Verlängerte antithrombozytäre Therapie nach ACS: welcher Patient profitiert?

Meinrad Gawaz
Innere Medizin III, Kardiologie und Kreislauferkrankungen
Eberhard Karls Universität Tübingen

7. Thromboseforum, Stuttgart 2017

Antithrombotische Therapie

Indikationen in der Herzmedizin

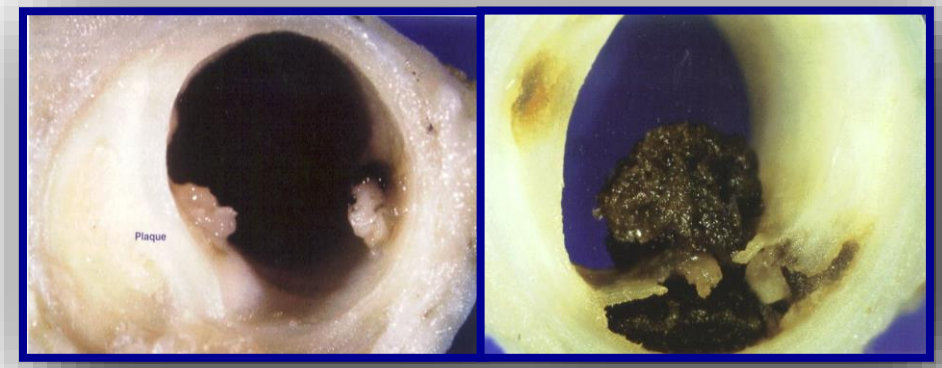
Koronare Herzerkrankung
(stabile KHK, PCI, ACS)

Vorhofflimmern
(Kunstklappen, TVT, LE)

Koronare Thrombose –

Akutes Koronarsyndrom und Stentthrombose

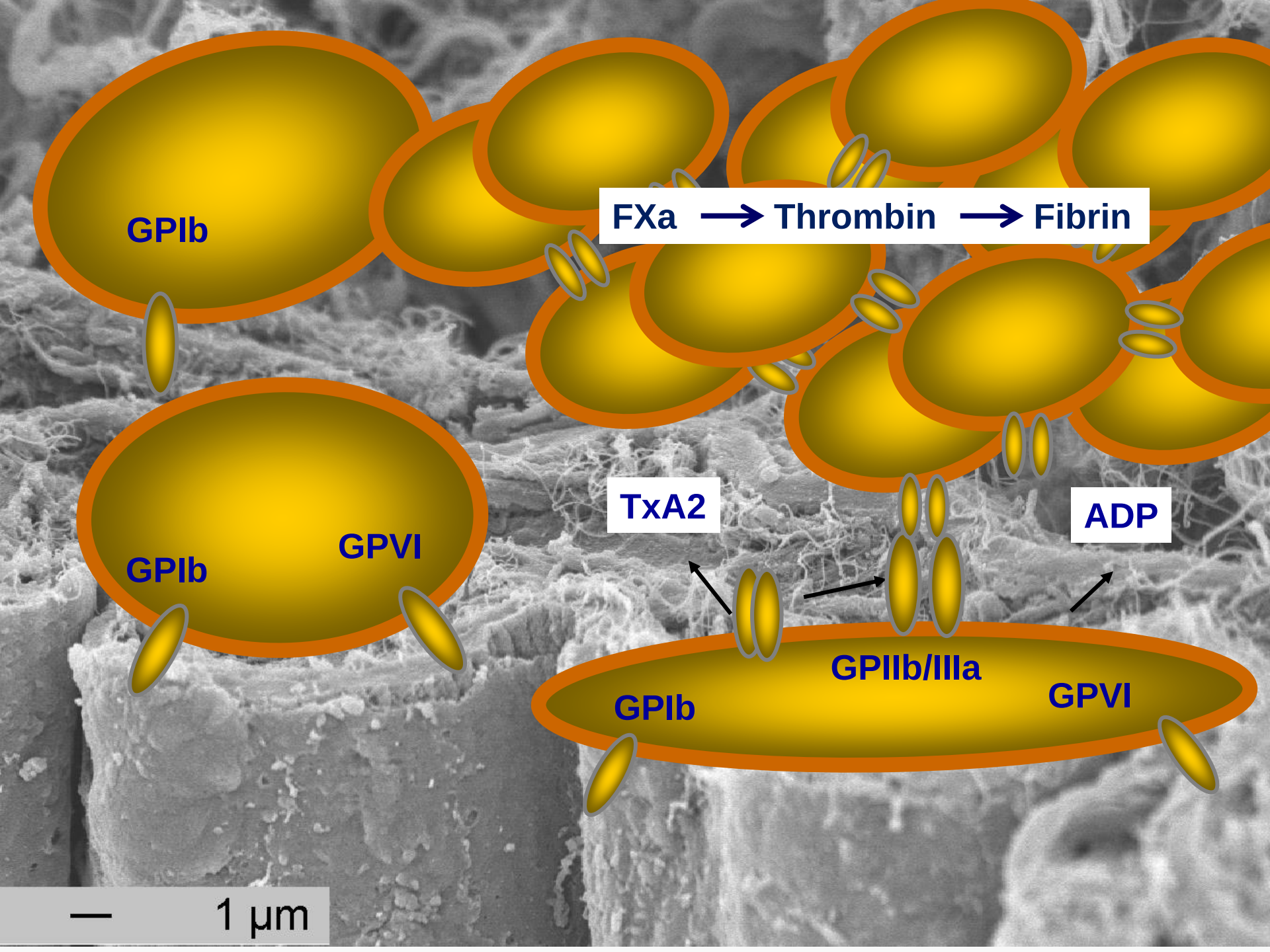
Davies, 2001



Plaque Ruptur und Thrombose

Stentthrombose

Akutes Koronarsyndrom (NSTEMI/ STEMI)


GPIb
FXa → Thrombin → Fibrin
GPIb
GPVI
TxA2
ADP
GPIIb/IIIa
GPIb
GPVI
— 1 µm

Orale Antithrombotische Therapie

	Antikoagulation	Antithrombozytäre Therapie
2008	**Vitamin K-Antagonisten** (Marcumar®)	**Acetylsalicylsäure** (Aspirin®) **Clopidogrel** (Plavix®, (Iscover®)
2017	**Rivaroxaban** (Xarelto®) **Dabigatran** (Pradaxa®) **Apixaban** (Eliquis®) **Edoxaban** (Lixiana®)	**Prasugrel** (Efient®) **Ticagrelor** (Brillique®) **Vorapaxar** (Zontivity®)

ESC Guideline NSTE-ACS

Recommendations for platelet inhibition

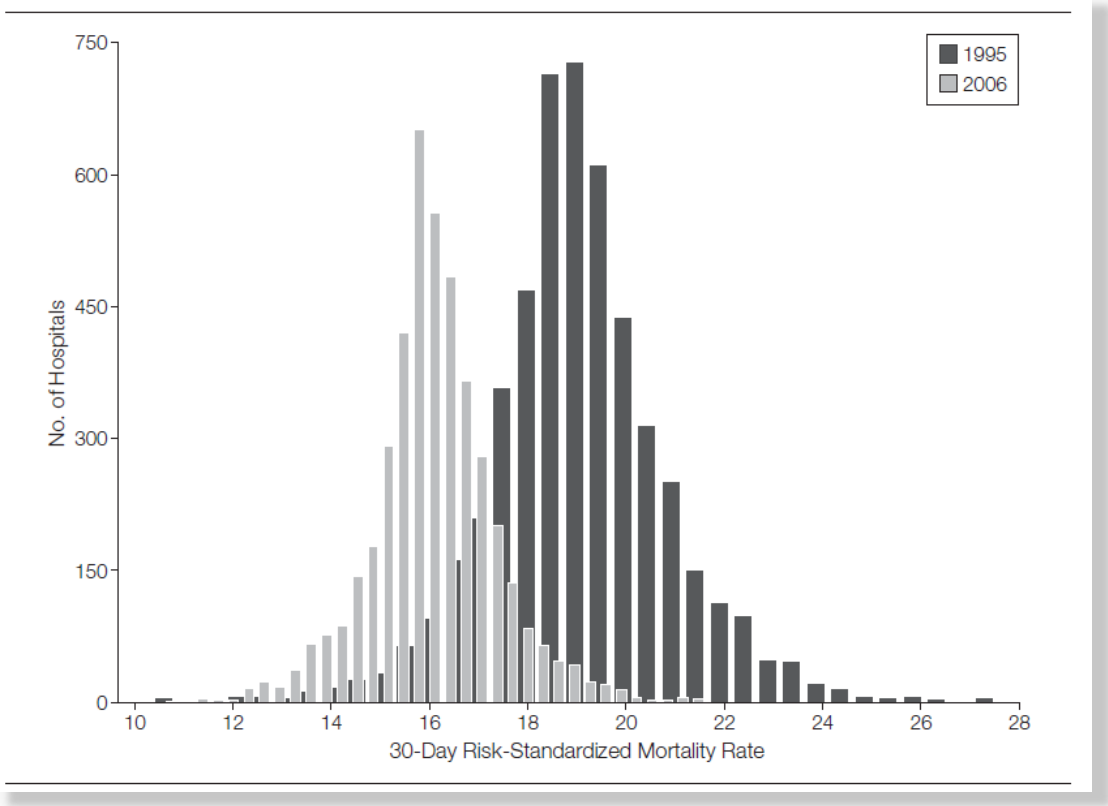
Oral antiplatelet therapy	Class	Level
A $P2Y_{12}$ inhibitor is recommended, in addition to aspirin, for 12 months unless there are contraindications such as excessive risk of bleeds.	I	A
• Ticagrelor (180 mg loading dose, 90 mg twice daily) is recommended, in the absence of contraindications,[e] for all patients at moderate-to-high risk of ischemic events (e.g. elevated cardiac troponins), regardless of initial treatment strategy and including those pretreated with clopidogrel (which should be discontinued when ticagrelor is started).	I	B
• Prasugrel (60 mg loading dose, 10 mg daily dose) is recommended in patients who are proceeding to PCI if no contraindication.[e]	I	B
• Clopidogrel (600 mg loading dose, 75 mg daily dose) is recommended for patients who cannot receive ticagrelor or prasugrel or who require oral anticoagulation.	I	B
$P2Y_{12}$ inhibitor administration for a shorter duration of 3–6 months after DES implantation may be considered in patients deemed at high bleeding risk	IIb	A
It is not recommended to administer prasugrel in patients in whom coronary anatomy is not known.	III	B
Long-term $P2Y_{12}$ inhibition		
$P2Y_{12}$ inhibitor administration in addition to aspirin beyond 1 year may be considered after careful assessment of the ischemic and bleeding risks of the patient.	IIb	A

Roffi M, ESC Guidelines
Roffi M et al., Eur Heart J, August 2015, doi:10.1093/eurheartj/ehv320,
http://eurheartj.oxfordjournals.org/content/ehj/33/20/2569.full.pdf

„short term risk“ - Myokardinfarkt

Reduction in Acute Myocardial Infarction Mortality in the United States
Risk-Standardized Mortality Rates From 1995-2006

(n=2.7 Mio)



30-Tage Mortalität

	Observed, Mean (SD)	
Year	In-Hospital	30-d
1995	14.6 (5.9)	18.9 (6.8)
1996	13.8 (5.8)	18.4 (6.7)
1997	13.2 (5.6)	18.0 (6.7)
1998	12.8 (5.4)	17.9 (6.3)
1999	14.1 (5.7)	19.5 (6.7)
2000	13.5 (5.3)	18.9 (6.4)
2001	13.2 (5.3)	18.7 (6.4)
2002	12.6 (5.0)	18.1 (6.2)
2003	12.0 (5.1)	17.8 (6.5)
2004	11.4 (5.1)	17.2 (6.6)
2005	10.8 (5.2)	16.8 (6.9)
2006	10.1 (5.2)	16.1 (7.0)

Krumholz et a. JAMA 2009

„short term risk“ - STEMI

Association of Changes in Clinical Characteristics and Management With Improvement in Survival Among Patients With ST-Elevation Myocardial Infarction

French Registry FAST-MI (n=6707, *1995-2010*)

Year	No. of Events	No. of Patients	30–Day Mortality, % (95% CI)		Multivariable Logistic Regression Analyses, OR (95% CI)[a]	*P* Value
			Observed	Standardized		
1995	210	1536	13.7 (12.0-15.4)	11.3 (9.5-13.2)	1 [Reference]	
2000	160	1844	8.7 (7.4-10.0)	7.6 (5.7-9.5)	0.64 (0.51-0.81)	.001
2005	111	1611	6.9 (5.7-8.2)	6.4 (5.1-7.7)	0.52 (0.40-0.68)	.001
2010	75	1716	4.4 (3.5-5.4)	4.4 (3.5-5.4)	0.39 (0.29-0.53)	.001

Conclusion In France, the overall rate of cardiovascular mortality among patients with STEMI decreased from 1995 to 2010, accompanied by an increase in the proportion of women younger than 60 years with STEMI, changes in other population characteristics, and greater use of reperfusion therapy and recommended medications.

JAMA. 2012;308(10):998-1006

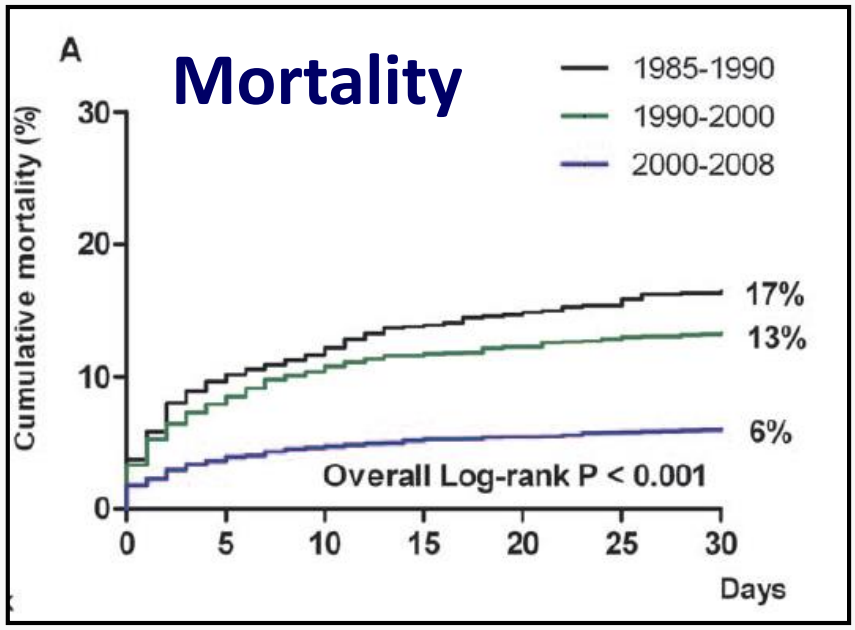
Puymirat et a. JAMA 2012

„long term risk“ - STEMI

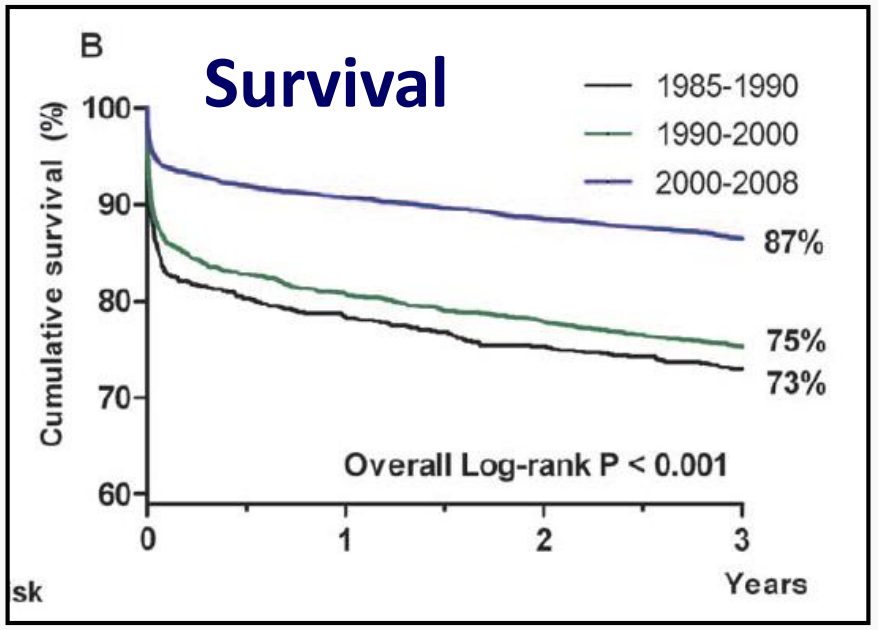
Changes in Clinical Profile, Treatment, and Mortality in Patients Hospitalised for Acute Myocardial Infarction between 1985 and 2008

Netherlands (n>6820, *1985-2008*)

„short term“



„long term“



approx. 1 of 8 will die after STEMI

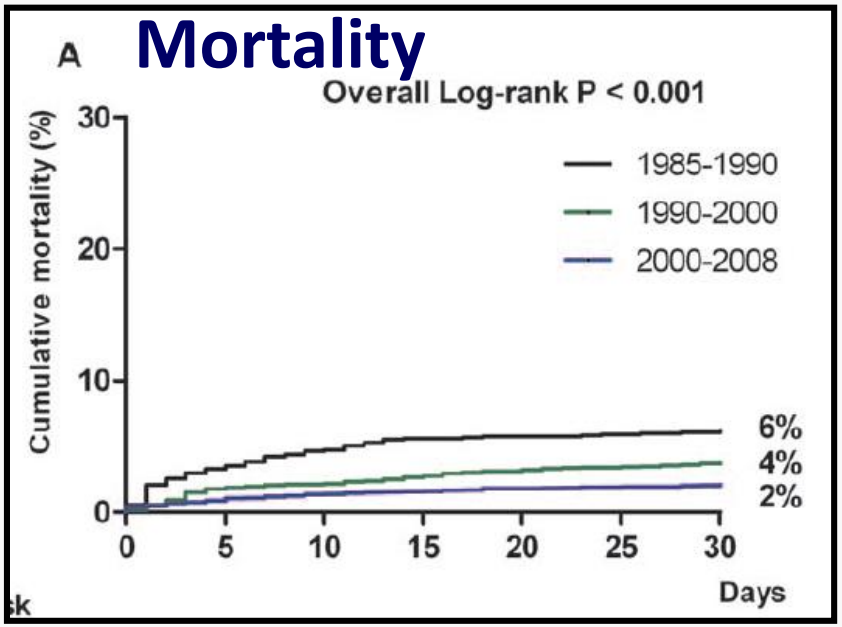
Nauta et al. PlosOne 2011

„long term risk“ – N-STEMI

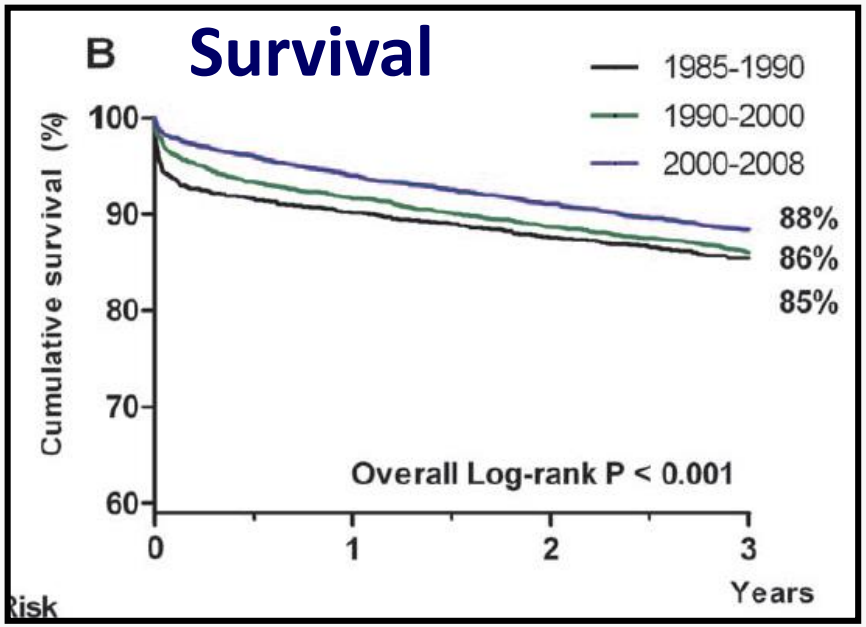
Changes in Clinical Profile, Treatment, and Mortality in Patients Hospitalised for Acute Myocardial Infarction between 1985 and 2008

Netherlands (n>7614, *1985-2008*)

„short term“

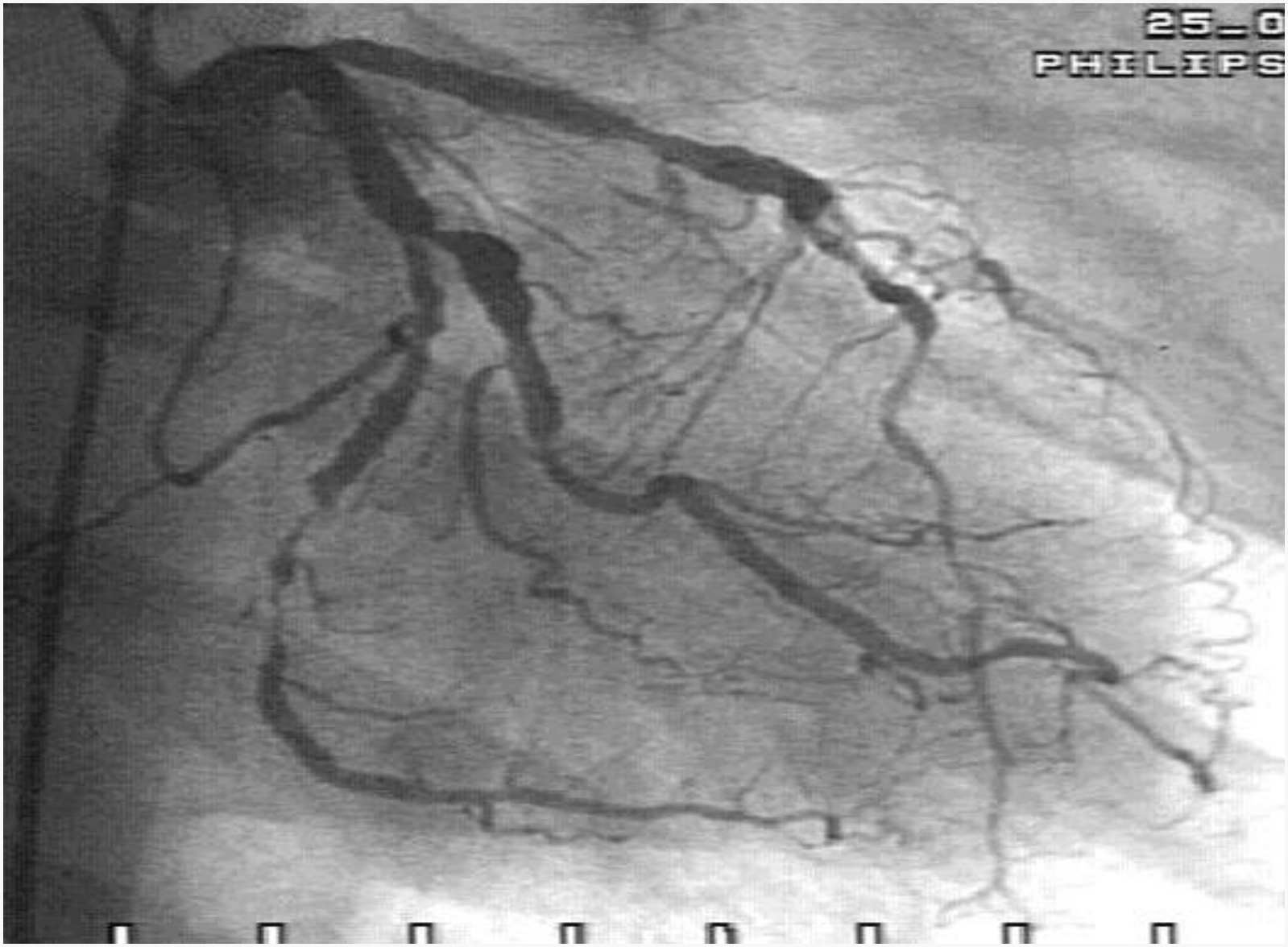


„long term“



approx. 1 of 8 will die after N-STEMI

Nauta et al. PlosOne 2011


25_0
PHILIPS

Duale Antithrombozytäre Therapie

- **12 Monate bei NSTEMI/STEMI**
- **bei allen?**

Duale Antiplättchen Therapie (DAPT)

Risikoadjustierte DAPT

Frühes und spätes ischämisches Risiko und Blutungsrisiko

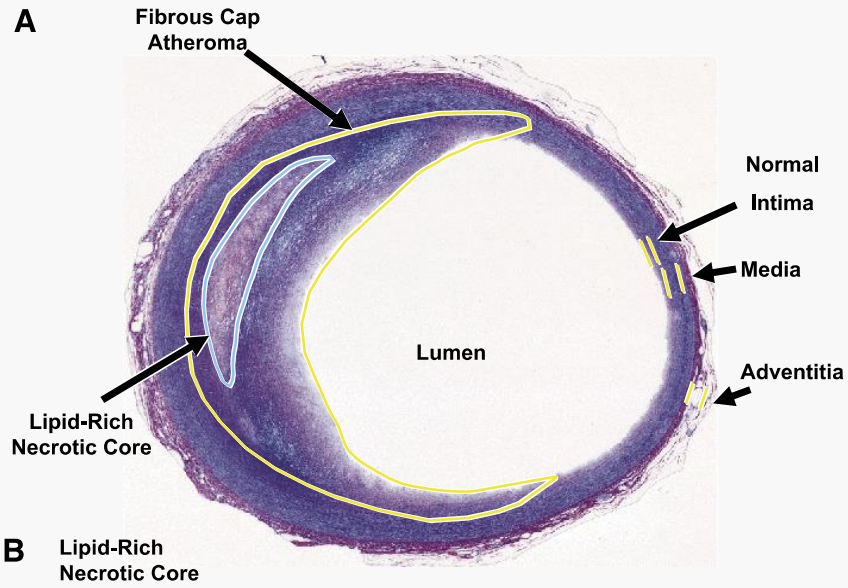
Stentthrombose

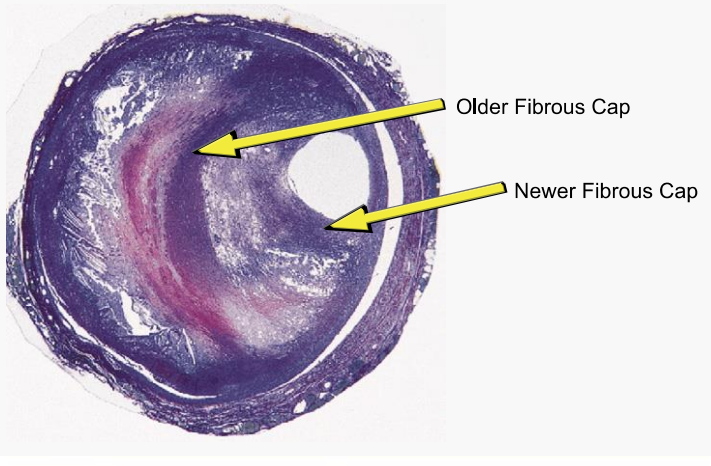
Tod und Myokardinfarkt

Komplikationen nach PCI

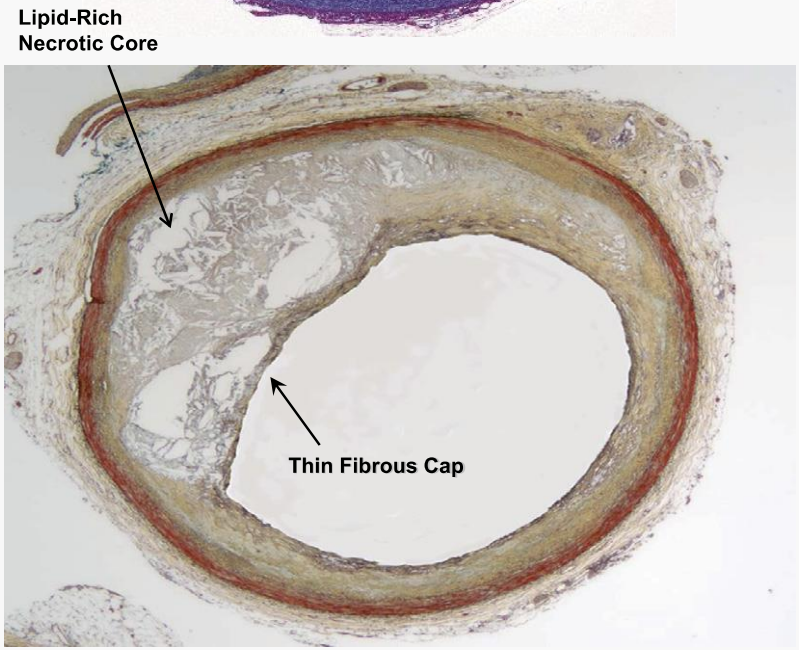
Komplikationen der Koronaren Herzerkrankung/Atherosklerose

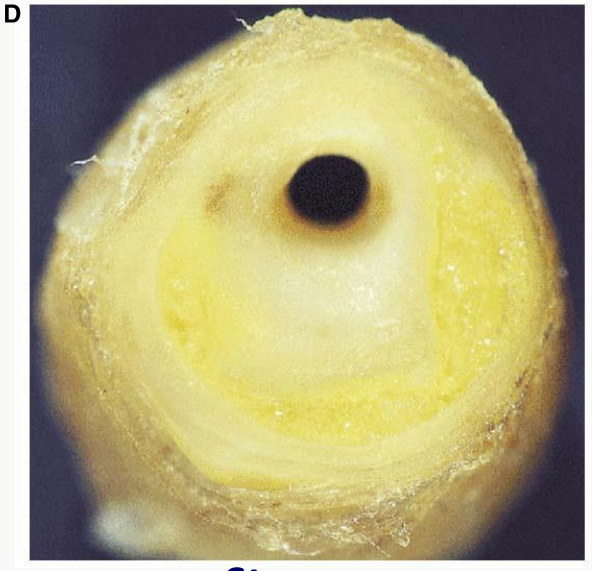
„fibrous cap“-Atherom („Fibröse Kappe“)





„Plaque rupture healing“

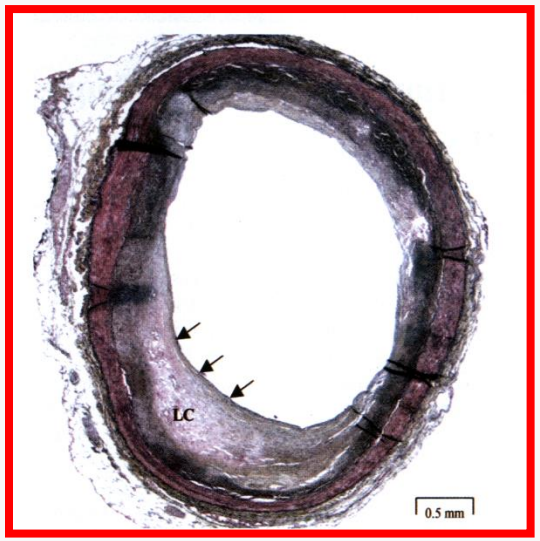




Insuli W, Am J Med 2009

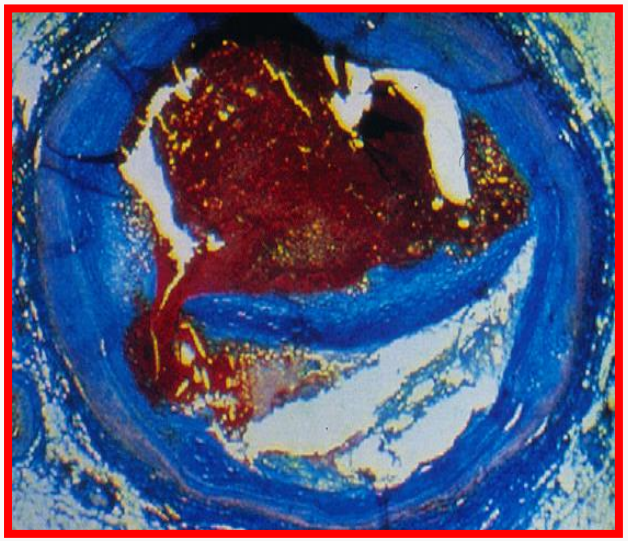
Stenose

Vulnerable Plaque



MacNeill et al.; ATVB 2003

„Trigger Event“



H.C. Stary, 1993

Plaque characteristics:

- thin, fibrous cap (<65µm)
- large, lipid rich pool
- increased macrophage activity
- T-cells, old hemorrhage, calcium

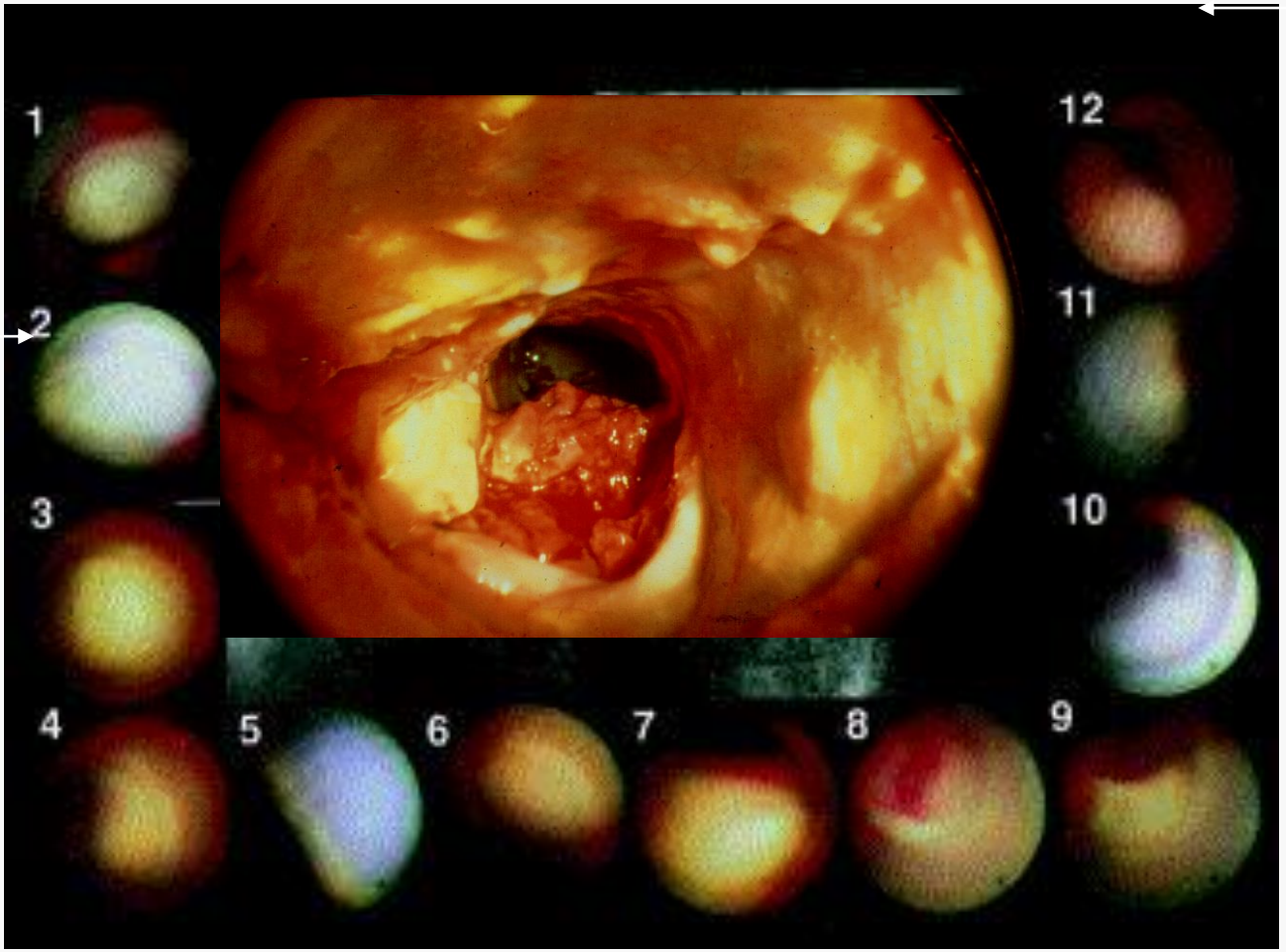
Predisposing cellular mechanisms:

- reduced collagen synthesis
- overexpression of collagenase
- smooth muscle cell apoptosis
- inflammatory cytokines

Contributing factors: local shear stress, systemic inflammation (CRP ↑)

Multiple vulnerable Plaques bei Patienten mit Akutem Koronarsyndrom

Angiographic & angioscopic images in a 58-year-old man with anterior MI[Asakura 2001]



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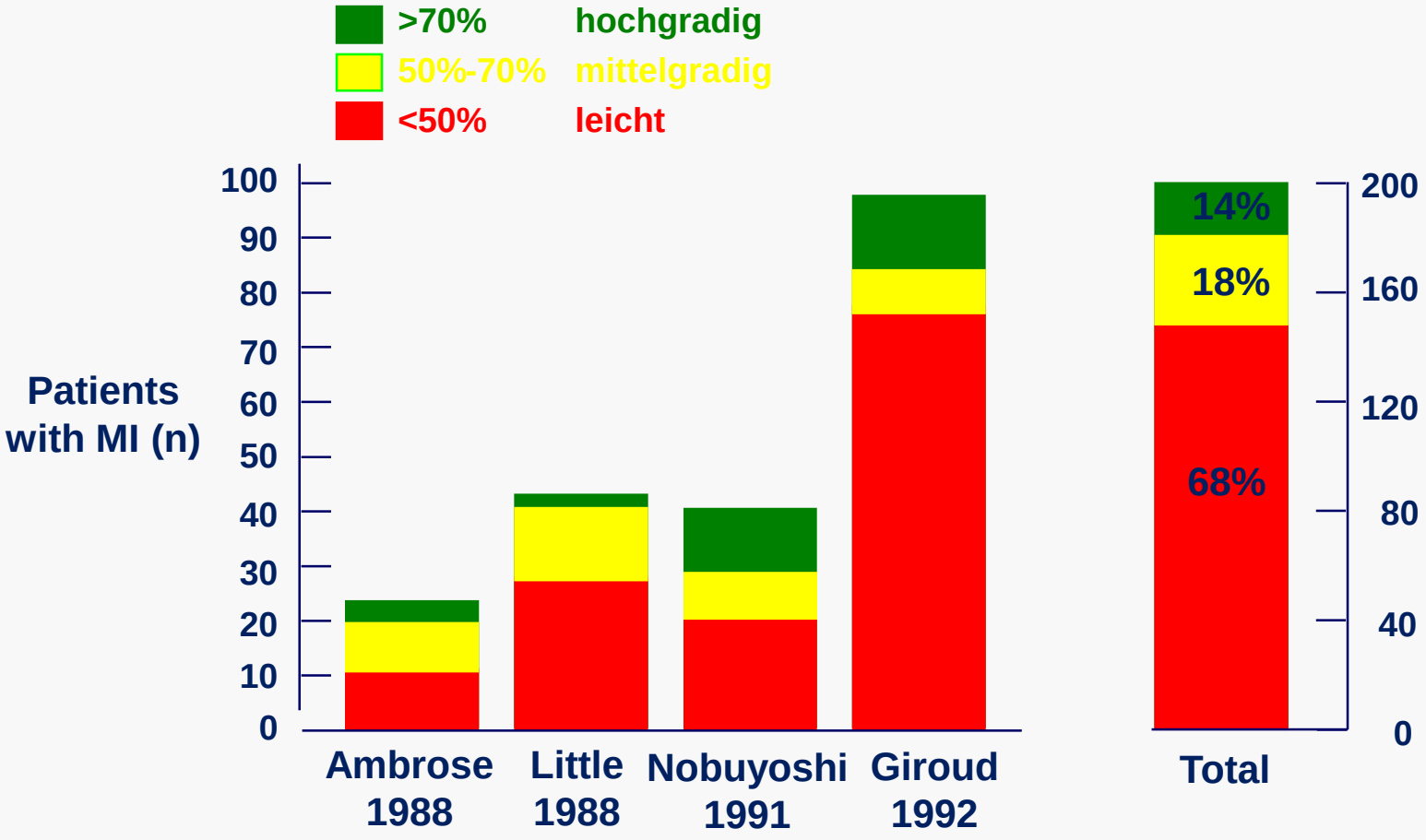
Asakura M *et al.* J Am Coll Cardiol 2001

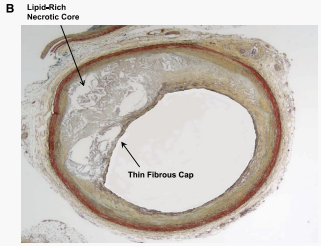
Stenosegrad der vulnerablen Plaque bei Myokardinfarkt



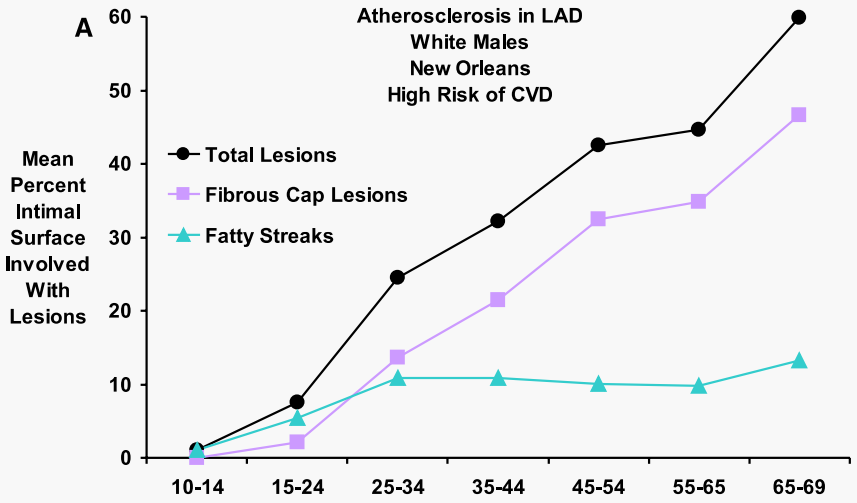
Falk et al. Circulation, 1995

Koronare “Plaquelast” in Abhängigkeit des kardiovaskulären Risikoprofils und des Alters

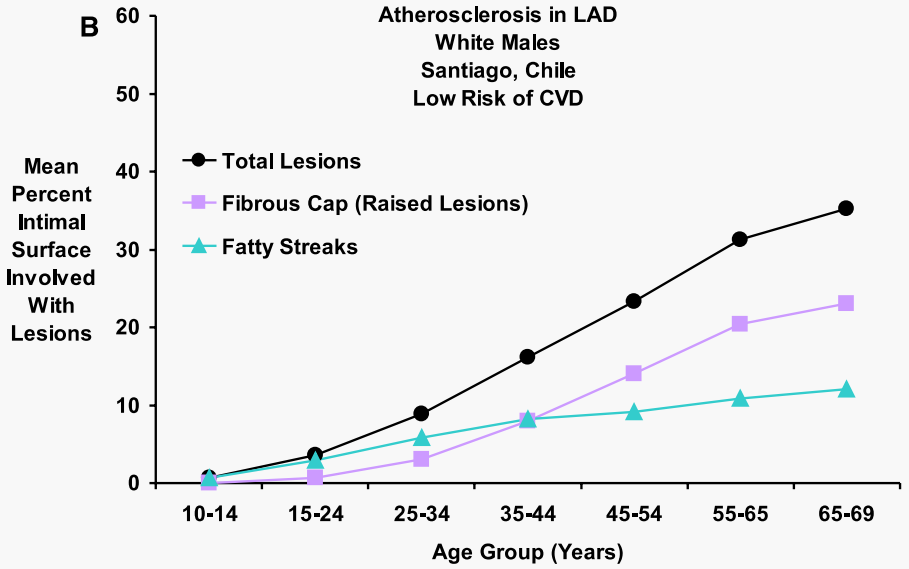
Hohes CV-Risiko



Niedriges CV-Risiko



Alter →



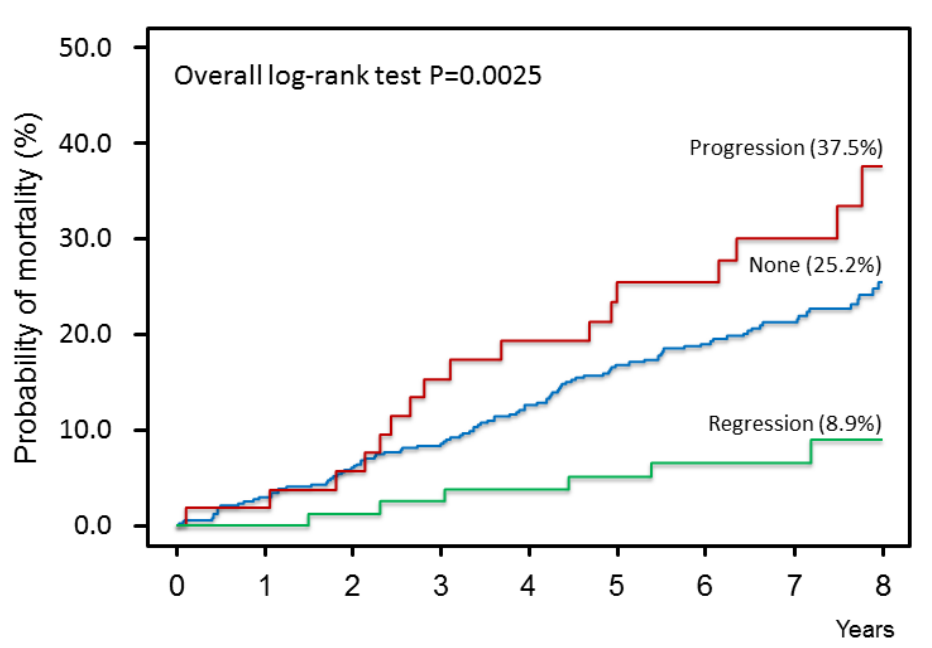
Alter →

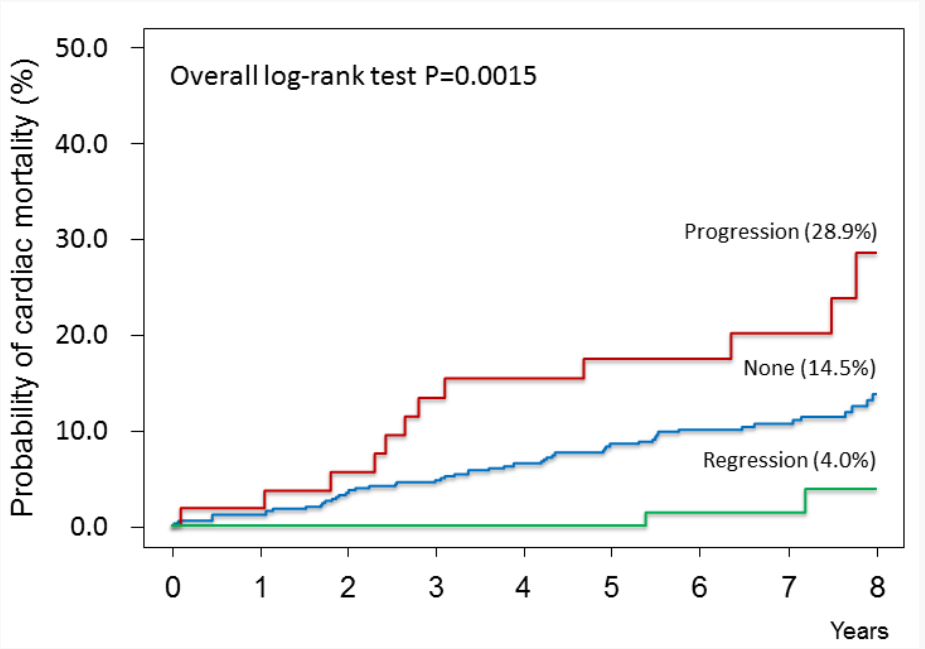
Insuli W, Am J Med 2009

Progression der Koronaren Herzerkrankung und Mortalität

Association of Progression or Regression of Coronary Artery Atherosclerosis with Long-term Prognosis

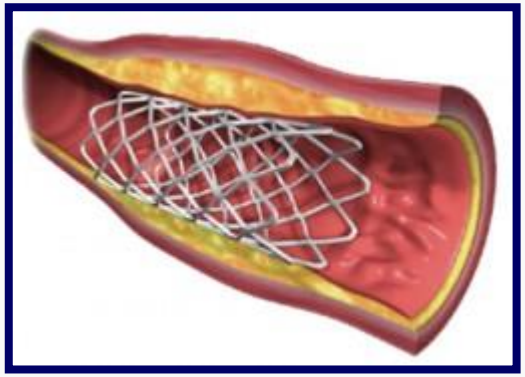
Gjin Ndrepepa MD, Raisuke Iijima MD, Sebastian Kufner MD, Siegmund Braun MD, Salvatore Cassese MD, Robert A. Byrne MD, Jonas Sorges, Stefanie Schulz-Schüpke MD, Petra Hoppmann MD, Massimiliano Fussaro MD, Karl-Ludwig Laugwitz MD, Heribert Schunkert MD, Adnan Kastrati MD



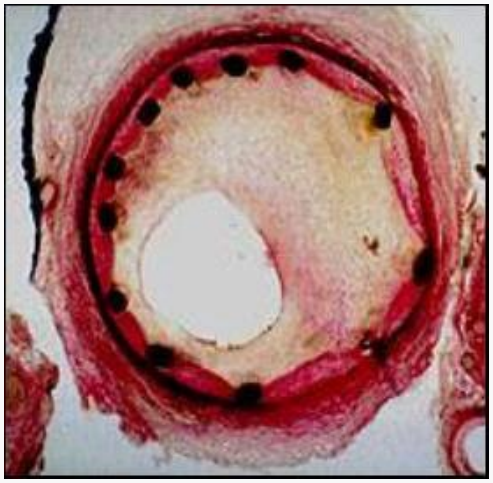


Ndrepepa et al., Am Heart J 2016

Koronare Determinanten des Langzeitrisikos nach Myokardinfarkt

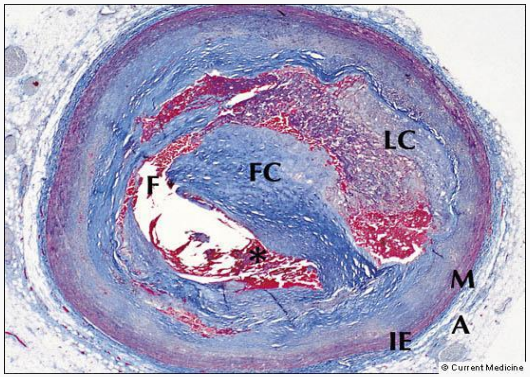


Stent-Thrombose



Restenose

Progression der KHK



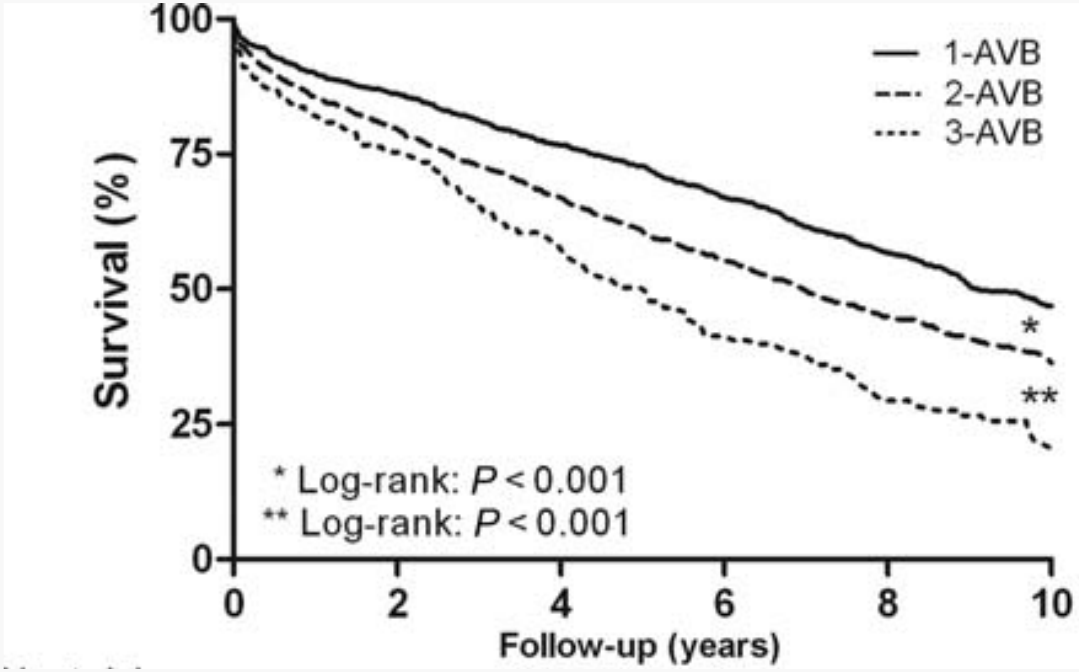
Anhaltender „Entzündungsprozess“

Long-term prognosis of patients with peripheral arterial disease with or without polyvascular atherosclerotic disease

Jan-Peter van Kuijk[1], Willem-Jan Flu[2], Gijs M.J.M. Welten[1], Sanne E. Hoeks[2], Michel Chonchol[3], Radosav Vidakovic[1], Hence J.M. Verhagen[1], Jeroen J. Bax[4], and Don Poldermans[1]*

Kaplan–Meier estimates for long-term all-cause mortality, stratified according to the number of affected vascular beds.

N= 2933



Van Kuijik et al., Eur H J 2010

Incidence, Predictors, and Subsequent Mortality Risk of Recurrent Myocardial Infarction in Patients Following Discharge for Acute Myocardial Infarction

Daisaku Nakatani, MD, PhD; Yasuhiko Sakata, MD, PhD; Shinichiro Suna, MD, PhD; Masaya Usami, MD; Sen Matsumoto, MD; Masahiko Shimizu, MD, PhD; Satoru Sumitsuji, MD, PhD; Shigeo Kawano, MD; Yasunori Ueda, MD, PhD; Toshimitsu Hamasaki, PhD; Hiroshi Sato, MD, PhD; Shinsuke Nanto, MD, PhD; Masatsugu Hori, MD, PhD; Issei Komuro, MD, PhD for the Osaka Acute Coronary Insufficiency Study (OACIS) Investigators

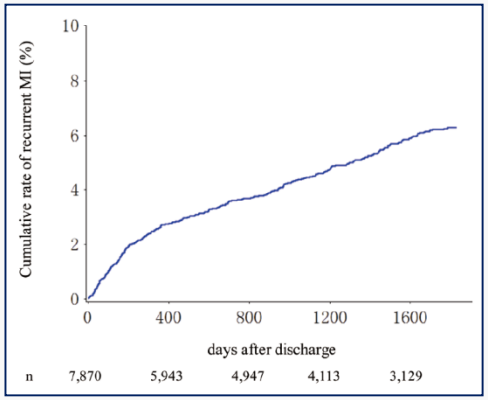
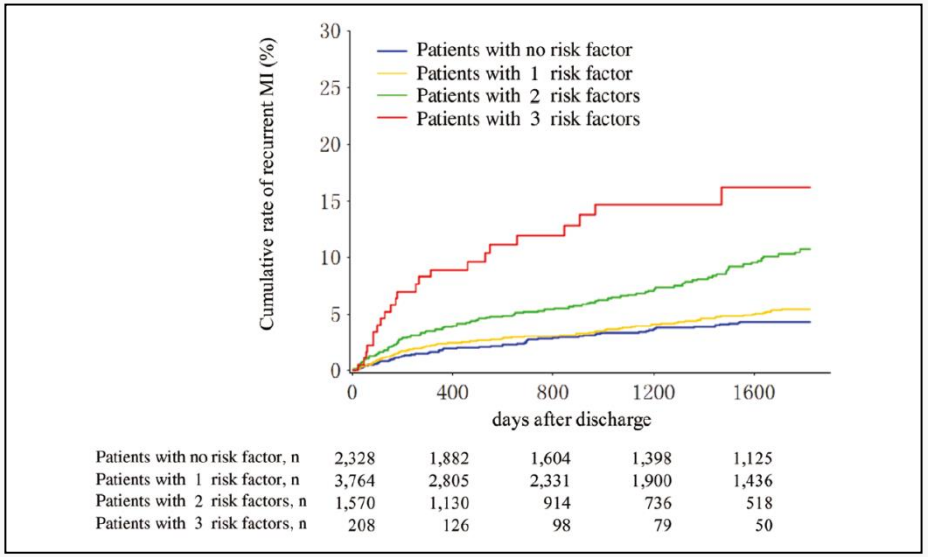


Table 3. Predictors of Re-MI by Multivariate Cox Regression Analyses

	Model 1a			Model 2a			Model 1b			Model 2b		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
Age	1.021	1.007–1.035	0.003	1.020	1.005–1.035	0.007	1.021	1.008–1.034	0.001	1.019	1.006–1.033	0.005
Male sex	1.344	0.937–1.928	0.108	1.467	0.993–2.169	0.054	–	–	–	–	–	–
Hypertension	1.242	0.926–1.665	0.148	1.214	0.892–1.652	0.217	–	–	–	–	–	–
Diabetes mellitus	2.013	1.528–2.653	<0.001	1.823	1.364–2.436	<0.001	2.079	1.584–2.73	<0.001	1.873	1.406–2.496	<0.001
History of MI	1.538	1.066–2.219	0.021	1.431	0.968–2.117	0.073	1.767	1.251–2.496	0.001	1.744	1.212–2.51	0.003



Nakatani et al. Circ J 2013; 77:439-446

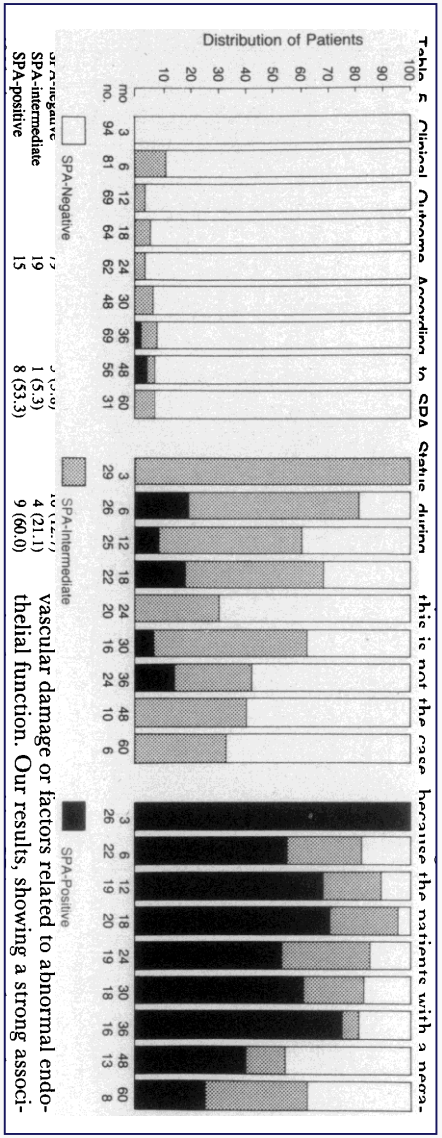
which platelets contribute to the acute manifestations of coronary artery disease is not fully understood. A causal role of platelet hyperreactivity or of local platelet activation in an acute coronary event has been suggested but never proved.[5] Platelet products in plasma (beta-thromboglobulin, thromboxane, and platelet factor 4) have been measured to determine platelet activation in patients with coronary artery disease.[6-9]

ease by reducing the risk of sudden death, myocardial infarction, and unstable angina.[11-15]

In two case reports, a syndrome characterized by peripheral ischemia of the fingers and toes has been described in patients with thrombocythemia and spontaneous platelet aggregation (SPA). Treatment with aspirin prevented the aggregation and the clinical signs of ischemia, both of which recurred after

Table 4. Logistic Multiple Regression Analysis of Mortality during Five Years of Follow-up.

VARIABLE	NO. OF PATIENTS	COEFFICIENT	SE	LOG LIKELIHOOD*	P VALUE
Cohort	149	−0.5	0.7	−54.9	
SPA-positive status	26	1.8	0.6	−49.0	0.001
Digitalis	14	1.4	0.7	−47.0	0.048



Trip et al. New Engl J Med 1990

Hohe individuelle Variabilität nach PCI

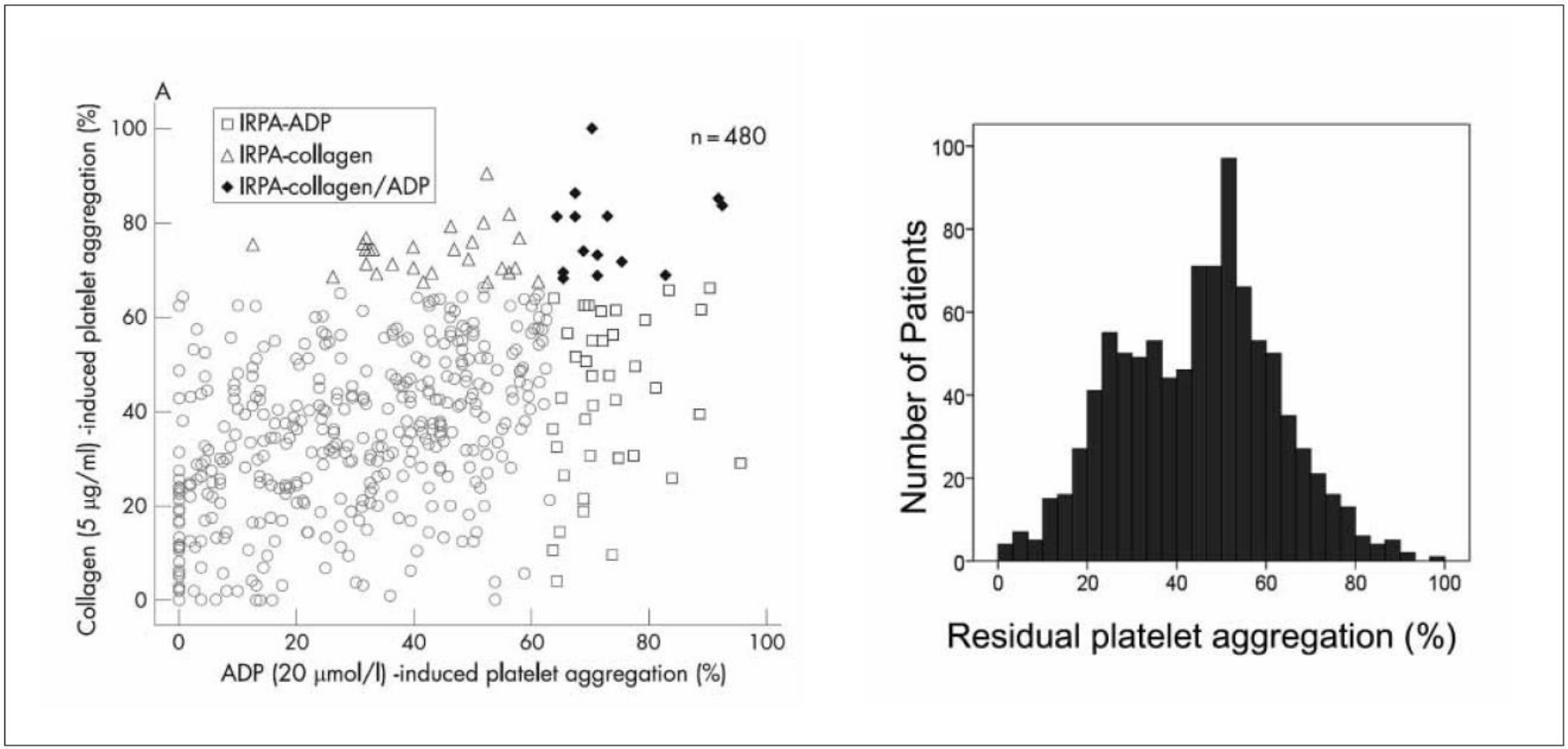
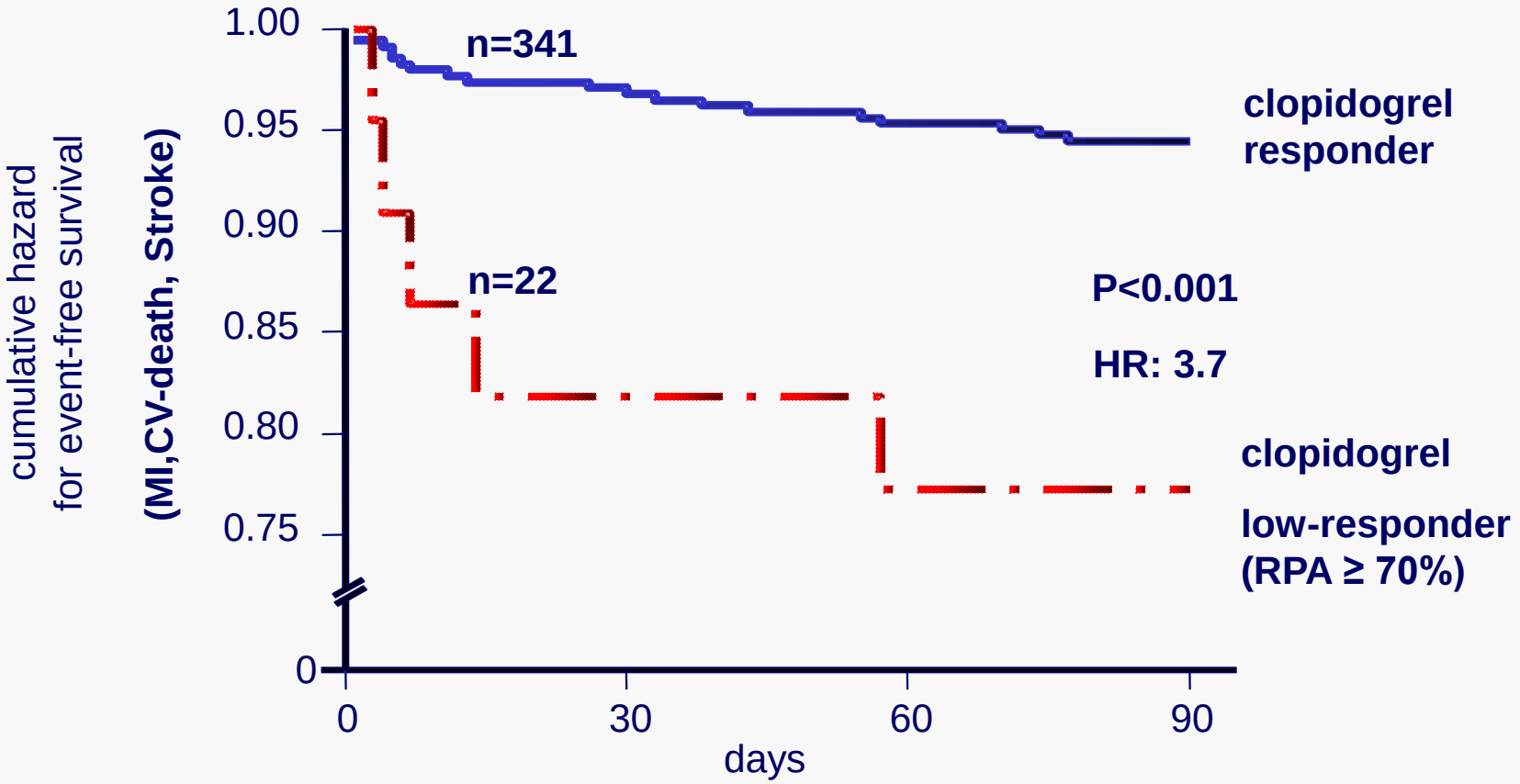


Figure 1: Distribution of platelet response to dual antiplatelet therapy. A) A scatter plot showing ADP- and collagen-induced post-treatment platelet aggregation in a study of 480 patients. IRPA, increased residual platelet aggregation. B) In the patient population, the residual platelet aggregation (RPA) shows a normal but wide-spread distribution. Adapted from Geisler et al. Heart 2008; 94: 743–747.

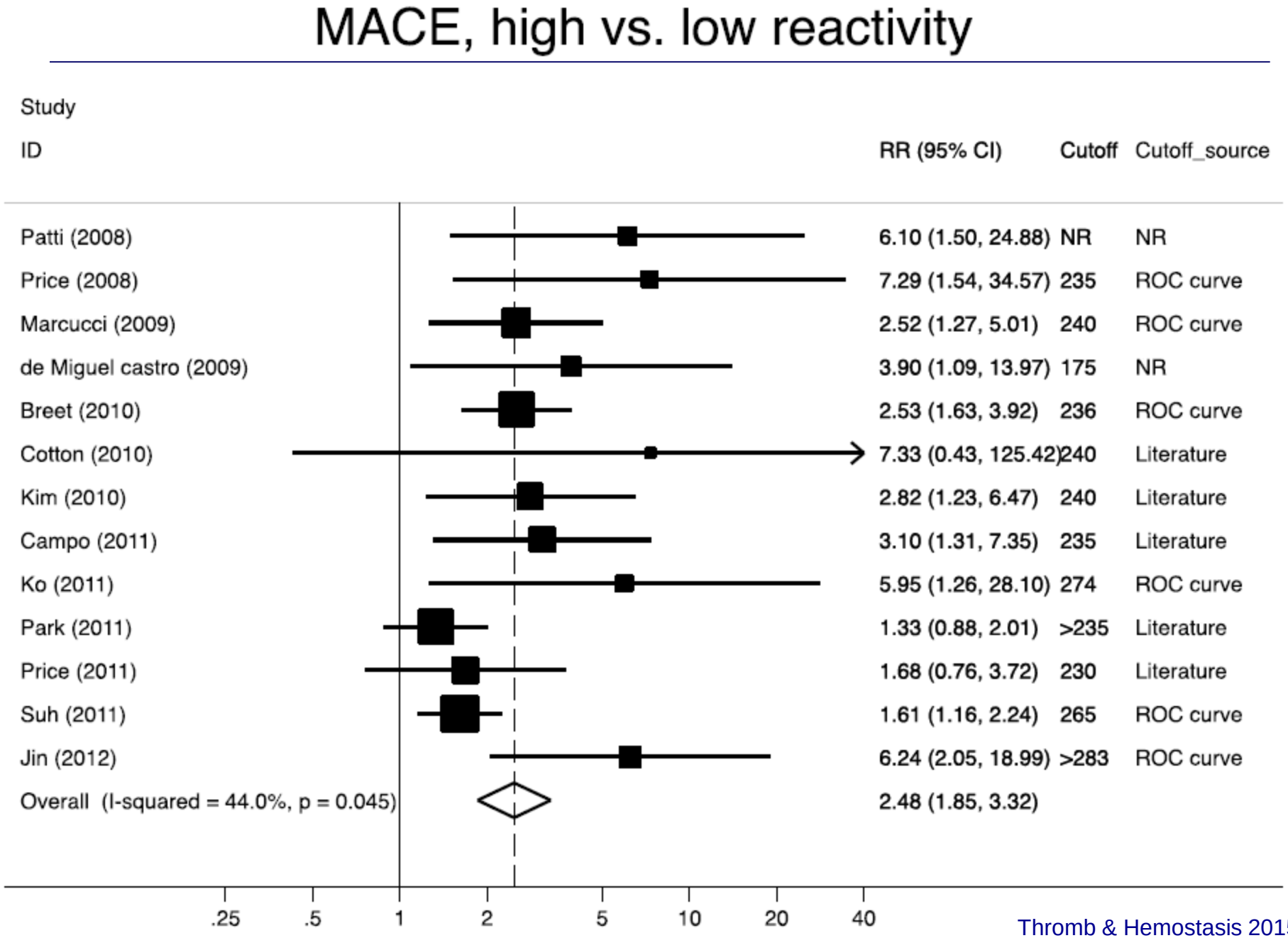
Geisler, Gawaz et al.; Heart 2008

Low response to Clopidogrel measured by residual platelet aggregation is associated with clinical prognosis



Geisler T. & Gawaz M. Eur Heart J 2006

Figure 25. Meta-analysis of major adverse cardiovascular events comparing patients with high versus low reactivity measured using the VerifyNow P2Y12 assay



RESEARCH ARTICLE

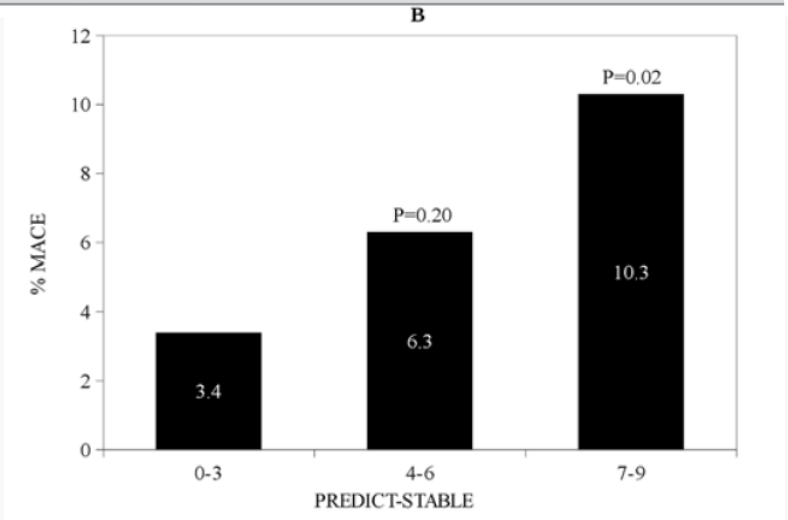
Evaluation of Clinical Risk Factors to Predict High On-Treatment Platelet Reactivity and Outcome in Patients with Stable Coronary Artery Disease (PREDICT-STABLE)

Michal Droppa[1], Dimitri Tschernow[1], Karin A. L. Müller[1], Elli Tavlaki[1], Athanasios Karathanos[1], Fabian Stimpfle[1], Elke Schaeffeler[2], Matthias Schwab[2,3], Alexander Tolios[4], Jolanta M. Siller-Matula[5], Meinrad Gawaz[1], Tobias Geisler[1]*

N=739

Table 3. Multivariate analysis of risk predictors for HPR.

Variables	Coefficient B	Odds ratio (95% CI)	P	PREDICT-STABLE
Age (> 63 years)	0.745	2.11 (1.26–3.53	0.005	3
Female gender	0.381	1.46 (0.93–2.31)	0.102	-
Diabetes mellitus	0.575	1.78 (1.19–2.65)	0.005	2
Adiposity (BMI>30)	0.622	1.86 (1.22–2.86)	0.004	2
Reduced left ventricular function EF<55	0.431	1.54 (1.03–2.31)	0.037	1
Reduced renal function (Serumcreatinin> 1.1 g/dL)	0.391	1.48 (0.97–2.25)	0.067	1



Droppa, Geisler et al., PlosOne 2015

Vascular risk levels affect predictive value of platelet reactivity for the occurrence of MACE in clopidogrel treatment

Systematic review and collaborative meta-analysis of individual patient data

Jean-Luc Reny[1,2]; Pierre Fontana[1,3]; Willibald Hochholzer[4]; Franz Josef Neumann[4]; Jurriën ten Berg[5]; Paul W. Janssen[5]; Tobias Geisler[6]; Meinrad Gawaz[6]; Rossella Marcucci[7]; Anna-Maria Gori[7]; Thomas Cuisset[8]; Marie-Christine Alessi[9]; Philippe Berdagué[10]; Paul A. Gurbel[11]; Gerald Yong[12]; Dominick J. Angiolillo[13]; Daniel Aradi[14]; Roy Beigel[15]; Gianluca Campo[16]; Christophe Combescure[17,18]

Study	Year of publication	Patients (n)	Age (years)	Male (%)	Diabetics (%)	Smokers (%)	Hypertension (%)	Hypercholesterolaemia (%)	ACS at inclusion (%)	PCI (%)	GpIIb/IIIa inhibitor (%)	Follow-up (months)*	ADP (µM)
Campo et al. (27)	2006	70	64±13	69	19	37	63	34	100	100	100	10 (15)	5, 20
Hochholzer et al. (28)	2006	765	66±9	78	24	11	82	92	0	100	0	12 (12)	5, 20
Angiolillo et al. (29)	2007	173	67±9	65	100	13	65	68	0	0	0	24 (36)	20
Cuisset et al. (30)	2007	190	65±12	76	33	48	58	53	87.4	100	14.7	1 (1)	10, 20
Geisler et al. (31)	2008	1,092	67±11	74	33	39	80	59	51.7	100	7.7	1 (1)	20
Gurbel et al. (32)	2008	297	65±12	65	41	55	74	82	0	100	42	24 (24)	5, 20
Cuisset et al. (33)	2009	598	65±12	78	35	39	56	55	100	100	9.9	1 (1)	10
Yong et al. (34)	2009												
Breet et al. (35)	2010												
Marcucci et al. (36)	2010												
Beigel et al. (37)	2011												
Aradi et al. (38)	2012												
Reny et al. (8)	2012												

Age, mean ± standard deviation; CAD, cor
telet reactivity. * Median (maximum).

Factors collected in studies	Adjusted HR [95 % CI]	p	Level of risk of MACE *	HR [95 % CI]	p
Current smoking status	0.92 [0.71;1.18]	0.50	*Low risk (n=579)*	1	
Age (> 75)	1.56 [1.25;1.95]	< 0.0001	*Intermediate risk (n=2444)*	1.61 [1.05;2.45]	0.03
Diabetes	1.58 [1.27;1.96]	< 0.0001	*High risk (n=3435)*	2.58 [1.69;3.94]	< 0.0001
Hypercholesterolaemia	0.86 [0.69;1.06]	0.15			
Hypertension	1.23 [0.98;1.54]	0.07			
ACS at inclusion	2.00 [1.27;3.16]	0.003			
Gender (Male)	1.11 [0.89;1.40]	0.35			

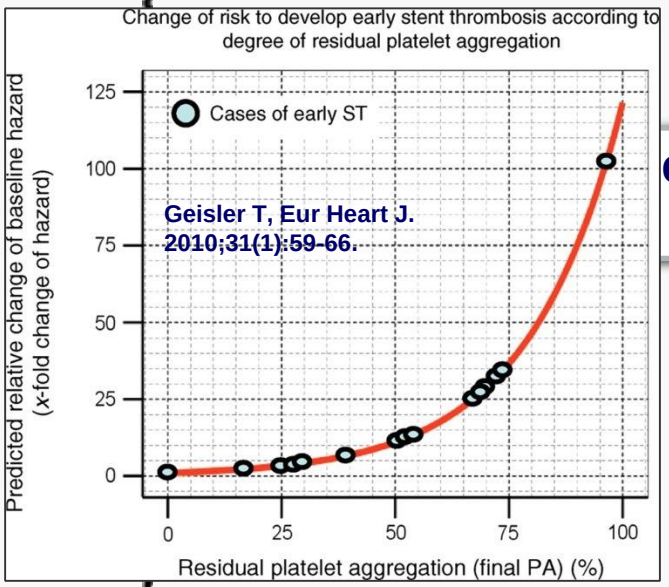
Reny et al., TH 2016

Beurteilung des Langzeitrisikos nach ACS?

Unterschiedliche Schwerpunkte antithrombozytärer Therapien im zeitlichen Verlauf

ACS Initialereignis

Akute Phase



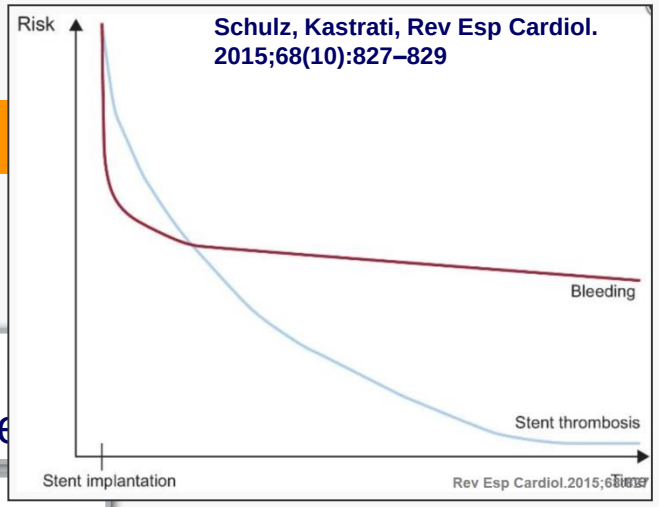
Langzeit Phase

Reduktion von Blutungen

Reduktion von stentbezogenen Ere

Inhibition der Thrombozyten abhängigen Inflammation

Niedrig dosierte Thrombin Inhibition



Zeit

REACH Registry [1]

Table 3. Four-Year Hazard Rates In Patients With a History at Enrollment of Prior Ischemic Events, Stable Atherosclerosis Without Prior Ischemic Events, or Risk Factors for Atherosclerosis Without Established Disease[a]

	Hazard Rate, % (95% CI)	
	Prior Ischemic Event at Baseline	
Event	Single Vascular Disease (n = 16 732)	Polyvascular Disease (n = 5158)
All-cause mortality	12.05 (11.23-12.86)	17.65 (16.26-19.00)
CV death	7.57 (6.89-8.24)	12.69 (11.42-13.94)
Nonfatal MI	4.13 (3.62-4.64)	6.01 (5.07-6.94)
Nonfatal stroke	5.92 (5.32-6.52)	10.74 (9.49-11.97)
CV hospitalization	20.70 (19.71-21.67)	35.48 (33.66-37.25)
CV death, MI, and stroke	15.72 (14.80-16.63)	25.02 (23.35-26.65)
CV death, MI, stroke, and CV hospitalization	29.89 (28.79-30.97)	47.14 (45.35-48.88)

Abbreviations: CI, confidence interval; CV, cardiovascular; MI, myocardial infarction.
[a] Ischemic events were defined as myocardial infarction or stroke.

[1] Bhatt et al. JAMA 2010; 304 (12):1350-1357

Einfluss der Atherothrombose auf weitere kardiovaskuläre Ereignisse

	Erhöhtes Risiko vs. Allgemeinbevölkerung (%)	
Erstereignis	**Myokardinfarkt**	**Schlaganfall**
Myokardinfarkt	**5–7 x größeres Risiko**	**3–4 x größeres Risiko**
Schlaganfall	**2–3 x größeres Risiko**	**9 x größeres Risiko**
pAVK	**4 x größeres Risiko**	**2–3 x größeres Risiko**

* innerhalb einer Stunde dokumentierter, auf eine KHK zurückzuführender Tod; † ausschließlich nicht-tödlicher MI

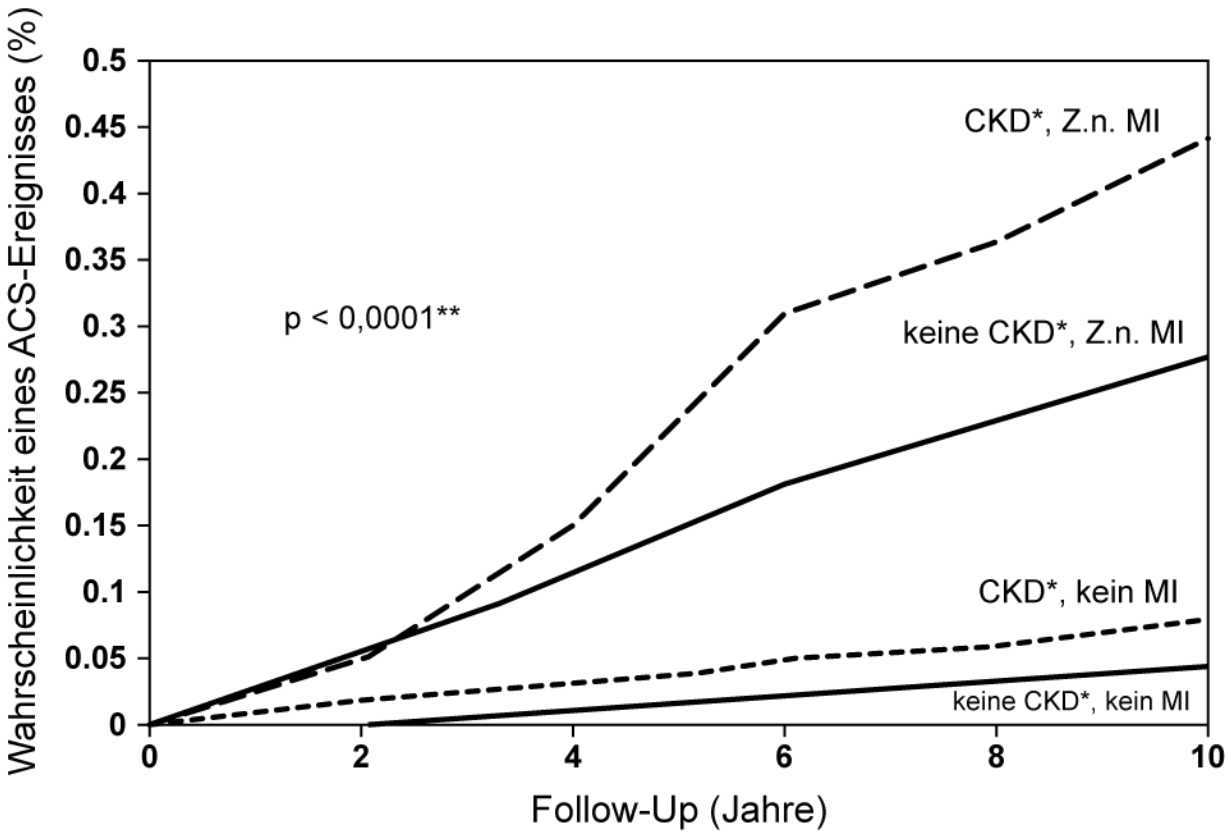
Patienten mit einer atherothrombotischen Erkrankung in einem Gefäßbett haben ein erhöhtes Risiko für kardiovaskuläre Folgeereignisse, die jedoch auch andere Gefäßbetten betreffen können.

TIA: Transitorische ischämische Attacke; MI: Myokardinfarkt; KHK: koronare Herzkrankheit

1. Adult Treatment Panel II. Circulation 1994; 89: 1333–1363; 2. Kannel WB. J Cardiovasc Risk 1994; 1: 333–339; 3. Criqui MH et al. N Engl J Med 1992; 326: 381–386; 4. Wilterdink JI et al. Arch Neurol 1992; 49: 857–863

Chronische NI erhöht kardiovaskuläres Risiko

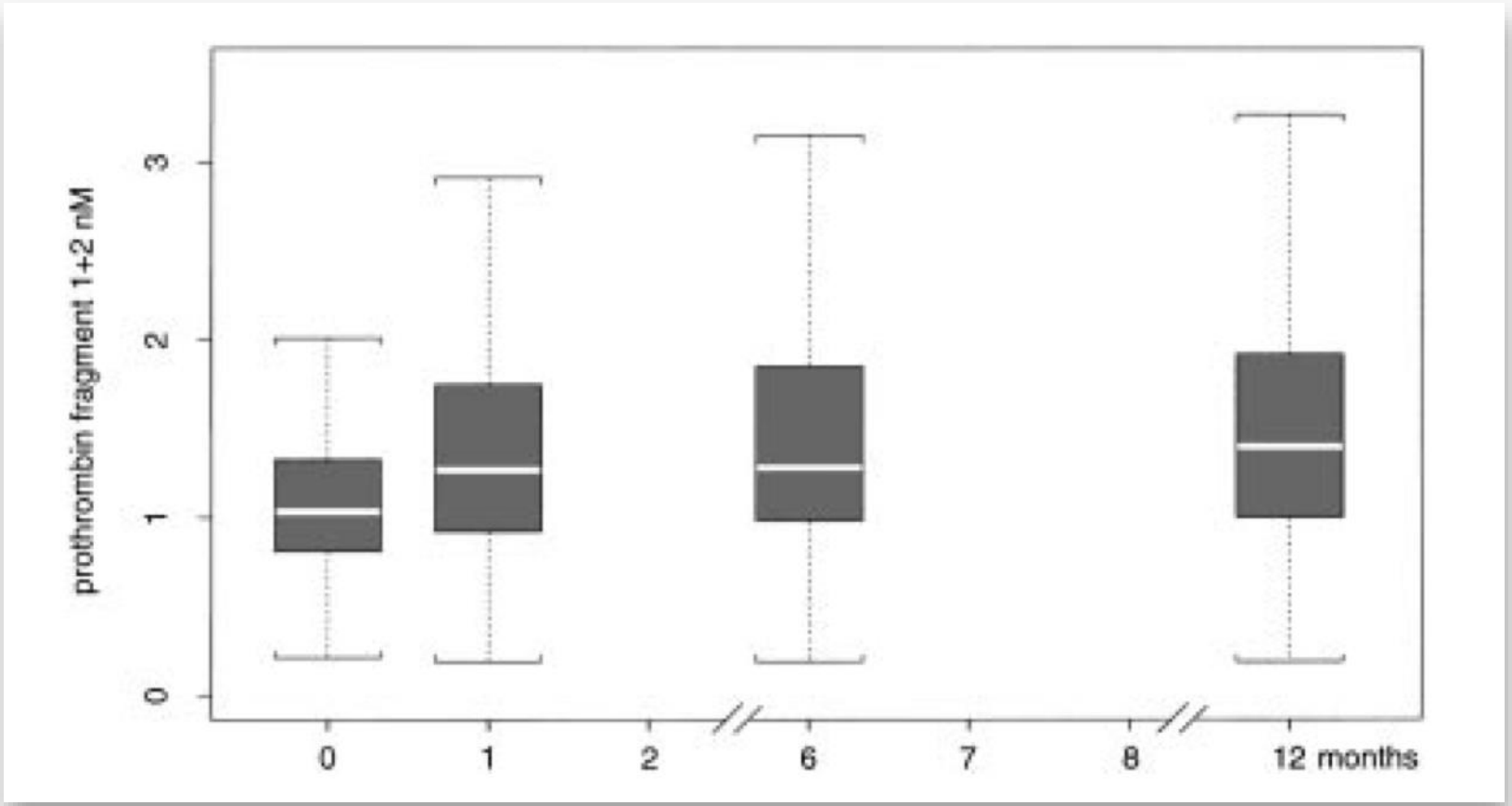
- Daten von über 12.000 Nicht-Diabetikern der ARIC-Studie
- Kategorisierung der Teilnehmer nach
  - Nierenfunktion (eGFR ≥ 60 ml/min vs. 30-59 ml/min)
  - Z.n. Myokardinfarkt (Ja oder Nein)
- Follow-Up: 10 Jahre



Eine chronische Niereninsuffizienz alleine erhöht das ACS-Risiko im Gegensatz zum Z.n. Myokardinfarkt kaum. Tritt die CKD allerdings als Komorbidität zum Z.n. Myokardinfarkt auf, steigt das Risiko für weitere akute Koronarereignisse erheblich.

*Grad 3; **keine CKD*, Z.n. MI vs. CKD*, kein MI
CKD: Chronic Kidney Disease; ARIC: Atherosclerosis Risk In Communities; eGFR: geschätzte glomeruläre Filtrationsrate; MI: Myokardinfarkt; ACS: Akutes Koronarsyndrom
Mod. nach Wattanakit K et al. J Am Coll Cardiol 2008;48(6):1183-1189

Persistierende Gerinnungsaktivierung / gesteigerte Thrombin Generierung in der Langzeitphase nach ACS



Ardissino D, Blood 2003

Was sagen die Leitlinien zur verlängerten Thrombozytenfunktionshemmung nach ACS?

Recommendations for platelet inhibition

Oral antiplatelet therapy	Class	Level
A $P2Y_{12}$ inhibitor is recommended, in addition to aspirin, for 12 months unless there are contraindications such as excessive risk of bleeds.	*I*	***A***
• Ticagrelor (180 mg loading dose, 90 mg twice daily) is recommended, in the absence of contraindications,[e] for all patients at moderate-to-high risk of ischemic events (e.g. elevated cardiac troponins), regardless of initial treatment strategy and including those pretreated with clopidogrel (which should be discontinued when ticagrelor is started).	*I*	*B*
• Prasugrel (60 mg loading dose, 10 mg daily dose) is recommended in patients who are proceeding to PCI if no contraindication.[e]	*I*	*B*
• Clopidogrel (600 mg loading dose, 75 mg daily dose) is recommended for patients who cannot receive ticagrelor or prasugrel or who require oral anticoagulation.	*I*	*B*
$P2Y_{12}$ inhibitor administration for a shorter duration of 3–6 months after DES implantation may be considered in patients deemed at high bleeding risk	*IIb*	*A*
It is not recommended to administer prasugrel in patients in whom coronary anatomy is not known.	*III*	*B*
Long-term $P2Y_{12}$ inhibition		
$P2Y_{12}$ inhibitor administration in addition to aspirin beyond 1 year may be considered after careful assessment of the ischemic and bleeding risks of the patient.	*IIb*	*A*

Roffi M, ESC Guidelines
Roffi M et al., Eur Heart J, August 2015, doi:10.1093/eurheartj/ehv320,
http://eurheartj.oxfordjournals.org/content/ehj/33/20/2569.full.pdf

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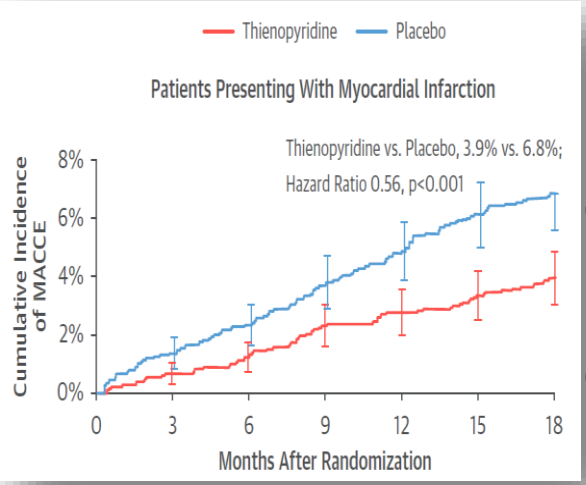
UNIVERSITÄT
TÜBINGEN

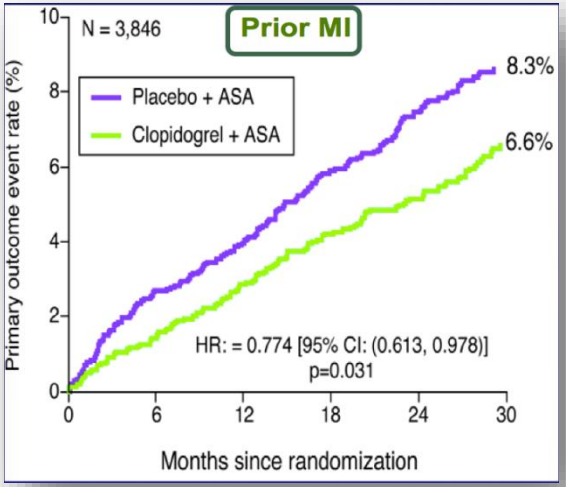
Hinweise aus RCTs für eine Vorteil einer prolongierten antithrombotischen TX bei ausgewählten Patienten nach ACS

DAPT



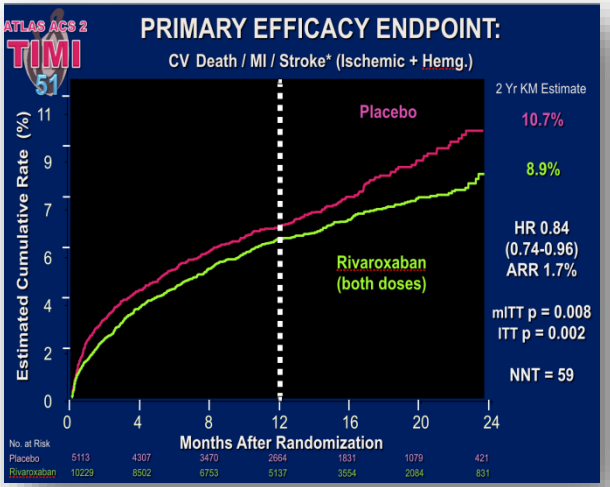
Yeh et al,JACC 2015

CHARISMA



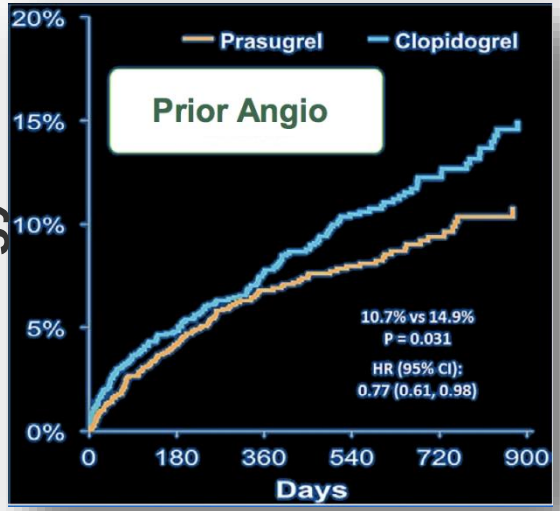
Bhatt DL et al, JACC 2007

ATLAS-TIMI 51



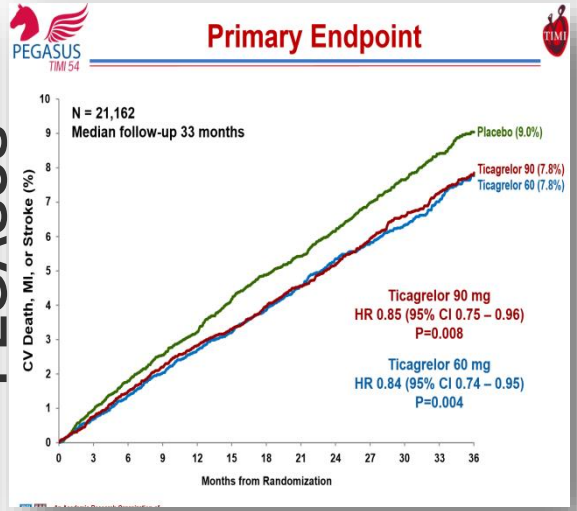
Mega JL, NEJM 2012

Trilogy



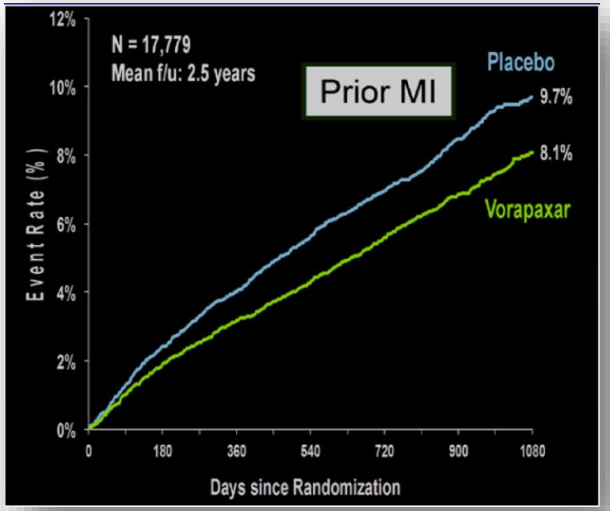
Wiviott SR et al, Lancet 2013

PEGASUS



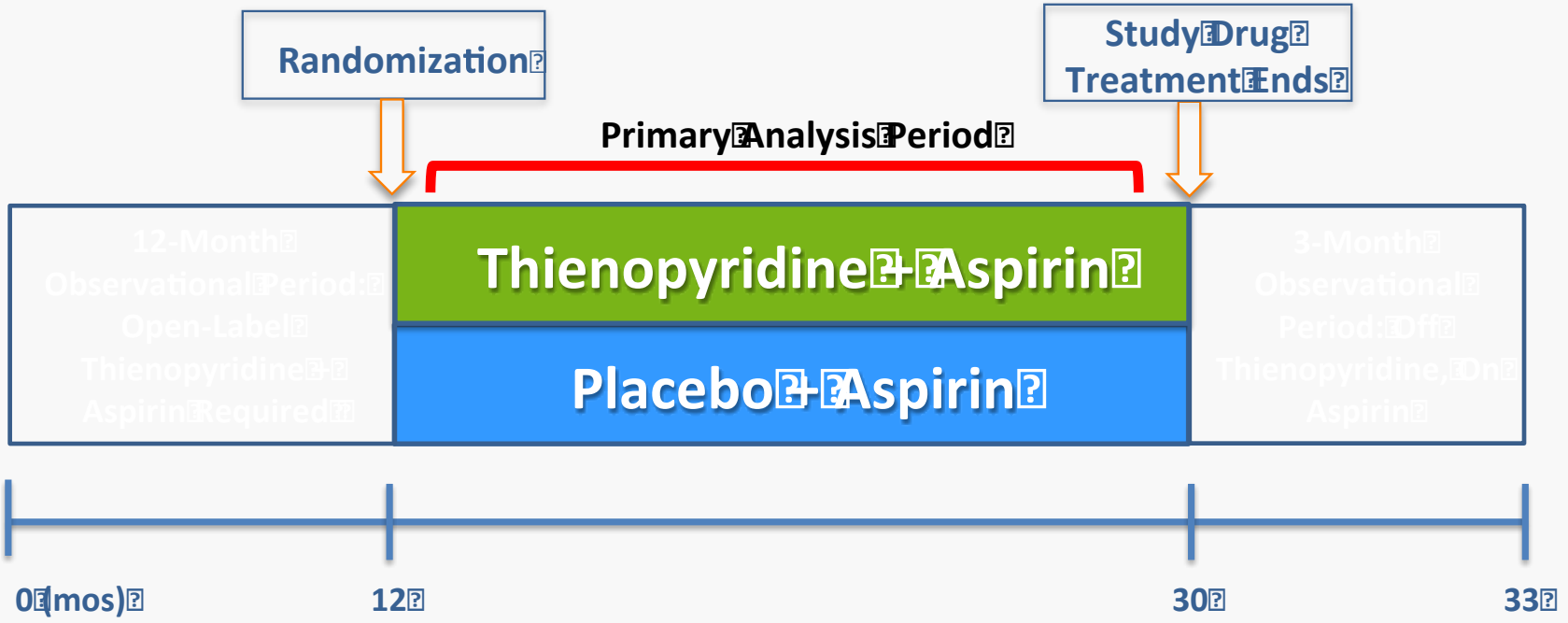
Bonaca MP et al, NEJM 2015

TRA 2P



Scirica B et al, Lancet 2013

DAPT Study - Design



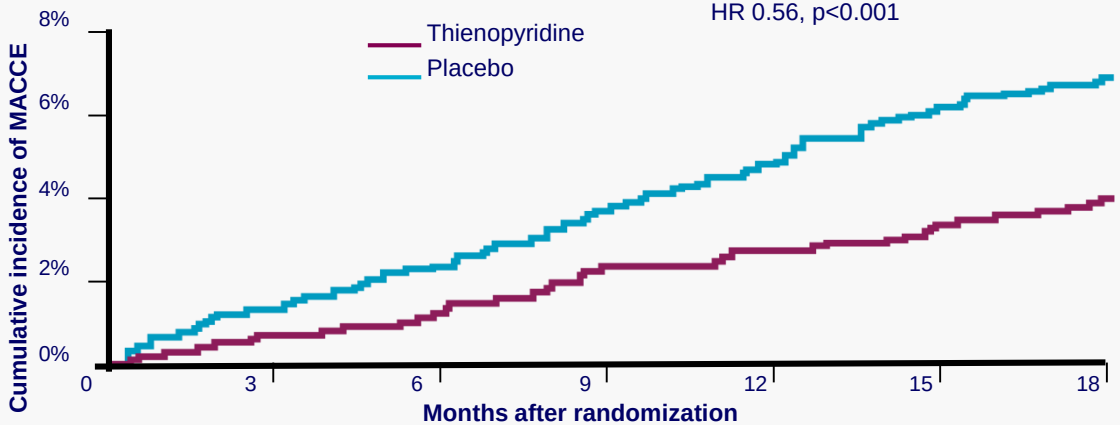
Mauri, Kereiakes et al. AHJ. 2010;160(6): 1035-41.

DAPT– Subanalysis for history of MI

Results – MACCE

Patients presenting with myocardial infarction

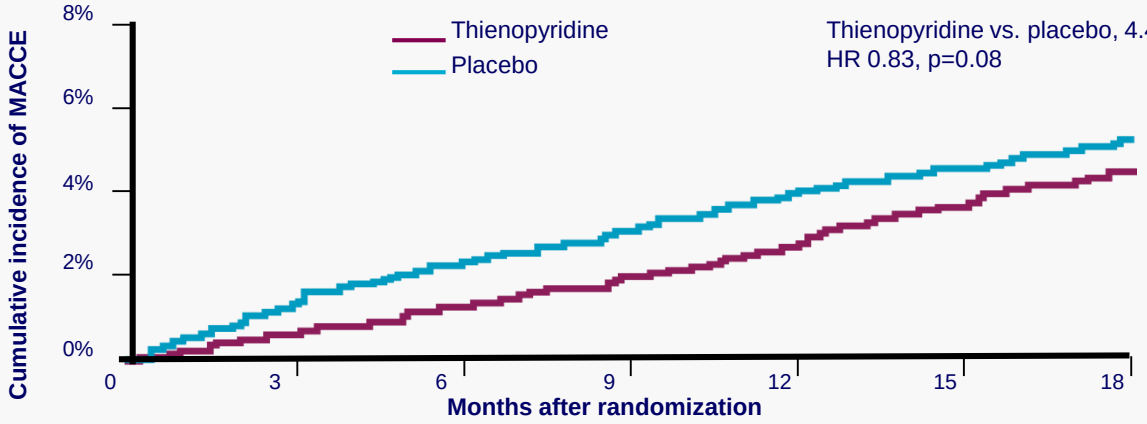
Thienopyridine vs. placebo, 3.9% vs. 6.8%;
HR 0.56, p<0.001



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, J Am Coll Cardiol. 2015;65(20):2211-21.

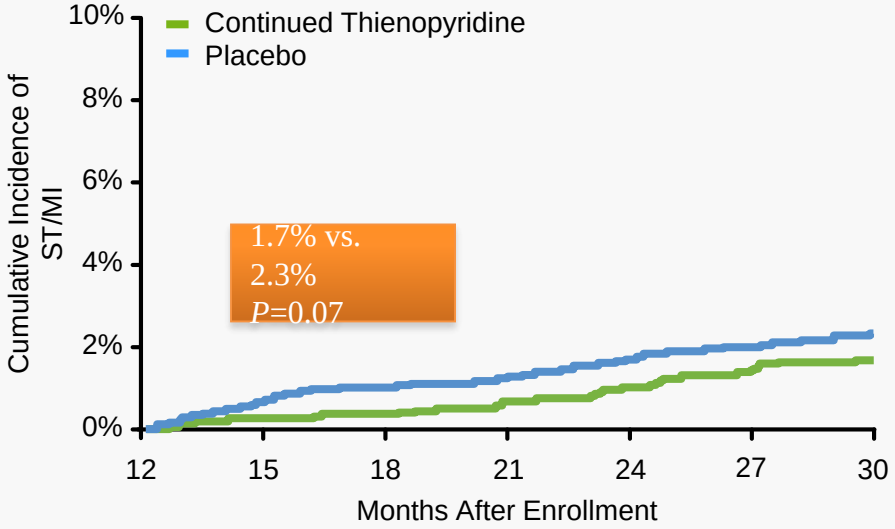
Predictors of Combined Treatment Effect

Characteristics	Impact on Combined Treatment Effect	% of Variation Explained	DAPT Score
Age ≥ 75	-1.2%	6.0%	**-2**
Age 65 - < 75	-0.5%	2.2%	**-1**
Age < 65 (reference)	-	-	**0**
Prior PCI or MI	1.1%	14.6%	**1**
Stent Diameter < 3 mm	0.9%	10.1%	**1**
CHF or LVEF < 30%	1.9%	9.9%	**2**
MI at Presentation	1.0%	9.6%	**1**
Paclitaxel-Eluting Stent	1.0%	8.8%	**1**
Cigarette Smoker	0.7%	4.3%	**1**
Diabetes	0.6%	4.3%	**1**
Vein Graft PCI	1.6%	3.7%	**2**
Hypertension	0.2%	0.4%	
Renal Insufficiency	0.4%	0.3%	
PAD	-0.1%	0.04%	

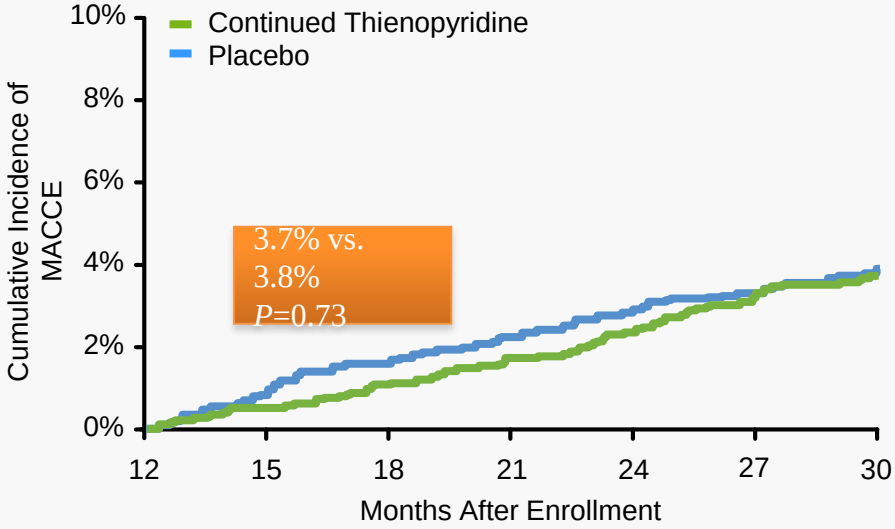
Yeh et al. JAMA 2016

Continued Thienopyridine vs. Placebo DAPT Score <2 (Low); N=5731

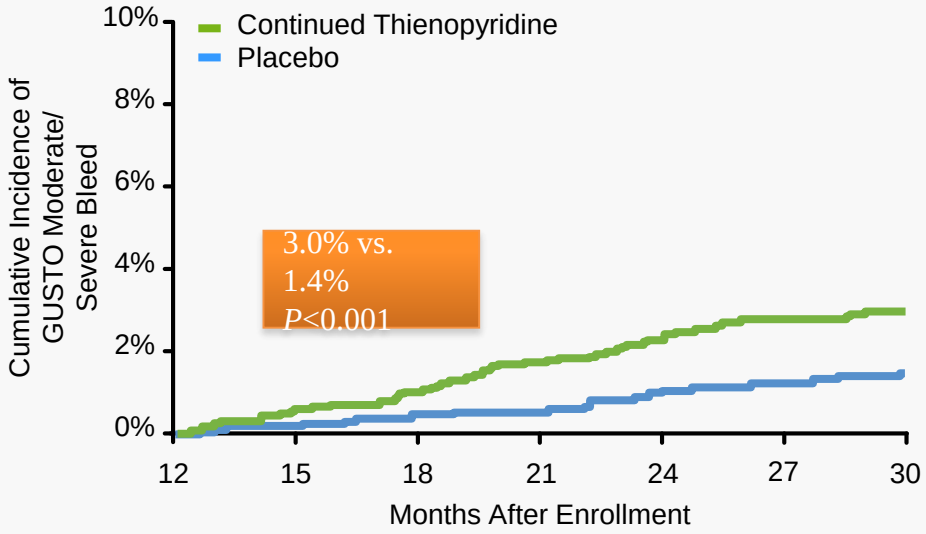
Stent Thrombosis or MI



MACCE



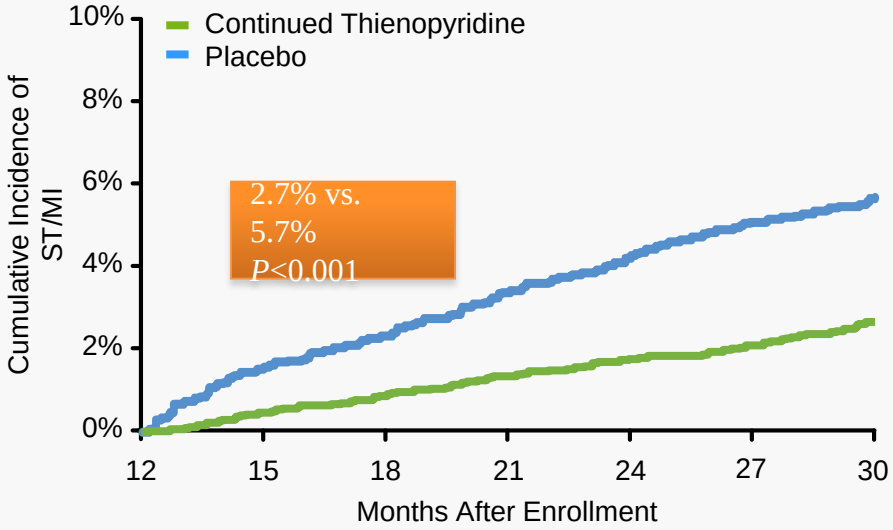
GUSTO Moderate/ Severe Bleeding



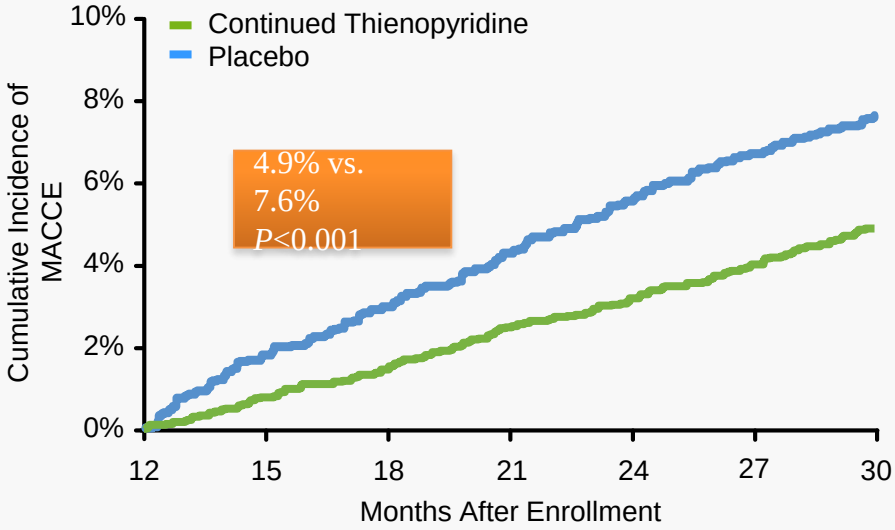
Yeh et al. JAMA 2016

Continued Thienopyridine vs. Placebo DAPT Score ≥ 2 (High); N=5917

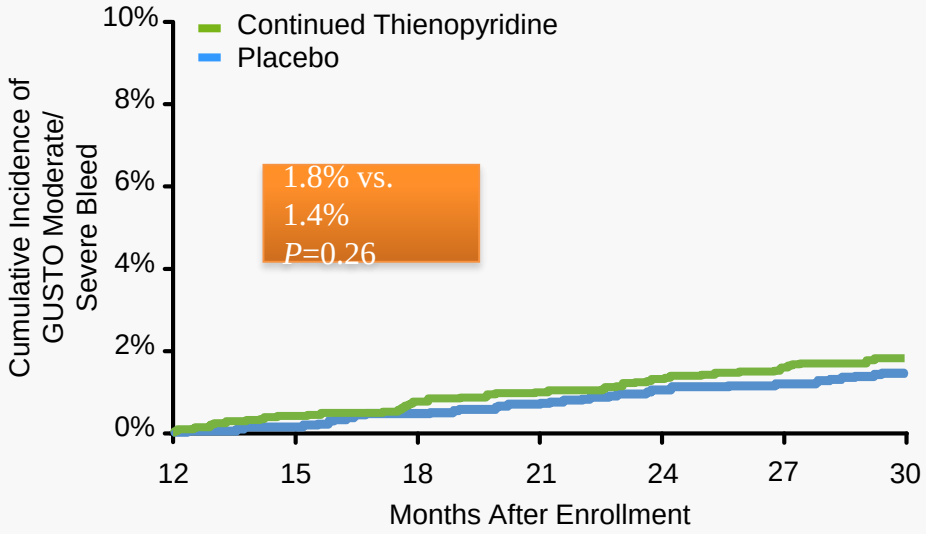
Stent Thrombosis or MI



MACCE

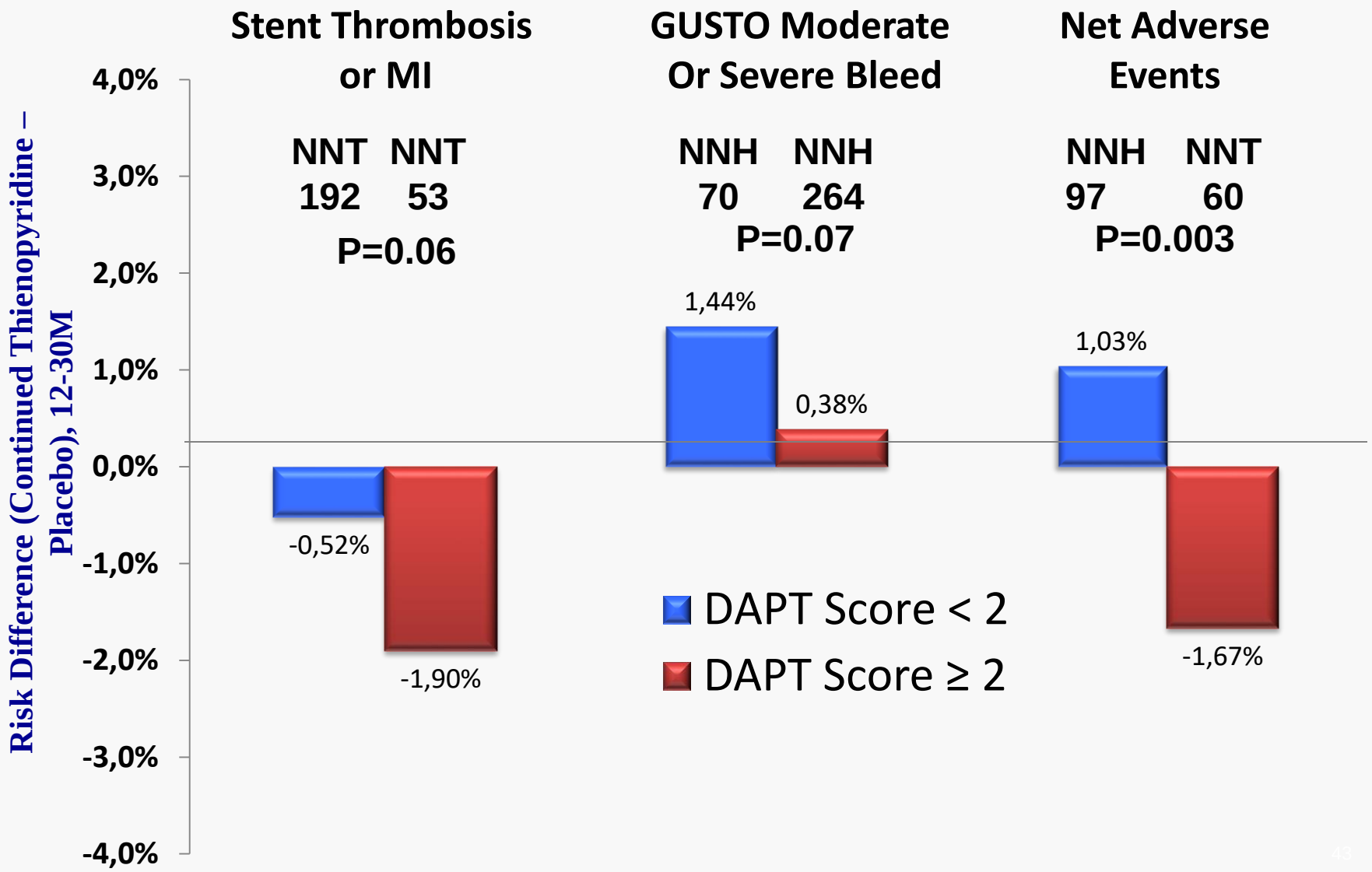


GUSTO Moderate/ Severe Bleeding



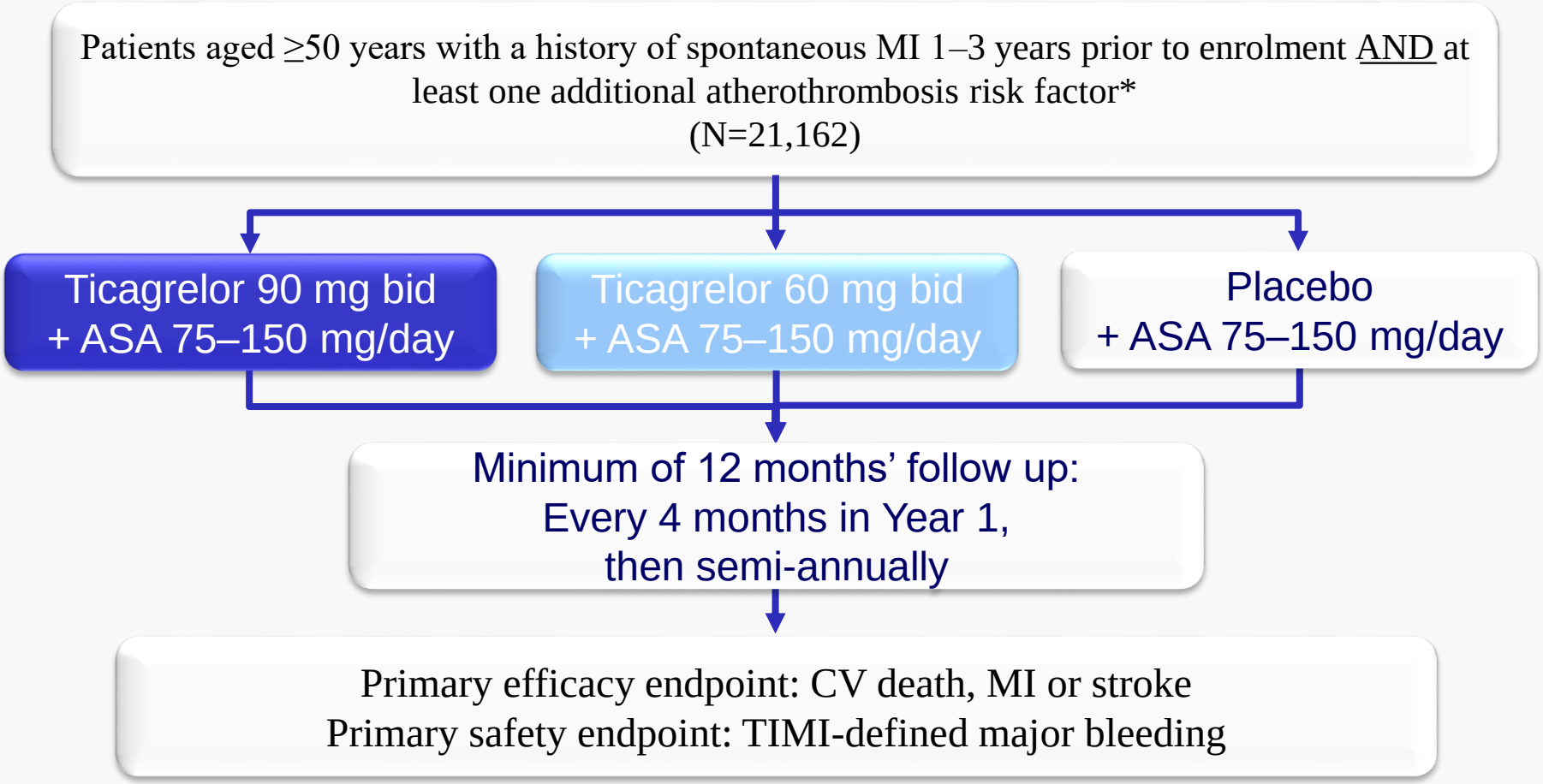
Yeh et al. JAMA 2016

Continued Thienopyridine vs. Placebo, by DAPT Score, Excluding Paclitaxel-Eluting Stent



Yeh et al. JAMA 2016

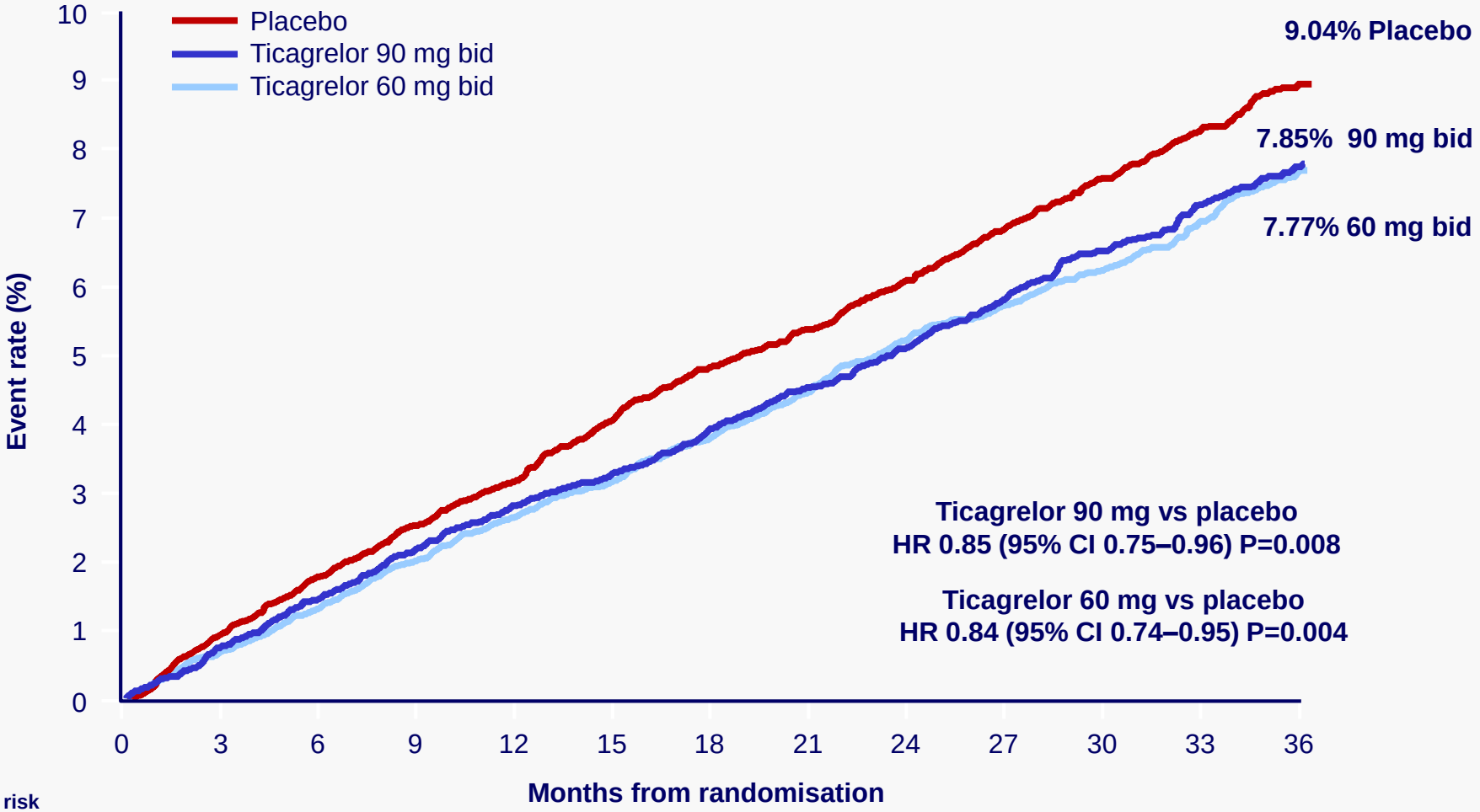
PEGASUS-TIMI 54: Study Design



*Age ≥65 years, diabetes mellitus, second prior MI, multivessel CAD or chronic non-end stage renal disease
bid, twice daily; CAD, coronary artery disease; TIMI, Thrombolysis in Myocardial Infarction

Bonaca MP *et al. Am Heart J* 2014;167:437–444
Bonaca MP *et al. N Engl J Med* 2015 [Epub ahead of print]

PEGASUS-TIMI 54: Primary Endpoint

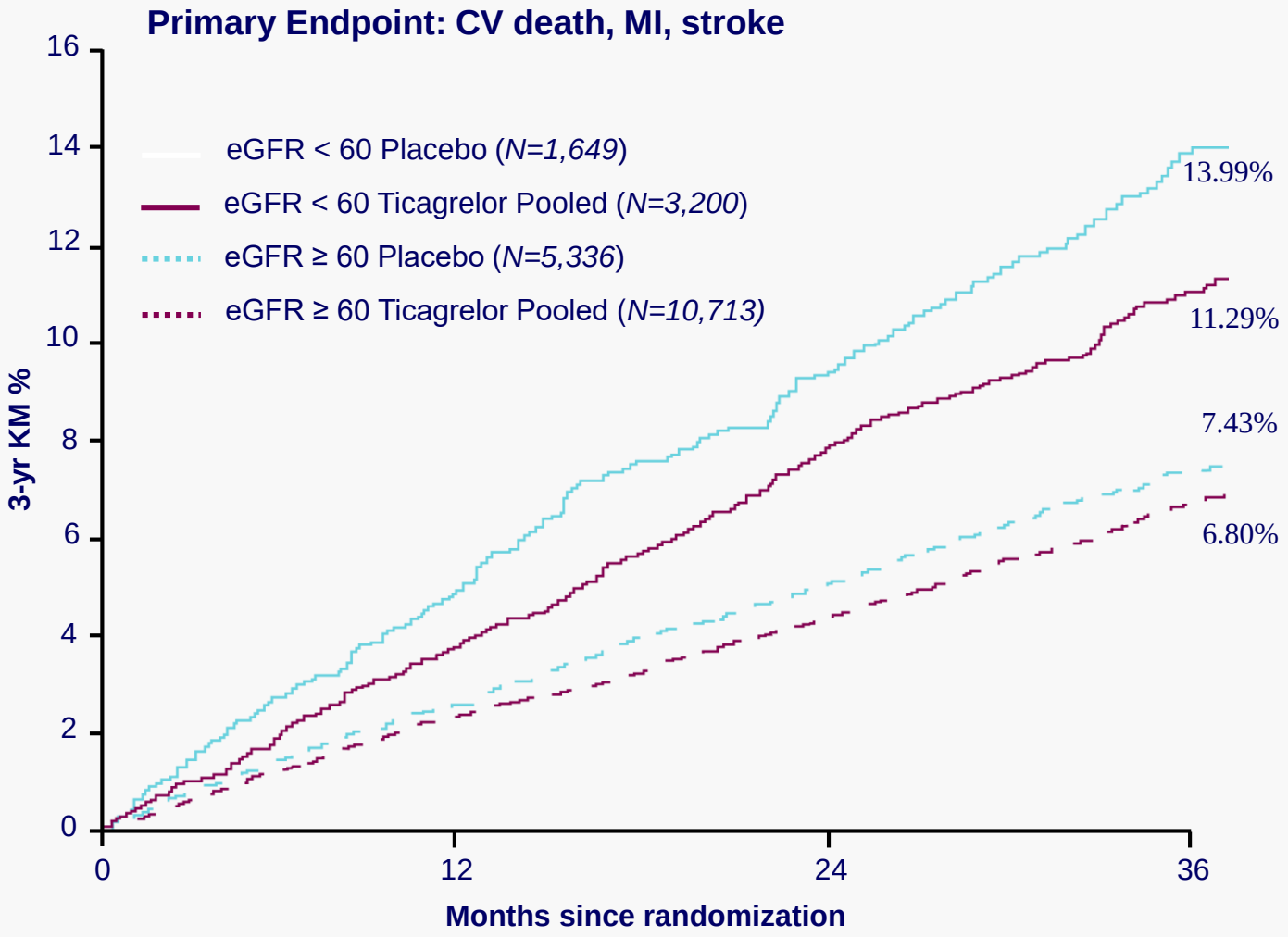


No. at risk													
Placebo	7067	6979	6892	6823	6761	6681	6508	6236	5876	5157	4343	3360	2028
90 mg bid	7050	6973	6899	6827	6769	6719	6550	6272	5921	5243	4401	3368	2038
60 mg bid	7045	6969	6905	6842	6784	6733	6557	6270	5904	5222	4424	3392	2055

CI, confidence interval; HR, hazard ratio

Bonaca MP *et al*. *N Engl J Med* 2015 [Epub ahead of print]

PEGASUS renal function: results by therapy

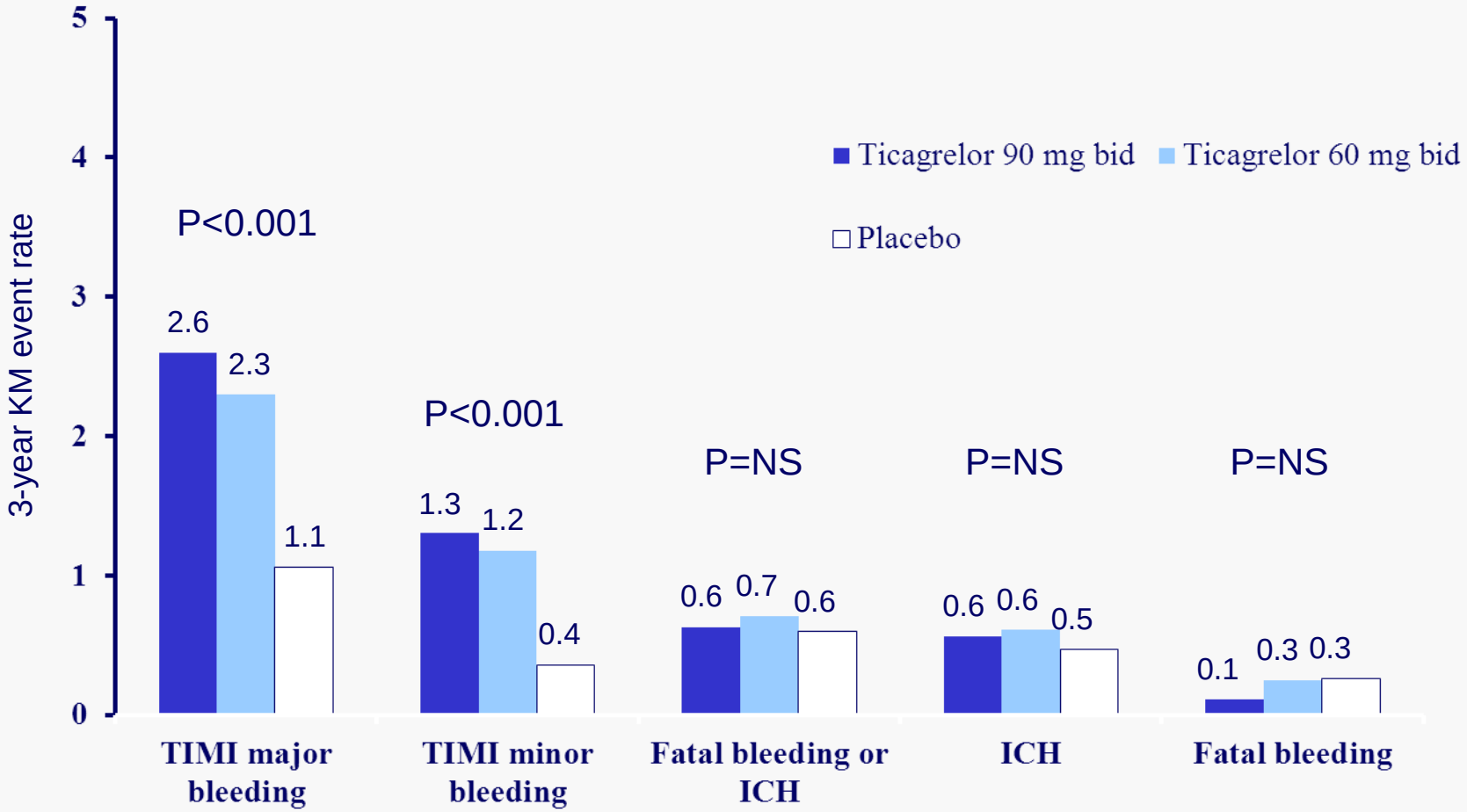


HR 95% CI
0.81 (0.68-0.96)
ARR = 2.70%

HR 95% CI
0.88 (0.77-1.00)
ARR = 0.63%

Magnani G, Antithrombotic Drugs – an ongoing story, 3032

PEGASUS-TIMI 54: Bleeding



Rates are presented as 3-year Kaplan-Meier estimates
P<0.026 indicates statistical significance

Bonaca MP *et al*. *N Engl J Med* 2015 [Epub ahead of print]

ESC Guideline NSTE-ACS

Recommendations for platelet inhibition

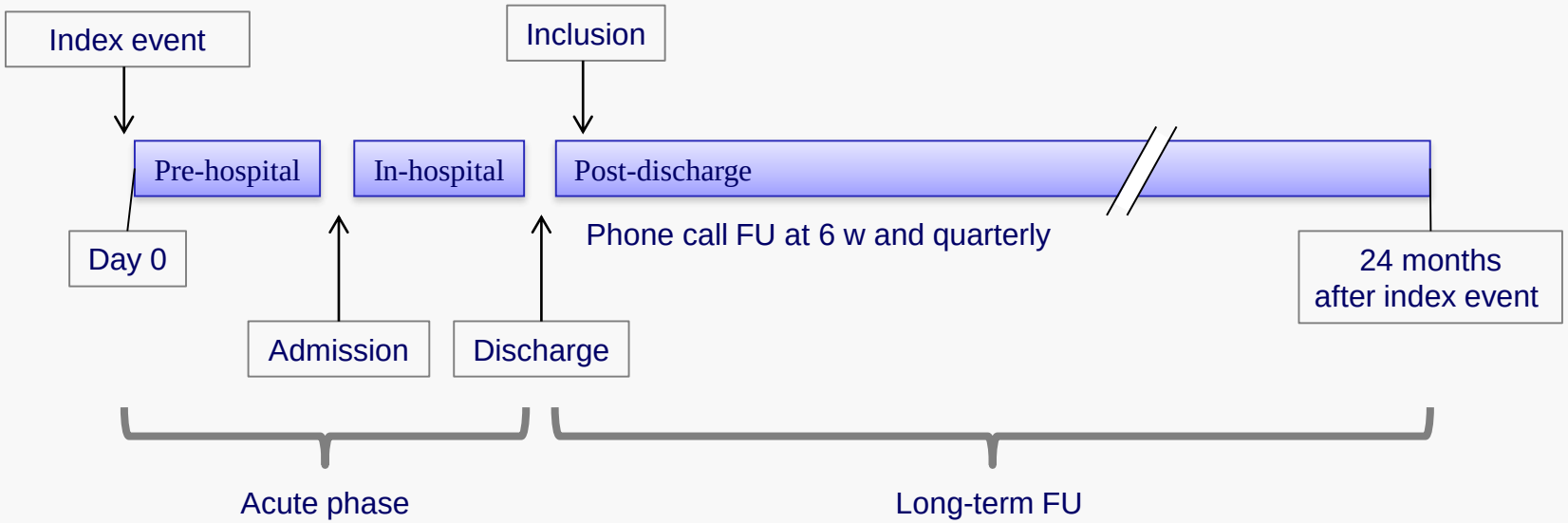
Oral antiplatelet therapy	Class	Level
A $P2Y_{12}$ inhibitor is recommended, in addition to aspirin, for 12 months unless there are contraindications such as excessive risk of bleeds.	I	A
• Ticagrelor (180 mg loading dose, 90 mg twice daily) is recommended, in the absence of contraindications,[e] for all patients at moderate-to-high risk of ischemic events (e.g. elevated cardiac troponins), regardless of initial treatment strategy and including those pretreated with clopidogrel (which should be discontinued when ticagrelor is started).	I	B
• Prasugrel (60 mg loading dose, 10 mg daily dose) is recommended in patients who are proceeding to PCI if no contraindication.[e]	I	B
• Clopidogrel (600 mg loading dose, 75 mg daily dose) is recommended for patients who cannot receive ticagrelor or prasugrel or who require oral anticoagulation.	I	B
$P2Y_{12}$ inhibitor administration for a shorter duration of 3–6 months after DES implantation may be considered in patients deemed at high bleeding risk	IIb	A
It is not recommended to administer prasugrel in patients in whom coronary anatomy is not known.	III	B
Long-term $P2Y_{12}$ inhibition		
$P2Y_{12}$ inhibitor administration in addition to aspirin beyond 1 year may be considered after careful assessment of the ischemic and bleeding risks of the patient.	IIb	A

Roffi M, ESC Guidelines
Roffi M et al., Eur Heart J, August 2015, doi:10.1093/eurheartj/ehv320,
http://eurheartj.oxfordjournals.org/content/ehj/33/20/2569.full.pdf

EPICOR

Background

Aim: to describe current international patterns of the use of DAPT after discharge in patients surviving hospitalization for ACS using data from the EPICOR study



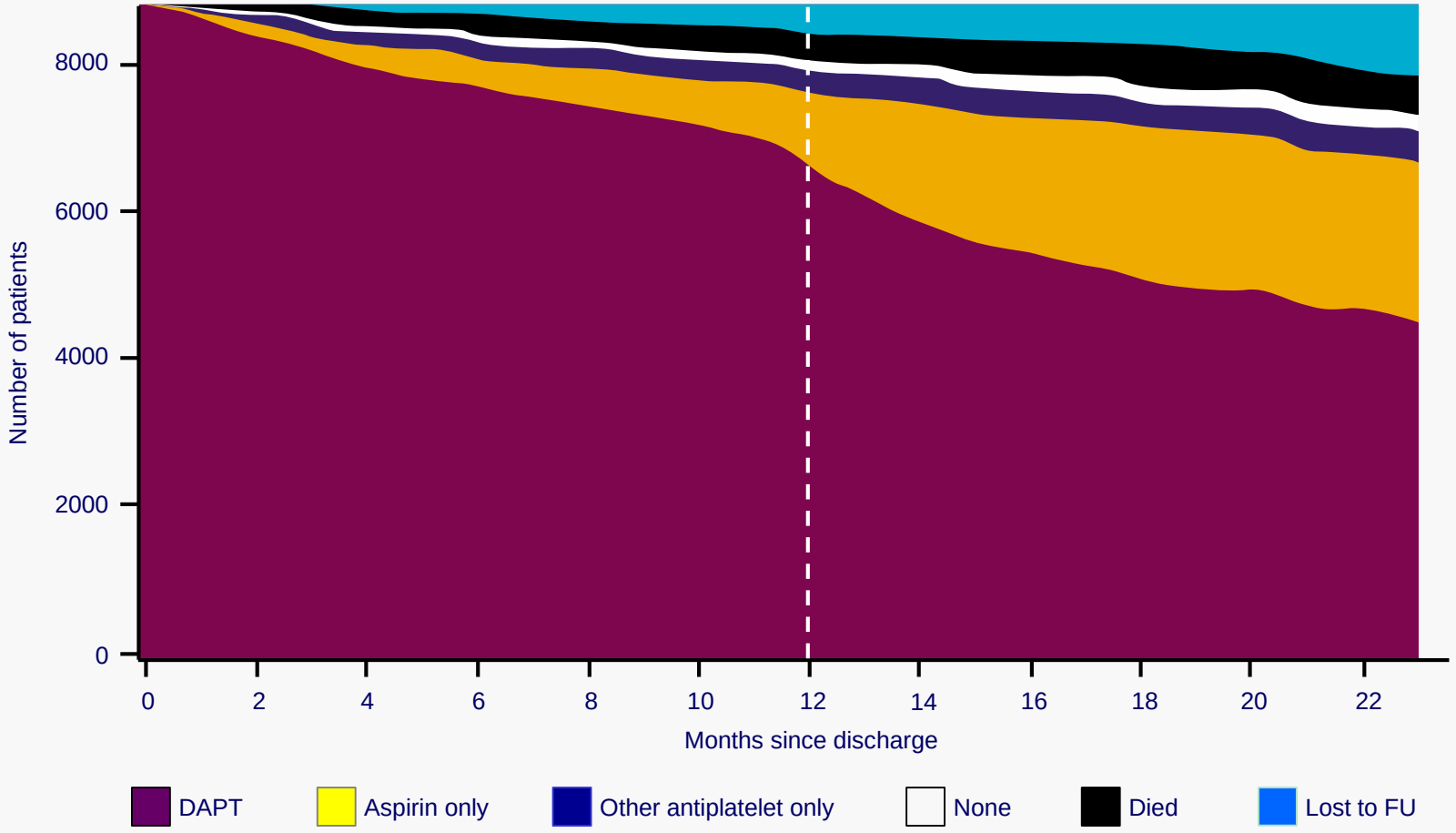
- Basline data
- Short-term medical management from symptoms onset: antithrombotics (dose + timing), invasive procedure
- Early clinical outcomes
- Economic evalutation

- Long-term medical management
- Post-discharge clinical outcomes
- QoL-assessment
- Persistence on antithrombotic treatment: planned + unplanned interruptions
- Economic evaluation

Bueno H et al., AHA 2014
Modified after: Bueno H et al., Am Heart J 2013;165:8-14

EPICOR

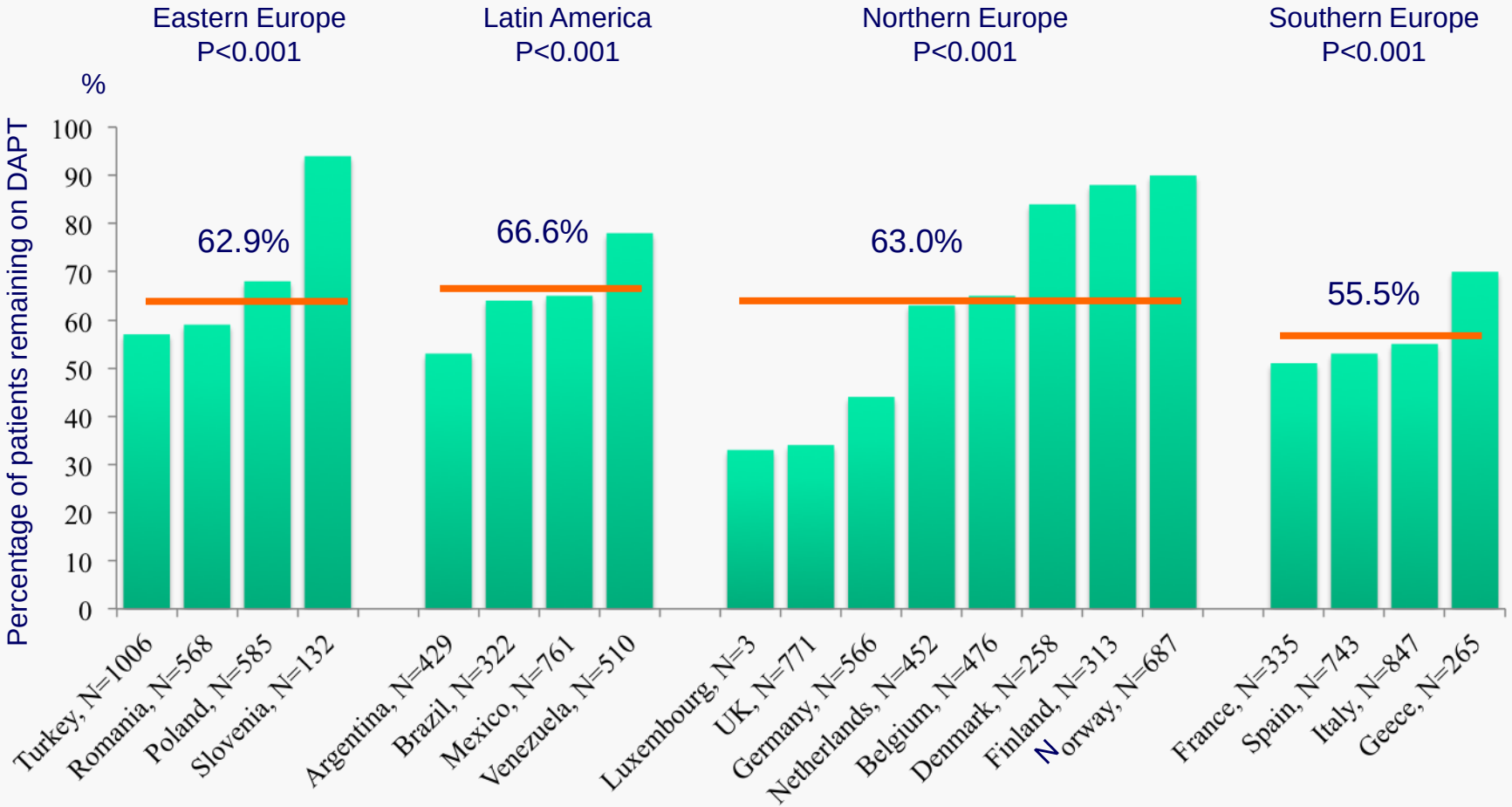
Results – changes in DAPT over time in patients discharged on DAPT



Bueno H et al., AHA 2014

EPICOR

Results – persistence on DAPT at the end of FU by country in patients discharged on DAPT



Bueno H et al., AHA 2014

Secondary prophylaxis after MI - individualized therapeutic concept

Balancing ischaemic versus bleeding risk:

bleeding risk ↑ ?

ischemic risk ↓ ?

platelet
adjustment of DAPT, Therapeutic Window?

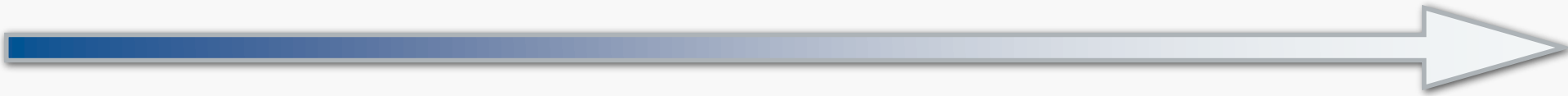
individual patient selection

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

ease in multiple
eart failure

Clinically / Genetic Risk Factors (Scores)

Biomarkers (hsTNT, hsCRP, other?)



1month **12 months** **indefinite??**

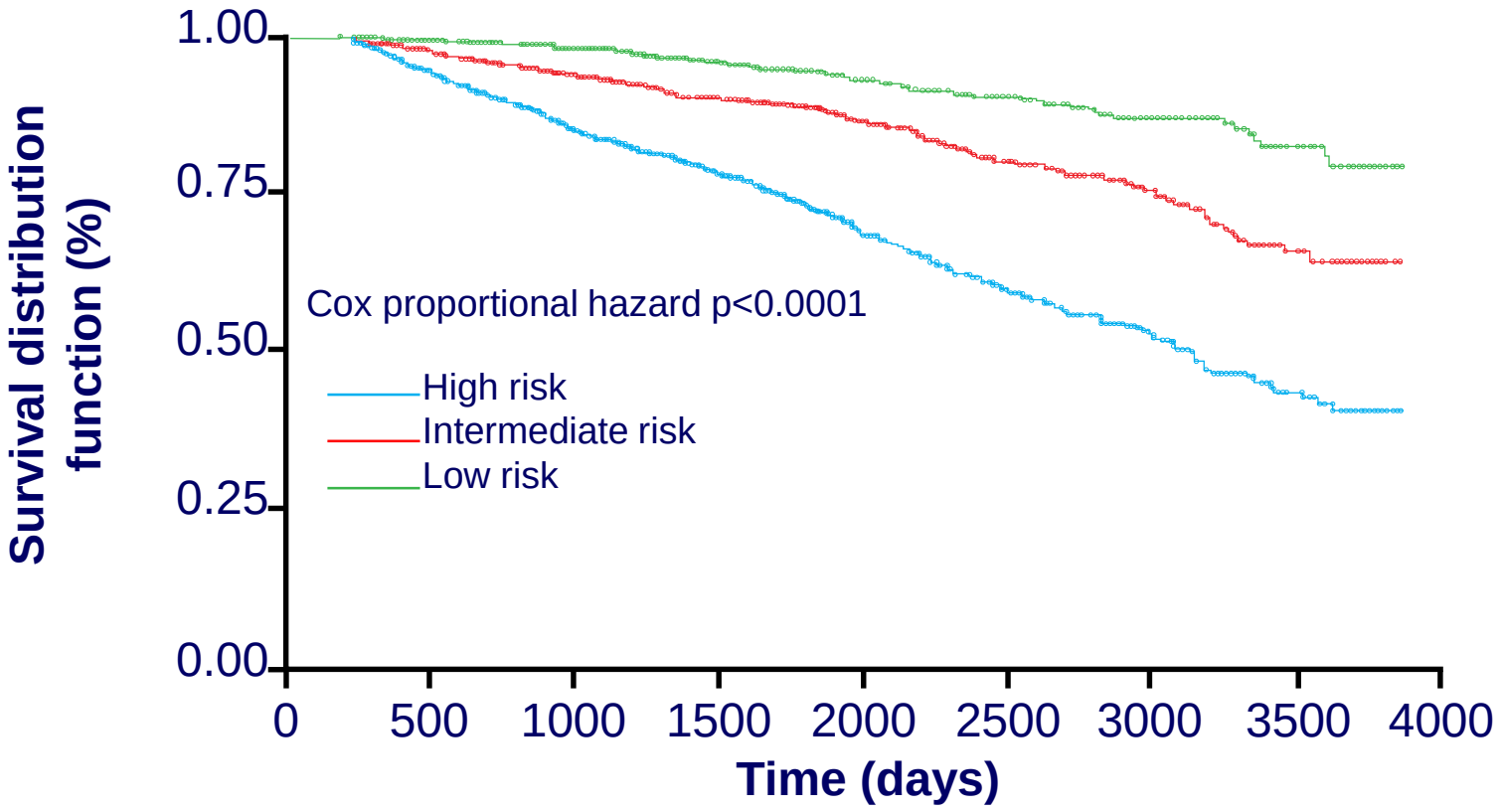
Verlängerte antithrombozytäre Therapie nach ACS: welcher Patient profitiert?

Meinrad Gawaz
Innere Medizin III, Kardiologie und Kreislauferkrankungen
Eberhard Karls Universität Tübingen

7. Thromboseforum, Stuttgart 2017

Risikoscores: GRACE UK–Belgian Study: Mortality in patients with prior MI

Analysis of UK and Belgian patients with ACS enrolled in the GRACE study



A residual risk of mortality is observed in ACS patients post-6-month survival

ACS, acute coronary syndromes; GRACE, Global Registry of Acute Coronary Events; MI, myocardial infarction.

Fox KA, et al. *Eur Heart J* 2010;31:2755–2764.