Дебат сесия
Индивидуализираната антиагрегантна терапия при ОКС е реалност

А. Постаджиян
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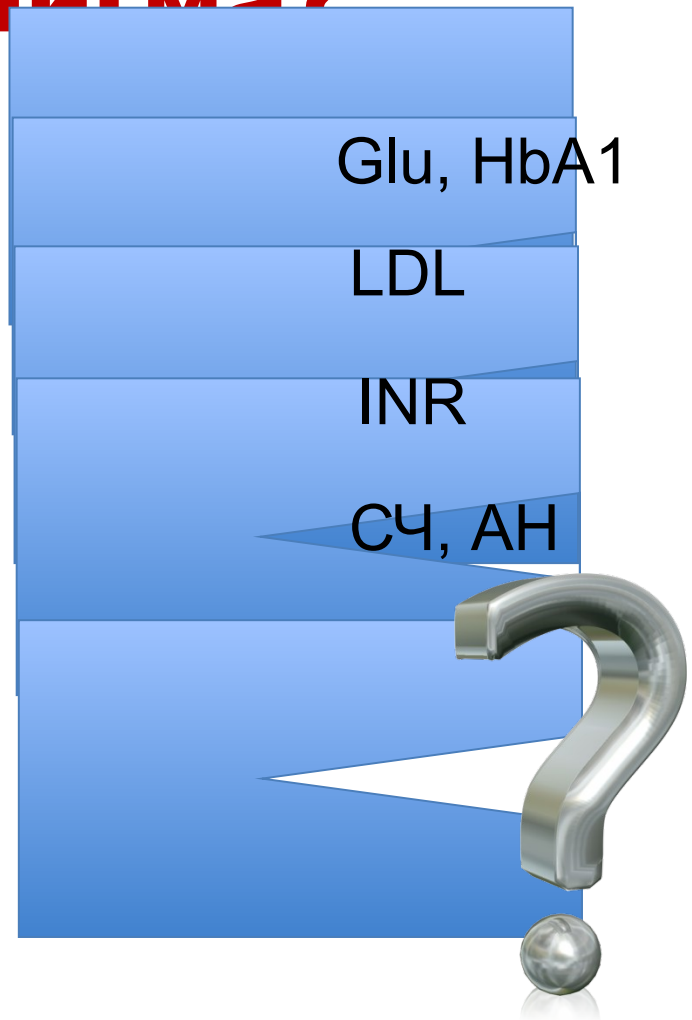
Смяна на терапевтичната парадигма?

- Инсулин
- Статини
- Антикоагуланти
- В-блокери
- Антиагреганти



A.Colombo
Operator techniques to reduce stent thrombosis

The stool stands only if each leg is solid: one leg with extra strength does not compensate for the broken one

- Lumen Leg: optimal MLD
- Run off leg: TIMI 3 flow
- Blood leg: optimal antiplatelet therapy

Оптимизиране на антиагрегантната терапия

- Оптимизиране, базирано на изследване на тромбоцитна реактивност
- Оптимизиране, базирано на генетичен анализ
- Оптимизиране, базирано на клиничната характеристика на пациента

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Как да се оптимизира антиагрегантната терапия чрез изследване на тромбоцитна реактивност

- Мониториране за ефикасност – резистентност
- Мониториране за безопасност и превенция на кървенето
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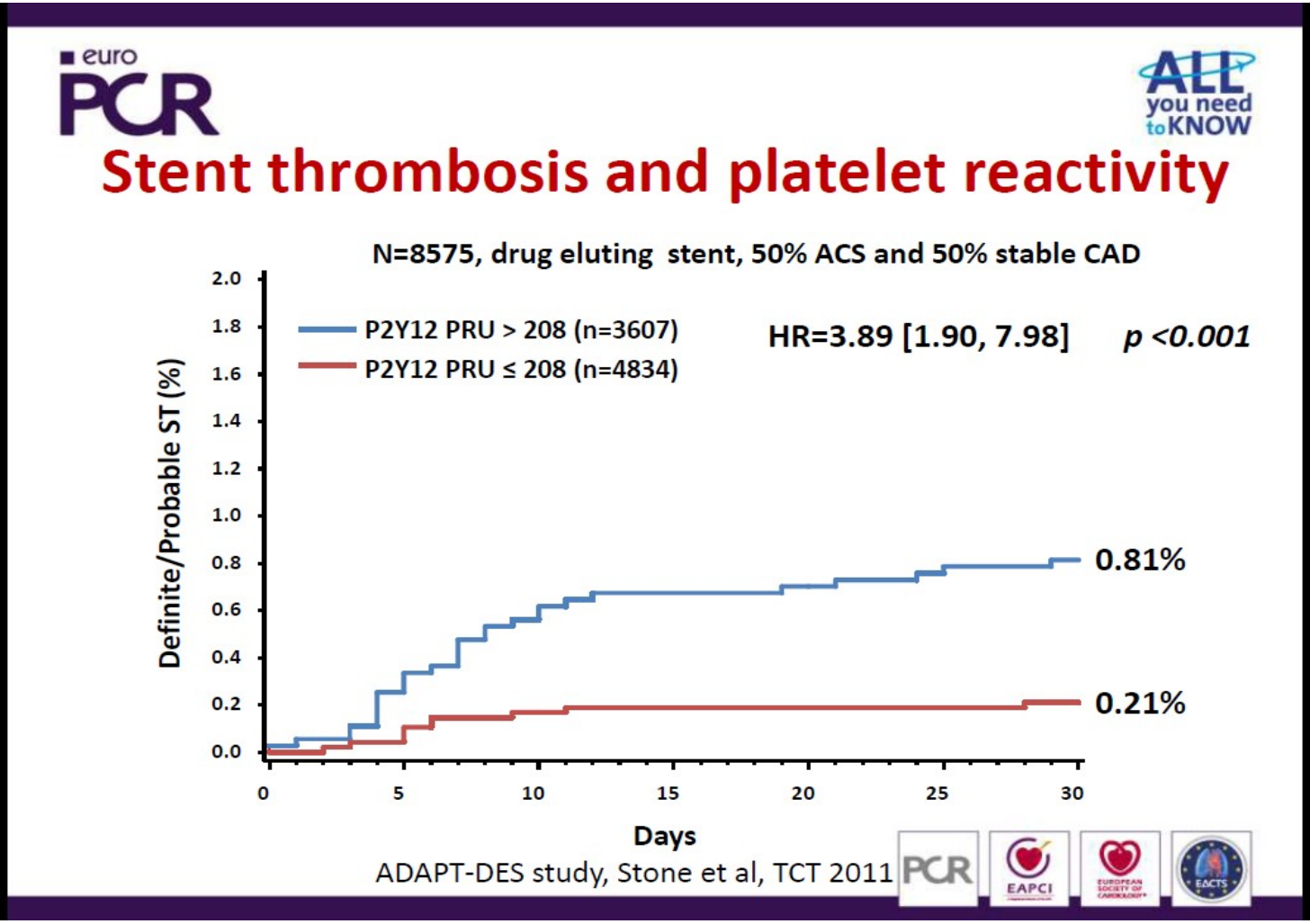
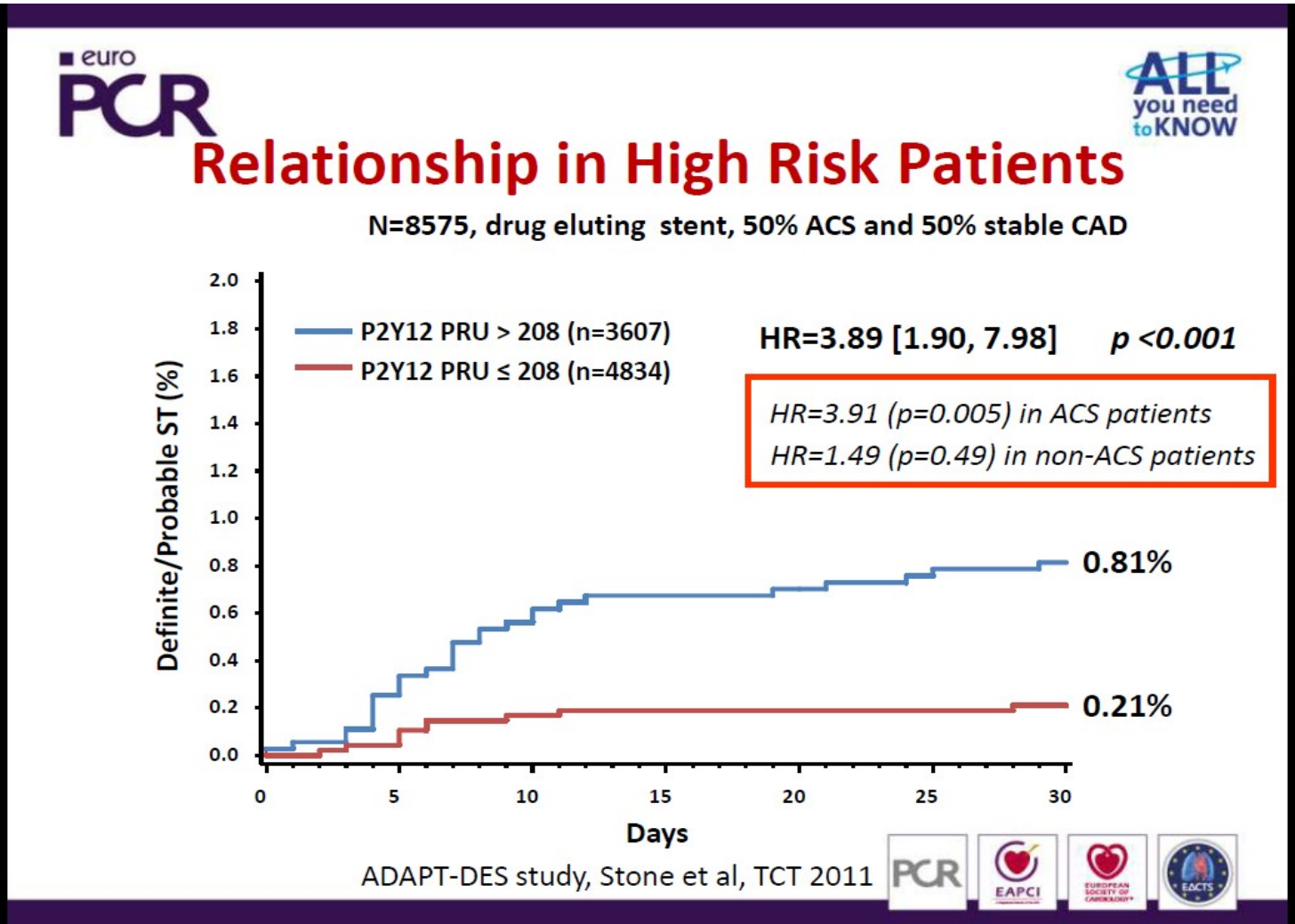
ADAPT DES – Стент тромбоза и тромбоцитна реактивност



ADAPT DES – Стент тромбоза и тромбоцитна реактивност – връзка при високорисковите

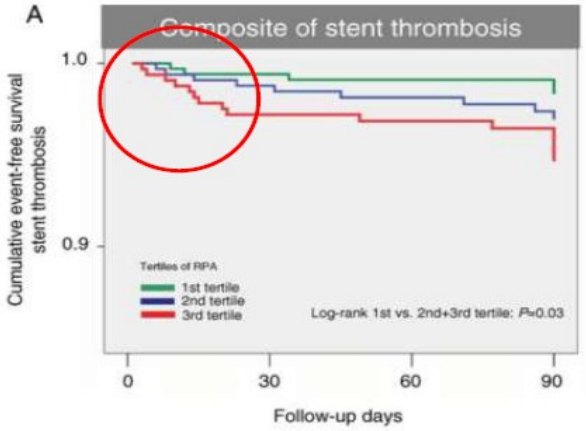


Персистиращо висока тромбоцитна реактивност - връзка с ранната дефинитивна стент тромбоза

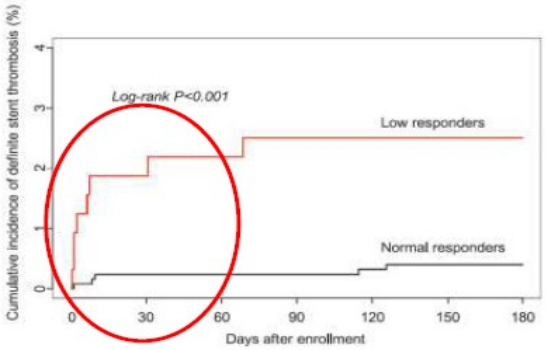
euro PCR

Relationship for early events

ALL you need to KNOW



Geisler et al, EHJ 2010

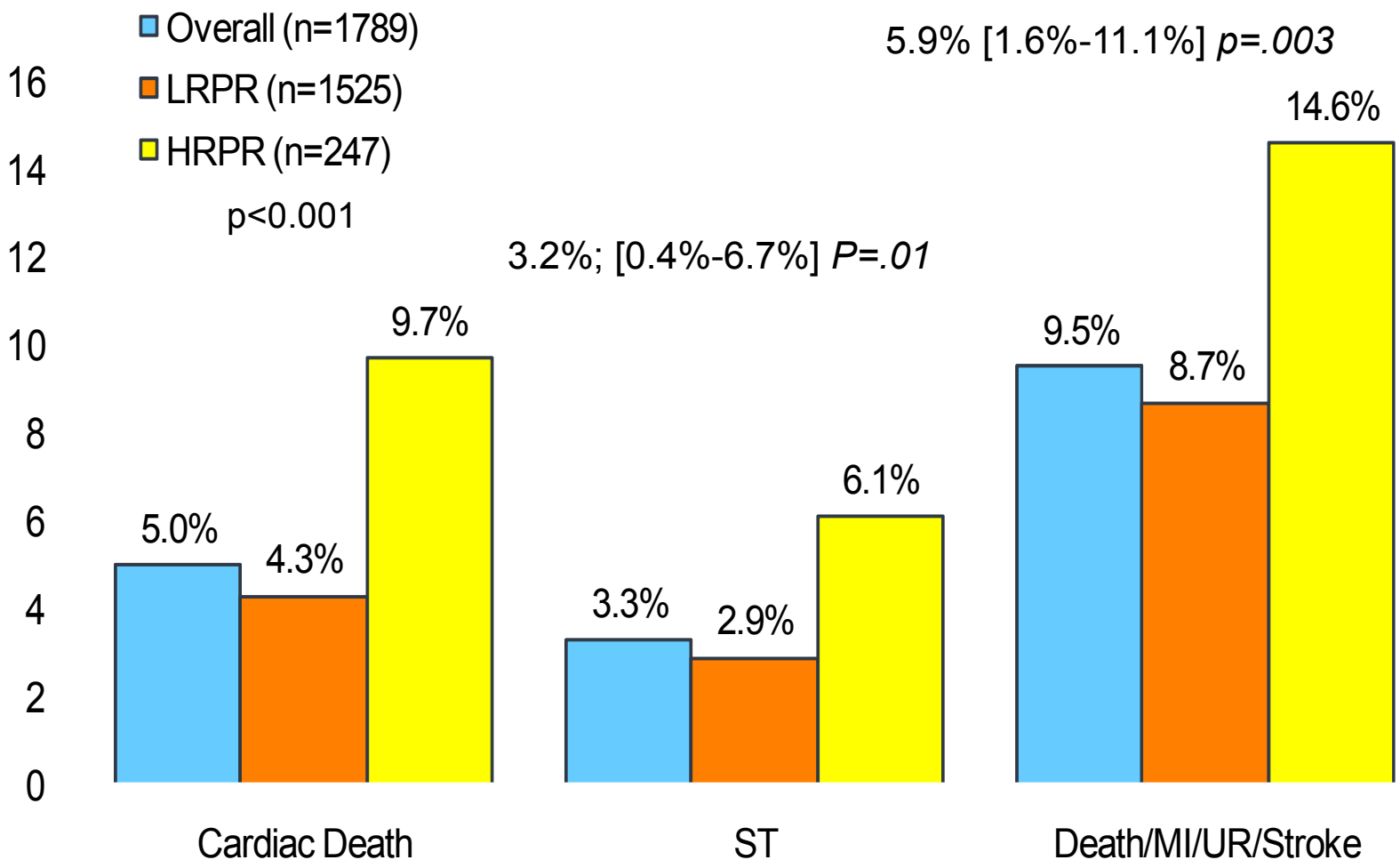


Sibbing et al, TH 2010

HTPR is good predictor of early thrombotic events

PCR EAPCI EACTS

The RECLOSE Study Смъртност



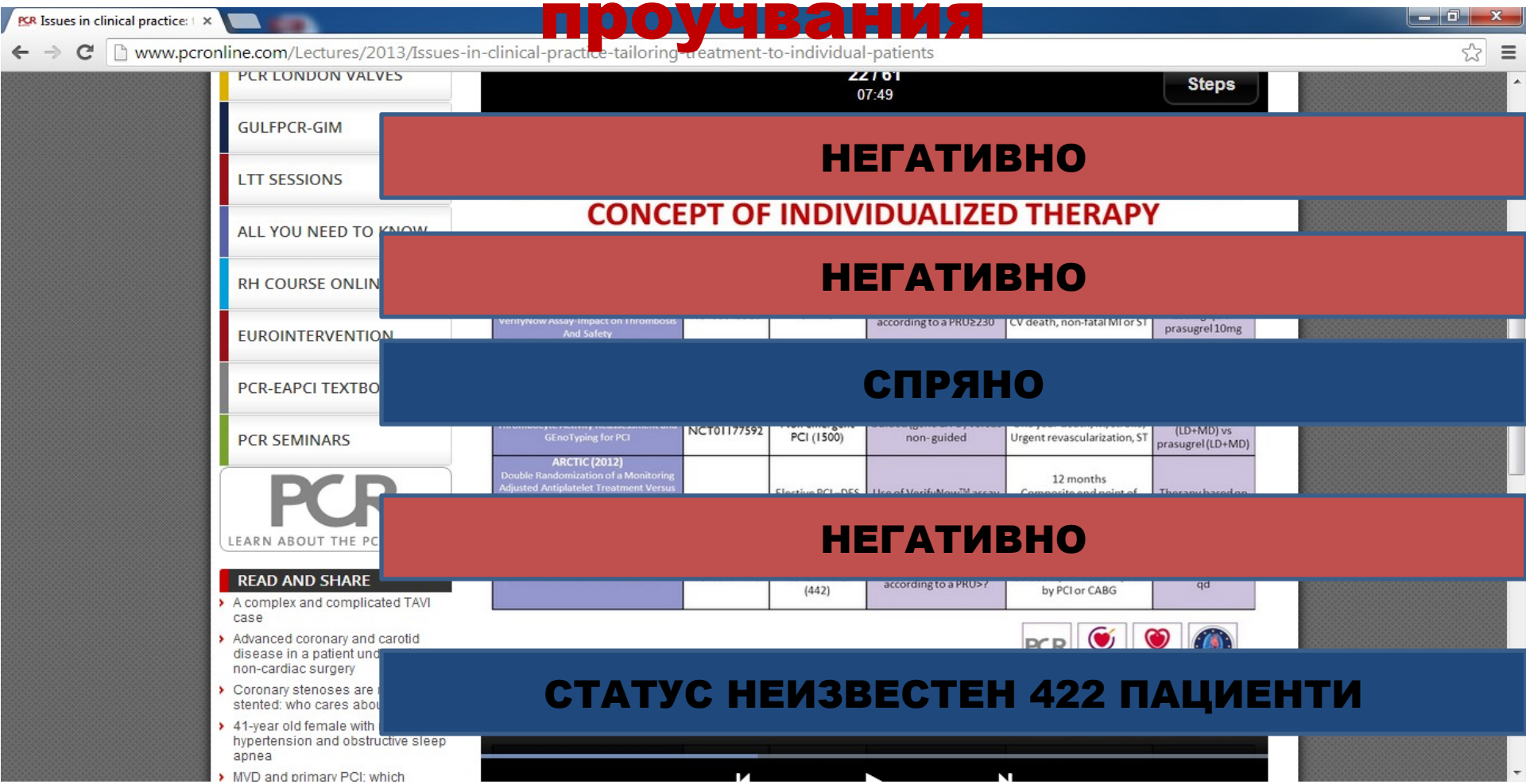
HRPR: независимо корелира със смъртност HR, 1.81; [1.18-2.76;] P=.006

JAMA. 2011;306(11):1215-1223

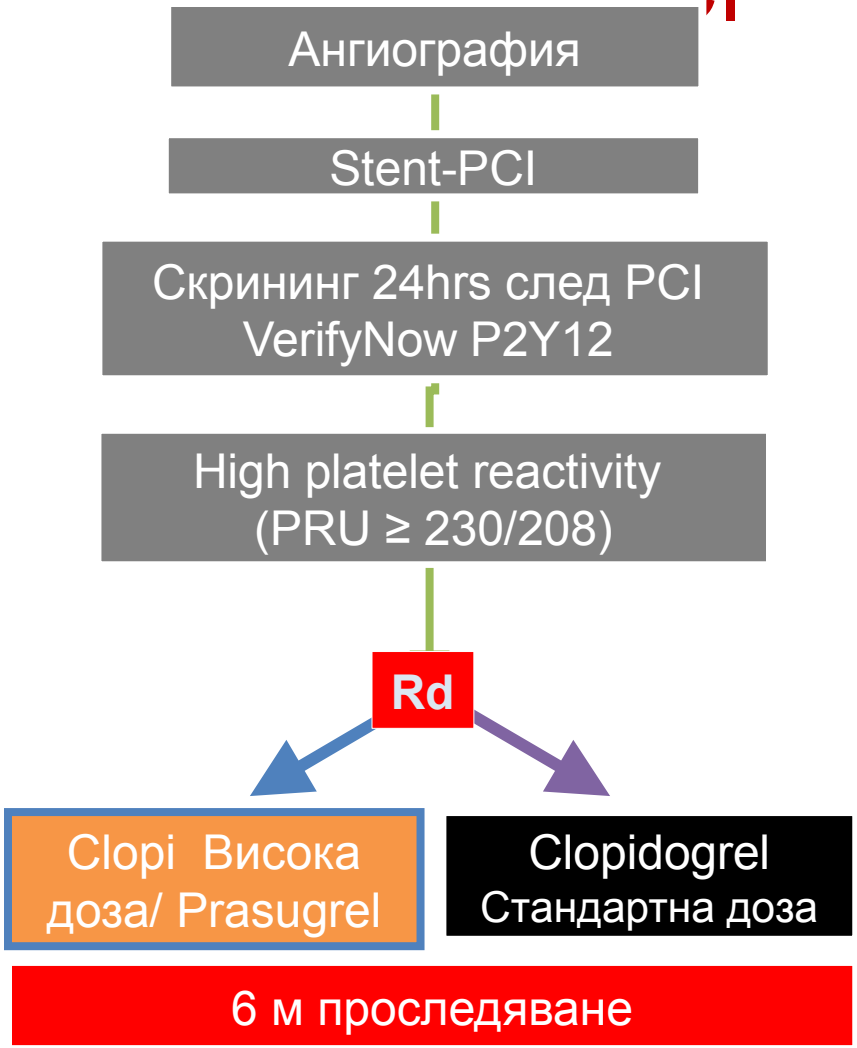
Мониториране за ефикасност – резистентност

- Ясна връзка за ранните тромботични инциденти
- Ясна връзка при високорисковите пациенти
- …Не означава, че тестуването и оптимизирането на терапията е свързано с подобряване на прогнозата…
- …Доказателства към 2013 год

Концепцията за индивидуализираната терапия с тестуване в клиничните проучвания

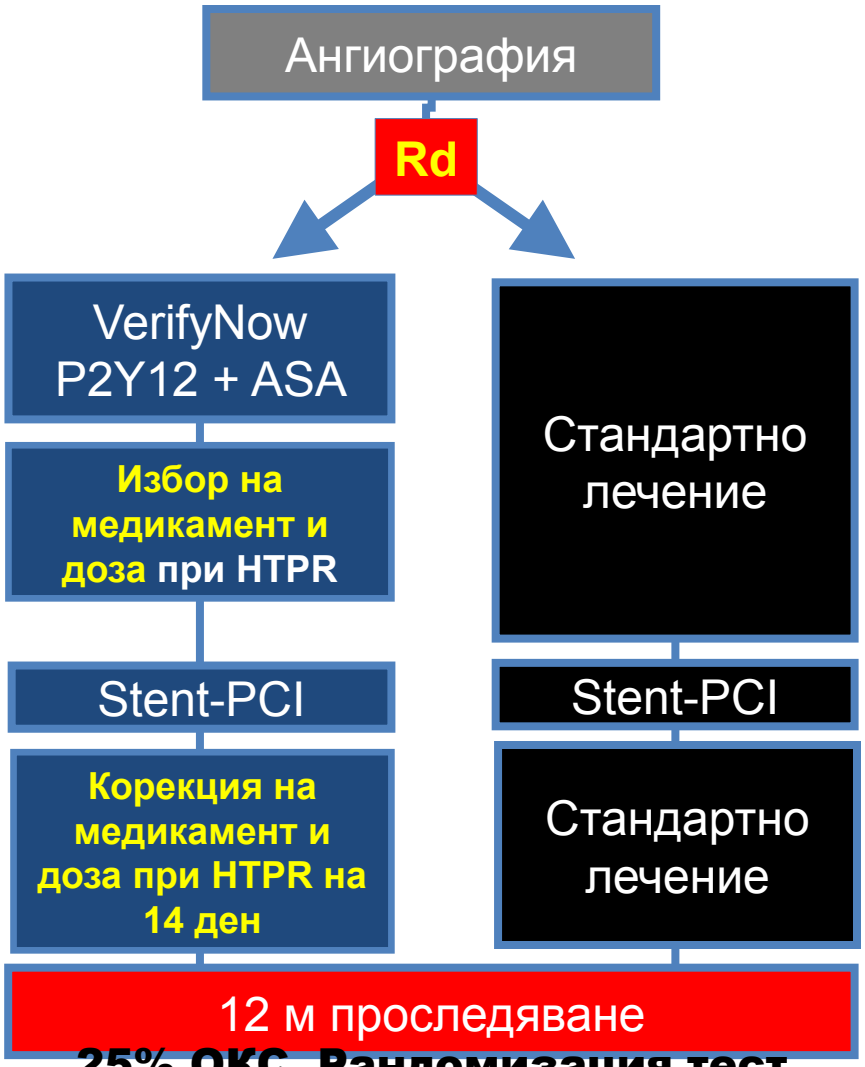


GRAVITAS / TRIGGER-PCI



Стабилни пациенти,
Рандомизация след теста,
Оптимизиране след PCI

ARCTIC

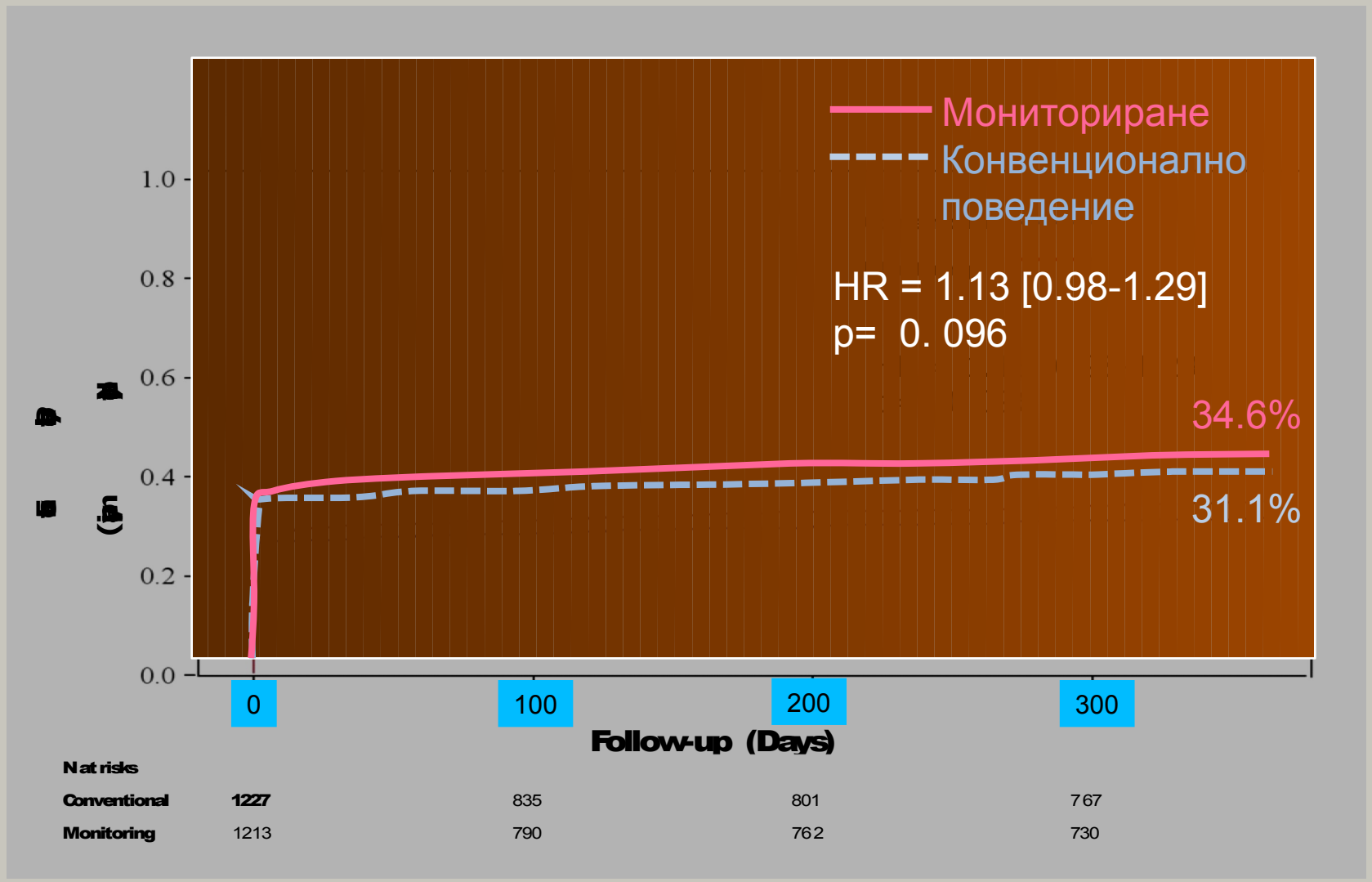


25% ОКС, Рандомизация тест или не

Оптимизиране преди PCI

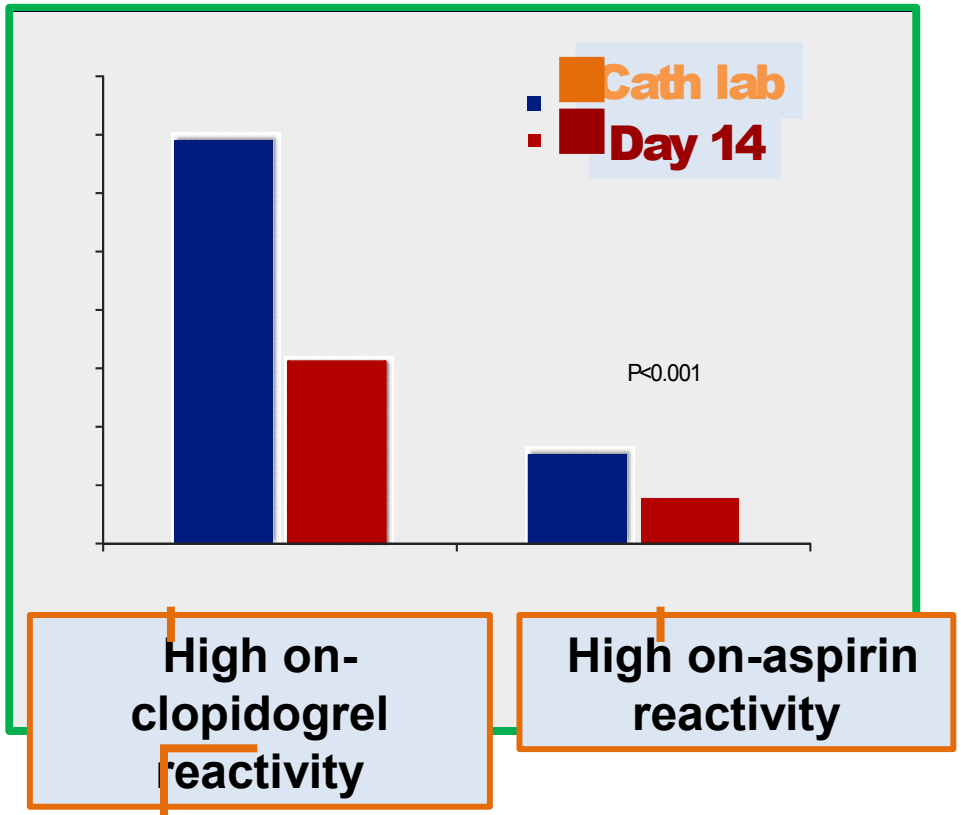
ARCTIC – първична крайна точка 1 год

Смърт/МИ/ Инсулт/стент тромбоза/спешна реваскуларизация



N Engl J Med. 2012 Nov 29;367(22):2100-9.

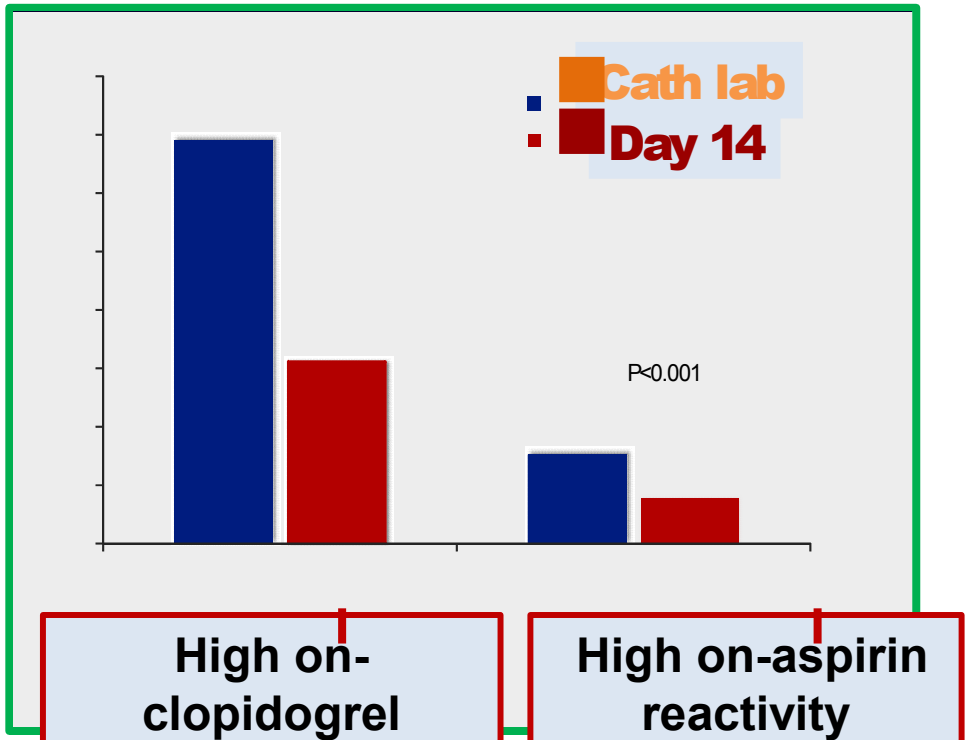
Оптимизиране преди PCI



80% нова натоварваща доза clopidogrel преди PCI
77% GP IIb/IIIa по време на PCI

N Engl J Med. 2012 Nov 29;367(22):2100-9.

Оптимизиране при проследяване



43% повишаване дозата на clopidogrel
17% prasugrel MD

N Engl J Med. 2012 Nov 29;367(22):2100-9.

Ограничения на ARCTIC

- Само 25% от пациентите са с ОКС
- Оптимизиране – 17% prasugrel при HTPR на фона на лечение с клопидогрел

Дизайн

- Оценка на отговора към клопидогрел
- Фокусирано върху HTPR/ превенция на исхемичните усложнения

Тромбоцитна реактивност за мониториране за ефикасност – резистентност

- Ниско рискова PCI/стабилни пациенти
- Високо рискова PCI/ОКС

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Comparison of Prasugrel and Ticagrelor Loading Doses in ST-Segment Elevation Myocardial Infarction Patients

RAPID (Rapid Activity of Platelet Inhibitor Drugs) Primary PCI Study

Guido Parodi, MD, PHD, Renato Valenti, MD, Benedetta Bellandi, MD, Angela Migliorini, MD, Rossella Marcucci, MD, Vincenzo Comito, MD, Nazario Carrabba, MD, Alberto Santini, MD, Gian Franco Gensini, MD, Rosanna Abbate, MD, David Antoniucci, MD

Florence, Italy

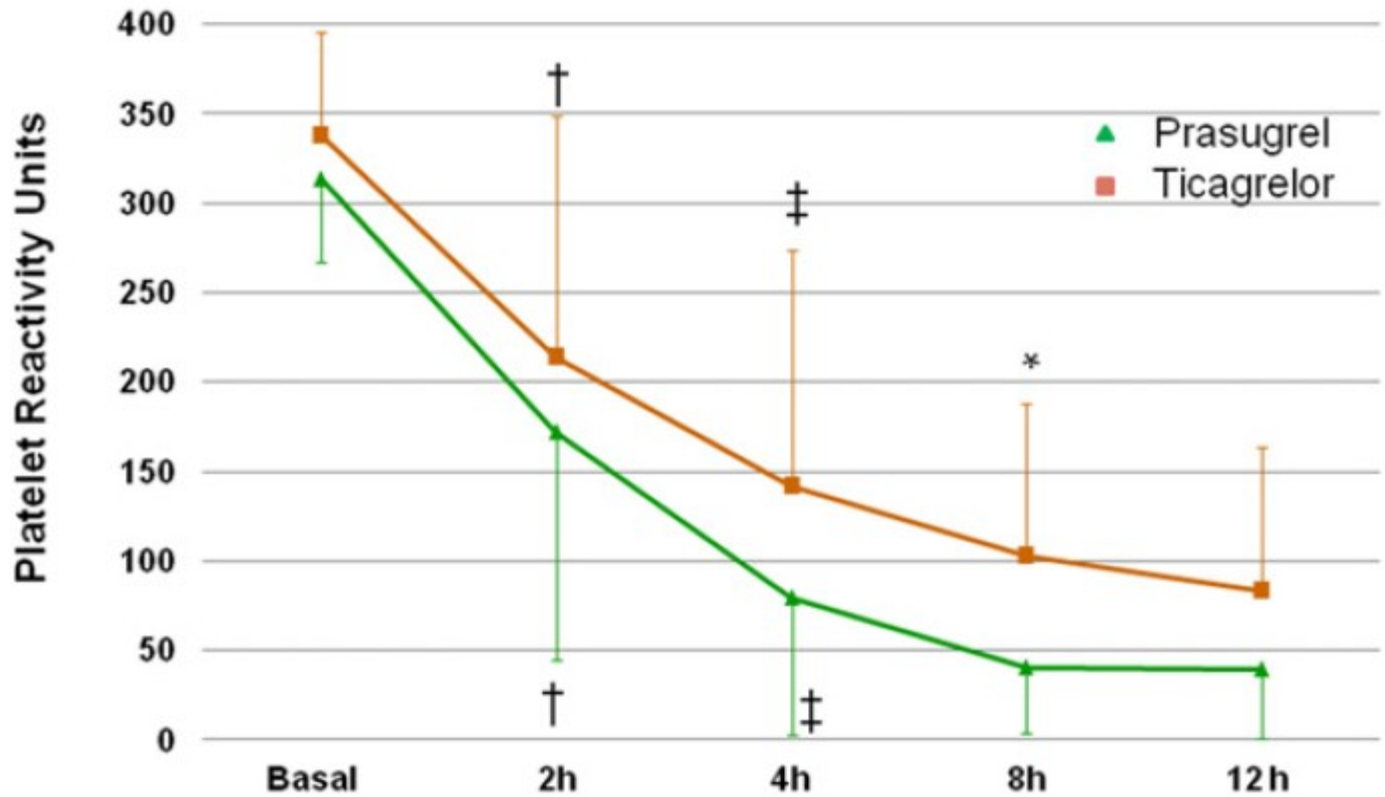
Objectives This study sought to compare the action of prasugrel and ticagrelor in ST-segment elevation myocardial infarction (STEMI) patients undergoin

Background It has been documented that pr loading dose (LD). However, the provided by assessing only heal

Methods Fifty patients with STEMI underg sugrel LD (n = 25) or 180 mg t baseline and 2, 4, 8, and 12 h a

Results Platelet reactivity units (PRU) 2 305) in the prasugrel and ticagr High residual platelet reactivity The mean time to achieve a PR tively. The independent predicto 1.44 to 19.49; p = 0.012) and p = 0.046).

Conclusions In patients with STEMI, prasugre platelet reactivity 2 h after the l half of patients, and at least 4 h tients. Morphine use is associat Drugs Study, NCT01510171) Cardiology Foundation



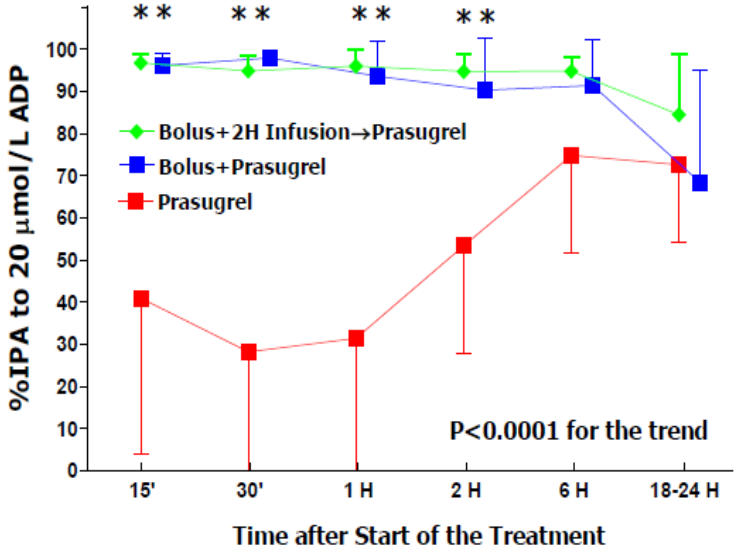
Имаме ли нужда от интравенозни антиагреганти през 2013 год?

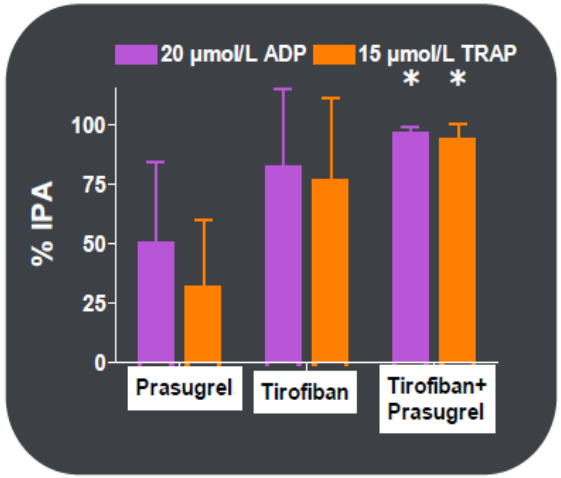
euro PCR 2013

Do we still need i.v. anti-platelet Tx in 2013 ?

ALL you need to KNOW

This question is relevant for our present (**GPI**) and future practice (**Cangrelor**)!





Valgimigli et al. JACC Cardiovasc Interv. 2012 Mar;5(3):268-77

Как да се оптимизира антиагрегантната терапия чрез изследване на тромбоцитна реактивност

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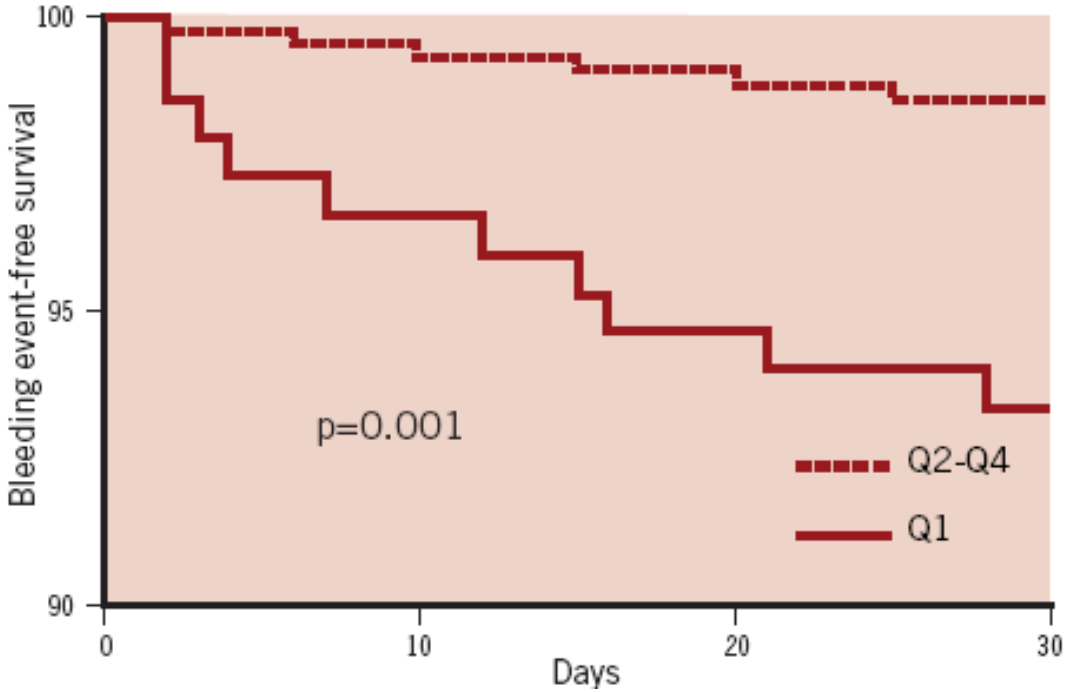
Промяна в парадигмата при мониториране

Тромбоцитна реактивност и кървене

597 NSTE ACS, clopidogrel 600 mg, Кървене след дехоспитализацията



Q1: Хиперреспондери,

ADP-Ag<40%

ADP 10 μmol/L, LTA

Повишен отговор към клопидогрел → Висок риск от кървене

<u>HR 5.3</u>, 95% CI 1.9 to 14.9; p<0.01

Cuisset et al. Eurointervention 2009

The NEW ENGLAND JOURNAL of MEDICINE

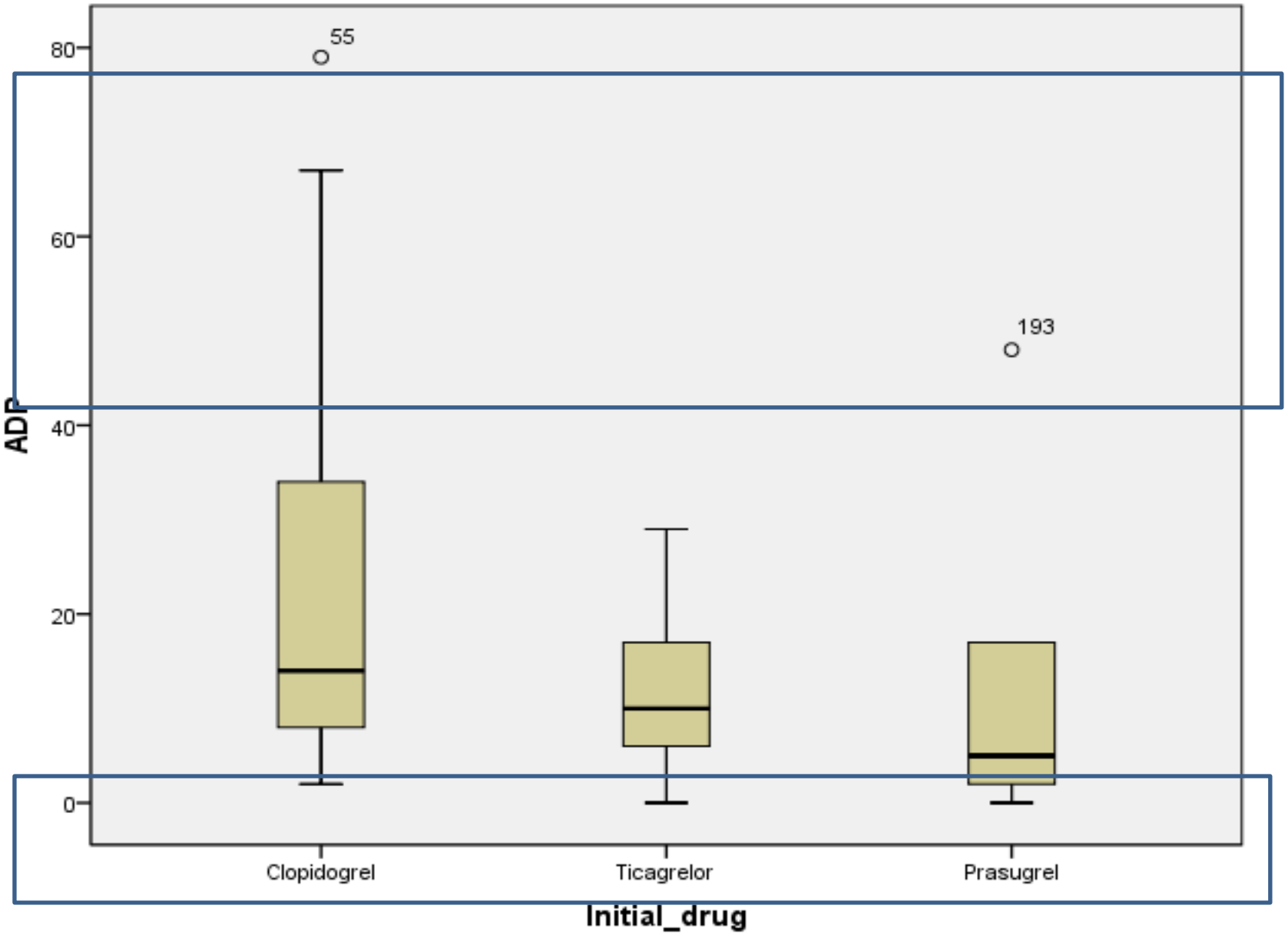
ORIGINAL ARTICLE

Bedside Monitoring to Adjust Antiplatelet Therapy for Coronary Stenting

Jean-Philippe Collet, M.D., Ph.D., Thomas Cuisset, M.D., Ph.D., Grégoire Rangé, M.D., Guillaume Cayla, M.D., Ph.D., Simon Elhadad, M.D., Christophe Pouillot, M.D., Patrick Henry, M.D., Ph.D., Pascal Motreff, M.D., Ph.D., Didier Carrié, M.D., Ziad Boueri, M.D., Ph.D., Loic Belle, M.D., Eric Van Belle, M.D., Ph.D., Hélène Rousseau, Ph.D., Pierre Aubry, M.D., Jacques Monségu, M.D., Pierre Sabouret, M.D., Stephen A. O'Connor, M.B., B.Ch., Jérémie Abtan, M.D., Mathieu Kerneis, M.D., Christophe Saint-Etienne, M.D., Olivier Barthélémy, M.D., Farzin Beygui, M.D., Ph.D., Johanne Silvain, M.D., Ph.D., Eric Vicaut M.D., Ph.D., and Gilles Montalescot, M.D., Ph.D., for the ARCTIC Investigators*

Table 3. Study End Points at 1 Year of Follow-up.*

End Point	Conventional Treatment (N=1227)	Monitoring (N=1213)	Hazard Ratio (95% CI)	P Value
Bleeding				
Major bleeding	40 (3.3)	28 (2.3)	0.70 (0.43–1.14)	0.15
Minor bleeding	21 (1.7)	12 (1.0)	0.57 (0.28–1.16)	0.12
Major or minor bleeding	55 (4.5)	38 (3.1)	0.69 (0.46–1.05)	0.08



Д-р Н.Стоянов, УМБАЛ Света Анна, София,
Собствени резултати

JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 6, NO. 8, 20
ISSN 1936-8798/$36.
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Clinical Implications of Very Low On-Treatment Platelet Reactivity in Patients Treated With Thienopyridine

The POBA Study (Predictor of Bleedings With Antiplatelet Drugs)

Thomas Cuisset, MD, PHD,*†‡ Charlotte Grosdidier, PHD,†‡§
Anderson Diendonné Loundou, PHD,‖ Jacques Quilici, MD,*†‡ Marie Loosveld, MD,†‡§
Laurence Camoin, PHD,‡§ Mathieu Pankert, MD,*‡ Shirley Beguin, PHD,¶
Marc Lambert, MD,*†‡ Pierre Emmanuel Morange, MD, PHD,†‡§
Jean-Louis Bonnet, MD,*†‡ Marie-Christine Alessi, MD, PHD†‡§

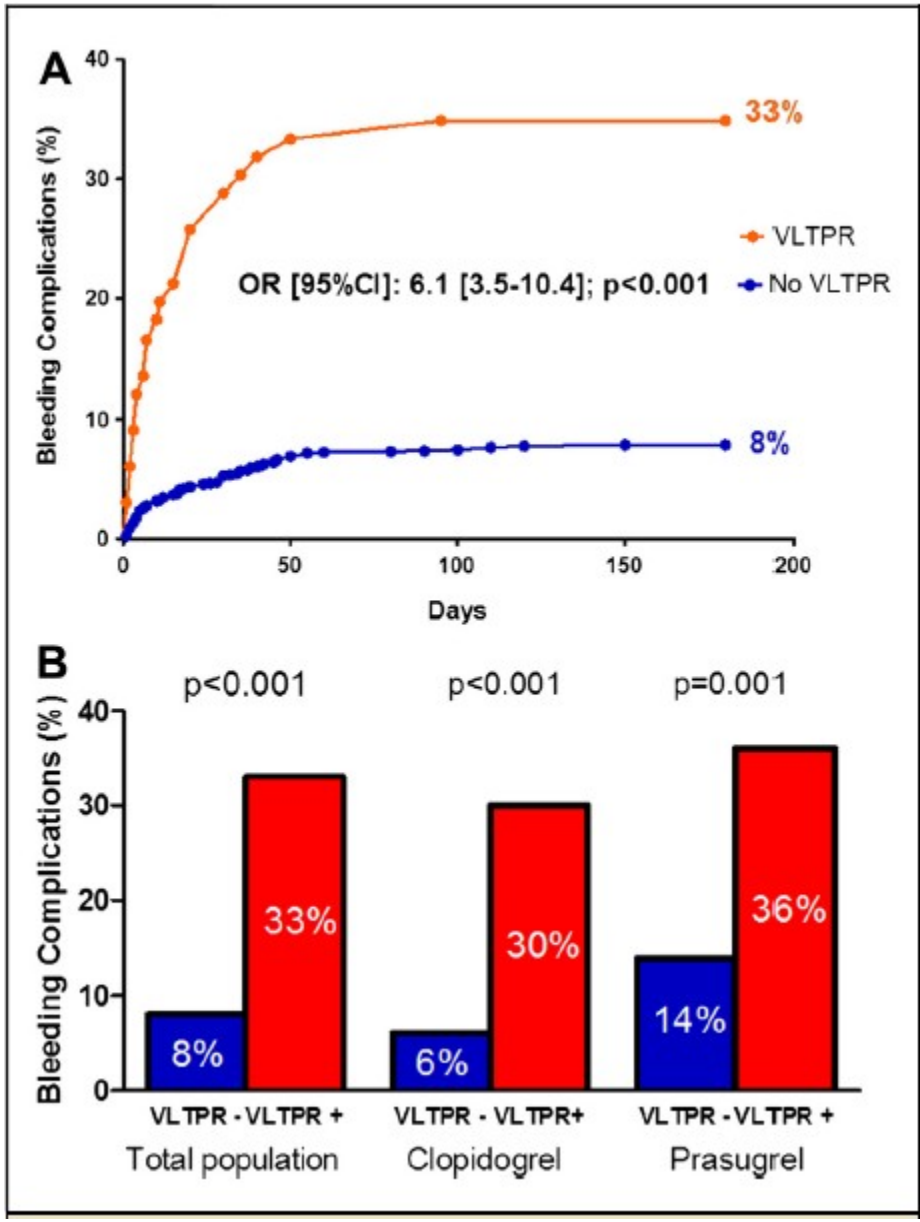
Marseille, France

Objectives This study was designed to define the hyperresponse to thienopyridine (very low on-treatment platelet reactivity [VLTPR]) as the most predictive threshold value of platelet reactivity index vasodilator-stimulated phosphoprotein (PRI VASP) for the prediction of non-access site–related bleeding events. We also aimed to identify predictors of bleeding and VLTPR in patients treated with thienopyridines.

Background New $P2Y_{12}$ blockers and platelet monitoring has been proposed to optimize platelet inhibition after acute coronary syndromes and improve ischemic outcomes. However, bleeding complications remain the Achilles' heel of antiplatelet therapy, and platelet monitoring could be useful to evaluate this risk.

Methods A total of 1,542 consecutive patients undergoing coronary stenting for ACS were included in the present study (287 taking clopidogrel 75 mg, 868 taking clopidogrel 150 mg, and 387 taking prasugrel 10 mg).

Results During 6-month follow-up, 9% of patients (n = 139) experienced nonaccess site–related Bleeding Academic Research Consortium bleeding complications. These patients were more often women and nondiabetic and had lower PRI VASP values than others ($p < 0.001$). Receiver-operating characteristic curve analysis (0.71, $p < 0.01$) identified a threshold value for VLTPR of PRI VASP ≤10% to predict bleeding events with a sensitivity of 17% and a specificity of 97%. Although prasugrel was the main predictor of VLTPR in the whole population (odds ratio: 10.2, 95% confidence interval: 3.0 to −34.2; $p < 0.001$), VLTPR was the strongest and independent predictor of bleeding (odds ratio: 4.7, 95% confidence interval: 2.7 to 8.3; $p < 0.001$).



Как да се оптимизира антиагрегантната терапия чрез изследване на тромбоцитна реактивност

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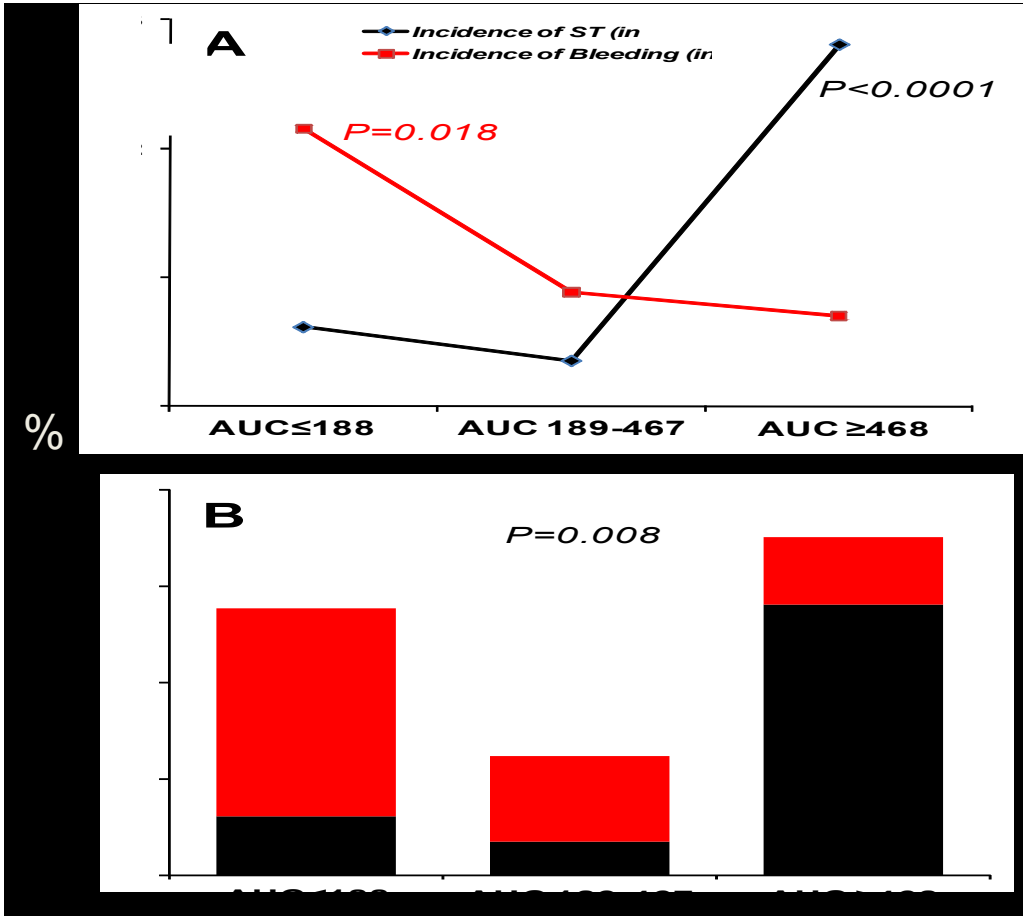
“Терапевтичен прозорец” на антиагрегантния ефект

2533 пациенти преди PCI (след 600 mg clopidogrel LD)
Тромбоцитната функция - Multiplate analyzer



Стент тромбоза:

n=22 – в рамките 30 дни

- 16 дефинитивна
- 6 възможна

Кървене:

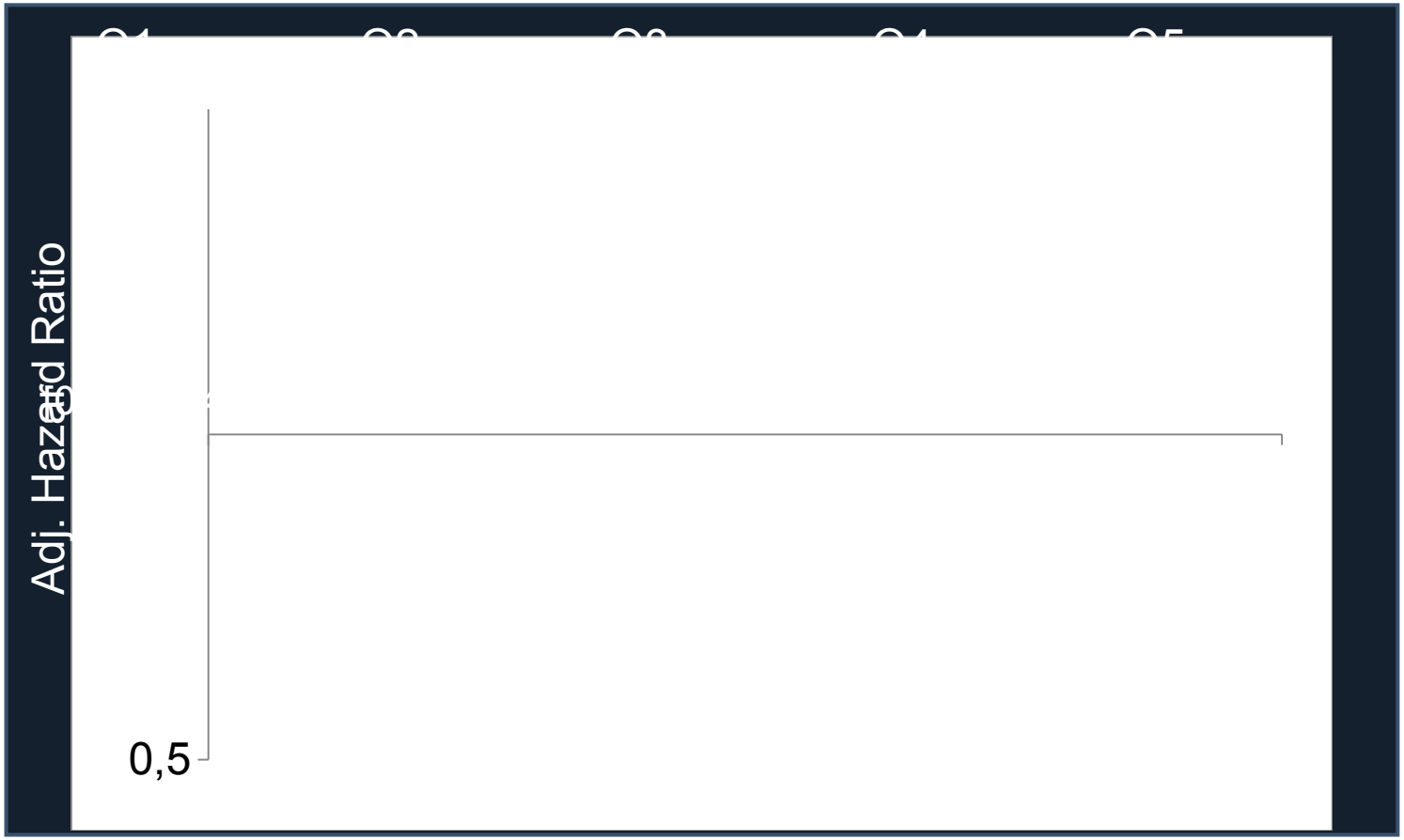
n=34 (вътреболнично)

- TIMI голямо кървене

Sibbing D et al, JACC 2010

ADAPT DES – Едногодишен анализ ST:

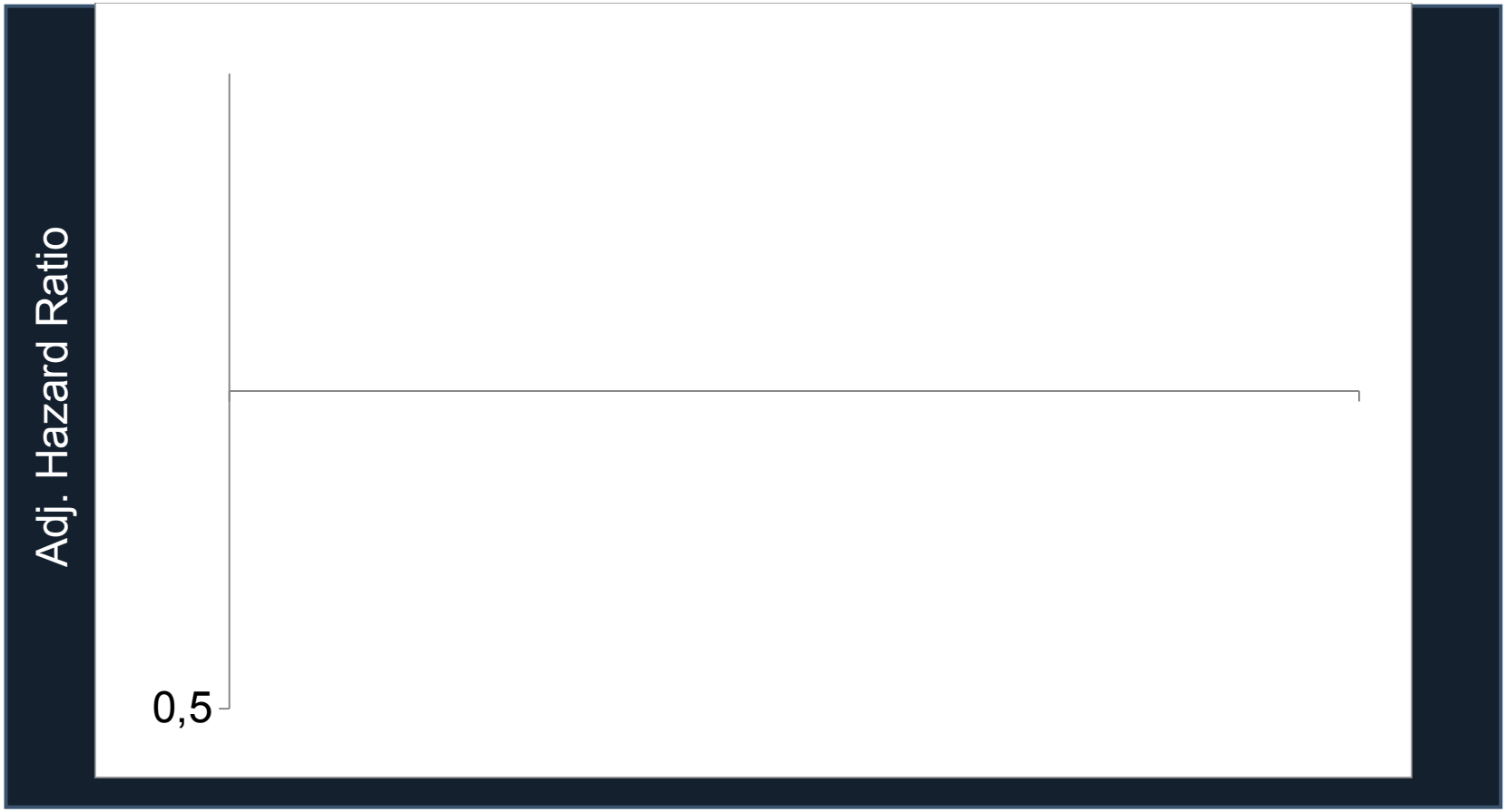
8,449 пациенти след PCI оценени с VerifyNow PRU след НД клопидогрел



A. Kirtane and G. Stone, ACC 2013

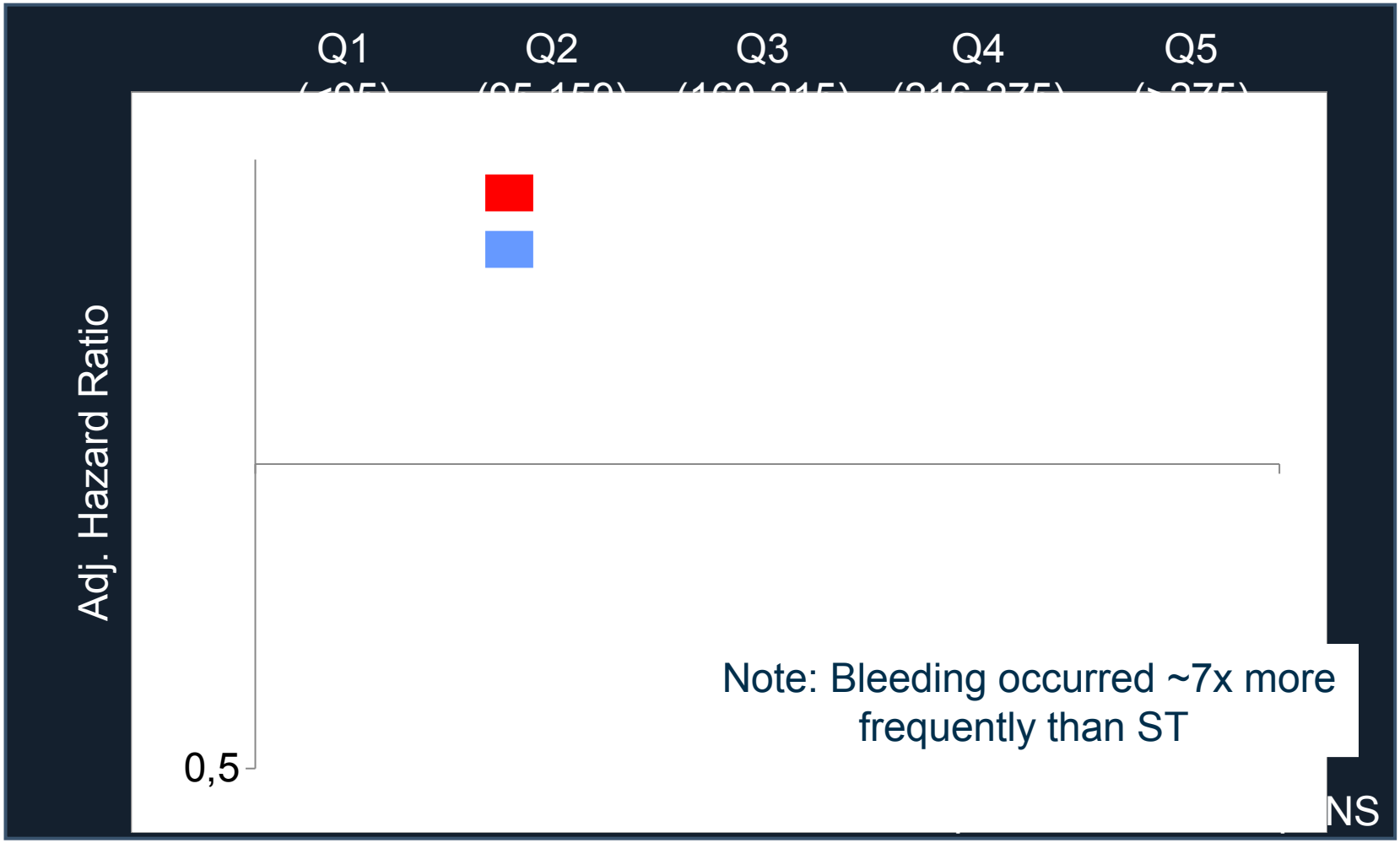
ADAPT DES – Едногодишен анализ голямо кървене:

8,449 пациенти след PCI оценени с VerifyNow PRU след НД клопидогрел

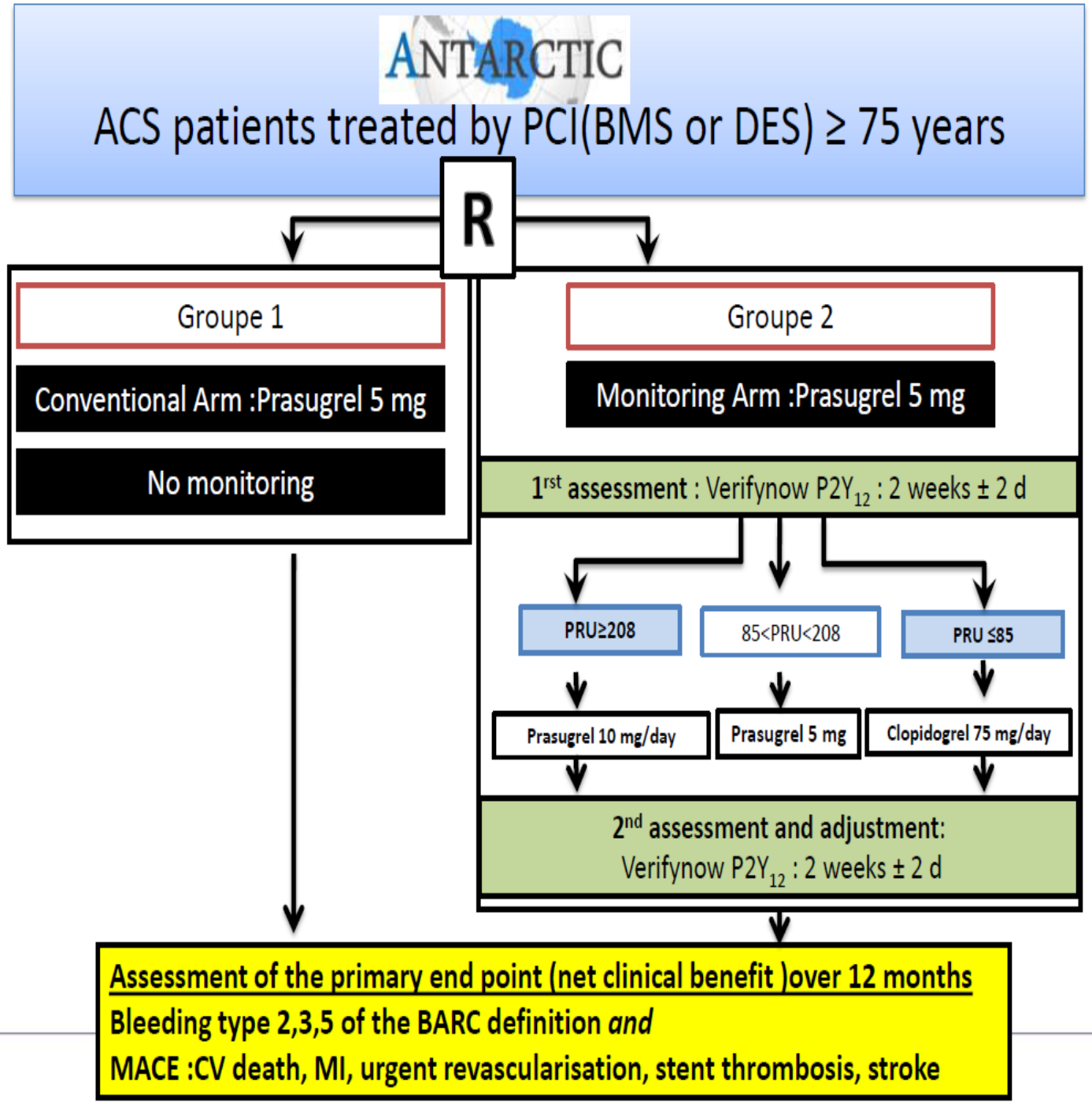


A. Kirtane and G. Stone, ACC 2013

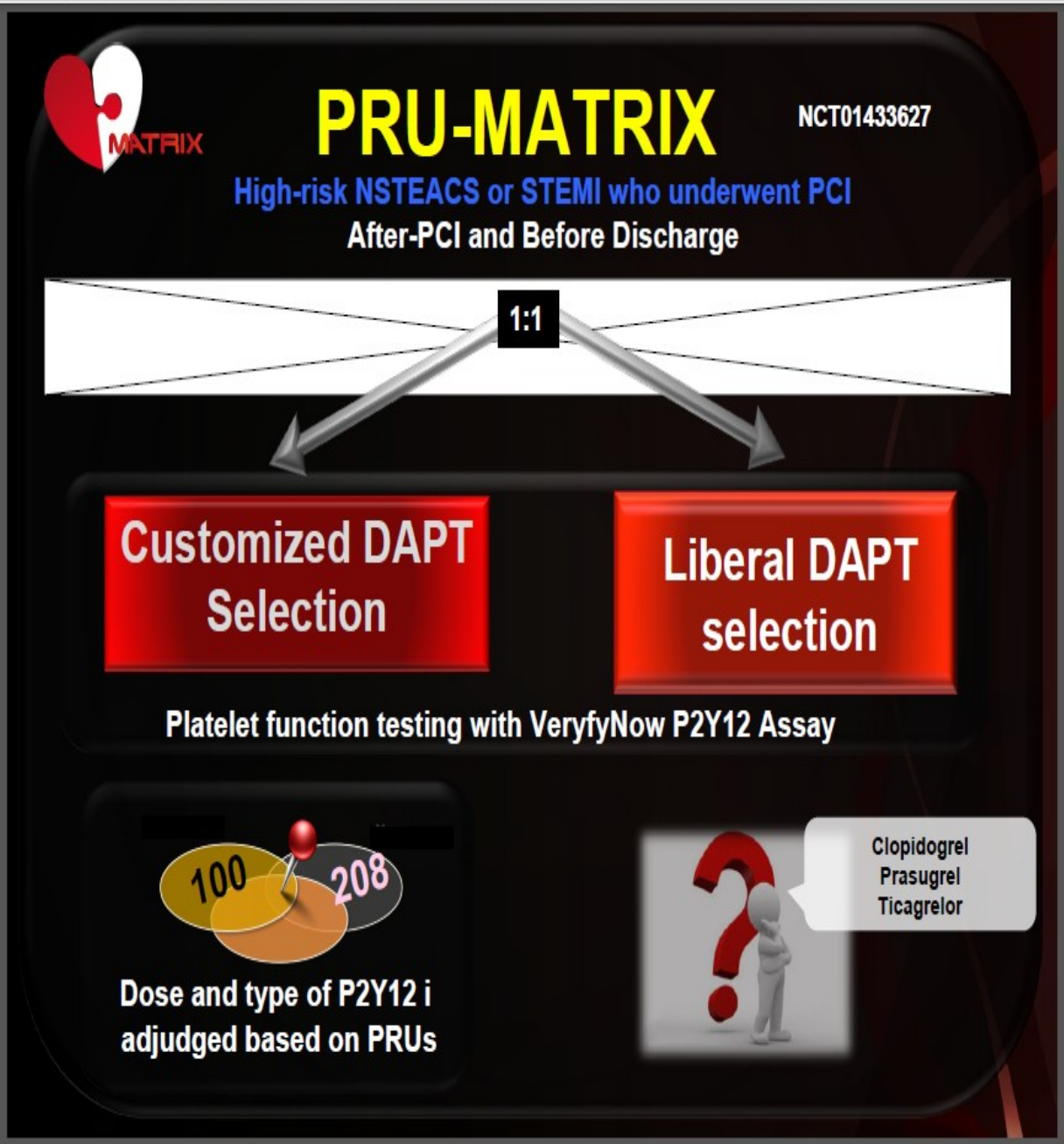
ADAPT DES – Едногодишен анализ ST и голямо кървене



A. Kirtane and G. Stone, ACC 2013

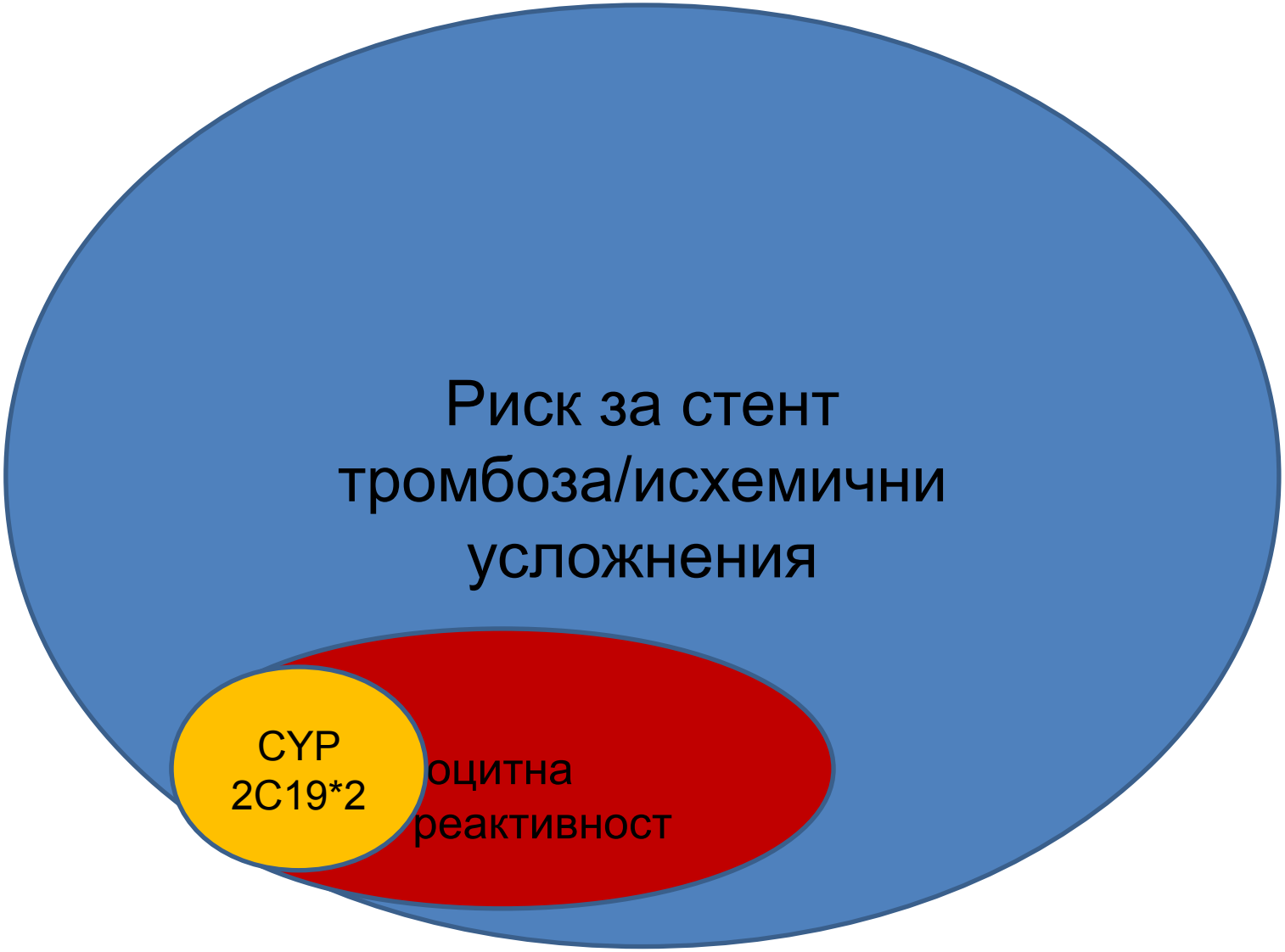

ANTARCTIC
ACS patients treated by PCI(BMS or DES) ≥ 75 years
R
Groupe 1
Conventional Arm :Prasugrel 5 mg
No monitoring
Groupe 2
Monitoring Arm :Prasugrel 5 mg
1rst assessment : Verifynow P2Y12 : 2 weeks ± 2 d
PRU≥208
85<PRU<208
PRU ≤85
Prasugrel 10 mg/day
Prasugrel 5 mg
Clopidogrel 75 mg/day
2nd assessment and adjustment:
Verifynow P2Y12 : 2 weeks ± 2 d
Assessment of the primary end point (net clinical benefit)over 12 months
Bleeding type 2,3,5 of the BARC definition and
MACE :CV death, MI, urgent revascularisation, stent thrombosis, stroke

File Edit View Window Help
8 / 8 77.6% Tools Sign Comment



Оптимизиране на антиагрегантната терапия

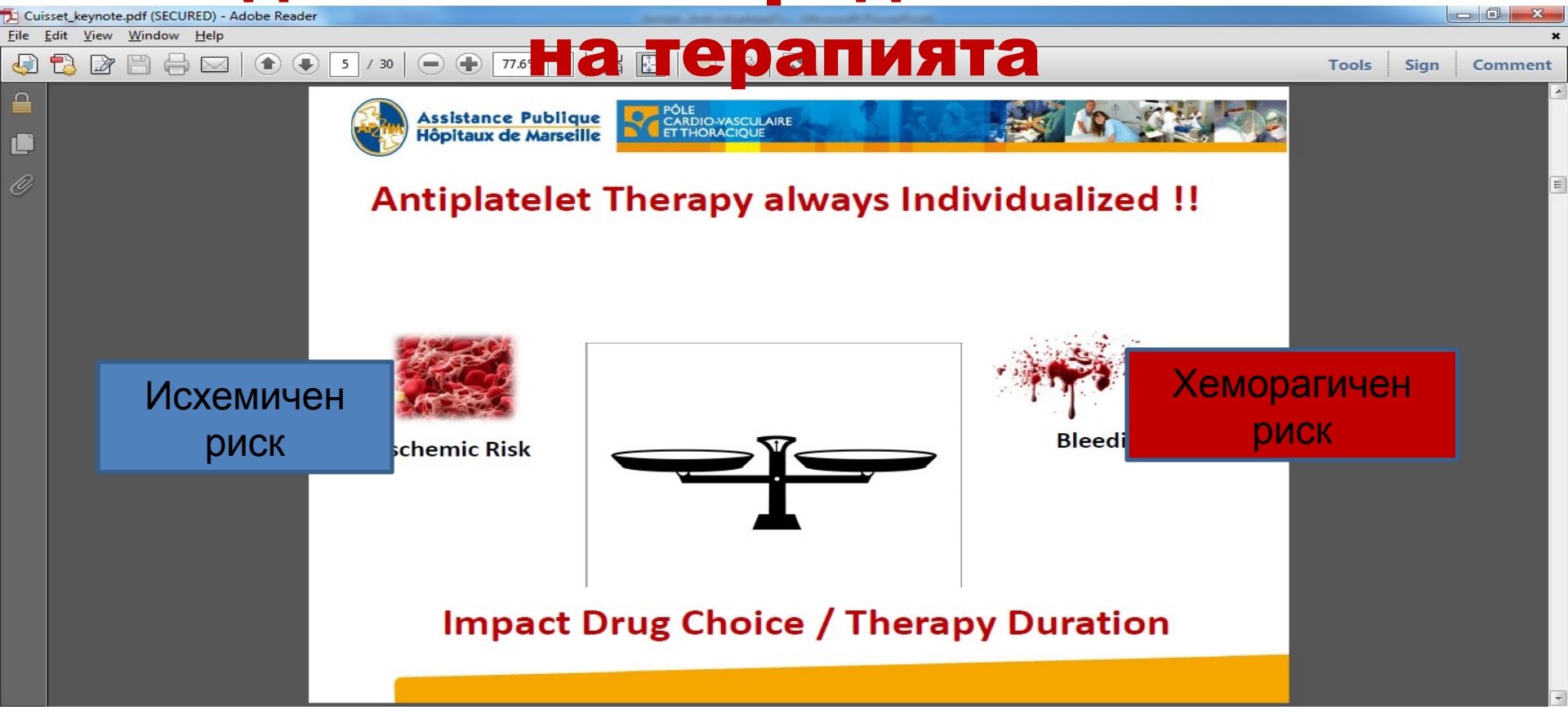
- Оптимизиране, базирано на изследване на тромбоцитна реактивност
- Оптимизиране, базирано на генетичен анализ
- Оптимизиране, базирано на клиничната характеристика на пациента


Риск за стент тромбоза/исхемични усложнения
оцитна реактивност
CYP 2C19*2

Оптимизиране на антиагрегантната терапия

- Оптимизиране, базирано на изследване на тромбоцитна реактивност
- Оптимизиране, базирано на генетичен анализ
- Оптимизиране, базирано на клиничната характеристика на пациента

Антиагрегантната терапия винаги е индивидуализирана – избор на медикамент и продължителност на терапията



Избор на P2Y12 рецепторен блокер

Choice of P2Y12 blockers

Ischemic Risk **ACS patients** *Bleeding Risk*	**High risk** STEMI Diabetes mellitus, CKD High-risk NSTE ACS (Tn + and/or ST changes) Recurrent event on clopidogrel Stent Thrombosis	**Low risk ACS** No ST changes No Troponin elevation **PCI for stable CAD** *(Patients not in Triton / Plato)*
High risk: Prior stroke/TIA* Age > 75 y.o, Weight < 60 kg Active bleeding Chronic OAC, Prior Bleeding	Individual Decision	Clopidogrel
Low risk No prior stroke/TIA/Bleeding Age < 75 y.o Weight > 60 kg No Chronic OAC	New P2Y12 Blockers	Clopidogrel

* CI Prasugrel

Избор на P2Y12 рецепторен блокер при ОКС

Prasugrel и Ticagrelor

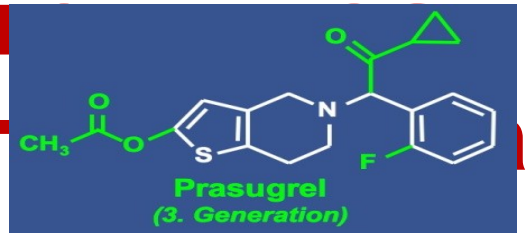
- NSEMI с висок риск
- STEMI
- Диабет
- Рекурентни инциденти clopidogrel

Ticagrelor

- Натоварване преди коронарна анатомия
- Консервативно лекувани пациенти с

Възможни опорни

разг не



	Prasugrel	Ticagrelor
Контраиндикации		
Мозък:	Преживян инсулт/ПНМК	Преживяна интракраниална хеморагия
Черен дроб:	Тежка чернодробна дисфункция	Умерена/тежка чернодробна дисфункция
	Разумно поведение	
	Модифициране на поддържащата доза при < 60 kg / ≥ 75 г	Брадикардия Високостепенен AV-Block

Efient, Summary of Product Characteristic, accessed at www.ema.europa.eu, Sept12;
Brilique, Summary of Product Characteristic, accessed at www.ema.europa.eu, Sept12

Индивидуализираната антиагрегантна терапия при ОКС е *реалност*

- Оптимизиране, базирано на изследване на тромбоцитна реактивност – ***Все още не***
  - ✓ Реалност - Стратифициране на исхемичния, хеморагичния и баланса исхемия-кървене
    - ✓ Не е доказано, но не е и отречено – помага в избора и дозировката на P2Y12
- Оптимизиране, базирано на генетичен анализ - ***Не***
- Оптимизиране, базирано на клиничната характеристика на пациента – ***Да***

Just do it...
NIKE

NOW
LATER

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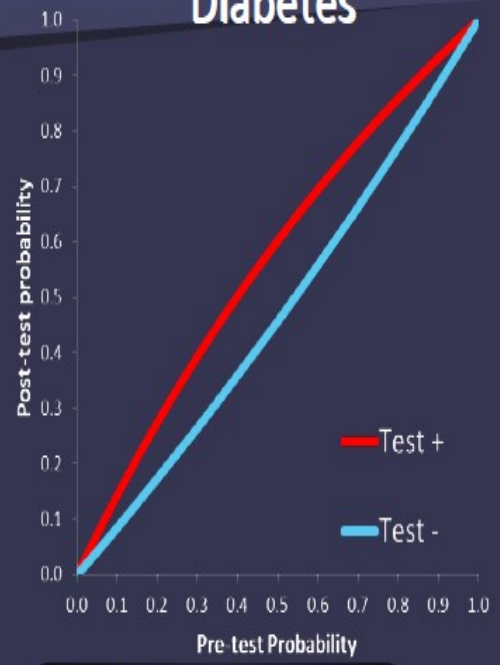
5 / 8 77.6% Tools Sign Comment

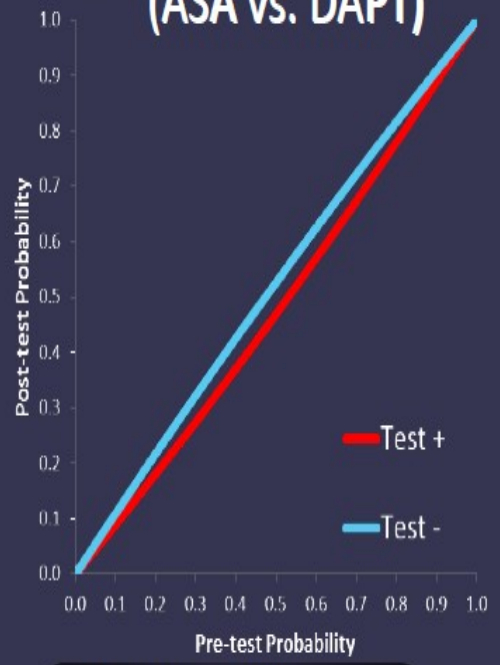
"Diagnostic" Performance of Other Accepted Risk Markers

Diabetes



Sensitivity = 35%
Specificity = 77%
PPV = 4%
NPV = 98%

P2Y12 Therapy in CURE (ASA vs. DAPT)



Sensitivity = 55%
Specificity = 50%
PPV = 9%
NPV = 89%

Adapted from Mathew et al. *Circulation* 2004;109:476-480; Yusuf S. et al. *N Engl J Med* 2001;345:494-502.

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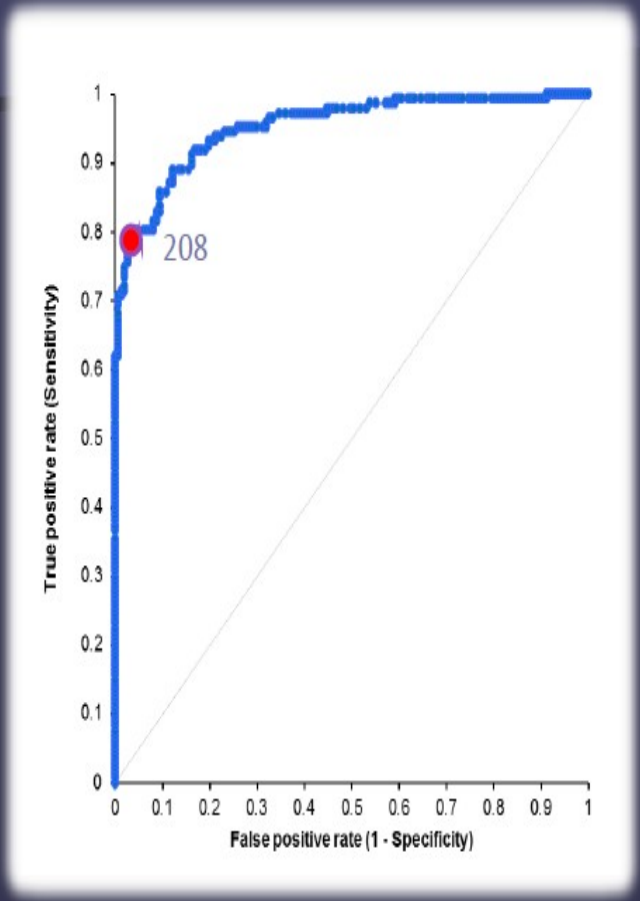
Diagnostic Performance of PRU Result



AUC: 0.92

Highest combination of sensitivity & specificity from ROC curve (208)

- Sensitivity = 79%
- Specificity = 97%

Brar SS et al. *J Am Coll Cardiol.* 2011 Nov 1; 58 (19):1945-54; Price MJ et al. *Am Heart J.* 2009 May; 157 (5):818-24; VerifyNow P2Y12 Test package insert, 2012.

Speakers: 100%

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Additive Value of PFT when properly assessed via prognostic statistics

Measurement	Number of Subjects	Referent Risk Classification	NRI
VerifyNow PRU (Brar et al JACC 2011)	3,059	Clinical Risk Score	23% ($p < 0.001$)
VerifyNow PRU (ADAPT-DES, ACC 2012)	8,575	ACS/Diabetes/Stent Length	29% ($p < 0.001$)
HDL Cholesterol	3,264	FRS	12% ($p < 0.001$)
C-reactive Protein	3,006	FRS	12% ($p = 0.009$)
Carotid Intima-Media Thickness	2,965	FRS	7.6% ($p = 0.01$)
Coronary Artery Calcification	4,129	FRS ATP III	22.4% ($p = 0.009$) 19.6% ($p = 0.004$)
Family History of premature CAD	22,841	FRS	-2.0%