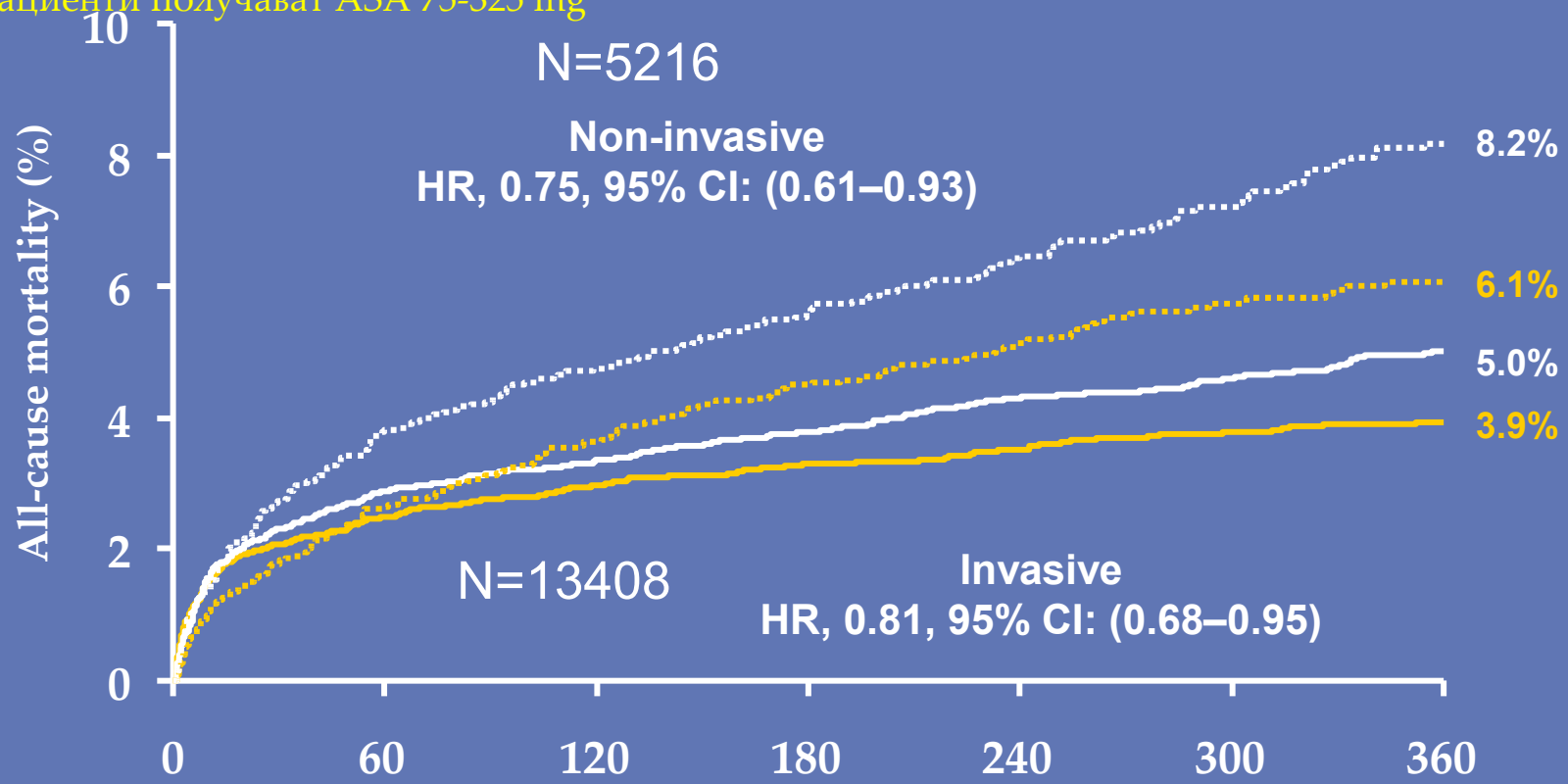
p-values adjusted for covariates

Erlinge JACC in press, 2012

Редукция на смъртността

Ticagrelor vs Clopidogrel

- 18,624 пациента
- Рандомизация:
  - Ticagrelor 180 mg loading dose, 90mg BID
  - Clopidogrel 300-600 mg loading dose, 75 mg QD
- Всички пациенти получават ASA 75-325 mg

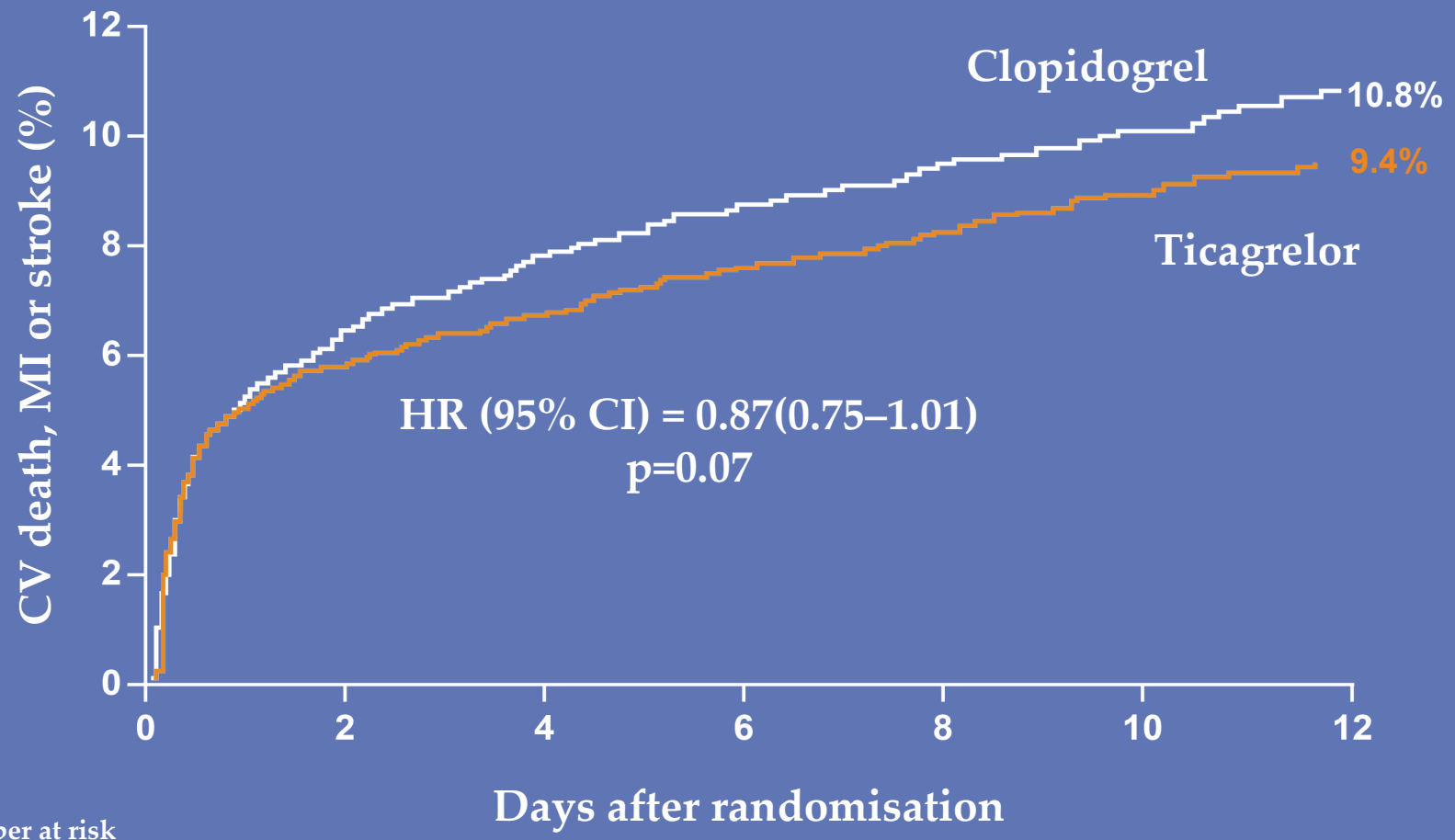


Number at risk							
Invasive							
Ticagrelor	6732	6439	6375	6241	5141	3951	3233
Clopidogrel	6676	6376	6331	6209	5114	3917	3164
Non-invasive							
Ticagrelor	2601	2485	2447	2385	1978	1531	1186
Clopidogrel	2615	2488	2448	2380	1965	1524	1200

James S et al. ESC abstract 2010

PLATO

STE-ACS scheduled for primary PCI

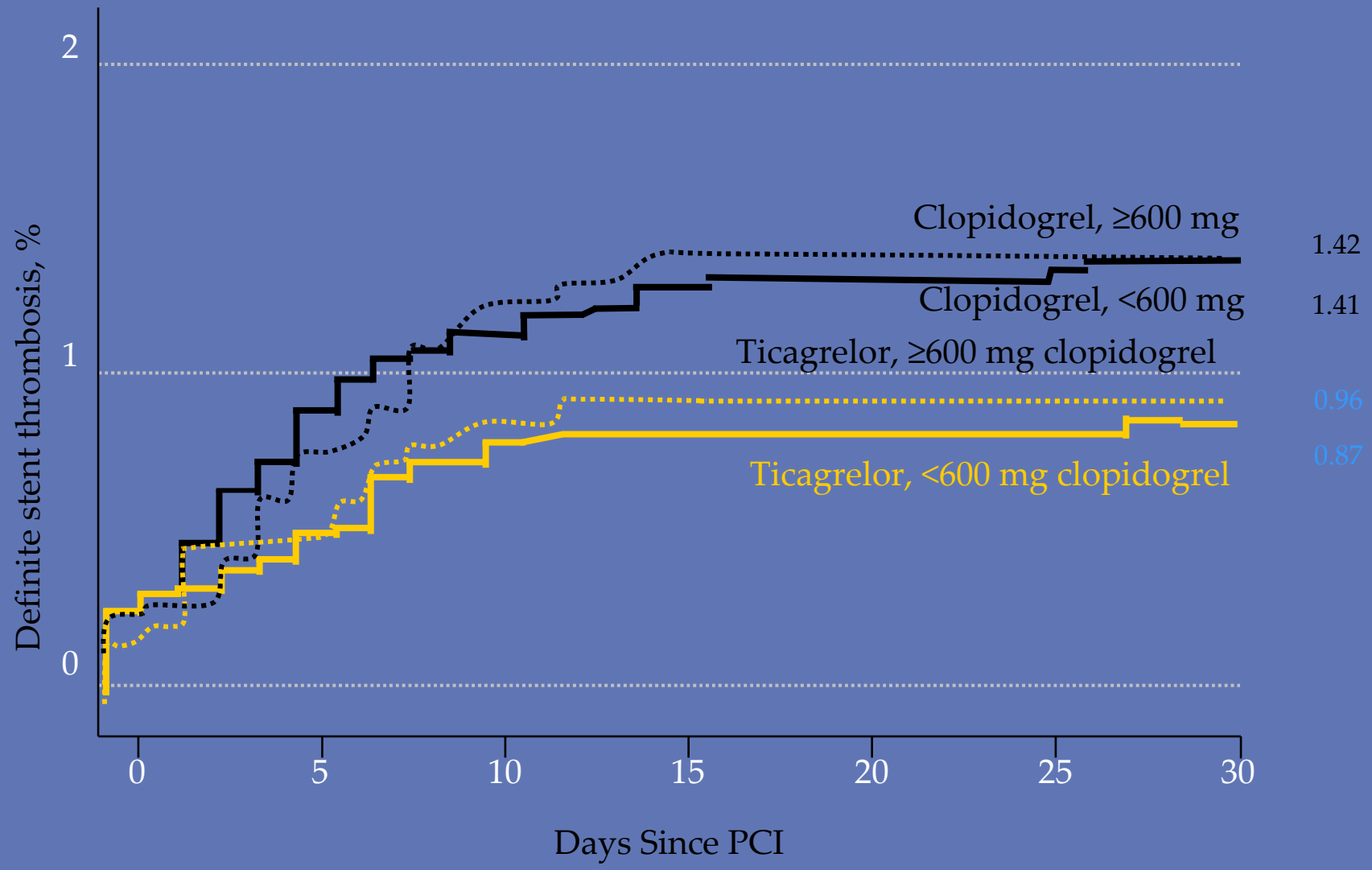


Number at risk							
STE-ACS							
Ticagrelor	3752	3476	3424	3331	2687	2049	1675
Clopidogrel	3792	3501	3438	3356	2726	2097	1679

ACS, acute coronary syndromes; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; STE, ST-segment elevated.
Steg PG, et al. *Circulation* 2010;122:2131–2141.

PLATO
Invasive

Definite Stent Thrombosis



Cannon CP, et al. Lancet. 2010;375:283-293.

EDITORIAL

Ticagrelor — Is There Need for a New Player in the Antiplatelet-Therapy Field?

Albert Schömig, M.D.

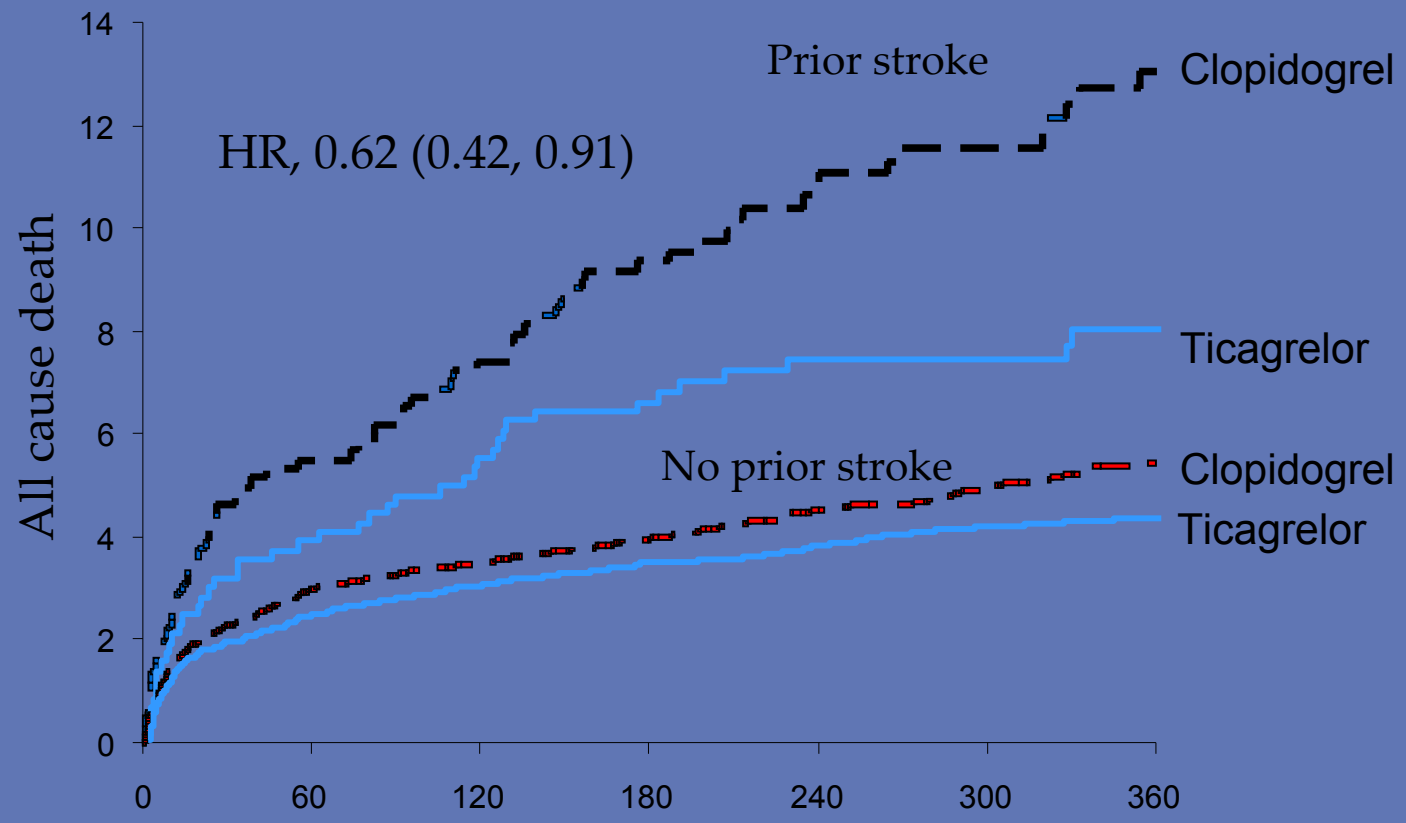
gery. Avoidance of the use of prasugrel in patients with a history of stroke or transient ischemic attacks has been advised.[10] It seems prudent to apply the same advice to ticagrelor. The use of prasugrel has been discouraged in patients with an excessively high risk of bleeding.[10] It might also be prudent to avoid the use of ticagrelor in patients with a high bleeding risk (presumably those with multiple risk factors). Ticagrelor therapy should be discouraged in patients who have chronic obstructive pulmonary disease, hyperuricemia, moderate or severe renal failure, bradyarrhythmias unprotected by pacemakers, a history of syncope, or a need for treatment with an ADP-receptor antagonist for more than 1 year. We should further recognize that the rapidly reversible effect of ticagrelor makes careful sur-

but

Prior stroke or TIA

Stroke

N=1052

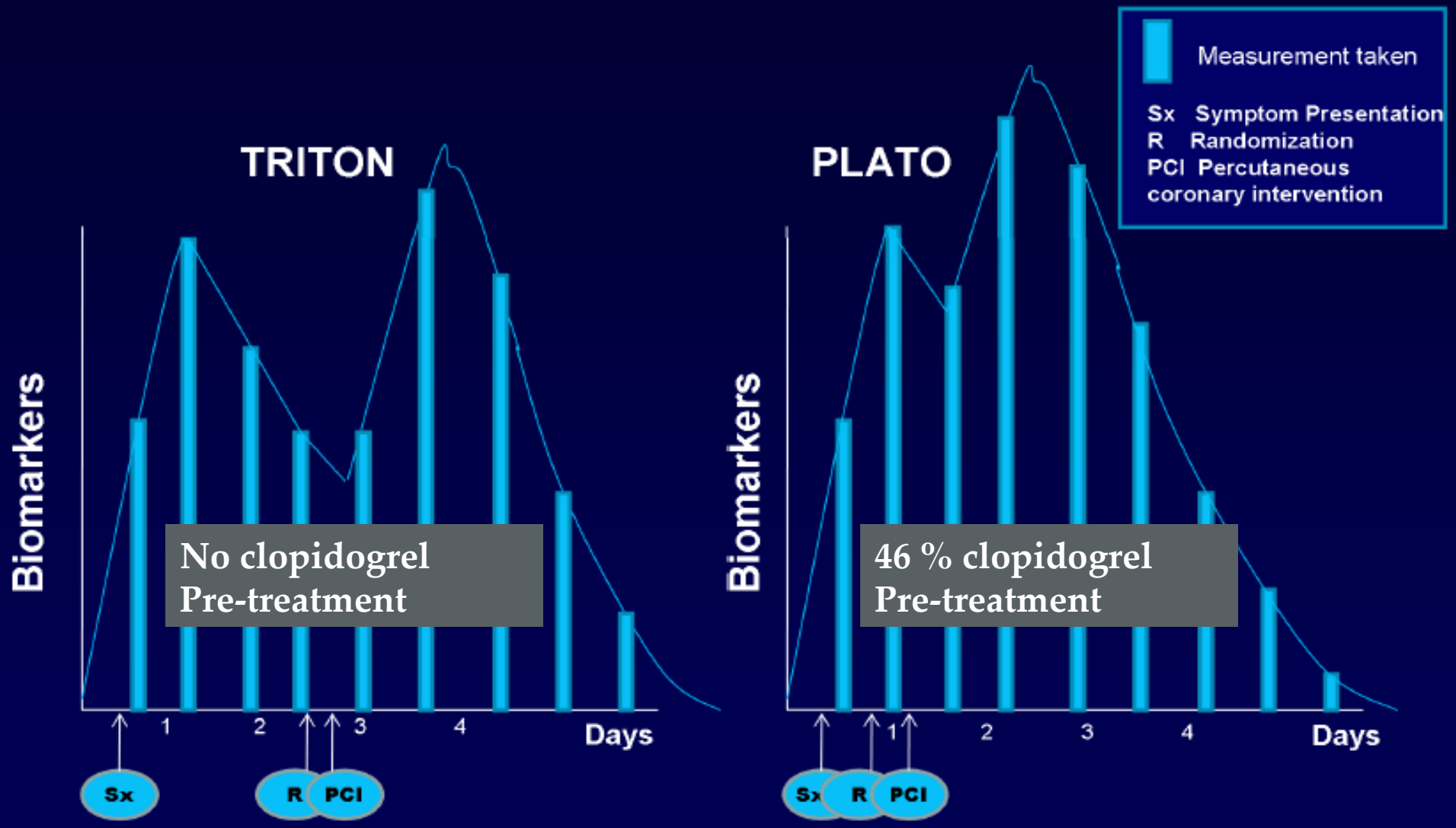


Patient at risk

Prior stroke	Clopidogrel	588	542	530	507	397	314	246
	Ticagrelor	564	534	525	511	411	332	254
No prior stroke	Clopidogrel	8699	8318	8245	8078	6679	5124	4115
	Ticagrelor	8761	8382	8289	8107	6701	5143	4162

James, S et al, ESC 2011

TRITON vs PLATO: Biomarkers and Index Events



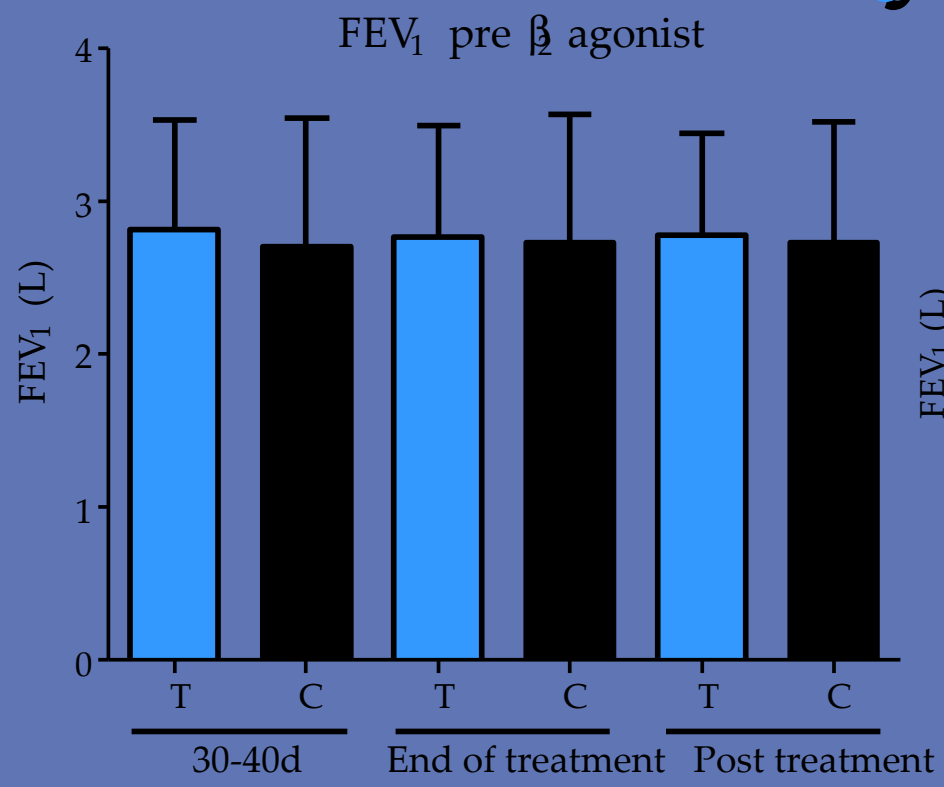
2 events detected: index and new MI

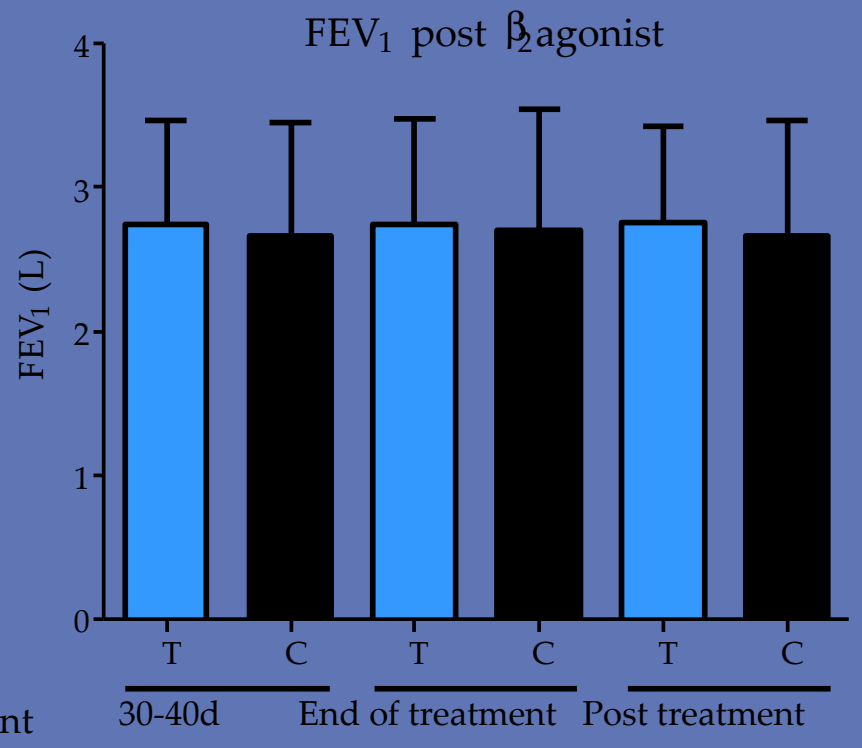
1 event detected: index

PLATO

Pulmonary

Pulmonary function





Storey, R et al, Am J Cardiol. 2011 Sep 3. [Epub ahead of print]

PLATO: Holter Мониторираща програма

All Patients	Ticagrelor (n=9235)	Clopidogrel (n=9186)	*P* value
Holter monitor first week	**Ticagrelor (n=1451)**	**Clopidogrel (n=1415)**	***P* value**
Ventricular pauses ≥3 seconds	5.8%	3.6%	0.01
Ventricular pauses ≥5 seconds	2.0%	1.2%	0.10
Holter monitor at 30 days	**Ticagrelor (n=985)**	**Clopidogrel (n=1006)**	***P* value**
Ventricular pauses ≥3 seconds	2.1%	1.7%	0.52
Ventricular pauses ≥5 seconds	0.8%	0.6%	0.60

Wallentin L, et al. *N Engl J Med*. 2009;361:1045–1057

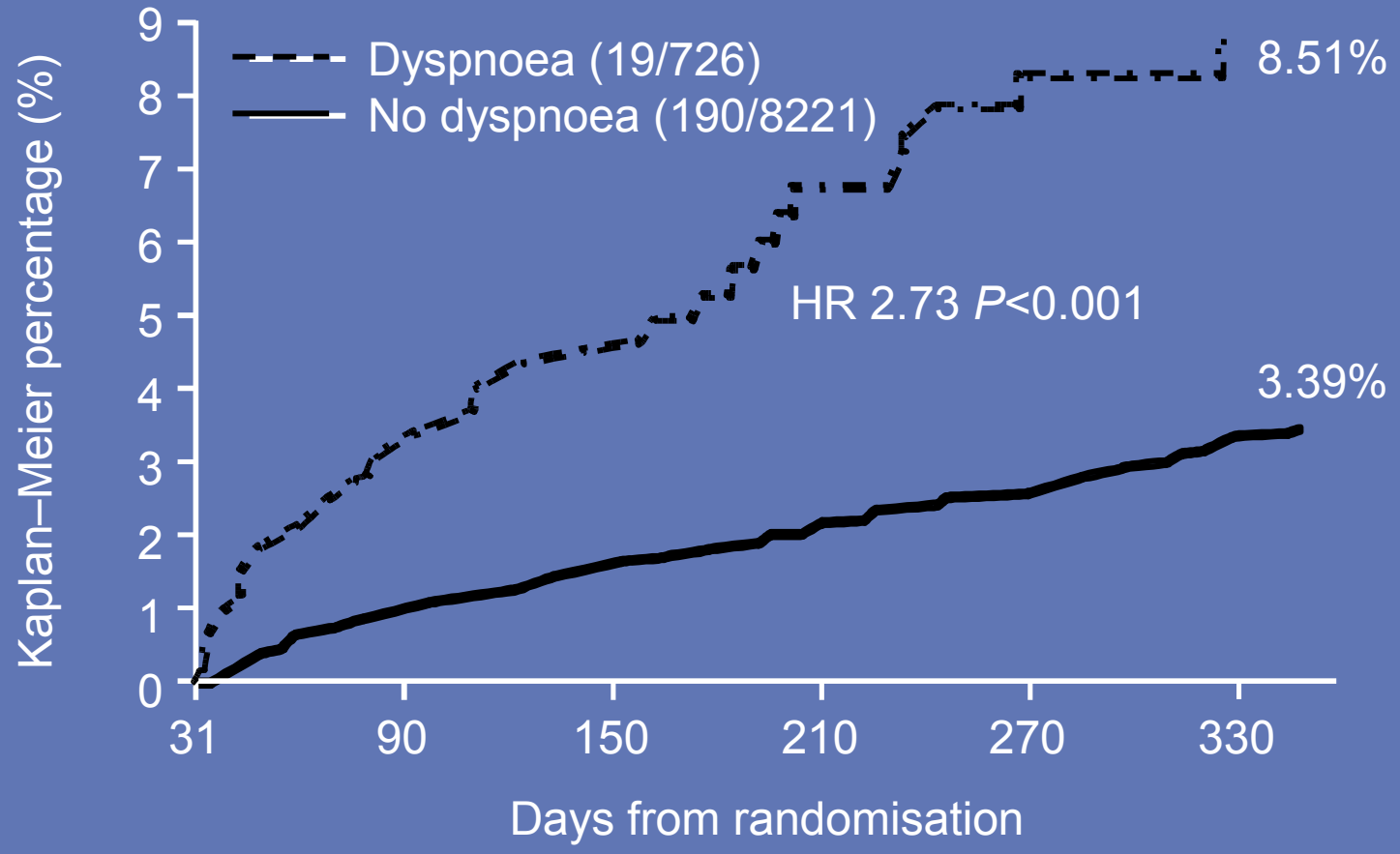
Dyspnea in PLATO

- Dyspnea was reported more frequently by patients on ticagrelor than clopidogrel (13.8% vs 7.8%; *P*<0.001)[Wallentin 2009:L,N]
  - Most episodes lasted less than a week
  - Ticagrelor-associated dyspnea was mostly mild to moderate and did not affect efficacy
- 1 in 9 patients discontinued study drug because of dyspnea (0.9% vs 0.1%, *P*<0.001)[Wallentin 2009:L,N]
- The higher frequency of dyspnea with ticagrelor was not associated with any detectable detrimental effect on pulmonary function compared with clopidogrel[Storey 2010:A]

Wallentin L, et al. *N Engl J Med*. 2009;361:1045-1057; Storey R, et al. *JACC*. 2010;55(Suppl 1):A108.E1007.

Total death

C

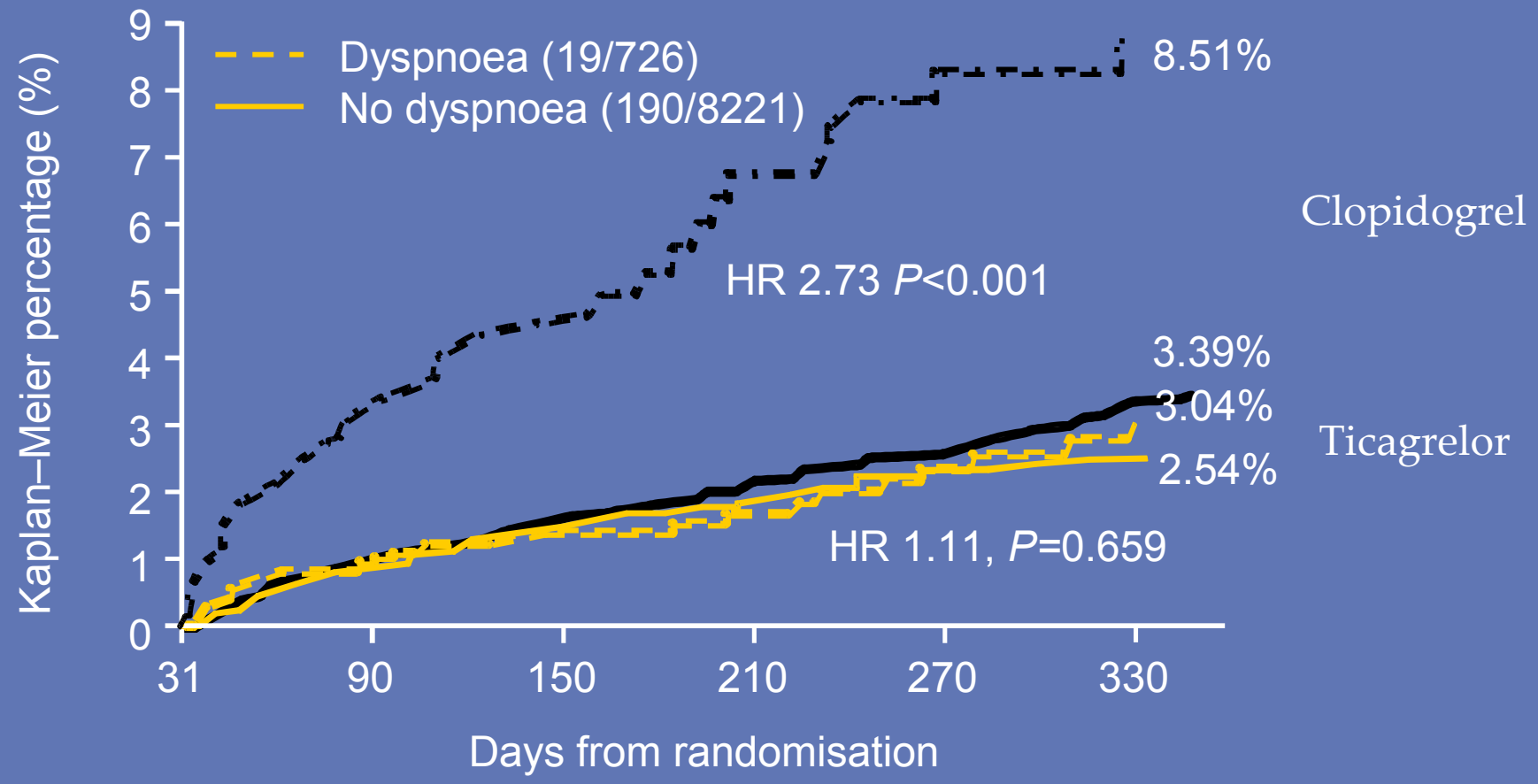


Clopidogrel

n at risk						
DE	726	717	713	628	582	431
NDE	8221	8089	8004	6711	6220	4666

Storey RF et al. Eur Heart J 2011.

Total death



n at risk						
DE	726	717	713	628	582	431
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Storey RF et al. Eur Heart J 2011.