Is Aspirin the Main Treatment in CV Disease?

No! We have a fancy alternative

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Classic….

A classic is an outstanding example of a particular style; *something of lasting worth or with a timeless quality*; of the first or highest quality, class, or rank – something that *exemplifies its class*.

To try to debate a classic drug…..

1. Hippocrates referred to their use of salicylic tea to reduce fevers around 400 BC

2. In 1897, Felix Hoffman/Friedrich succeed in synthesizing aspirin (Bayer)

3. Since 1900, the most widely used drug in the world.

To go against Dr. Serebruany……

雪上加霜

疊疊山中

When it rains, it pours….

I acknowledge that

1. Currently, aspirin is one of the most common medications to be prescribed to patients with CV disease…..

2. It is probably one of the cheapest medications as well….

However…. Let me raise a few questions

- Is aspirin a perfect medicine? What are the pitfalls of aspirin therapy?
- Was aspirin efficacious when used on top of another antiplatelet agent?
- What about head-to-head comparisons?
- If this is such a forgone conclusion, why is it being tested in so many new RCTs?

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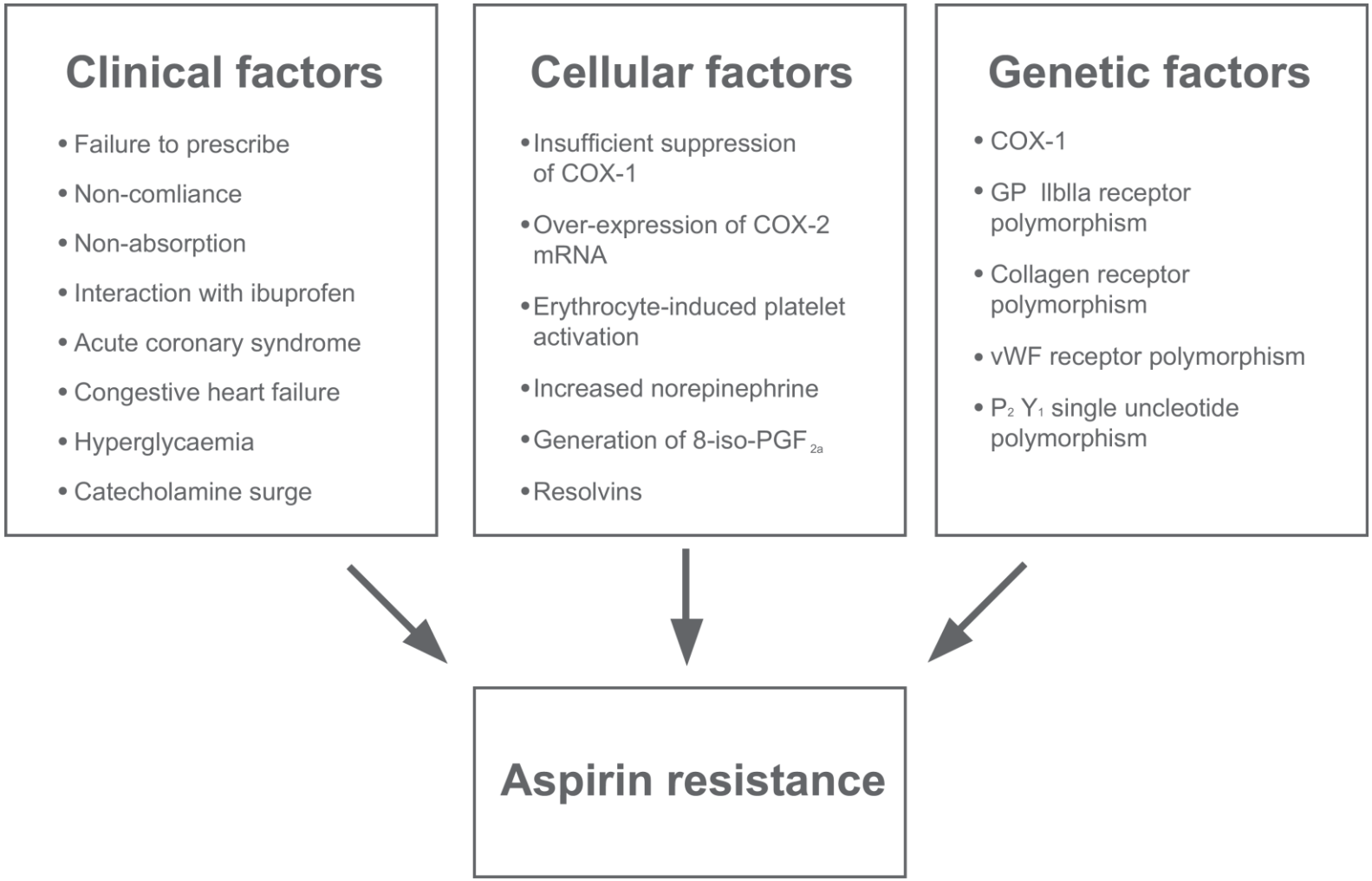
Clinical Issues with Aspirin

- Treatment Failure (“aspirin resistance”)
- Drug-drug interaction
- Various side effects.
- Gastrotoxicity and GI bleeding
- Bleeding risk

Mechanisms of Aspirin Resistance



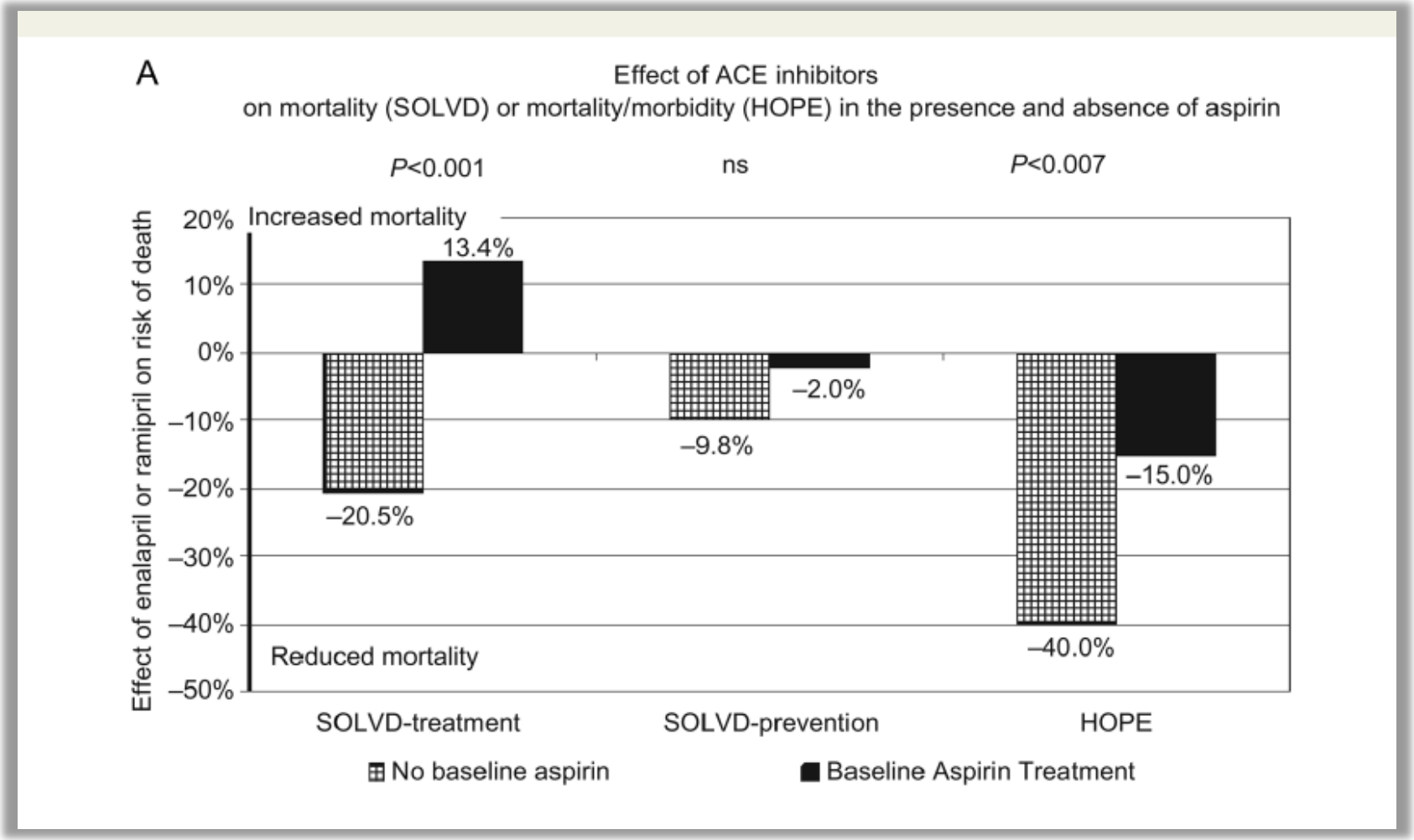
ADAPT-DES :
Aspirin Resistance (1 Year Outcome)

VerifyNow test	Def/ prob ST (n=70)	No def/ prob ST (n=8,513)	p-value
Aspirin ARU	426 ± 58	419 ± 55	0.30
- ARU ≥ 550	7.2%	5.6%	0.54
P2Y12 Base	305 ± 60	310 ± 58	0.56
P2Y12 PRU	234 ± 97	188 ± 97	<0.0001
- PRU > 208	65.2%	42.5%	0.0002
- PRU ≥ 230	53.6%	34.9%	0.001
P2Y12 % Inhibition	24.8 ± 27.0	40.1 ± 28.2	<0.0001
- Inhibition ≤ 11%	44.9%	19.9%	<0.0001
IIb/IIIa PAU	194 ± 56	193 ± 54	0.92

- Aspirin resistance was unrelated to ST, MI or death, but may be related to bleeding (HR0.65, p=0.04), questioning the utility of aspirin in pts with DES.

Stone GW, et al. Lancet. 2013 Aug 17;382(9892):614-23.

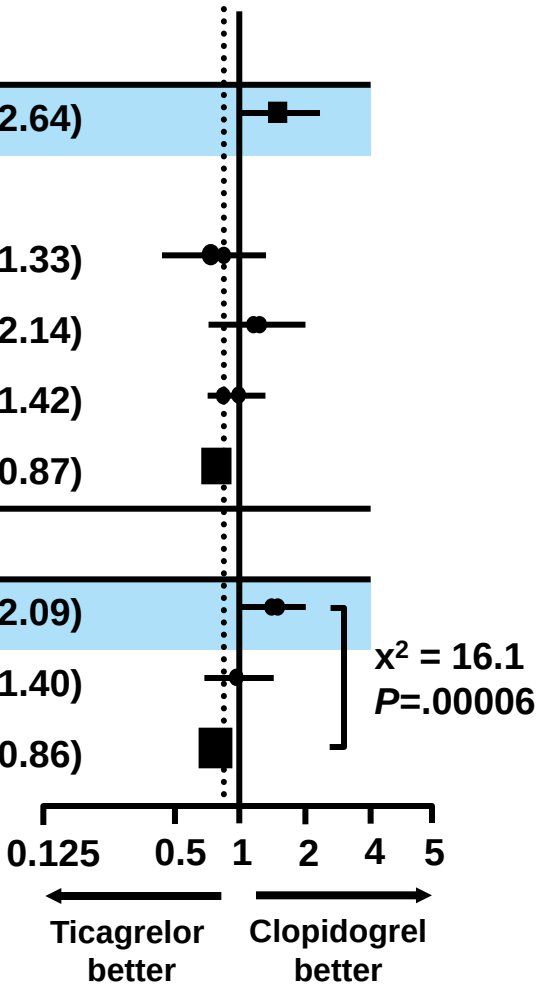
Aspirin Interaction with ACE-Inhibitors



Cleland JG. Eur Heart J 2013

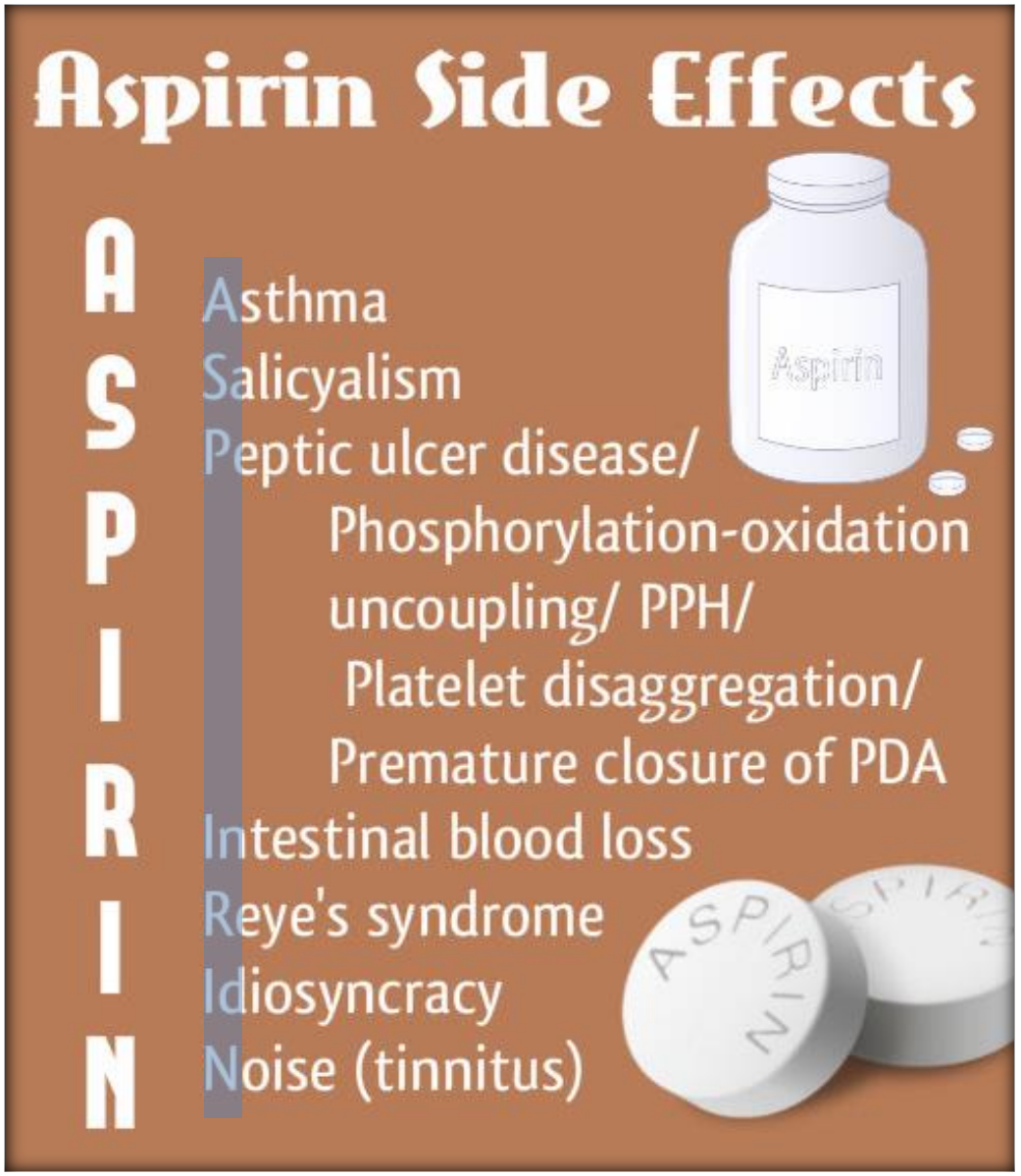
Aspirin interaction with Ticagrelor

Region	ASA Dose (mg)	Ticagrelor N	Ticagrelor E	Clopidogrel N	Clopidogrel E	HR (95% CI)
US	≥ 300	324	40	352	27	1.62 (0.99, 2.64)
	> 100 - < 300	22	2	16	2	
	≤ 100	284	19	263	24	0.73 (0.40, 1.33)
Non-US	≥ 300	140	28	140	23	1.23 (0.71, 2.14)
	> 100 - < 300	503	62	511	63	1.00 (0.71, 1.42)
	≤ 100	7449	546	7443	699	0.78 (0.69, 0.87)
Overall						
	≥ 300	464	68	492	50	1.45 (1.01, 2.09)
	> 100 - < 300	525	64	527	65	0.99 (0.70, 1.40)
	≤ 100	7733	565	4406	723	0.77 (0.69, 0.86)



Circulation 2011;124:544

Various Side Effects Of Aspirin



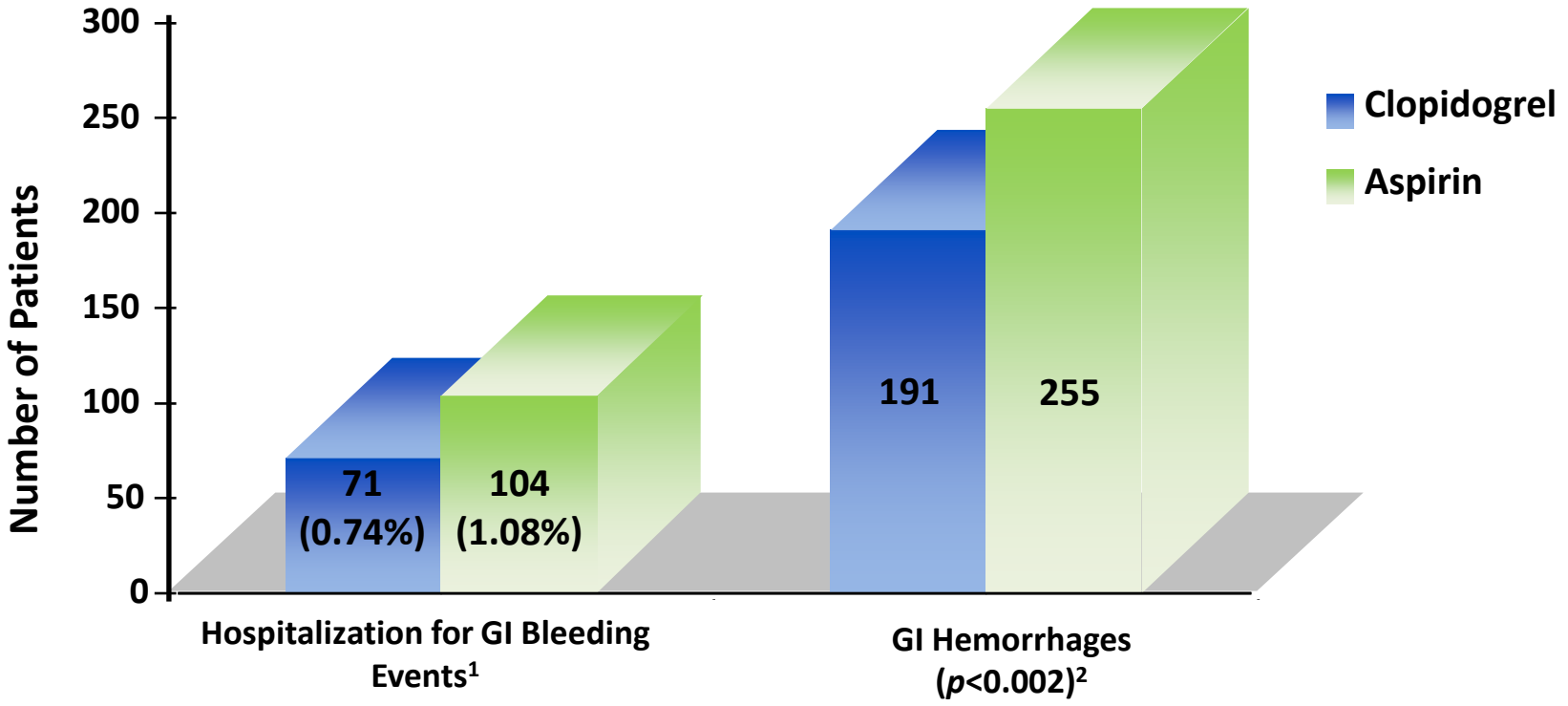
CAPRIE: Safety Profile
Increased Gastrotoxicity

Adverse experiences†	ASA (n = 9,586)	Clopidogrel (n = 9,599)	*p*-value
Diarrhoea (severe)[1]	0.11%	0.23%	NS
Gastritis[2]	1.32%	0.75%	< 0.001
Gastrointestinal ulcer[2]	1.15%	0.68%	0.001
Gastrointestinal haemorrhage (severe)[1]	0.71%	0.49%	< 0.05
Intracranial haemorrhage[1]	0.49%	0.35%	NS
Rash (severe)[1]	0.10%	0.26%	< 0.05
Neutropenia[2]	0.17%	0.10%	NS

*Patients with ASA intolerance were excluded.
†Clinically severe or resulting in early drug discontinuation

1CAPRIE Steering Committee. Lancet 1996;348:1329–1339
2Harker LA et al. Drug Safety 1999;21:325–335

CAPRIE Safety: Hemorrhagic Events



- Trend to more cerebral hemorrhages, fatal or non-fatal, and more hemorrhagic deaths in aspirin group: 37 versus 51 (0.39% vs. 0.53%)

1. Bogousslavsky. Cerebrovasc Dis 1998;8(suppl 4):43. Abstract CLI 76.
2. CAPRIE Steering Committee. Lancet 1996;348:1329-1339.

Gastrointestinal Hemorrhage

Meta-analysis of 66,000 patients

Aspirin increased risk of GI bleed ~70%

2.5% with aspirin

1.4% with control

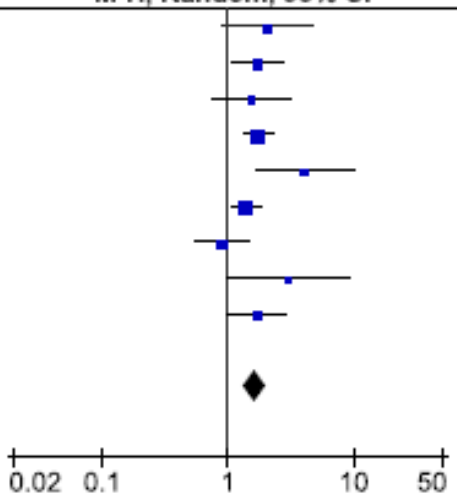
Derry S, et al. BMJ 2000

Aspirin and Major Bleeding

Study or Subgroup	Aspirin Events	Aspirin Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
BDT	29	3429	7	1710	5.5%	2.07 [0.91, 4.71]	1988
PHS	48	11037	28	11034	12.9%	1.71 [1.08, 2.73]	1989
TPT	20	2545	13	2540	7.2%	1.54 [0.77, 3.08]	1998
HOTT	136	9399	78	9391	21.9%	1.74 [1.32, 2.30]	1998
PPP	24	2226	6	2269	4.8%	4.08 [1.67, 9.96]	2001
WHS	127	19934	91	19942	22.4%	1.40 [1.07, 1.83]	2005
POPADAD	28	638	31	638	11.8%	0.90 [0.55, 1.49]	2008
JPAD	12	1262	4	1277	3.1%	3.04 [0.98, 9.39]	2008
AAA	34	1675	20	1675	10.4%	1.70 [0.98, 2.94]	2010
Total (95% CI)		**52145**		**50476**	**100.0%**	**1.62 [1.31, 2.00]**	
Total events	458		278				

Heterogeneity: Tau² = 0.03; Chi² = 12.36, df = 8 (*P* = .14); I² = 35%

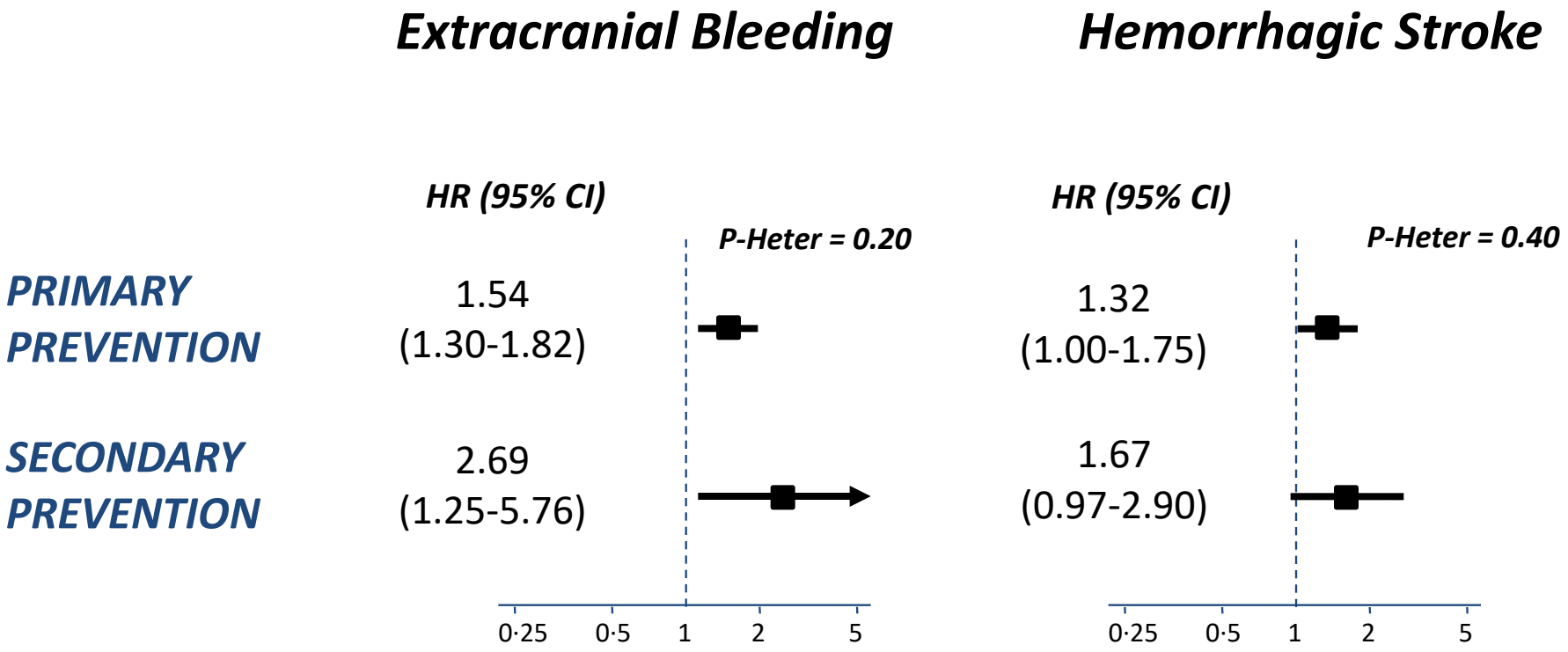
Test for overall effect: Z = 4.50 (*P* < .00001)



Berger JS. Am Heart J 2011

Risk of Bleeding With Aspirin

Antithrombotic Trialists Collaboration. Lancet 2009; 373:1849–60



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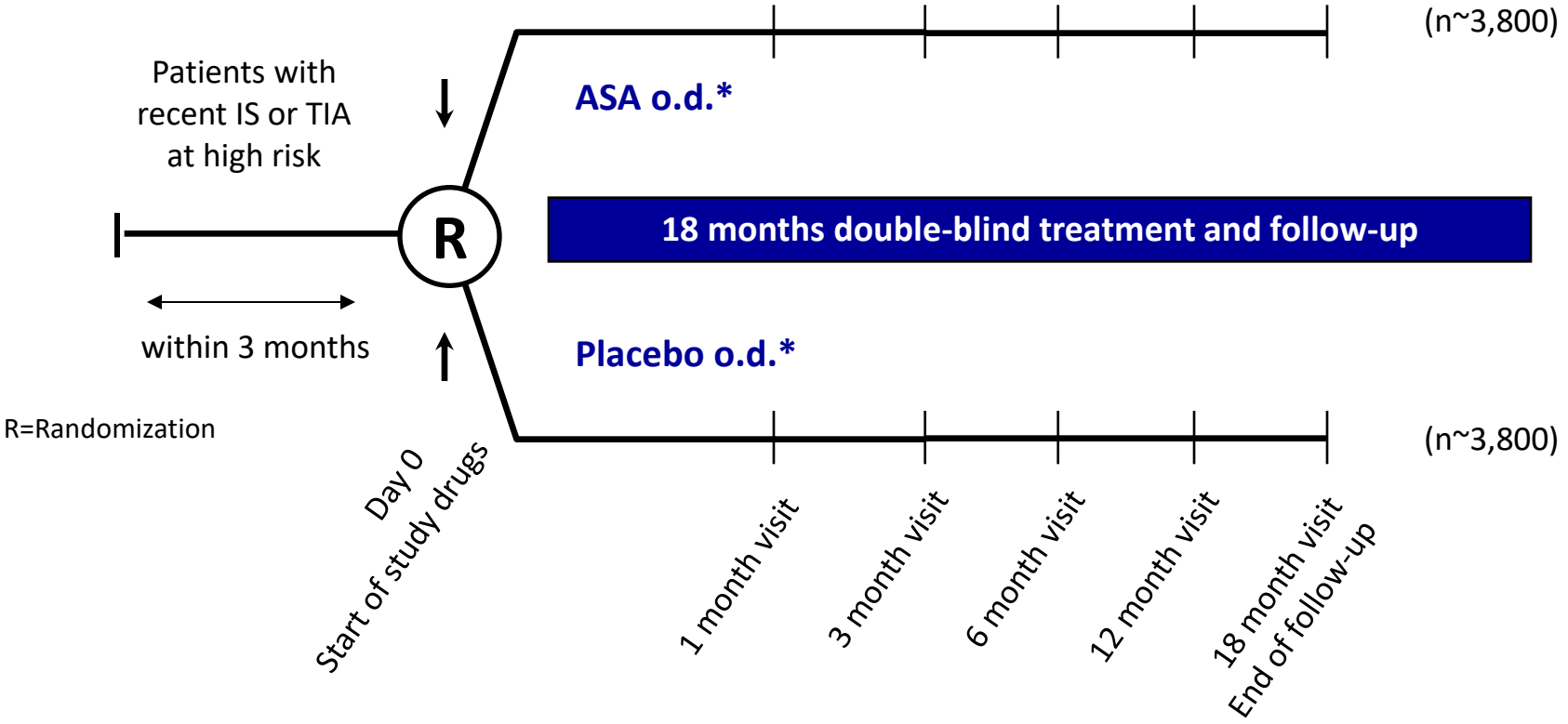
The MATCH Trial: Study Objectives and Design

The MATCH Trial is designed to determine the efficacy and safety of ASA compared to placebo in high-risk cerebrovascular patients receiving clopidogrel 75 mg and other standard therapies

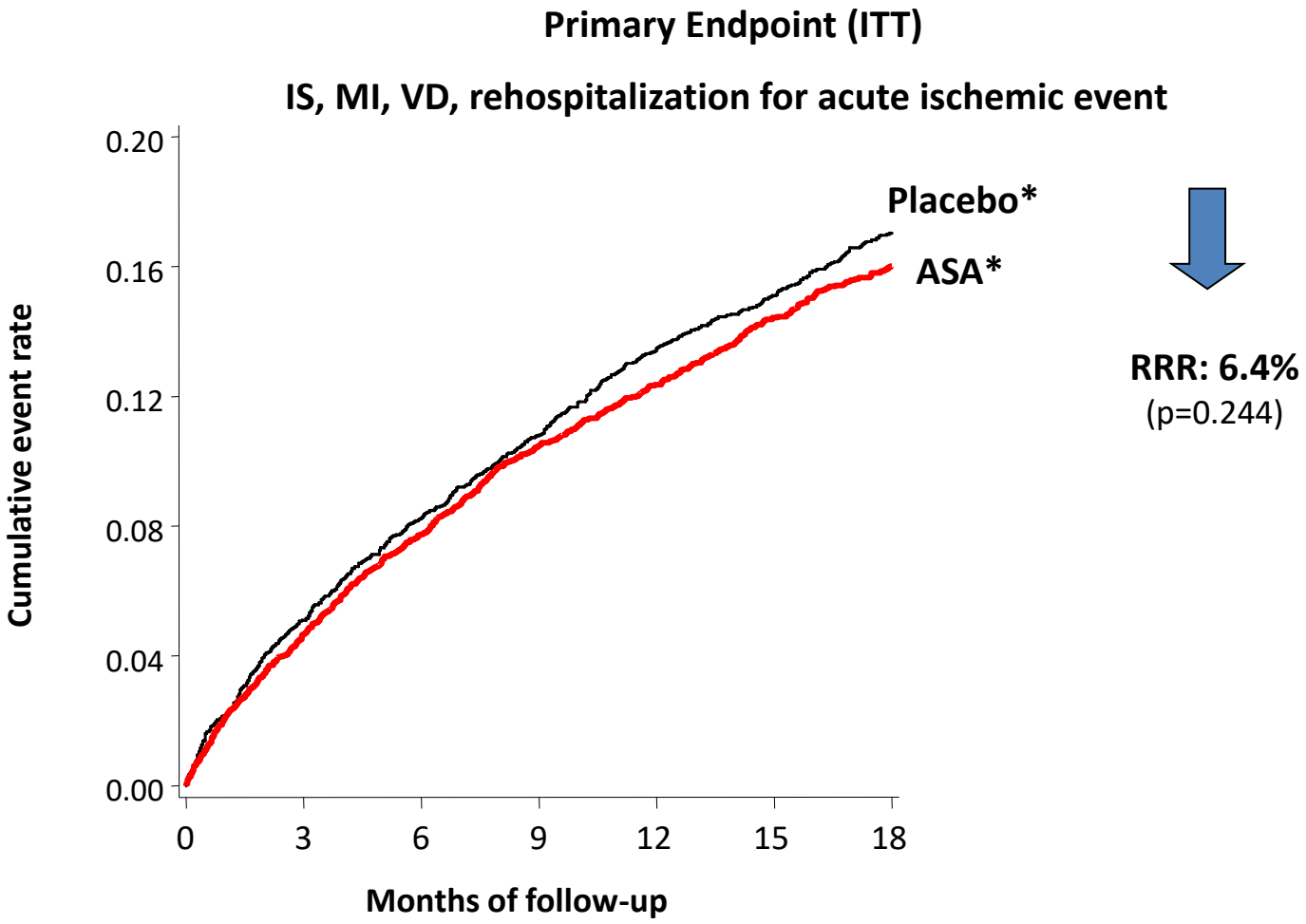


***All patients received clopidogrel and other standard therapies**

1. Diener H-C, *et al*. *Lancet* 2004; **364:** 331–337.

Aspirin on top of Clopidogrel:

No Significant Benefit in reduction of Major Vascular Events

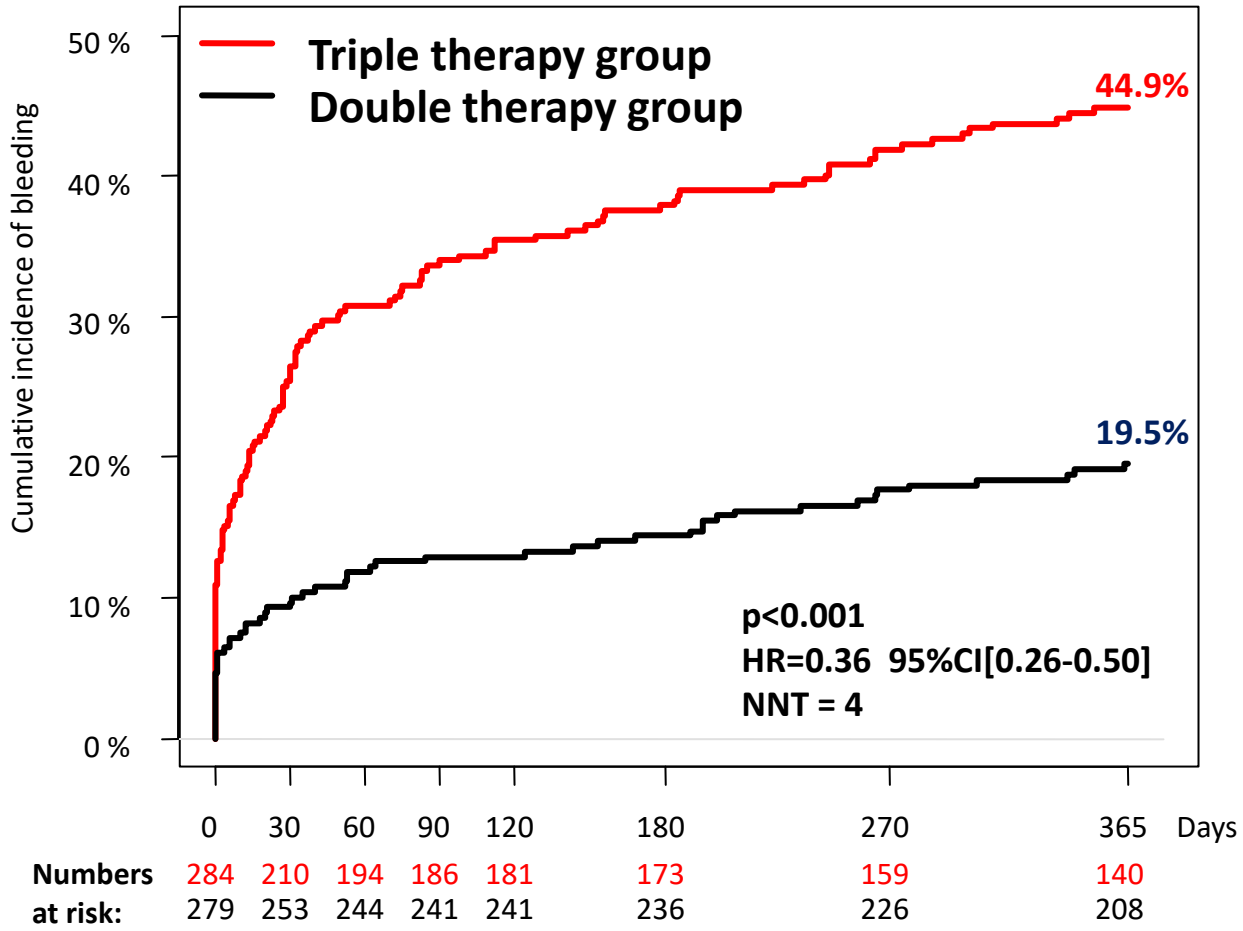


*All patients received clopidogrel and other standard therapies

Diener H-C, *et al*. *Lancet* 2004; **364:** 331–337.

A+C+W vs. C+W: WOEST Trial

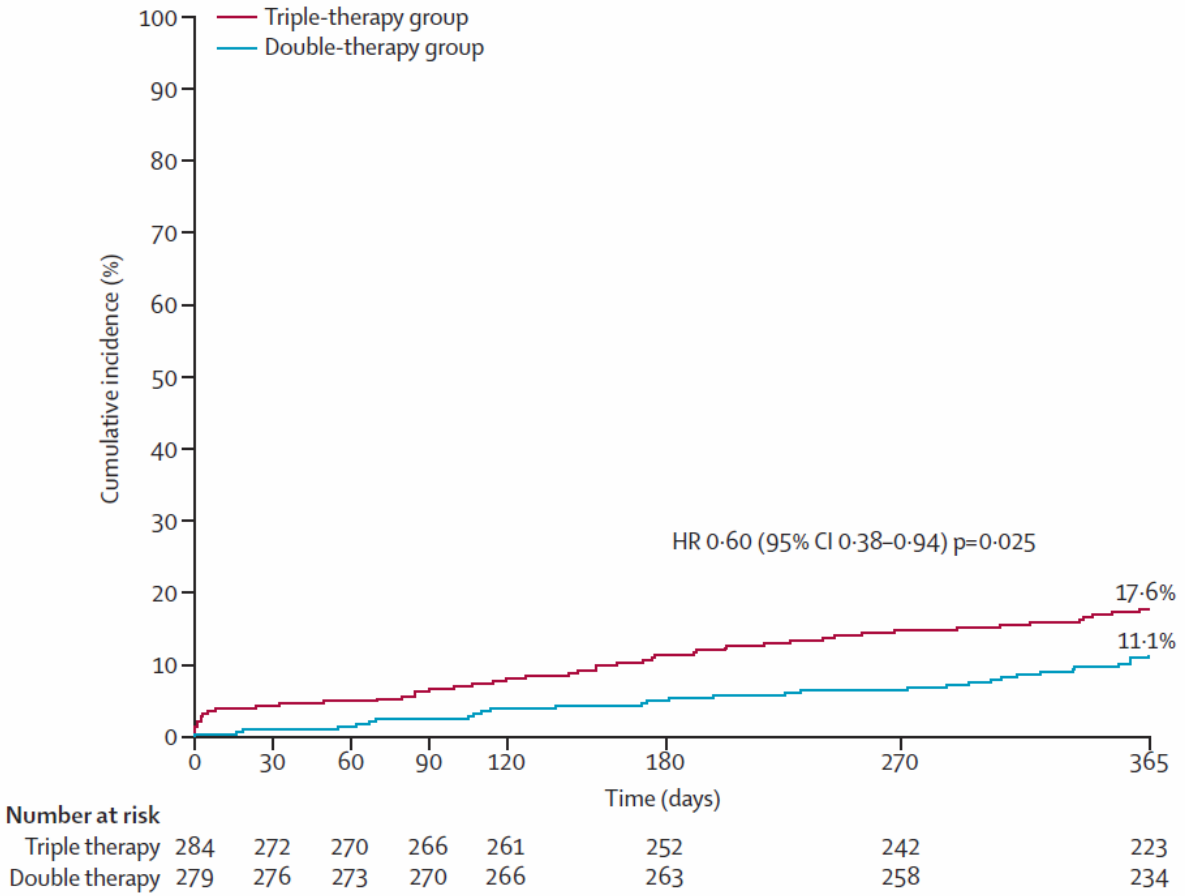
Primary Endpoint: Total number of bleeding events



Lancet 2013:381:1107-1115

A+C+W vs. C+W: WOEST Trial

Major 2ndary Endpoint: Death, MI, stroke, TVR or ST



Lancet 2013:381:1107-1115

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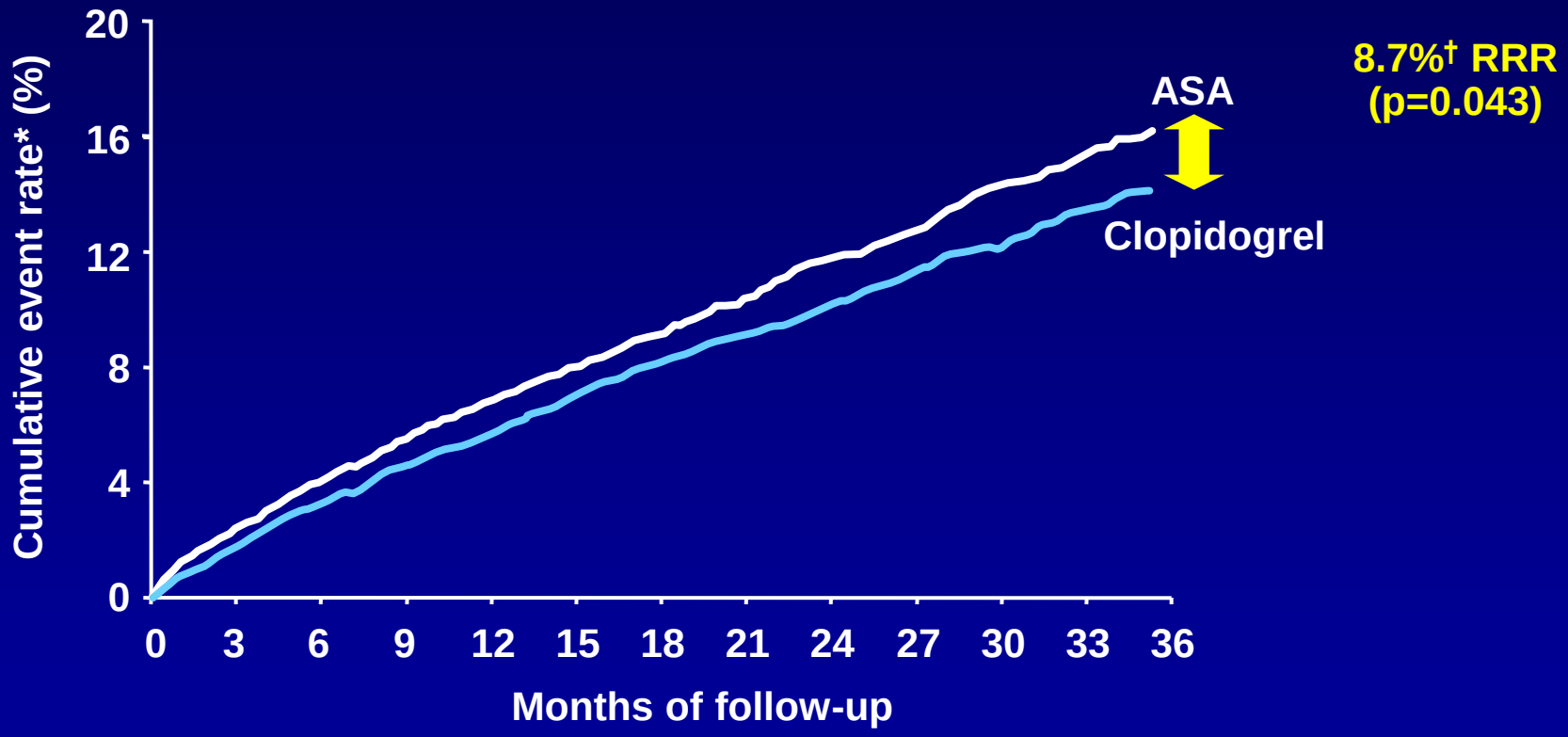
CAPRIE: Superior Efficacy of Clopidogrel versus ASA

Patients with recent MI, ischemic stroke, or symptomatic PAD



*MI, ischemic stroke or vascular death

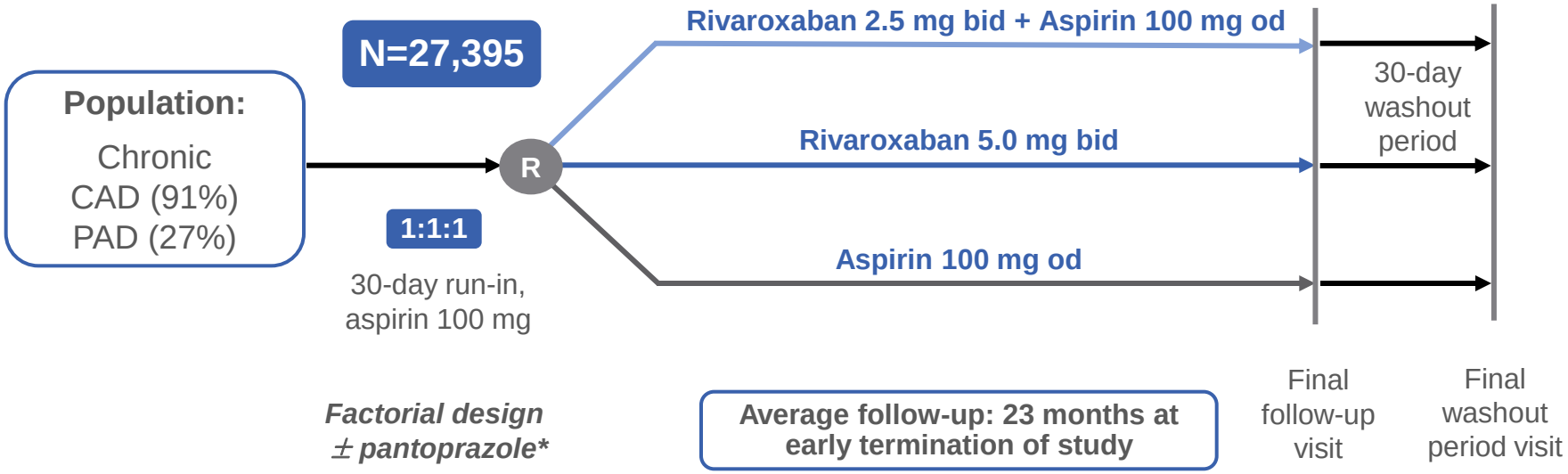
†Intent-to-treat analysis (n=19,185)

CAPRIE Steering Committee. *Lancet* 1996; 348: 1329.

CAD PAD

A Dual Pathway Approach Targeting Chronic Patients with CAD or PAD was Investigated in COMPASS

Objective: To determine the efficacy and safety of rivaroxaban, vascular dose of rivaroxaban plus aspirin or aspirin alone for reducing the risk of MI, stroke and cardiovascular death in CAD or PAD



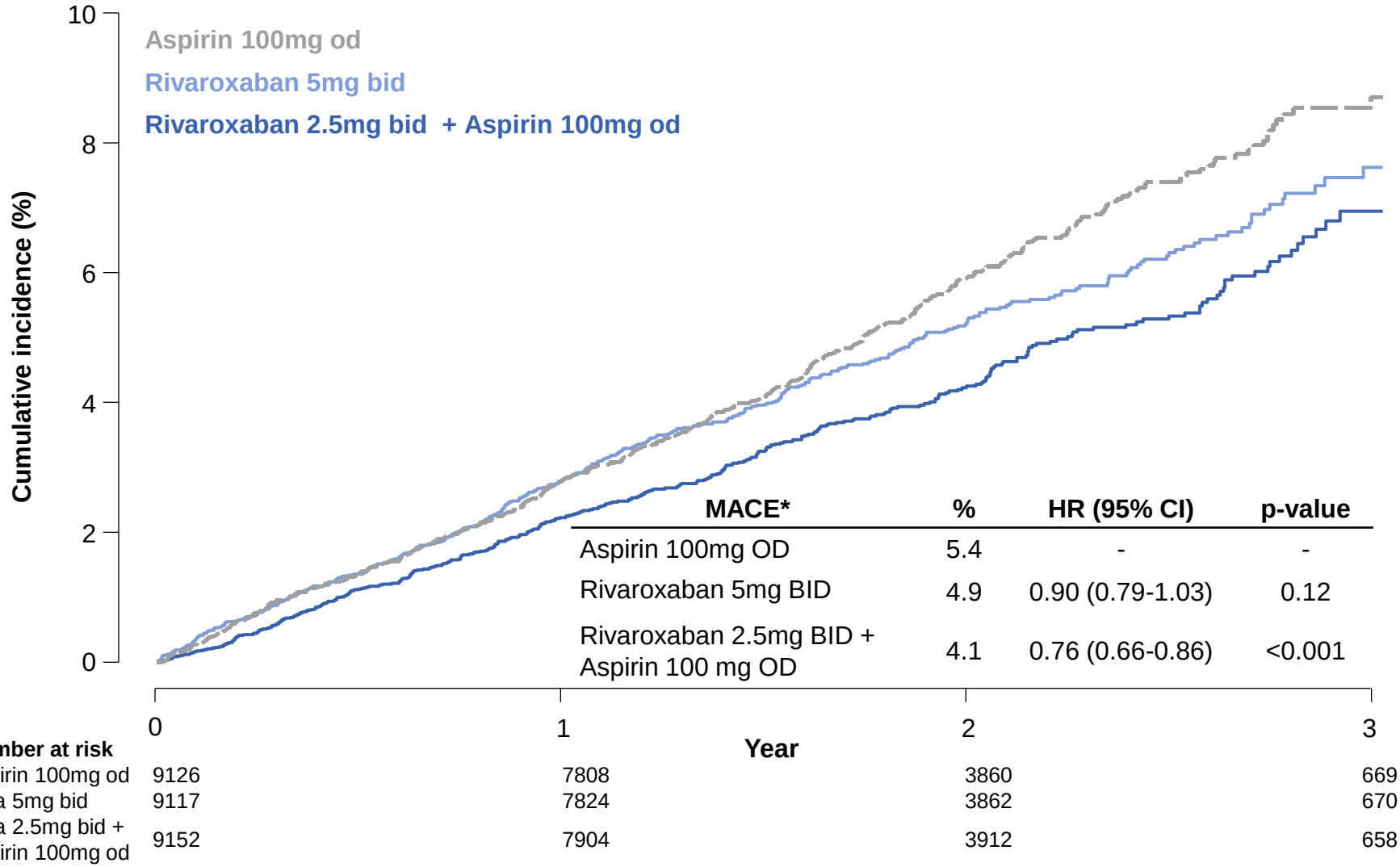
Antithrombotic investigations* were stopped 1 year ahead of expectations in Feb 2017 due to overwhelming efficacy in the rivaroxaban 2.5 mg bid + aspirin arm

*Patients who were not receiving a proton pump inhibitor (PPI) were randomized to pantoprazole or placebo (partial factorial design); the PPI pantoprazole component of the study is continuing; data will be communicated once complete

1. Eikelboom JW *et al. N Engl J Med* 2017; DOI: 10.1056/NEJMoa1709118;
2. Bosch J *et al. Can J Cardiol* 2017;33(8):1027–1035

COMPASS

Dual Pathway Inhibition with Rivaroxaban Vascular Dose 2.5 mg bid + Aspirin Reduced CV Death, Stroke and MI



MACE*	%	HR (95% CI)	p-value
Aspirin 100mg OD	5.4	-	-
Rivaroxaban 5mg BID	4.9	0.90 (0.79-1.03)	0.12
Rivaroxaban 2.5mg BID + Aspirin 100 mg OD	4.1	0.76 (0.66-0.86)	<0.001

Number at risk				
Aspirin 100mg od	9126	7808	3860	669
Riva 5mg bid	9117	7824	3862	670
Riva 2.5mg bid + Aspirin 100mg od	9152	7904	3912	658

*Rates as at mean follow up of 23 months

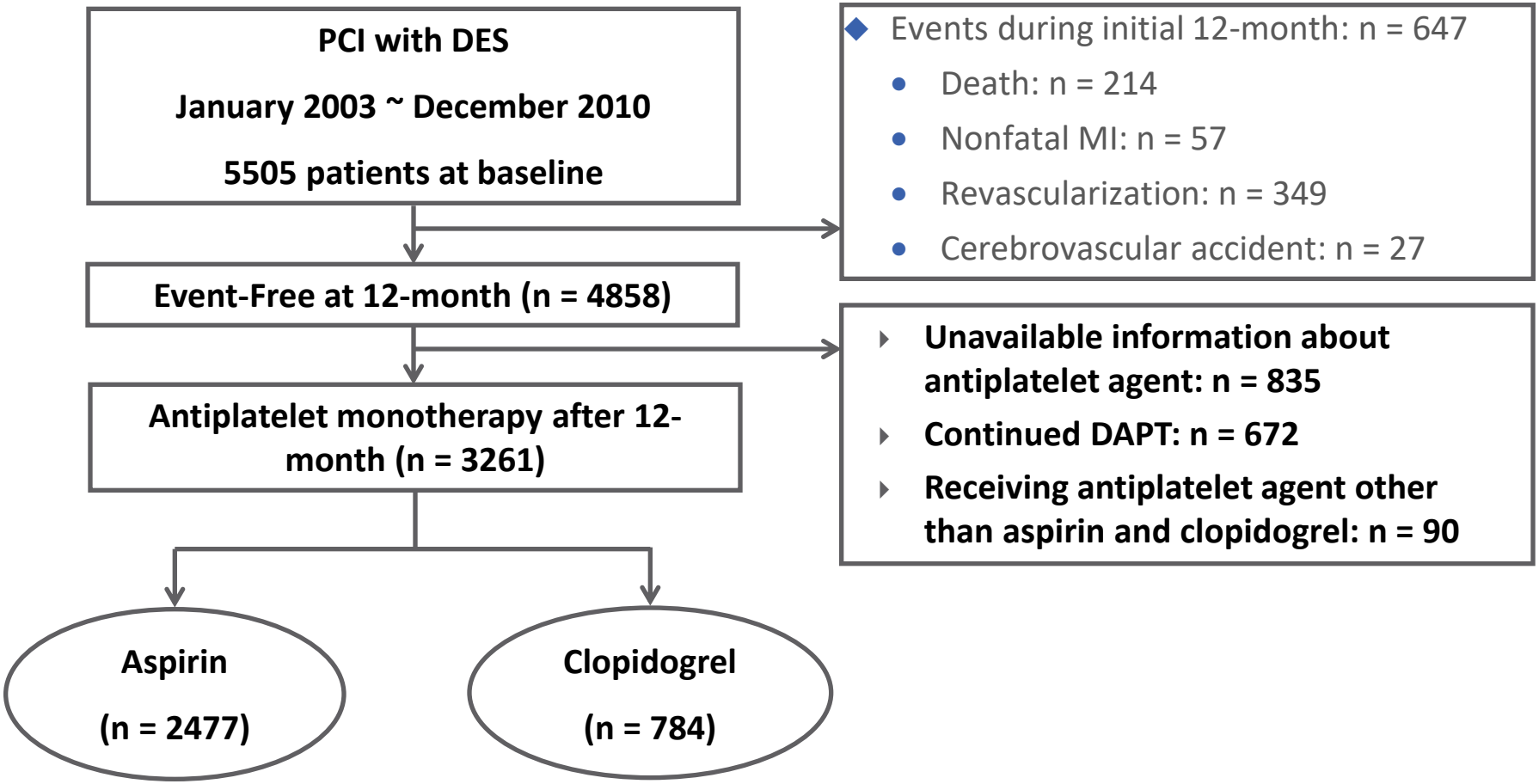
Eikelboom JW *et al. N Engl J Med* 2017; DOI: 10.1056/NEJMoa1709118

COMPASS

Monotherapy after PCI: A vs. C

Single center, observational study

Choice of antiplatelet agent → the operator's discretion



Park TK, Song YB et al. ACC 2014

Monotherapy after PCI: A vs. C

Clinical outcomes

Median f/u duration: 59 months

	Aspirin (n=2477)	Clopidogrel (n=784)	Before weighting		After IPTW	
			HR* (95% CI)	P value	HR* (95% CI)	P value
Total death	131 (5.3)	26 (3.3)	0.85 (0.55-1.33)	0.48	0.89 (0.61-1.31)	0.56
Cardiac death	50 (2.0)	7 (0.9)	0.51 (0.22-1.16)	0.11	0.54 (0.25-1.15)	0.11
MI	51 (2.1)	7 (0.9)	0.68 (0.30-1.54)	0.36	0.42 (0.17-1.04)	0.06
Stent thrombosis	18 (0.7)	1 (0.1)	0.29 (0.04-2.29)	0.24	0.12 (0.01-2.19)	0.15
TLR	109 (4.4)	14 (1.8)	0.71 (0.40-1.26)	0.24	0.63 (0.37-1.08)	0.09
TVR	**184 (7.4)**	**23 (2.9)**	**0.64 (0.41-0.99)**	**0.05**	**0.53 (0.34-0.82)**	**0.004**
CVA	60 (2.4)	11 (1.4)	0.73 (0.37-1.42)	0.36	0.62 (0.32-1.20)	0.16
Cardiac death or MI	**93 (3.8)**	**13 (1.7)**	**0.61 (0.33-1.11)**	**0.11**	**0.51 (0.28-0.93)**	**0.03**
Cardiac death, MI, or CVA	**144 (5.8)**	**22 (2.8)**	**0.65 (0.41-1.04)**	**0.07**	**0.51 (0.32-0.83)**	**0.006**

Values are expressed as number of patients (%).

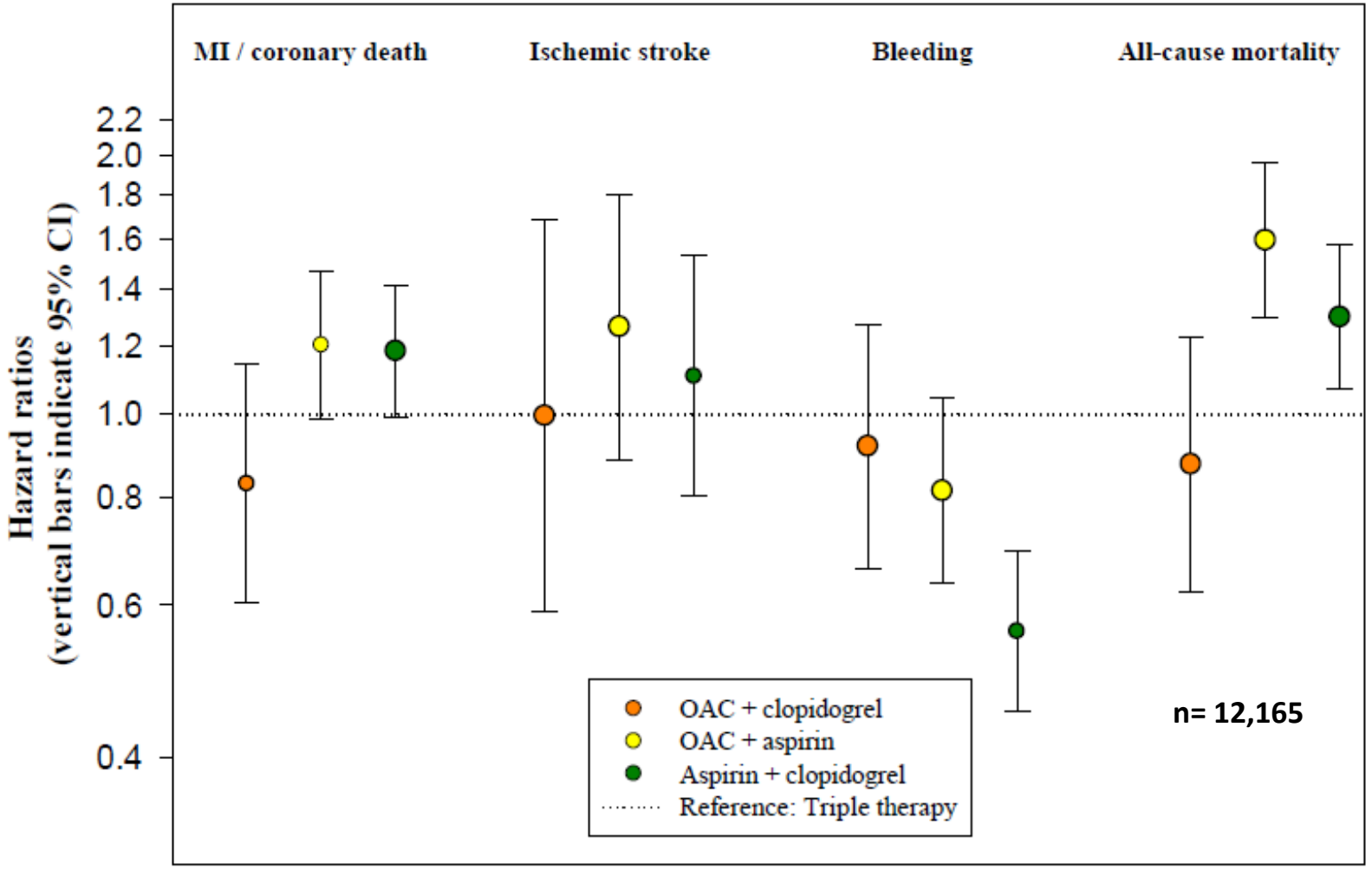
IPTW indicates inverse probability of treatment weighting; MI, myocardial infarction; TLR, target lesion revascularization; TVR, target vessel revascularization; CVA, cerebrovascular accident.

*Adjusted covariates included age, sex, clinical presentation, diabetes mellitus, hypertension, dyslipidemia, current smoker, chronic renal failure, previous MI, previous percutaneous coronary intervention, previous bypass surgery, previous CVA, angiographic disease extent, number of treated lesion, number of stent used, stent diameter, total stent length, left main or left anterior descending artery as a treated vessel, and type of drug-eluting stent.

Park TK, Song YB et al. ACC 2014

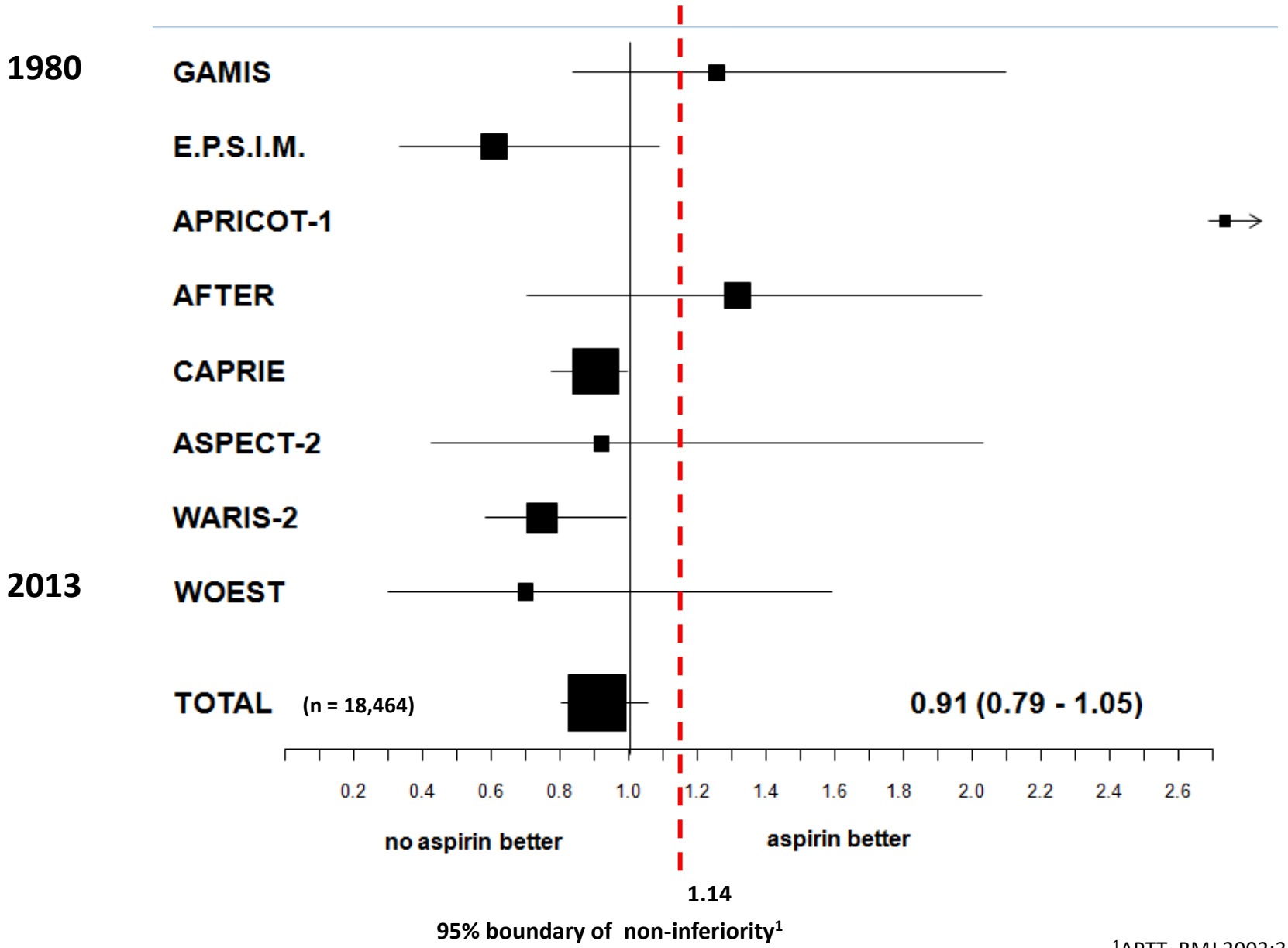
Dual vs Triple therapy in AF after PCI for MI

Clopidogrel better than Aspirin (both on top of OAC)



Lamberts M. J Am Coll Cardiol 2013;62:981-989

Aspirin vs non-Aspirin based Antithrombotic RCTs post MI



[1]APTT. BMJ 2002;324:71–86

Verheugt FWA. Eur Heart J 2014;35:Abstr Suppl:997

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Ongoing RCTs testing whether antiplatelet should really be based on aspirin….

1. HOST-EXAM (EXtended Antiplatelet Monotherapy)
2. TWILIGHT Trial
3. GLOBAL LEADERS Trial
4. STOP-DAPT 2

HOST EXAM: Trial Design

Prospective, open label, randomized multi-center trial

Assumption
: 12% vs. 9.6%
Superiority Design
Sampling ratio= 1:1
Alpha:1-sided 5%
Power 80%
5,530 pts needed

5,530 Patients that received PCI with DES without events for 12 (± 6) months

42 centers in Korea
PI: HS Kim

Randomization
1:1

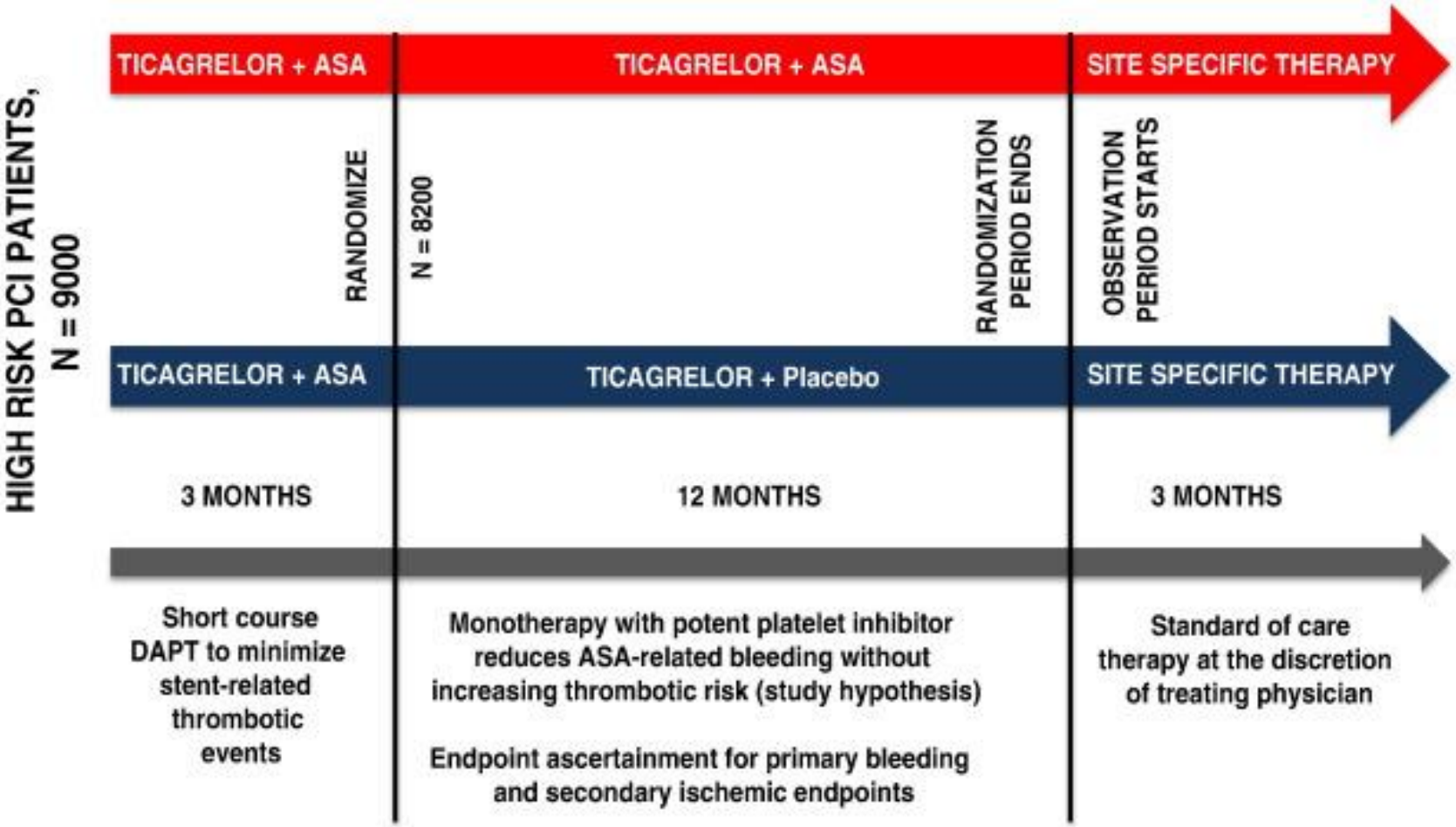
Aspirin Monotherapy
N=2,765

Clopidogrel Monotherapy
N=2,765

Outpatient Clinic-based Clinical Trial

Composite of
All cause death, MI, stroke, readmission due to ACS, urgent revascularization, bleeding

TWILIGHT Trial



Baber U, et al. Am Heart J. 2016;182:125.

GLOBAL LEADERS

All-comers PCI population
ACS and Elective/Stable patients
(n=16,000)

Biolimus-eluting stent(s)

1:1 randomization

1 month DAPT
(ASA + ticagrelor)

23 months mono Rx
(ticagrelor)

12 months DAPT
(ASA + ticagrelor)
(ASA + clopidogrel

12 months mono Rx
(ASA)

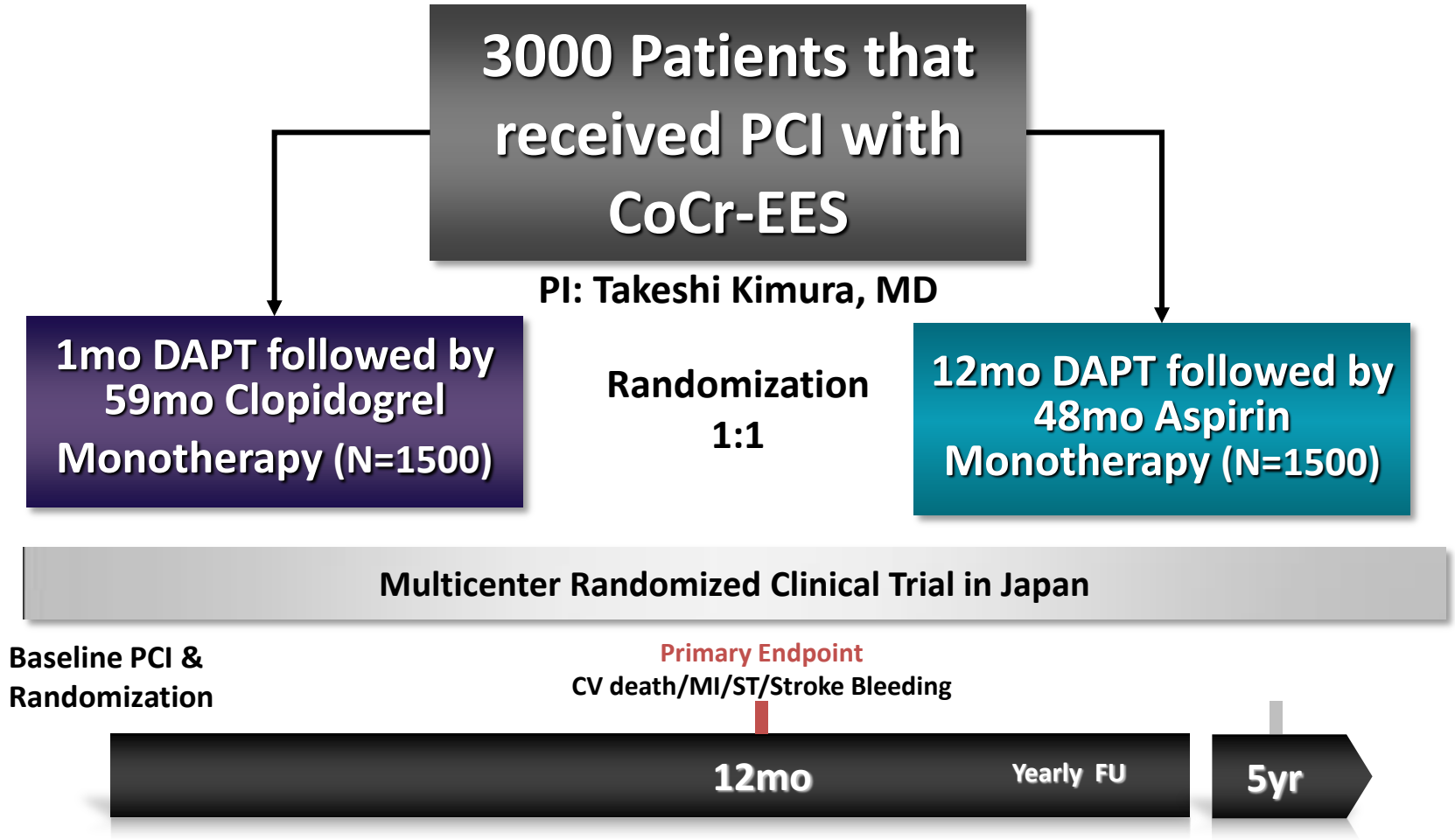
Primary Efficacy Endpoint – Death / Q-wave MI at 2 years

Primary Safety Endpoint – Major Bleeding (BARC)

Vranckx P, et al. EuroIntervention. 2016;12:1239.

STOP-DAPT 2: Trial Design

Prospective, open label, randomized multi-center trial



Summary

1. Aspirin is currently the mainstay of antiplatelet therapy in patients with CV disease.
2. However, it is not a perfect drug. There are issues such as whether aspirin actually has a role in primary and secondary prevention in the era of statin therapy, interaction with various drug, and several S/E including GI toxicity and bleeding.
3. Therefore we must keep ourselves open for the role of other treatments such as clopidogrel or newer P2Y12 inhibitors.
4. Many ongoing studies are addressing this issue, so be on the look out for new data.

Thank you

for your attention!!