Evolving Paradigm of Antiplatelet Therapy Following PCI or ACS

Usman Baber, MD MS
Associate Professor of Medicine (Cardiology)
Director, Cardiac Catheterization Laboratory
University of Oklahoma Health Sciences Center

Disclosures

Speakers' Bureau:

- **Astra Zeneca**: Antithrombotic Therapy post MI
- **Amgen**: Lipoproteins
- **Abbott**: Optical Coherence Tomography (OCT)
- **Boston Scientific**: Drug eluting stent

All relevant financial relationships have been mitigated.

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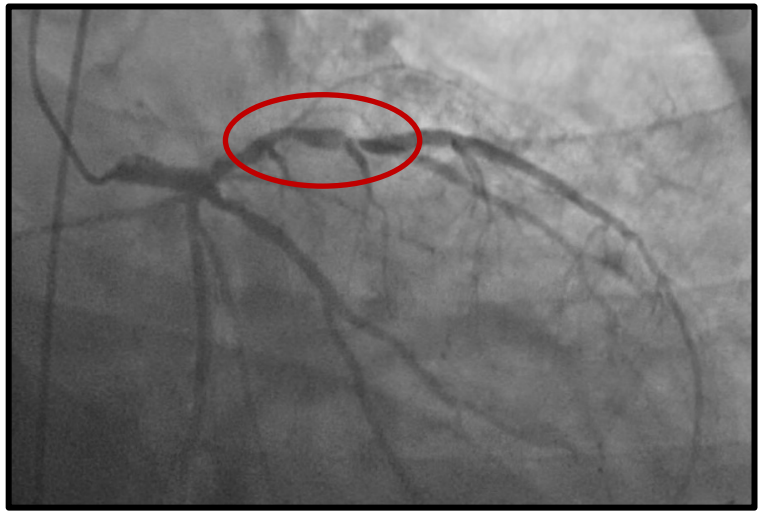
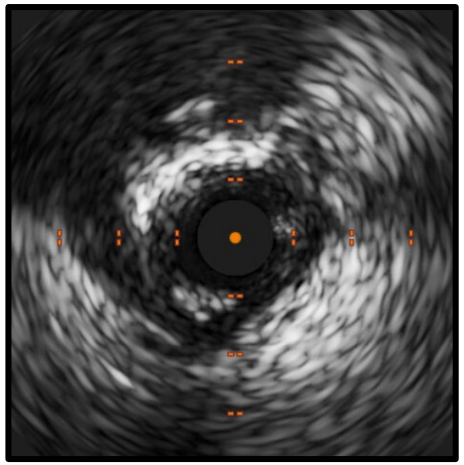
Case Presentation

- 74 y/o male presents with NSTEMI
  - Fe deficiency anemia with baseline Hgb 8 – 9; unrevealing work-up with endoscopy
  - HFpEF; moderate AS and AI
  - Advanced, oxygen-dependent CKD
  - CKD (eGFR ~ 45 ml/min)



Calcific prox/mid LAD culprit



Eccentric calcification

Is this patient considered high bleeding risk?

Should he be treated with DAPT for 1, 3, 6, > 6 months?

How does one weigh thrombotic risk (NSTEMI; prox/mid LAD; complex lesion) versus bleeding risk (anemia; CKD)

What is optimal long-term therapy?

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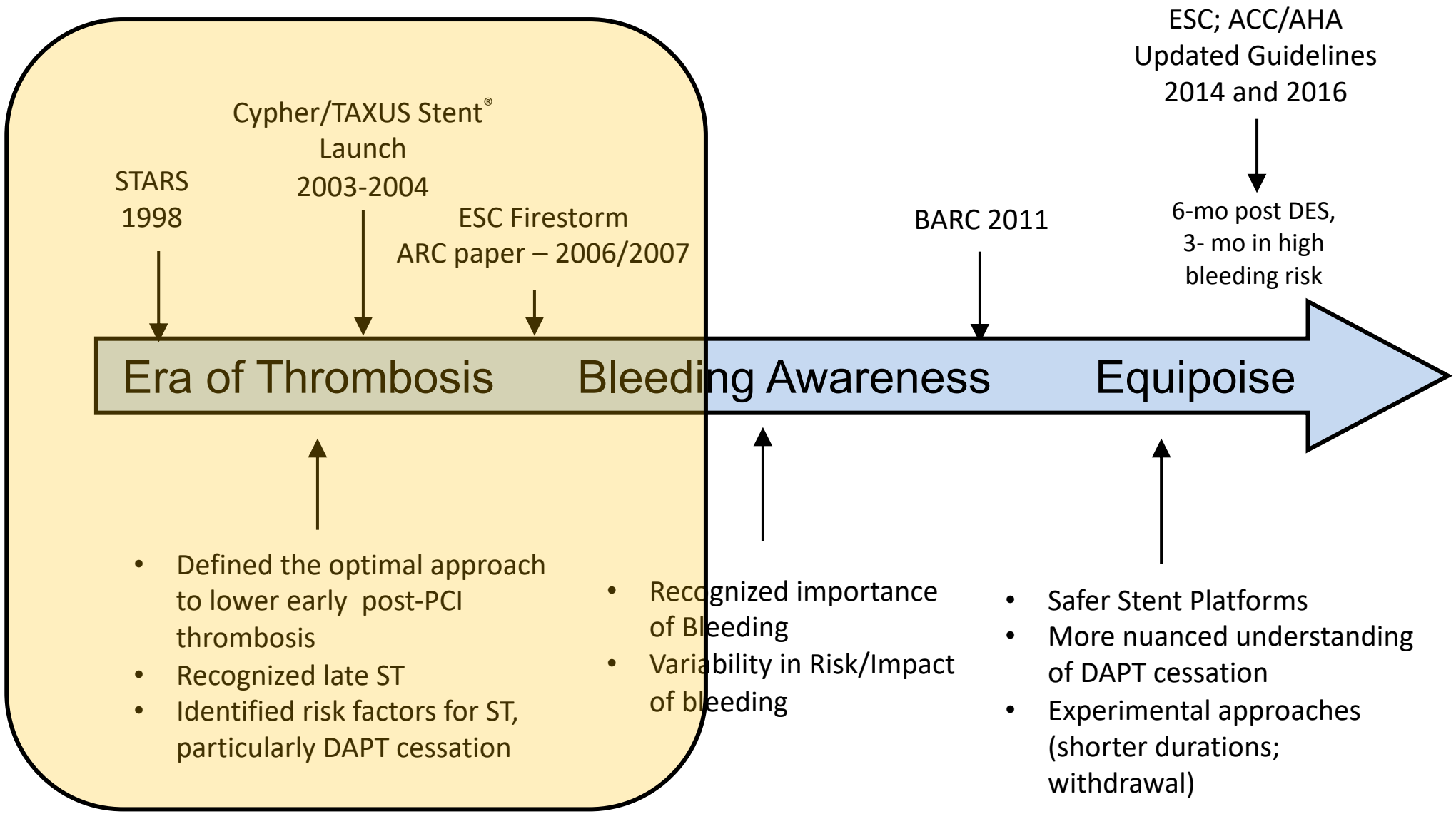
DAPT: Evolution over time



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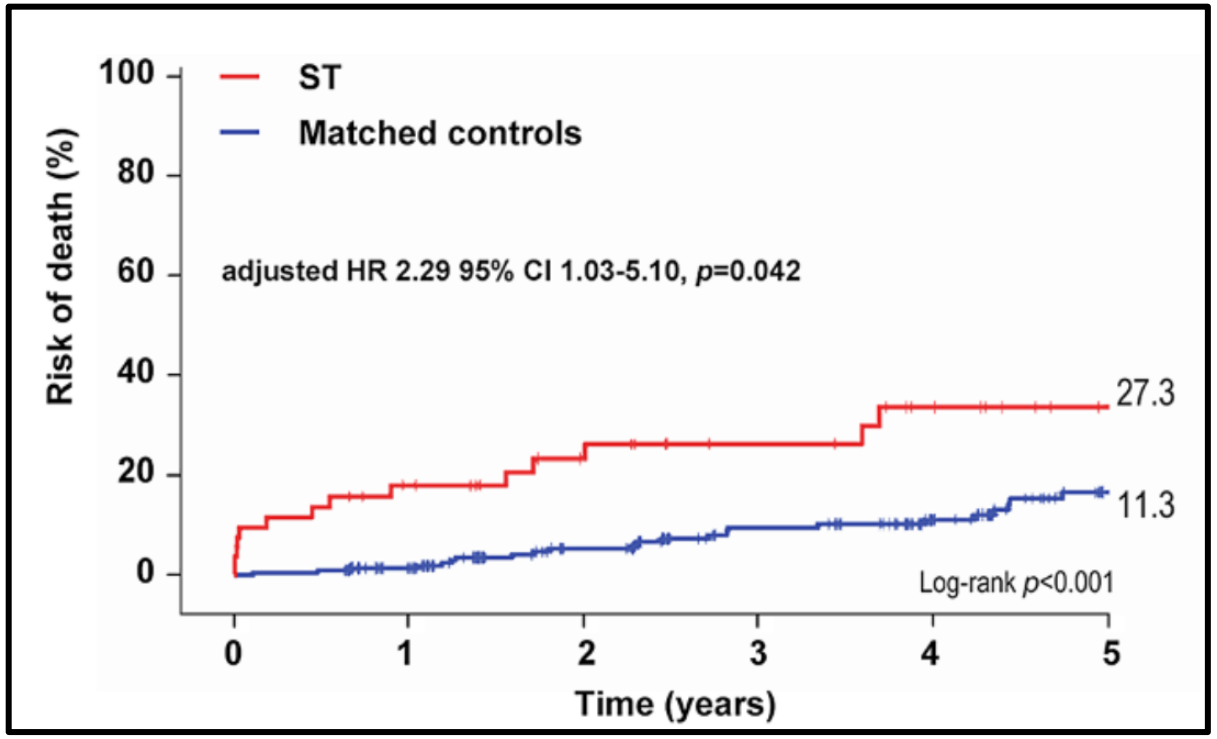
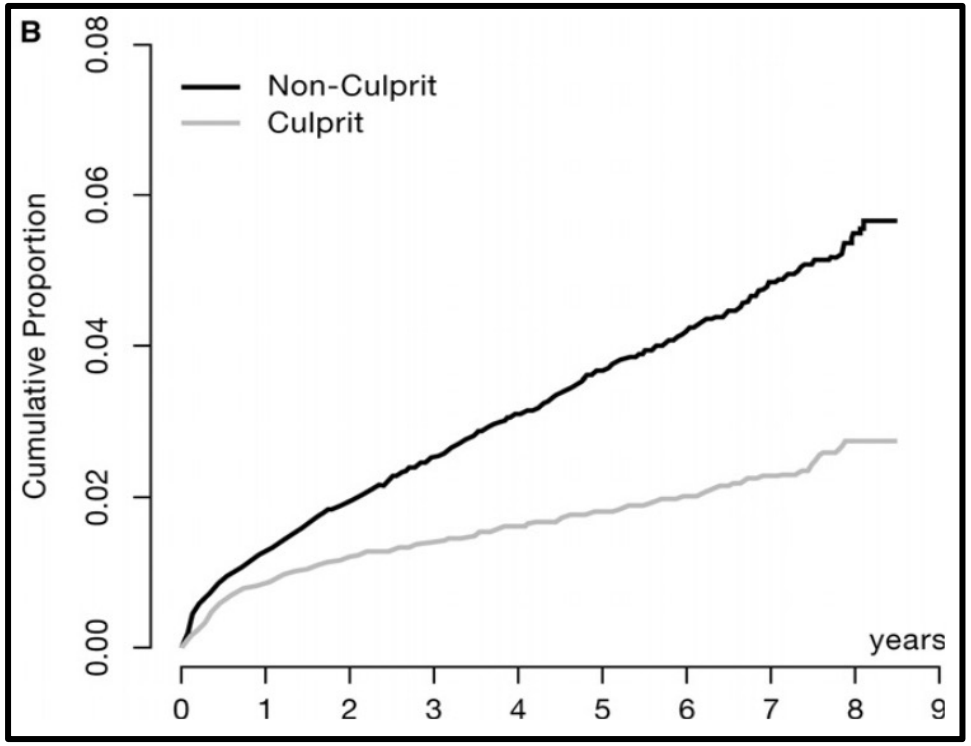
Need for DAPT After PCI (or ACS)

Mortality risk after ST compared with controls



Risk of MI from non-culprit versus culprit lesion



Prevent focal thrombosis (early)

Prevent systemic thrombosis (late)

Rozemeijer et al., 2019; Varenhorst et al., 2018

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STARS Trial

A CLINICAL TRIAL COMPARING THREE ANTITHROMBOTIC-DRUG REGIMENS AFTER CORONARY-ARTERY STENTING

A CLINICAL TRIAL COMPARING THREE ANTITHROMBOTIC-DRUG REGIMENS AFTER CORONARY-ARTERY STENTING

MARTIN B. LEON, M.D., DONALD S. BAIM, M.D., JEFFREY J. POPMA, M.D., PAUL C. GORDON, M.D., DONALD E. CUTLIP, M.D., KALON K.L. HO, M.D., ALEX GIAMBARTOLOMEI, M.D., DANIEL J. DIVER, M.D., DAVID M. LASORDA, D.O., DAVID O. WILLIAMS, M.D., STUART J. POCOCK, PH.D., AND RICHARD E. KUNTZ, M.D., FOR THE STENT ANTICOAGULATION RESTENOSIS STUDY INVESTIGATORS*

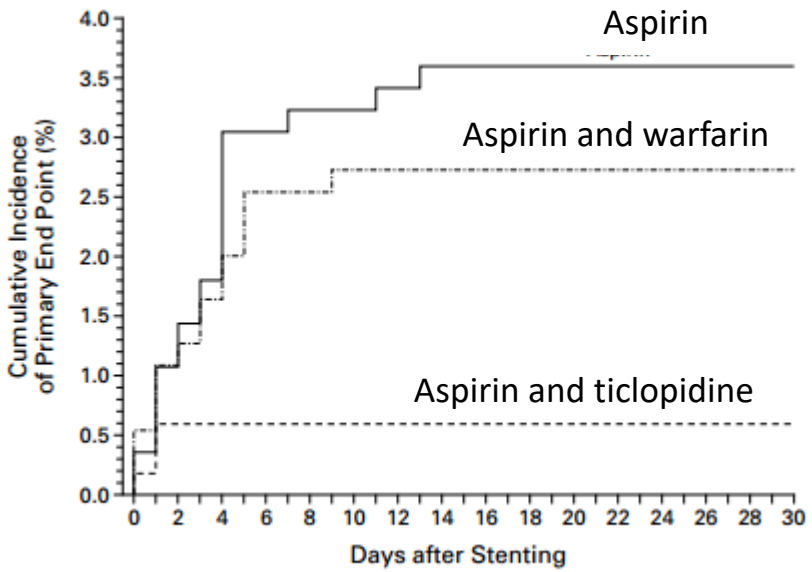

Figure 1. Cumulative Incidence of the Primary End Point in the Three Treatment Groups.

Landmark trial that showed DAPT was optimal antithrombotic approach to prevent early thrombosis

and

Aspirin served as foundation for DAPT

N Engl J Med 1998;339:1665-71

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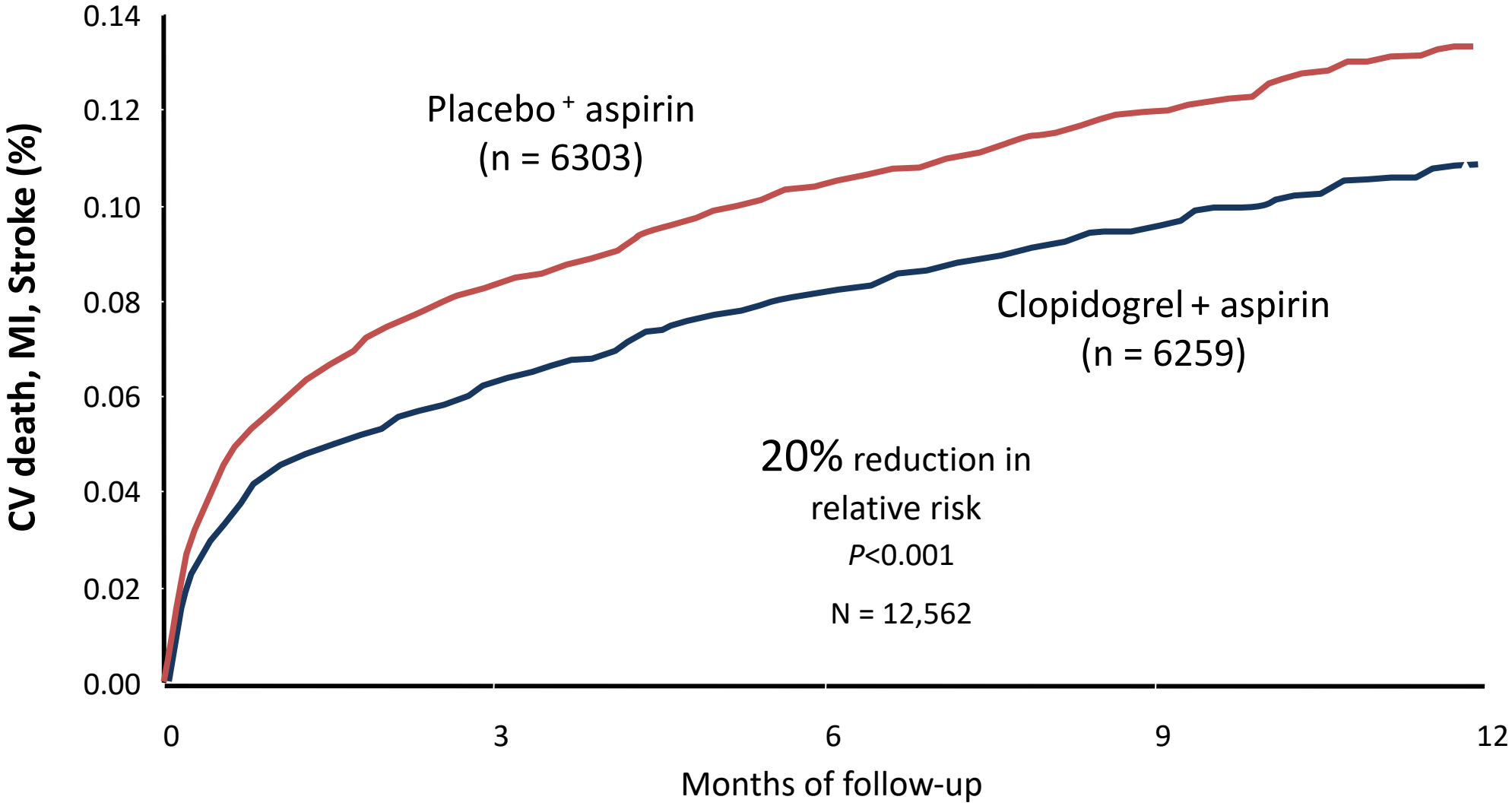
CURE Trial: Clop vs. Placebo

~ 67% treated medically; 33% PCI/CABG



Yusuf et al., NEJM 2001

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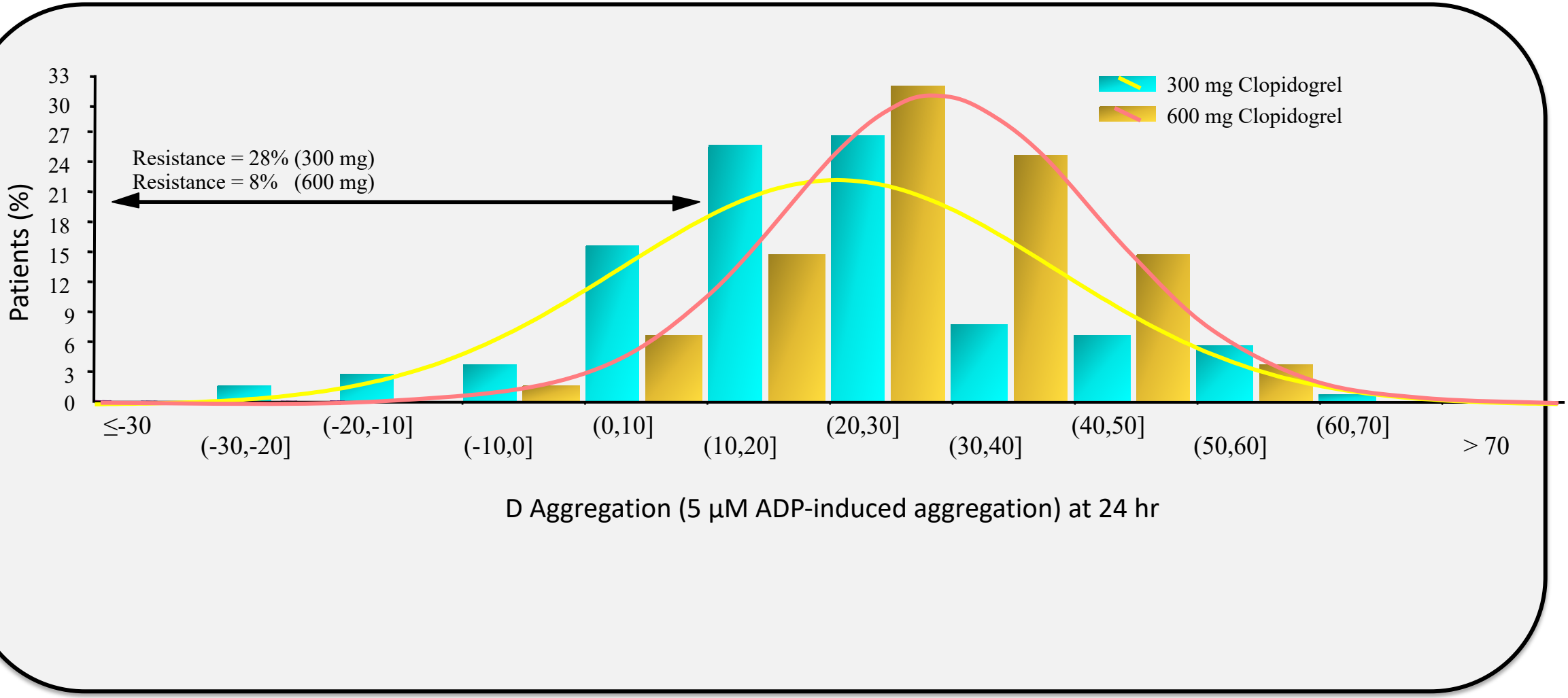
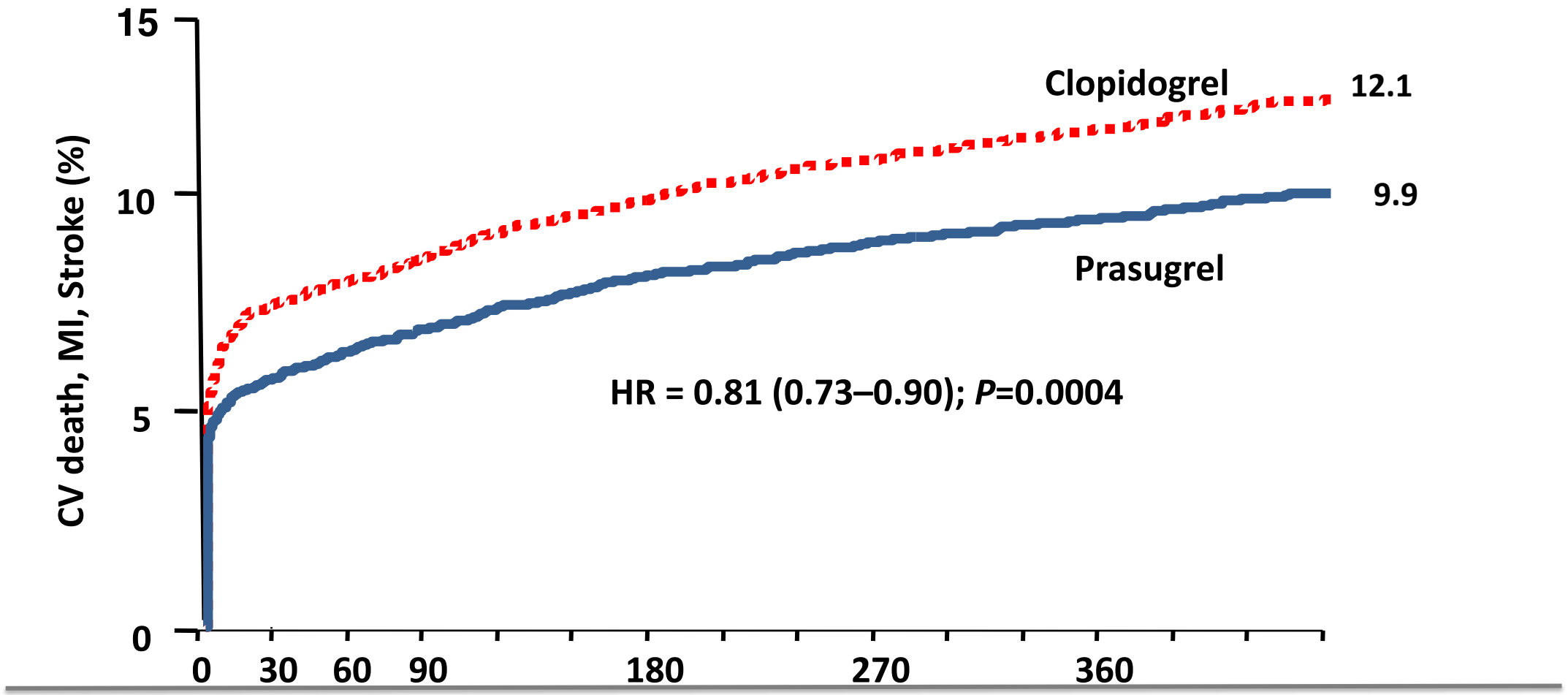
Variability in response to clopidogrel



Gurbel PA et al. J Am Coll Cardiol. 2005;45:1392-6.

TRITON TIMI 38: Pras vs. Clop in ACS

All patients underwent PCI



Wiviott SD et al. N Engl J Med. 2007;357:2001-2015.

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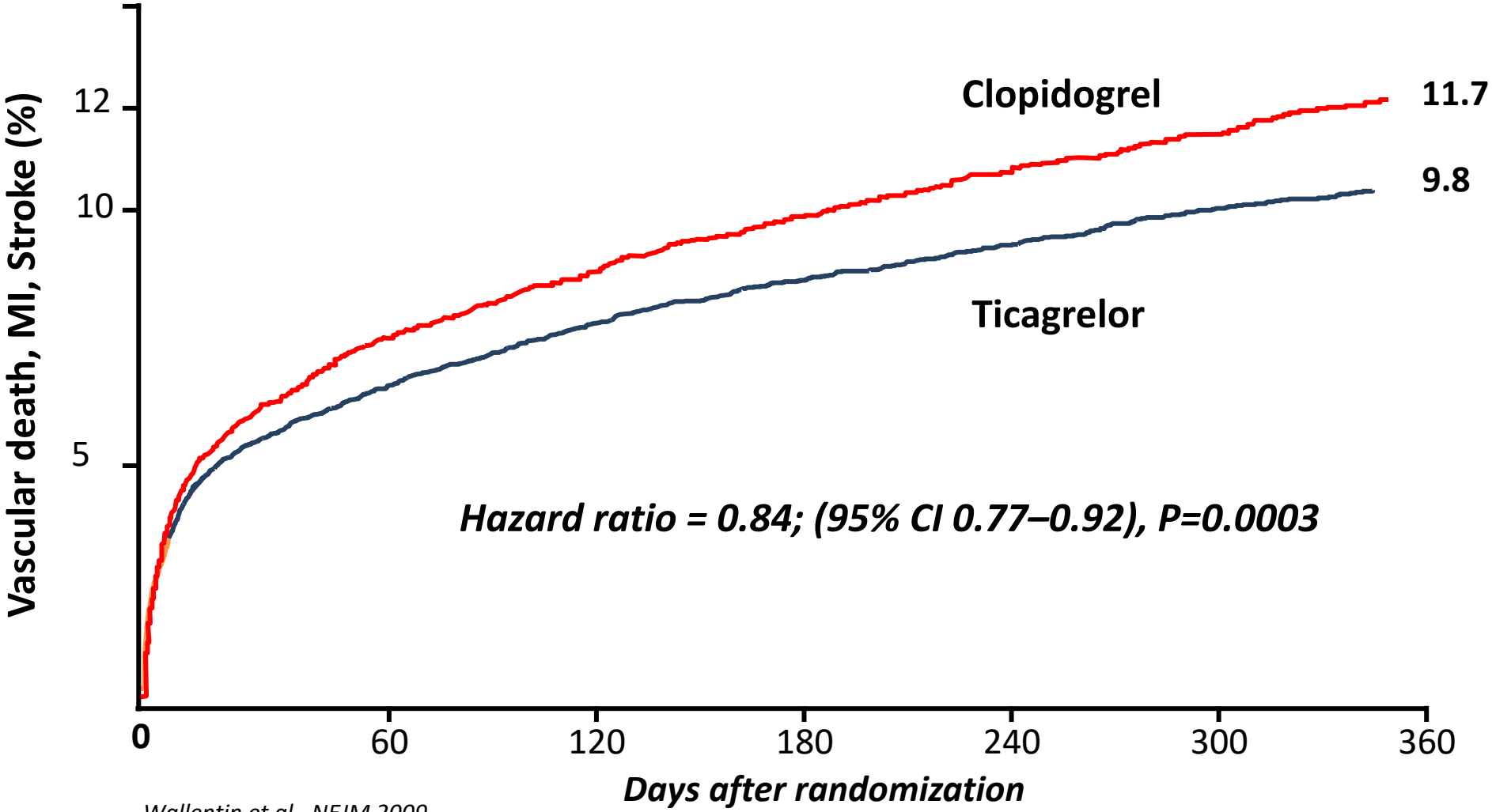
PLATO: Tica vs. Clop in ACS

~ 25% treated medically; 10% CABG



Wallentin et al., NEJM 2009

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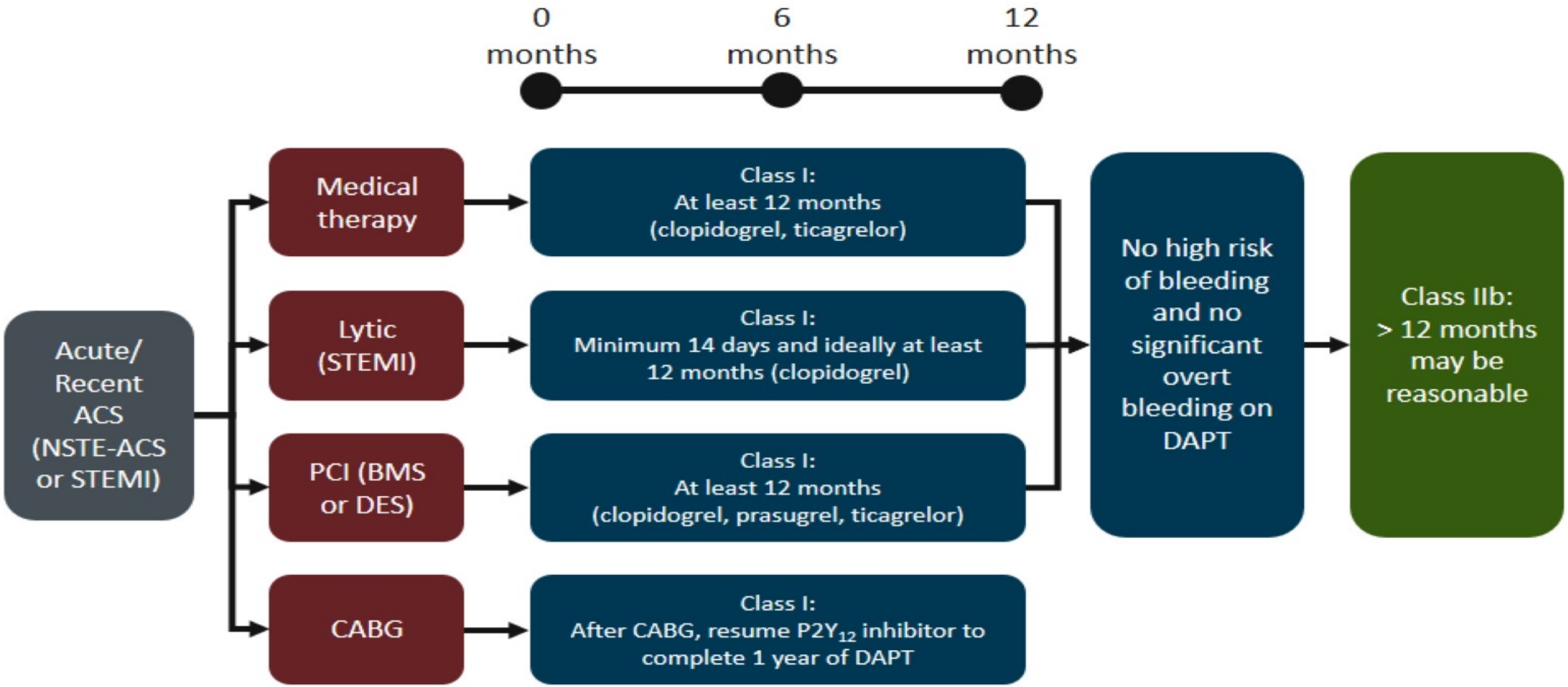
2016 ACC/AHA DAPT Guidelines

DAPT Duration



Levine GN, et al. *JACC.* 2016. 68:1082-1115.

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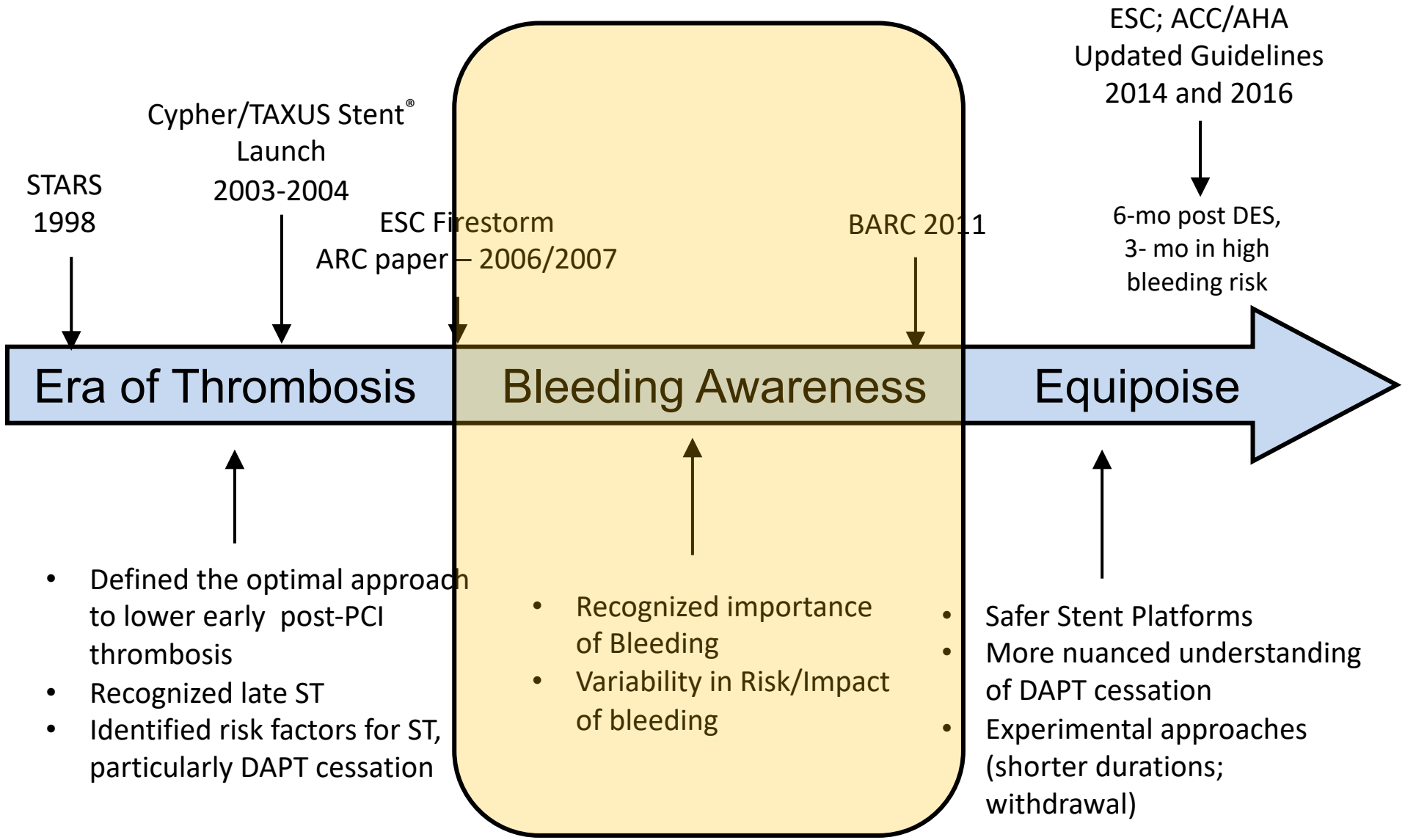
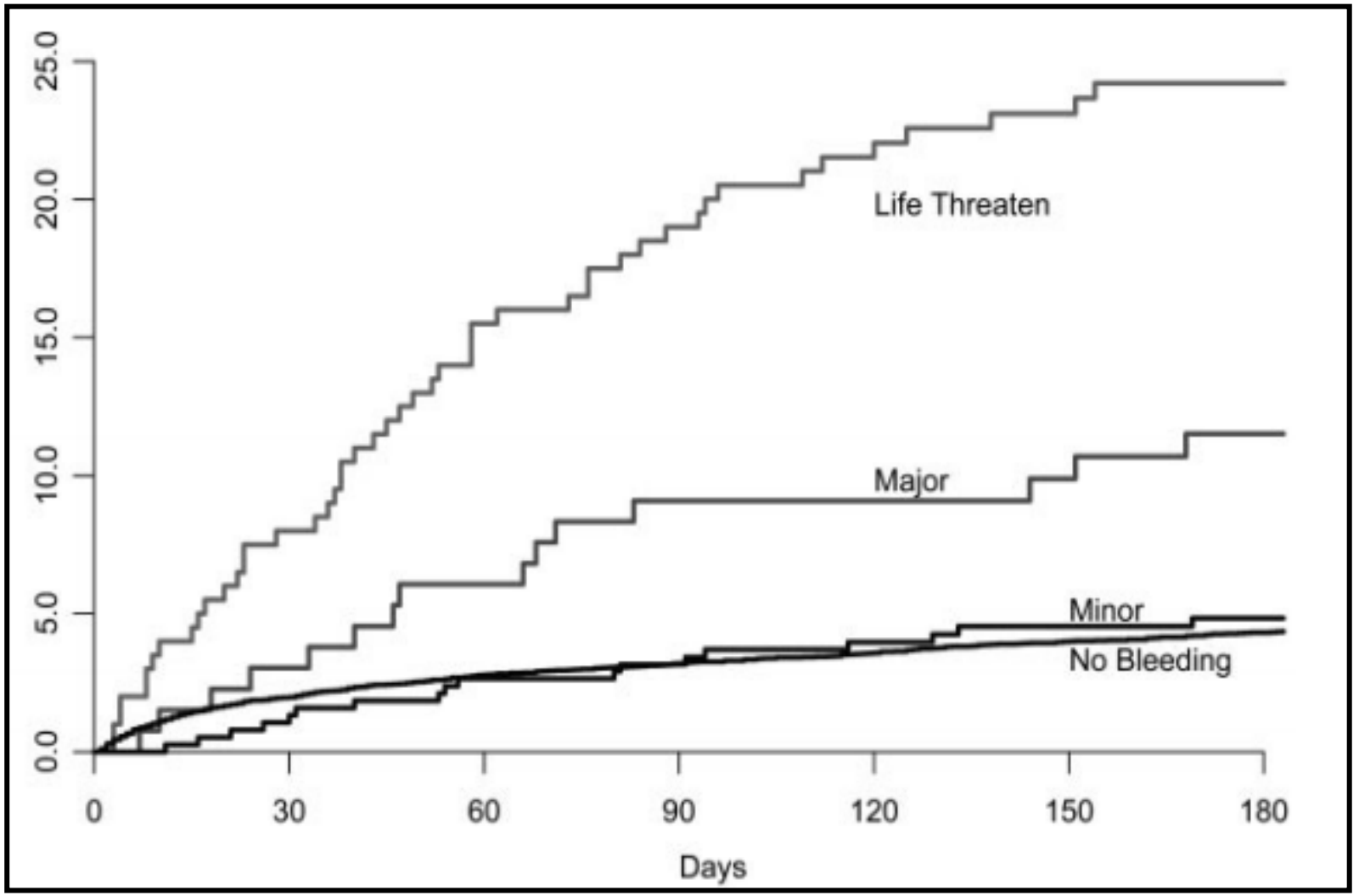
DAPT: Evolution over time



Bleeding and Mortality



ACS cohort

n = 34,136

Impact of bleeding on mortality over 6 months

Mortality first 30 days
12.8% vs. 2.5%

Eikelboom et al, Circulation. 2006;114:774-782

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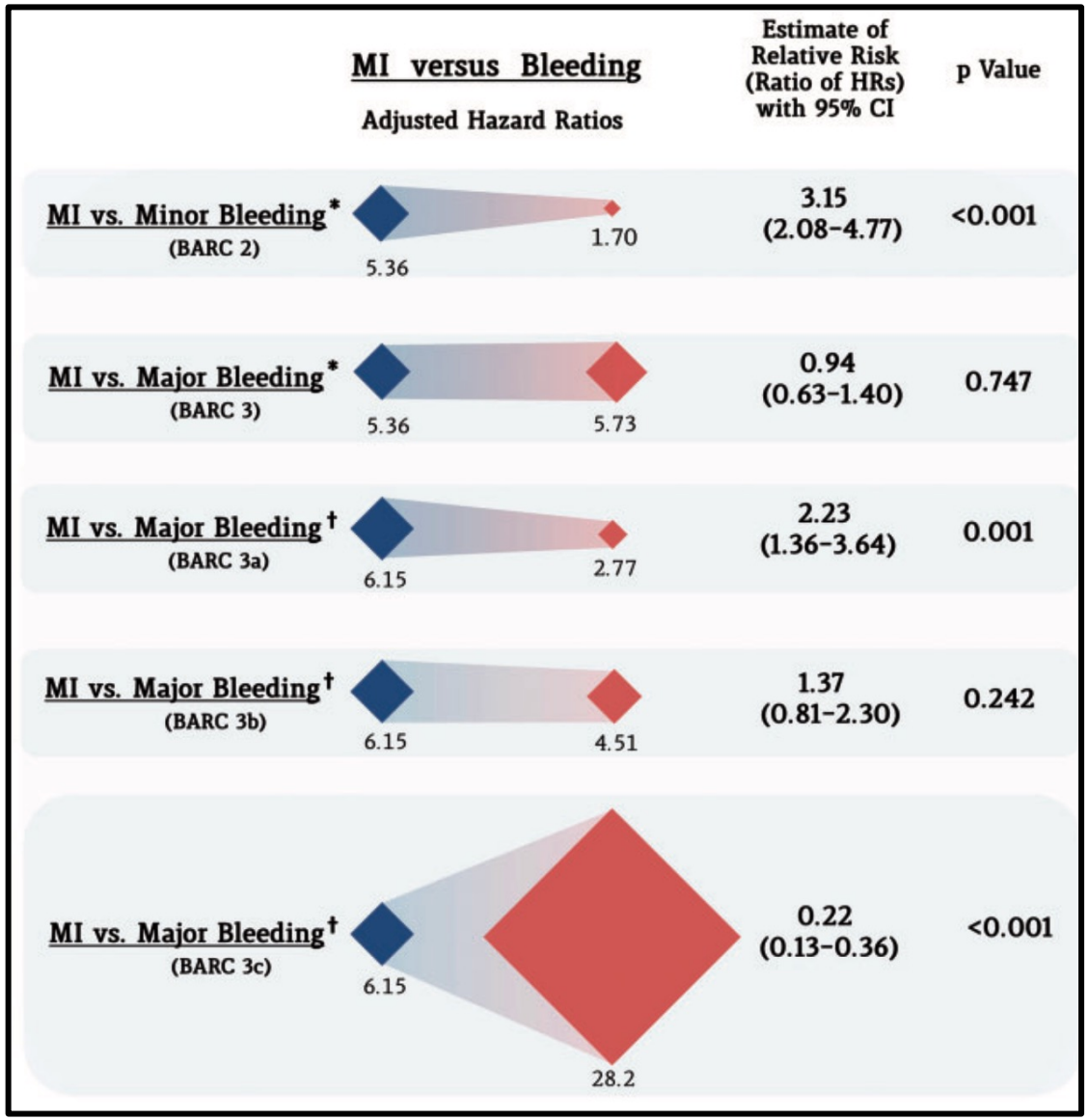
Bleeding versus MI: Mortality Impact



Valgimigli et al., 2017

RCT involving NSTE-ACS

n=12,994

BARC type 2 and 3 bleeding associated with excess mortality

"… the risk of mortality was equivalent between BARC 3b bleeding and MI,…"

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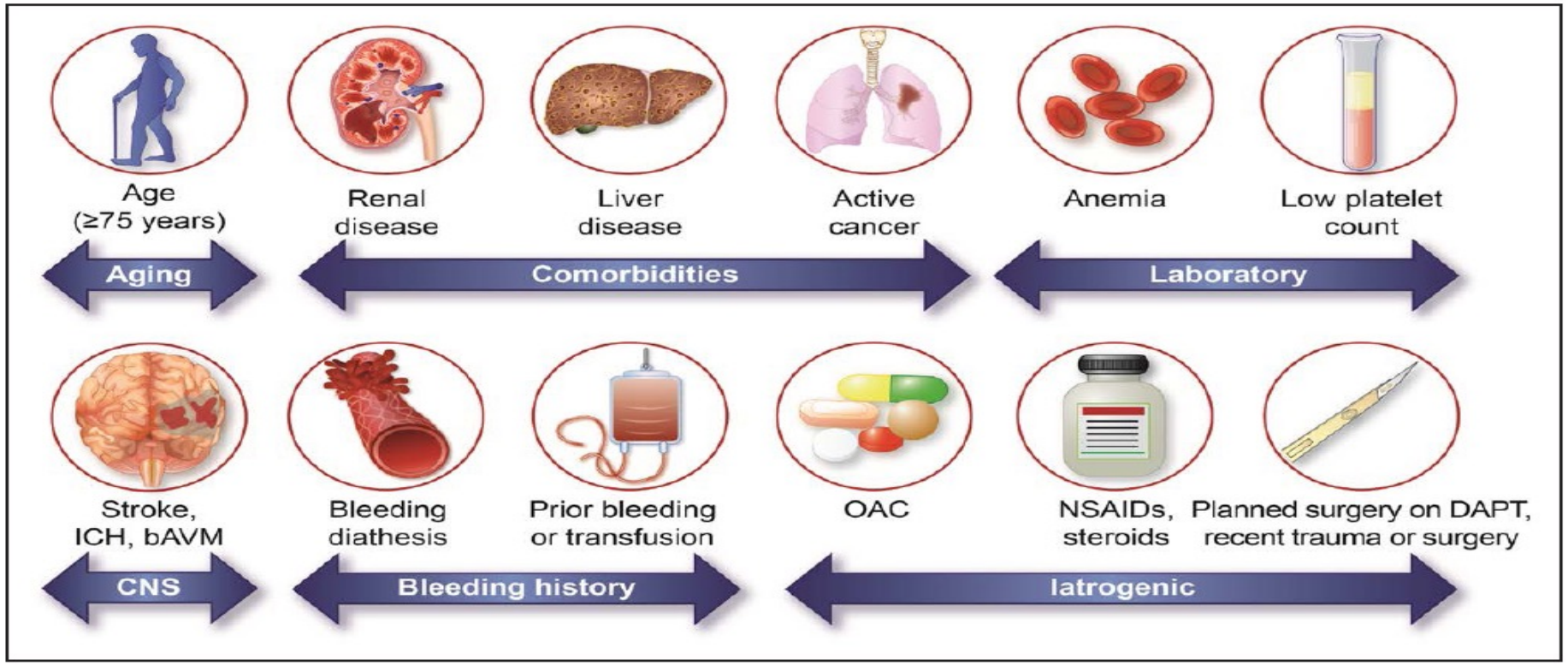
Mechanisms linking Bleeding to Mortality

- Interruption of antiplatelet or other therapies
- Alterations in blood viscosity and thrombogenicity
- Risk marker for patients at elevated risk for subsequent thrombosis

Defining High Bleeding Risk in Patients Undergoing Percutaneous Coronary Intervention

A Consensus Document From the Academic Research Consortium for High Bleeding Risk



"HBR is defined as a BARC 3 or 5 bleeding risk of ≥ 4% at 1 year…"

Urban et al. Circulation 2019

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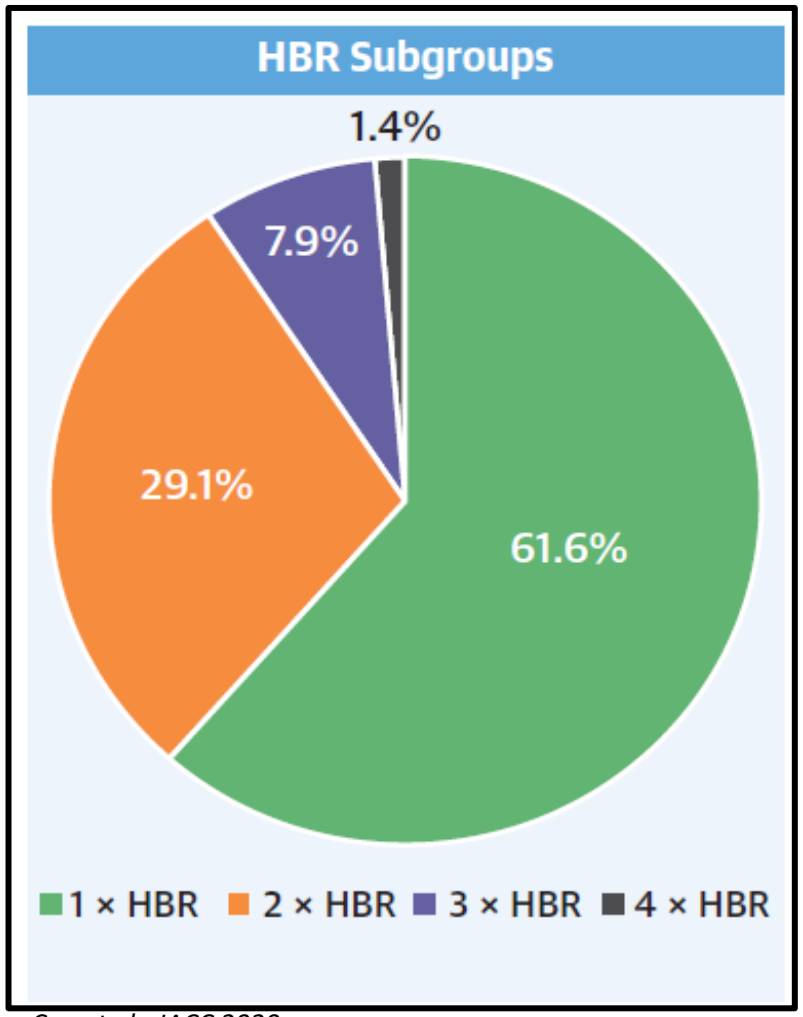
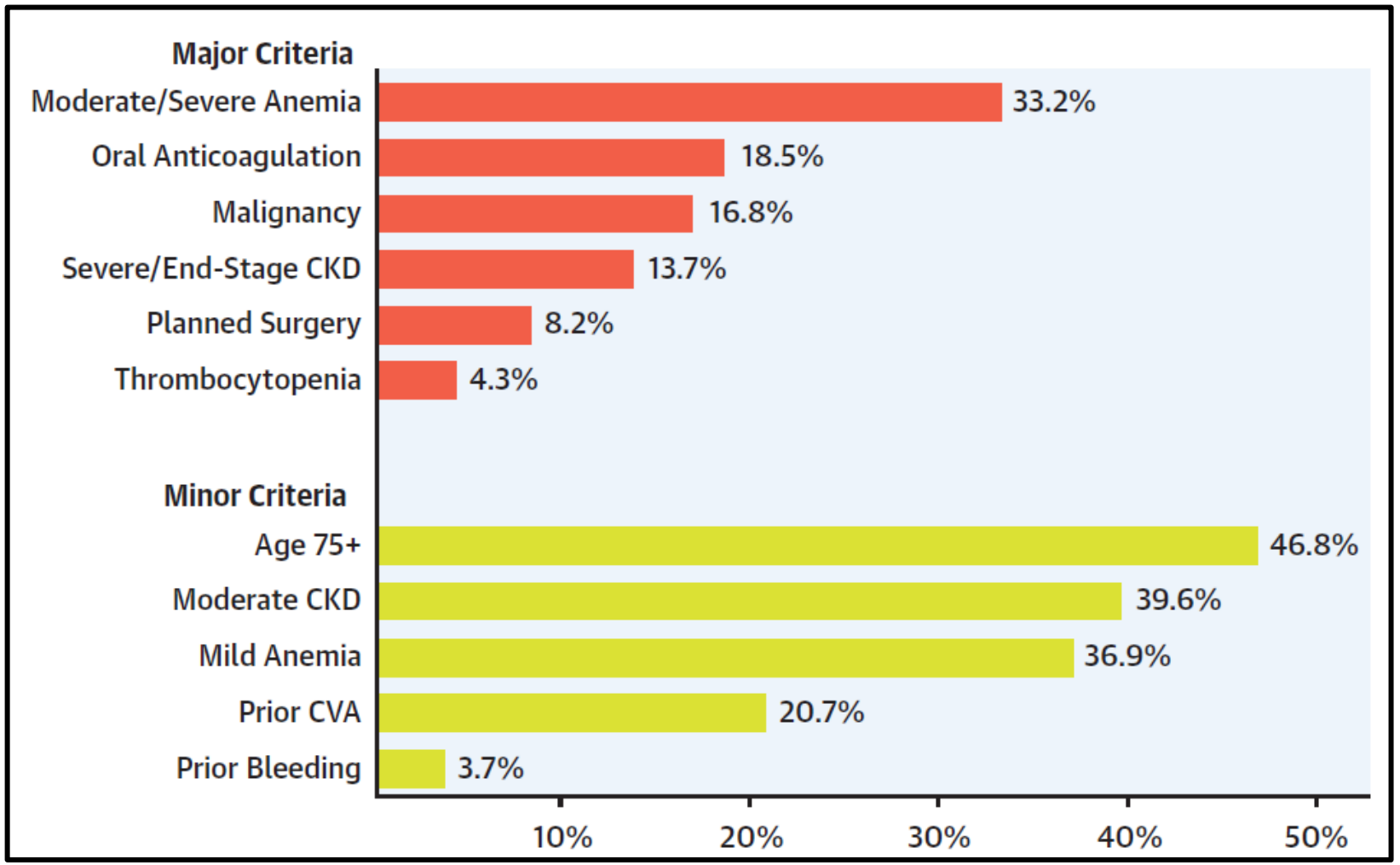
HBR Prevalence

Mount Sinai PCI Registry; HBR prevalence 44%
n= 9623; 2014 - 2017

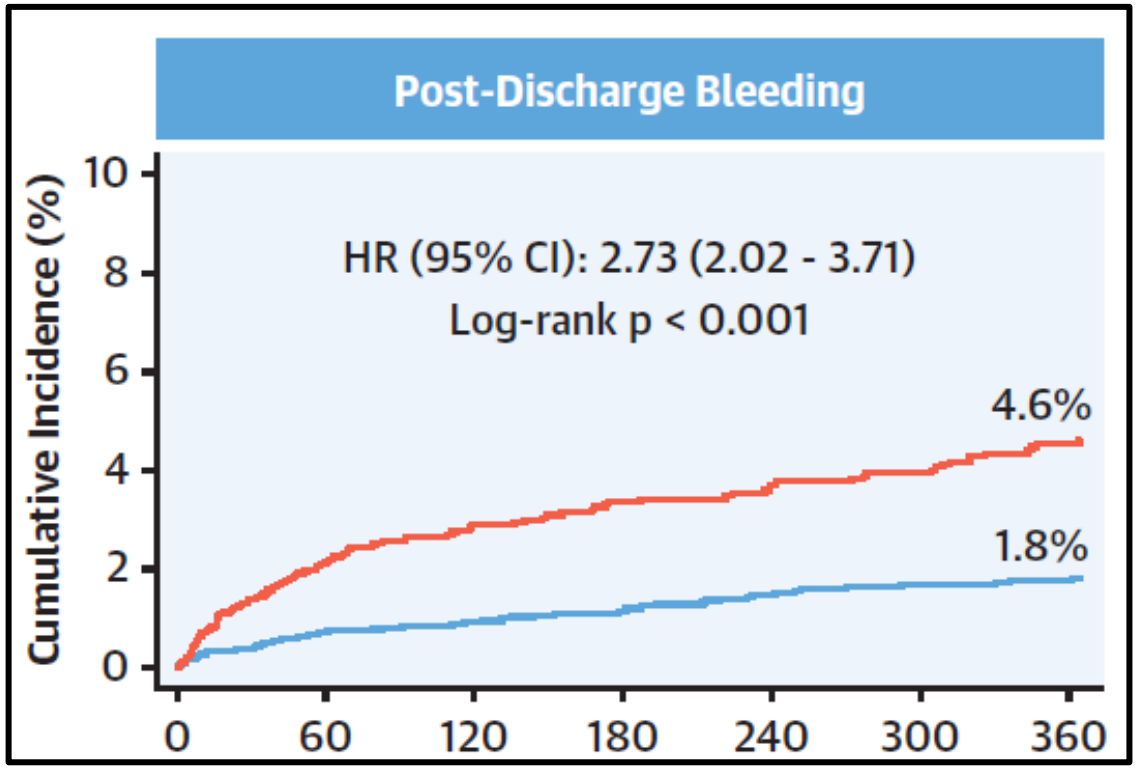


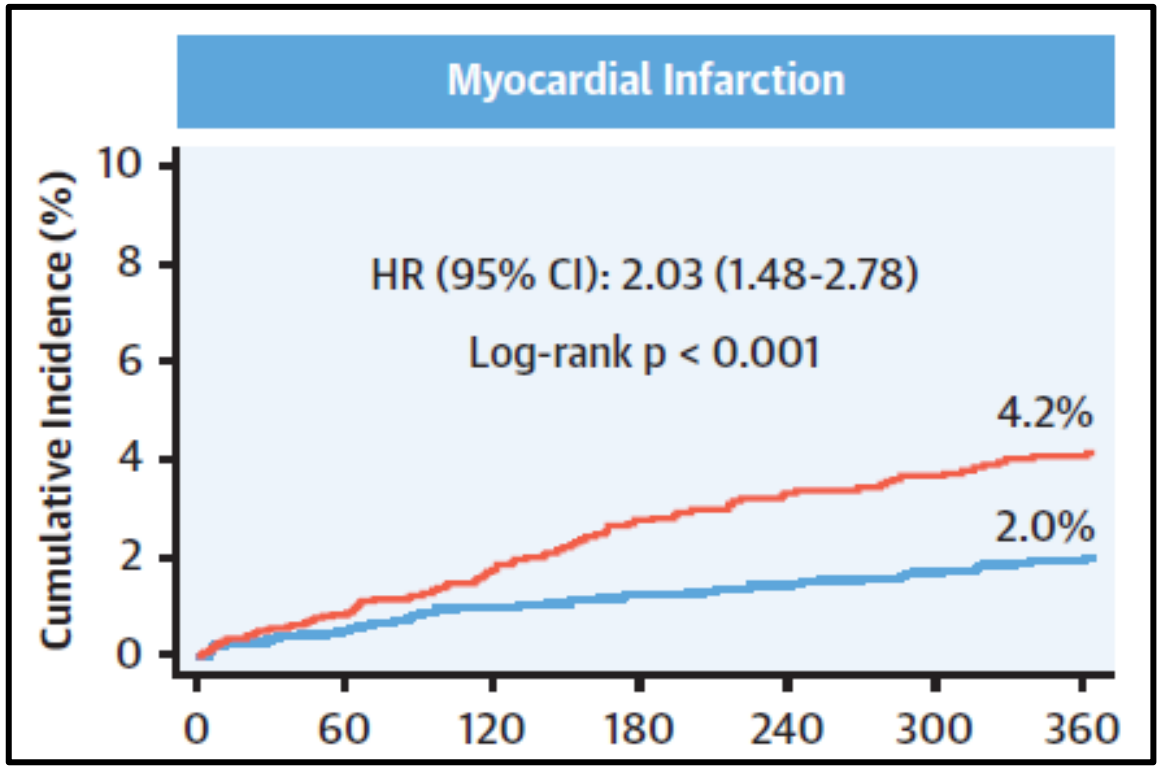


Cao et al., JACC 2020

HBR: Bleeding and Thrombotic Risk

Mount Sinai PCI Registry; n= 9623; 2014 - 2017





Cao et al., JACC 2020

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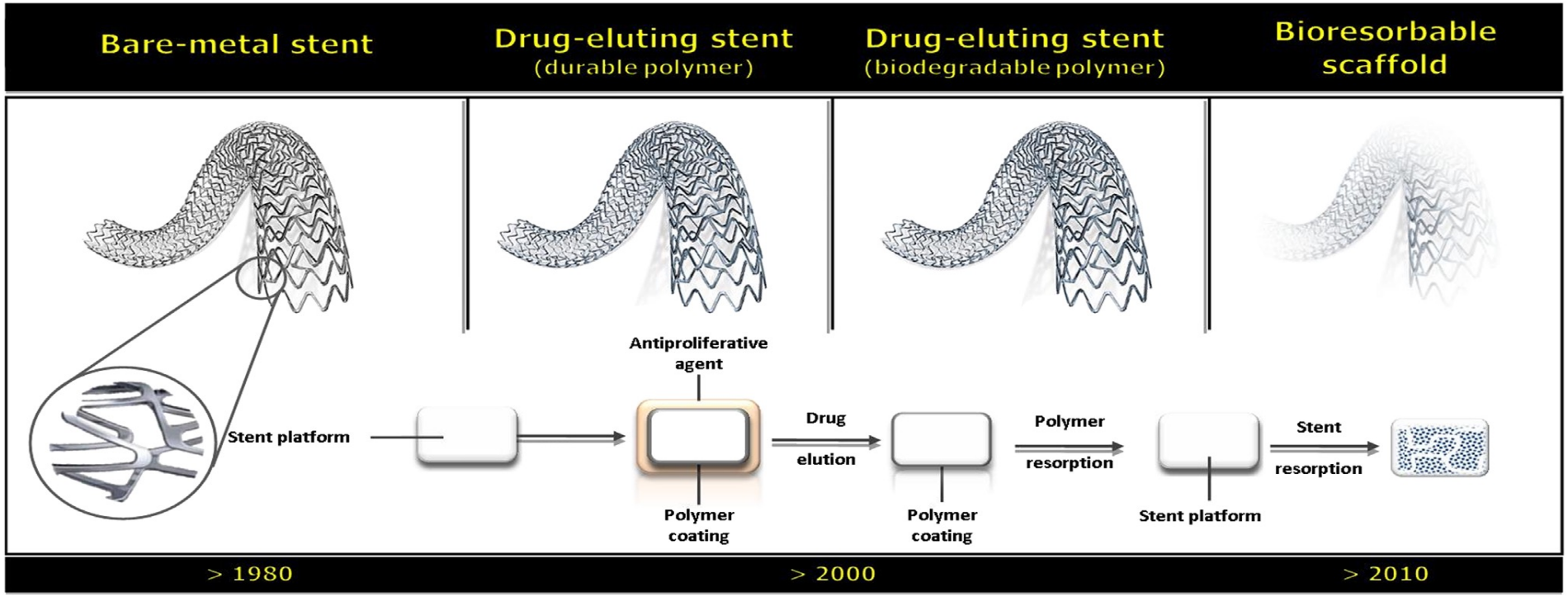
Evolution of coronary stents



Strut thickness

THICK (~ 130 um) → ***THIN (~ 80 um)*** → ***ULTRATHIN (60 um)***

Polymer

Inflammatory → ***Biocompatible*** → ***Biodegradable/Polymer free***

Gogas et al. Trends in Cardiovascular Medicine24 (2014) 305–313

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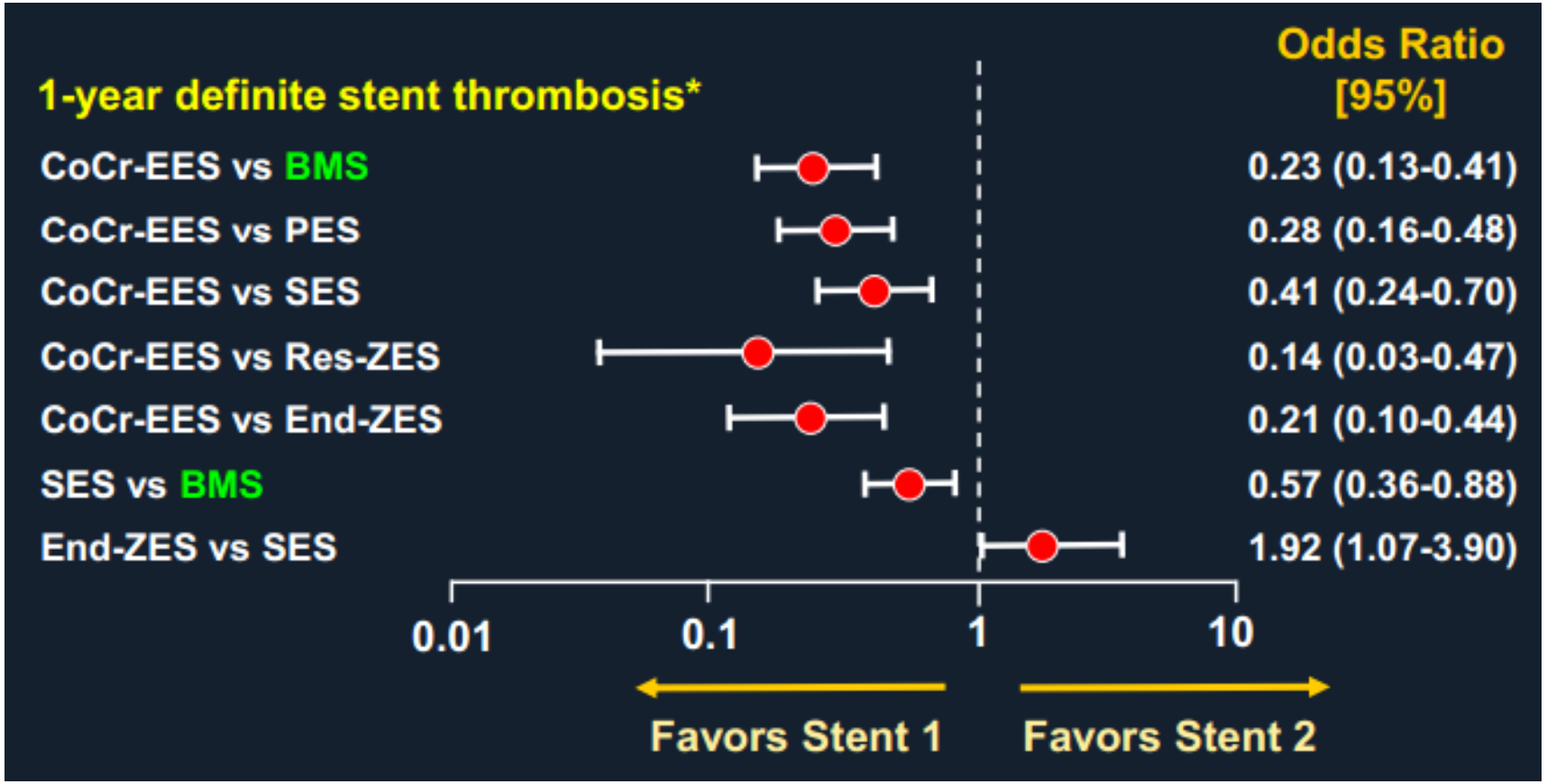
THE LANCET
Volume 379, Issue 9824, 14–20 April 2012, Pages 1368–1369



Newer-generation DES reduce ST when compared to 1st generation devices and BMS

Palmerini T et al. Lancet 2012

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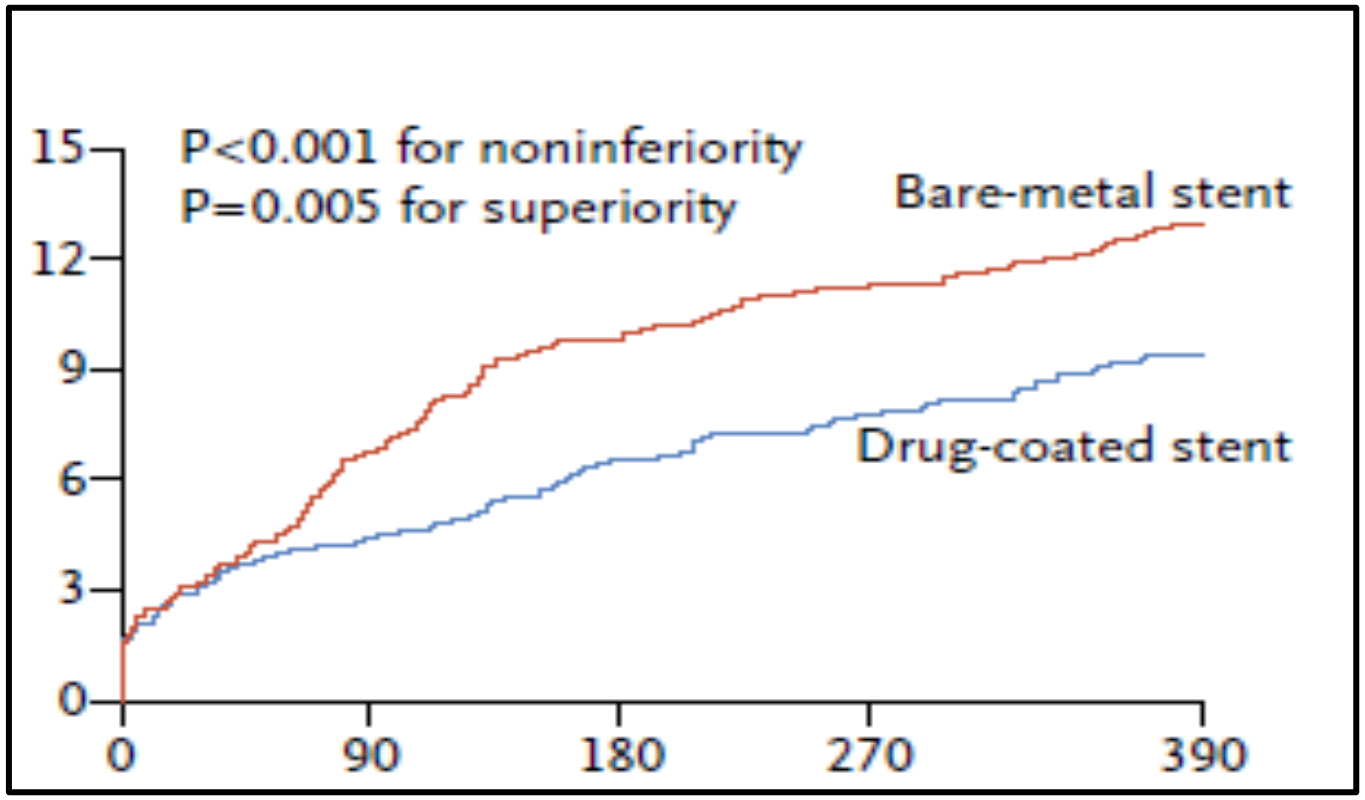
LEADERS FREE Trial (n=2466)



Polymer free DES versus BMS in "high-bleeding risk" patients (~27% ACS)

DAPT for one month

DES preferred over BMS in ESC and ACC/AHA guidelines

Urban et al, NEJM 2015

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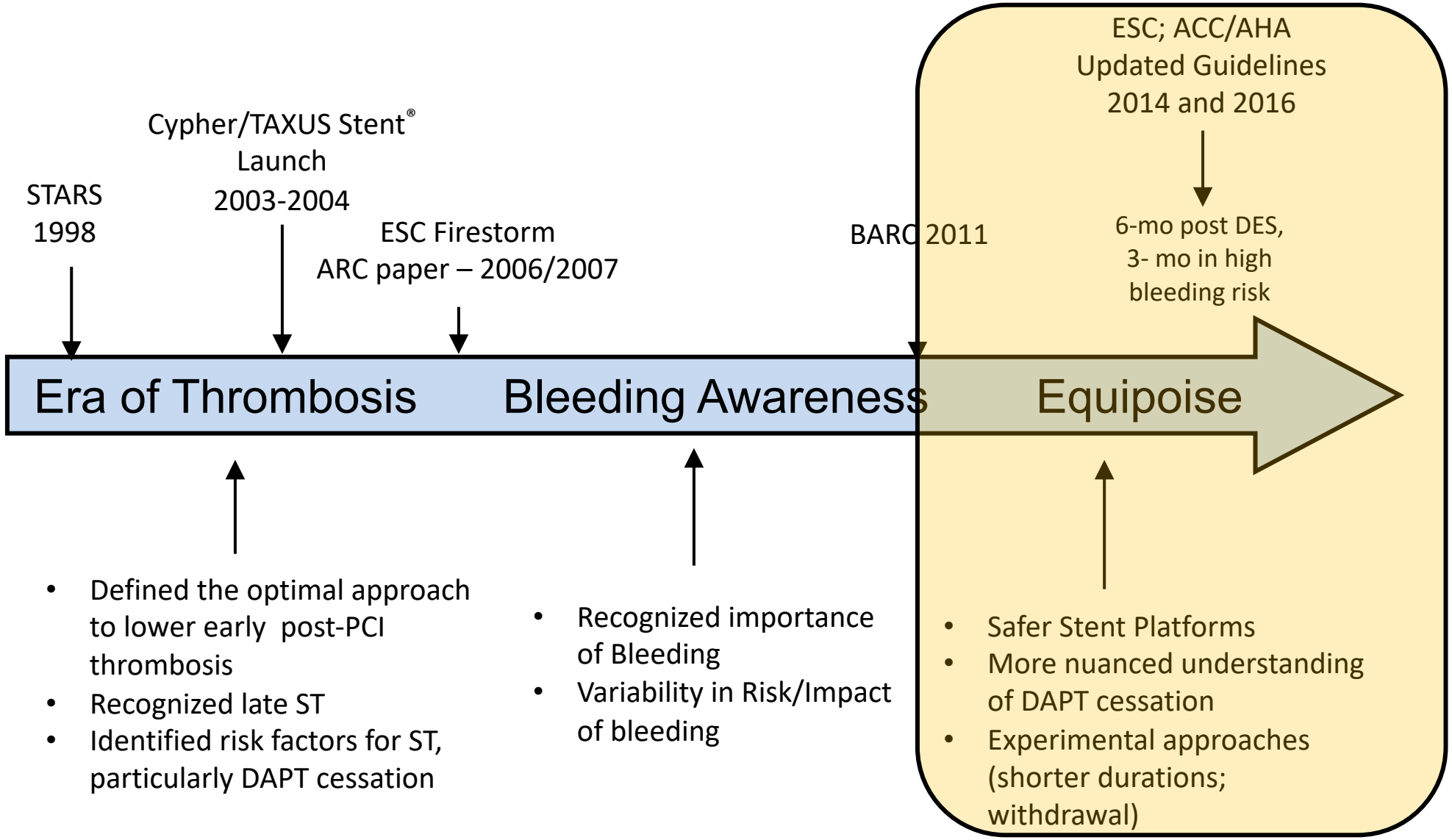
DAPT: Evolution over time



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Bleeding Reduction Strategies

- Shorten DAPT duration
  - Typically stop $P2Y_{12}$ inhibitor
  - Tested in HBR patients
- Aspirin withdrawal
  - Examined in non-HBR cohorts
  - Primarily tested in patients receiving ticagrelor
- De-escalation

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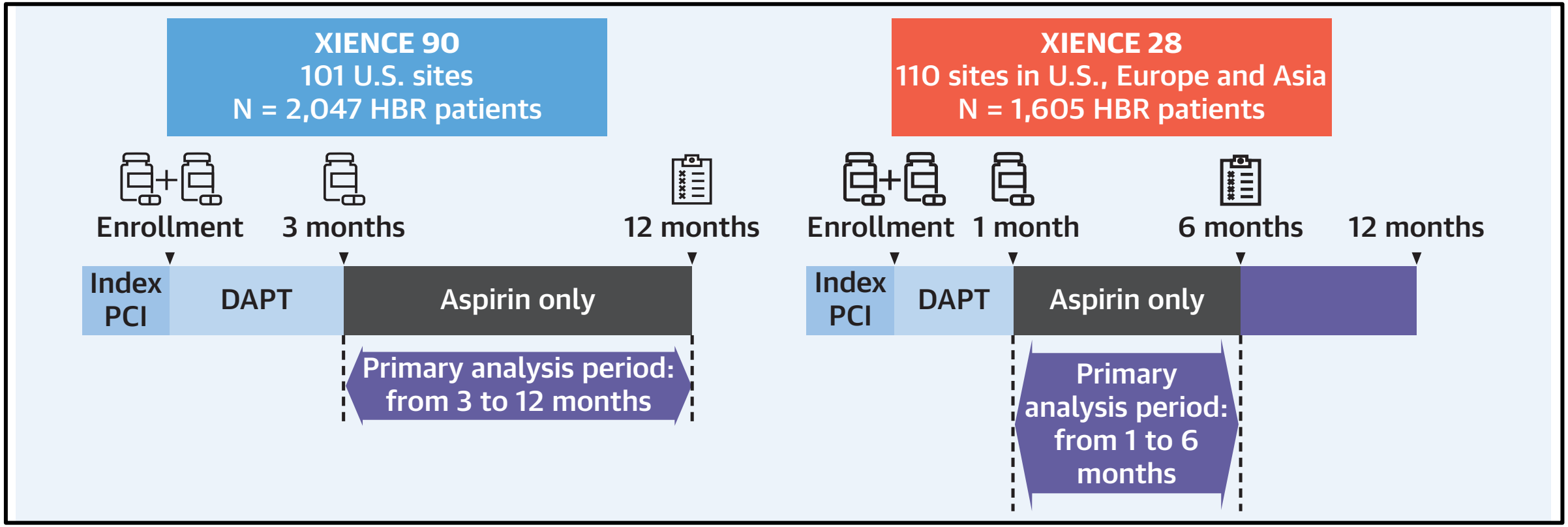
XIENCE – Short DAPT

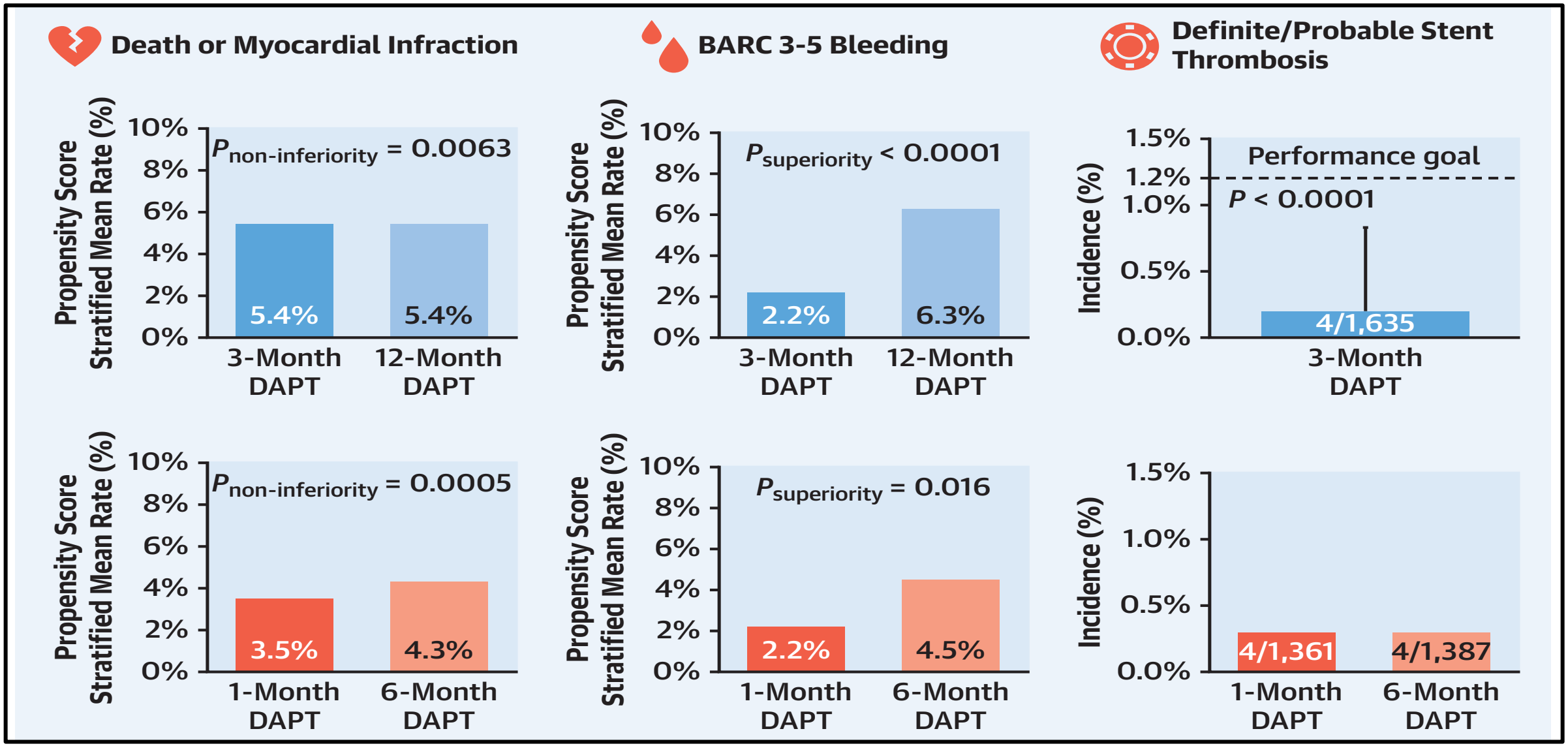


Single arm; compared with historical control

Mean age ~ 75 years; ~ 40% OAC; ~ 13% Tn (+) ACS

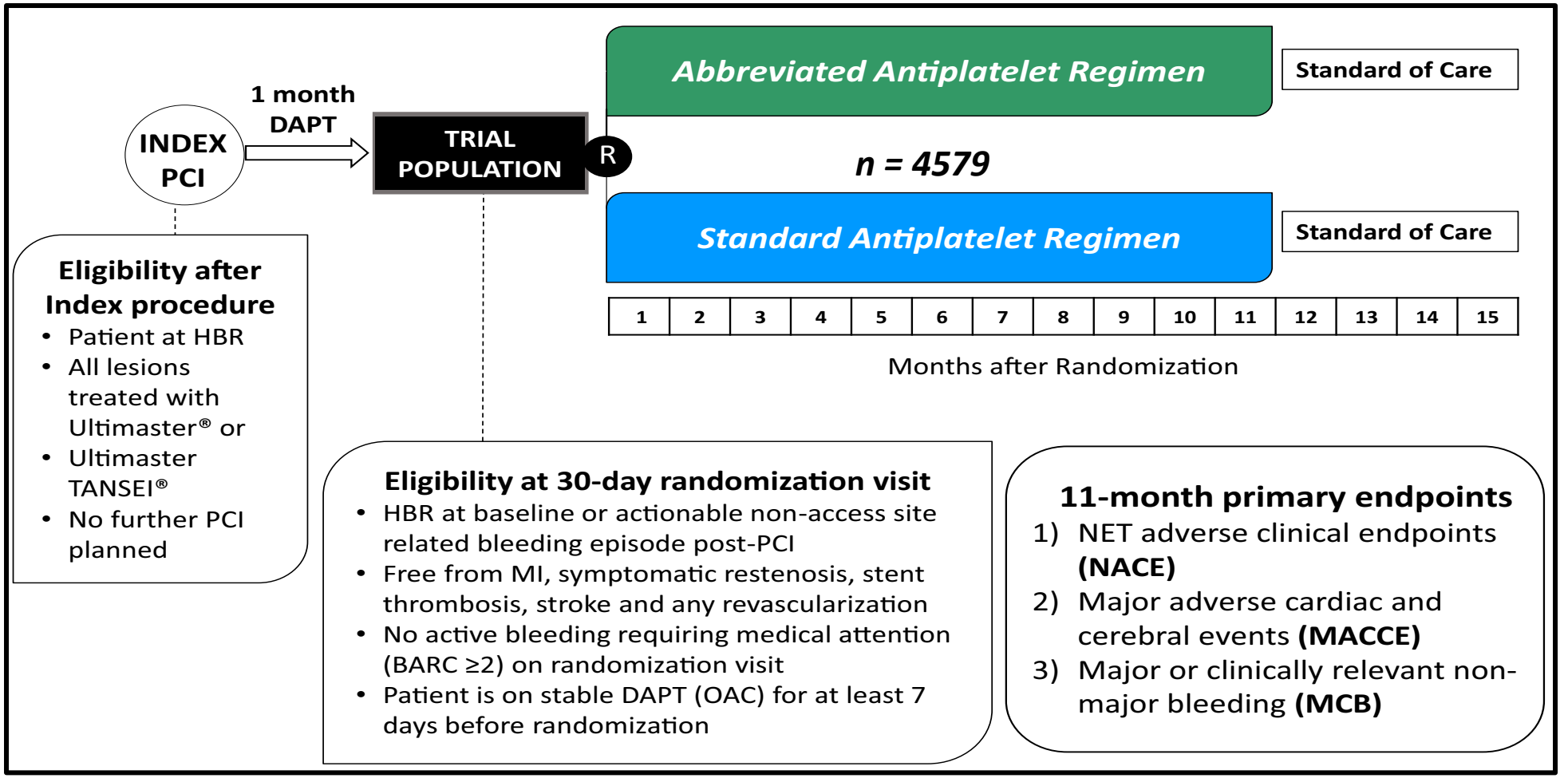
Mehran et al. JACC Int 2021

XIENCE – Short DAPT Results



Mehran et al. JACC Int 2021

MASTER DAPT Trial



Mean age ~ 76 years; ~ 36% OAC ; ~ 35% Tn (+) ACS

Frigoli et al. AHJ2019

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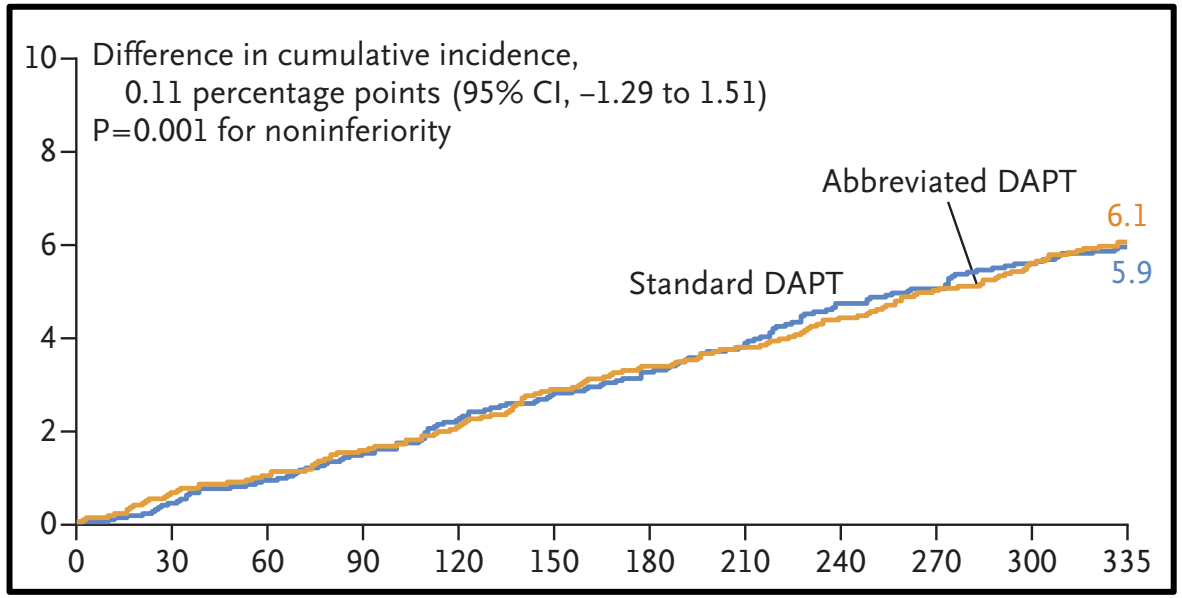
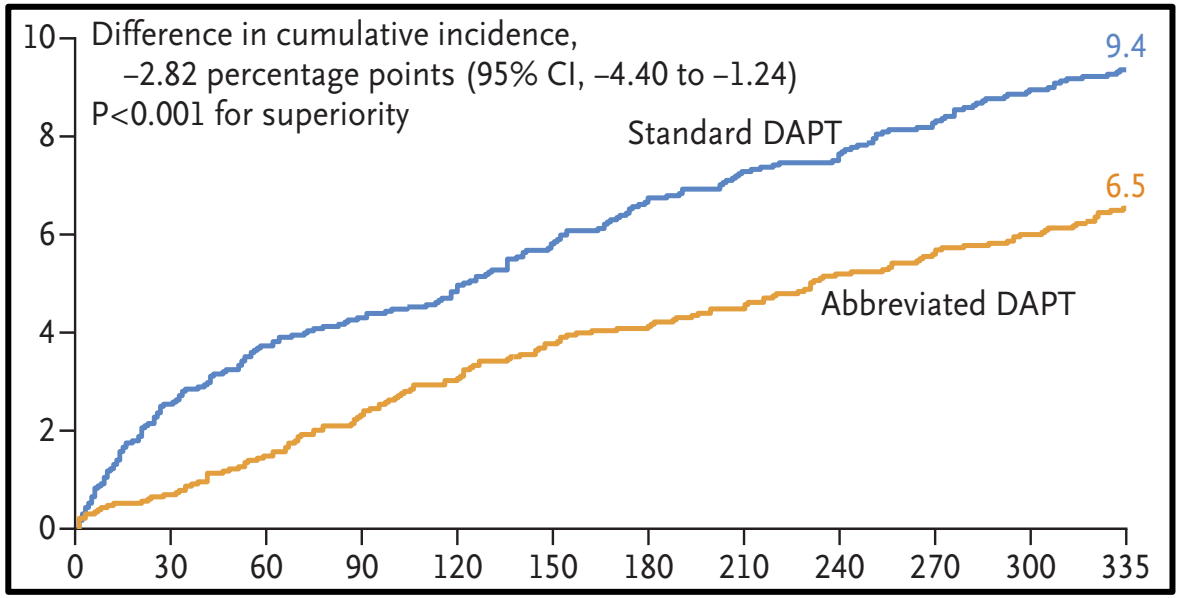
MASTER DAPT Trial - Results

MACCE



BLEEDING



All patient received biodegradable SES

Ischemic event rates lower than expected

Monotherapy mixture of P2Y12i (predominant clopidogrel) and Aspirin

Valgimigli et al. NEJM 2021

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ACC/ACHA 2016 DAPT Guideline Update

Duration of DAPT in Patients With SIHD Treated With PCI

COR	LOE	Recommendations
IIb	C-LD	In patients with SIHD treated with DAPT after DES implantation who develop a high risk of bleeding (e.g., treatment with oral anticoagulant therapy), are at high risk of severe bleeding complication (e.g., major intracranial surgery), or develop significant overt bleeding, ***discontinuation of $P2Y_{12}$ inhibitor therapy after 3 months may be reasonable.***

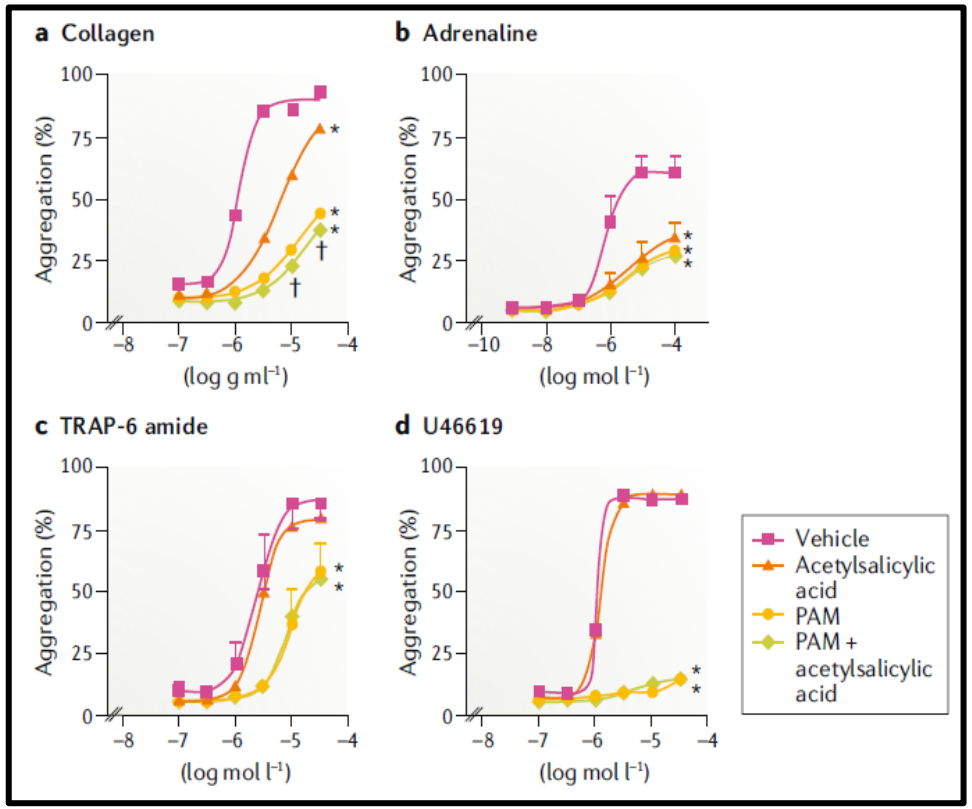
Duration of DAPT in Patients With ACS Treated With PCI

COR	LOE	Recommendations
IIb	C-LD	In patients with ACS treated with DAPT after DES implantation who develop a high risk of bleeding (e.g., treatment with oral anticoagulant therapy), are at high risk of severe bleeding complication (e.g., major intracranial surgery), or develop significant overt bleeding, ***discontinuation of $P2Y_{12}$ inhibitor therapy after 6 months may be reasonable.***

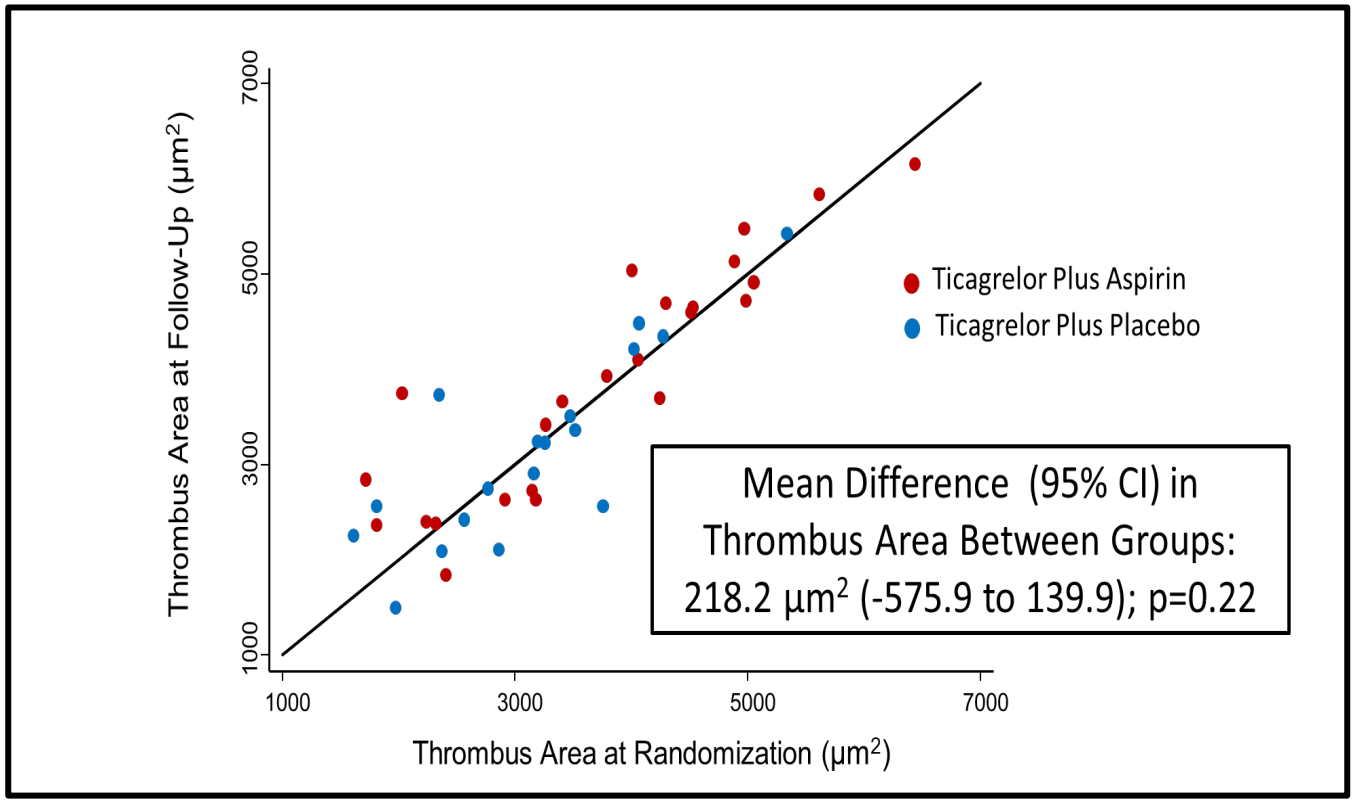
Levine et al., JACC 2016

Aspirin Free Strategies

In vitro platelet aggregation



Ex-vivo thrombus formation: TWILIGHT Platelet Substudy



In the presence of strong $P2Y_{12}$ inhibitor blockade, acetylsalicylic acid provides little additional inhibition of platelet aggregation

Capodanno et al, Nature Reviews 2018; Baber et al., JACC 2020

Aspirin Withdrawal in ACS

Trial	$P2Y_{12}$	Sample size	Timing of ASA withdrawal	Design	Major Bleeding (n)	MACE (n)
GLOBAL LEAD						161
TWILIGHT A						198
TICO						70
STOPDAPT-2						94
SMART CHO						49
MASTER DAF						144

Accumulated Evidence Base

Randomized Patients ~ 23,000

Major Bleeding Events – 368

Ischemic Events - 716

Tomaniak et al. 2019; Kim et al. 2020; Hahn et al. 2019; Baber et al. 2020; Watanabe et al. 2022; Smits et al. 2022

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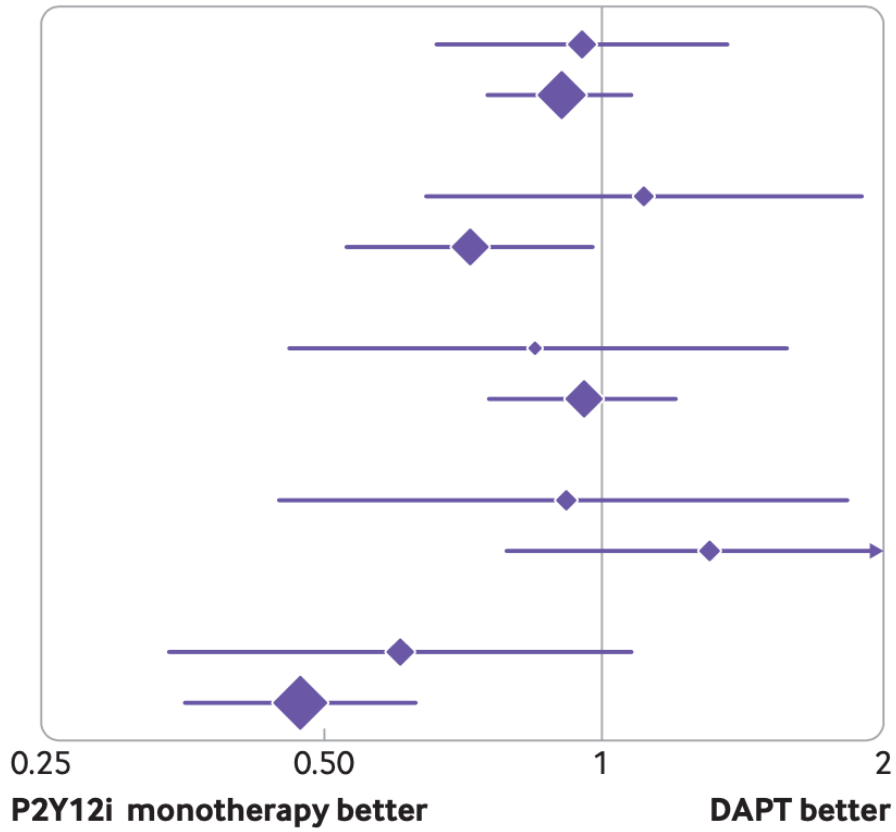
P2Y12 inhibitor monotherapy or dual antiplatelet therapy after coronary revascularisation: individual patient level meta-analysis of randomised controlled trials

	P2Y12i monotherapy (%) (n=11 634)	DAPT (%) (n=11 674)	Hazard ratio (95% CI)	P value for interaction	Hazard ratio (95% CI)
Primary outcome					
Clopidogrel	60/2618 (2.5)	65/2650 (2.7)		0.16	0.94 (0.66 to 1.33)
Newer P2Y12i	243/9016 (2.9)	273/9024 (3.4)			0.89 (0.75 to 1.06)
All cause mortality					
Clopidogrel	29/2618 (1.2)	27/2650 (1.1)		0.16	1.09 (0.65 to 1.84)
Newer P2Y12i	78/9016 (0.9)	110/9024 (1.4)			0.71 (0.53 to 0.95)
Myocardial infarction					
Clopidogrel	19/2618 (0.8)	23/2650 (1.0)		0.23	0.84 (0.46 to 1.54)
Newer P2Y12i	148/9016 (1.8)	158/9024 (1.9)			0.94 (0.75 to 1.17)
Stroke					
Clopidogrel	15/2618 (0.6)	17/2650 (0.7)		0.40	0.90 (0.45 to 1.79)
Newer P2Y12i	36/9016 (0.5)	28/9024 (0.3)			1.29 (0.79 to 2.11)
BARC 3 or 5					
Clopidogrel	19/2618 (0.8)	32/2650 (1.3)		0.41	0.60 (0.34 to 1.06)
Newer P2Y12i	78/9016 (0.9)	165/9024 (1.9)			0.47 (0.36 to 0.62)



Valgimigli et al. 2021

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Aspirin Withdrawal: Guidelines

- ESC Myocardial Revasc (2018)

  P2Y12i monotherapy after 6 months DAPT (IIa)

- ESC NSTE-ACS (2020)

  P2Y12i monotherapy after 3-6 months DAPT (IIa)

- ACC/AHA Revasc (2021)

  P2Y12i monotherapy after 1-3 months DAPT (IIa)

Neumann et al. 2018; Collet et al. 2020; Lawton et al. 2021

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De-escalation

- Switch from tica/pras to clopidogrel
  - Guided (genotype or platelet function testing)
  - Unguided

- Transition to lower dose of tica/pras
  - Tica 90 - > 60
  - Pras 10 -> 5

- DAPT is maintained at lower bleeding risk

Neumann et al. 2018; Collet et al. 2020; Lawton et al. 2021

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De-escalation Evidence Base

Trial	$P2Y_{12}$	Sample size	Strategy	Design	Major Bleeding (n)	MACE (n)
BLESS						3
HOST-REDUCE POLYTECH AC						17
HOPE-TAILOR						2
ANTARCTIC						70
TROPICAL-AC						37
POPular Gen						75
TOPIC						67
TALOS-AMI						65
A-MATCH	Prasugrel	255	½ dose or guided	N/A	2	5

Accumulated Evidence Base

Randomized Patients ~ 12,000

Major Bleeding Events – 309

Ischemic Events – 341

Carrabba et al. 2016; Kim et al. 2020; Kim et al. 2021; Cuisset et al. 2017; Claassens et al., 2019; Sibbing et al. 2017; Cayla et al., 2016; Jin et al. 2021; Jeong et al., 2021

De-escalation: Results

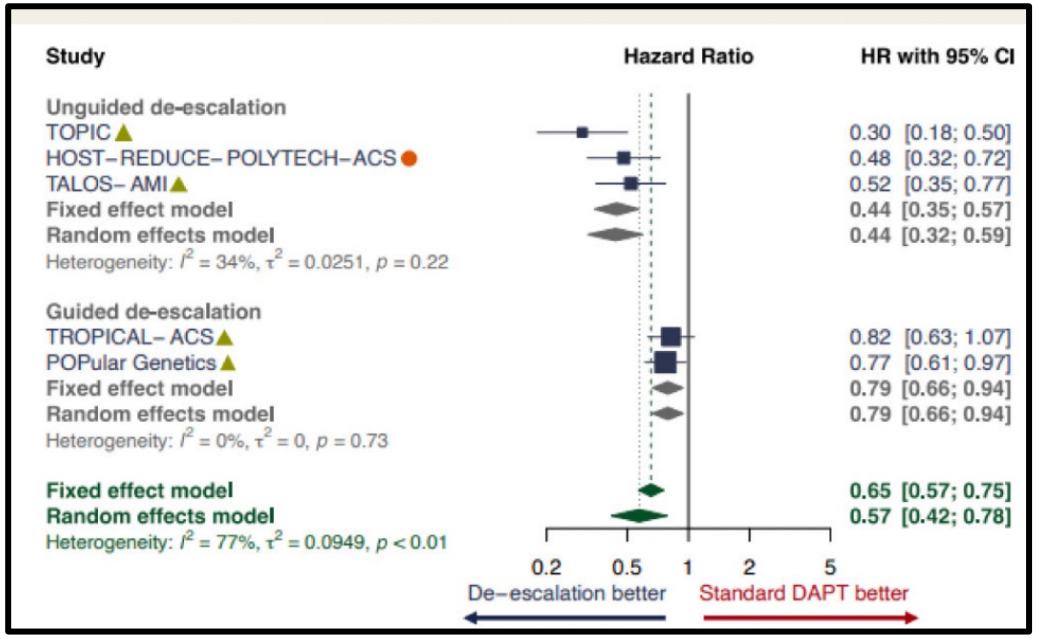
Meta-analysis; 5 RCT; 10,779 patients

De-escalation (guided; unguided; lower dose) versus standard DAPT

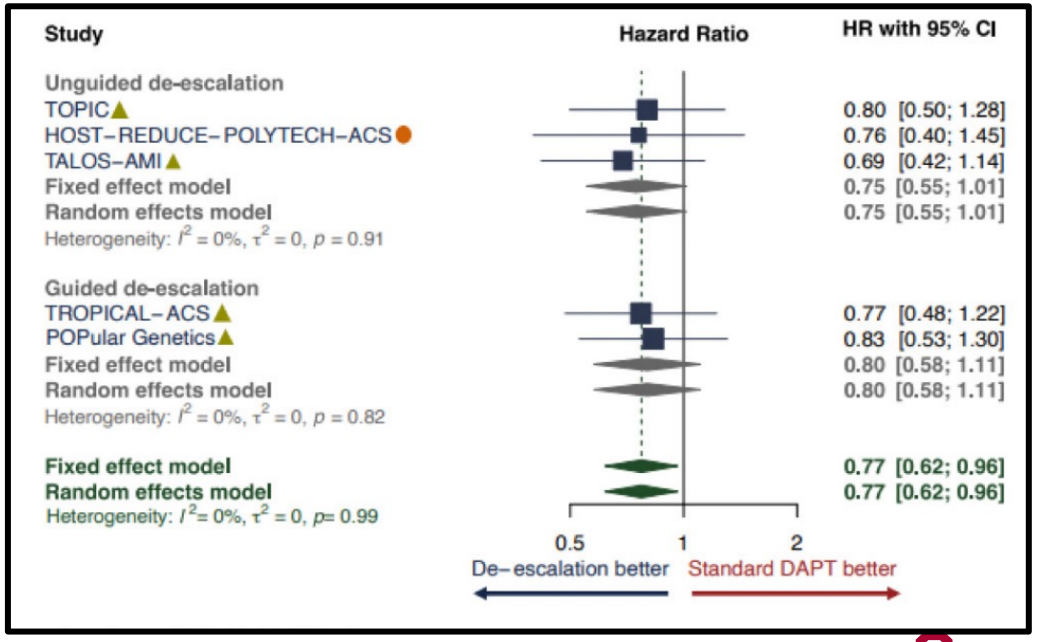
De-escalation reduced bleeding and MACE

Results consistent guided/unguided approaches

Clinically relevant bleeding



MACE



Laudani et al., 2022

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De-Escalation: Guidelines

- ESC Myocardial Revasc (2018)

  Guided (IIb)

- ESC NSTE-ACS (2020)

  Guided or unguided (IIb)

- ACC/AHA Revasc (2021)

  Not mentioned

Neumann et al. 2018; Collet et al. 2020; Lawton et al. 2021

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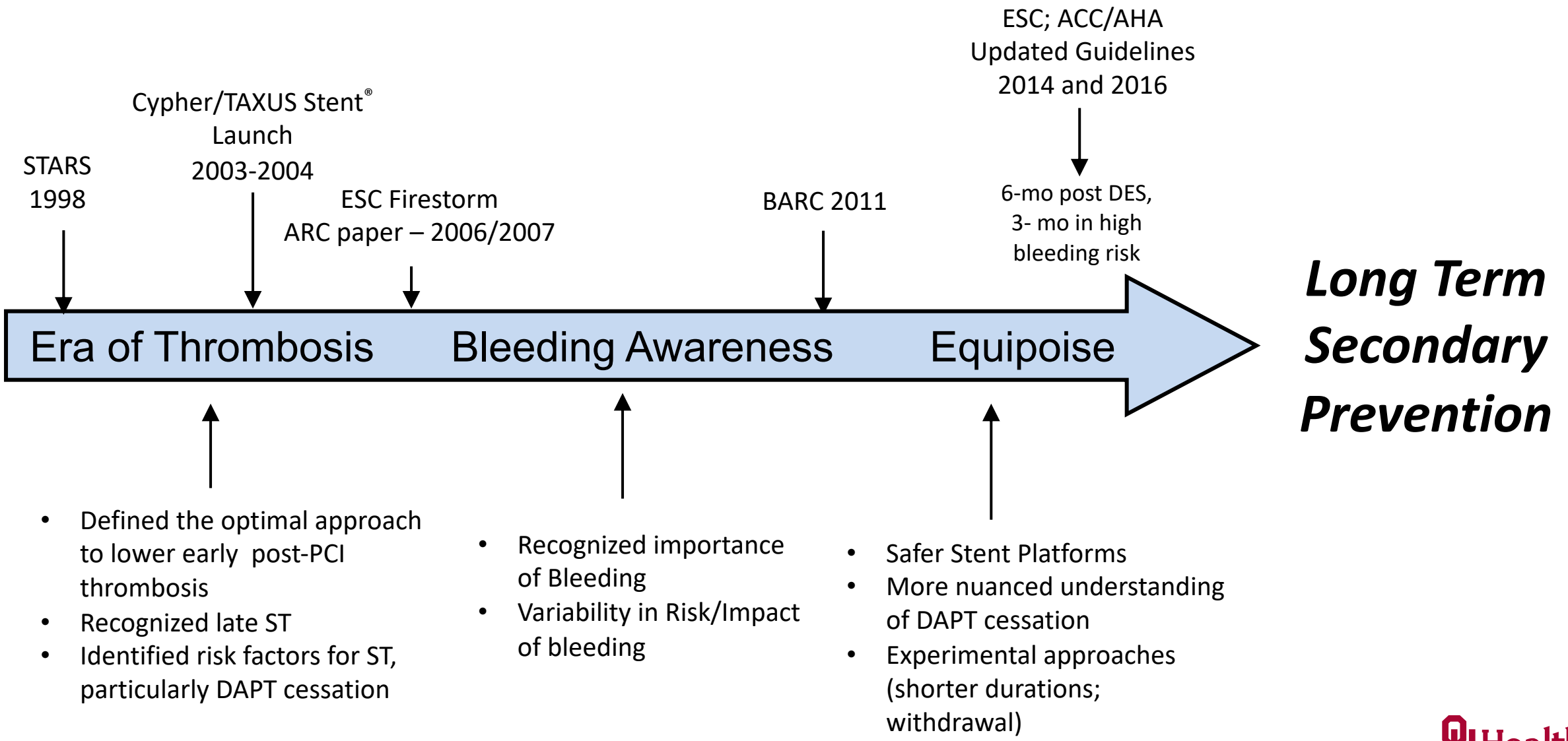
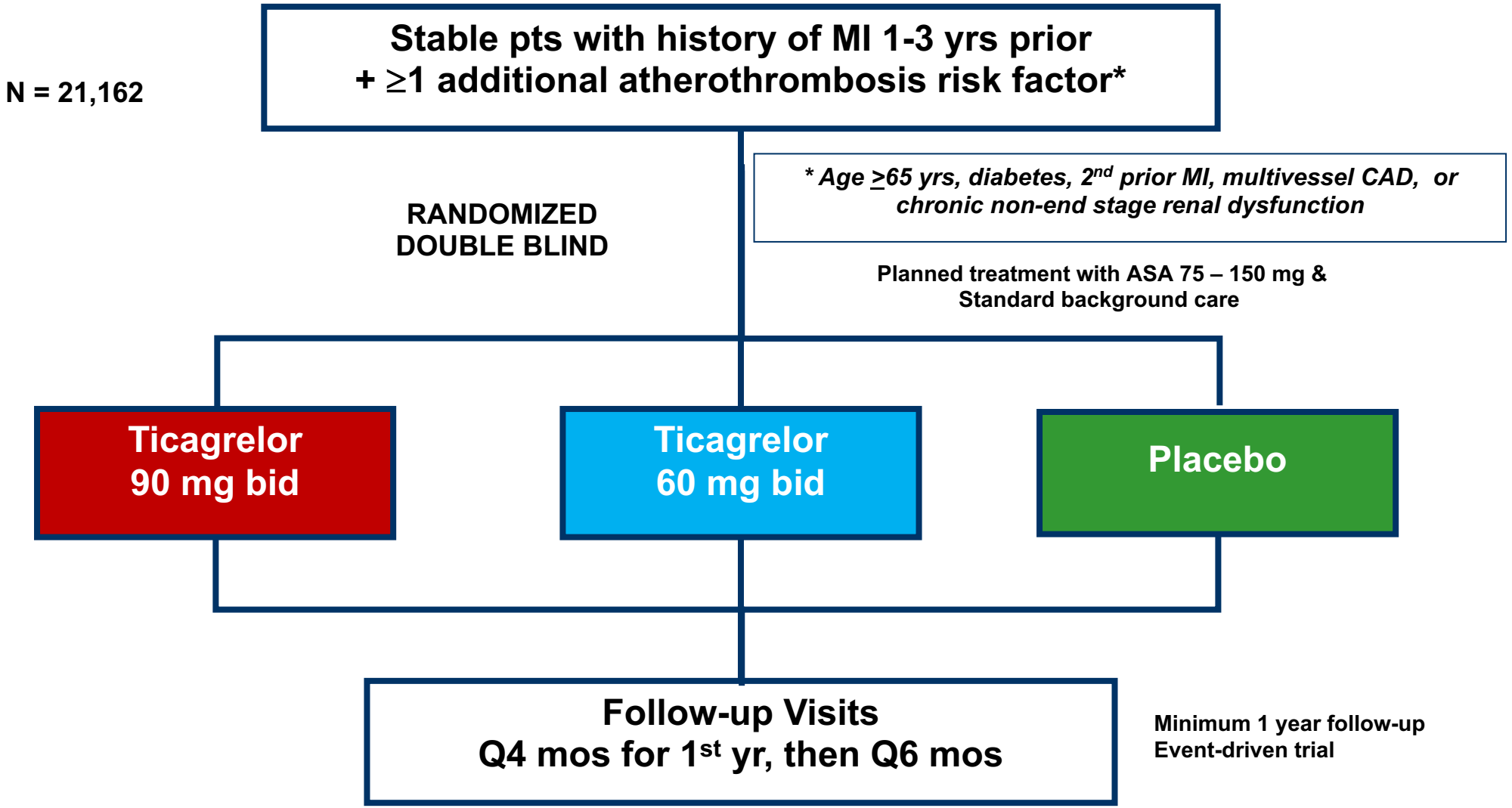
DAPT: Evolution over time

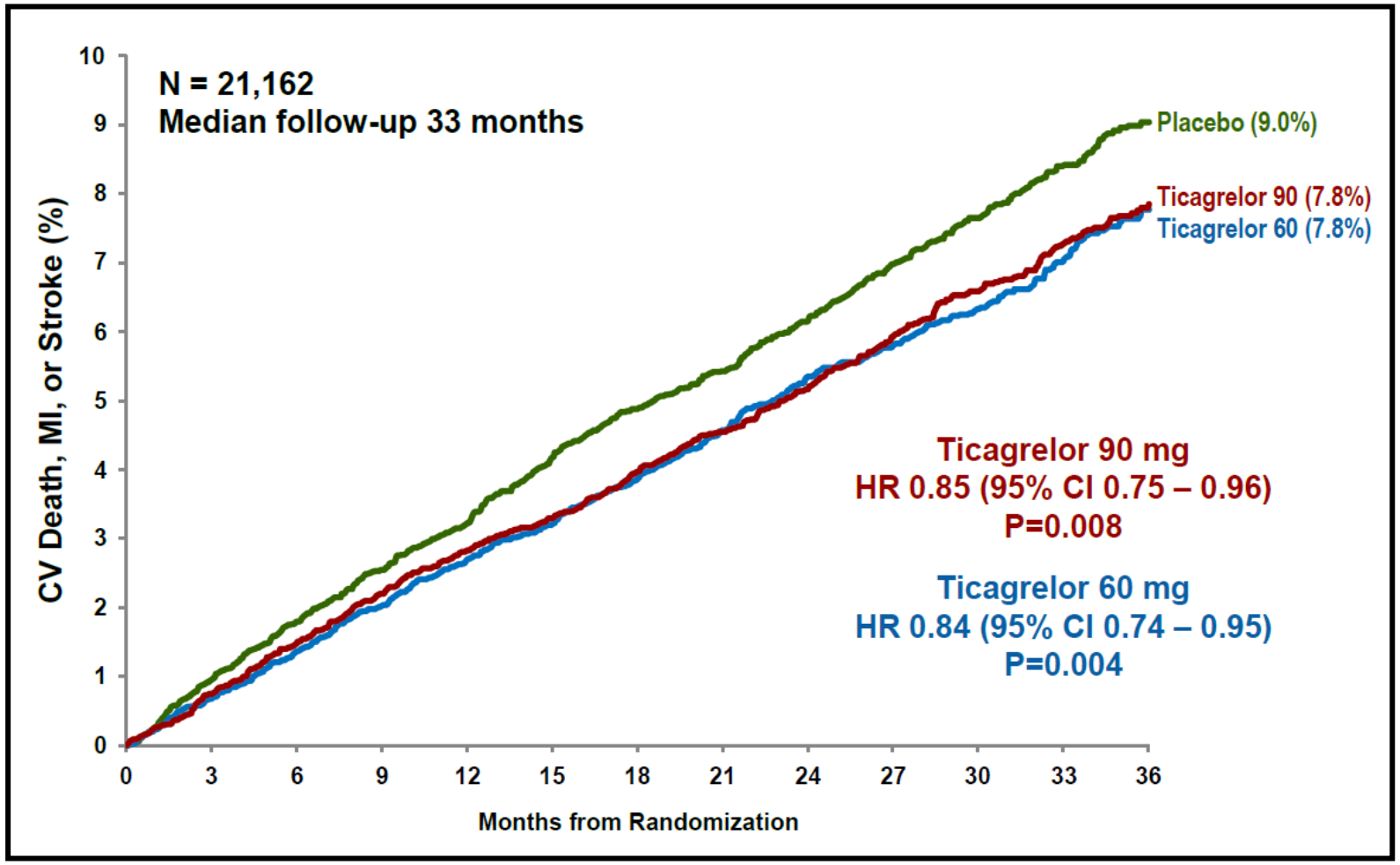


PEGASUS (Prior MI)



Bonaca et al., AHJ 2014

PEGASUS (Prior MI)



Major bleeding increase by absolute ~ 1.3%

No significant difference in fatal bleeding or ICH

FDA label for ticagrelor expanded for use in patients with prior MI at 60 mg twice daily dose in 2015

Bonaca et al., NEJM 2015

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THEMIS (Diabetes Mellitus)

- Study population: Stable CAD (~ 60% prior PCI) and DM. ***Prior MI excluded***
- n = 19,220
- Ticagrelor plus ASA vs. ASA alone
- Primary efficacy EP: CV death, MI , stroke
- Primary safety EP: Major Bleeding
- Median f/u 40 months

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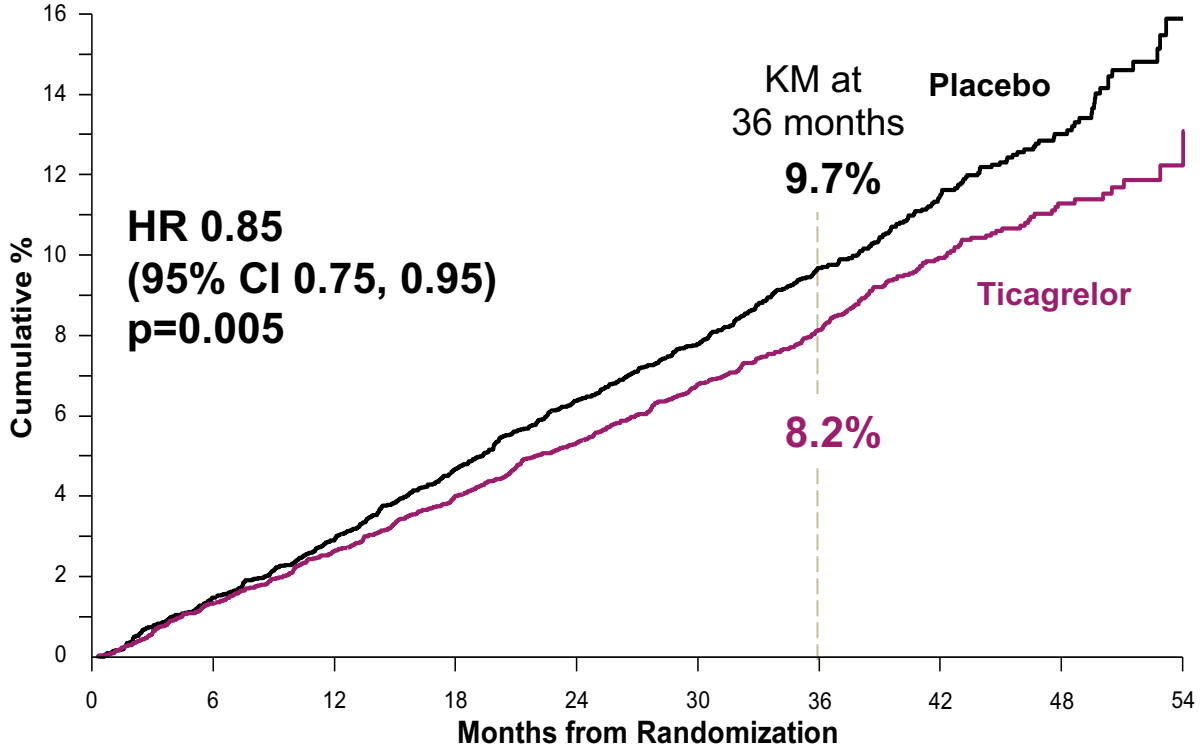
Net Clinical Benefit

All cause death, MI, stroke, fatal bleed, or ICH (ITT)*

History of PCI

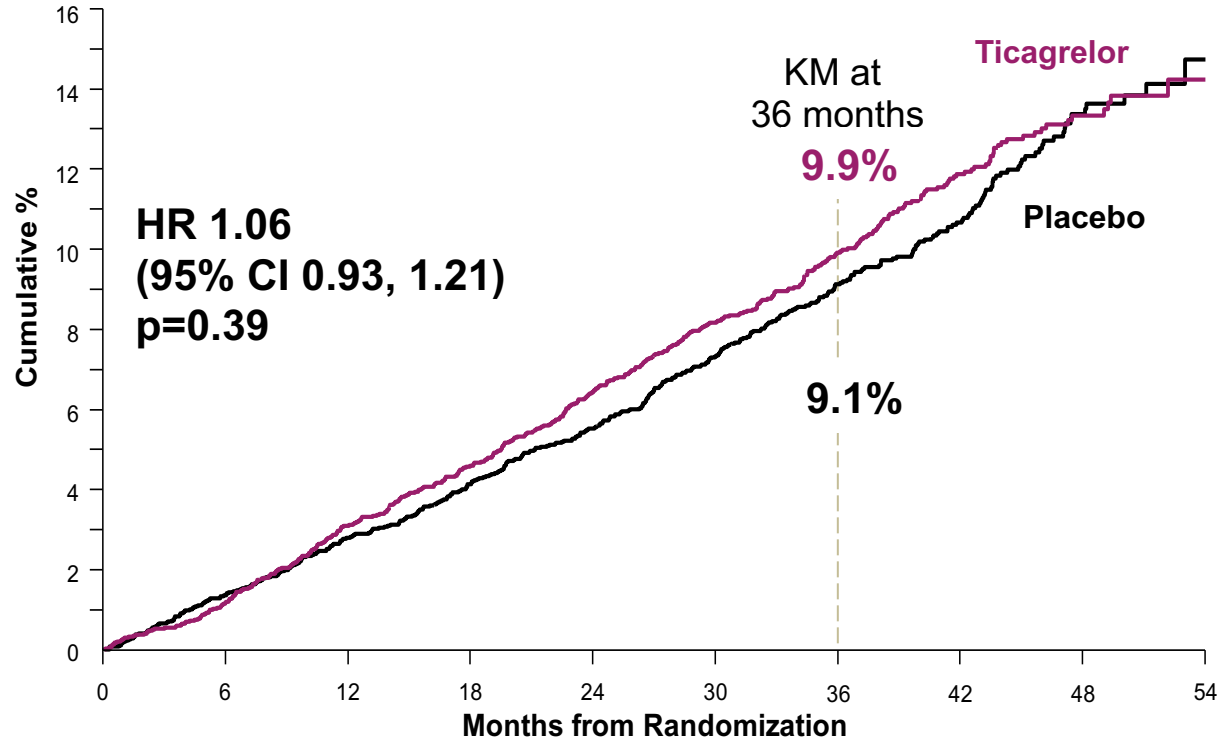
Interaction p=0.012

No history of PCI



Number at risk

Ticagrelor	5558	5433	5339	5240	5153	5037	3484	2124	981	100
Placebo	5596	5480	5390	5274	5166	5060	3470	2128	993	102



Number at risk

Ticagrelor	4061	3978	3881	3813	3728	3620	2471	1527	696	68
Placebo	4005	3932	3859	3799	3737	3628	2455	1549	690	70

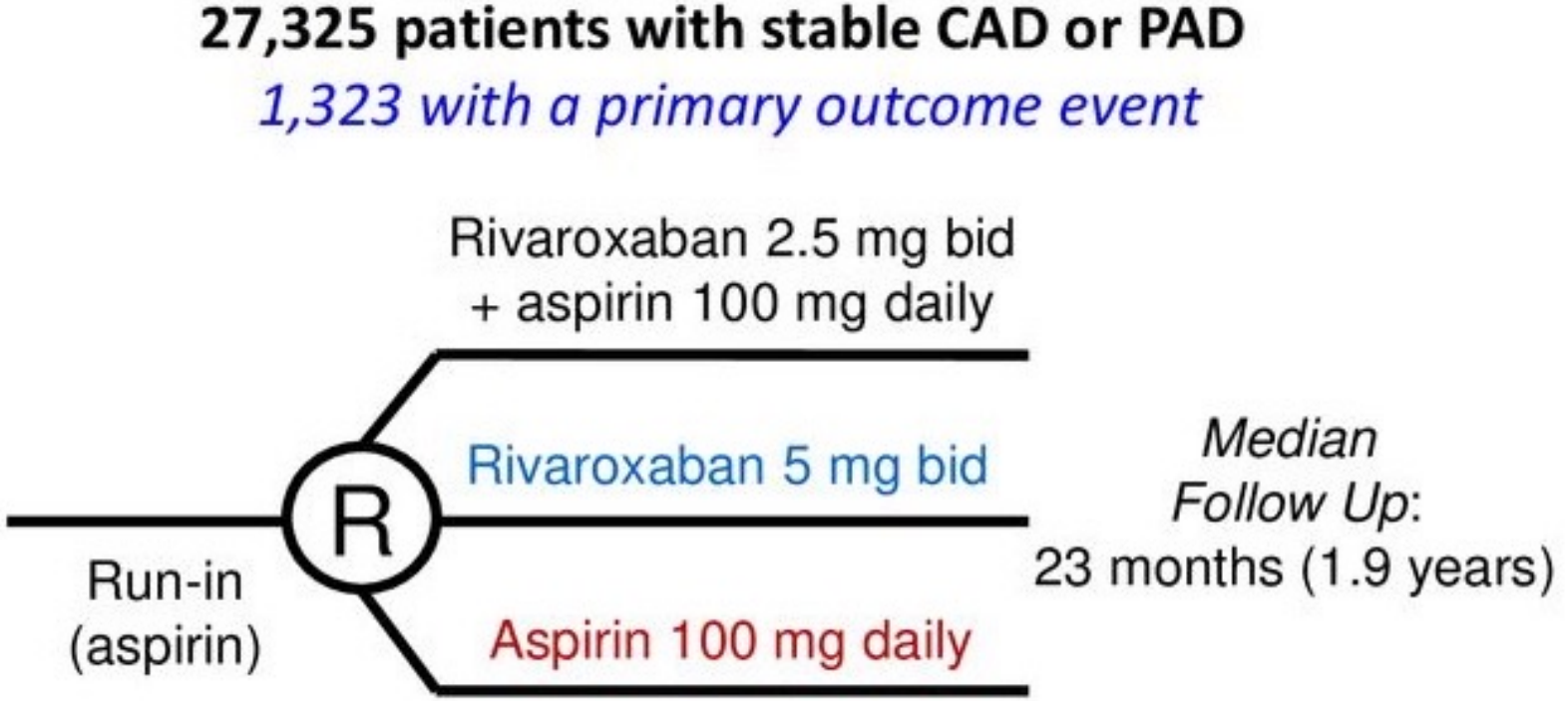
*Prespecified definition of net clinical benefit.

CI=confidence interval; HR=hazard ratio; ICH=intracranial hemorrhage; ITT=intention to treat; MI=myocardial infarction; PCI=percutaneous coronary intervention

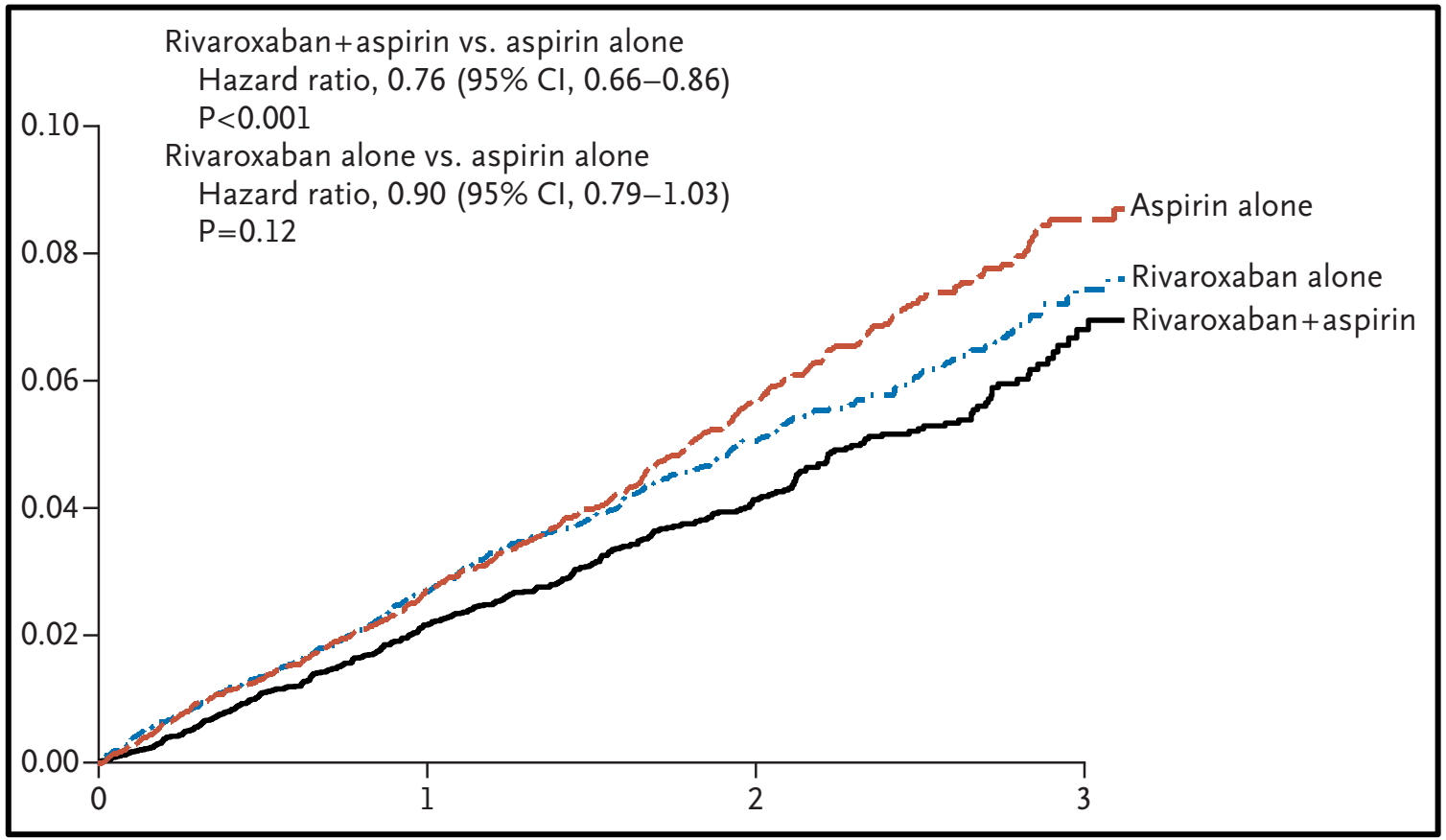
Bhatt DL, Steg PG, et al. Lancet 2019 http://dx.doi.org/10.1016/ S0140-6736(19)31887-2.

COMPASS (Dual Pathway Inhibition)

- Randomized, placebo controlled, double blinded trial
- Ongoing arm testing proton pump inhibitor pantoprazole versus placebo (PPI arm)



COMPASS (Dual Pathway Inhibition)



Major bleeding increase by absolute ~ 70%

No significant difference in fatal bleeding or ICH

Reduction in all-cause mortality with riva + aspirin

Trial terminated early due to efficacy

Eikelboom et al., NEJM 2017

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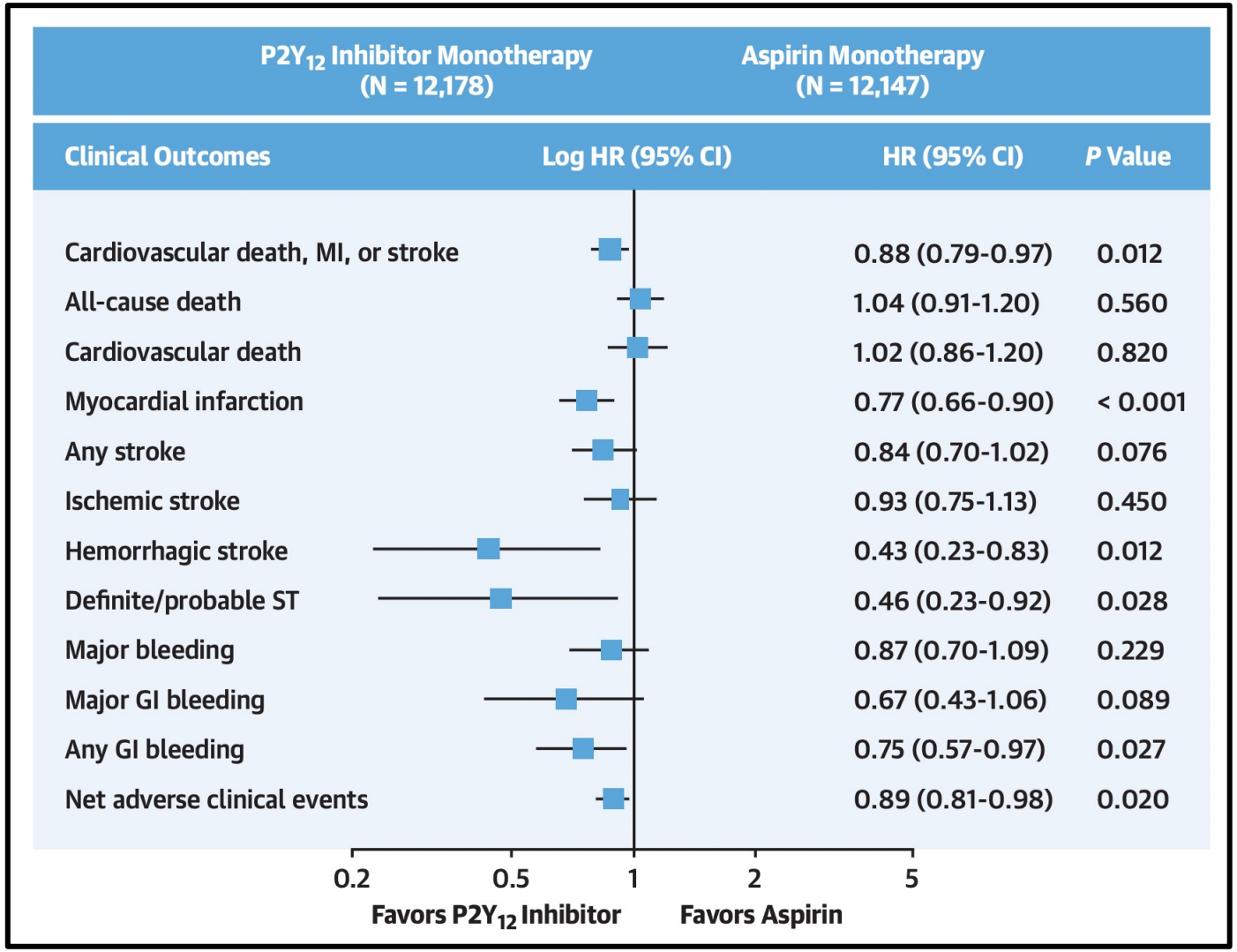
Aspirin versus $P2Y_{12}$ inhibitor monotherapy?



Patient-level meta-analysis

7 trials; 24,325 patients

Majority received clopidogrel (62%)

Less MI, hemorrhagic stroke and GI bleeding with $PY_{12}i$ monotherapy

"…$P2Y_{12}$ inhibitor monotherapy might be preferred over aspirin monotherapy for long-term secondary prevention in patients with established CAD."

Gragnano et al., JACC 2023

ESC 2019 Guidelines

Adding a second antithrombotic drug to aspirin for long-term secondary prevention should be considered in patients with a **high risk** of ischaemic events[c] and without high bleeding risk[d] (see *Table 9* for options).[289,296,297,307]	**IIa**
Adding a second antithrombotic drug to aspirin for long-term secondary prevention may be considered in patients with at least a **moderately increased risk** of ischaemic events[e] and without high bleeding risk[d] (see *Table 9* for options).[289,296,297,307]	**IIb**

High ischemic risk: MV CAD plus DM requiring medication; recurrent MI; PAD; CKD

Drug option	Dose	Indication	Additional cautions	References
Clopidogrel	75 mg o.d.	Post-MI in patients who have tolerated DAPT for 1 year		289,290
Prasugrel	10 mg o.d or 5 mg o.d.; if body weight <60 kg or age >75 years	Post-PCI for MI in patients who have tolerated DAPT for 1 year	Age >75 years	289,290,313
Rivaroxaban	2.5 mg b.i.d.	Post-MI >1 year or multivessel CAD	Creatinine clearance 15 - 29 mL/min	297
Ticagrelor	60 mg b.i.d.	Post-MI in patients who have tolerated DAPT for 1 year		291–293,307,314

Knuuti et al., EHJ 2019

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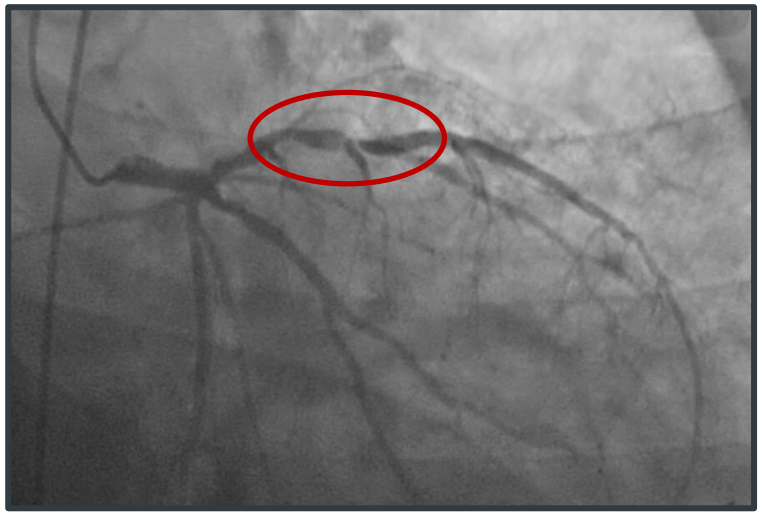
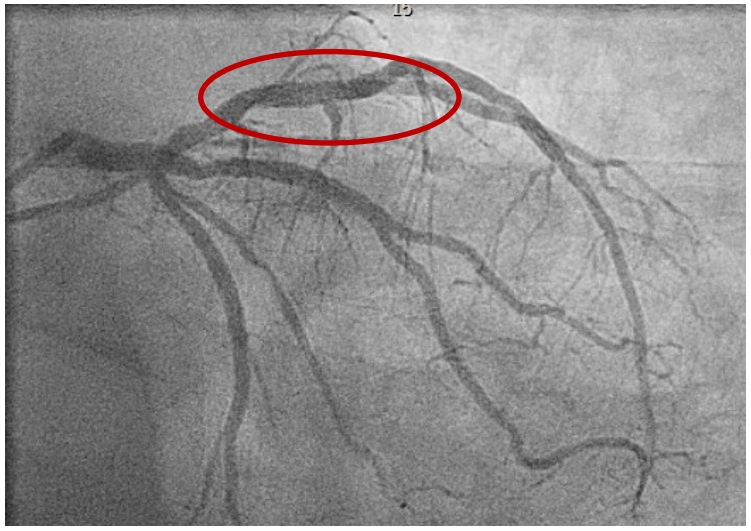
Case Resolution

Pre



Post



Underwent cutting balloon angioplasty and DES x 1

Discharged on aspirin + clopidogrel

After 30 days switch to clopidogrel monotherapy

Conclusions

- A short course of DAPT is necessary to prevent near-term atherothrombotic events
- Major bleeding is common and associates with a comparable mortality risk to that of myocardial infarction
- “True” HBR patients may be treated with a 4-week course of DAPT followed by single antiplatelet therapy (aspirin or clopidogrel)
- Aspirin withdrawal followed by $P2Y_{12}$ inhibitor monotherapy or de-escalation has emerged as an alternative to DAPT in the setting of ACS
- Long-term secondary prevention with DAPT or aspirin + low-dose DOAC provides a net clinical benefit in appropriate patients

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THANK YOU!!