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Datenlage zur Plättchenaggregationshemmung, Dual, triple oder vierfach?

Welche Kombination wie lange?

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Disclosures

Company Name	*Relationship*
Eli Lilly / Daiichi Sankyo	*Research / educational grants, honoraria, consultant*
Astra Zeneca	*Honoraria, consultant*
MSD	*Honoraria*
The Medicines Company	*Research grants, honoraria*
Bristol Myers Squibb	*Research / educational grants, honoraria, consultant*
Bayer HealthCare	*Research / educational grants, honoraria, consultant*
Boehringer Ingelheim	*Consultant, Honoraria*

Guideline recommendations Antiplatelet therapy - Stable CAD/ Elective stenting

Clopidogrel (600 mg loading dose or more, 75 mg daily maintenance dose) is recommended for elective stenting.	I A
DAPT is indicated for at least 1 month after BMS implantation	I A
DAPT is indicated for 6 months after DES implantation	I B
Shorter DAPT duration (<6 months) may be considered after DES implantation in patients at high bleeding risk.	IIb A
Life-long single anti platelet therapy, usually ASA, is recommended	I A
DAPT may be used for more than 6 months in patients at high ischaemic risk and low bleeding risk	IIb C

Windecker S, et al. European Heart Journal (2014): 35, 2541–2619

Art der antithrombozytären Therapie nach ACS - Guidelines

ESC Myocardial Revascularization Guidelines 2014

NSTEMI

Prasugrel in patients in whom coronary anatomy is known and whom are preceding to PCI if no contraindication	I	B
Ticagrelor (180 mg loading dose, 90 mg twice daily) for patients at moderate-to-high risk of ischaemic events, regardless of initial treatment strategy including those pre-treated with clopidogrel if no contraindication.	I	B
Clopidogrel (600 mg loading dose, 75 mg daily dose), only when prasugrel or ticagrelor are not available or are contraindicated.	I	B

STEMI

Prasugrel (60mg loading dose, 10mg daily dose) if no contraindication	I	B
Ticagrelor (180mg loading dose, 90mg twice daily) if no contraindication	I	B
Clopidogrel (600mg loading dose, 75mg daily dose) only when prasugrel or ticagrelor are not available or are contraindicated	I	B

SOP: Anwendung ADP-Rezeptorblocker beim ACS – bevorzugte Substanz nach Kontraindikationen

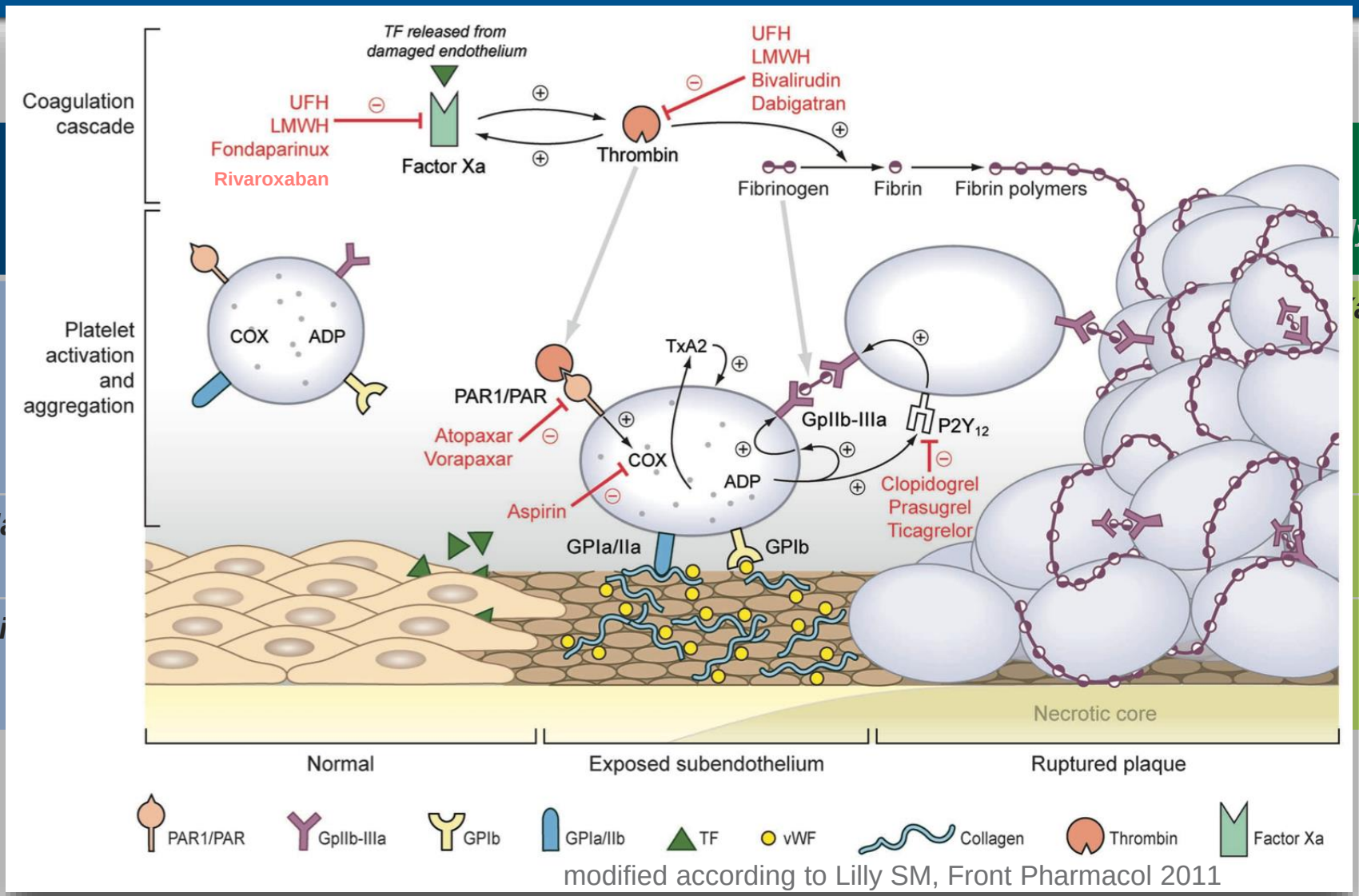
	Ticagrelor	Prasugrel
STEMI	+	++
Niereninsuffizienz	++	+
konservativ behandeltes ACS	++	+
Geplante Bypass-OP	++	+
Leberfunktions-störung (CHILD B)	+	-

Kein Head-to-Head Vergleich, Empfehlungen basierend auf z. T. nicht gepowerten Subgruppenanalysen im Vergleich zu Clopidogrel aus den entsprechenden Landmark-Studien

* nur, wenn Prasugrel und Ticagrelor keine Option

Geisler T, Gawaz M, Positionspapier DGK 2012

Approved anti platelet /antithrombotic compounds for longterm secondary prophylaxis after ACS



modified according to Lilly SM, Front Pharmacol 2011

Class

Formula

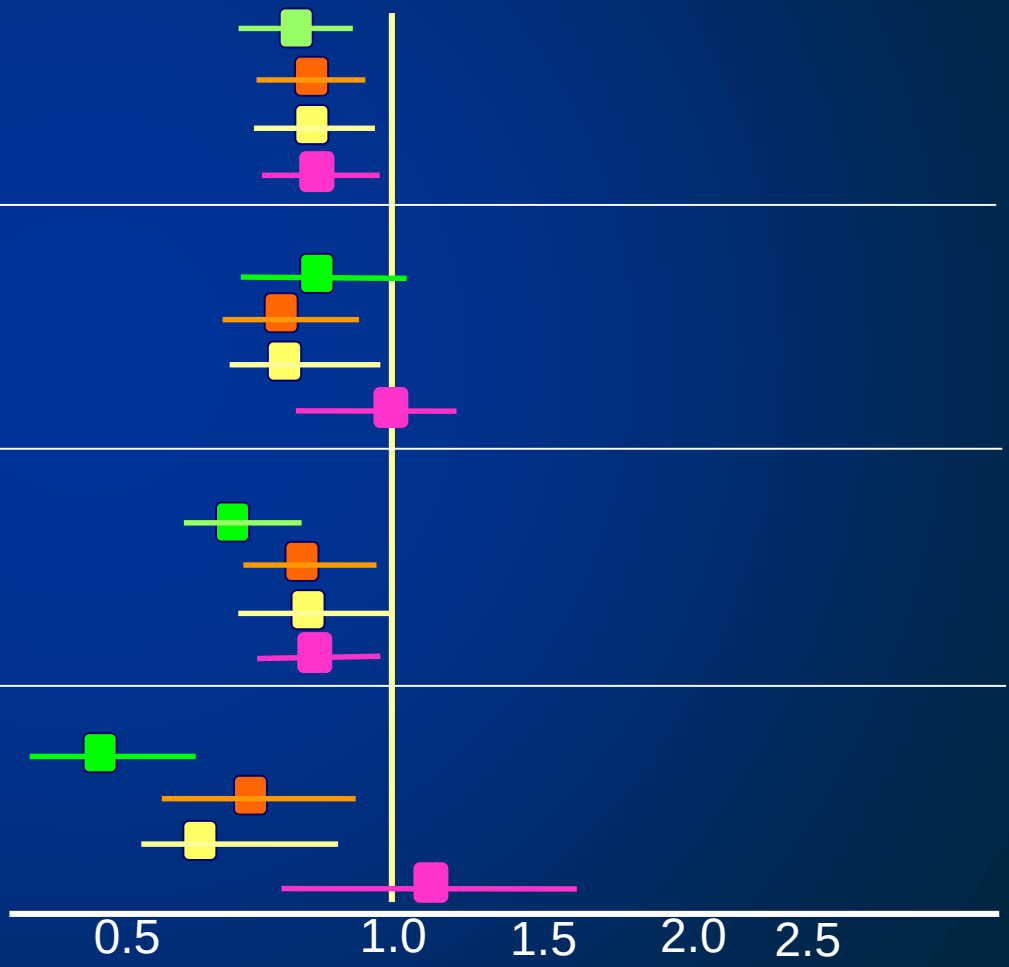
Reversi

y)

a

Efficacy of novel oral antithrombotics after ACS – current state

	HR
CV-Death, MI or Stroke	
TRITON	0.81 (0.73-0.90)
PLATO	0.84 (0.77-0.92)
ATLAS2-ACS	0.84 (0.74-0.96)
TRACER	0.89 (0.81-0.98)
CV-Death	
TRITON	0.89 (0.70-1.12)
PLATO	0.79 (0.69-0.91)
ATLAS2-ACS	0.80 ((0.65-0.99)
TRACER	1.00 (0.83-1.22)
MI	
TRITON	0.76 (0.67-0.85)
PLATO	0.84 (0.75-0.95)
ATLAS2-ACS	0.85 (0.72-1.00)
TRACER	0.88 (0.79-0.98)
Stent thrombosis (Defi/Probab)	
TRITON	0.48 (0.36–0.64)
PLATO	0.75 (0.59–0.95)
ATLAS2-ACS	0.69 (0.51–0.93)
TRACER	1.12 (0.78-1.62)

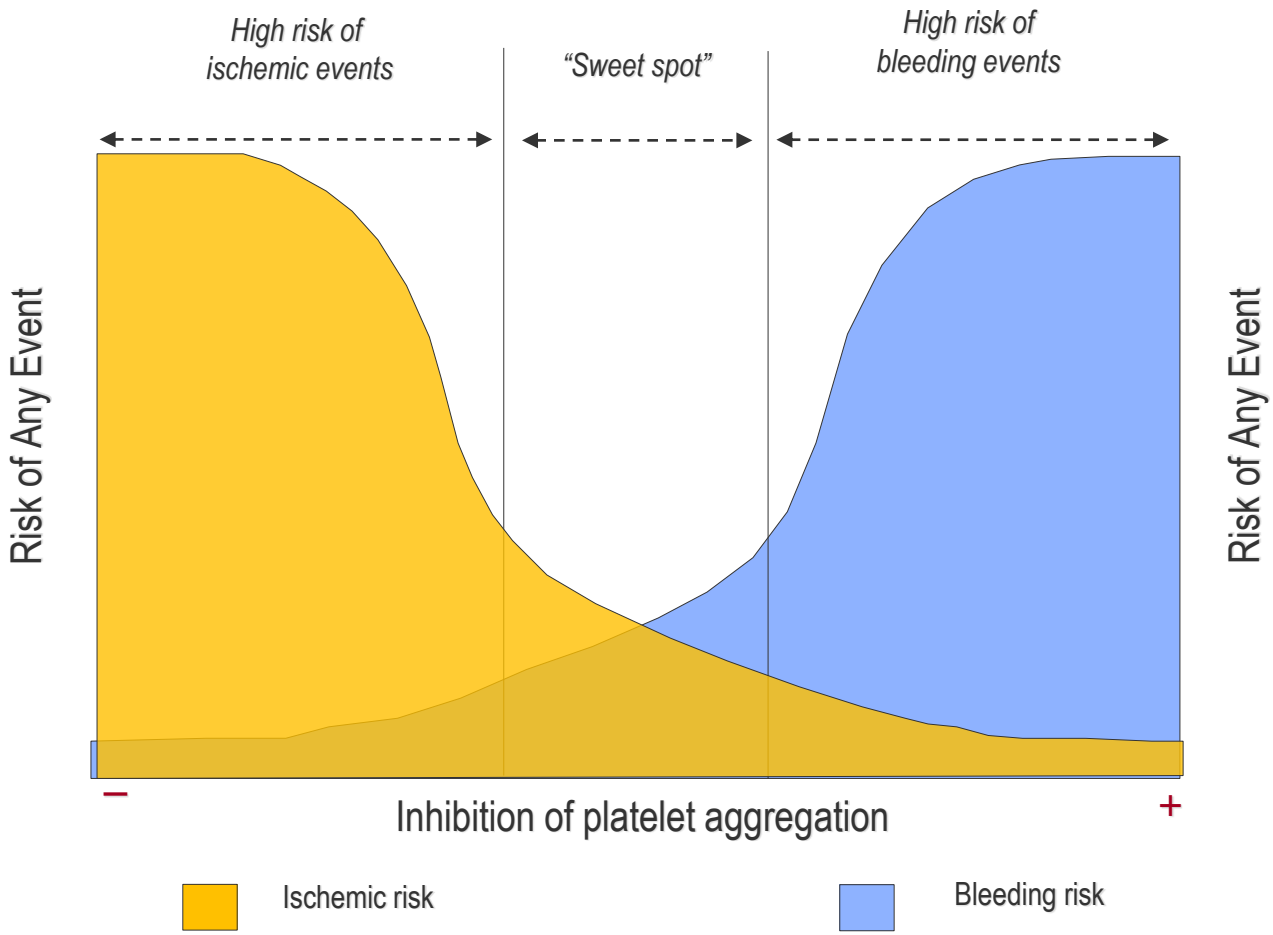


TRITON, NEJM 2007 *Plato NEJM 2009* *ATLAS2-ACS NEJM 2012* *TRACER NEJM 2011*

Favours higher degree of antithrombotic TX

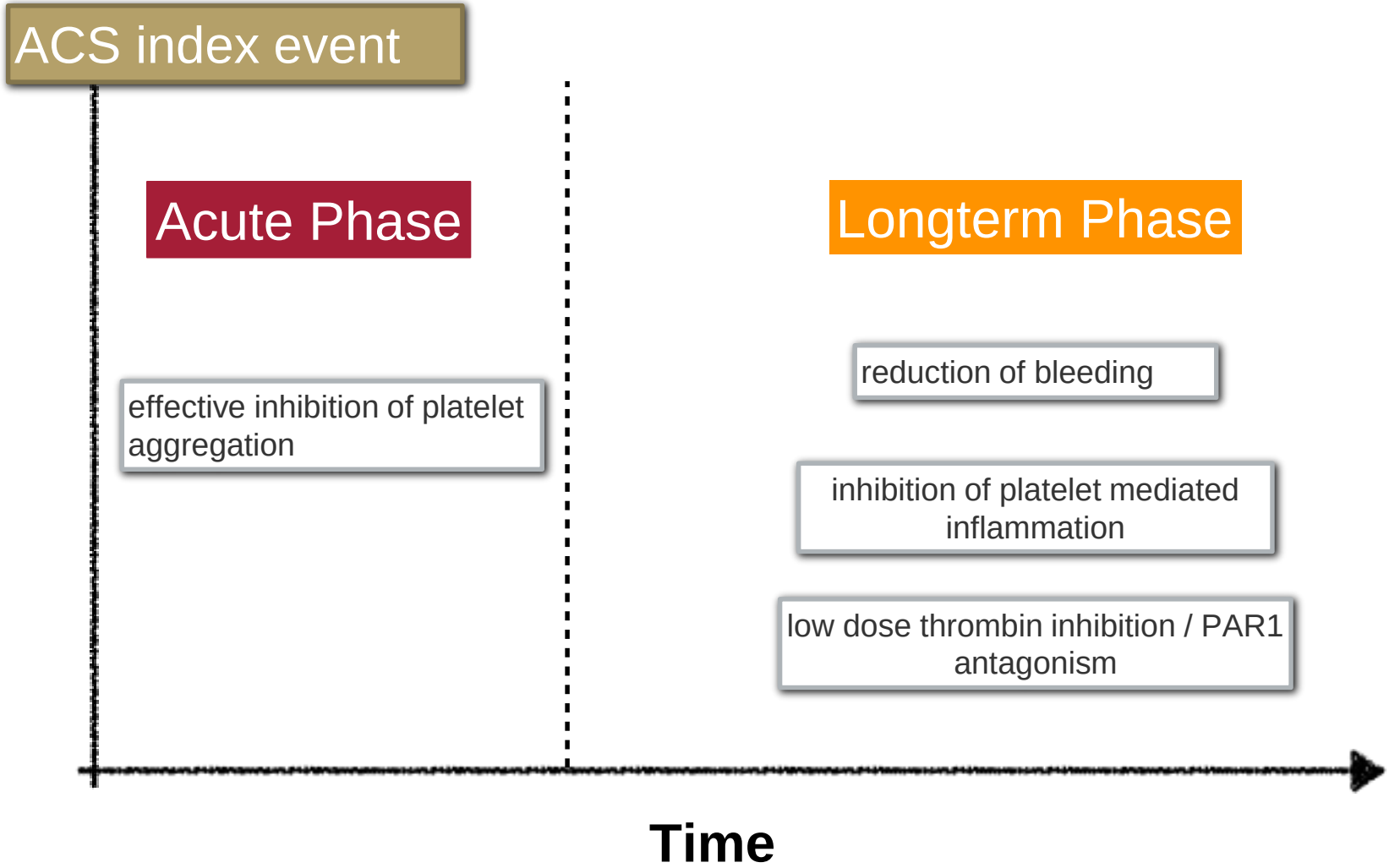
Favours Comparator

Platelet Inhibition Related to the Risk of Ischemic and Bleeding Events

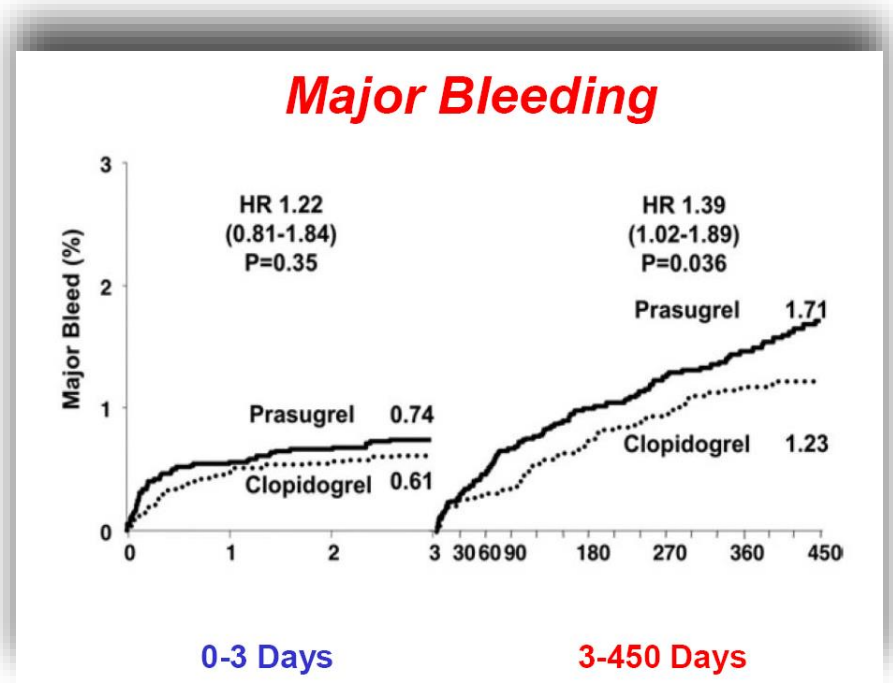


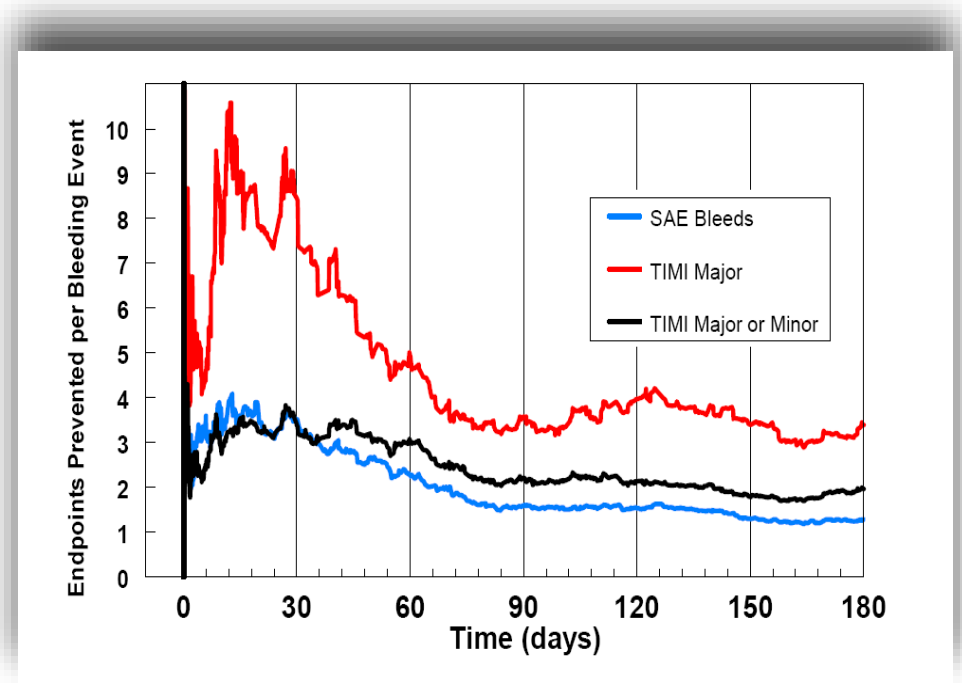
Ferreiro JL et al. *Thromb Haemost.* 2010;103:1-8.

Different focus on platelet targeted strategies according to time



Time dependence of benefit-risk ratio - Prasugrel





Antmann, J Am Coll Cardiol 2008

Unger E, FDA 2011

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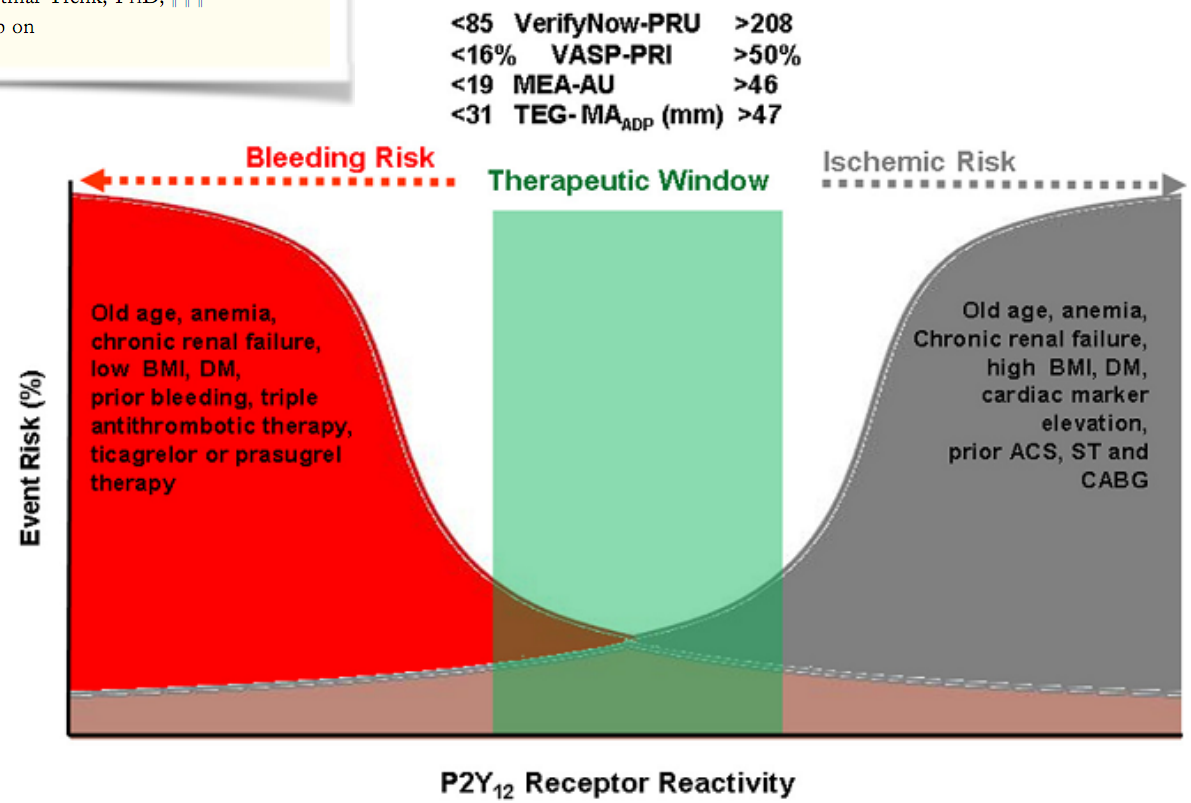
STATE-OF-THE-ART PAPER

Consensus and Update on the Definition of On-Treatment Platelet Reactivity to Adenosine Diphosphate Associated With Ischemia and Bleeding

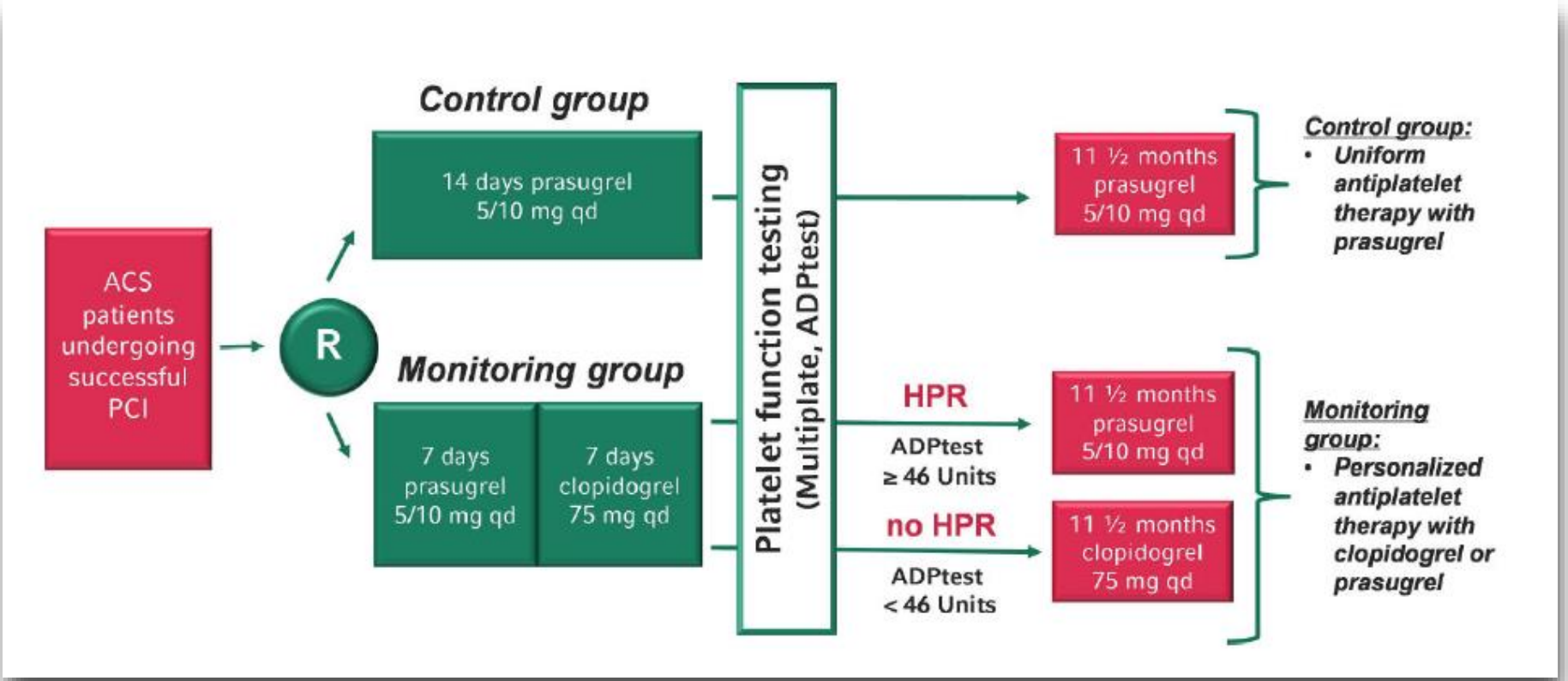
Udaya S. Tantry, PhD,* Laurent Bonello, MD, PhD,† Daniel Aradi, MD, PhD,‡ Matthew J. Price, MD,§ Young-Hoon Jeong, MD, PhD,‖ Dominick J. Angiolillo, MD, PhD,¶ Gregg W. Stone, MD,# Nick Curzen, BM (hons), PhD,** Tobias Geisler, MD,†† Jurrien ten Berg, MD, PhD,‡‡ Ajay Kirtane, MD, SM,# Jolanta Siller-Matula, MD, PhD,§§ Elisabeth Mahla, MD,‖‖ Richard C. Becker, MD,¶¶ Deepak L. Bhatt, MD, MPH,## Ron Waksman, MD,*** Sunil V. Rao, MD,††† Dimitrios Alexopoulos, MD,‡‡‡ Rossella Marcucci, MD, PhD,§§§ Jean-Luc Reny, MD, PhD,‖‖‖ Dietmar Trenk, PhD,¶¶¶ Dirk Sibbing, MD,### Paul A. Gurbel, MD,* for the Working Group on On-Treatment Platelet Reactivity



J Am Coll Cardiol. 2013;62(24):2261-73.

TROPICAL ACS

TESTING **R**ESP**O**NSIVENESS TO **P**LATELET **I**NHIBITION ON **C**HRONIC **A**NTIPLATE**L**ET TREATMENT FOR **A**CUTE **C**ORONARY **S**YNDROMES **(TROPICAL-ACS)** TRIAL



Primary Endpoint: Composite primary endpoint consisting of death from cardiovascular cause, myocardial infarction, stroke and bleeding at 12 months

ClinicalTrials.gov Identifier: NCT01959451

ECRI
European Cardiovascular Research Institute

GLOBAL LEADERS flowchart

All-comers PCI population (ACS and Stable CAD patients)
(N = 16,000)

Bivalirudin* - supported
BioMatrix Flex™ stent implantation

1 : 1 Randomization, Open-Label Design

Experimental Treatment Strategy

- **ASA** — 1 month
- **Ticagrelor** — 24 months

Reference Treatment Strategy

- **ASA** — 24 months
- **Ticagrelor** — 12 months — not allowed in stable PTS
- OR
- **Clopidogrel** — 12 months — only allowed in stable PTS

Primary endpoint (Effectiveness):
Experimental treatment strategy superior to reference treatment strategy on cumulative 2 year composite of all cause mortality and new Q-wave MI

Scientific Grants to ECRI: Biosensors, AstraZeneca and The Medicines Company

* In countries where available

Guideline recommendations Antiplatelet therapy - Myocardial infarction

Guidelines:

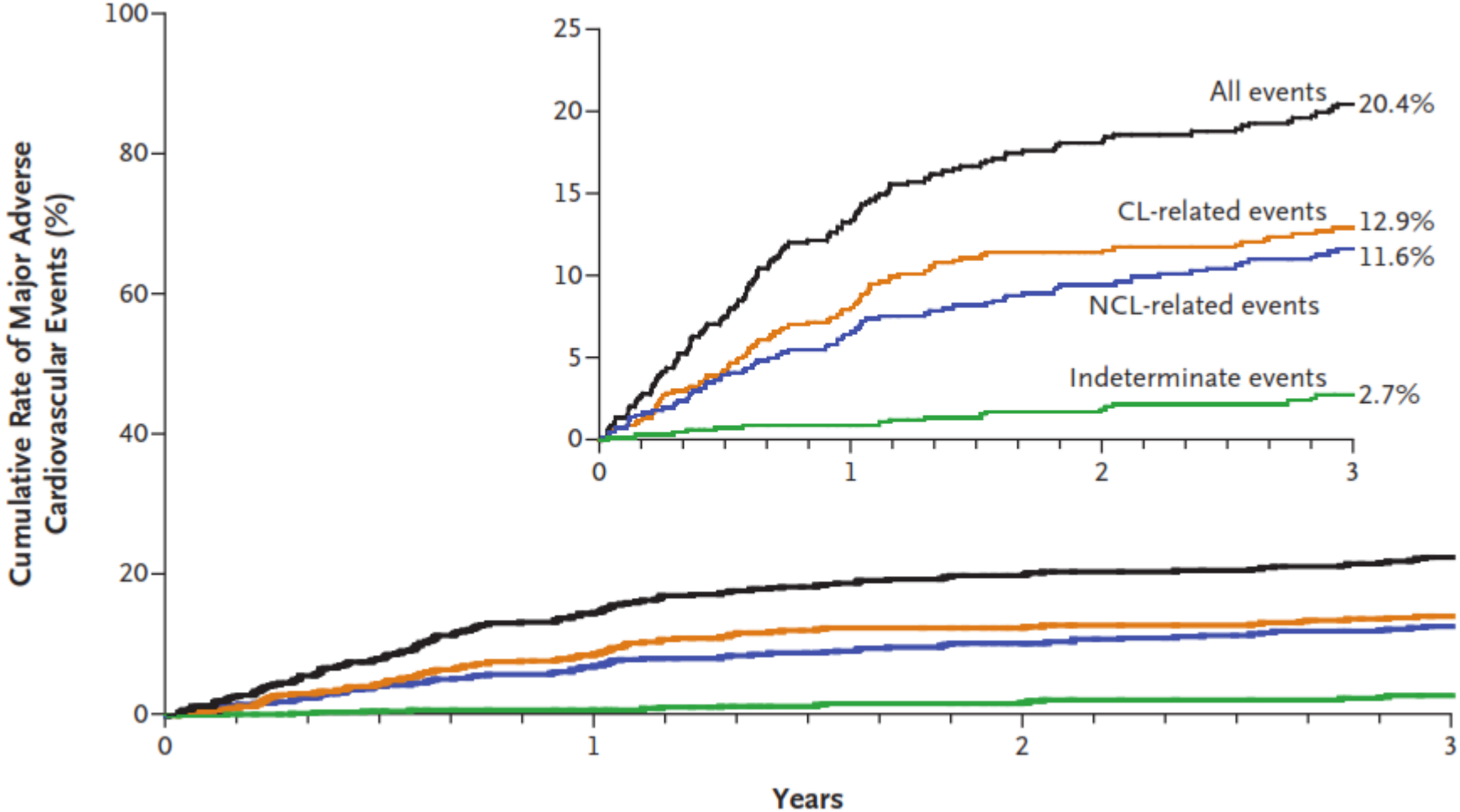
NSTEMI: A P2Y12 inhibitor should be added to aspirin as soon as possible and maintained over 12 months, unless there are contraindications such as excessive risk of bleeding.	I A
STEMI: DAPT with aspirin and an oral ADP receptor antagonist must be continued for up to 12 months after STEMI, with a strict minimum of: • 1 month for patients receiving BMS • 6 months for patients receiving DES	I C I C IIb B

Hamm CW, et al, Eur Heart J. 2011;32(23):2999-3054 and
Steg G et al, Eur Heart 2012;33:2569-2619

New Trials: challenging one size fits all strategy

Cardiovascular Risk after ACS is not linked to culprit lesion only, cumulative risk over time

Treat the patient, not the stent: The PROSPECT study



Stone GW et al. ***N Engl J Med*** 2011;364:226-235

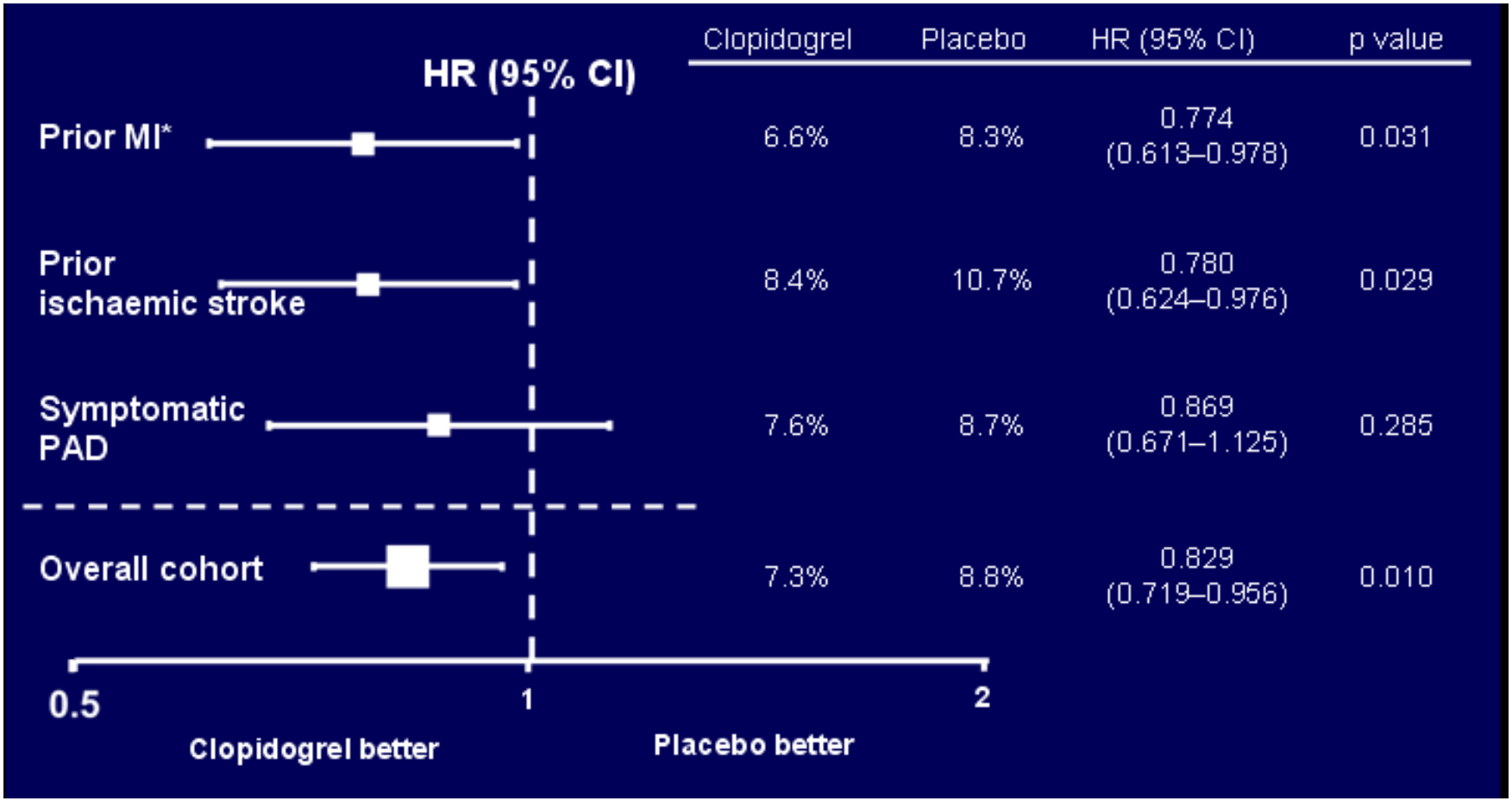
Studies examining extended DAPT in high risk patients

- CAPRIE[CAPRIE steering committee 1996]
  - Clopidogrel versus ASA in patients at risk of ischaemic events
- CHARISMA[Bhatt 2006]
  - Clopidogrel plus ASA versus ASA alone for the prevention of atherothrombotic events
- CHARISMA: *Post-hoc* subgroup analysis[Bhatt 2007]
  - Patients with prior MI, prior stroke or symptomatic PAD
- TRA2ºP TIMI 50[Morrow 2012]
  - Vorapaxar for the secondary prevention of atherothrombotic events
- TRA2ºP TIMI 50: Pre-specified subgroup analysis[Scirica 2012]
  - Vorapaxar for the secondary prevention of thrombotic events in patients with a recent MI
- DAPT[Mauri 2014]
  - 12 v 18m of DAPT post DES in a mixed patient population comprising CAD and ACS
- PEGASUS[Bonaca 2014]
  - Ticagrelor in patients with a history of MI and at least one additional thrombotic risk factor
- TRILOGY [Roe MT 2013]
  - Prasugrel in patients medically managed ACS patients

ASA, acetylsalicylic acid; CV, cardiovascular; DAPT, dual antiplatelet therapy; MI, myocardial infarction; PAD, peripheral artery disease.

Bhatt DL, et al. *J Am Coll Cardiol* 2007;49:1982–1988; Bhatt DL, et al. *N Engl J Med* 2006;354:1706–1717; Bonaca MP, et al. In preparation; CAPRIE steering committee. *Lancet* 1996;348:1329–1339; Mauri L, et al. *N Engl J Med.* Nov 16, 2014. DOI: 10.1056/NEJMe1413297 Morrow DA, et al. *N Engl J Med* 2012;366:1404–1413; Scirica SM, et al. *Lancet* 2012;380:1317–1324.

CHARISMA: Risk of primary endpoint in patients with symptomatic CV disease



	Clopidogrel	Placebo	HR (95% CI)	p value
Prior MI*	6.6%	8.3%	0.774 (0.613–0.978)	0.031
Prior ischaemic stroke	8.4%	10.7%	0.780 (0.624–0.976)	0.029
Symptomatic PAD	7.6%	8.7%	0.869 (0.671–1.125)	0.285
Overall cohort	7.3%	8.8%	0.829 (0.719–0.956)	0.010

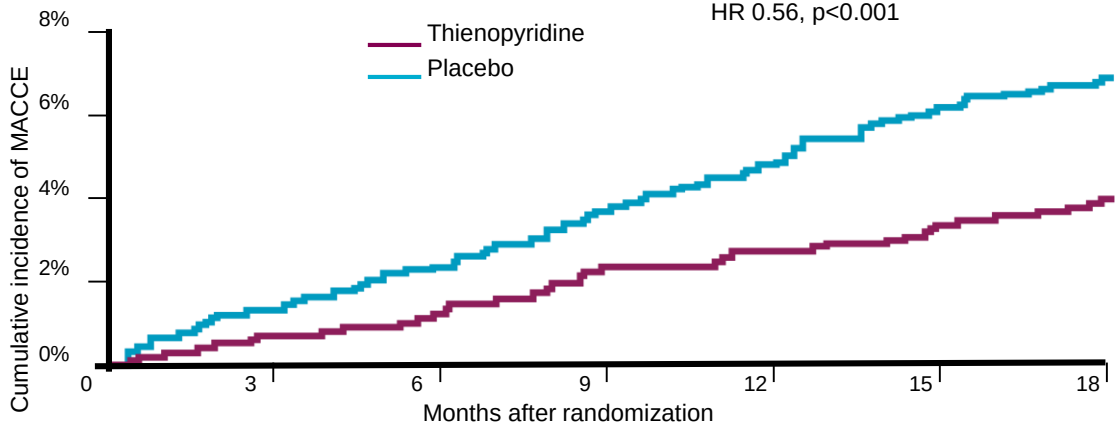
*3846 patients had a prior MI, with a median time from the qualifying event to randomisation of 23.6 months.
CI, confidence interval; CV, cardiovascular; HR, hazard ratio;MI, myocardial infarction; PAD, peripheral artery disease.
Bhatt DL, et al. *J Am Coll Cardiol* 2007;49:1982–1988.

DAPT– Subanalysis for history of MI

Results – MACCE

Patients presenting with myocardial infarction

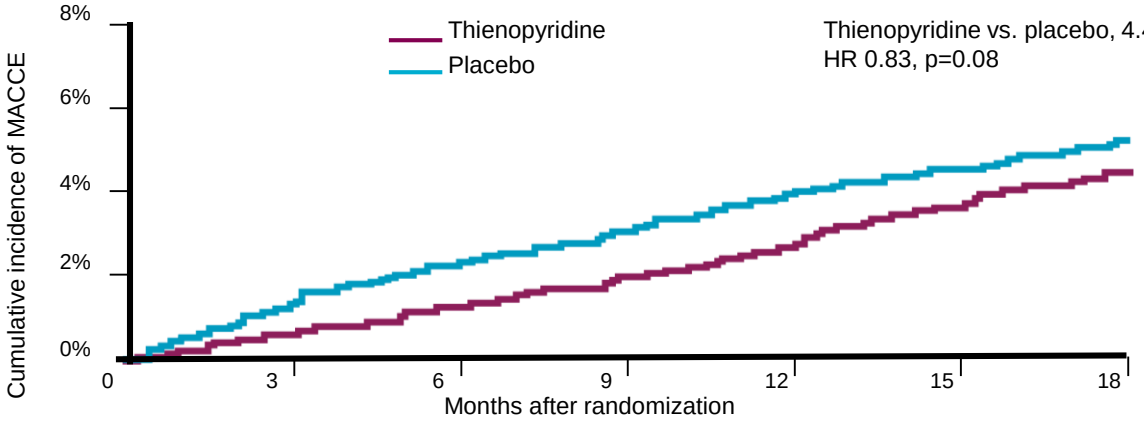
Thienopyridine vs. placebo, 3.9% vs. 6.8%;
HR 0.56, p<0.001



Thienopyridine	1802	1791	1761	1737	1704	1676	1649
Placebo	1766	1749	1706	1676	1632	1592	1553

Patients presenting without myocardial infarction

Thienopyridine vs. placebo, 4.4% vs. 5.3%;
HR 0.83, p=0.08



Thienopyridine	4050	4020	3951	3900	3851	3786	3718
Placebo	4008	3982	3893	3830	3772	3705	3660

Yeh R | ACC 2015

DAPT– Subanalysis for history of MI

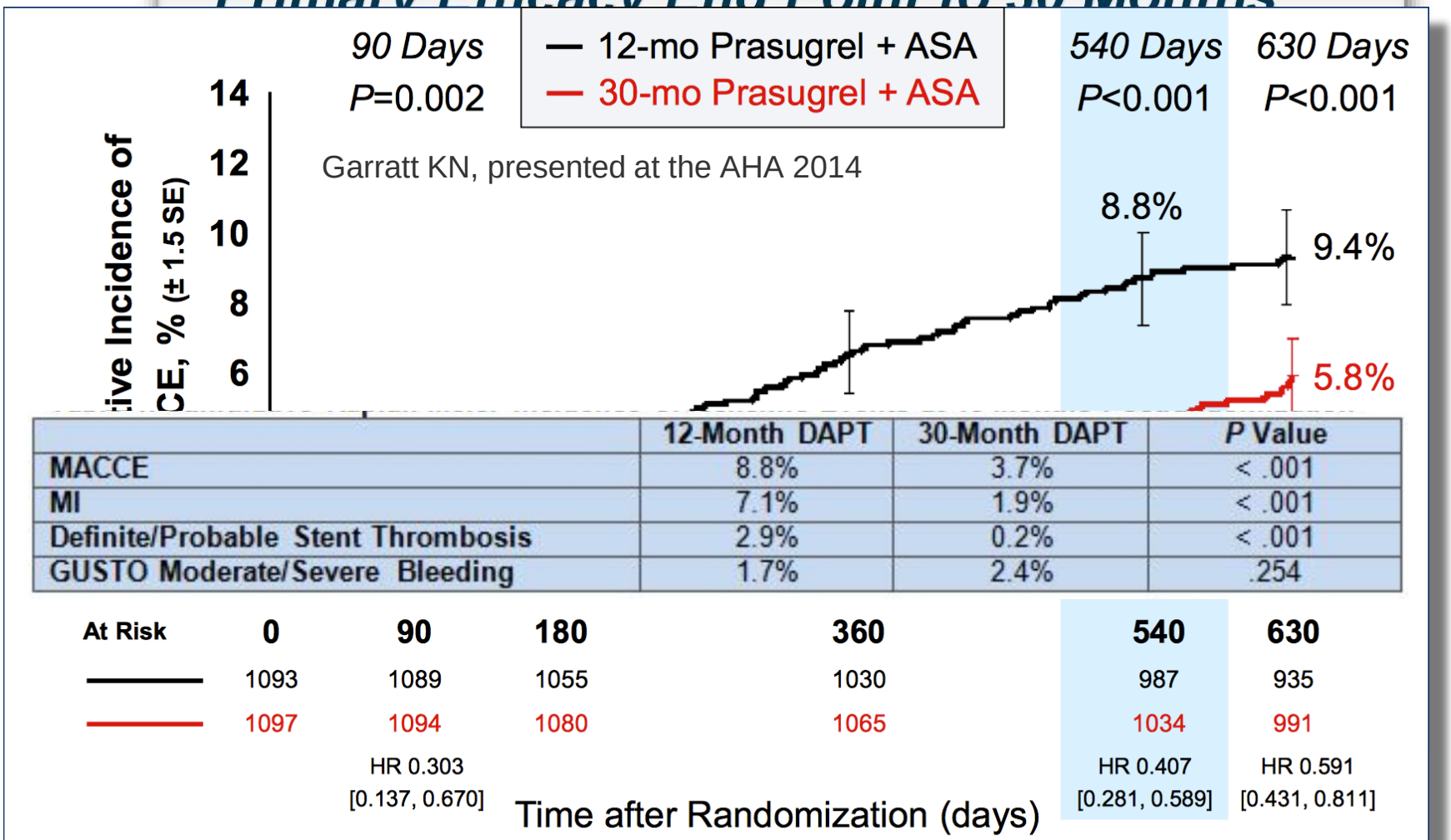
Results – bleeding outcomes

	Continued Thienopyridine N (%)	Placebo N (%)	Hazard ratio (95% CI)	Stratified log-rank P-value	P-value for interaction
GUSTO moderate bleeding					***0.06***
MI Group	***21 (1.2%)***	***5 (0.3%)***	***4.10 (1.55-10.87)***	***0.002***	
No MI Group	***70 (1.8%)***	***47 (1.2%)***	***1.48 (1.03-2.15)***	***0.04***	
GUSTO severe bleeding					***0.86***
MI Group	***13 (0.7%)***	***9 (0.5%)***	***1.41 (0.60-3.29)***	***0.43***	
No MI Group	***31 (0.8%)***	***20 (0.5%)***	***1.54 (0.88-2.70)***	***0.13***	
BARC 2,3 or 5					***0.666***
MI Group	***76 (4.3%)***	***35 (2.1%)***	***2.14 (1.43-3.19)***	***<0.001***	
No MI Group	***223 (5.7%)***	***116 (3.0%)***	***1.93 (1.55-2.42)***	***<0.001***	

GUSTO, Global Utilization of Streptokinase and TPA for Occluded Arteries. Percentages are Kaplan-Meier estimates

TRILOGY-ACS

Primary Efficacy End Point to 30 Months



	12-Month DAPT	30-Month DAPT	*P* Value
MACCE	8.8%	3.7%	< .001
MI	7.1%	1.9%	< .001
Definite/Probable Stent Thrombosis	2.9%	0.2%	< .001
GUSTO Moderate/Severe Bleeding	1.7%	2.4%	.254

Cumulative KM Event Rate ± 1.5 SE; log-rank *P* value; HR=Hazard Ratio [95% confidence interval]

PEGASUS – TIMI 54

Study design

Stable patients with history of MI 1-3 yrs prior
+ ≥ 1 additional atherothrombosis risk factor
21,162 patients randomized

Ticagrelor
90 mg bid
N=7050

Ticagrelor
60 mg bid
N=7045

Placebo
N=7067

FU visits Q4 months for 1st yr, then Q6 months
median FU: 33 months (IQR 28-37)
min 16 months, max 47 months

Premature permanent drug discontinuation	12%/yr	11%/yr	8%/yr
Withdrew consent	0.7% total	0.7% total	0.7% total
Lost to follow-up	3 patients	6 patients	1 patient

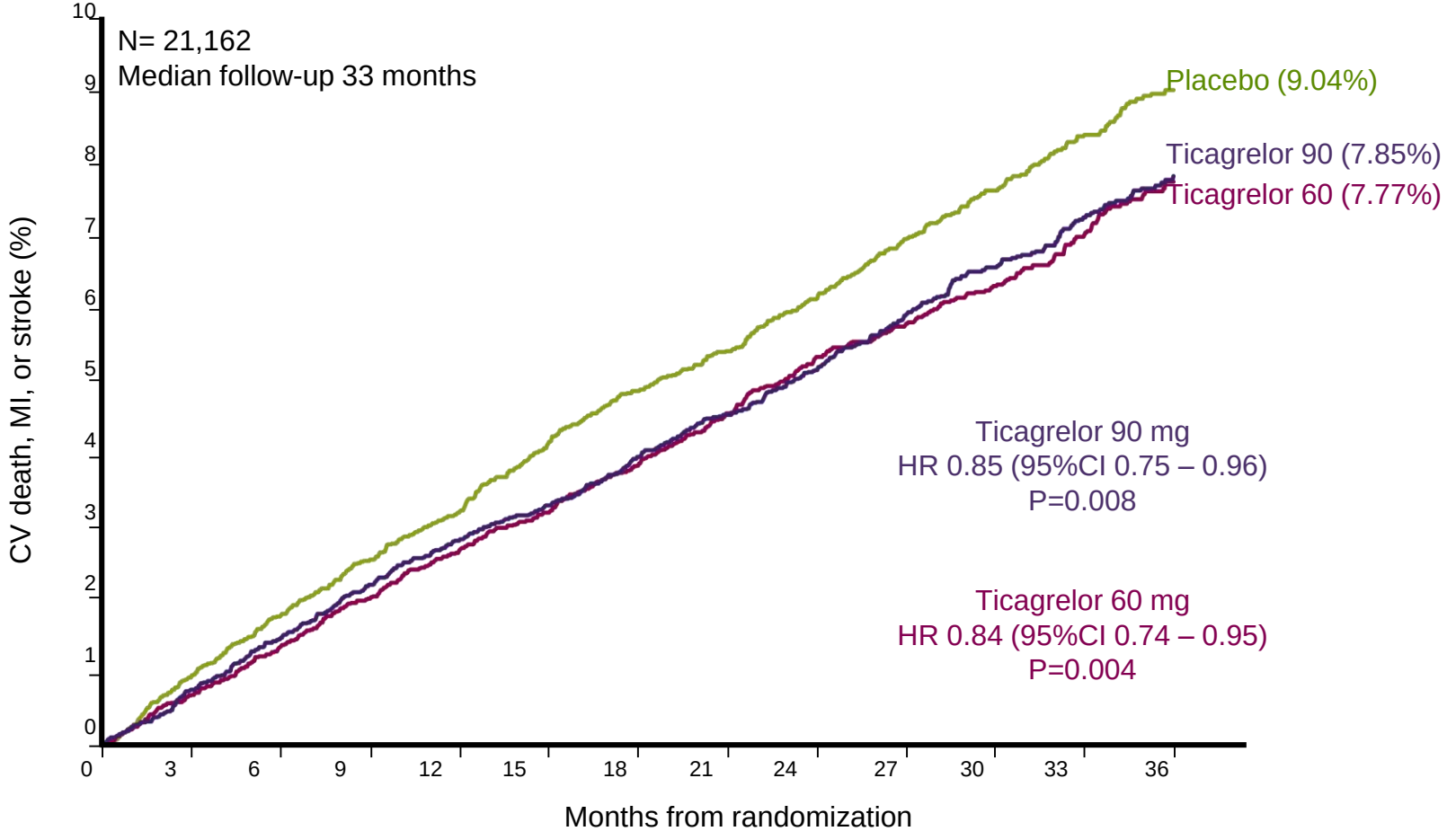
Ascertainment for primary endpoint was complete for 99% of potential patient-years of follow-up

Sabatine M | ACC 2015

Bonaca M et al. N Engl J Med 2015 DOI 0.1056/NEJMoa1500857

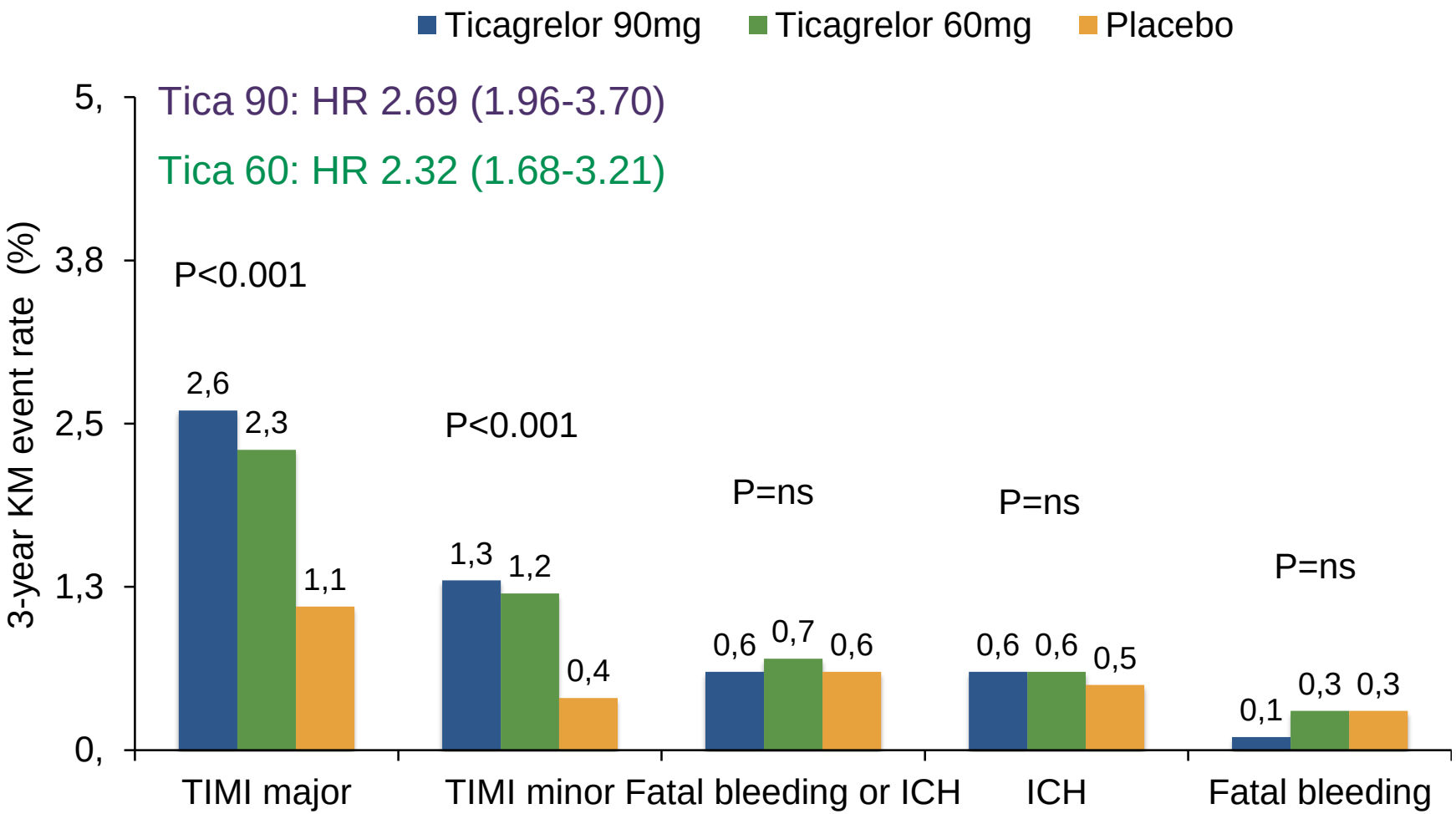
PEGASUS – TIMI 54

Results – primary efficacy endpoint



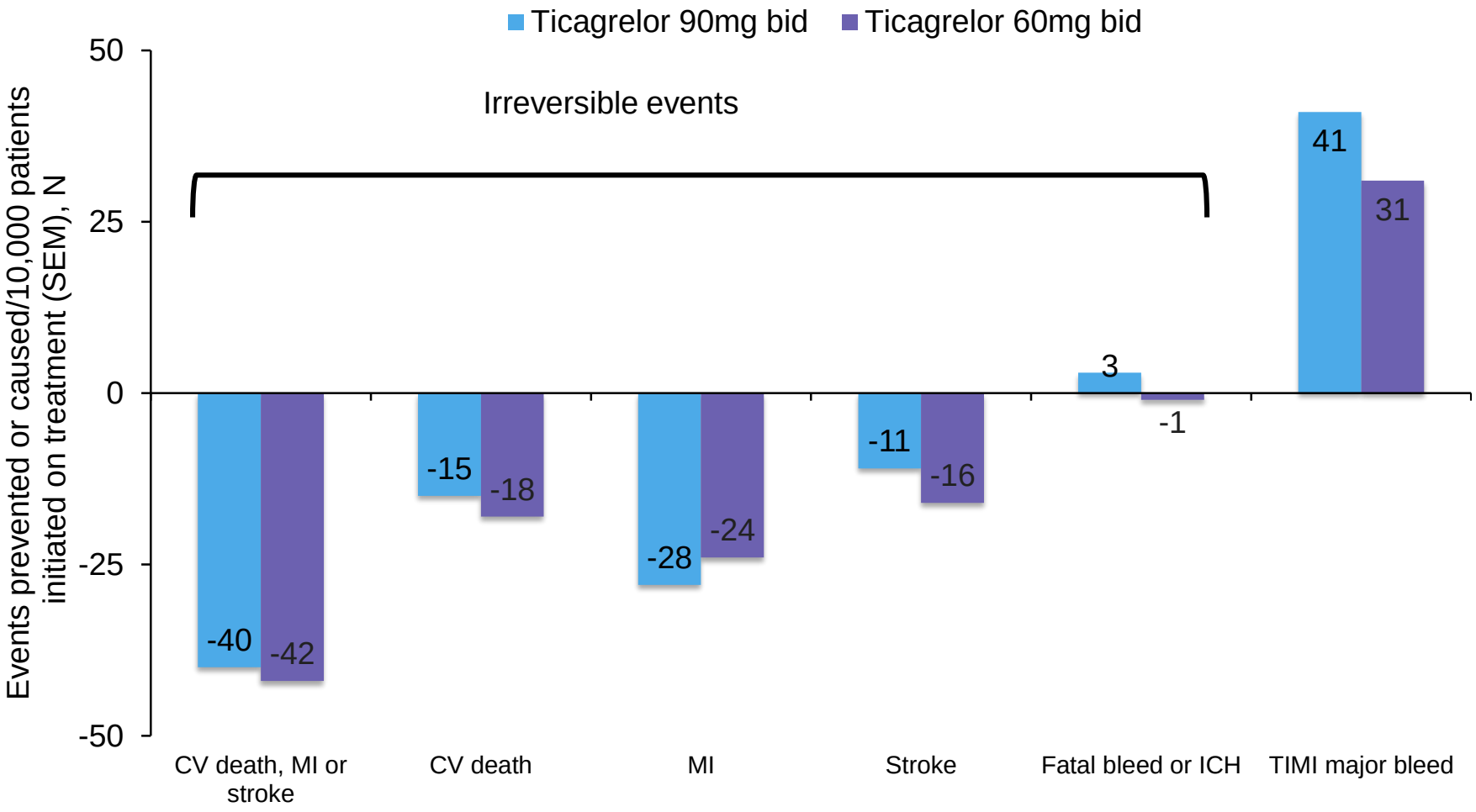
PEGASUS – TIMI 54

Results – bleeding



PEGASUS – TIMI 54

Results – outcomes for 10,000 patients treated for 1 year



Bonaca MP et al. N Engl J Med 2015, Supplementary Appendix [Epub ahead of print]
Bonaca MP et al. N Engl J Med 2015 [Epub ahead of print]; data on file

PEGASUS – TIMI 54

Results – analyses of net clinical benefit

	Ticagrelor 90 mg bid vs. placebo			Ticagrelor 60 bid vs placebo		
Characteristics	***RRR***	***HR (95%CI)***	***P value***	***RRR***	***HR (95%CI)***	***P value***
Net clinical benefit: *CV death, MI, stroke, or TIMI major bleeding*	*0%*	*1.00 (0.90-1.22)*	*0.9563*	*5%*	*0.95 (0.85-1.06)*	*0.3412*
Irreversible harm: ***CV death, MI, stroke, ICH and fatal bleeding***	*12%*	*0.88 (0.78-0.99)*	*0.0372*	*14%*	*0.86 (0.77-0.97)*	*0.0160*

Rates are annualised from 3-year Kaplan-Meier rates in the intention-to-treat population
RRR: relative risk reduction
Data on file

“Tripple Therapy” with Platelet inhibitors (Vorapaxar + ASA + Clopidogrel)

TRA2°P- TIMI 50
Design

MI, stroke, or PAD
Stratify by CAD, CVD, or PAD and intent to use thienopyridine

Vorapaxar
2.5 mg daily

Placebo

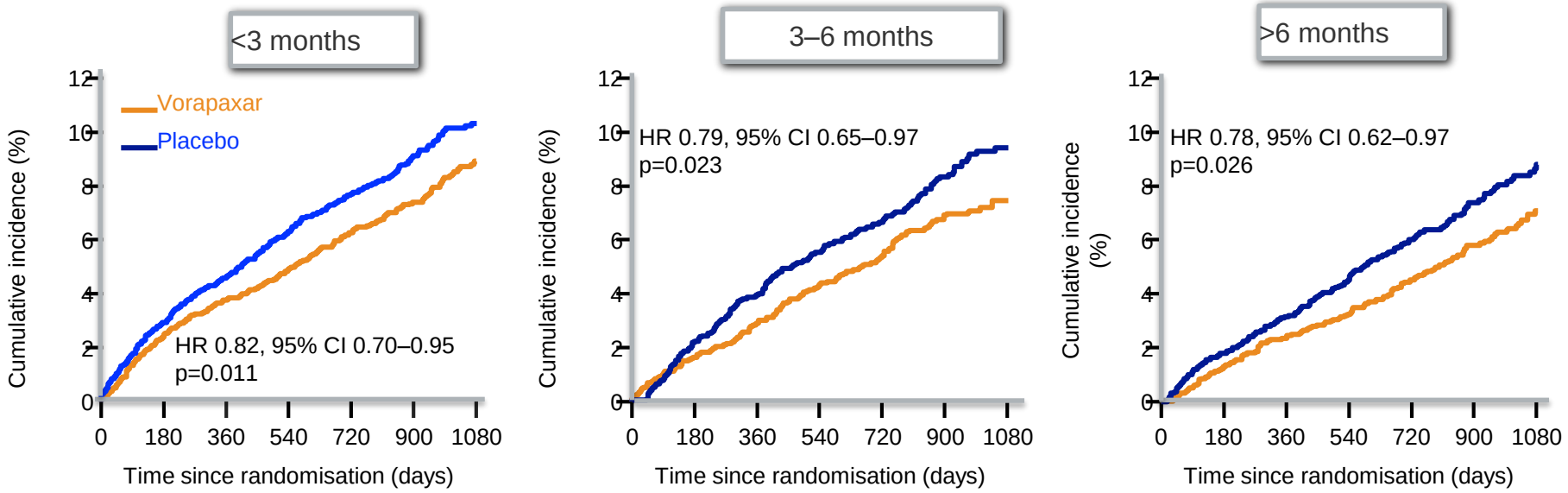
Follow-up: minimum 1 y

Primary end point: CV death, MI, stroke, urgent revascularization

Secondary end point: CV death, nonfatal MI, nonfatal stroke

Morrow DA, et al. *Am Heart J.* 2009;158:335-341.

TRA2°P-TIMI 50 recent MI subgroup: Cumulative incidence of CV death, MI or stroke (primary endpoint) by time to randomisation



No. at risk																			
Placebo	3938	3779	3673	3574	2873	1760	730	2592	2501	2434	2372	1897	1230	585	2284	2223	2179	2131	1752	1255	576
Vorapaxar	3863	3730	3648	3575	2878	1793	781	2559	2492	2437	2372	1868	1178	536	2419	2358	2322	2286	1879	1325	608

CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction.
Scirica SM, et al. *Lancet* 2012;380:1317–1324.

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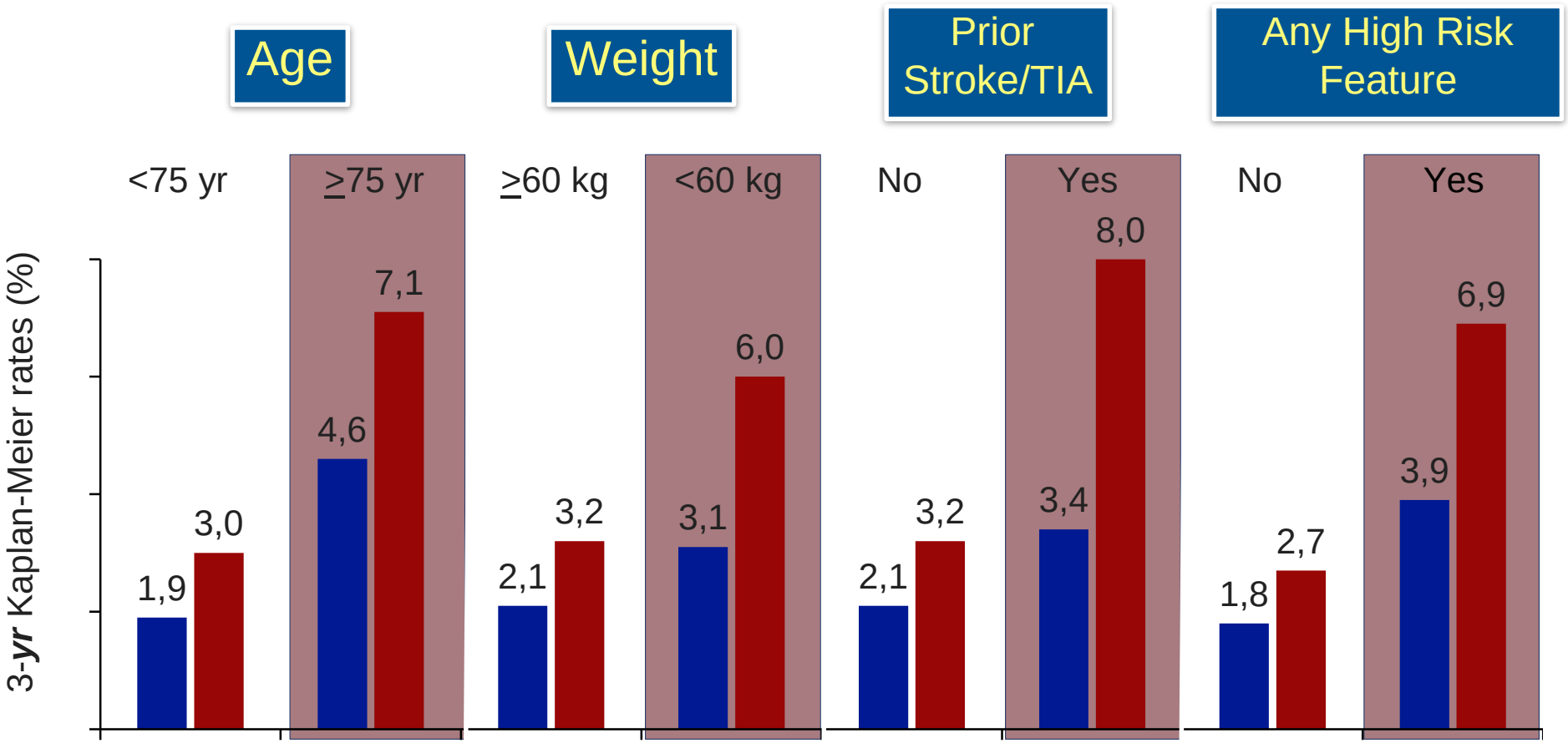
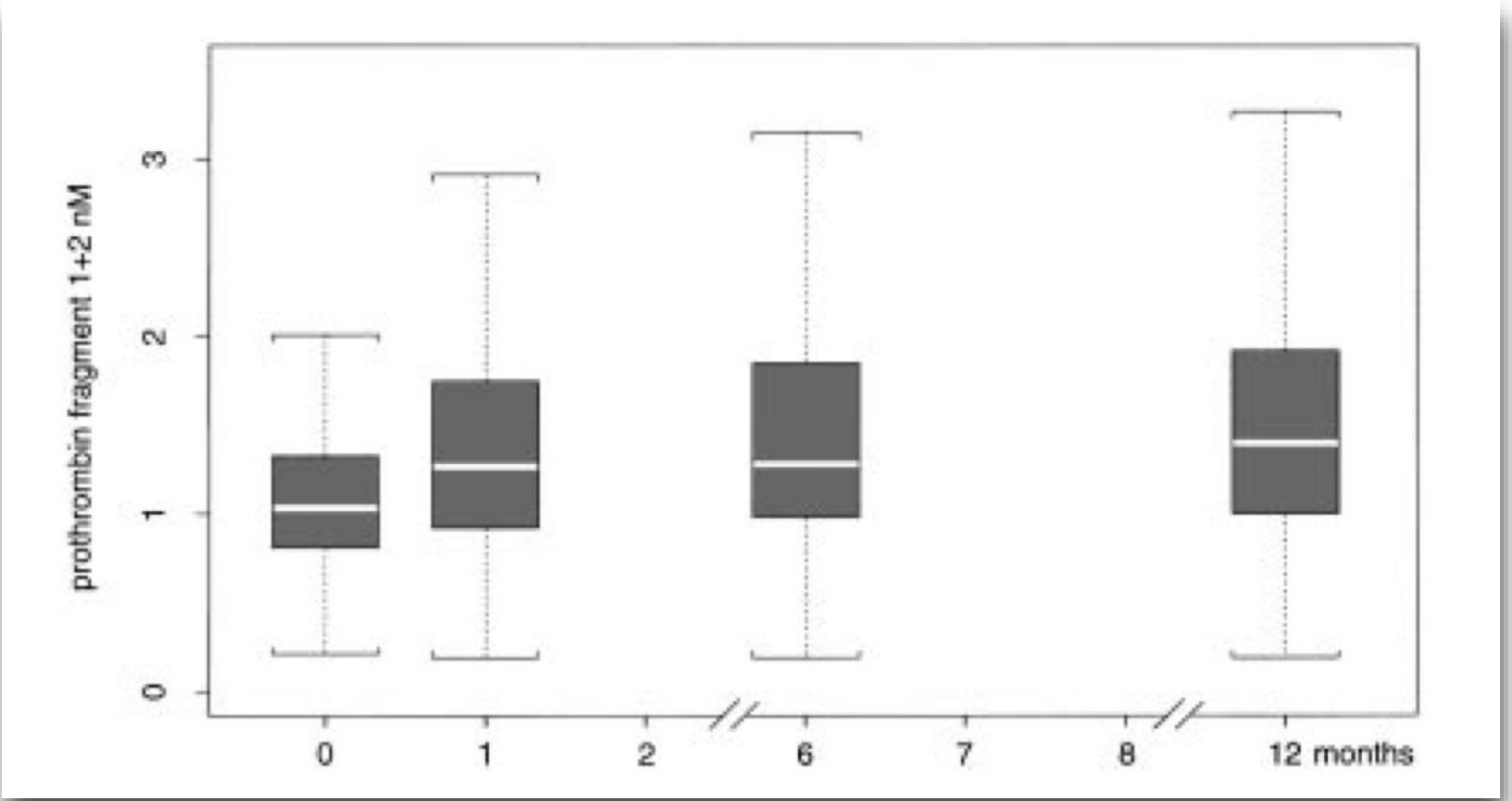
MI Cohort

GUSTO Mod/Severe Bleeding



TIMI

Persistent Elevation of Thrombin Generation in Post-ACS Patients



Ardissino D, Blood 2003

ATLAS-TIMI 51 - Low Dose Rivaroxaban after ACS -Prognostic benefit in label population

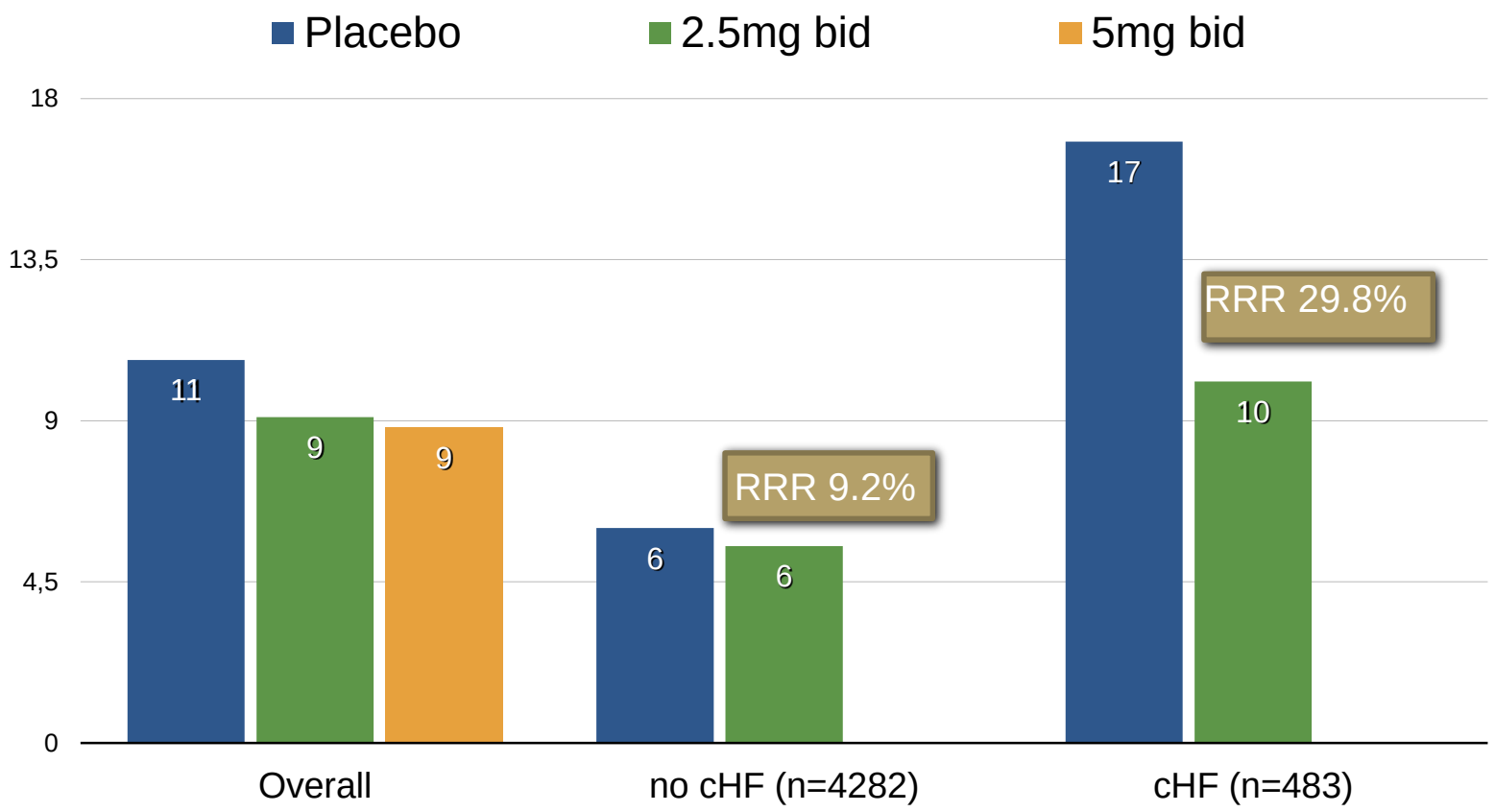
Table 1. Biomarker Elevation and no Prior Stroke/TIA Population

Bleeding	Placebo N=4,157	Rivaroxaban 2.5 mg Twice Daily N=4,096
Non-CABG TIMI Major KM rate (Number of Events)	0.7% (16)	1.9% (54) (P<0.001)
Fatal KM rate (Number of Events)	0.3% (8)	0.1% (3) (P=NS)
ICH KM rate (Number of Events)	0.2% (4)	0.4% (10) (P=NS)
Fatal ICH KM rate (Number of Events)	0.2% (3)	0.1% (2) (P=NS)

Days

Mega JL, presented at ESC 2014

ATLAS-TIMI 51 - Low Dose Rivaroxaban after ACS - Prognostic benefit in ACS patients with heart failure



Mega JL, N Engl J Med. 2012 Jan 5;366(1):9-19.

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Platelet inhibition after MI - mono/dual/triple? individualized therapeutic concept

bleeding risk ↑ ?

ischemic risk ↓ ?

platelet function guided adjustment of DAPT, Therapeutic Window?

Dual (ASA + Prasugrel/Ticagrelor/Clopidogrel), Triple (ASA + Clopidogrel + Vorapaxar, ASA+Clopidogrel + low dose Rivaroxaban)

Balancing ischaemic versus bleeding risk:

ideal candidates: patients with low bleeding risk and high ischaemic risk

Vessel Disease in multiple locations, heart failure

Clinically / Genetic Risk Factors (Scores)

Biomarkers (hsTNT, hsCRP, other?)

1month

12 months

indefinite??

Triple Therapie - Datenlage, wenig Evidenz

Datenlage:

Die optimale Dauer der Tripletherapie nach DE-Stent Implantation i

- das Risiko einer Stentthrombose am höchsten ist in der Frühpha
- das Blutungsrisiko abhängig ist von der Dauer und der Intensitä

Kombination OAK plus Plättchenhemmung: EHRA Guidance

Lip GY, Eur Heart J. 2014 Dec 1;35(45):3155-79.

Recommendations for antithrombotic treatment in patients undergoing PCI who require oral anticoagulation

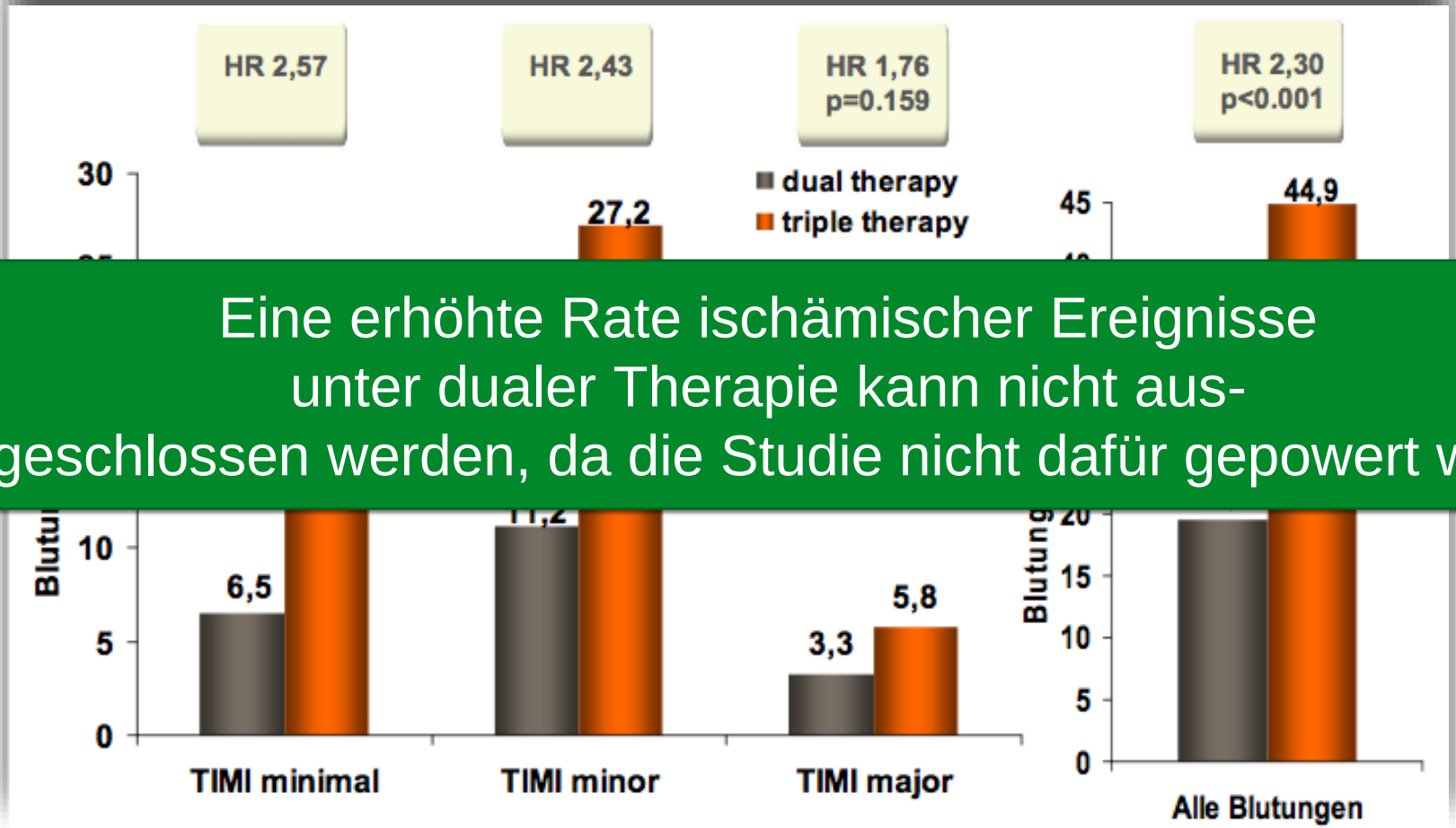
Recommendations	Class[a]	Level[b]	Ref[c]
In patients with a firm indication for oral anticoagulation (e.g. atrial fibrillation with CHA_2DS_2-VASc score ≥2, venous thromboembolism, LV thrombus, or mechanical valve prosthesis), oral anticoagulation is recommended in addition to antiplatelet therapy.	I	C	
New-generation DES are preferred over BMS among patients requiring oral anticoagulation if bleeding risk is low (HAS-BLED ≤2).	IIa	C	
In patients with SCAD and atrial fibrillation with CHA_2DS_2-VASc score ≥2 at low bleeding risk (HAS-BLED ≤2), initial triple therapy of (N)OAC and ASA (75–100 mg/day) and clopidogrel 75 mg/day should be considered for a duration of at least one month after BMS or new-generation DES followed by dual therapy with (N)OAC and aspirin 75–100 mg/day or clopidogrel (75 mg/day) continued up to 12 months.	IIa	C	
DAPT should be considered as alternative to initial triple therapy for patients with SCAD and atrial fibrillation	IIa	C	
immediately after primary PCI.	IIa	C	

Einzige Empfehlung auf Klasse I Niveau: eine antithrombozytäre Therapie sollte mit einer oralen Antikoagulation bei AFIB CHA2DS2-Vasc Score >=2 kombiniert werden sollte (Art der Kombination, Dauer der Kombination, DOAK versus VKA in Kombination mit APT —> keine klare Empfehlungen), meiste Empfehlungen LOE C: (Only consensus opinion of experts,case studies, or standard-of-care)

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
ACS = acute coronary syndrome; ASA = acetylsalicylic acid; BMS = bare-metal stent; CHA_2DS_2-VASc = Cardiac failure, Hypertension, Age ≥75 [Doubled], Diabetes, Stroke [Doubled]–Vascular disease, Age 65–74 and Sex category [Female]); DAPT = dual antiplatelet therapy; DES = drug-eluting stent; (N)OAC = (non-vitamin K antagonist) oral anticoagulant; HAS-BLED = hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly, drug/alcohol; INR = international normalized ratio; LV = left ventricular; PCI = percutaneous coronary intervention; SCAD = stable coronary artery disease; UFH = unfractionated heparin.

2014 **ESC**/EACTS **Guidelines** on **myocardial revascularization**: The Task Force on **Myocardial Revascularization** of the Europ

erapie (OAK + Clopidogrel) vs. Tripel- Therapie nach DE-



Eine erhöhte Rate ischämischer Ereignisse unter dualer Therapie kann nicht aus-geschlossen werden, da die Studie nicht dafür gepowert war.

Dewilde WJ et al., Lancet 2013

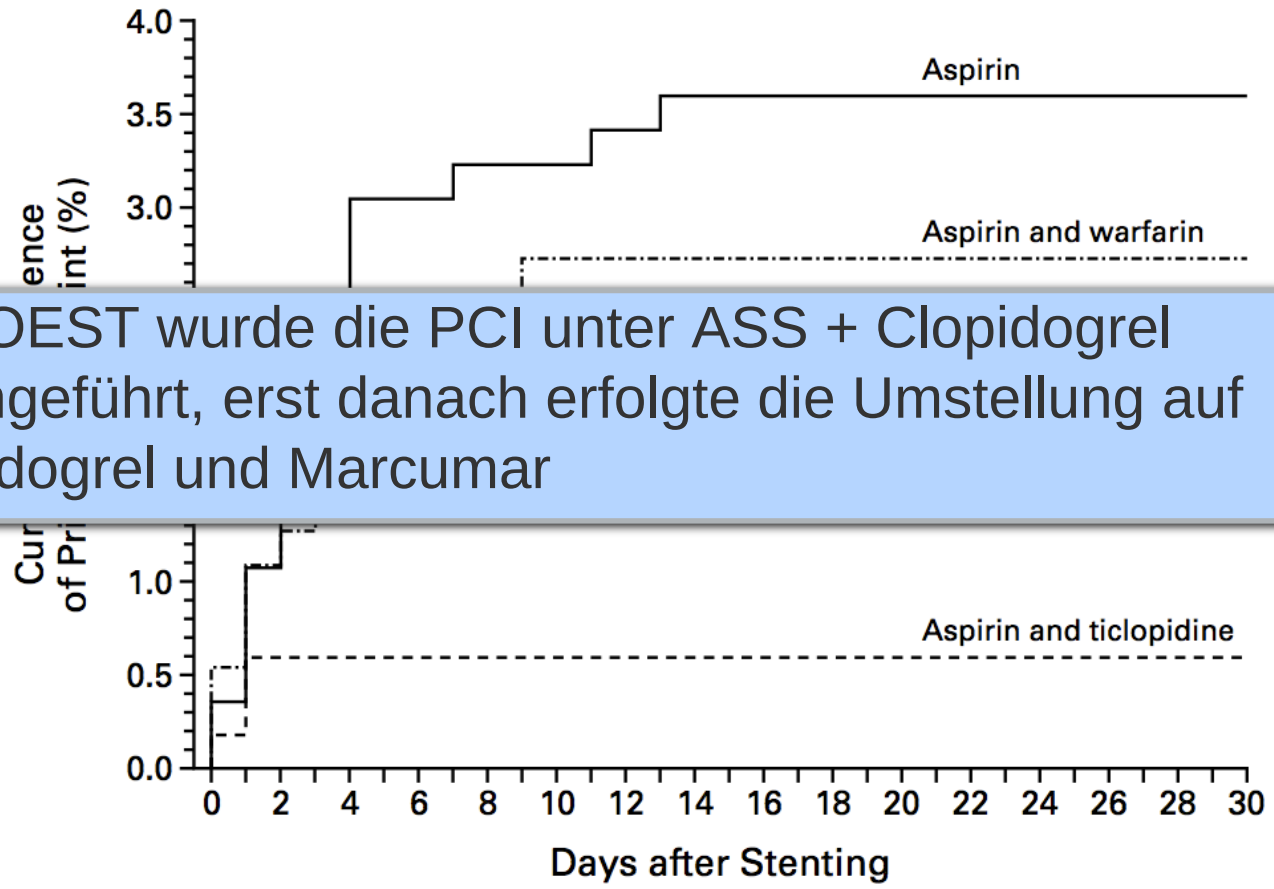
Kleine unverblindete Studien müssen repliziert werden bevor sie die Routine ändern!

Behandlung	SIMPLICITY HTN-2 (Lancet 2010)		SIMPLICITY HTN-3 (NEJM 2014)	
	Renale Denervation (N=52)	Kontrolle (N=54)	Renale Denervation (N=364)	Sham Kontrolle (N=171)
RDN for HTN (Δ, SBP, mmHg)	-32±23	-1±21	-14±24	-12±26
	-33, P<0.0001		-2.4 (-6.9, 2.1), P=0.26	

Behandlung	WOEST (Lancet 2013)		? WOEST 2 (NEJM ????)	
	Dual (N=284)	Triple (N=279)	Dual (N=1500)	Triple (N=1500)
Kein Aspirin bei DES+OAC (Blutung)	54 (19.5%)	126 (44.4%)	?	?
	0.36 (0.26, 0.50), P<0.0001		?	

adaptiert nach Kaul, präsentiert auf dem TCT 2014

Bedeutung der dualen Plättchenhemmung zur Vermeidung von frühen Stentthrombosen - Kombination einfache APT + OAK nicht ausreichend



In WOEST wurde die PCI unter ASS + Clopidogrel durchgeführt, erst danach erfolgte die Umstellung auf Clopidogrel und Marcumar

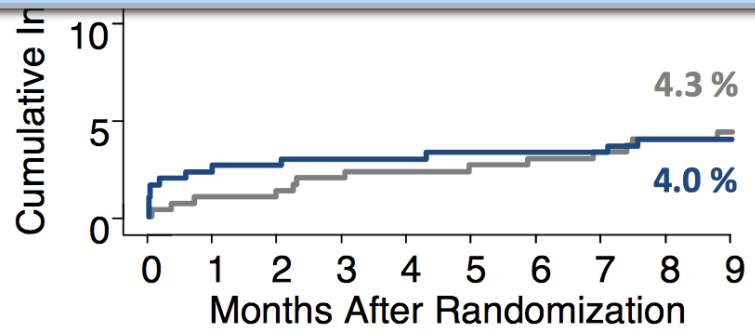
Leon et al, NEJM 1998; 339: 1665

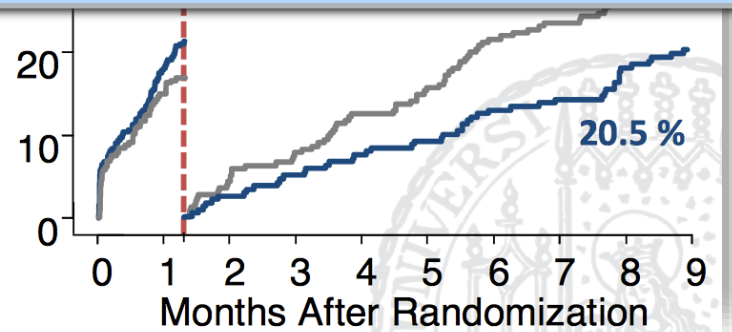
Dauer der Therapie – ISAR TRIPLE
TRIPLE Therapie über 6 Wochen hinaus keine Vorteil, jedoch mit zusätzlichem Blutungsrisiko behaftet

Cardiac death, myocardial infarction, stent thrombosis or ischemic stroke

Post-hoc landmark analysis of any BARC Bleeding before and after 6 weeks (6w)

ISAR-TRIPLE zeigt keine erhöhte Rate ischämischer Ereignisse unter dualer Th
Verkürzte Tripletherapie auf 6 Wochen scheint sicher mit den modernen DE- St





Fiedler....Sarafoff; presented at TCT 2014

Indikation zur Kombination OAK + APT - Einfluß auf die Wahl des Stents (BMS versus DES)

Recommendations for antithrombotic treatment in patients undergoing PCI who require oral anticoagulation

Recommendations	Class[a]	Level[b]	Ref[c]
In patients with a firm indication for oral anticoagulation (e.g. atrial fibrillation with CHA_2DS_2-VASc score ≥2, venous thromboembolism, LV thrombus, or mechanical valve prosthesis), oral anticoagulation is recommended in addition to antiplatelet therapy.	I	C	
New-generation DES are preferred over BMS among patients requiring oral anticoagulation if bleeding risk is low (HAS-BLED ≤2).	IIa	C	
In patients with SCAD and atrial fibrillation with CHA_2DS_2-VASc score ≥2 at low bleeding risk (HAS-BLED ≤2), initial triple therapy of (N)OAC and ASA (75–100 mg/day) and clopidogrel 75 mg/day should be considered for a duration of at least one month after BMS or new-generation DES followed by dual therapy with (N)OAC and aspirin 75–100 mg/day or clopidogrel (75 mg/day) continued up to 12 months.	IIa	C	
DAPT should be considered as alternative to initial triple therapy for patients with SCAD and atrial fibrillation with a CHA_2DS_2-VASc score ≤1.	IIa	C	
In patients with ACS and atrial fibrillation at low bleeding risk (HAS-BLED≤2), initial triple therapy of (N)OAC and ASA (75–100 mg/day) and clopidogrel 75 mg/day should be considered for a duration of 6 months irrespective of stent type followed by (N)OAC and aspirin 75–100 mg/day or clopidogrel (75 mg/day) continued up to 12 months.	IIa	C	
In patients requiring oral anticoagulation at high bleeding risk (HAS-BLED ≥3), triple therapy of (N)OAC and ASA (75–100 mg/day) and clopidogrel 75 mg/day should be considered for a duration of one month followed by (N)OAC and aspirin 75–100 mg/day or clopidogrel (75 mg/day) irrespective of clinical setting (SCAD or ACS) and stent type (BMS or new-generation DES).	IIa	C	
Dual therapy of (N)OAC and clopidogrel 75 mg/day may be considered as an alternative to initial triple therapy in selected patients.	IIb	B	865,870
The use of ticagrelor and prasugrel as part of initial triple therapy is not recommended	III	C	
Anticoagulation therapy after PCI in ACS patient			
In selected patients who receive ASA and clopidogrel, low-dose rivaroxaban (2.5 mg twice daily) may be considered in the setting of PCI for ACS if the patient is at low bleeding risk.	IIb	B	855
Anticoagulation during PCI in patients on oral anticoagulation			
It is recommended to use additional parenteral anticoagulation, regardless of the timing of the last dose of (N)OAC.	I	C	
Periprocedural parenteral anticoagulants (bivalirudin, enoxaparin or UFH) should be discontinued immediately after primary PCI.	IIa	C	

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
ACS = acute coronary syndrome; ASA = acetylsalicylic acid; BMS = bare-metal stent; CHA_2DS_2-VASc = Cardiac failure, Hypertension, Age ≥75 [Doubled], Diabetes, Stroke [Doubled]–Vascular disease, Age 65–74 and Sex category [Female]); DAPT = dual antiplatelet therapy; DES = drug-eluting stent; (N)OAC = (non-vitamin K antagonist) oral anticoagulant; HAS-BLED = hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly, drug/alcohol; INR = international normalized ratio; LV = left ventricular; PCI = percutaneous coronary intervention; SCAD = stable coronary artery disease; UFH = unfractionated heparin.

2014 **ESC**/EACTS **Guidelines** on **myocardial revascularization**: The Task Force on **Myocardial Revascularization** of the Europ

Tripel-Therapie mit NOACs ist möglich, auch wenn noch wenig Daten vorliegen - ESC Guidance

Consensus recommendations

Consensus recommendations on the management of AF patients with ACS and/or undergoing PCI/stenting are summarized in *Table* 4 and *Figure* 1.

In general, the period of triple therapy should be as short as possible, followed by OAC plus a single antiplatelet therapy (preferably clopidogrel 75 mg/day, or as an alternative, aspirin 75–100 mg/day). The duration of triple therapy is dependent on a number of considerations: acute vs. elective procedures, bleeding risk (as assessed by the HAS-BLED score), type of stent (with a preference for new generation DES or BMS). In these consensus recommendations for patients with non-valvular AF, where we refer to OAC, this can either be with well-controlled adjusted dose VKA (with TTR >70%) or with a NOAC.

Lip G, et al. Eur Heart J 2014

Dabigatran und kardiovaskuläres Risiko - Stellungnahme der EHRA

… Given the absence of new data from RCTs and the outcome data coming from 'real-world' registries,[79,80] it appears questionable to consider the potential risk of MI as a criterion for selecting the most appropriate NOAC agent in a patient with non-valvular AF. The available data do not suggest that there is a need to switch patients on dabigatran to one of the other NOACs in the event of an ACS developing in a patient with AF. …

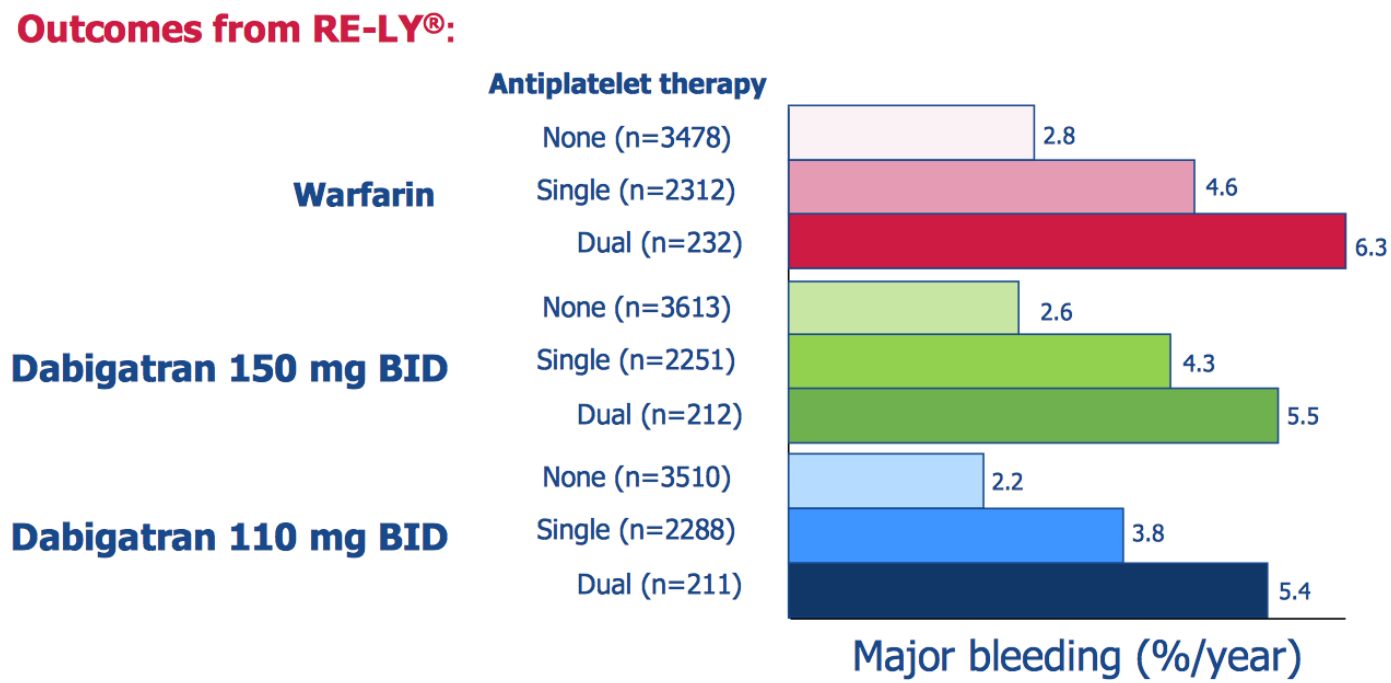
Lip GY, Eur Heart J. 2014 Dec 1;35(45):3155-79.

Kombination DOAK + antithrombozytäre Therapie bei Vorhofflimmern, verfügbare Studiendaten

Antiplatelet Agents	ARISTOTLE (Apixaban)	RELY (Dabigatran)	ROCKET-AF (Rivaroxaban)
ASA	< 165 mg/d	Ja	< 100 mg/d
Clopidogrel	Ja	Ja	Ja
Kombination	Nein	Ja	Nein
Aspirin (%)	31%	40%	36%
Prasugrel	Nein	Nein	Nein
Ticagrelor	Nein	Nein	Nein

Granger et al, New Engl J Med 2009;361:1139-51; Connoly et al, New Engl J Med 2011;365:883-91, Patel et al., New Engl J Med 2011;365:981-92

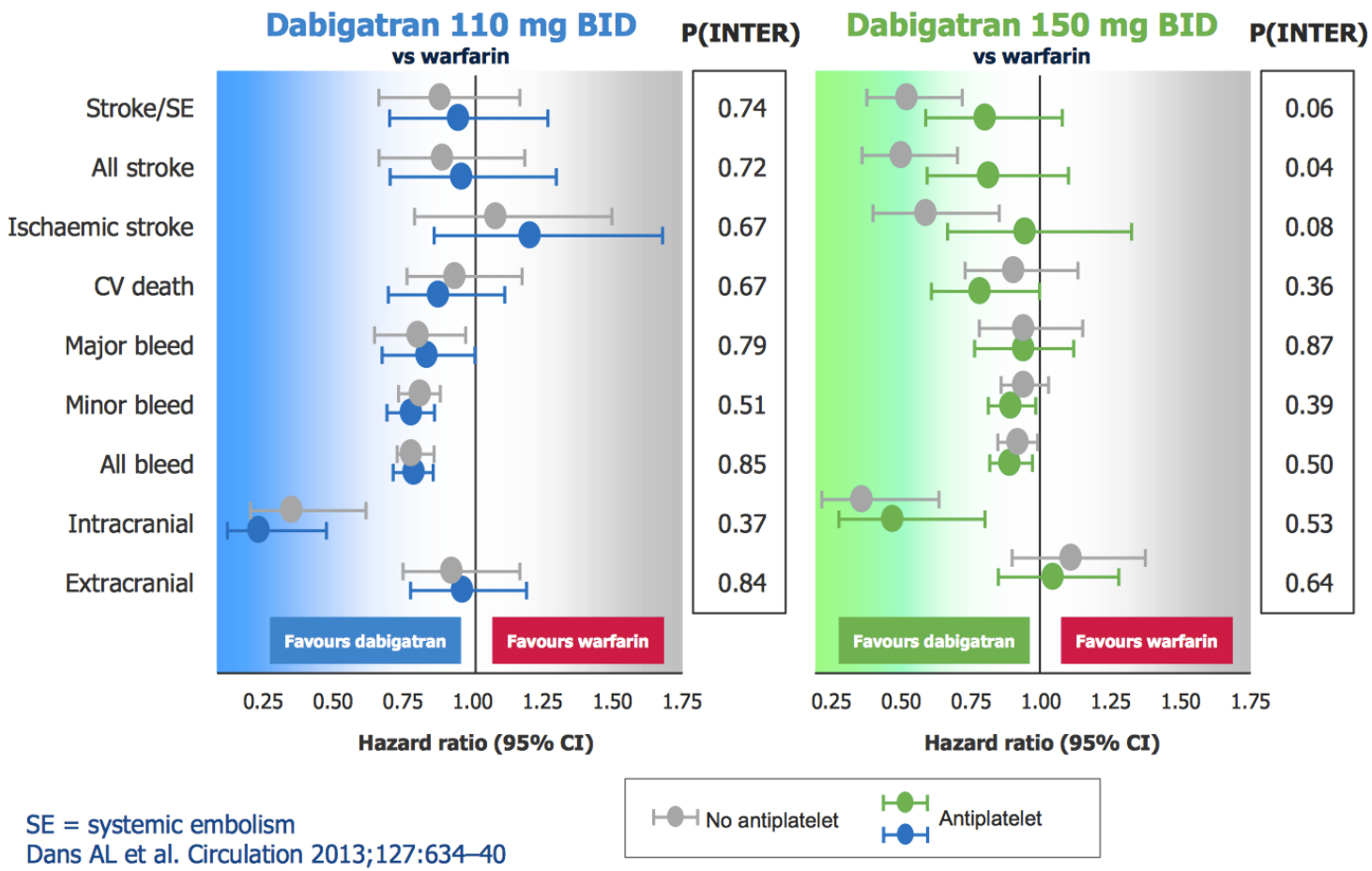
Kombination OAK/DOAK + antithrombozytäre Therapie führt zu vermehrten Blutungen - RE-LY



Triple Therapie führt zum höchsten Risiko für Blutungen sowohl unter Dabigatran als auch Warfarin, aber das Risiko ist nicht höher mit Dabigatran (tendentiell eher niedriger)

Dans AL, et al., Circulation 2013;127:634-640.

Effekte von Dabigatran im Vgl zur VKA sind konsistent und unabhängig von Kombination mit einer antithrombozytären Therapie



SE = systemic embolism
Dans AL et al. Circulation 2013;127:634–40

RE-DUAL PCI™: design

Assessment of high-risk vs non-high-risk characteristics (bridging therapy at physician's discretion)

Screening

R

n=2840 patients per arm

Dabigatran 150 mg BID + P2Y12 inhibitor

Dabigatran 110 mg BID + P2Y12 inhibitor

Warfarin (INR 2.0–3.0) + P2Y12 inhibitor + ASA

1° EP

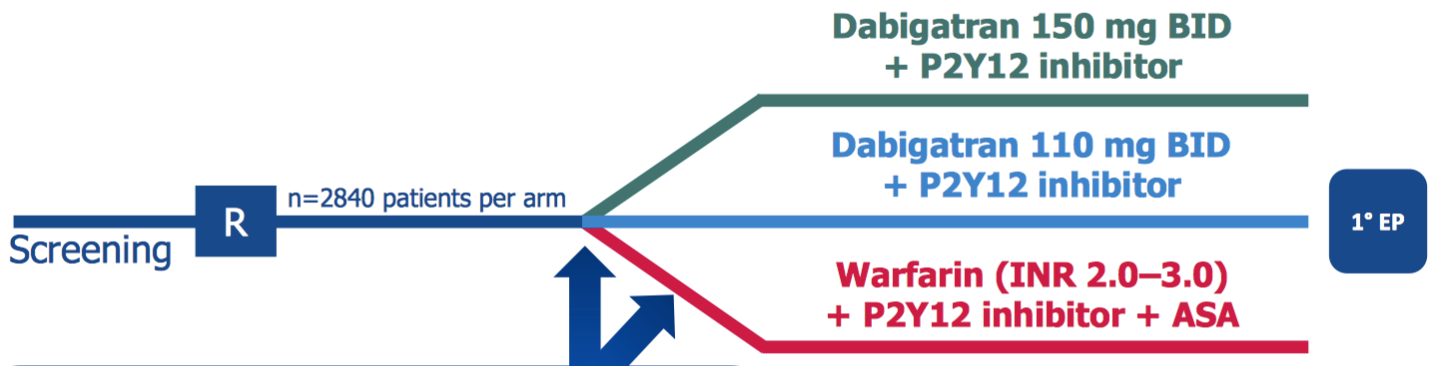
Randomization can occur ≤72 hours post-PCI
Study drug should be administered 6 hours after sheath removal, ≤72 hours post-PCI

Follow-up visits at month 1, 3, 6, 9, 12, and 15; and 18, 24, and 30 post-randomization or end of trial

Minimum treatment duration: 6 months

DAT = dual antithrombotic therapy; EP = endpoint
Adapted from Cannon C. AHA 2013 and Boehringer Ingelheim data on file

RE-DUAL PCI™: design



ASA discontinuation:

- Dabigatran arms: immediately after successful procedure (immediate initiation of DAT)
- Warfarin arm: 1 month after BMS or 3 months after DES

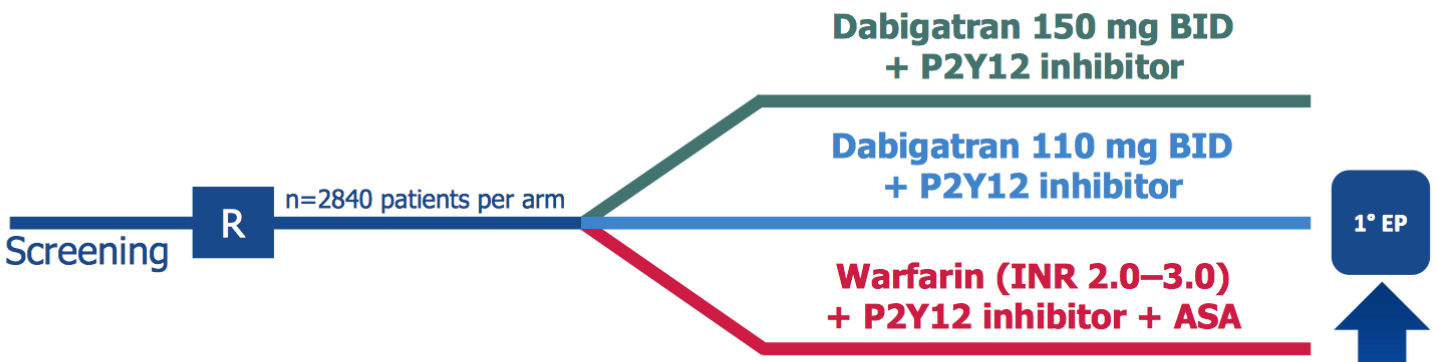
P2Y12 inhibitor can be discontinued after month 12 at physician's discretion

Follow-up visits at month 1, 3, 6, 9, 12, and 15; and 18, 24, and 30 post-randomization or end of trial

Minimum treatment duration: 6 months

DES = drug-eluting stent
Adapted from Cannon C. AHA 2013 and Boehringer Ingelheim data on file

RE-DUAL PCI™: design



Dual primary endpoints of efficacy and safety

- Time to death or first thrombotic event (death, MI, stroke/SE)
- Time to first ISTH major bleeding event

ISTH = International Society on Thrombosis and Haemostasis
Adapted from Cannon C. AHA 2013 and Boehringer Ingelheim data on file

Zusammenfassung - “TRIPLE” Therapie (OAK plus DAPT)

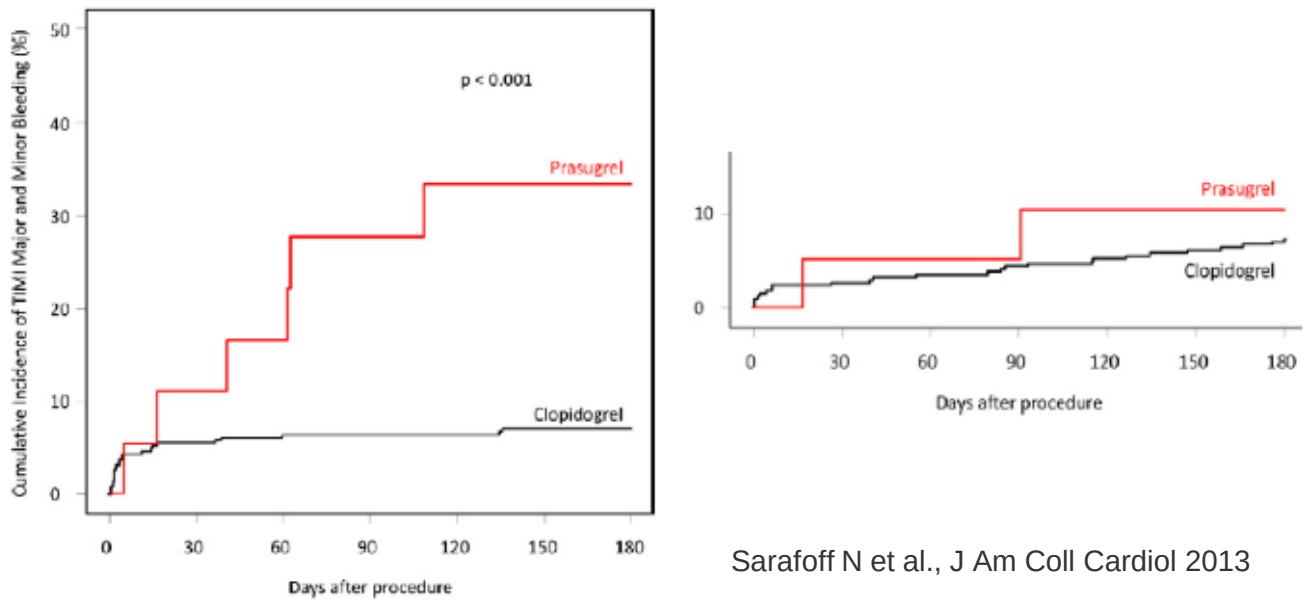
Eine duale antithrombozytäre Therapie in der frühen Phase nach (elektiver) Stentimplantation (d..h. ersten 4 Wochen) scheint unumgäng

DES der neuen Generation

Die Triple Therapie sollte hi
Blutungsrisiko) gehalten we
auch für DOAKs.

Es ist pharmakologisch nich
Gesamtblutungsraten, nicht
Therapie (auch zur VKA in

Wenn Kombination mit NO



Sarafoff N et al., J Am Coll Cardiol 2013

Laufende Studien evaluieren, ob duale Therapien aus Clopidogrel/neuere P2Y12 Inhibitor und oraler Antikoagulation mit DOAKs ausreichende Sicherheit und Effektivität bieten (Dabigatran: RE-DUAL, RIVAROXABAN: PIONEER, Edoxaban: EVOLVE-PCI, APIXABAN: 2x2 faktorielle Studie)

Für eine vierfach antithrombotische Therapie (3 fach Antiaggregation plus Antikoagulanz) gibt es derzeit keine ausreichende Evidenz insbesondere zur Sicherheit und diese sollte daher nicht angewendet werden

SOP: Dauer der antithrombozytären Therapie und Kombination mit OAK bei KHK/PCI mit und ohne Vorhofflimmern (modifiziert nach 2014 ESC/EACTS Guidelines on myocardial revascularization und LIP GY, et al Eur Heart J. 2014;35(45):3155-79.)

KHK ohne Vorhofflimmern + Indikation für PCI

- DES*
  - Stabile KHK
    - ASS 100mg/d + Clopidogrel für 6 Monate
  - ACS
    - Prasugrel/Ticagrelor für 12 Monate nach Anordnung im HK**

KHK mit Vorhofflimmern + Indikation für PCI

- DES*
  - Stabile KHK
  - ACS
- **CHA_2DS_2-Vasc Score = 1**
  - ASS 100mg/d + Clopidogrel für 6 Monate, danach OAK (VKA/DOAK) Monotherapie
  - Prasugrel/Ticagrelor für 12 Monate nach Anordnung im HKL danach OAK (DOAK/Marcumar) Monotherapie
- **CHA_2DS_2-Vasc Score >1 + HASBLED-Score < 3**
  - Triple-Therapie: ASS + Clopidogrel + OAK (Marcumar (INR 2-2,5) oder DOAK (Dabigatran 110mg/2xtgl oder Rivaroxaban 15mg/1xtgl oder Apixaban 2,5mg/2xtgl,) entsprechend des vorhergehenden OAK*** — 4 Wochen / 6 Monate
  - Clopidogrel + Marcumar(INR 2-2,5)/DOAK in niedriger Dosis (s.o.), *** — Weitere 5 Monate / Weitere 6 Monate
  - **OAK (präferentiell DOAK oder Marcumar INR 2-3)** in maximal verträglicher Dosis **dauerhaft**
- **CHA_2DS_2-Vasc Score >1 + HASBLED-Score ≥ 3**
  - **Triple-Therapie (s.o)** — 4 Wochen / 4 Wochen
  - Clopidogrel + Marcumar(INR 2-2,5)/DOAK in niedriger Dosis (s.o.), *** — Weitere 5 Monate / Weitere 11 Monate
  - **OAK (präferentiell DOAK oder Marcumar INR 2-3)** in maximal verträglicher Dosis **dauerhaft**

**BMS nur wenn Kontraindikationen gegen APT ≥1 Monat, oder notwendige OP mit erhöhtem perioperativen Blutungsrisiko innerhalb der ersten 3 Monate nach PCI*

*** (s. SOP intrahospitale antithrombotische Therapie beim ACS)*

**** (Behandlung mit PPI während der Dauer der Kombination OAK olus antithrombozytäre Therapie)*

Geisler Stand 04/2015

Vielen Dank für die Aufmerksamkeit