Предимства и ограничения при избора на Clopidogrel в лечението на пациентите с ОКС

Доц. Добрин Василев д.м.
Национална Кардиологична Болница

UA/NSTEMI

NSTEMI

Recommendations for oral antiplatelet agents (2)

Recommendations	Class	Level
Clopidogrel (300 mg loading dose, 75 mg daily dose) is recommended for patients who cannot receive ticagrelor or prasugrel.	I	A
A 600 mg loading dose of clopidogrel (or a supplementary 300 mg dose at PCI following an initial 300 mg loading dose) is recommended for patients scheduled for an invasive strategy when ticagrelor or prasugrel is not an option.	I	B
A higher maintenance dose of clopidogrel 150 mg daily should be considered for the first 7 days in patients managed with PCI and without increased risk of bleeding.	IIa	B
Increasing the maintenance dose of clopidogrel based on platelet function testing is not advised as routine, but may be considered in selected cases.	IIb	B
Genotyping and/or platelet function testing may be considered in selected cases when clopidogrel is used.	IIb	B
In patients pre-treated with $P2Y_{12}$ inhibitors who need to undergo non-emergent major surgery (including CABG), postponing surgery at least for 5 days after cessation of ticagrelor or clopidogrel, and 7 days for prasugrel, if clinically feasible and unless the patient is at high risk of ischaemic events should be considered.	IIa	C
Ticagrelor or clopidogrel should be considered to be (re-)started after CABG surgery as soon as considered safe.	IIa	B
The combination of aspirin with an NSAID (selective COX-2 inhibitors and non-selective NSAID) is not recommended.	III	C

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

Periprocedural anti thrombotic medication in primary PCI

STEMI

Recommendations	Class	Level
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.

European Heart Journal (2012) 33, 2569–2619
doi:10.1093/eurheartj/ehs215

Doses of anti-platelet co-therapies

Doses of antiplatelet co-therapies	
With primary PCI	
Aspirin	Loading dose of 150-300 mg orally or of 80-150 mg i.v. if oral ingestion is not possible, followed by a maintenance dose of 75-100 mg/day.
Clopidogrel	Loading dose of 600 mg orally, followed by a maintenance dose of 75 mg/day.
Prasugrel	Loading dose of 60 mg orally, followed by a maintenance dose of 10 mg/day. In patients with body weight <60 kg, a maintenance dose of 5 mg is recommended. In patients > 75 years, prasugrel is generally not recommended, but a dose of 5 mg should be used if treatment is deemed necessary.
Ticagrelor	Loading dose of 180 mg orally, followed by a maintenance dose of 90 mg b.i.d.
Abciximab	Bolus of 0.25 mg/kg i.v. and 0.125 μg/kg/min infusion (maximum 10 μg/min) for 12 h.
Eptifibatide	Double bolus of 180 μg/kg i.v. (given at a 10-min interval) followed by an infusion of 2.0 μg/kg/min for 18 h.
Tirofiban	25 μg/kg over 3 min i.v., followed by a maintenance infusion of 0.15 μg/kg/min for 18 h.
With fibrinolytic therapy	
Aspirin	Starting dose 150-500 mg orally or i.v. dose of 250 mg if oral ingestion is not possible.
Clopidogrel	Loading dose of 300 mg orally if aged ≤ 75 years, followed by a maintenance dose of 75 mg/day.
Without reperfusion therapy	
Aspirin	Starting dose 150-500 mg orally.
Clopidogrel	75 mg/day orally.

European Heart Journal (2012) 33, 2569–2619
doi:10.1093/eurheartj/ehs215

Routine therapies in the acute, subacute and long term phase of STEMI

Recommendations	Class	Level
Active smokers with STEMI must receive counselling and be referred to a smoking cessation programme	I	B
Each hospital participating in the care of STEMI patients must have a smoking cessation protocol.	I	C
Exercise-based rehabilitation is recommended	I	B
Antiplatelet therapy with low dose aspirin (75-100 mg) is indicated indefinitely after STEMI.	I	A
In patients who are intolerant to aspirin, clopidogrel is indicated as an alternative to aspirin.	I	B
DAPT with a combination of aspirin and prasugrel or aspirin and ticagrelor is recommended (over aspirin and clopidogrel) in patients treated with PCI	I	A
DAPT with aspirin and an oral ADP receptor antagonist must be continued for up to 12 months after STEMI, with a strict minimum of:	I	C
• 1 month for patients receiving BMS;	I	C
• 6 months for patients receiving DES.	IIb	B

European Heart Journal (2012) 33, 2569–2619
doi:10.1093/eurheartj/ehs215

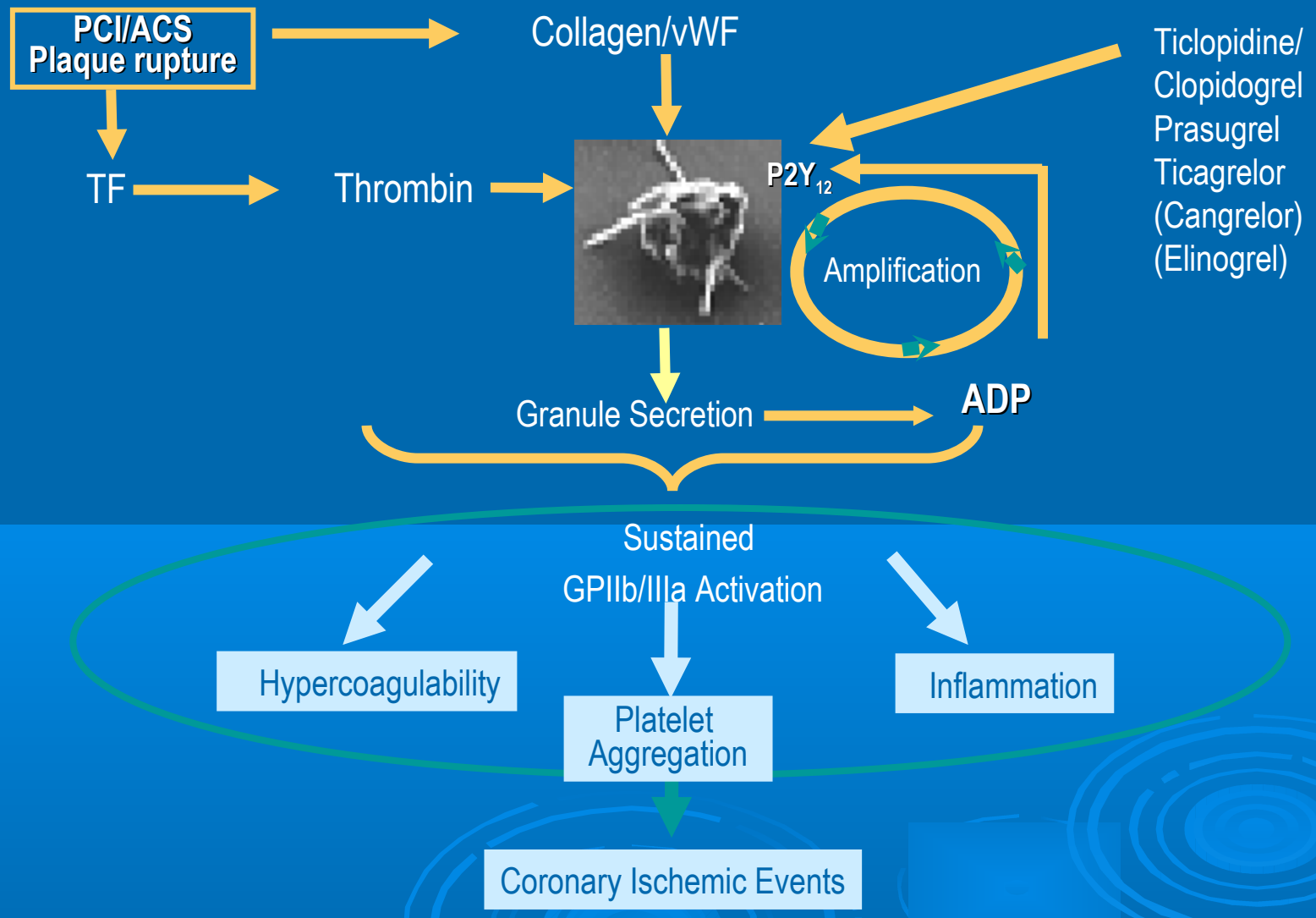
Благодаря за вниманието!

Нищо не е толкова просто в този живот.....

Идеалният антиагрегант

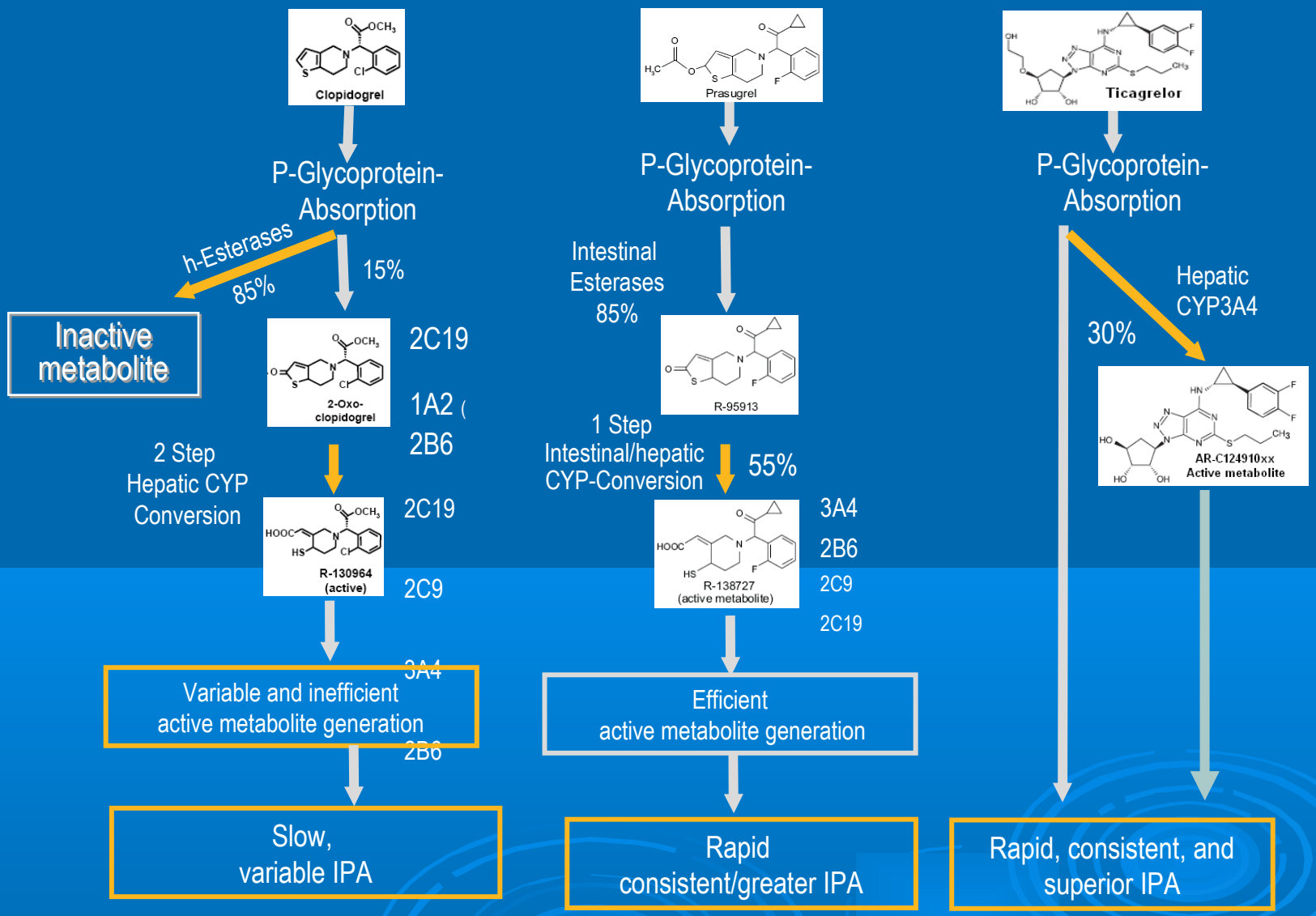
- Бърз ефект и продължително действие
- Пълно блокиране на агрегацията
- Без взаимодействие с други медикаменти
- Минимални странични ефект – кървене
- С ефективен, бързодействащ антидот
- Еднократен прием

МЯСТО НА ДЕЙСТВИЕ НА АДФ - БЛОКЕРИТЕ

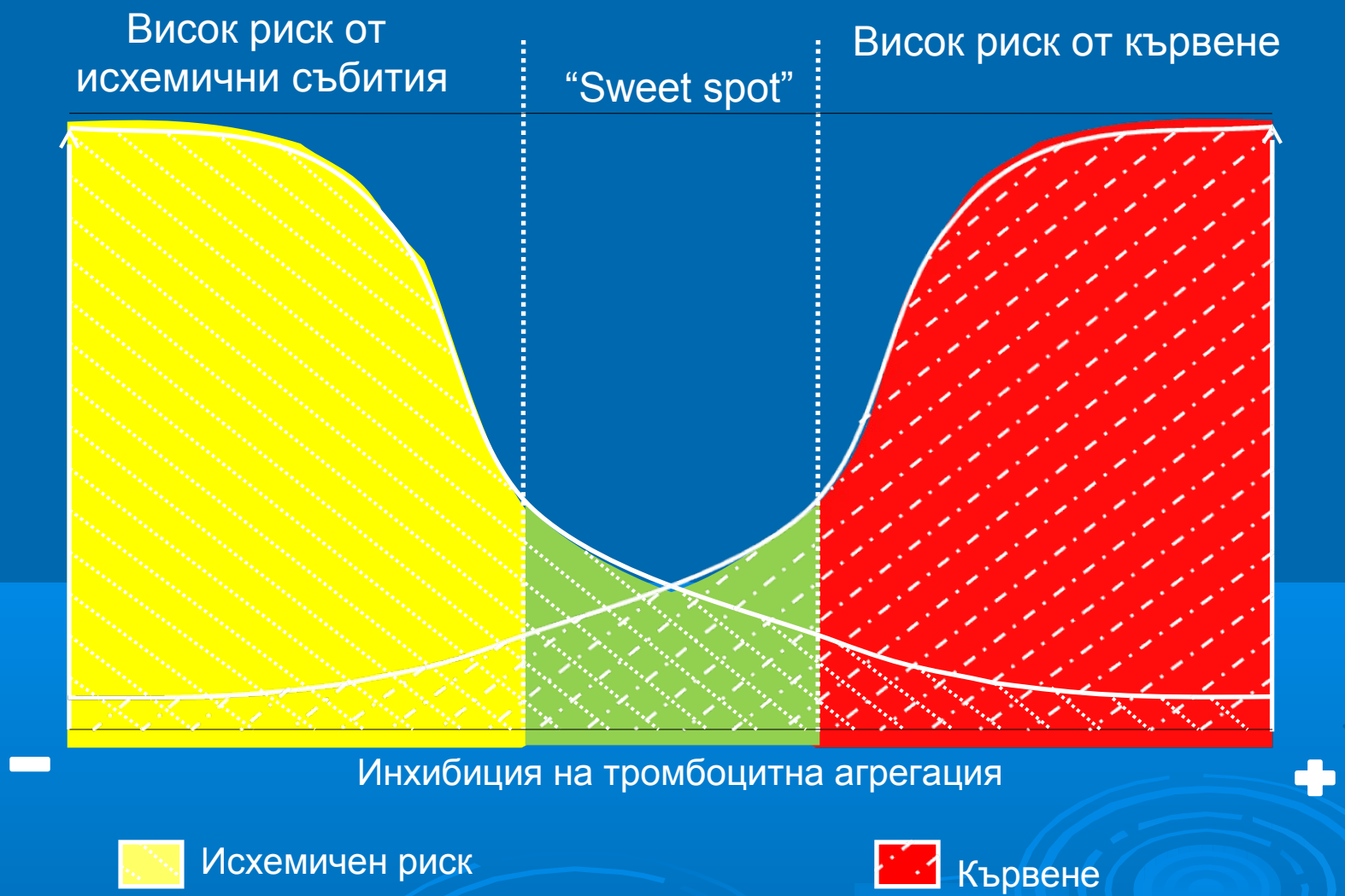


Gurbel PA et al. *Rev Cardiovasc Med*. 2006;7:S20-S28.

МЕТАБОЛИЗЪМ НА АДФ - БЛОКЕРИТЕ



Чак толкова ли е неефикасен клопидогрела?!?!?!



Ferreiro & Angiolillo. Thromb Haemost 2010

Ефект на клопидогрел при различни клинични ситуации

- CLARITY ***MACE***: 21.7% vs. 15% (RRR 36%)
- CURE ***MACE***: 11.4% vs. 9.3% (RRR 20%)
  - ***BLEEDING***: 2.7 vs. 3.7% (RRI 38%)
- PCI – CURE ***MACE***: 6.4% vs. 4.5% (RRR 30%)
- CREDO ***MACE***: 11.5% vs. 8.5% (RRR 27%)
- CURRENT – OASIS 7 ***MACE***: 4.5% vs. 3.9% (RRR 15%)

Thomas & Storey Current Treatment Options in Cardiovascular Medicine (2012)

Ticagrelor & prasugrel

- PLATO ***MACE***: 11.7% vs. 9.8% (RRR 16%)
  - ***Bleeding***: 3.5% vs. 4.8% (RRI 37%)

- TRITON – TIMI 38 ***MACE***: 12.1% vs. 9.9% (RRR 19%)
  - ***Bleeding***: 1.8% vs. 2.4% (RRI 32%)

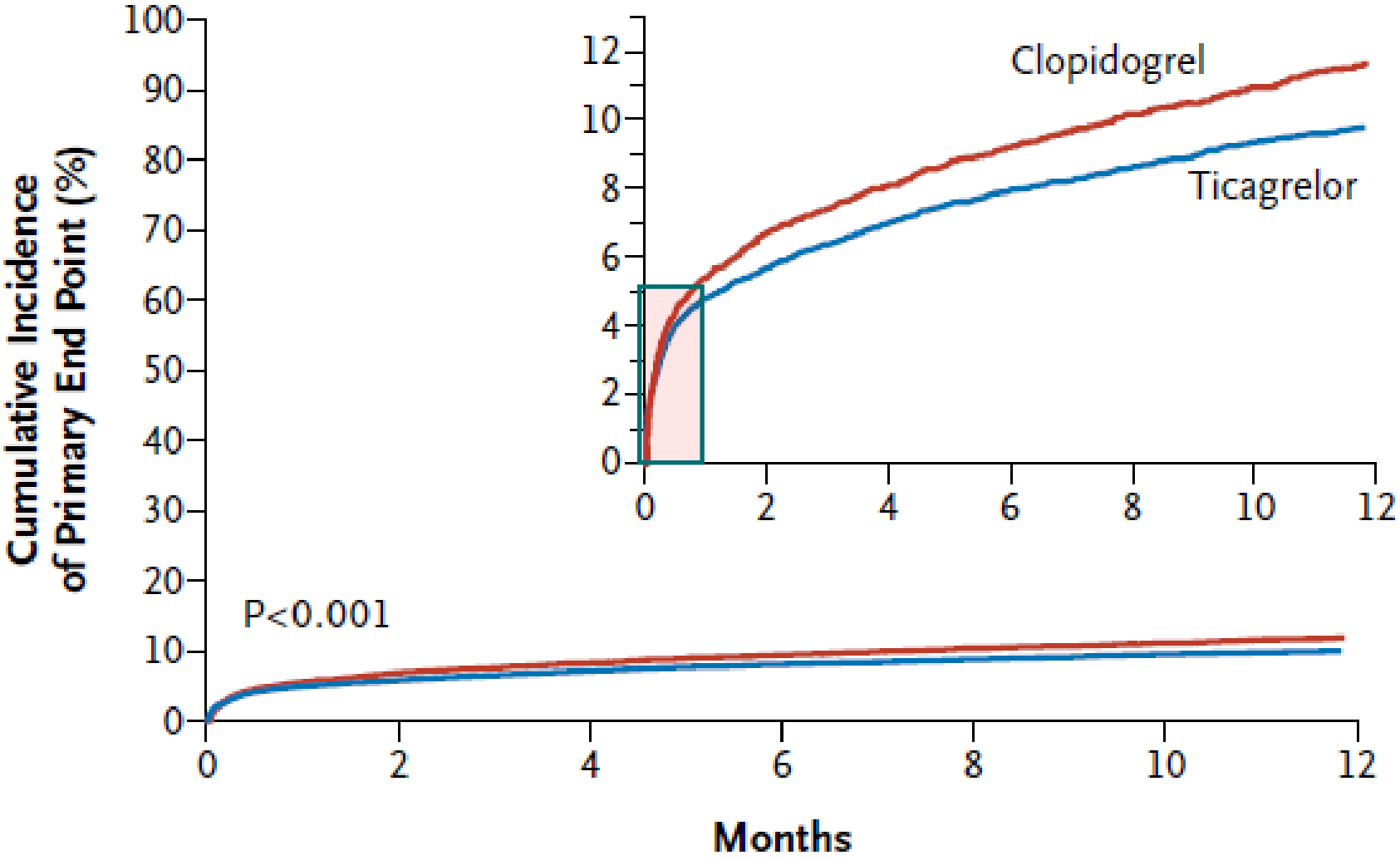
Thomas & Storey Current Treatment Options in Cardiovascular Medicine (2012)

Честота на сърдечно-съдовите инциденти

Table 1
Major adverse cardiovascular events (MACE) as reported in studies comparing standard clopidogrel loading (300 mg) versus alternatives, specifically clopidogrel 600 mg, prasugrel or ticagrelor which are shown under italicized headings. *ns*, not stated in original publication.

Study		Alternative to standard clopidogrel			Standard clopidogrel loading (300 mg)			HR	95% CI	p value
		Total	n	%	Total	n	%			
Clopidogrel 600 mg, MACE at 30 days										
2005	ARMYDA-2	126	5	4	129	15	12	*ns*	*ns*	0.041
2006	Cuisset et al.	146	7	5	146	18	12	*ns*	*ns*	0.02
2006	ALBION (300 mg vs 600 mg)	34	2	5.9	35	4	11.4	*ns*	*ns*	ns
2008	Abuzahra et al.	77	8	10.3	42	10	23.8	ns	ns	0.04
2008	Bonello et al.	3146	91	2.9	959	50	5.2	*ns*	*ns*	<0.001
2008	Jung et al.	73	1	1.4	98	11	11.2	*ns*	*ns*	0.013
2009	HORIZONS-AMI	2158	93	4.3	1153	81	7	*ns*	*ns*	<0.001
2010	CURRENT-OASIS 7 (PCI)	8560	330	3.9	8703	392	4.5	0.86	0.74–0.99	0.039
2010	CURRENT-OASIS 7 (All)	12,520	522	4.2	12,566	557	4.4	0.94	0.83–1.06	0.3
2010	ARMYDA-4 RELOAD	109	7	6.4	98	16	16.3	0.35	*0.12–0.96*	0.041
2011	ARMYDA-6MI	103	6	5.8	98	15	15	*ns*	*ns*	0.049
2011	Choi et al.	1217	92	7.6	1447	111	7.7	*ns*	*ns*	0.977
Clopidogrel 600 mg, MACE at 1 year										
2010	Mangiacapra et al.	157	26	17	98	26	27	0.62	*0.38–1.00*	0.05
2011	Choi et al.	1217	155	12.7	1447	198	13.7			0.473
Prasugrel										
2007	TRITON-TIMI-38 (15 months)	6813	643	9.9	6795	781	12.1	0.81	0.73–0.90	<0.001
	TRITON-TIMI-38 (30 days)		–	–		–	–	0.78	0.69–0.89	<0.001
Ticagrelor										
2009	PLATO (12 months)	9333	864	9.8	9291	1014	11.7	0.84	0.77–0.92	<0.001
	PLATO (30 days)		443	4.8		502	5.4	0.88	0.77–1.00	0.045
	PLATO (Invasive Only, 12 months)	6732	569	9	6676	668	10.7	0.84	0.75–0.94	0.0025

Nijjer ет ал. International Journal of Cardiology 158 (2012) 181–185



No. at Risk

Ticagrelor	9333	8628	8460	8219	6743	5161	4147
Clopidogrel	9291	8521	8362	8124	6650	5096	4047

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

CLOPIDOGREL 600 mg vs. 300 mg

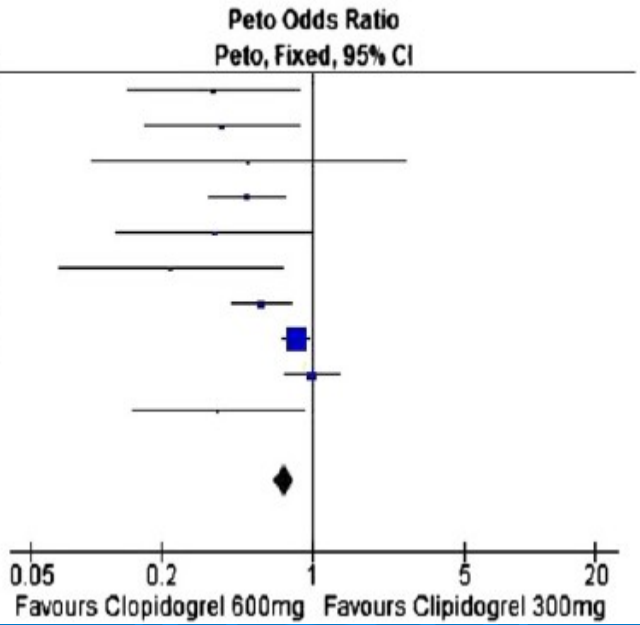
OR 0.74 (0.66–0.82, p=0.00001)

A. Major adverse cardiovascular events

Study or Subgroup	Clopidogrel 600mg LD Events	Total	Clopidogrel 300mg LD Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI	Year
Patti 2005	5	126	15	129	1.5%	0.35 [0.14, 0.87]	2005
Cuisset 2006	7	146	18	146	1.9%	0.38 [0.17, 0.87]	2006
Montalescot 2006	2	34	4	35	0.5%	0.50 [0.10, 2.65]	2006
Bonello 2008	91	3146	50	959	8.0%	0.50 [0.33, 0.74]	2008
Abuzahra 2008	8	77	10	42	1.2%	0.35 [0.12, 1.01]	2008
Jung 2008	1	73	11	98	0.9%	0.22 [0.07, 0.73]	2008
HORIZONS-AMI	93	2158	81	1153	12.3%	0.58 [0.42, 0.80]	2009
CURRENT-OASIS 7 (PCI)	330	8560	392	8560	56.9%	0.84 [0.72, 0.97]	2010
Choi 2011	92	1217	111	1447	15.3%	0.98 [0.74, 1.31]	2011
ARMYDA-6MI	6	103	15	98	1.6%	0.36 [0.15, 0.90]	2011
Total (95% CI)		**15640**		**12667**	**100.0%**	**0.74 [0.66, 0.82]**	
Total events	635		707				

Heterogeneity: $Chi^2 = 25.99$, df = 9 (P = 0.002); $I^2 = 65\%$

Test for overall effect: Z = 5.34 (P < 0.00001)



Nijjer et al. International Journal of Cardiology 158 (2012) 181–185

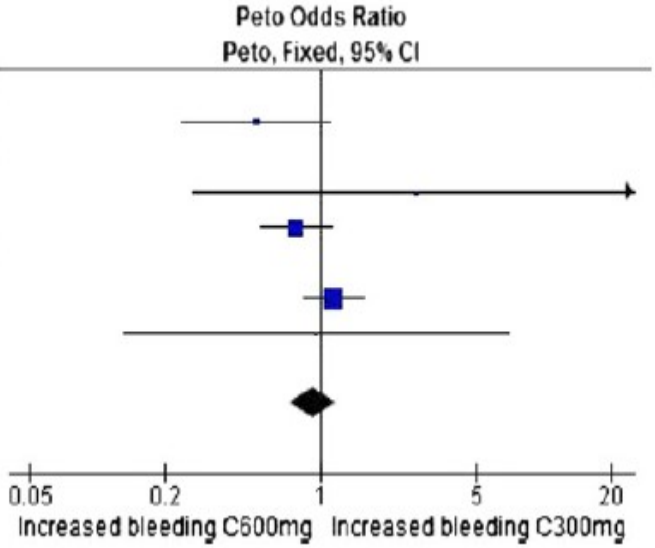
CLOPIDOGREL 600 mg vs. 300 mg

C. TIMI-defined major bleeding

Study or Subgroup	Clopidogrel 600mg LD Events	Clopidogrel 600mg LD Total	Clopidogrel 300mg LD Events	Clopidogrel 300mg LD Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI	Year
Patti 2005	0	126	0	129		Not estimable	2005
Bonello 2008	24	3146	13	959	8.8%	0.52 [0.24, 1.11]	2008
Abuzahra 2008	77	1	42	1		Not estimable	2008
Jung 2008	2	73	1	98	1.0%	2.70 [0.27, 26.92]	2008
HORIZONS-AMI	78	2158	53	1153	38.2%	0.77 [0.54, 1.11]	2009
Di Sciascio 2010	0	252	0	251		Not estimable	2010
CURRENT-OASIS 7 (PCI)	81	8560	72	8703	50.7%	1.15 [0.83, 1.57]	2010
ARMYDA-6MI	2	103	2	98	1.3%	0.95 [0.13, 6.85]	2011
Total (95% CI)		**14419**		**11392**	**100.0%**	**0.92 [0.74, 1.16]**	
Total events	264		183				

Heterogeneity: $Chi^2 = 5.74$, df = 4 (P = 0.22); $I^2 = 30\%$

Test for overall effect: Z = 0.69 (P = 0.49)



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Честота на кървене

Table 2
Major bleeding events reported in studies comparing clopidogrel 600 mg loading dose, prasugrel or ticagrelor with clopidogrel 300 mg in patients with acute coronary syndromes
TIMI – thrombolysis in myocardial infarction criteria; GUSTO-global utilization of streptokinase and tissue plasminogen activator for occluded coronary arteries. *ns* – not stated in original publication.

Clopidogrel vs. prasugrel HR 1.32, 1.03–1.68, p=0.03

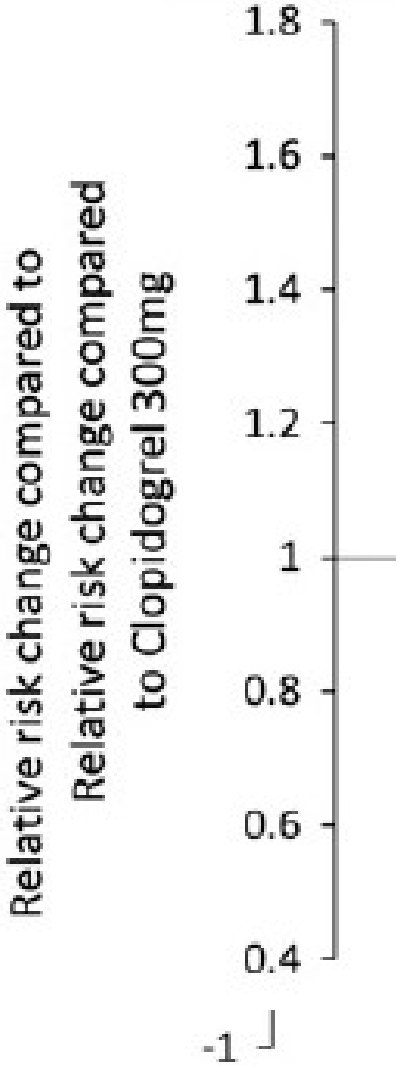
Clopidogrel vs. ticagrelor HR 1.25, 1.03–1.53, p=0.03

HORIZONS-AMI	GUSTO	2158	78	3.6	1153	62	5.4	*ns*	*ns*	0.02
CURRENT-OASIS 7 (PCI)	Study-defined	8560	139	1.6	8703	99	1.1	1.41	1.09–1.83	0.009
CURRENT-OASIS 7 (PCI)	TIMI	8560	81	1	8703	72	0.8	1.36	0.97–1.90	0.074
CURRENT-OASIS 7	Study-defined	12,520	313	2.5	12,566	255	2	1.24	1.05–1.46	0.01
CURRENT-OASIS 7	TIMI	12,520	210	1.7	12,566	168	1.3	1.26	1.03–1.54	0.03
ARMYDA-4 RELOAD	TIMI	252	0	0	25[illegible]	0	0	*ns*	*ns*	*ns*
ARMYDA-6MI	TIMI	103	2	1.9	98	2	2	*ns*	*ns*	*ns*
Choi et al. 2011	Study-defined	1217	5	0.4	1447	6	0.4	*ns*	*ns*	0.977
Overall for TIMI								*0.92*	*0.74–1.16*	0.85
Prasugrel										
TRITON-TIMI-38 (15 months) TIMI	6813	146	2.4	6795	11[illegible]	1.8	1.32	1.03–1.68	0.03	
Ticagrelor										
PLATO (12 months)	TIMI	9333	221	2.8	9291	177	2.2	1.25	1.03–1.53	0.03

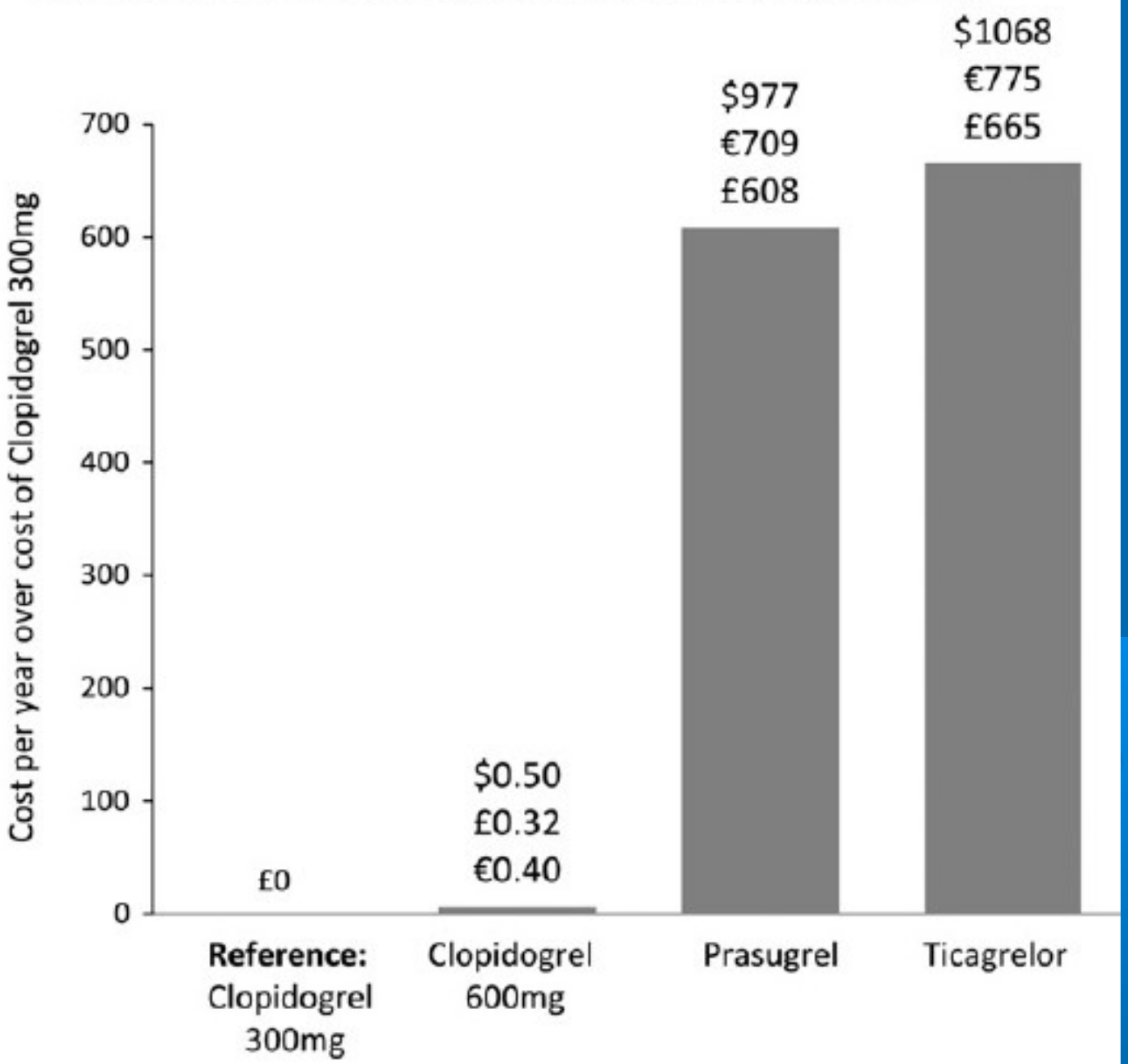
Nijjer et ал. International Journal of Cardiology 158 (2012) 181–185

A. Relative risk r
relative to Clo

B. Relative ris
relative to



C. Additional financial cost per year, relative to Clopidogrel 300mg



International Journal of Cardiology 158 (2012) 181–185

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International Journal of Cardiology

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Editorial

Quantitative comparison of clopidogrel 600 mg, prasugrel and ticagrelor, against clopidogrel 300 mg on major adverse cardiovascular events and bleeding in coronary stenting: Synthesis of CURRENT-OASIS-7, TRITON-TIMI-38 and PLATO☆

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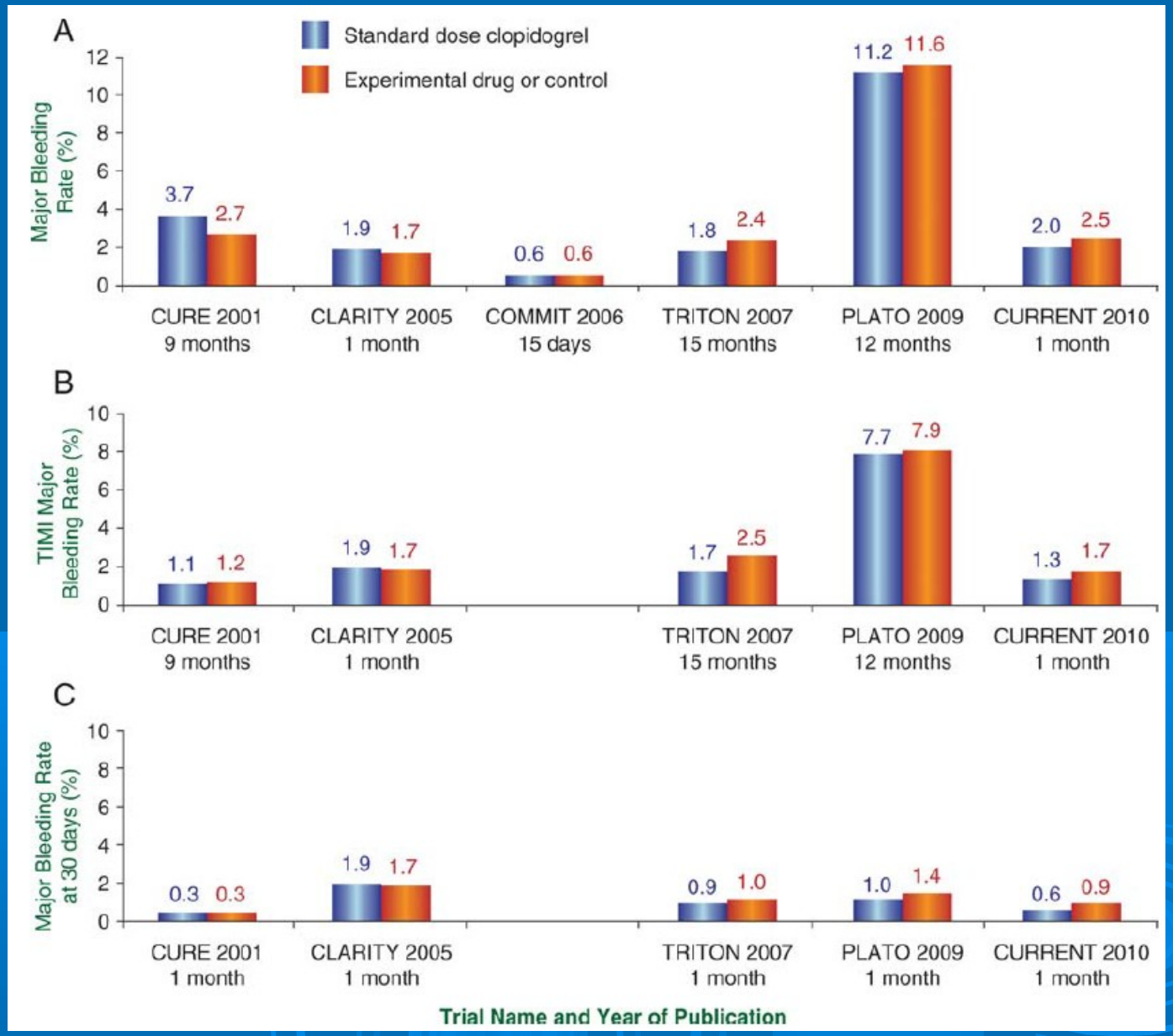
hold clinical trial purse-strings. Second, to detect a difference one-third as large requires a study 9 times as large, with attendant very large costs. Third, the large size and/or prolonged duration of such a trial, starting from this late stage in the patent lifespan of each of the two new drugs, would leave commercial sponsors with little or no remaining duration of commercial monopoly. With headline figures less superficially impressive, recruitment vastly more difficult, and time to return investment severely curtailed, commercial trials with these endpoints are triply unlikely.

It is unwise to await head-to-head trials on every question [22]: they may not materialise for a long time, or ever. First, the difference

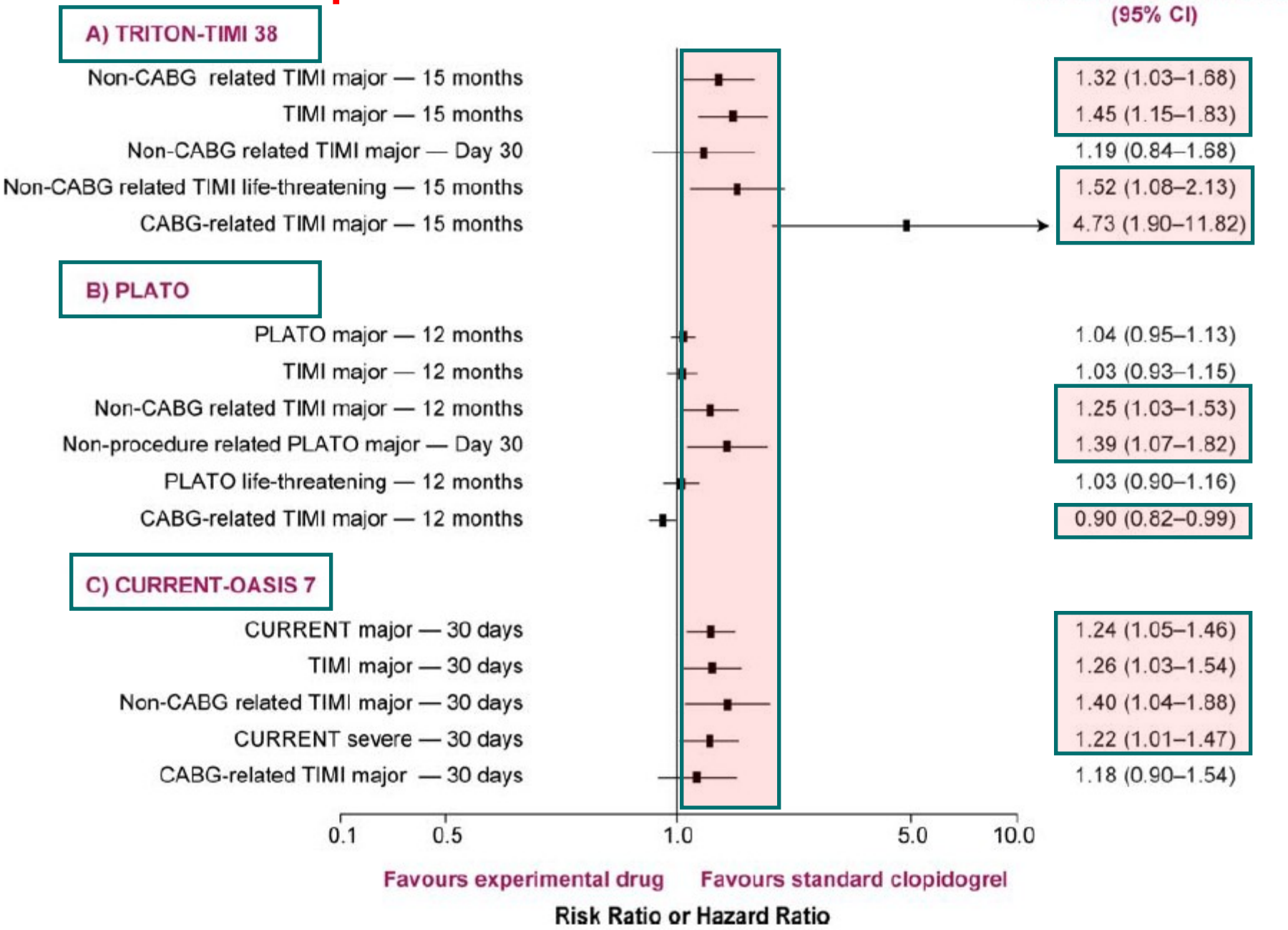
The three new competing strategies all have merit with reduction in MACE compared to clopidogrel 300 mg/75 mg, at some incremental

Колко е важна дефиницията на кървенето?



Quinlan et al. Eur. Heart Jour. 2011; 32: 2256-2265

Риск от кървене съгласно ТИМИ скала



Quinlan et al. Eur. Heart Jour. 2011; 32: 2256-2265

Значение на дозата на АСА

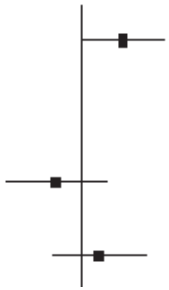
Table 2. Clinical Events Committee–Adjudicated Primary Efficacy End Points and Bleeding in the United States and the Rest of the World by Treatment

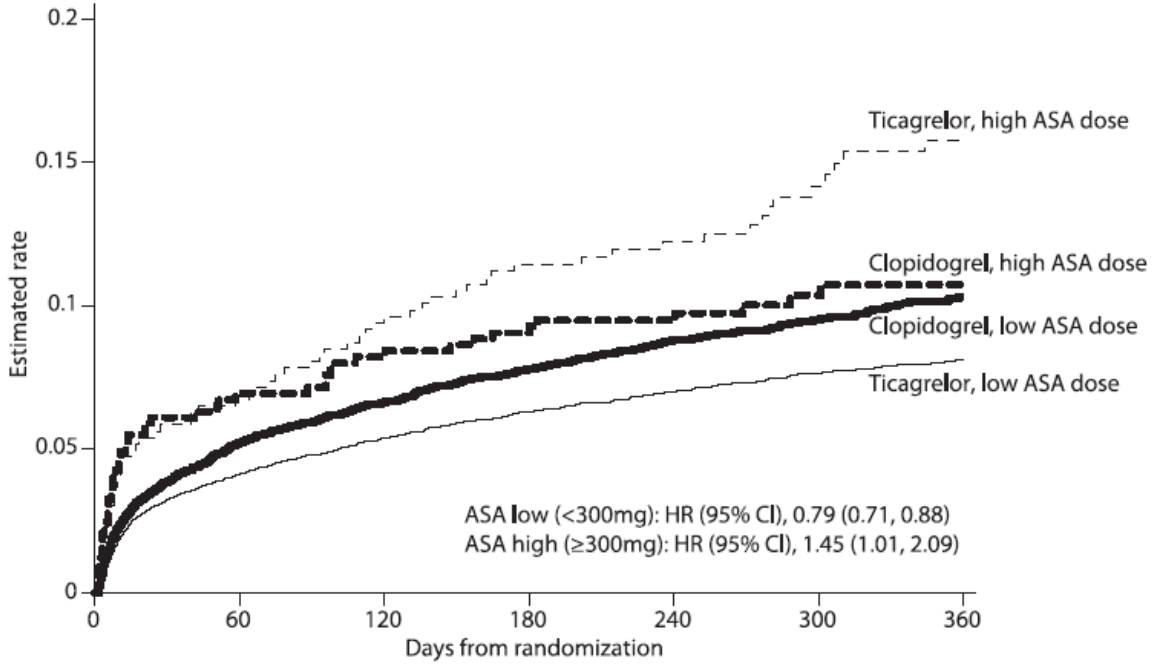
		Ticagrelor (n=9333)			Clopidogrel (n=9291)				
End Point	Region	n	Patients With Events, n (%)	KM, %	n	Patients With Events, n (%)	KM, %	HR (95% CI)	*P*
Cardiovascular death/MI*/stroke	US	707	84 (11.9)	12.6	706	67 (9.5)	10.1	1.27 (0.92–1.75)	0.1459
	ROW	8626	780 (9.0)	9.6	8585	947 (11.0)	11.8	0.81 (0.74–0.90)	<0.0001
Cardiovascular death	US	707	24 (3.4)	3.7	706	19 (2.7)	2.7	1.26 (0.69–2.31)	0.4468
	ROW	8626	329 (3.8)	4.0	8585	423 (4.9)	5.3	0.77 (0.67–0.89)	0.0005
MI*	US	707	64 (9.1)	9.6	706	47 (6.7)	7.2	1.38 (0.95–2.01)	0.0956
	ROW	8626	440 (5.1)	5.5	8585	546 (6.4)	6.9	0.80 (0.70–0.90)	0.0004
Stroke	US	707	7 (1.0)	1.0	706	4 (0.6)	0.6	1.75 (0.51–5.97)	0.3730
	ROW	8626	118 (1.4)	1.5	8585	102 (1.2)	1.3	1.15 (0.88–1.50)	0.2964
All-cause mortality	US	707	28 (4.0)	4.2	706	24 (3.4)	3.6	1.17 (0.68–2.01)	0.5812
	ROW	8626	371 (4.3)	4.6	8585	482 (5.6)	6.1	0.77 (0.67–0.88)	0.0001
PLATO major bleeding	US	682	77 (11.3)	12.2	675	74 (11.0)	11.9	1.05 (0.76–1.45)	0.7572
	ROW	8553	884 (10.3)	11.5	8511	855 (10.1)	11.1	1.04 (0.94–1.14)	0.4696
PLATO non-CABG major bleeding	US	682	29 (4.3)	5.1	675	25 (3.7)	4.3	1.20 (0.70–2.04)	0.5115
	ROW	8553	333 (3.9)	4.4	8511	281 (3.3)	3.7	1.19 (1.01–1.39)	0.0330
PLATO major/minor bleeding	US	682	101 (14.8)	16.4	675	92 (13.6)	15.2	1.11 (0.84–1.48)	0.4599
	ROW	8553	1238 (14.5)	16.1	8511	1123 (13.2)	14.6	1.11 (1.02–1.20)	0.0114

Mahaffey et al Circulation. 2011;124:544-554

Значение на дозата на АСА
НЕТНА КЛИНИЧНА ПОЛЗА

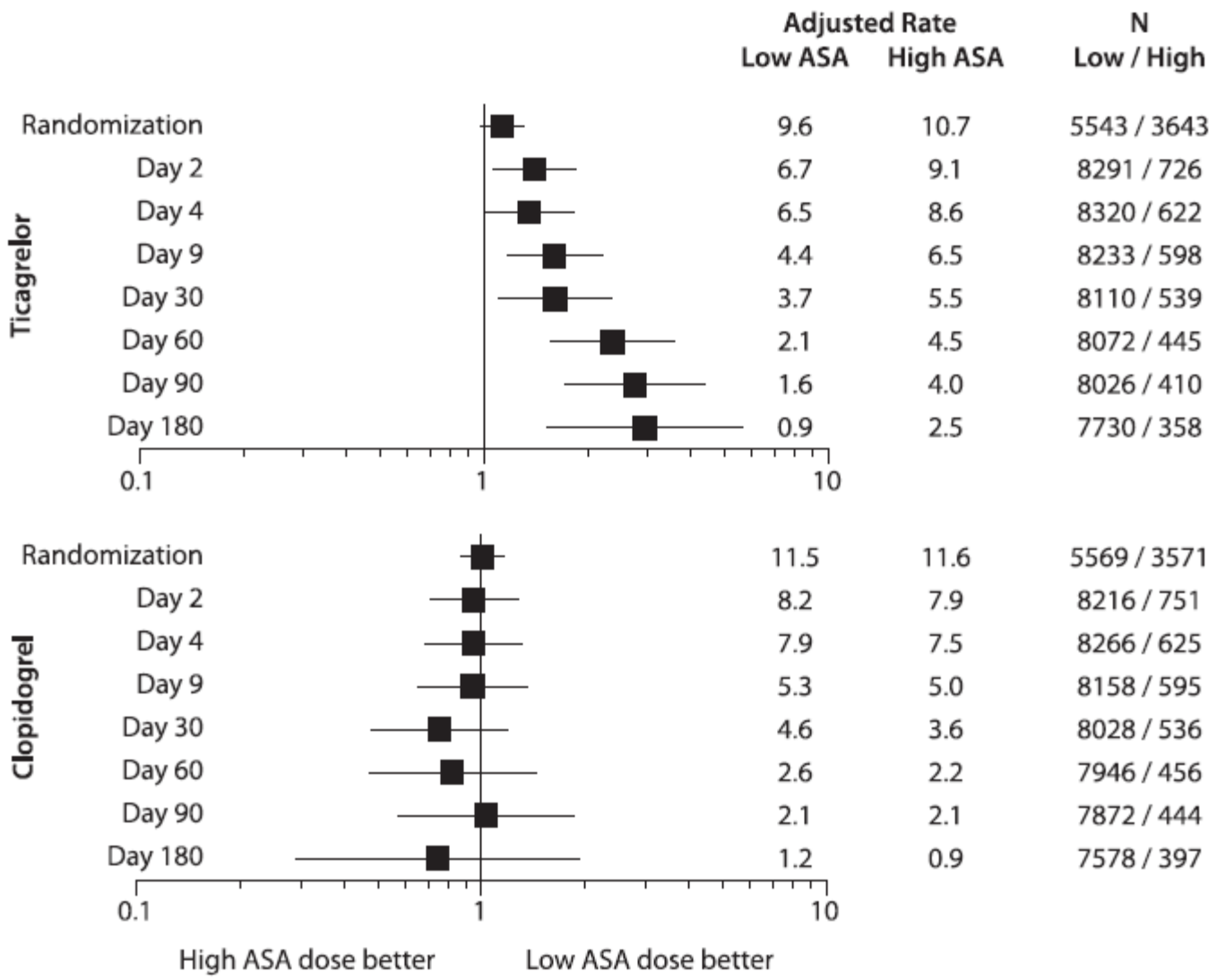
Region	ASA Dose (mg)	Ticagrelor N	Ticagrelor E	Clopidogrel N	Clopidogrel E	HR (95% CI)
US	≥300	324	40	352	27	1.62 (0.99, 2.64)
	>100–<300	22	2	16	2	*
	≤100	284	19	263	24	0.73 (0.40, 1.33)
Non-US	≥300	140	28	140	23	1.23 (0.71, 2.14)
	>100–<300	503	62	511		
	≤100	7449	546	7443		





Mahaffey et al Circulation. 2011;124:544-554

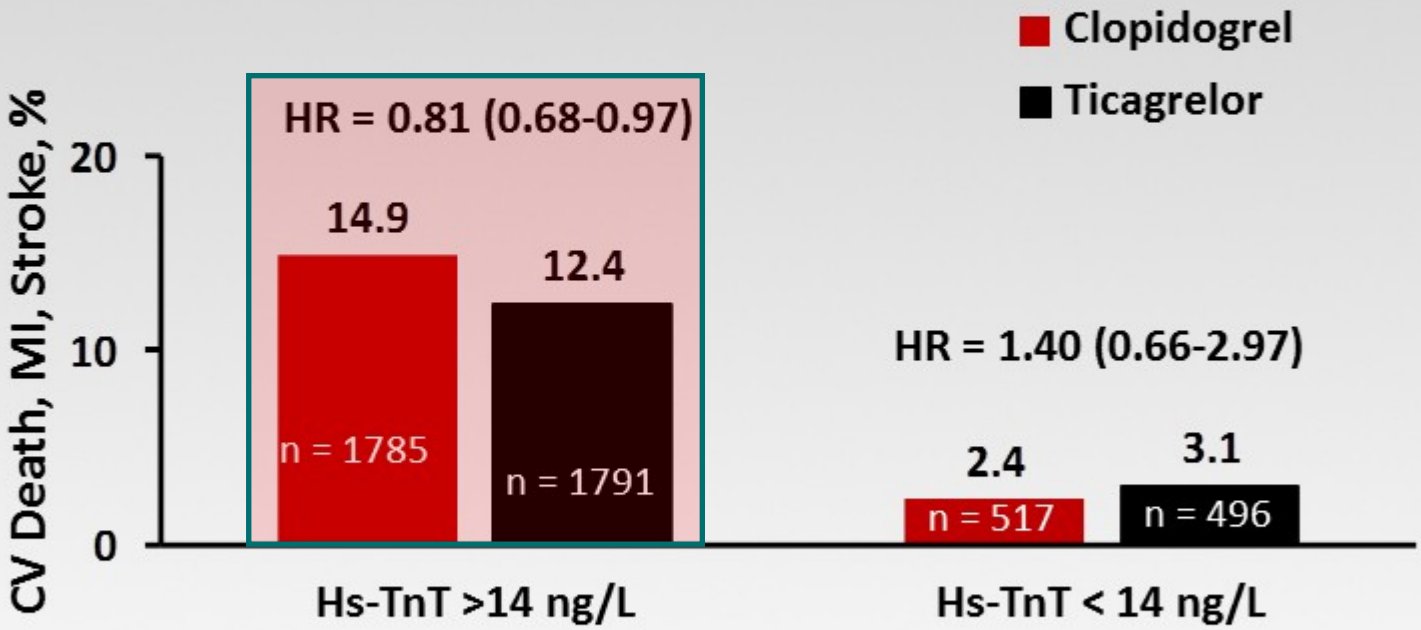
НЕТНА КЛИНИЧНА ПОЛЗА



Mahaffey et al Circulation. 2011;124:544-554

PLATO hs-TnT: Noninvasive Group

No benefit for ticagrelor vs clopidogrel in hs-TnT negative subgroups

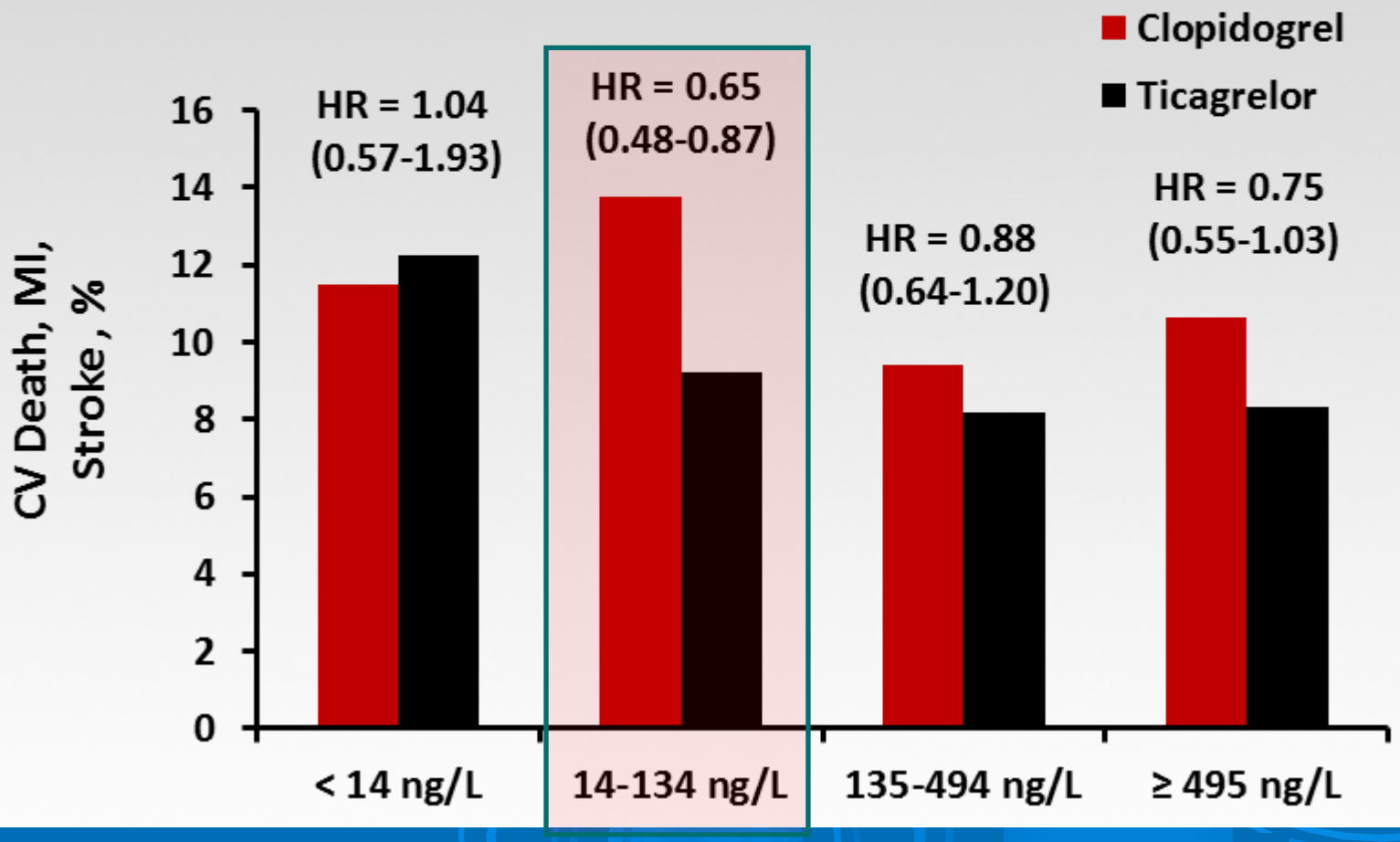


Clopidogrel = 300-600 mg load, 75 mg daily
Ticagrelor = 180 mg load, 90 mg twice daily

PLATO: hs-TnT and Outcomes Invasively Managed Patients

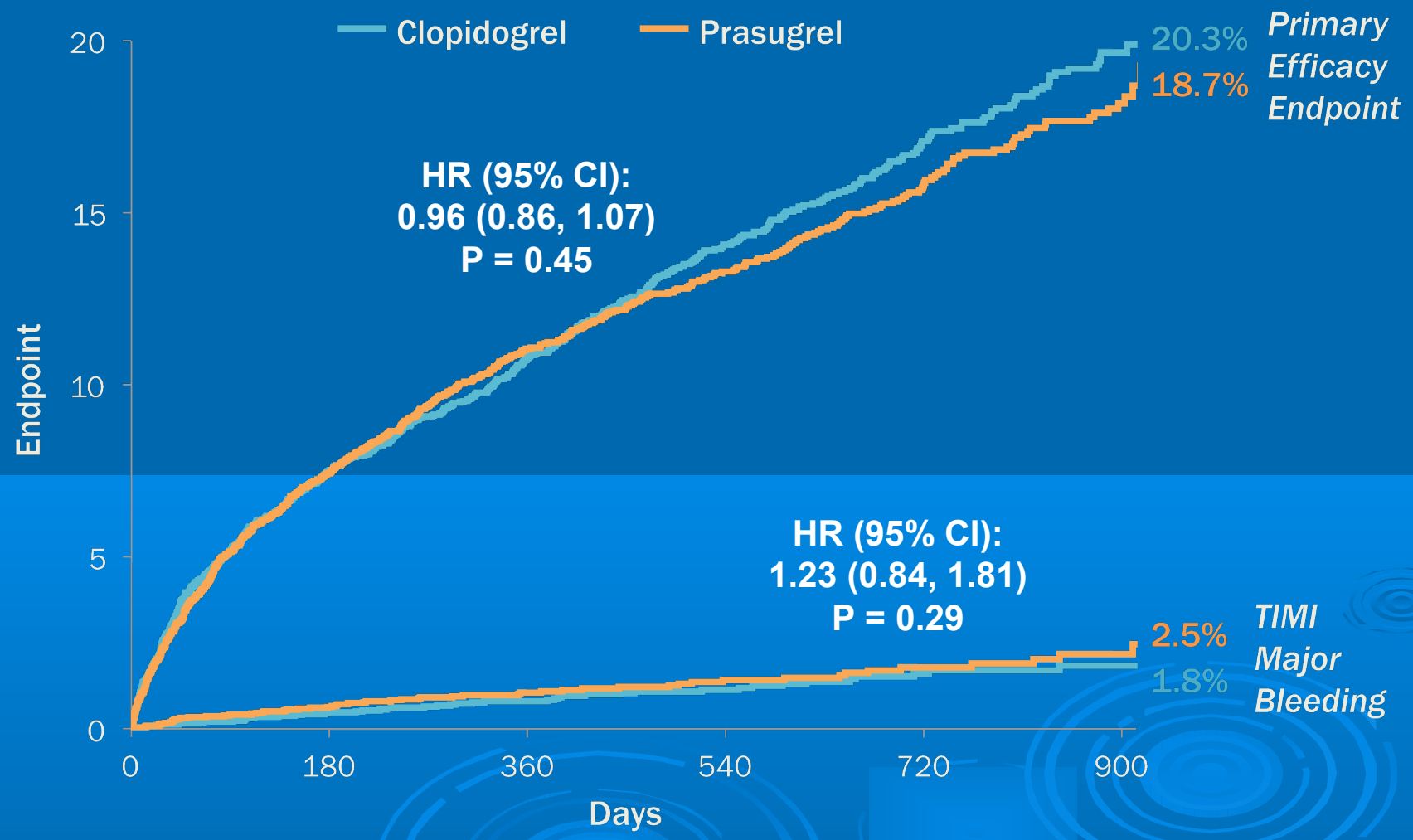
hs-TnT and outcome, *P* = 0.09

Interaction between hs-TnT and ticagrelor vs clopidogrel and outcome, *P* = 0.39



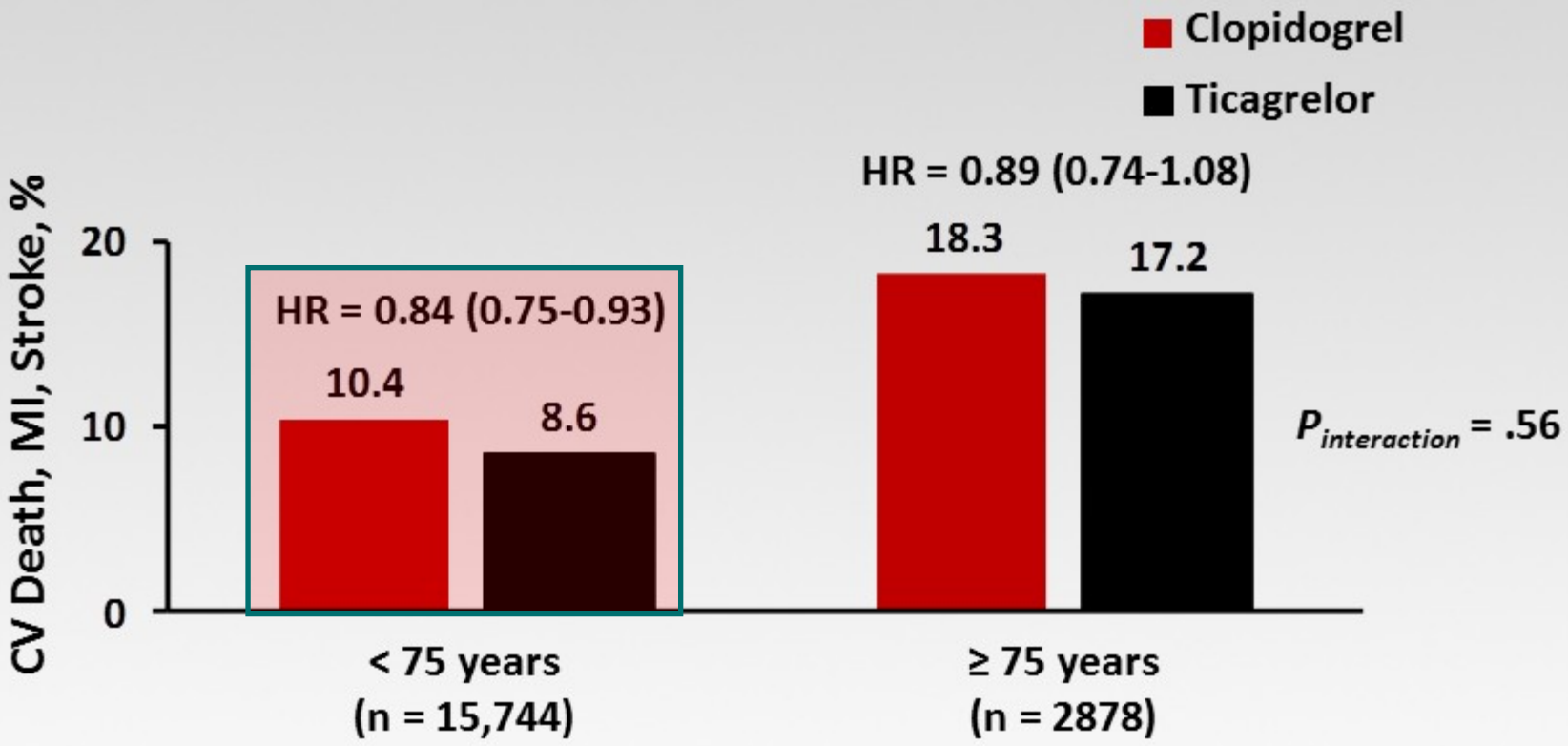
Primary Efficacy Endpoint (CV Death, MI, Stroke) and TIMI Major Bleeding Through 30 Months

(Overall TRILOGY population)



PLATO Elderly: Primary End Point

Absolute reduction in all-cause mortality greater in elderly vs younger patients (2.6% vs 1.2%)



Clopidogrel = 300-600 mg load, 75 mg daily
Ticagrelor = 180 mg load, 90 mg twice daily

Резистентност спрямо клопидогрел

Дефиниция на клопидогреловата резистентност

Antiplatelet Drug Non-responsiveness/Resistance = **Failure to Inhibit Target/ Persistent Activity of the Target**

Clopidogrel

1. Absolute change in (ADP) aggregation ≤ 10%

Δ Aggregation = Max. baseline aggregation - Max. post-drug aggregation.[1]

2. Relative platelet inhibition < 10% [2]

3 . > 50% PRI ($P2Y_{12}$ Reactivity- VASP-P assay)[3]

1. Gurbel et al. *Circulation*. 2003;107:2908-13., 2. Muller et al. *Thromb Haemost.* 2003;89:783,
3. Barragan et. al. *Catheter Cardiovasc Interv*. 2003;59:295;

Genetic Factors

- Polymorphisms of CYP
- Polymorphisms of GPIa
- Polymorphisms of $P2Y_{12}$
- Polymorphisms of GPIIIa
- Polymorphisms of CYP 3A4
- Polymorphisms of CYP 2C19

Вариабилност на отговора с/о Clopidogrel

Clinical Factors

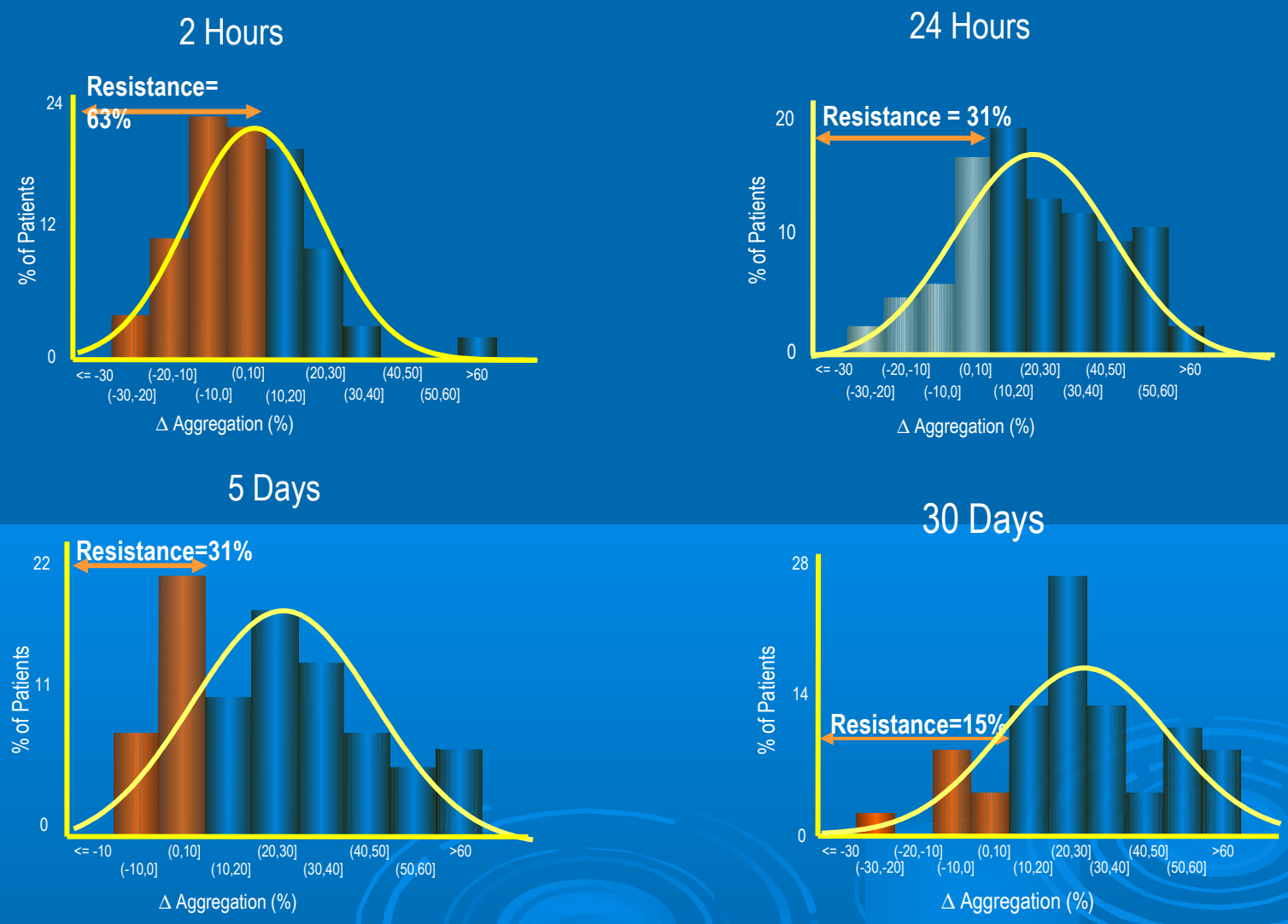
- Failure to prescribe/poor compliance
- Under-dosing
- Poor absorption
- Drug-drug interactions involving CYP3A4
- Acute coronary syndrome
- Diabetes mellitus/insulin resistance
- Elevated body mass index

Cellular Factors

- Accelerated platelet turnover
- Reduced CYP3A metabolic activity
- Increased ADP exposure
- Up-regulation of the $P2Y_{12}$ pathway
- Up-regulation of the $P2Y_1$ pathway
- Up-regulation of the P2Y-independent pathways (collagen, epinephrine, TXA_2, thrombin)

Angiolillo DJ et al. *J Am Coll Cardiol.* 2007;49:1505-1516.

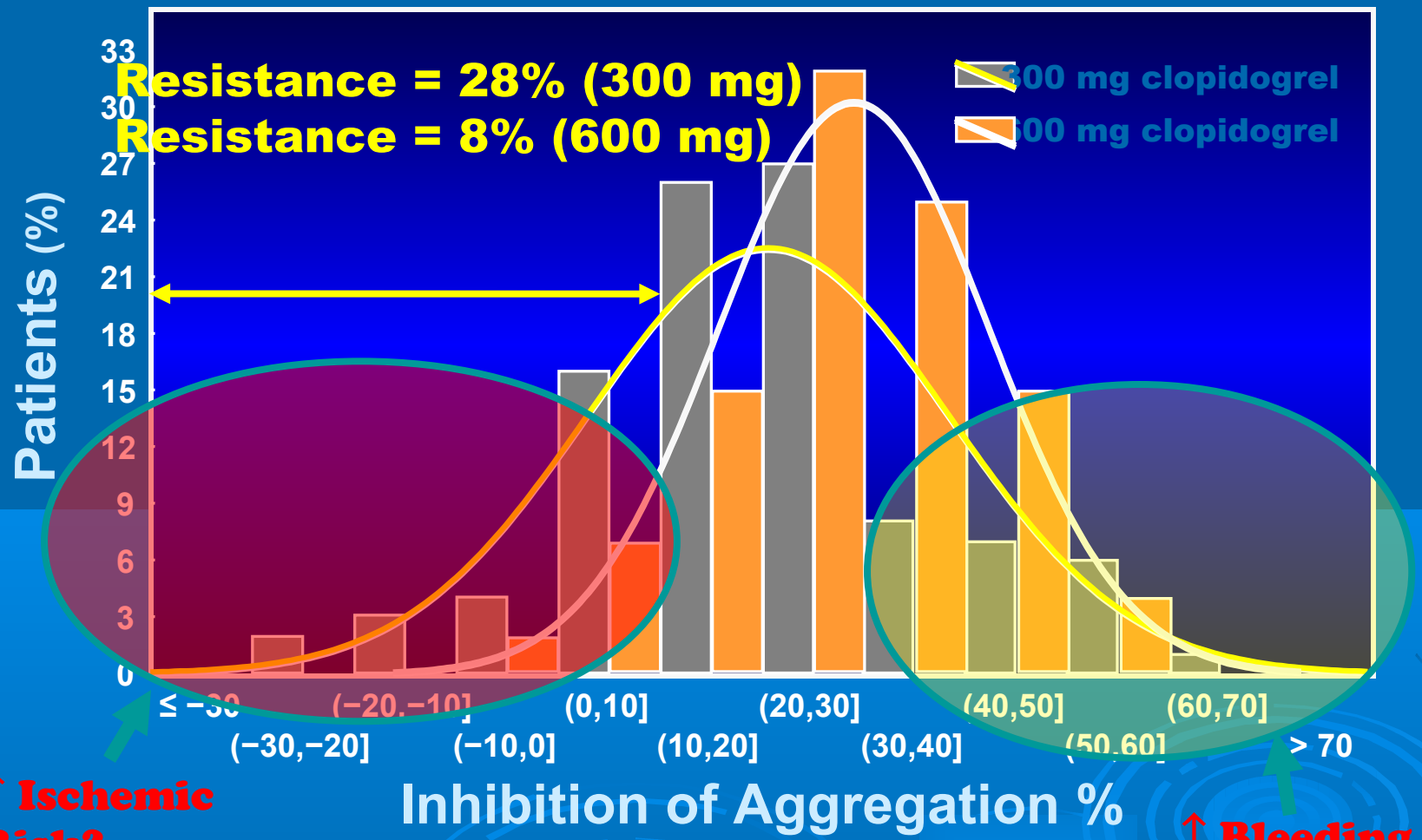
ВАРИАБИЛНОСТ НА ИНХИБИЦИЯТА В ЗАВИСИМОСТ ОТ ПРОДЪЛЖИТЕЛНОСТТА НА ПРИЛОЖЕНИЕ



Gurbel et al. *Circulation*. 2003;107:2908-2913.

ВАРИАБИЛНОСТ НА ОТГОВОРА КЪМ КЛОПИИДОГРЕЛ

5 μM ADP-induced Aggregation at 24 h



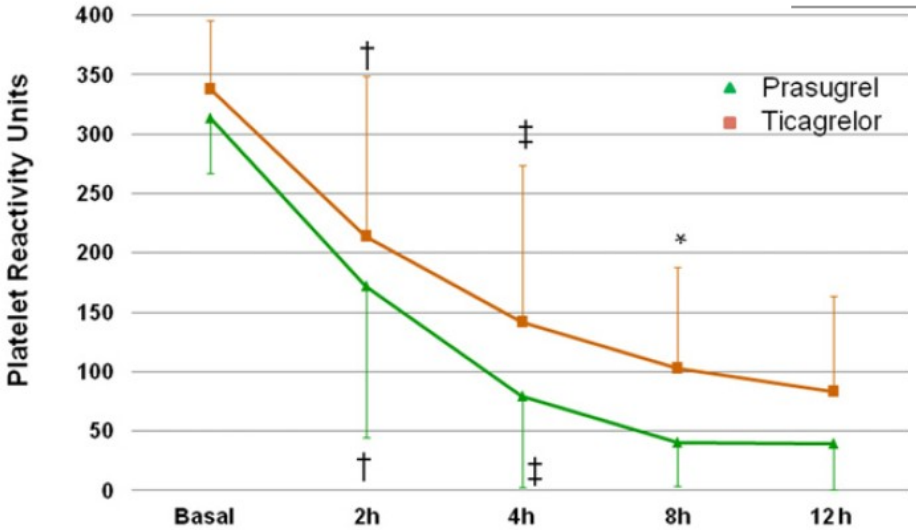
↑ Ischemic Risk?

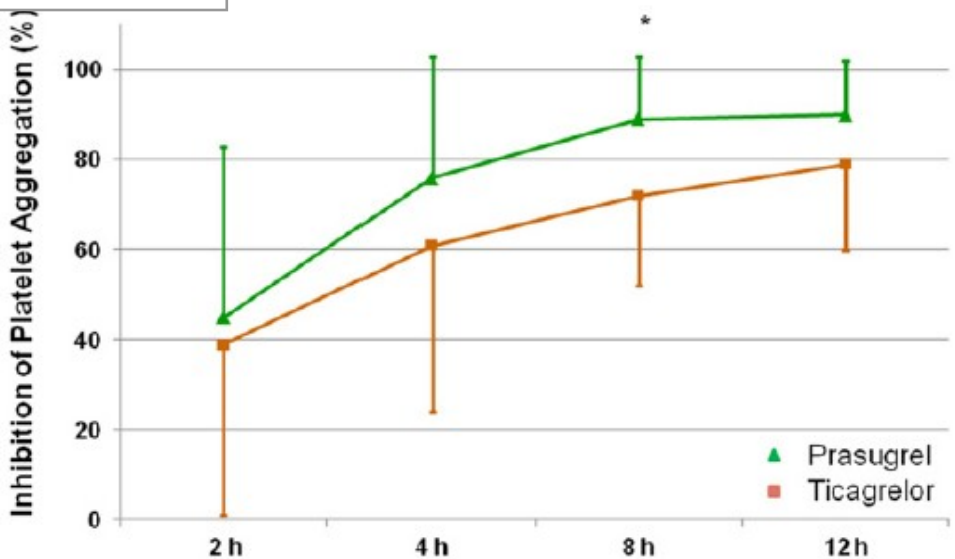
↑ Bleeding Risk?

Gurbel et al. *Circulation.* 2003;107:2908-2913.
Gurbel et al. *J Am Coll Cardiol.* 2005;45:1392-1396.

Пациенти с ОКС със СТ елевация

RAPID STUDY





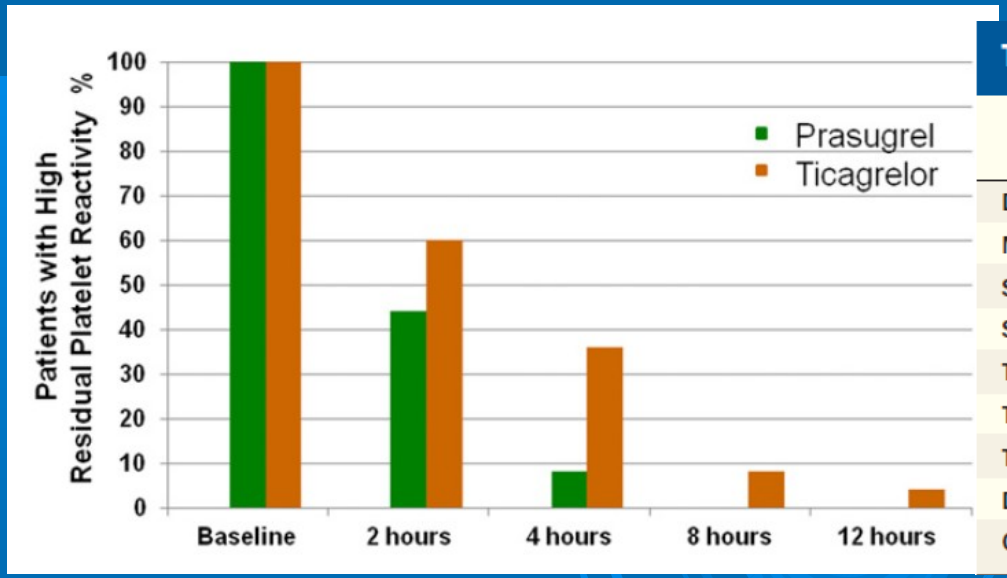


Table 2 In-Hospital Outcomes

In-Hospital Events	Prasugrel (n = 25)	Ticagrelor (n = 25)	p Value
Death	0 (0%)	2 (8%)	0.149
Myocardial infarction	1 (4%)	0 (0%)	0.312
Stent thrombosis	1 (4%)	0 (0%)	0.312
Stroke	0 (0%)	0 (0%)	1.000
TIMI major bleeding	0 (0%)	0 (0%)	1.000
TIMI minor bleeding	0 (0%)	3 (12%)	0.074
TIMI minimal bleeding	0 (0%)	2 (8%)	0.149
Dyspnoea	0 (0%)	5 (20%)	0.018
Contrast-induced nephropathy	0 (0%)	5 (20%)	0.018

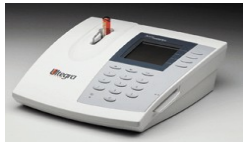
Parodi et al. JACC Vol. 61, No. 15, 2013:1601–6

КЛОПИДОГРЕЛОВА РЕЗИСТЕНТНОСТ НАЦИОНАЛНА КАРДИОЛОГИЧНА БОЛНИЦА

- 603 pts – UA, STEMI, NSTEMI
- Jan 2008 – June 2010
- PCI with BMS/DES
- 300 + 75 mg loading (24h) + maintenance dose + 100 mg ASA.
- When GP IIb/IIIa applied during the procedure the pt was excluded

Multiple Platelet Function Analyzer
Impedance aggregometry

Platelet function testing
Newest consensus paper

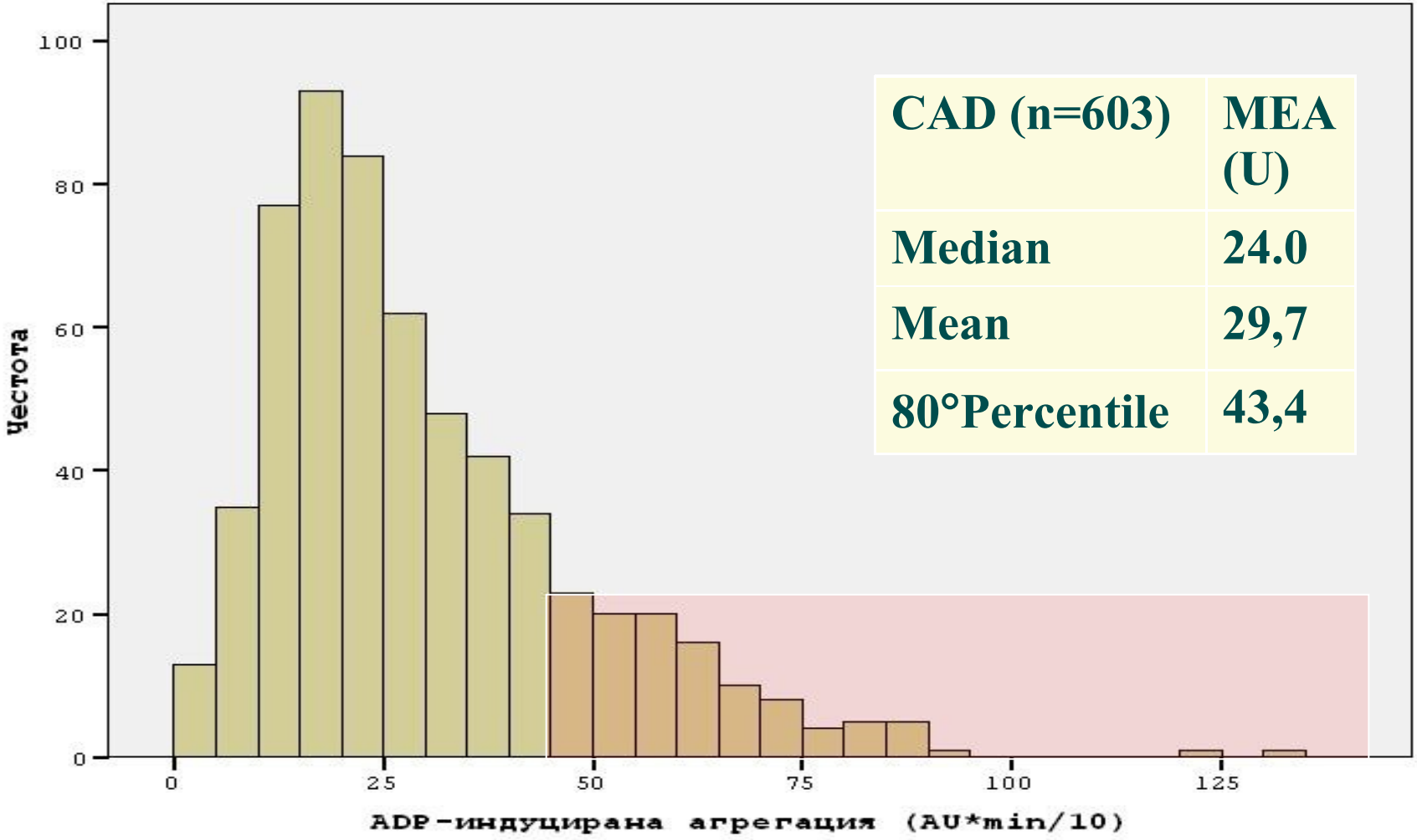
		Odds ratio
	Verifynow	2-3
	VASP	1.16
	LTA	2-6
	Multiplate	12

→ **highest relative risk for clopidogrel „resistant“ patients using the Multiplate analyzer**

Andreas Calatzis, calatzisa@gmail.com

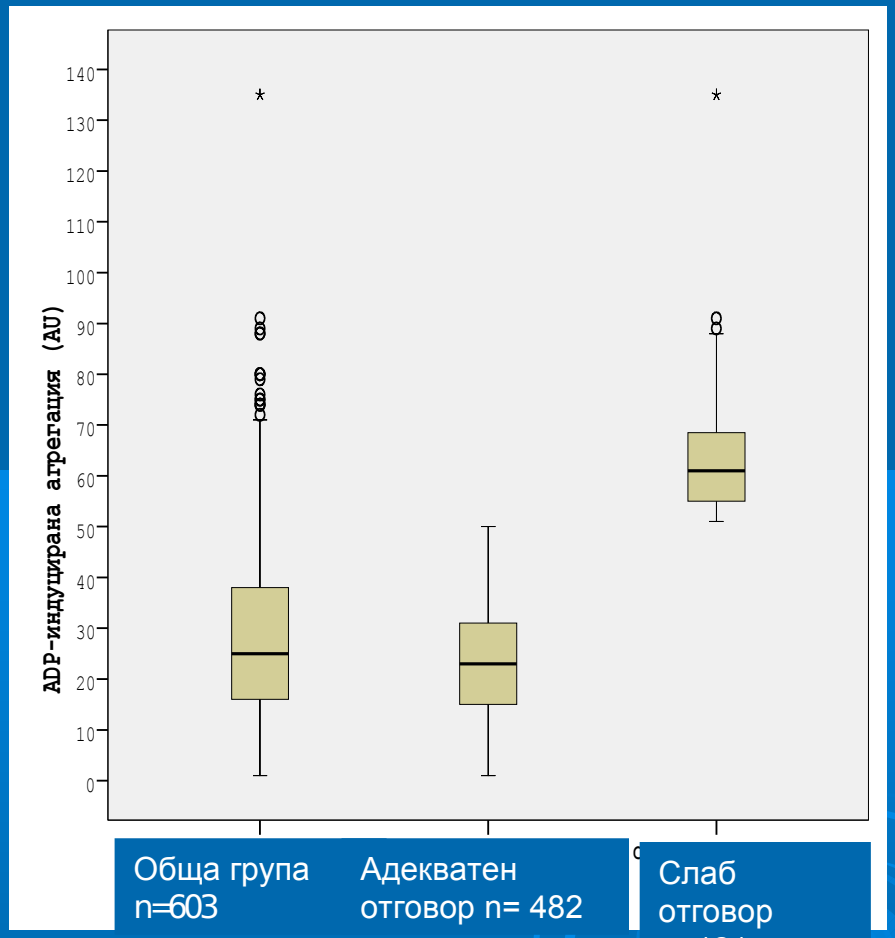
09.2010 г. JACC White Paper

Разпределение на АДФ-индуцирана тромбоцитна агрегация (N=603)



CAD (n=603)	MEA (U)
Median	24.0
Mean	29,7
80°Percentile	43,4

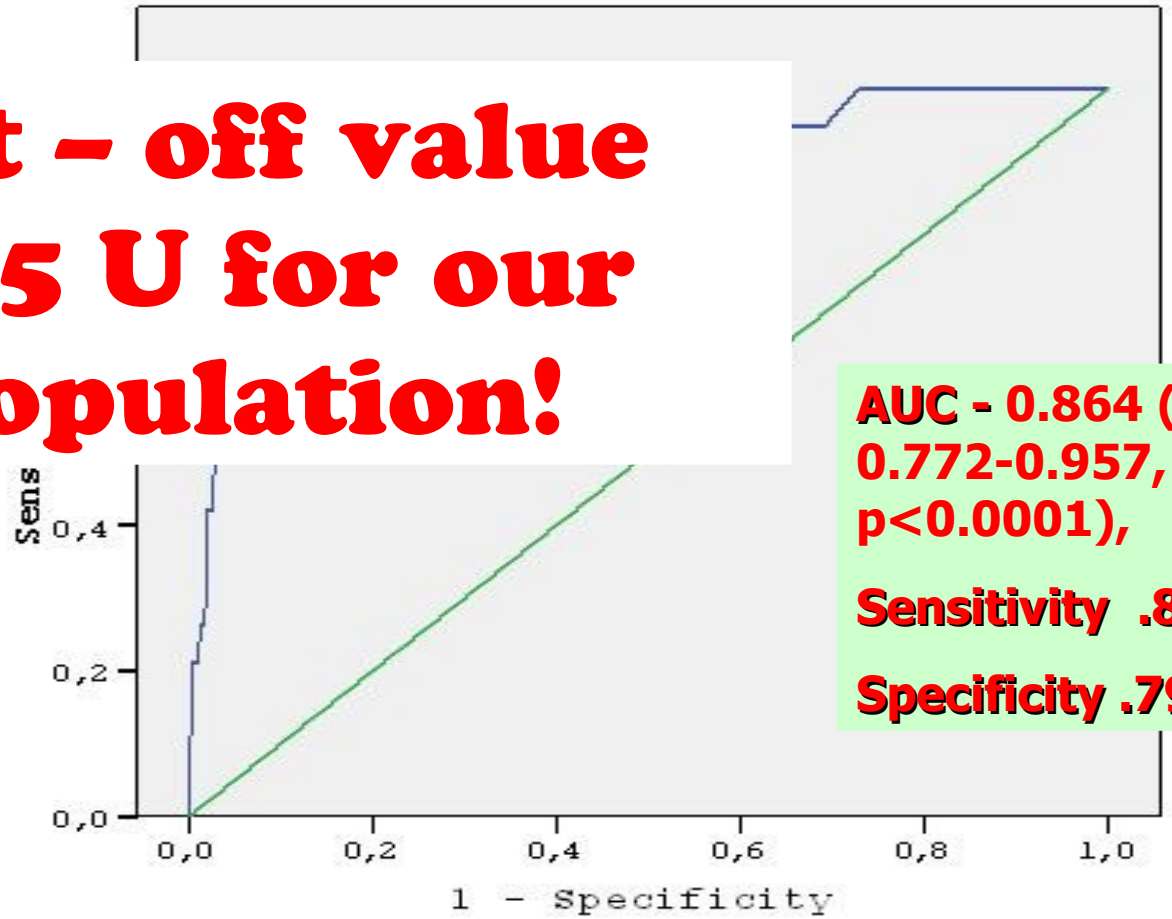
Остатъчна тромбоцитна активност след ПКИ



- 121/603 (20%) pts > 53 U - unsatisfactory responce.
- ST: 16/121 (13,2%) – high residual activity >98 percentile (> 70 U) vs. 3/482 (0,6%) adequate reaction – < p 001

Гранична стойност за клопидогрелова резистентност (резидуална тромбоцитна активност)

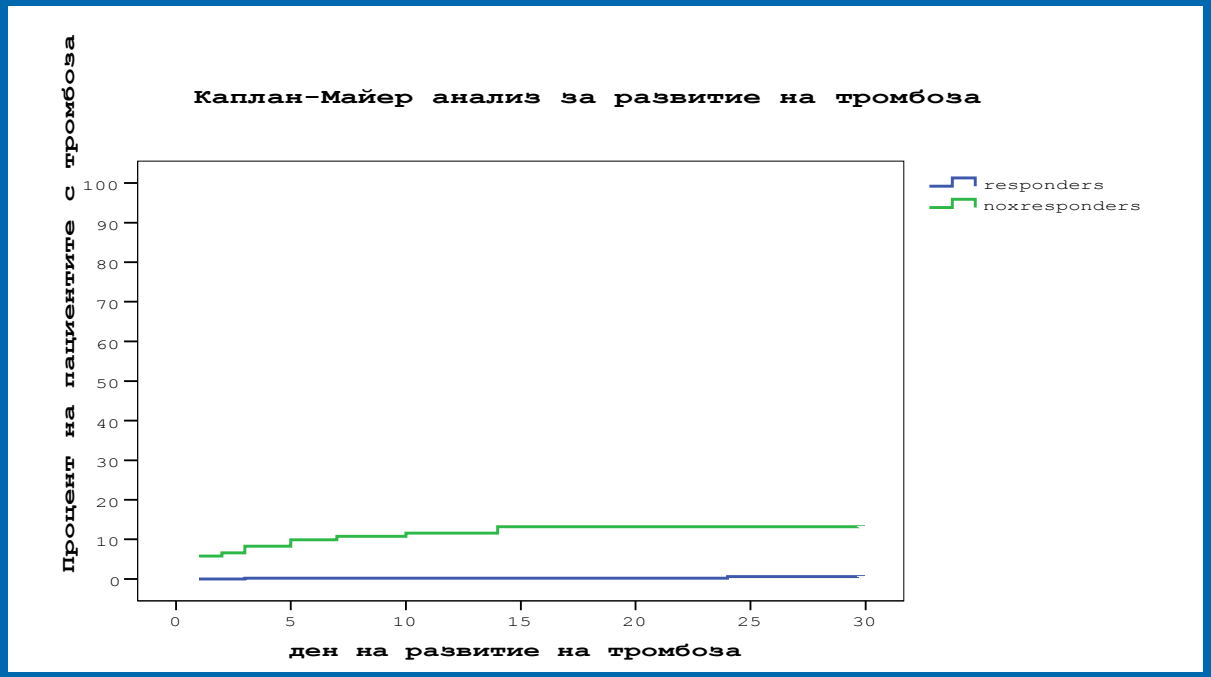
Cut – off value 45.5 U for our population!

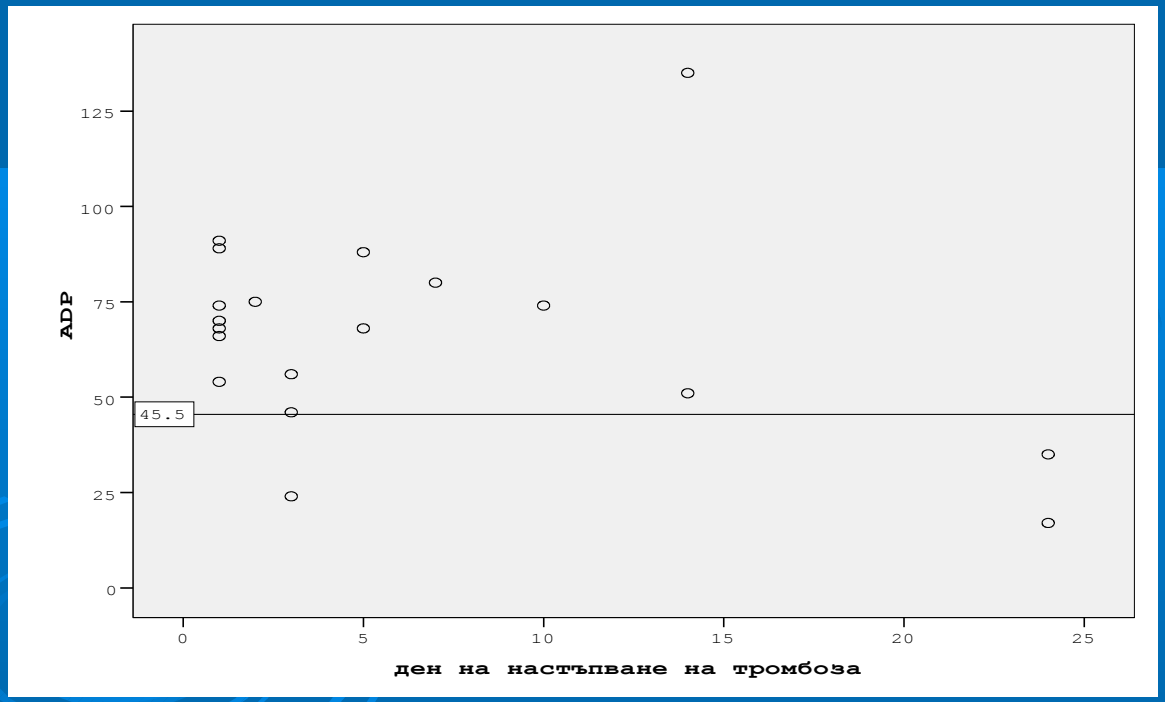


AUC - 0.864 (95% CI 0.772-0.957, p<0.0001),

Sensitivity .84

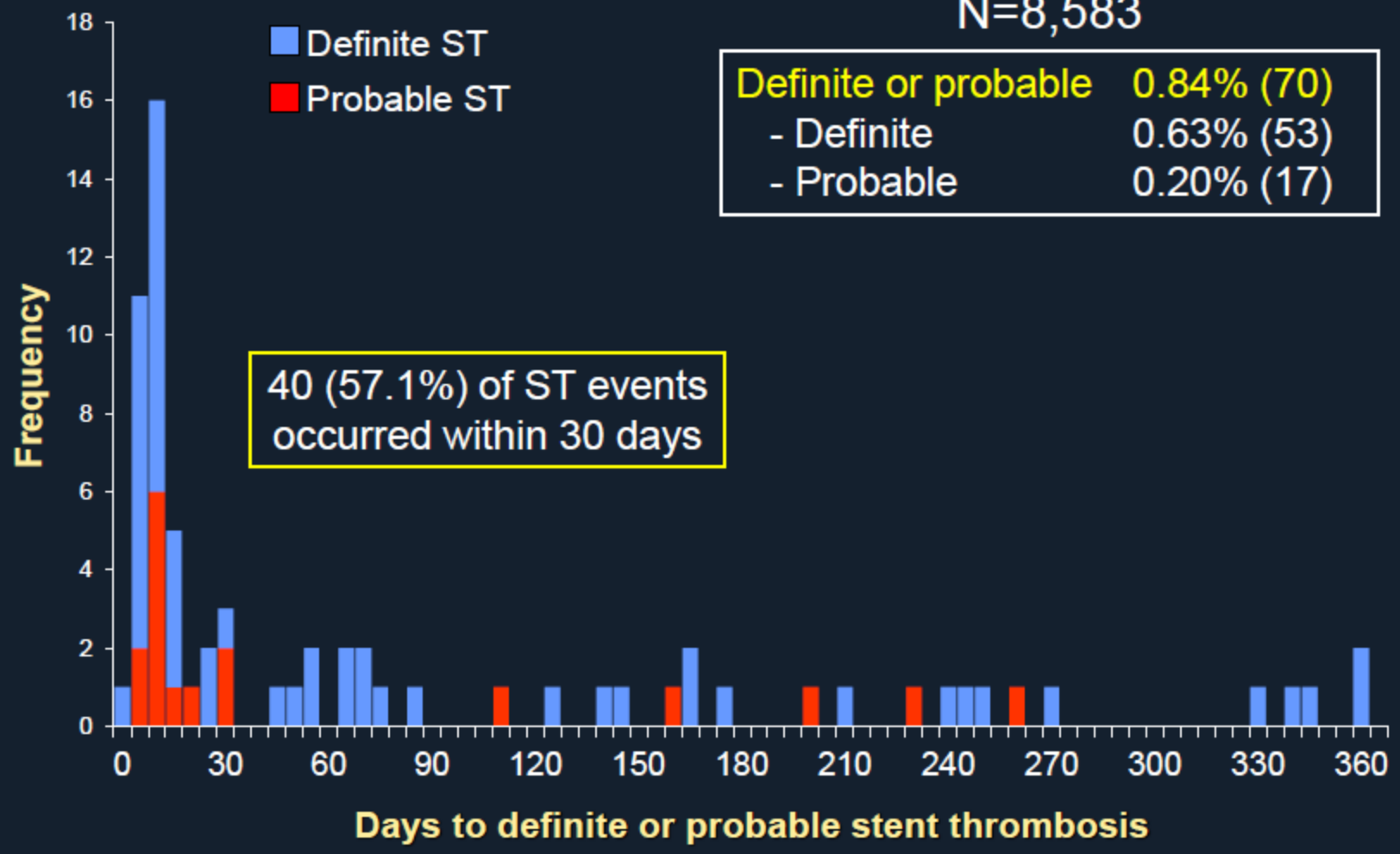
Specificity .79


Каплан-Майер анализ за развитие на тромбоза
Процент на пациентите с тромбоза
100
90
80
70
60
50
40
30
20
10
0
0
5
10
15
20
25
30
ден на развитие на тромбоза
responders
noxresponders

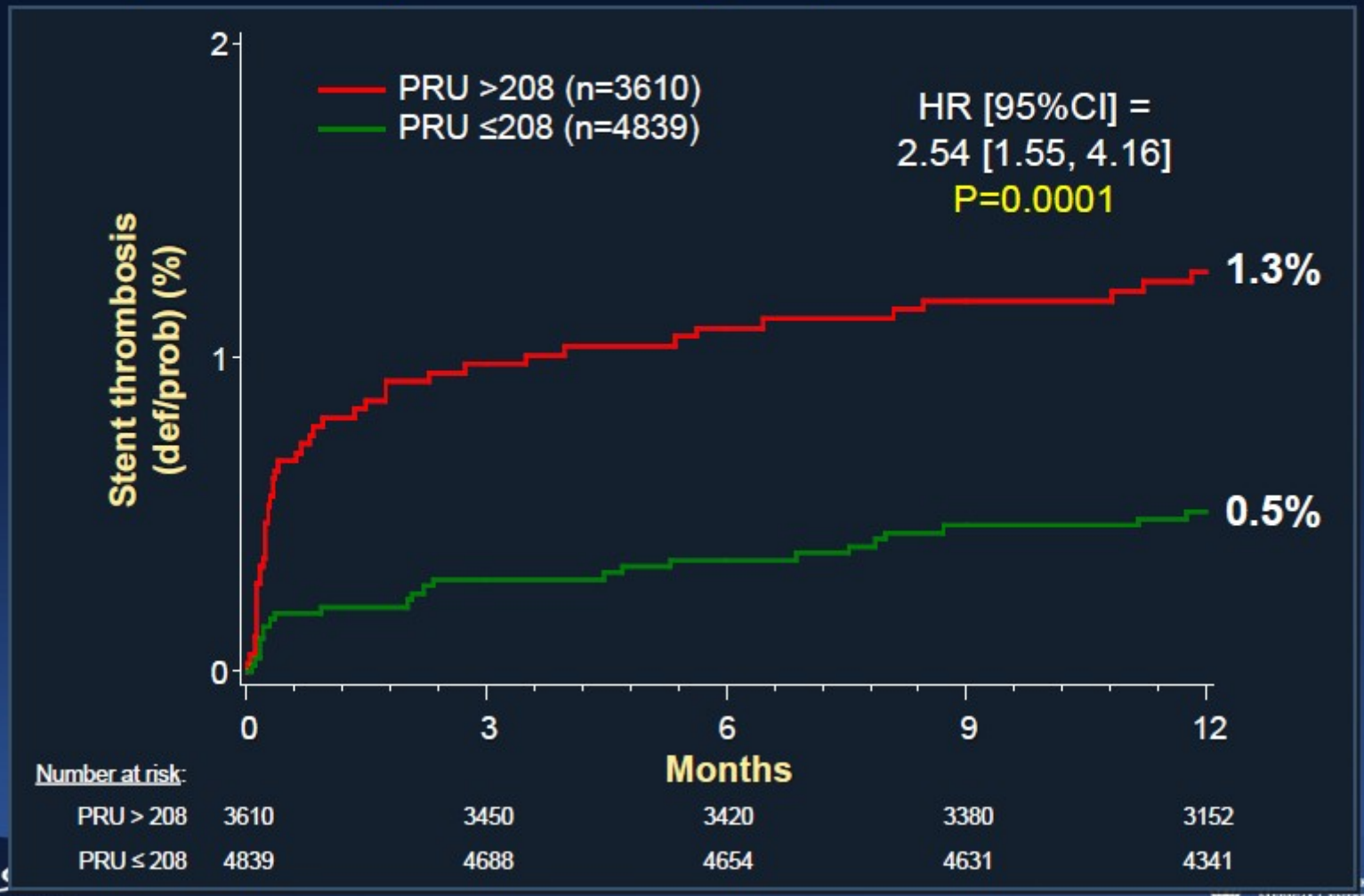

ADP
125
100
75
50
25
0
45.5
0
5
10
15
20
25
ден на настъпване на тромбоза

ADAPT-DES: Time to First Stent Thrombosis

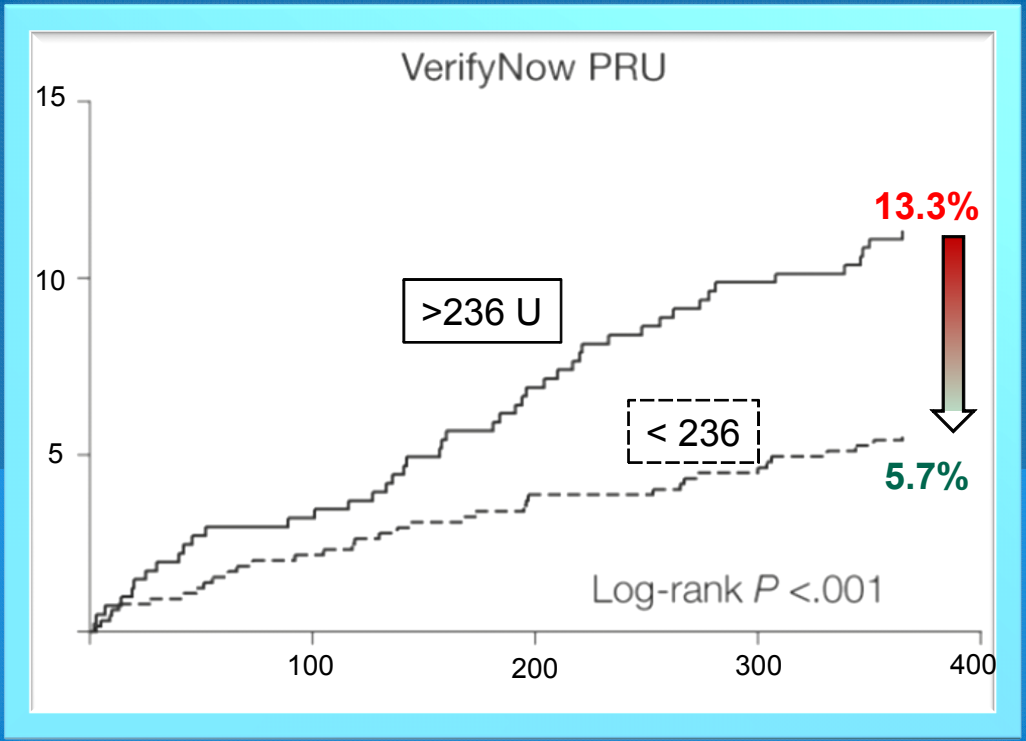
70 patients (0.84%) developed 74 ST events (ARC def/prob)



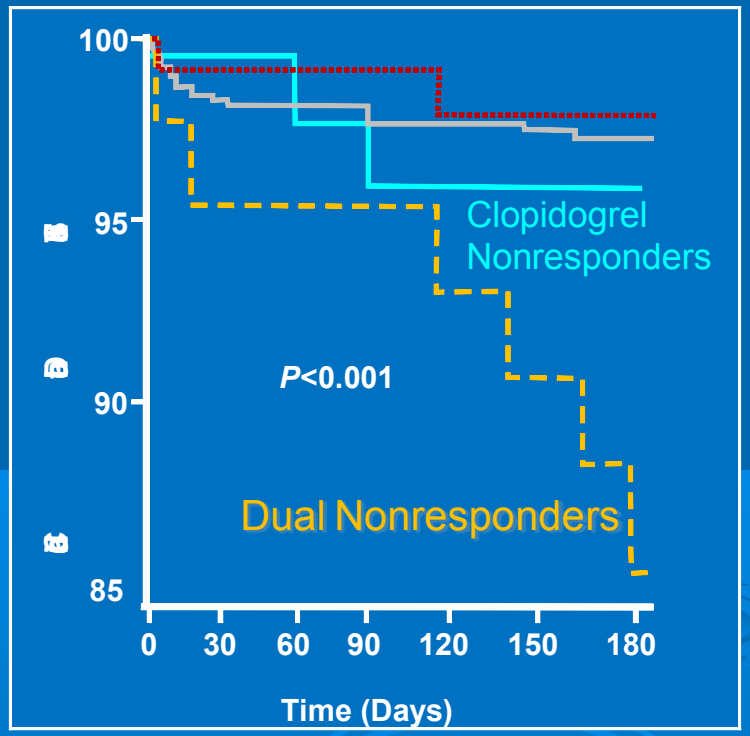
ADAPT-DES: Stent thrombosis (definite or probable) according to post-PCI PRU



Clopidogrel poor responsiveness is associated with MACEs



Breet N. JAMA 2010 Feb 24;303:754-62

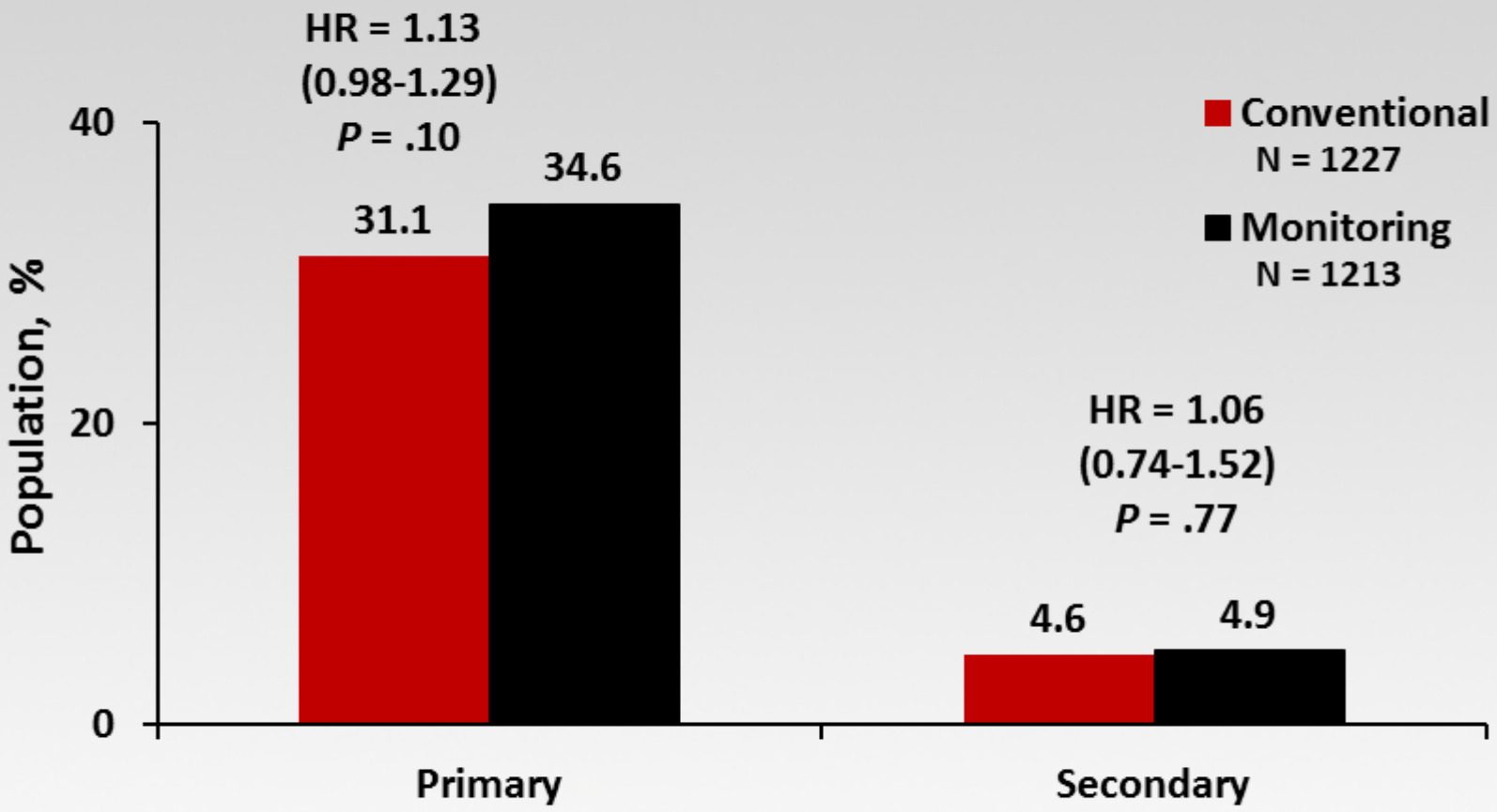


Gori AM, et al. *J Am Coll Cardiol.* 2008;52:734 -739

Как да се преодолее клопидогреловата резистентност?

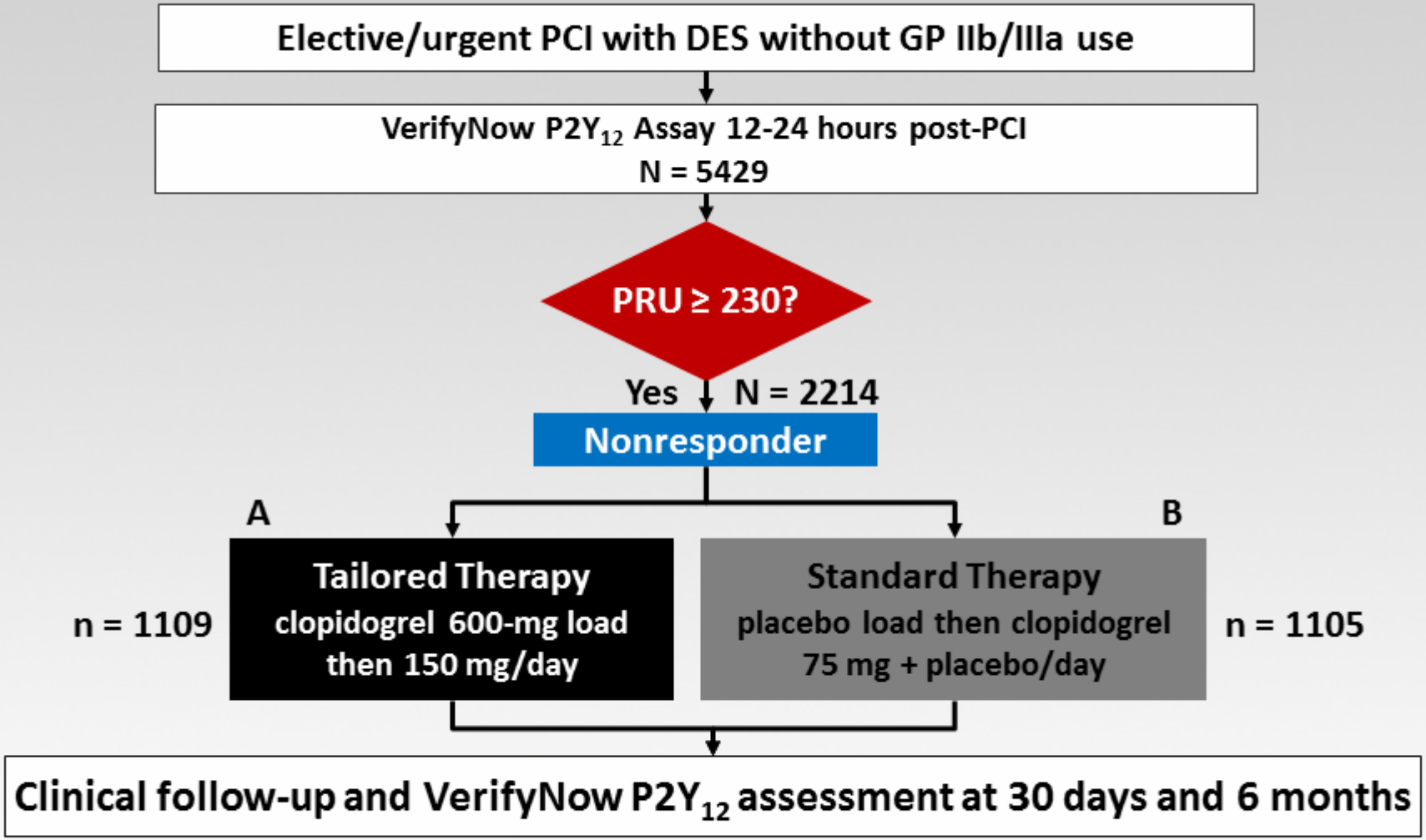
- 240 pts included with unsatisfactory clopidogrel response
- Clopidogrel loading and maintenance doses doubled (600 + 150 mg)
- 18% still resistant: 72 ±13U
- All of them switched to prasugrel -> good PRT achieved 27±12 U
- At 90 days – 0% ST

ARCTIC: Primary & Secondary End Points



- Primary end point: Death, MI, stroke, urgent revascularization and stent thrombosis
- Secondary end point: Urgent revascularization and stent thrombosis

GRAVITAS: Trial Design and Results

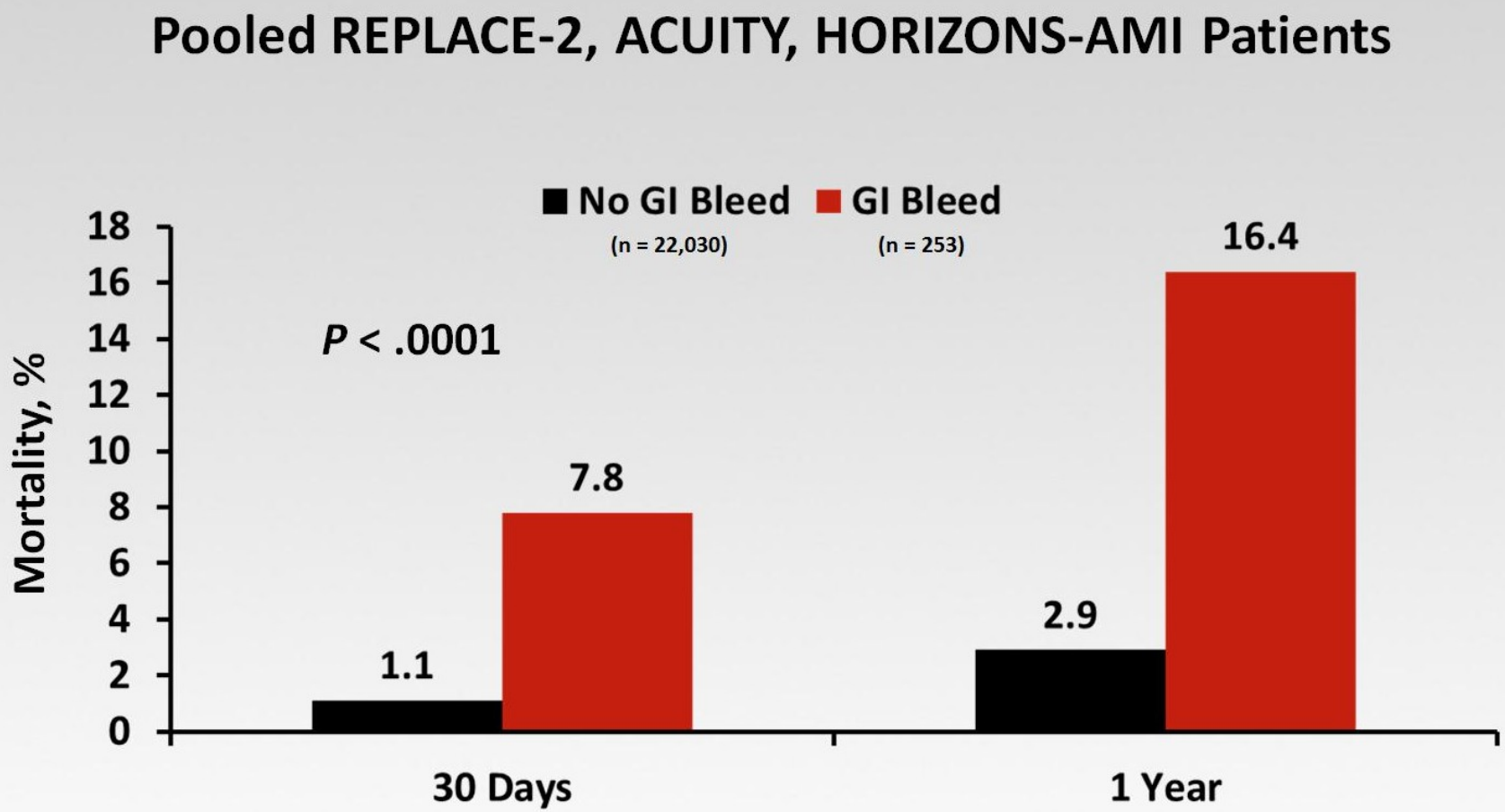


- Primary end point: 6-month CV death, MI, ARC definite/probable ST

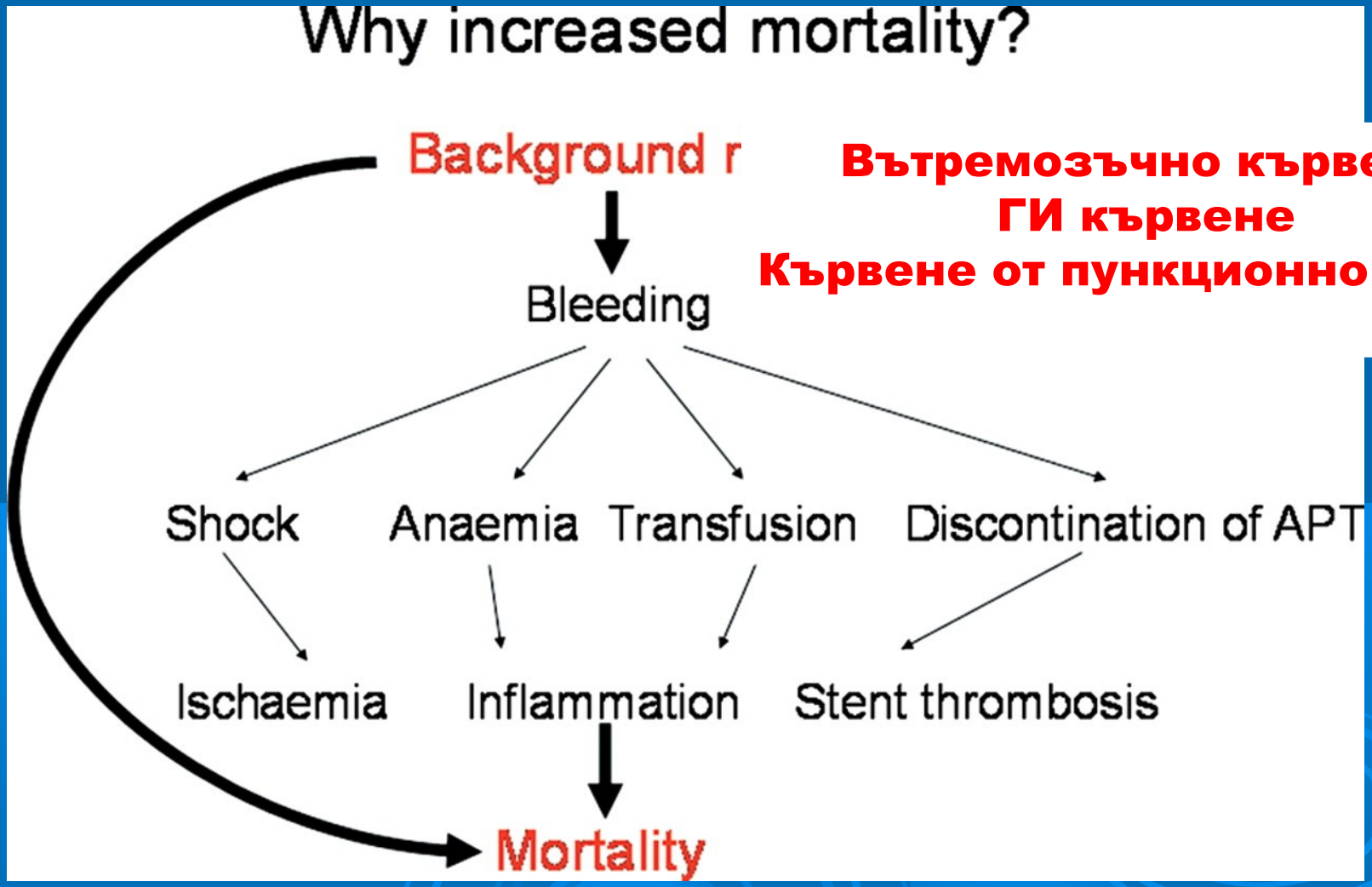
2.3% in both groups, HR = 1.01 (0.58-1.76), *P* = .97

Риск от кървене и взаимодействие с ИПП

GI Bleeding Increases Mortality



Връзка между кървене и смъртност



Вътремозъчно кървене
ГИ кървене
Кървене от пункционно място

Steg P G et al. Eur Heart J 2011;32:1854-1864

Исхемия - кървене

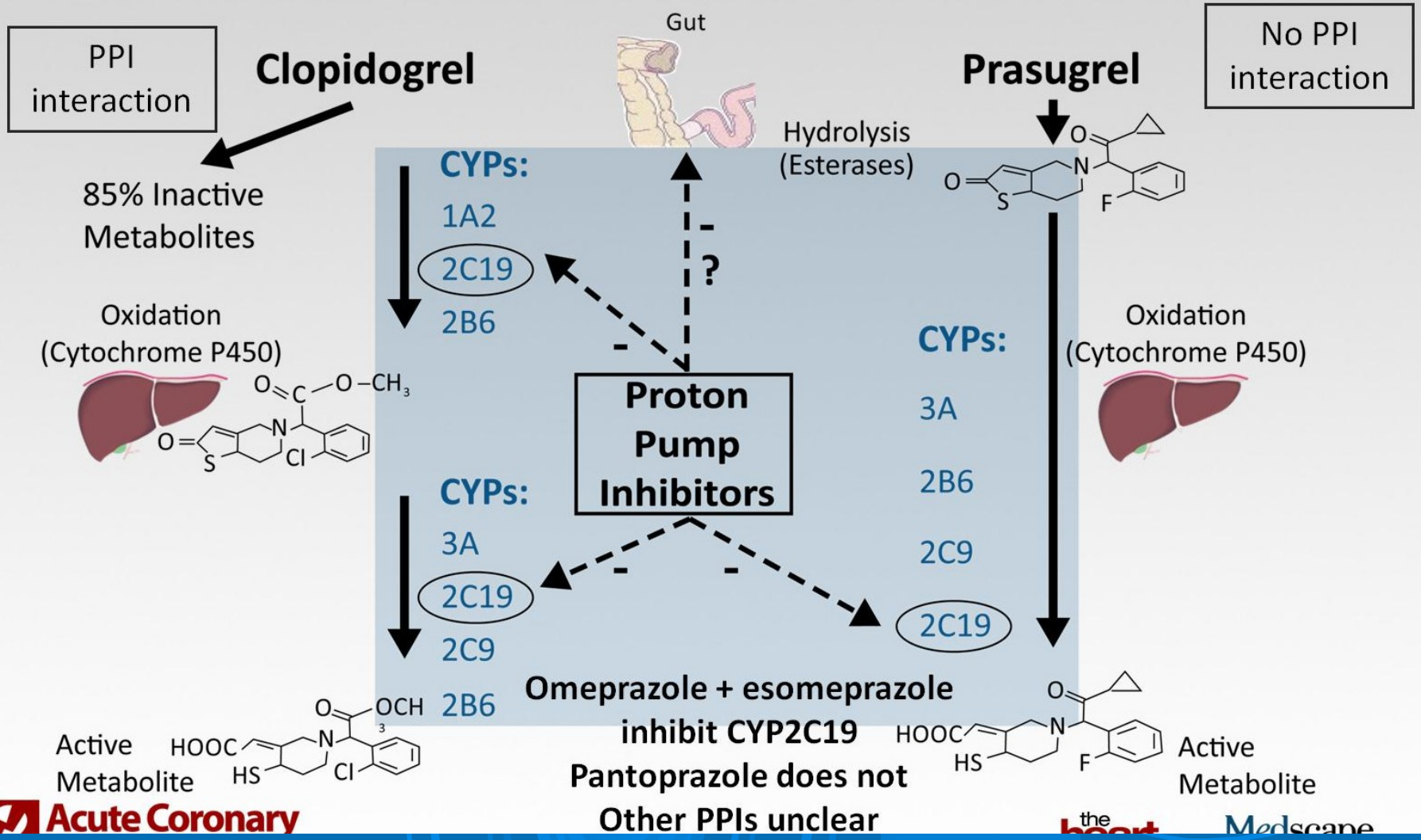
GRACE Рискова скала (Смърт/МИ):	CRUSADE Скала (кървене)
• Възраст	• Възраст
• Killip клас	• Killip клас
• Сърдечна честота	• Сърдечна честота
• САН	• САН (U-shape)
• Женски пол	• Женски пол
• Креатининов клирънс	• Креатининов клирънс
• Захарен диабет	• Захарен диабет
• + Тропонин	• Хематокрит
• Промяна в ST-сегмента	• Анамнеза за съдова болест
• Сърдечен арест	

Granger et al, JAMA 2004
Subherwal et al, Circulation 2009

Potential PPI Interaction With

Potential PPI Interaction With

Formation of Thienopyridine Active Metabolites



Специфични рискови фактори за кървене от ГИТ

Table 1
Demonstrated risk factors for ulcers on antiplatelet therapies[a]

Aspirin	Clopidogrel
Prior ulcer complication	Prior ulcer complication
Prior ulcer disease	Combination of clopidogrel with NSAID
Advanced age	Combination of clopidogrel with aspirin
H pylori	Combination of clopidogrel with anticoagulant
Dose of cardioprotective aspirin	
Combination of aspirin with NSAID	
Combination of aspirin with anticoagulant	

Cryer Gastroenterol Clin N Am 38 (2009) 289–30

Алгоритъм за приложение на ИПП при ОКС

ACS treated with DAPT in patients with a history of gastrointestinal haemorrhage or peptic ulcer, and/or high CRUSADE score or multiple other risk factors for GI bleeding (*Helicobacter pylori* infection, age ≥65 years, concurrent use of anticoagulants or steroids)

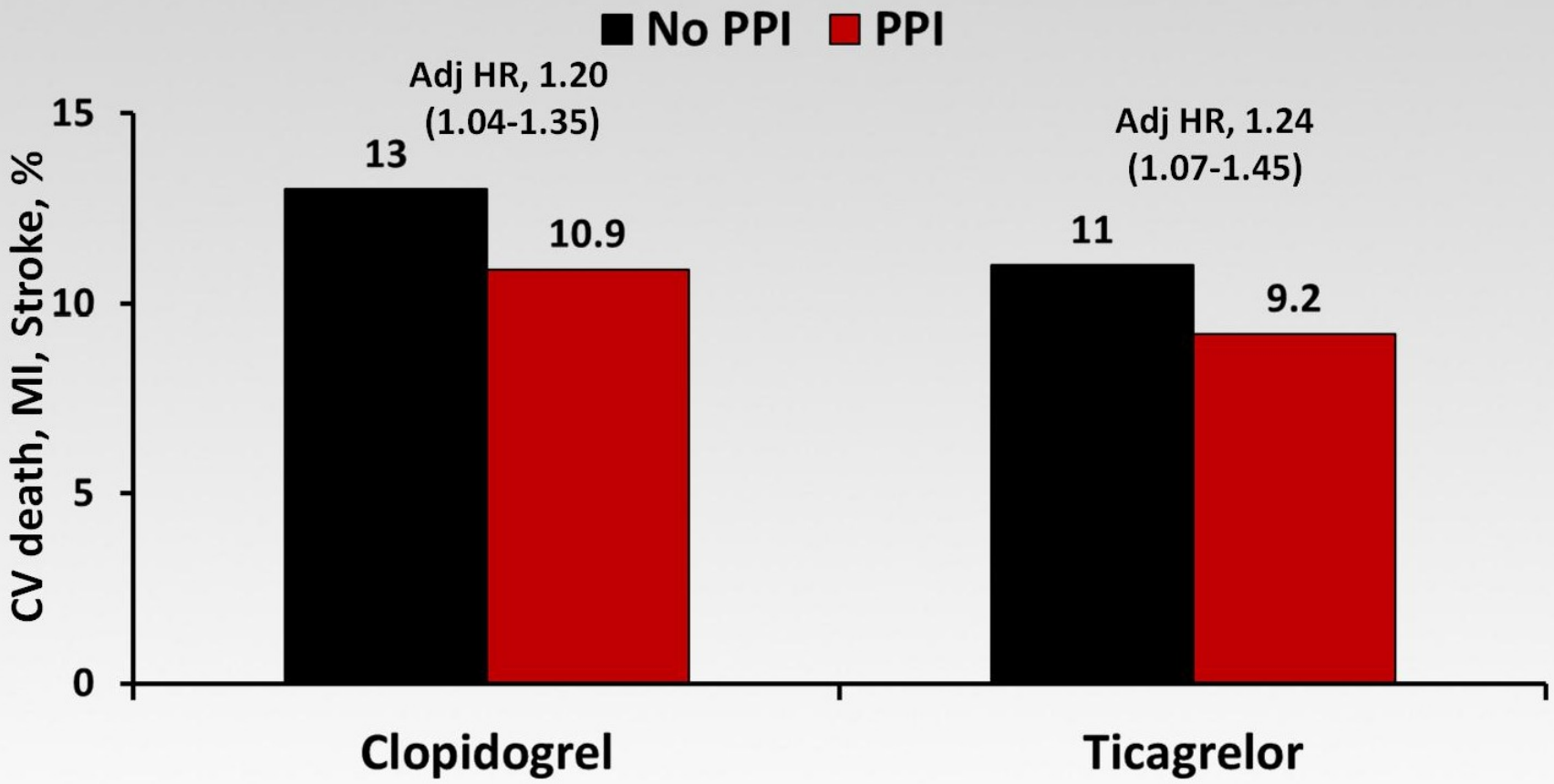
ПОНЕ 12 ЧАСА РАЗЛИКА ВЪВ ВРЕМЕТО ЗА ПРИЕМАНЕ НА КЛОПИДОГРЕЛ И ИПП!!!

than a PPI with high CYP2C19 inhibitory capacity (omeprazole)

Agewall S et al. Eur Heart J 2013;eurheartj.eht042

PLATO: Primary End Point by PPI Use

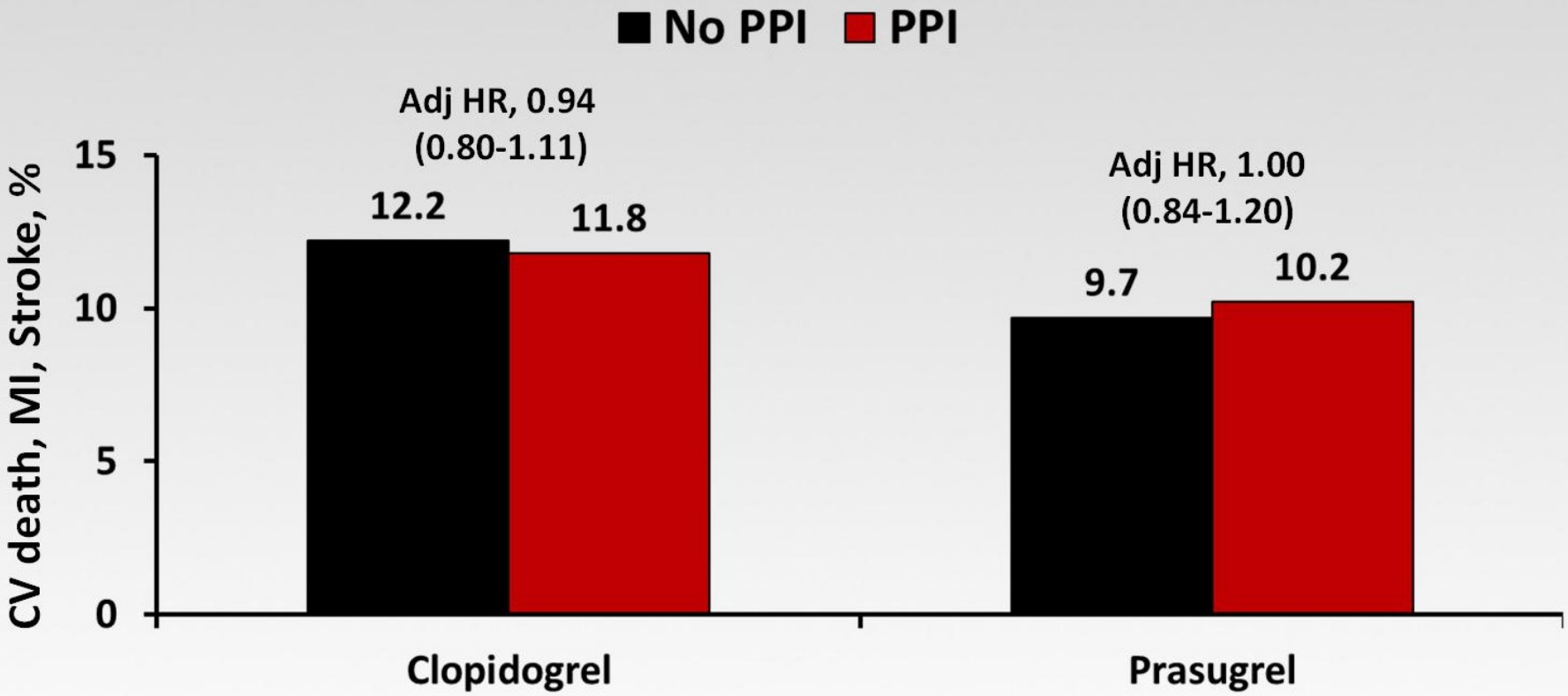
N = 18,599 (6539 on PPI; PPI use at physician discretion)



Clopidogrel = 300-600 mg LD, 75 mg MD
Ticagrelor = 180 mg LD, 60 mg BID MD

TRITON-TIMI 38: Primary End Point by PPI Use

N = 13,608 (33% on PPI; PPI use at physician discretion)



Clopidogrel = 300 mg load, 75 mg daily
Prasugrel = 60 mg load, 10 mg daily

FDA Warning: PPIs and Clopidogrel

11/17/2009

- Concomitant use of omeprazole and clopidogrel should be avoided because of the effect on clopidogrel's active metabolite levels and anti-clotting activity.
- Separating the dose of clopidogrel and omeprazole in time will not reduce this drug interaction.

10/27/2010 Update

- With regard to PPI drug class, this recommendation applies only to omeprazole and not to all PPIs. Not all PPIs have the same inhibitory effect on the enzyme (CYP2C19) that is crucial for conversion of clopidogrel into its active form.

11/2012 Labeling Update

- Avoid concomitant use of esomeprazole/omeprazole with clopidogrel.

Изводи

- Клопидогрел при ОКС се предпочита:
  - Пациенти с риск от кървене
  - Пациенти с ХОББ
  - Пациенти с бъбречна недостатъчност
  - Над 75 год.
  - С предходен ИМИ/ ПНМК
  - Пациенти с ниска телесна маса (жени?)
  - Пациенти с необходимост от ОАК
  - Цена на лечението?

Изводи

- И при всички останали – ако имате възможност за изследване на АДФ тест (истинската резистентност е много ниска!)
  - Насищаща доза – поне 600 мг
  - Поддържаща доза 150 мг за минимум 7 дни (най-добре 30 дни)

БЛАГОДАРЯ ЗА ВНИМАНИЕТО!