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ESC NSTEMI Guidelines

An Update

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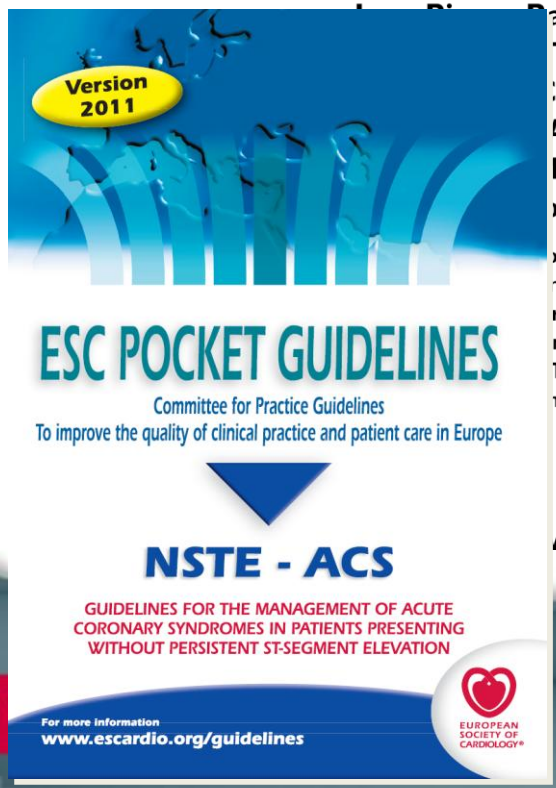
European Heart Journal
doi:10.1093/eurheartj/ehr236

ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation

The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC)

Authors/Task Force Members: Christian W. Hamm (Chairperson) (Germany)*, assand (Co-Chairperson)*, (France), Stefan Agewall (Norway), he Netherlands), Eric Boersma (The Netherlands), Hector Bueno aso (Italy), Dariusz Dudek (Poland), Stephan Gielen (Germany), Austria), Magnus Ohman (USA), Mark C. Petrie (UK), Frank Sonntag liguel Sousa Uva (Portugal), Robert F. Storey (UK), William Wijns ron Zahger (Israel).

r Practice Guidelines: Jeroen J. Bax (Chairperson) (The Netherlands), Angelo Auricchio mut Baumgartner (Germany), Claudio Ceconi (Italy), Veronica Dean (France), Christi Deaton rd (Belgium), Christian Funck-Brentano (France), David Hasdai (Israel), Arno Hoes (The ni Knuuti (Finland), Philippe Kolh (Belgium), Theresa McDonagh (UK), Cyril Moulin (France), The Netherlands), Bogdan A. Popescu (Romania), Željko Reiner (Croatia), Udo Sechtem nton Sirnes (Norway), Adam Torbicki (Poland), Alec Vahanian (France), Stephan Windecker



European Heart Journal
vance Access published August 26, 2011

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What was new?

- **Diagnostic**
  - High-sensitive troponin introduced
  - Echocardiography standard
  - Coronary CT for rule-out in low/intermediate risk patients
- **Risk Stratification**
  - 3-hour fast rule-out protocol
  - Bleeding risk score (CRUSADE)
- **Medical Treatment**
  - Ticagrelor and prasugrel introduced
- **Revascularization**
  - Timing of revascularization

What is new 2013 ?

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- hs-Troponin: more data
- CT: new studies
- Invasive strategy: new metaanalysis
- Prasugrel new study: TRILOGY
- Vorapaxar: new antiplatelet drug
- Rivaroxaban: new anticoagulation

Recommendations for diagnosis and risk stratification

Recommendations	Class	Level
Blood has to be drawn promptly for troponin (cardiac troponin T or I) measurement.The result should be available within 60 min.The test should be repeated 6-9 h after initial assessment if the first measurement is not conclusive. Repeat testing after 12-24 h is advised if the clinical condition is still suggestive	I	A
An echocardiogram is recommended for all patients to evaluate regional and global LV function and to rule in or rule out differential diagnoses.	I	C
Coronary angiography is indicated in patients in whom the extent of CAD or the culprit lesion has to be determined.	I	C
Coronary CT angiography should be considered as an alternative to invasive angiography to exclude ACS when there is a low to intermediate likelihood of CAD and when troponin and ECG are inconclusive.	IIa	B
In patients without recurrence of pain, normal ECG findings, negative troponins tests, and a low risk score, a non-invasive stress test for inducible ischaemia is recommended before deciding on an invasive strategy.	I	A

A rapid rule-out protocol (0 and 3 h) is recommended when highly sensitive troponin tests are available.

www.escardio.org/guidelines

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

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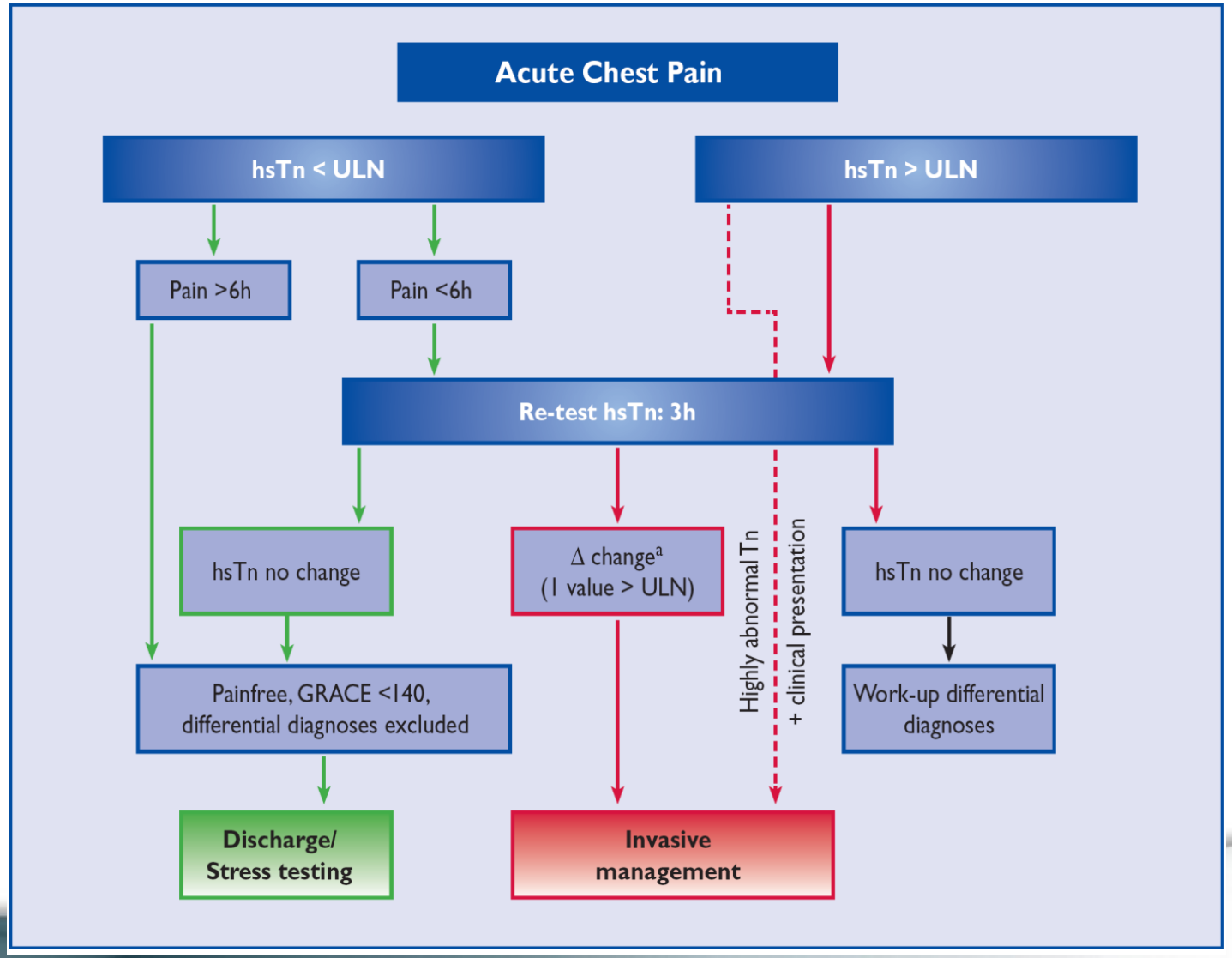
Rapid rule-out of ACS with high-sensitivity troponin.



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Evolution of the cardiac troponin (cTn) assays

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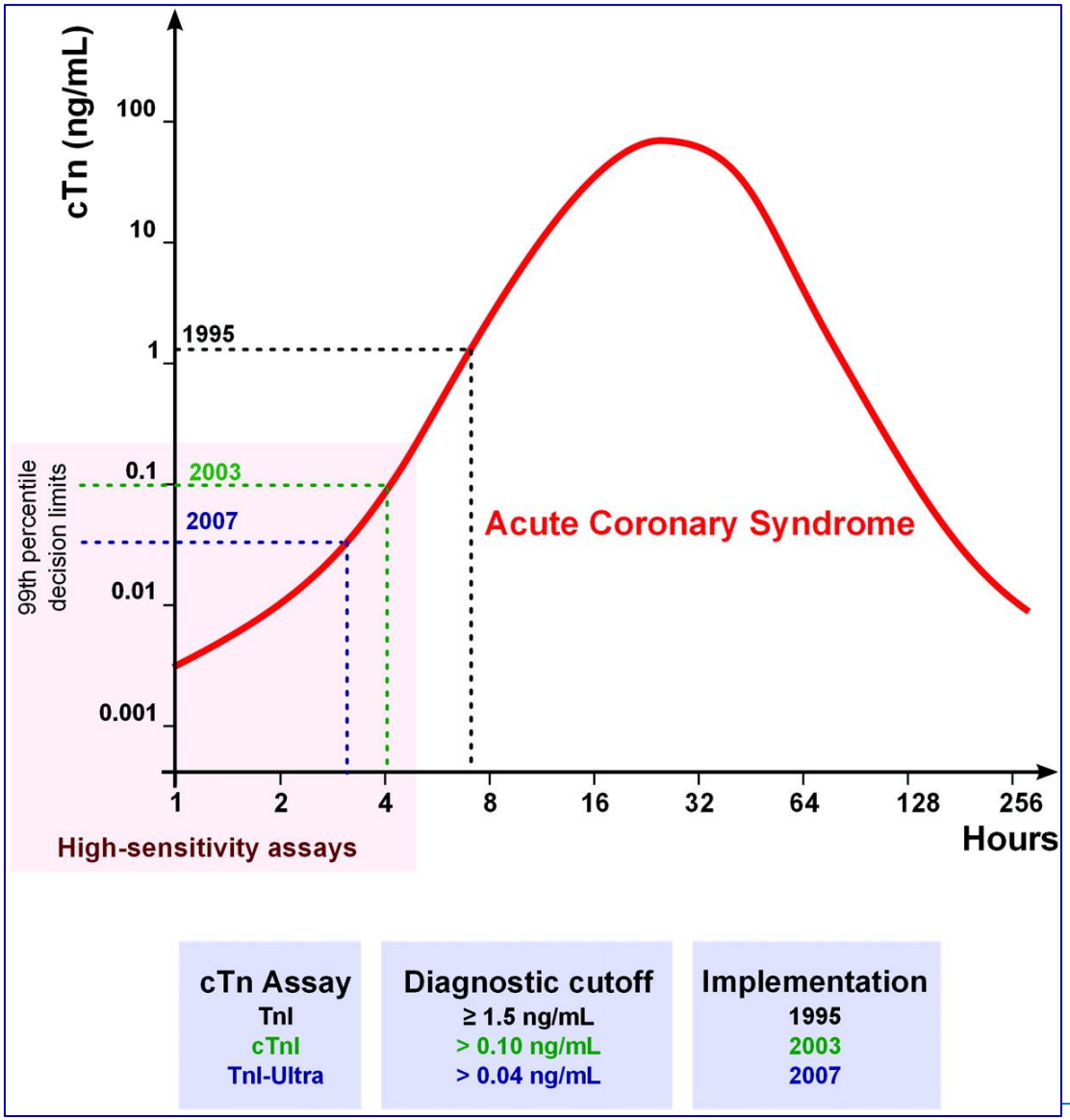

cTn Assay	Diagnostic cutoff	Implementation
TnI	≥ 1.5 ng/mL	1995
cTnI	> 0.10 ng/mL	2003
TnI-Ultra	> 0.04 ng/mL	2007

Mahajan V S , Jarolim P Circulation 2011;124:2350-2354

Hs-Troponin Elevation on Admission

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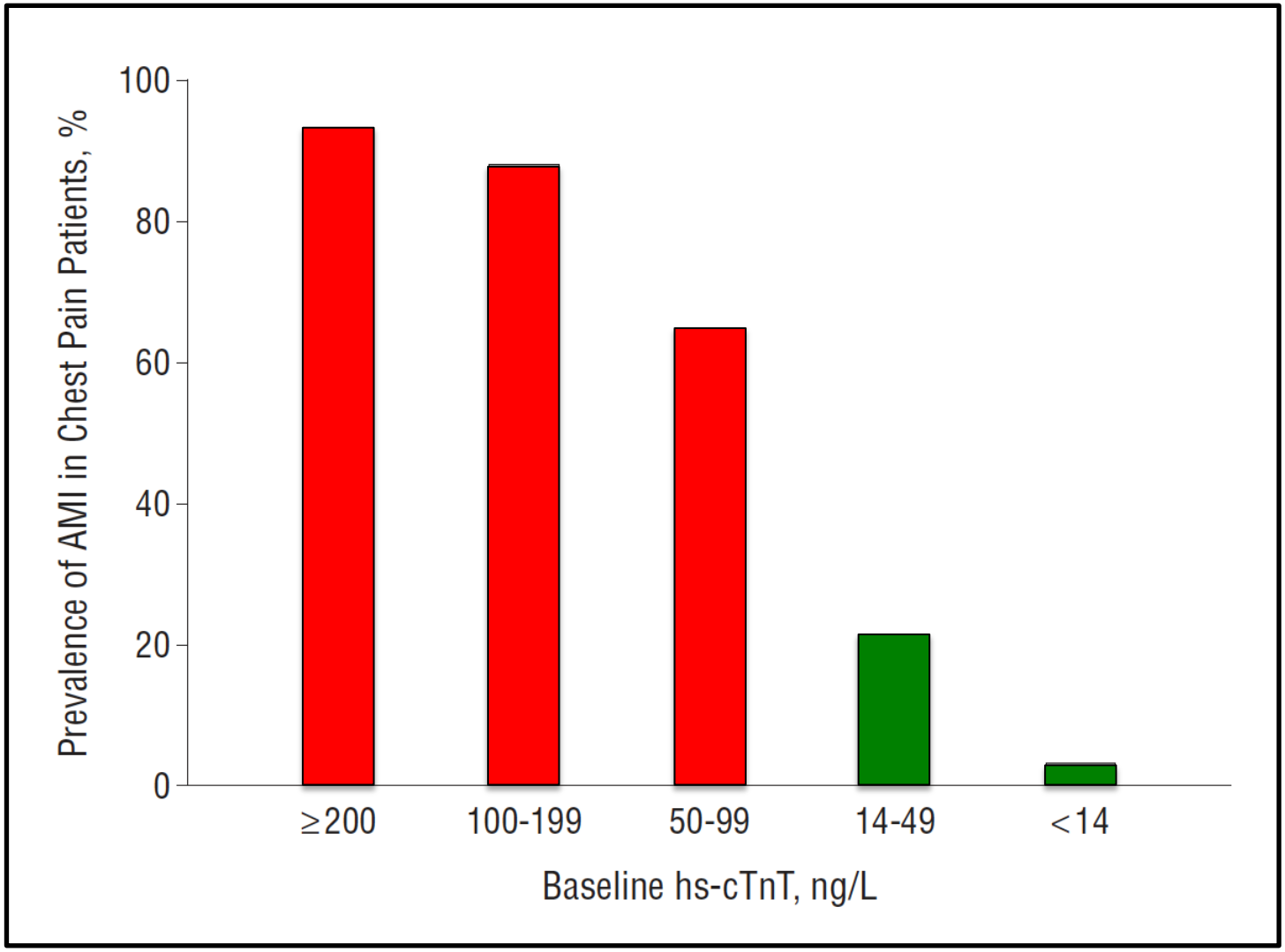

T. Reichlin, Arch Intern Med. 2012

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European Heart Journal (2012) **33**, 2252–2257
doi:10.1093/eurheartj/ehs154

CURRENT OPINION

How to use high-sensitivity cardiac troponins in acute cardiac care†

Kristian Thygesen*, Johannes Mair, Evangelos Giannitsis, Christian Mueller, Bertil Lindahl, Stefan Blankenberg, Kurt Huber, Mario Plebani, Luigi M. Biasucci, Marco Tubaro, Paul Collinson, Per Venge, Yonathan Hasin, Marcello Galvani, Wolfgang Koenig, Christian Hamm, Joseph S. Alpert, Hugo Katus, and Allan S. Jaffe, the Study Group on Biomarkers in Cardiology of the ESC Working Group on Acute Cardiac Care

Department of Cardiology, Aarhus University Hospital, Tage-Hansens Gade 2, DK-8000 Aarhus C, Denmark

Received 19 February 2012; revised 13 April 2012; accepted 7 May 2012; online publish-ahead-of-print 21 June 2012

Algorithm for Rapid Rule-in

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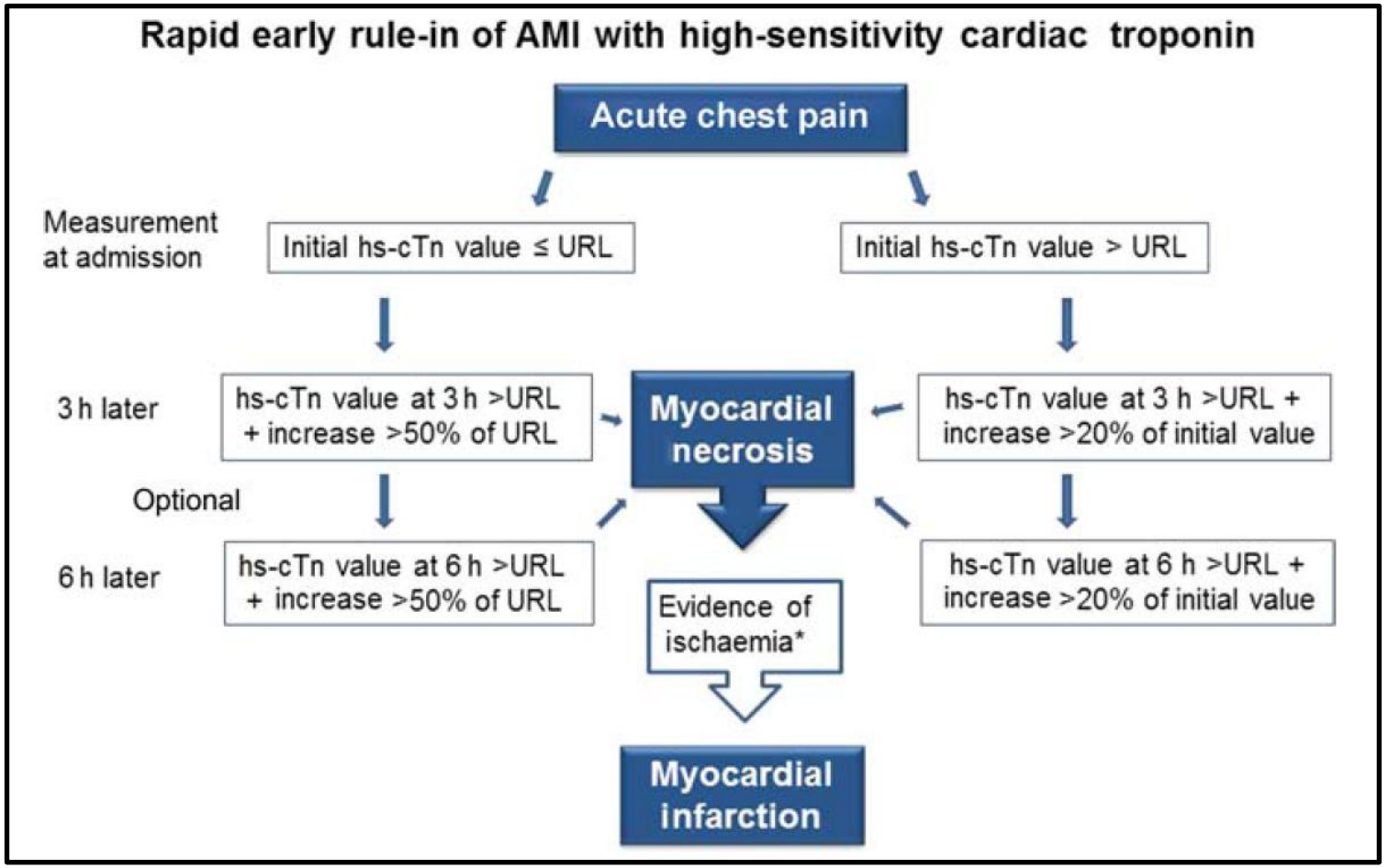

Recommendations for diagnosis and risk stratification (2)

Recommendations	Class	Level
Blood has to be drawn promptly for troponin (cardiac troponin T or I) measurement.The result should be available within 60 min.The test should be repeated 6-9 h after initial assessment if the first measurement is not conclusive. Repeat testing after 12-24 h is advised if the clinical condition is still suggestive of ACS.	I	A
Coronary CT angiography should be considered as an alternative to invasive angiography to exclude ACS when there is a low to intermediate likelihood of CAD and when troponin and ECG are inconclusive.	IIa	B
In patients without recurrence of pain, normal ECG findings, negative troponins tests, and a low risk score, a non-invasive stress test for inducible ischaemia is recommended before deciding on an invasive strategy.	I	A

Coronary CT angiography should be considered as an alternative to invasive angiography to exclude ACS when there is a low to intermediate likelihood of CAD and when troponin and ECG are inconclusive.

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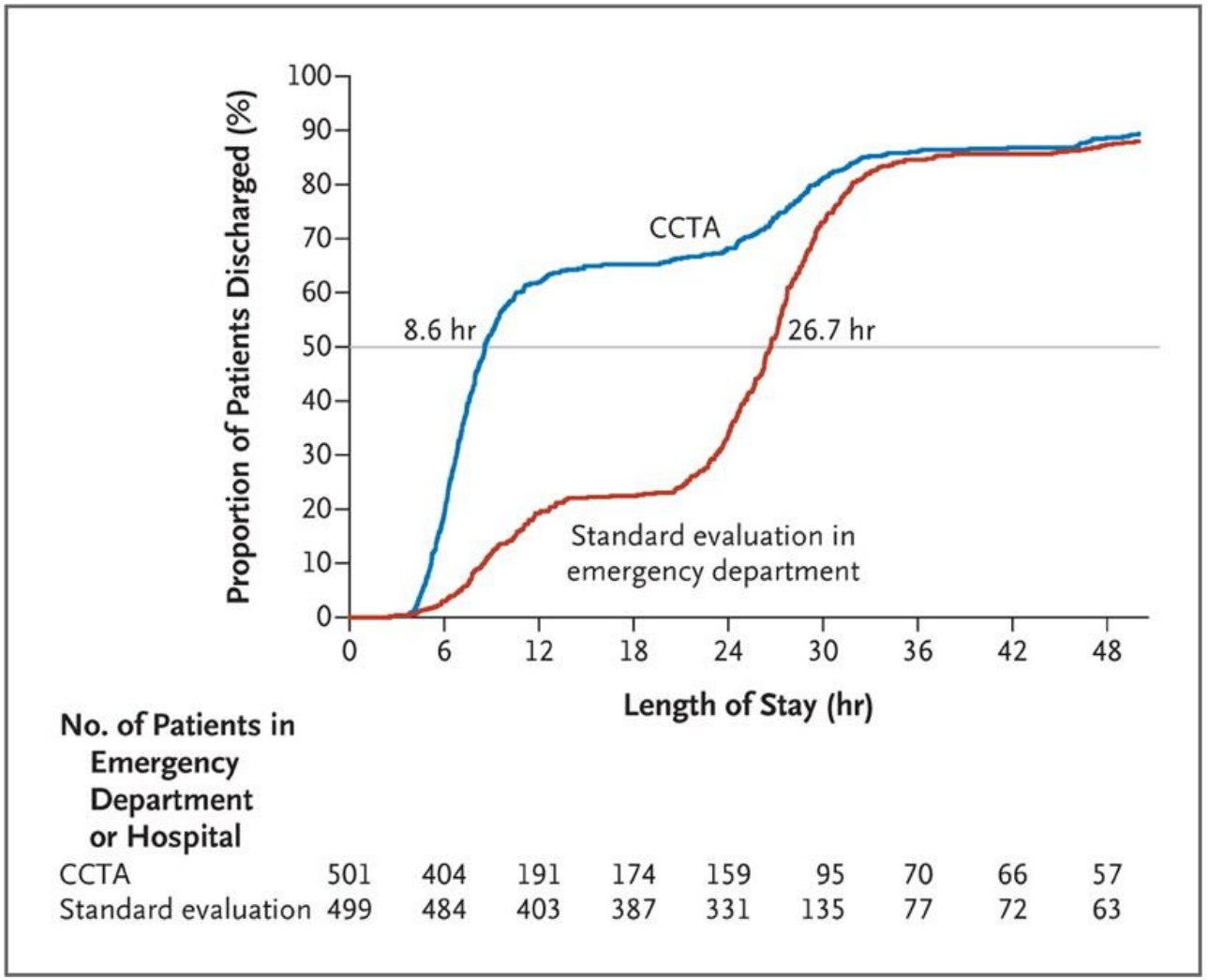
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 26, 2012 VOL. 367 NO. 4

Coronary CT Angiography versus Standard Evaluation in Acute Chest Pain

Udo Hoffmann, M.D., M.P.H., Quynh A. Truong, M.D., M.P.H., David A. Schoenfeld, Ph.D., Eric T. Chou, M.D., Pamela K. Woodard, M.D., John T. Nagurney, M.D., M.P.H., J. Hector Pope, M.D., Thomas H. Hauser, M.D., M.P.H., Charles S. White, M.D., Scott G. Weiner, M.D., M.P.H., Shant Kalanjian, M.D., Michael E. Mullins, M.D., Issam Mikati, M.D., W. Frank Peacock, M.D., Pearl Zakroysky, B.A., Douglas Hayden, Ph.D., Alexander Goehler, M.D., Ph.D., Hang Lee, Ph.D., G. Scott Gazelle, M.D., M.P.H., Ph.D., Stephen D. Wiviott, M.D., Jerome L. Fleg, M.D., and James E. Udelson, M.D., for the ROMICAT-II Investigators

Length of Stay in the Hospital and Proportion of Patients Discharged.



No. of Patients in Emergency Department or Hospital									
CCTA	501	404	191	174	159	95	70	66	57
Standard evaluation	499	484	403	387	331	135	77	72	63

Hoffmann U et al. N Engl J Med 2012;367:299-308.

Criteria for high risk with indication for invasive management

Primary
• Relevant rise or fall in troponin. • Dynamic ST- or T-wave changes (symptomatic or silent).
Secondary
• Diabetes mellitus. • Renal insufficiency (eGFR < 60 mL/min/1.73 m^2). • Reduced LV function (ejection fraction < 40%). • Early post infarction angina. • Recent PCI. • Prior CABG. • Intermediate to high GRACE risk score.

Meta-analysis in Diabetes

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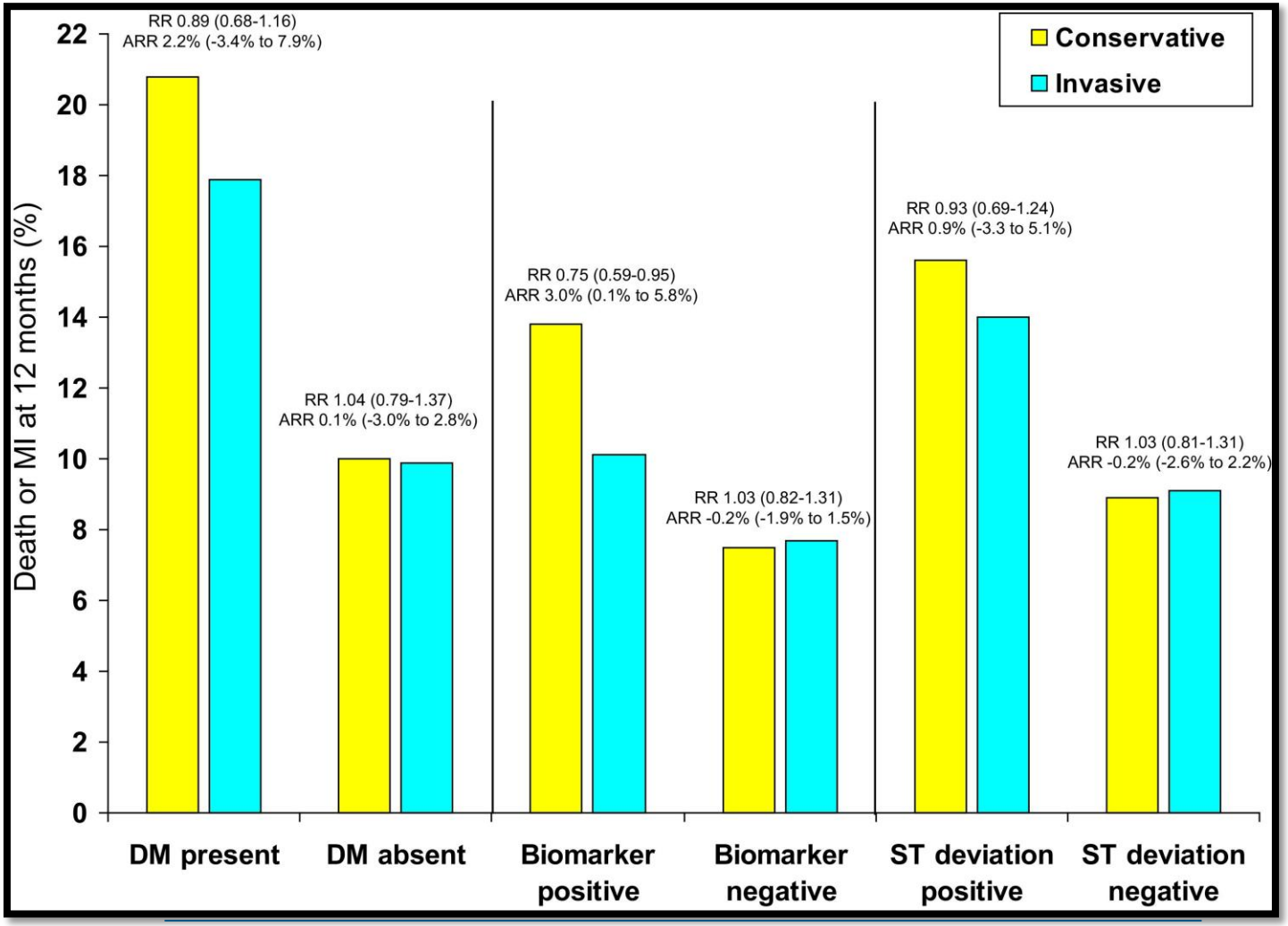
Invasive vs conservative Management



Michelle L. O'Donoghue , JACC, Volume 60, Issue 2 2012 106 - 111

Recommendations for oral antiplatelet agents

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*	I	A

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.

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

www.escardio.org/guidelines

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Prasugrel vs. Clopidogrel for Acute Coronary Syndromes Patients Managed without Revascularization — the TRILOGY ACS trial

On behalf of the TRILOGY ACS Investigators

Duke Clinical Research Institute

www.clinicaltrials.gov Identifier: NCT00699998

TRILOGY ACS Study Design

Medically Managed UA/NSTEMI Patients

Randomization Stratified by:
Age, Country, Prior Clopidogrel Treatment
(Primary analysis cohort — Age < 75 years)

Median Time to Enrollment = 4.5 Days

Medical Management Decision ≤72 hrs
(No prior clopidogrel given) — 4% of total

- **Clopidogrel**[1]: 300 mg LD + 75 mg MD
- **Prasugrel**[1]: 30 mg LD + 5 or 10 mg MD

Medical Management Decision ≤ 10 days
(Clopidogrel started ≤ 72 hrs in-hospital OR on chronic clopidogrel) — 96% of total

- **Clopidogrel**[1]: 75 mg MD
- **Prasugrel**[1]: 5 or 10 mg MD

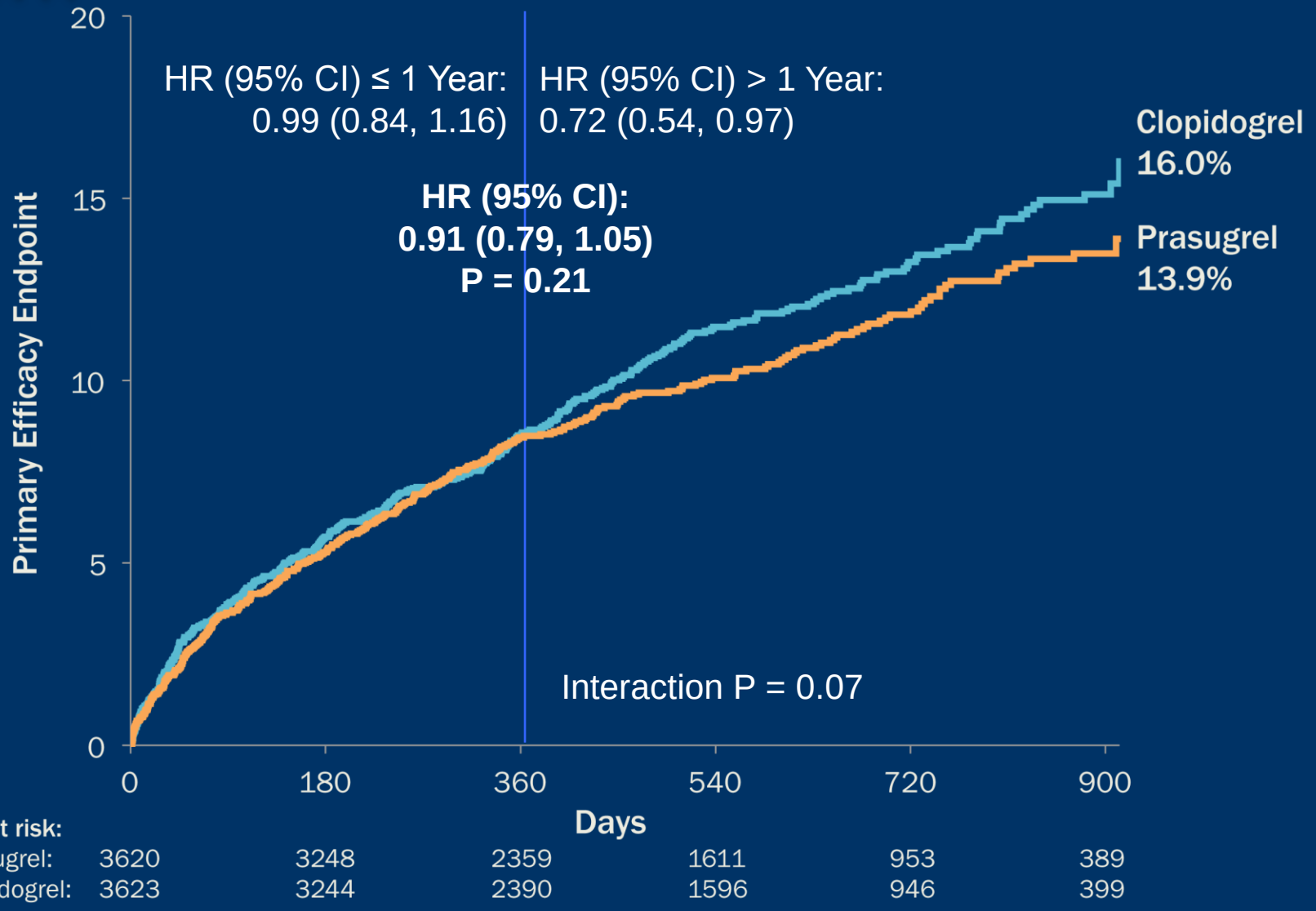
Minimum Rx Duration: 6 months; Maximum Rx Duration: 30 months

Primary Efficacy Endpoint: CV Death, MI, Stroke

1. All patients were on aspirin and low-dose aspirin (< 100 mg) was strongly recommended. For patients <60 kg or ≥75 years, 5 mg MD of prasugrel was given. Adapted from Chin CT et al. *Am Heart J* 2010;160:16-22.e1.

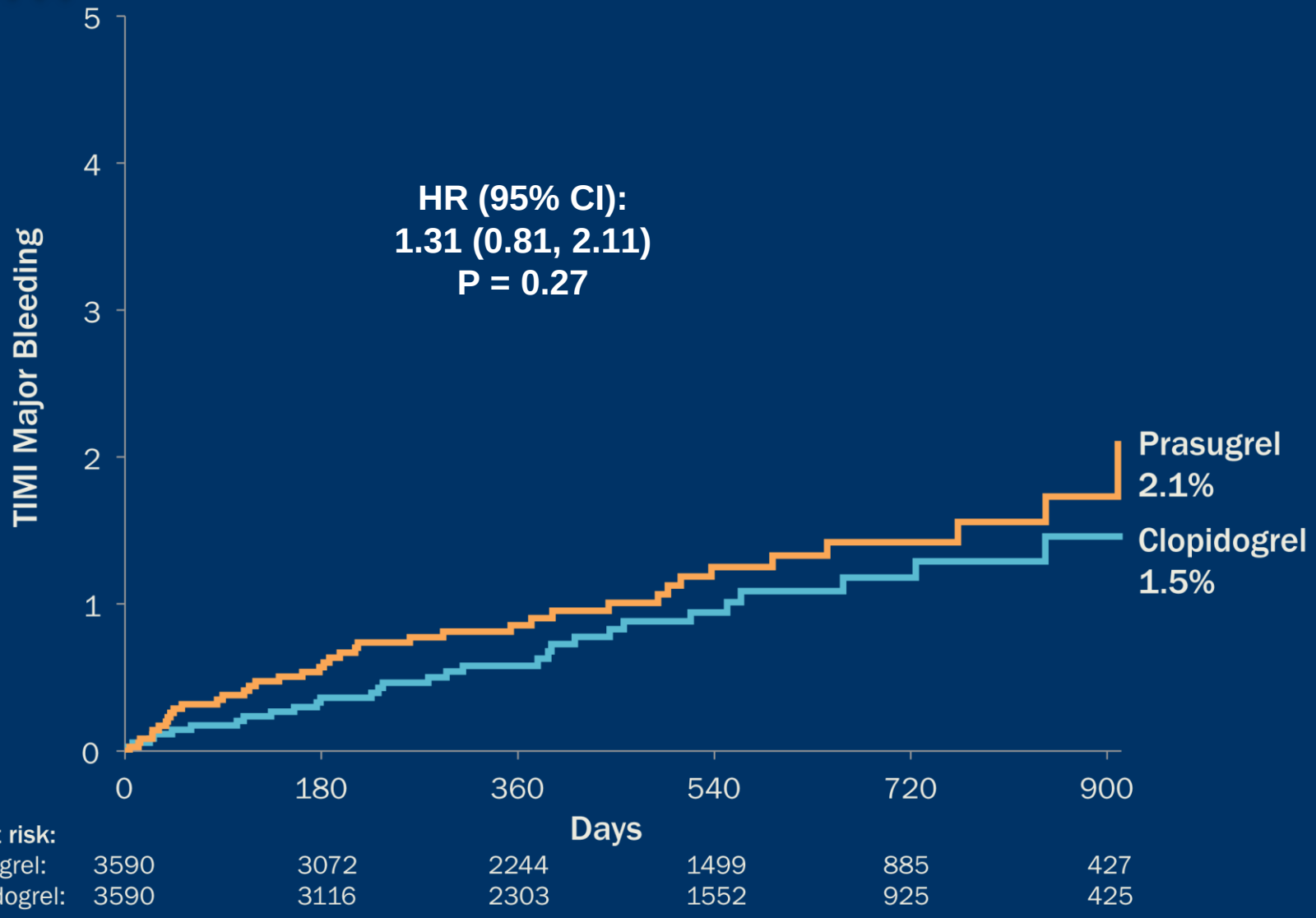
Primary Efficacy Endpoint to 30 Months

(Age < 75 years)

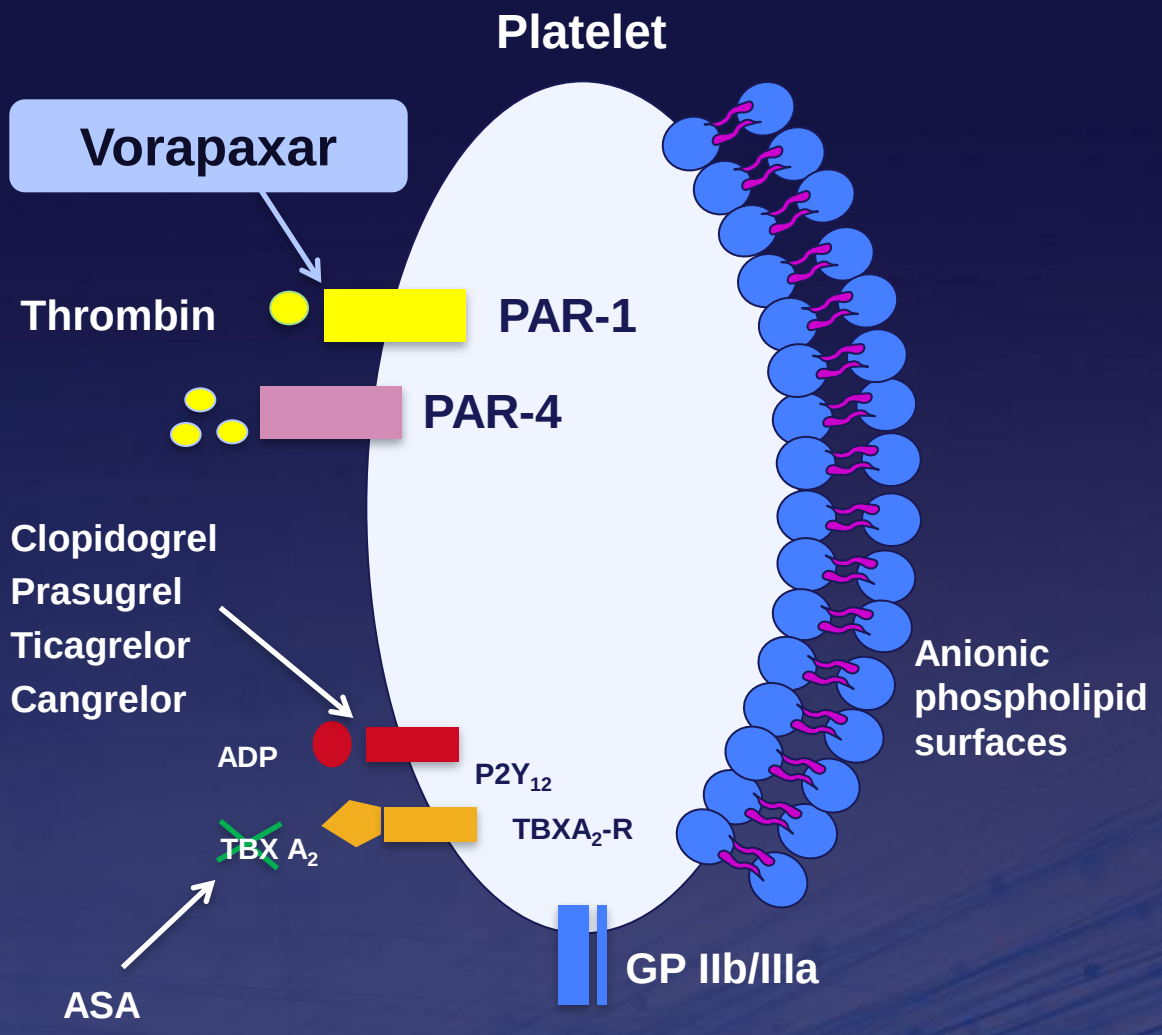


TIMI Major Bleeding to 30 Months

(Age < 75 years)



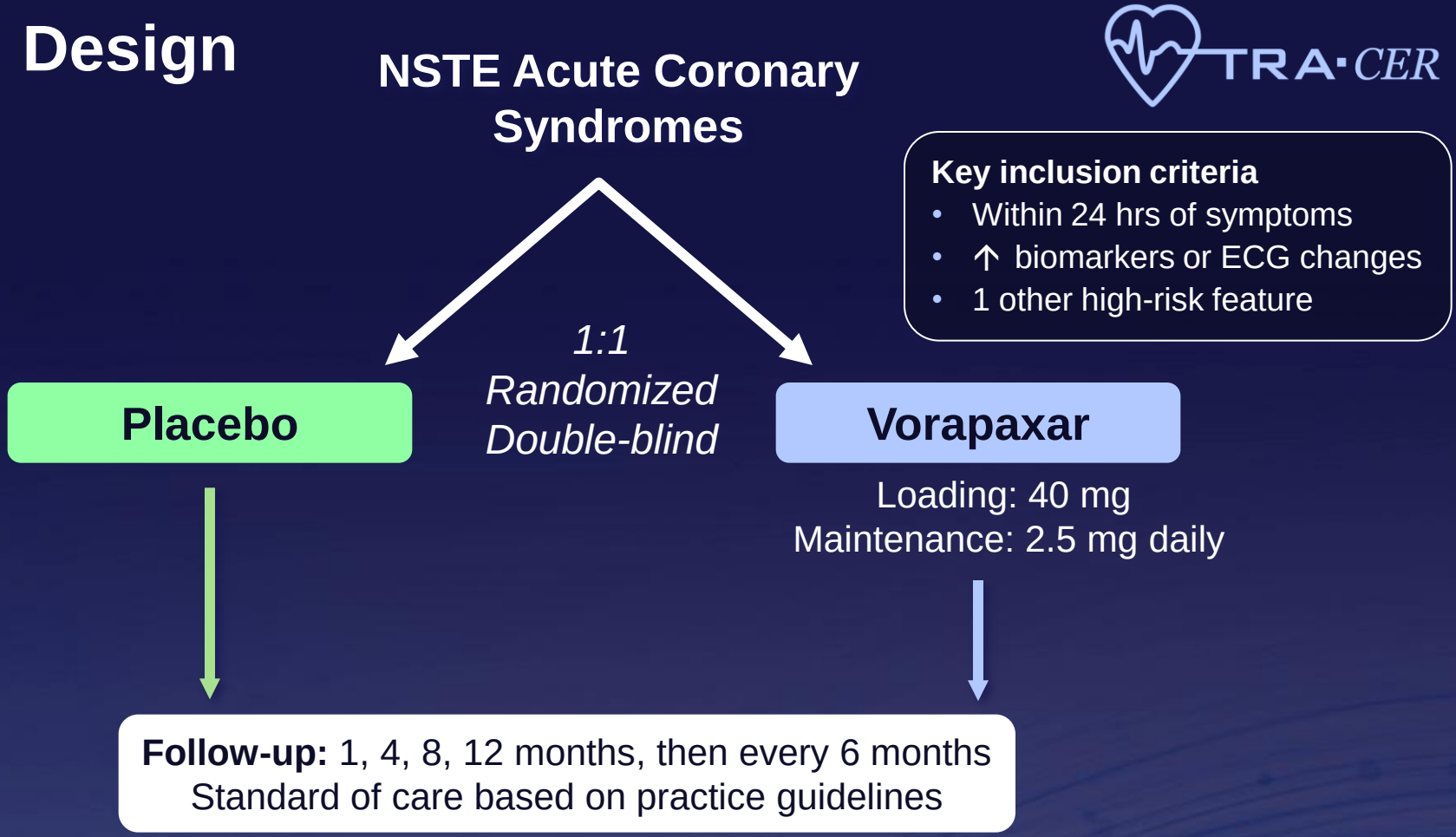
New Anti-Platelet Agent



- Vorapaxar:
  - First-in-class
  - Oral PAR-1 inhibitor
- Metabolism:
  - Primarily hepatic via CYP 3A4
  - Terminal half-life: ~126–269 hrs
- Prior trials:
  - No increase in bleeding and fewer MIs

Chackalamannil S, J Med Chem, 2006

Trial Design



Key inclusion criteria

- Within 24 hrs of symptoms
- ↑ biomarkers or ECG changes
- 1 other high-risk feature

Efficacy Endpoints

Primary: CV death, MI, stroke, hospitalization for ischemia, urgent revascularization

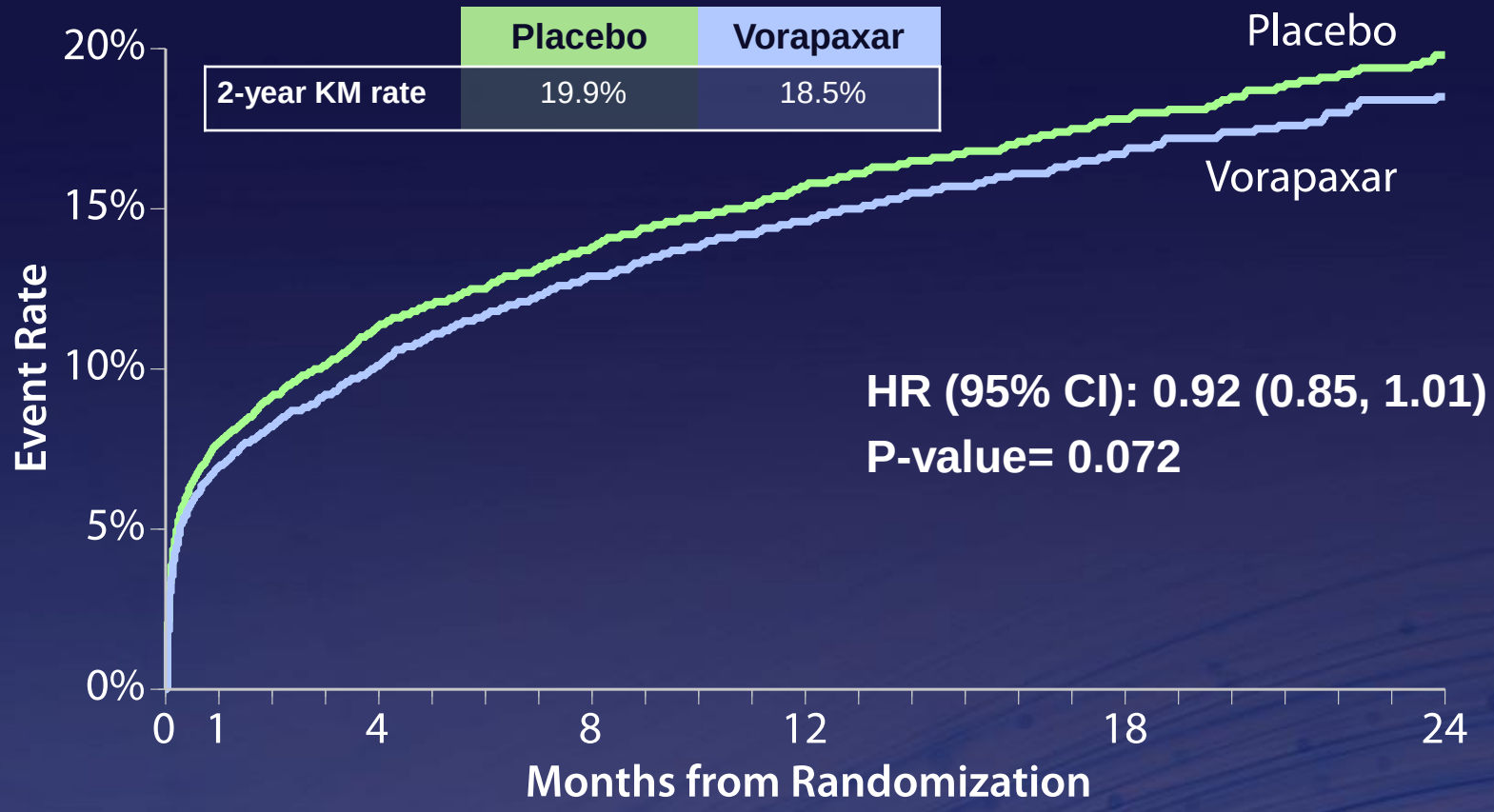
Key Secondary: CV death, MI, stroke

Bleeding Endpoints: GUSTO moderate or severe and clinically significant TIMI bleeding

Primary Endpoint

CV Death, MI, Stroke, Hospitalization for Ischemia, Urgent Revascularization

TRA·CER

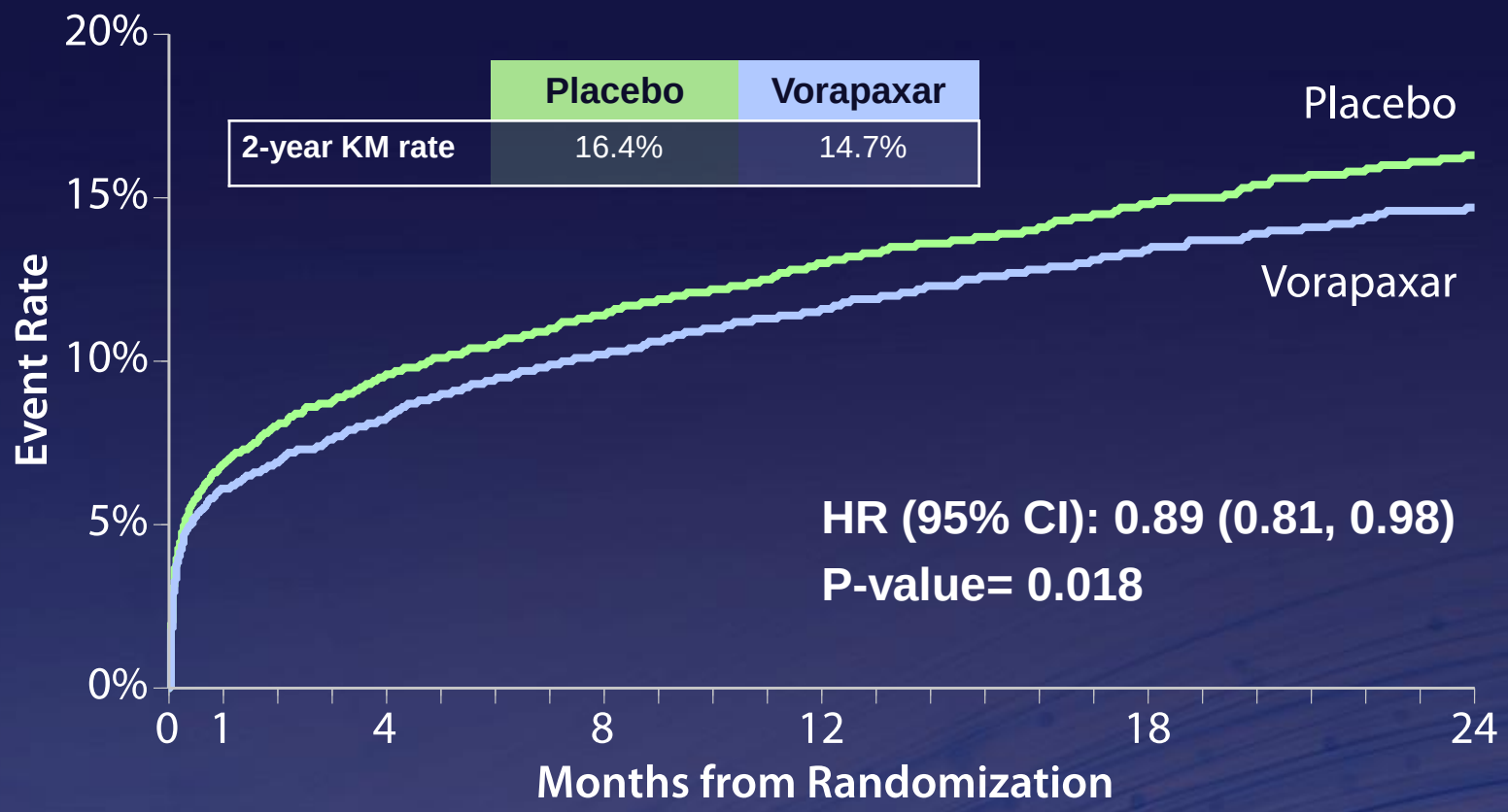


No. at risk							
Placebo	6471	5844	5468	5121	3794	2291	795
Vorapaxar	6473	5897	5570	5199	3881	2318	832

Key Secondary Endpoint

CV Death, MI, Stroke

TRA·CER



No. at risk							
Placebo	6471	5895	5575	5263	3922	2383	830
Vorapaxar	6473	5949	5684	5356	4023	2427	868

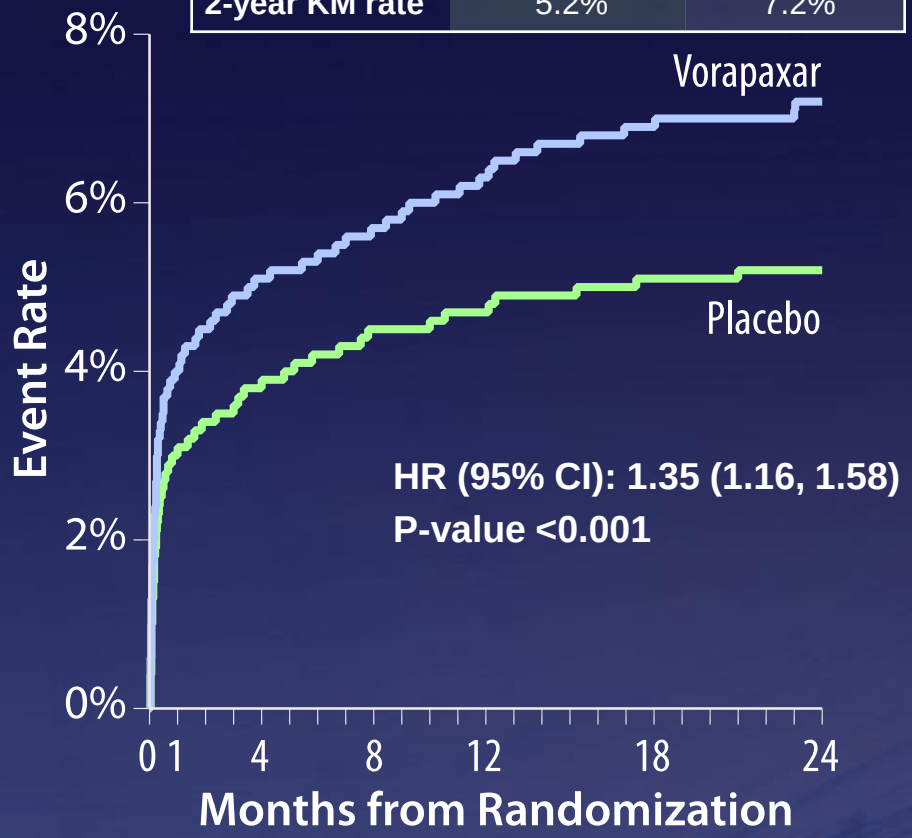
Duke Clinical Research Institute

Bleeding Outcomes

TRA·CER

GUSTO Moderate/Severe

	Placebo	Vorapaxar
2-year KM rate	5.2%	7.2%

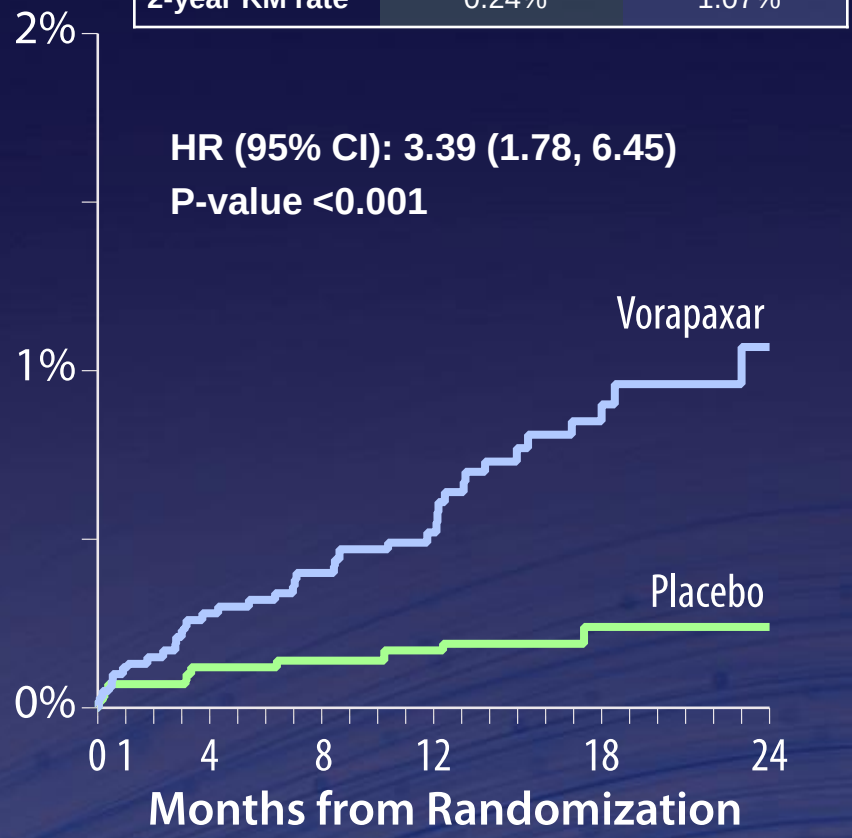


No. at risk

6441	5536	5137	4674	3393	1972	650
6446	5529	5108	4598	3278	1883	625

ICH

	Placebo	Vorapaxar
2-year KM rate	0.24%	1.07%



No. at risk

6441	5673	5281	4823	3511	2038	678
6446	5694	5272	4760	3411	1965	657

Recommendations for anticoagulants

Recommendations	Class	Level
Anticoagulation is recommended for all patients in addition to antiplatelet therapy.	I	A
The anticoagulation should be selected according to both ischaemic and bleeding risks, and according to the efficacy-safety profile of the chosen agent.	I	C
Fondaparinux (2.5 mg subcutaneously daily) is recommended as having the most favourable efficacy-safety profile with respect to anticoagulation.	I	A
If the initial anticoagulant is fondaparinux, a single bolus of UFH (85 IU/kg adapted to ACT, or 60 IU in the case of concomitant use of GPIIb/IIIa receptor inhibitors) should be added at the time of PCI.	I	B
Enoxaparin (1 mg/kg twice daily) is recommended when fondaparinux is not available.	I	B
If fondaparinux or enoxaparin are not available, UFH with a target aPTT of 50-70 s or other LMWHs at the specific recommended doses are indicated.	I	C
Bivalirudin plus provisional GPIIb/IIIa receptor inhibitors are recommended as an alternative to UFH plus GPIIb/IIIa receptor inhibitors in patients with an intended urgent or early invasive strategy, particularly in patients with a high risk of bleeding.	I	B

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

C. Michael Gibson, M.S., M.D., Jessica Mega, M.P.H., M.D., & Eugene Braunwald, M.D.
on behalf of the ATLAS ACS 2 TIMI 51 Investigators

Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome – Thrombolysis in Myocardial Infarction 51 Trial (ATLAS-ACS 2 TIMI 51):

A Randomized, Double-Blind, Placebo Controlled Study to Evaluate the Efficacy and Safety of Rivaroxaban in Subjects with Acute Coronary Syndrome

Funded by a Research Grant from Johnson and Johnson and Bayer to Brigham & Women's Hospital. Dr. Gibson has received honoraria & consulting fees from J&J and Bayer.

Recent ACS: STEMI, NSTEMI, UA

No increased bleeding risk, No warfarin, No ICH, No prior stroke if on ASA + Thienopyridine

Stabilized 1-7 Days Post-Index Event

Stratified by Thienopyridine use at MD Discretion

+ ASA 75 to 100 mg/day

Placebo
N=5,176
ASA + Thieno, n=4,821
ASA, n=355

RIVAROXABAN
2.5 mg BID
n=5,174
ASA + Thieno, n=4,825
ASA, n=349

RIVAROXABAN
5.0 mg BID
N=5,176
ASA + Thieno, n=4,827
ASA, n=349

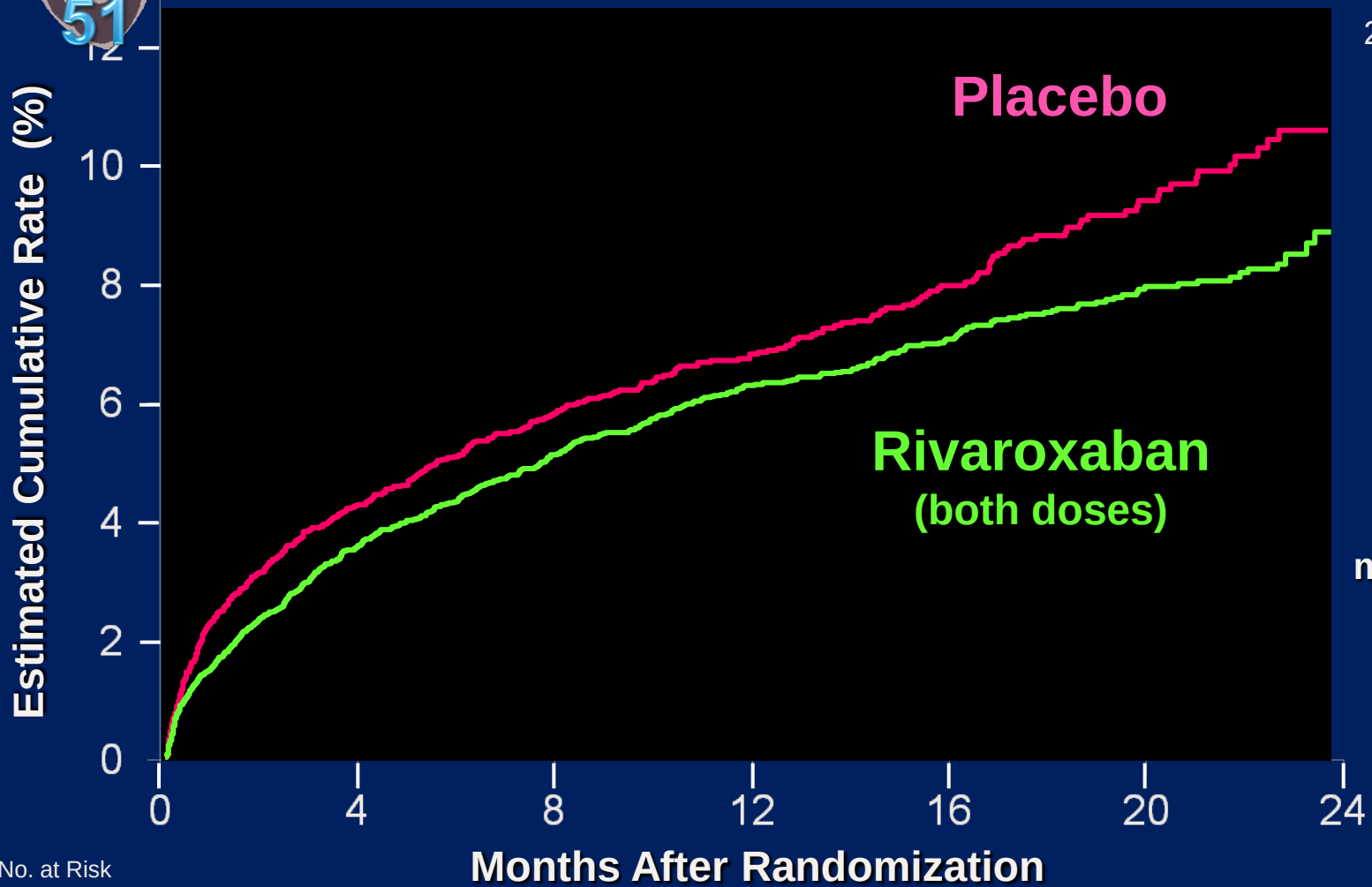
PRIMARY ENDPOINT:
EFFICACY: CV Death, MI, Stroke* (Ischemic + Hemg.)
SAFETY: TIMI major bleeding not associated with CABG
Event driven trial of 1,002 events in 15,342 patients**

* Stroke includes ischemic stroke, hemorrhagic stroke, and uncertain stroke
** 184 subjects were excluded from the efficacy analyses prior to unblinding

ATLAS ACS 2 TIMI 51

PRIMARY EFFICACY ENDPOINT:

CV Death / MI / Stroke* (Ischemic + Hemg.)



2 Yr KM Estimate

10.7%

8.9%

HR 0.84
(0.74-0.96)
ARR 1.7%

mITT p = 0.008
ITT p = 0.002

NNT = 59

No. at Risk

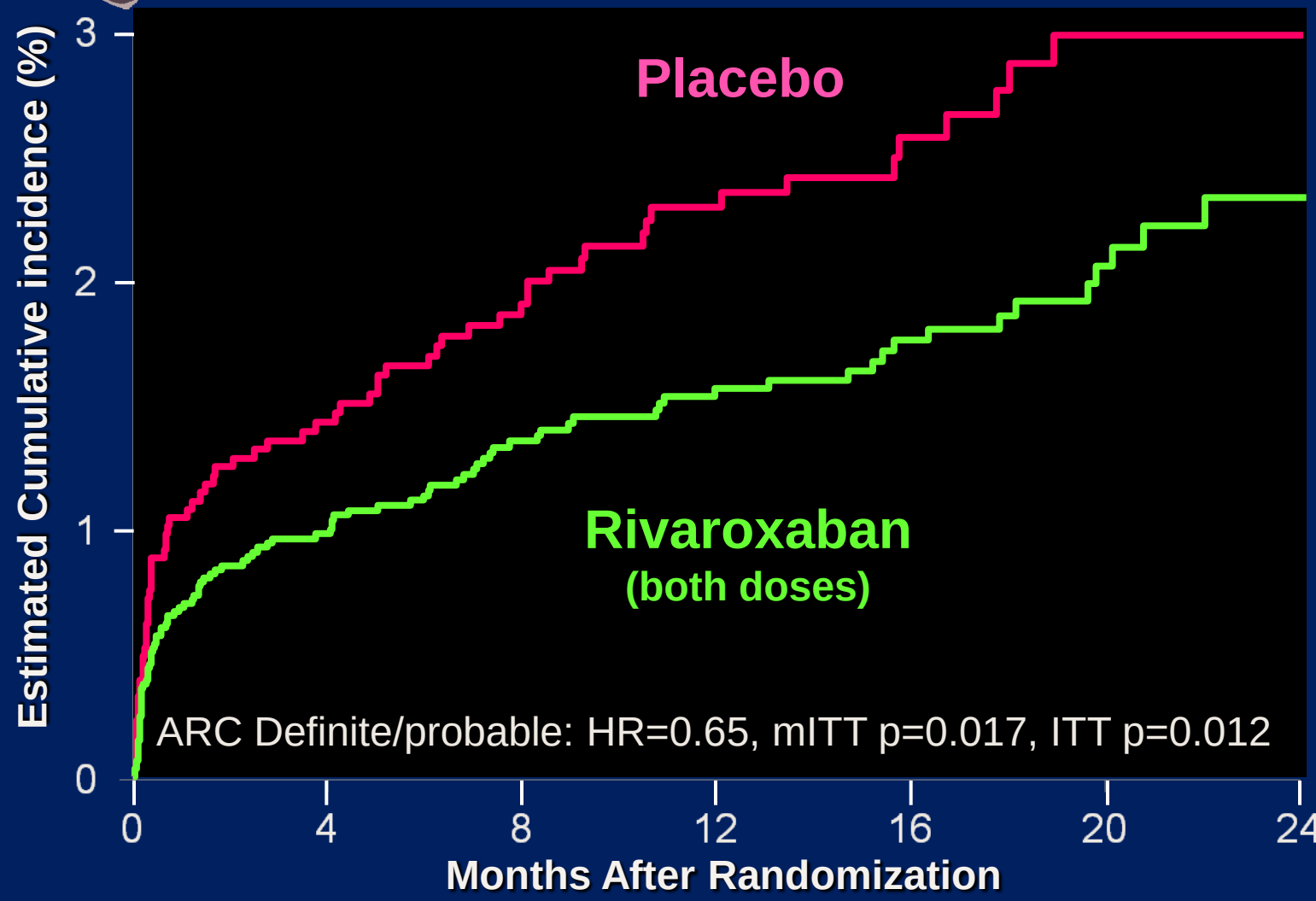
Placebo	5113	4307	3470	2664	1831	1079	421
Rivaroxaban	10229	8502	6753	5137	3554	2084	831

*: First occurrence of cardiovascular death, MI, stroke (ischemic, hemorrhagic, and uncertain) as adjudicated by the CEC across thienopyridine use strata
Two year Kaplan-Meier estimates, HR and 95% confidence interval estimates from Cox model stratified by thienopyridine use are provided per mITT approach; Stratified log-rank p-values are provided for both mITT and ITT approaches; ARR=Absolute Relative Reduction; NNT=Number needed to treat; Rivaroxaban=Pooled Rivaroxaban 2.5 mg BID and 5 mg BID.

ATLAS ACS 2 TIMI 51

STENT THROMBOSIS*

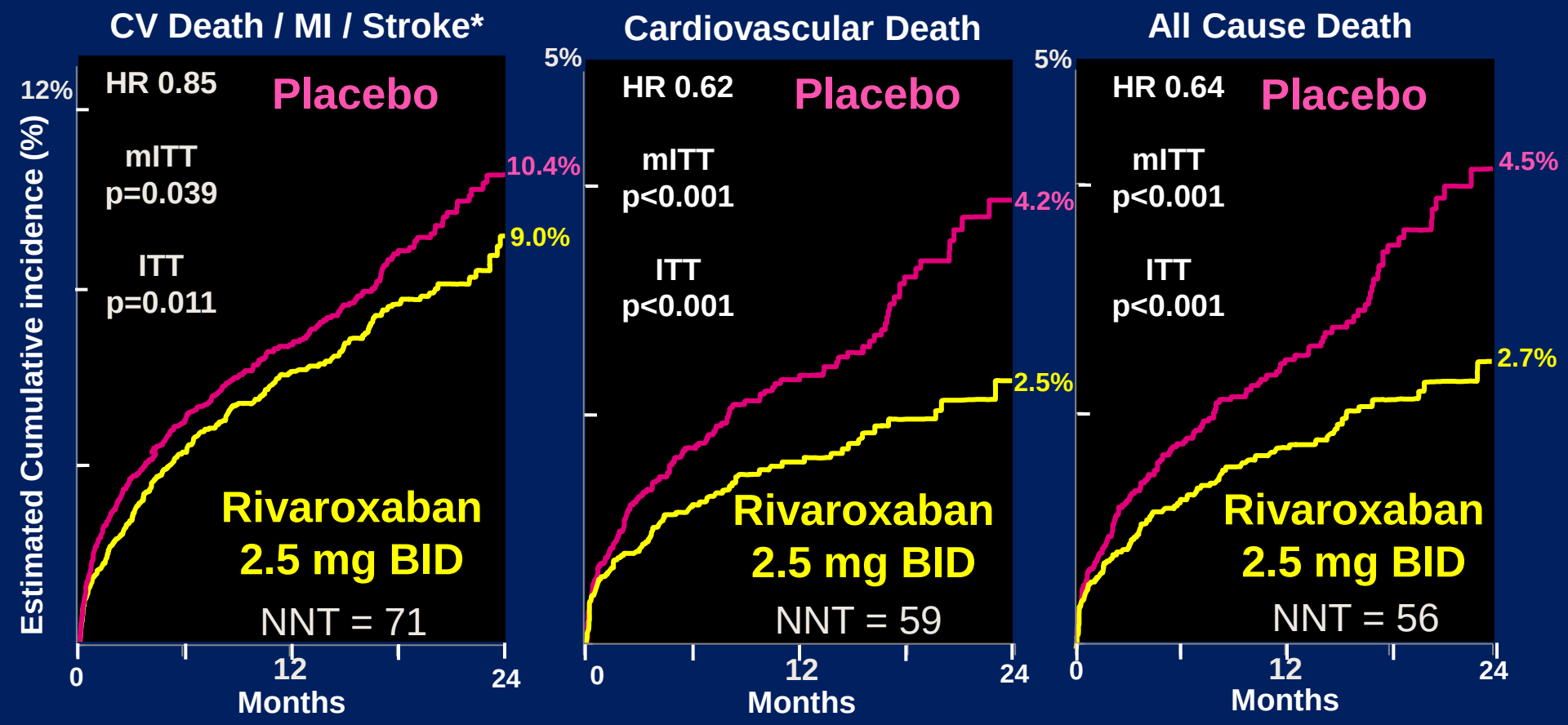
ARC Definite, Probable, Possible



* End point events are as adjudicated by the CEC across thienopyridine use strata

Two year Kaplan-Meier estimates, HR and 95% confidence interval estimates from Cox model stratified by thienopyridine use are provided per mITT approach; Stratified log-rank p-values are provided for both mITT and ITT approaches; Rivaroxaban=Pooled Rivaroxaban 2.5 mg BID and 5 mg BID.

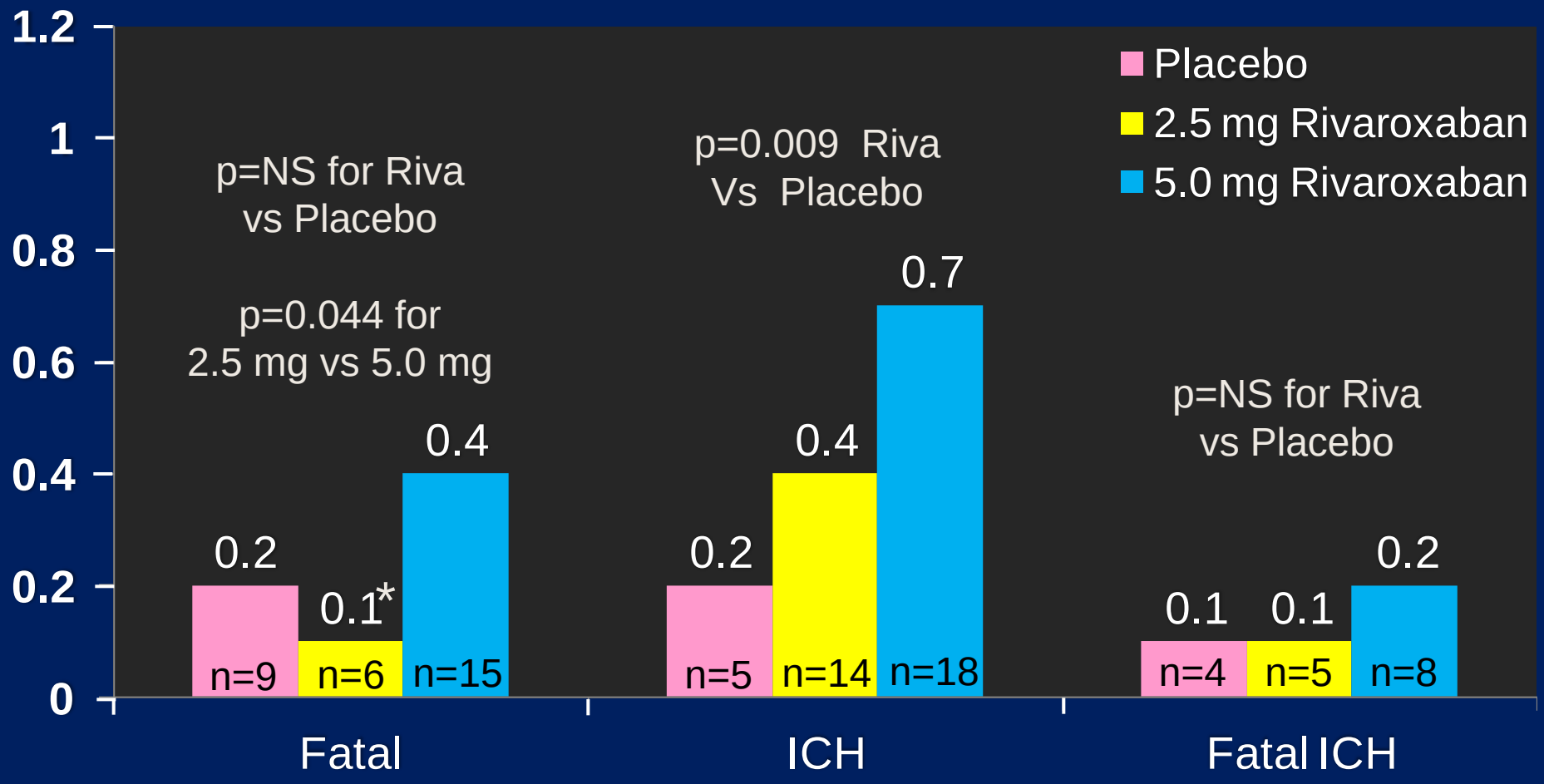
PRIMARY EFFICACY ENDPOINTS: 2.5 mg PO BID In Patients Treated with ASA + Thienopyridine



*: First occurrence of cardiovascular death, MI, stroke (ischemic, hemorrhagic, and uncertain) as adjudicated by the CEC
Two year Kaplan-Meier estimates, HR and 95% confidence interval estimates from Cox model stratified by thienopyridine use are provided per mITT approach; Stratified log-rank p-values are provided for both mITT and ITT approaches; NNT=Number needed to treat.

ATLAS ACS 2 TIMI 51

TREATMENT-EMERGENT FATAL BLEEDS AND ICH



*Among patients treated with aspirin + thienopyridine, there was an increase in fatal bleeding among patients treated with 5.0 mg of Rivaroxaban (15/5110) vs 2.5 mg of Rivaroxaban (5/5115) (p=0.02)

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Conclusion

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- Many interesting new data
- Nothing to change our current strategy

Thank you !

$P2Y_{12}$ Inhibitors

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

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

Recommendations for oral antiplatelet agents (1)

Recommendations	Class	Level
Aspirin should be given to all patients without contraindications at an initial loading dose of 150-300 mg, and at a maintenance dose of 75-100 mg daily long-term regardless of treatment strategy.	I	A
A $P2Y_{12}$ inhibitor should be added to aspirin as soon as possible and maintained over 12 months, unless there are contraindications such as excessive risk of bleeding.	I	A
$P2Y_{12}$-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

PLATO

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).

www.escardio.org/guidelines

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doi:10.1093/eurheartj/ehr236

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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

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Recommendations for oral Antiplatelet Agents 2

Recommendations	Class [a]	Level [b]
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

Decision-making algorithm in ACS