Secondary stroke prevention - Update

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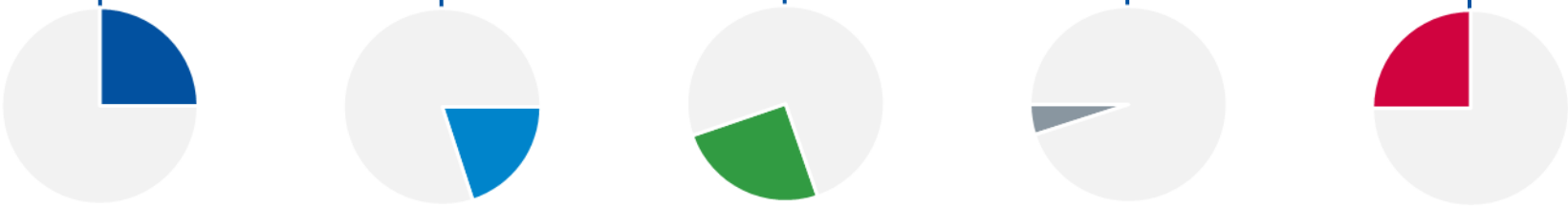
SHAARE ZEDEK MEDICAL CENTER
Jerusalem's Hospital

TOAST classification of acute ischaemic stroke subtypes

Ischaemic stroke



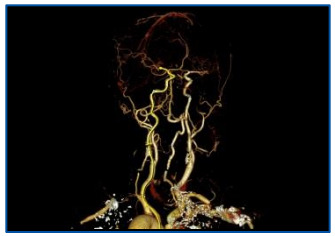
25%
large-artery atherosclerotic

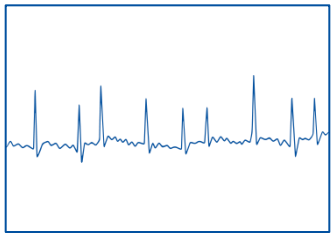
20%
cardioembolic

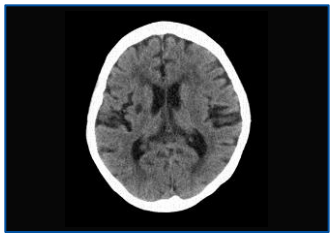
25%
lacunar

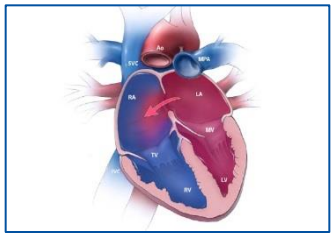
5%
other/rare
(e.g. dissections, arteritis, etc.)

25%
Cryptogenic
(not investigated, multiple causes, truly cryptogenic)



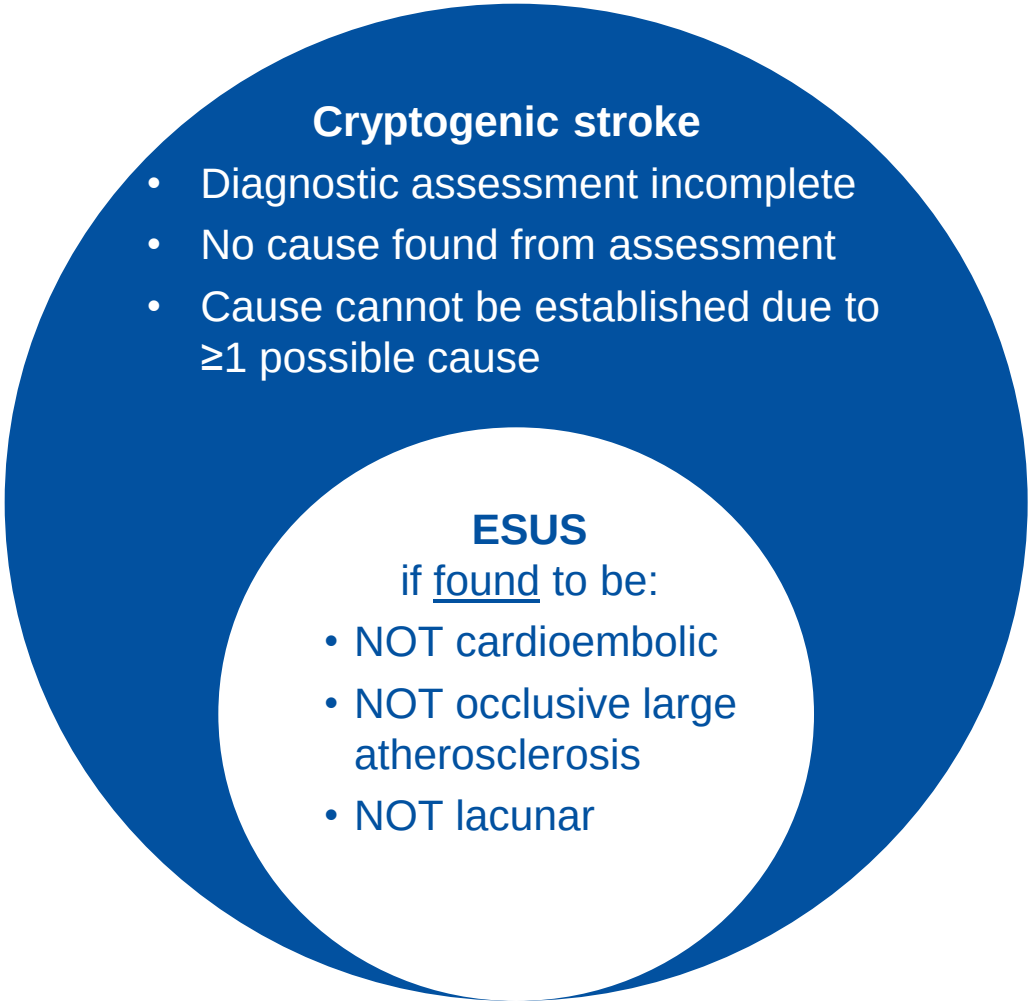






Adams et al. Stroke 1993; Hart et al. Lancet Neurol 2014
TOAST, Trial of ORG 10172 in Acute Stroke Treatment

ESUS is a subset of cryptogenic stroke

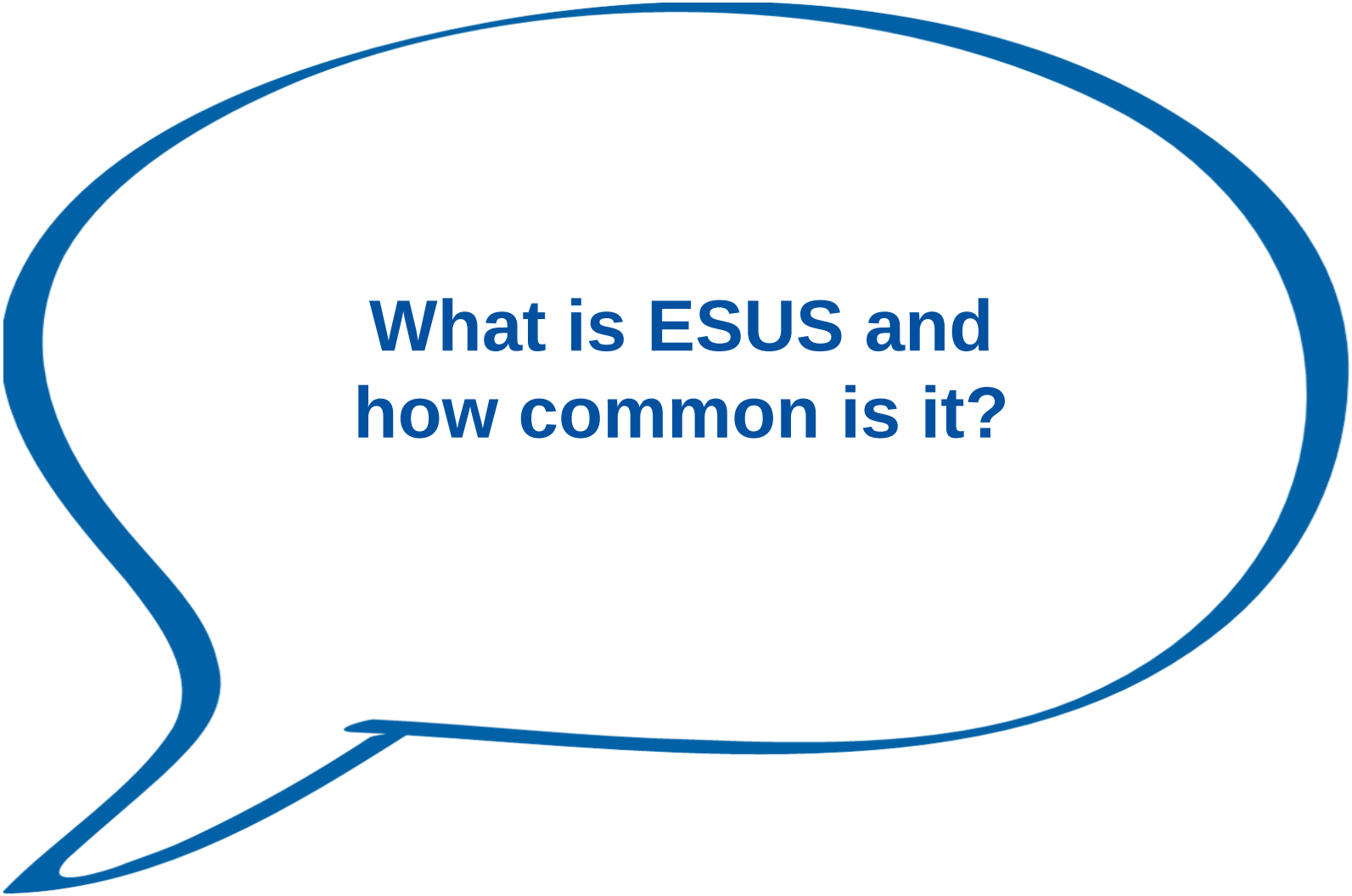


The dominant underlying mechanism of cryptogenic stroke is likely an embolism from an unestablished source

ESUS is a non-lacunar brain infarct without large artery stenosis or cardioembolic sources

ESUS, embolic stroke of undetermined source

Hart et al. Lancet Neurol 2014


What is ESUS and
how common is it?

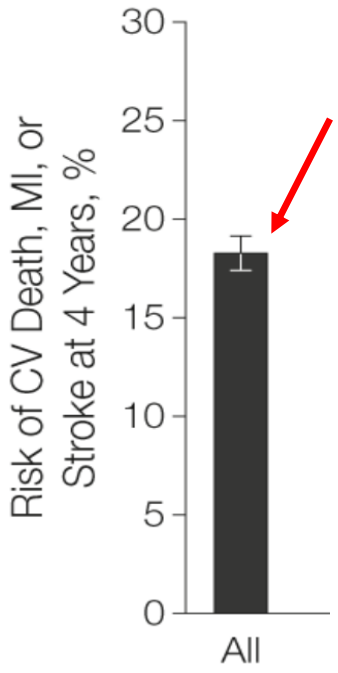
Estimates of long term risk after Stroke or TIA

	After TIA (%)[1]	After Stroke(%)[2]
30 days	4-8	3-10
1 year	12-13	10-14
5 years	24-29	25-40

1. Feinberg WM et al. Stroke. 1994;25(6):1320
2. Sacco RL. Neurology. 1997;49(suppl 4):S39

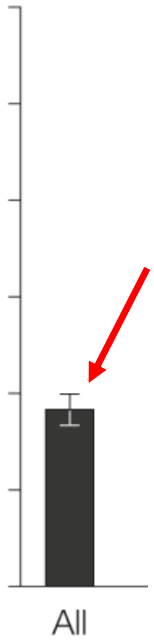
4 years risk with and without prior ischemic events

Prior ischemic event



Patients, No. 21 890

Only risk factors



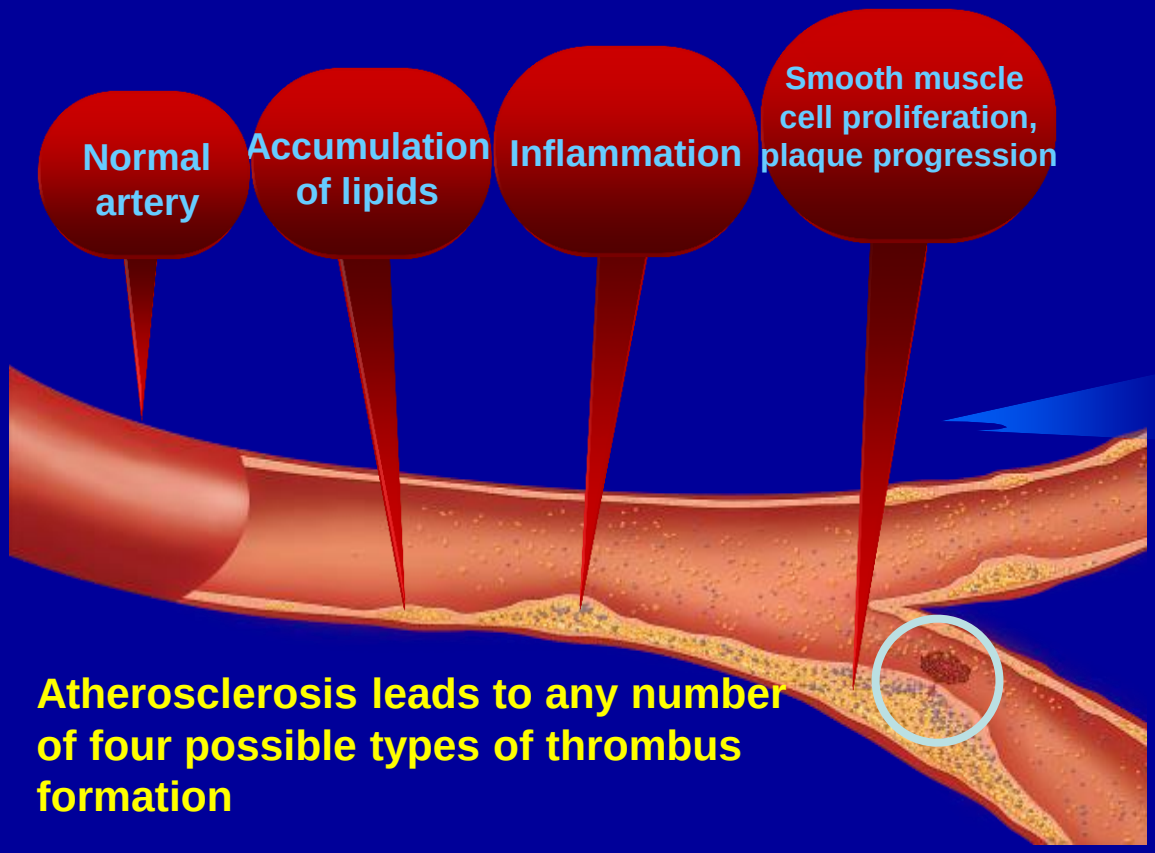
8073

JAMA. 2010;304(12):1350-1357. doi:10.1001/jama.2010.1322

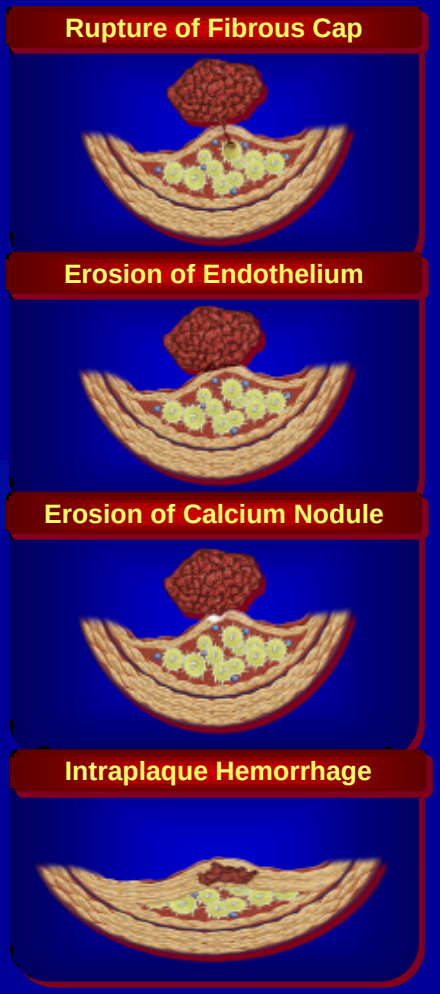
Targeted approach

Pathophysiology of Atherothrombosis

Atherosclerosis + **Thrombus Formation**

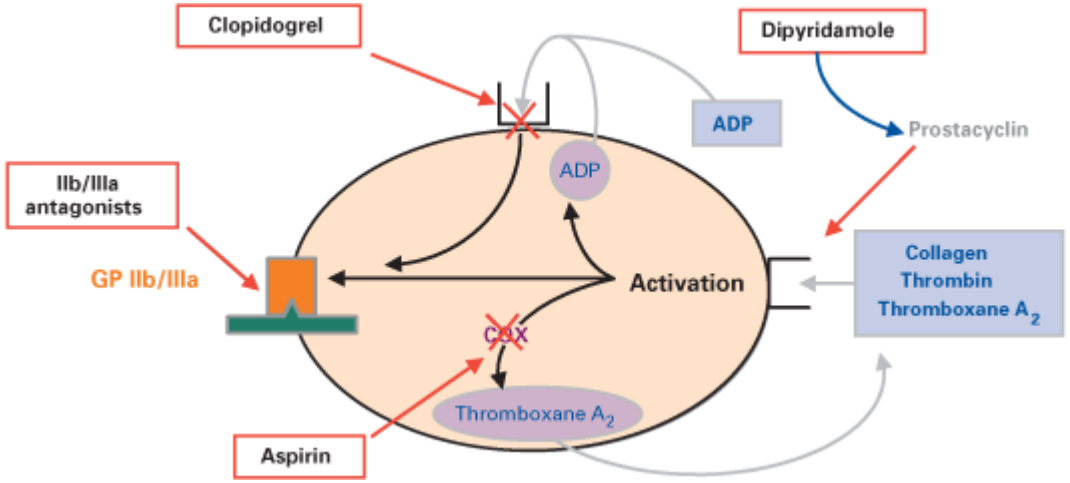


Atherosclerosis leads to any number of four possible types of thrombus formation



1. Munger MA et al. *J Am Pharm Assoc*. 2004;44(suppl 1):S5-S13.
2. Libby P et al. *Circulation*. 2005;111:3481-3488

Antiplatelets



Clopidogrel

Block ADP receptors

Aspirin

Inhibits cyclooxygenase and thromboxane A_2

Dipyridamole

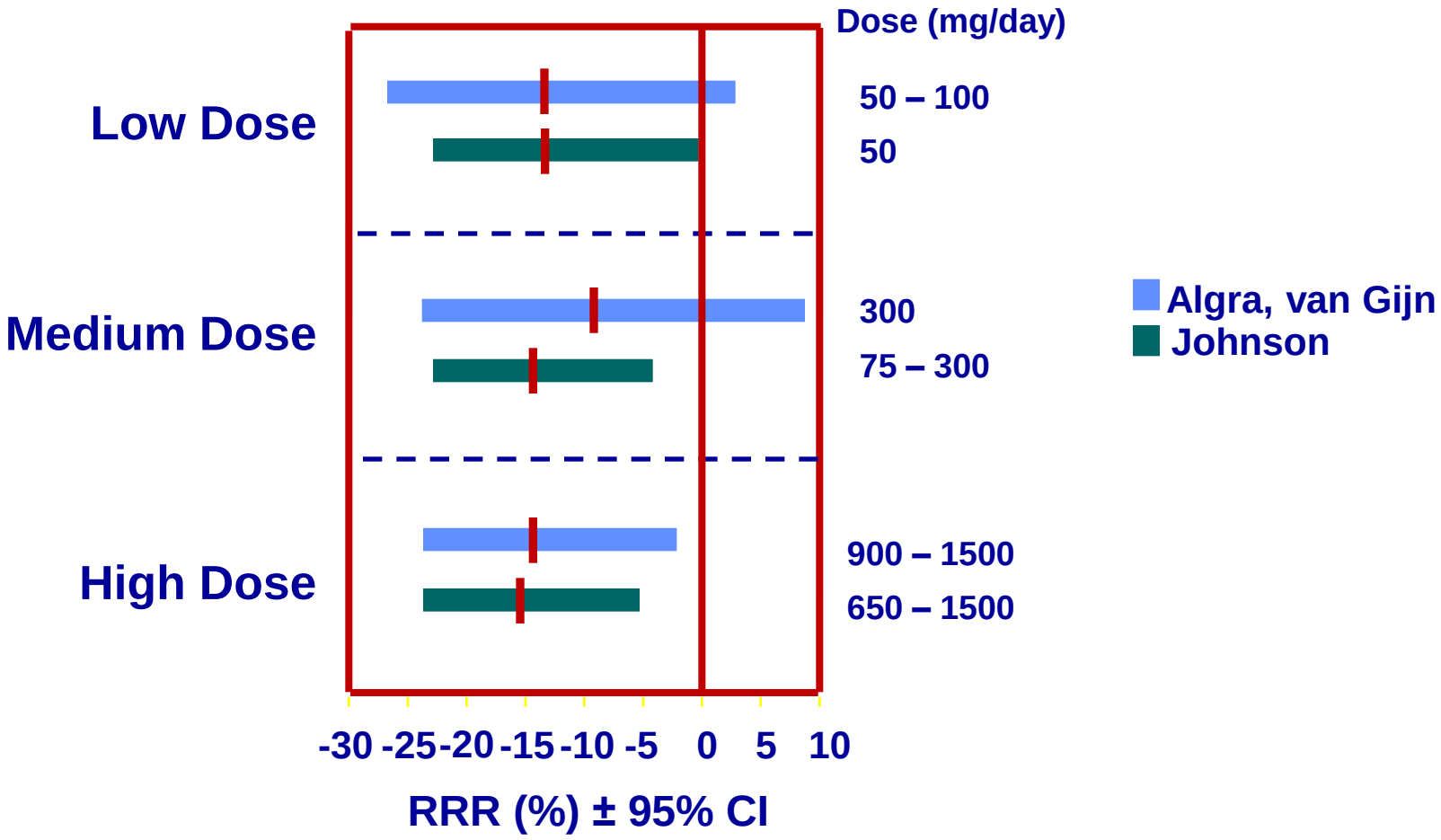
Increases plasma adenosine

Inhibits platelet phosphodiesterase

Inhibition of platelet activation and aggregation

Aspirin Efficacy by Dose:

*Meta-Analyses in Patients With Stroke/TIA**



** Endpoint: stroke, MI, or vascular death.*

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EDITORIAL

Should Aspirin Be Used for Primary Prevention in the Post-Statin Era?

Paul M Ridker, M.D., M.P.H.

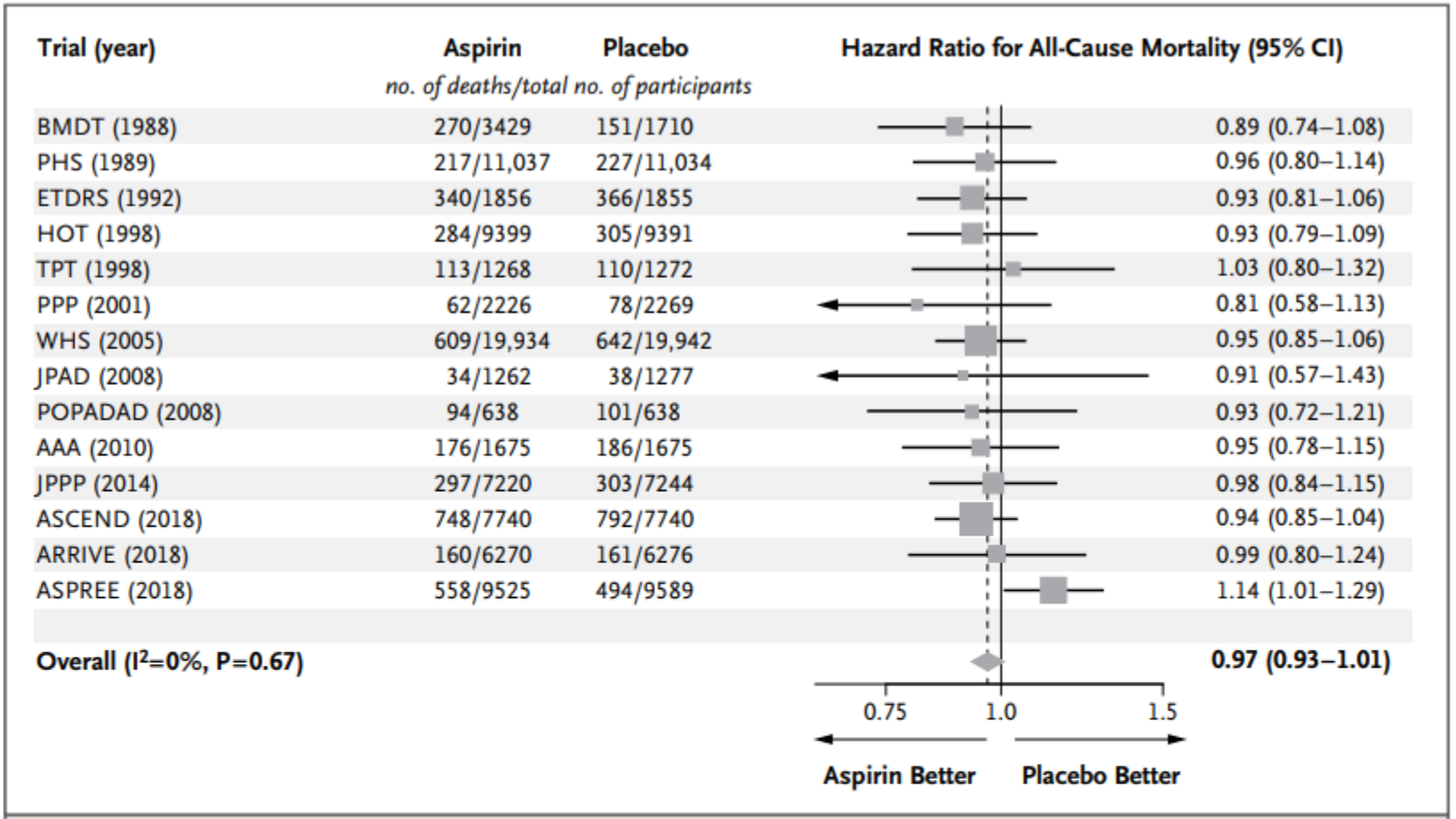


Figure 1. Aspirin and All-Cause Mortality in 14 Primary Prevention Trials.

BMDT denotes British Male Doctors Trial, PHS Physicians' Health Study, ETDRS Early Treatment Diabetic Retinopathy Study, HOT Hypertension Optimal Treatment, TPT Thrombosis Prevention Trial, PPP Primary Prevention Project, WHS Women's Health Study, JPAD Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes, POPADAD Prevention of Progression of Arterial Disease and Diabetes, AAA Aspirin for Asymptomatic Atherosclerosis, JPPP Japanese Primary Prevention Project, ASCEND A Study of Cardiovascular Events in Diabetes, ARRIVE Aspirin to Reduce Risk of Initial Vascular Events, and ASPREE Aspirin in Reducing Events in the Elderly. The meta-analysis was performed with a random effects model (I^2=0% for heterogeneity, P=0.67). The boxes indicate the hazard ratio for all-cause mortality in each trial, with box size proportional to sample size. The diamond indicates the overall hazard ratio and its confidence interval. Arrows on the lines for 95% confidence intervals indicate that the limit is beyond the scale.

Editorial

January 22, 2019

Aspirin for Primary Prevention
Clinical Considerations in 2019

J. Michael Gaziano, MD, MPH[1,2]

» Author Affiliations | Article Information

JAMA. 2019;321(3):253-255. doi:10.1001/jama.2018.20577

Research

JAMA | Original Investigation

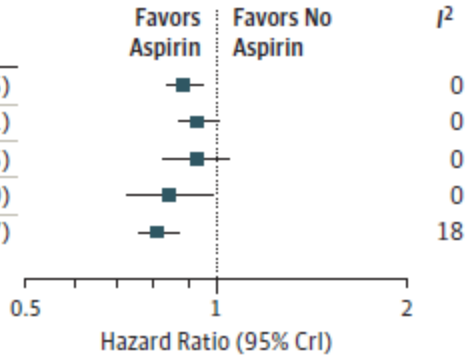
Association of Aspirin Use for Primary Prevention With Cardiovascular Events and Bleeding Events

A Systematic Review and Meta-analysis

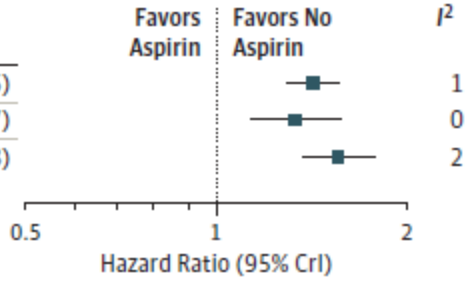
Sean L. Zheng, BM, BCh, MA, MRCP; Alistair J. Roddick, BSc

Figure 1. Cardiovascular and Bleeding Outcomes in all Participants

Cardiovascular Outcomes	No. of Studies	Aspirin		No Aspirin		Absolute Risk Reduction, % (95% CI)	HR (95% CrI)	I^2
		No. of Events	No. of Participants	No. of Events	No. of Participants			
Composite CV outcome	11	2911	79 717	3072	78 147	0.38 (0.20 to 0.55)	0.89 (0.84-0.95)	0
All-cause mortality	13	3622	81 623	3588	80 057	0.13 (-0.07 to 0.32)	0.94 (0.88-1.01)	0
CV mortality	13	995	81 623	997	80 057	0.07 (-0.04 to 0.17)	0.94 (0.83-1.05)	0
Myocardial infarction	13	1469	81 623	1599	80 057	0.28 (0.05 to 0.47)	0.85 (0.73-0.99)	0
Ischemic stroke	10	831	65 316	942	63 752	0.16 (0.06 to 0.30)	0.81 (0.76-0.87)	18



Bleeding Outcomes	No. of Studies	Aspirin		No Aspirin		Absolute Risk Increase, % (95% CI)	HR (95% CrI)	I^2
		No. of Events	No. of Participants	No. of Events	No. of Participants			
Major bleeding	11	1195	74 715	834	73 143	0.47 (0.34 to 0.62)	1.43 (1.30-1.56)	1
Intracranial bleeding	12	349	80 985	257	79 419	0.11 (0.04 to 0.18)	1.34 (1.14-1.57)	0
Major GI bleeding	10	593	70 336	380	70 465	0.30 (0.20 to 0.41)	1.56 (1.38-1.78)	2



The composite cardiovascular (CV) outcome consisted of cardiovascular mortality, nonfatal myocardial infarction, and nonfatal stroke. Hazard ratios (HRs) and 95% credible interval variables (CrIs) were calculated using Bayesian meta-analysis of trial-level event counts. The absolute risk reductions and increases were calculated by multiplying the control event risk by the relative risk and 95% CIs derived by frequentist meta-analysis (eFigure 4 in Supplement 2). GI indicates gastrointestinal.

IMPORTANCE The role for aspirin in cardiovascular primary prevention remains controversial, with potential benefits limited by an increased bleeding risk.

OBJECTIVE To assess the association of aspirin use for primary prevention with cardiovascular events and bleeding.

DATA SOURCES PubMed and Embase were searched on Cochrane Library Central Register of Controlled Trials from the earliest available date through November 1, 2018.

STUDY SELECTION Randomized clinical trials enrolling at least 1000 participants with no known cardiovascular disease and a follow-up of at least 12 months were included. Included studies compared aspirin use with no aspirin (placebo or no treatment).

DATA EXTRACTION AND SYNTHESIS Data were screened and extracted independently by both investigators. Bayesian and frequentist meta-analyses were performed.

MAIN OUTCOMES AND MEASURES The primary cardiovascular outcome was a composite of cardiovascular mortality, nonfatal myocardial infarction, and nonfatal stroke. The primary bleeding outcome was any major bleeding (defined by the individual studies).

RESULTS A total of 13 trials randomizing 164 225 participants with 1 050 511 participant-years of follow-up were included. The median age of trial participants was 62 years (range, 53-74), 77 501 (47%) were men, 30 361 (19%) had diabetes, and the median baseline risk of the primary cardiovascular outcome was 9.2% (range, 2.6%-15.9%). Aspirin use was associated with significant reductions in the composite cardiovascular outcome compared with no aspirin (57.1 per 10 000 participant-years with aspirin and 61.4 per 10 000 participant-years with no aspirin) (hazard ratio [HR], 0.89 [95% credible interval, 0.84-0.95]; absolute risk reduction, 0.38% [95% CI, 0.20%-0.55%]; number needed to treat, 265). Aspirin use was associated with an increased risk of major bleeding events compared with no aspirin (23.1 per 10 000 participant-years with aspirin and 16.4 per 10 000 participant-years with no aspirin) (HR, 1.43 [95% credible interval, 1.30-1.56]; absolute risk increase, 0.47% [95% CI, 0.34%-0.62%]; number needed to harm, 210).

CONCLUSIONS AND RELEVANCE The use of aspirin in individuals without cardiovascular disease was associated with a lower risk of cardiovascular events and an increased risk of major bleeding. This information may inform discussions with patients about aspirin for primary prevention of cardiovascular events and bleeding.

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November 28, 2017; 89 (22) ARTICLE

Low-dose aspirin and risk of intracranial bleeds

An observational study in UK general practice

Lucía Cea Soriano, David Gaist, Montse Soriano-Gabarró, Susan Bromley and Luis A. García Rodríguez

Abstract

OBJECTIVE: To quantify the risk of intracranial bleeds (ICBs) associated with new use of prophylactic low-dose aspirin using a population-based primary care database in the United Kingdom.

METHODS: A cohort of new users of low-dose aspirin (75-300 mg; n = 199,079) aged 40-84 years and a 1:1 matched cohort of nonusers of low-dose aspirin at baseline were followed (maximum 14 years, median 5.4 years) to identify incident cases of ICB, with validation by manual review of patient records or linkage to hospitalization data. Using 10,000 frequency-matched controls, adjusted rate ratios (RRs) with 95% confidence intervals (CIs) were calculated for current low-dose aspirin use (0-7 days before the index date [ICB date for cases, random date for controls]); reference group was never used.

RESULTS: There were 1,611 cases of ICB (n = 743 for intracerebral hemorrhage [ICH], n = 483 for subdural hematoma [SDH], and n = 385 for subarachnoid hemorrhage [SAH]). RRs (95% CI) were 0.98 (0.84-1.13) for all ICB, 0.98 (0.80-1.20) for ICH, 1.23 (0.95-1.59) for SDH, and 0.77 (0.58-1.01) for SAH. No duration of use or dose-response association was apparent. RRs (95% CI) for ≥1 year of low-dose aspirin use were 0.90 (0.72-1.13) for ICH, 1.20 (0.91-1.57) for SDH, and 0.69 (0.50-0.94) for SAH.

CONCLUSION: Low-dose aspirin is not associated with an increased risk of any type of ICB and is associated with a significantly decreased risk of SAH when used for ≥1 year.

THE ROLE OF CLOPIDOGREL

CAPRIE - Clopidogrel/ASA in Patients at Risk of Ischemic Events

CAPRIE Study: Primary Analysis

Treatment Group	Ischemic Stroke		MI		Other Vascular Death	Total First Events	Event Rate / Yr
	Non-fatal	Fatal	Non-fatal	Fatal			
Clopidogrel	405	33	226	49	226	939	5.32%
Aspirin	430	32	270	63	226	1021	5.83%

Relative Risk Reduction: 8.7% ($p = 0.043$)

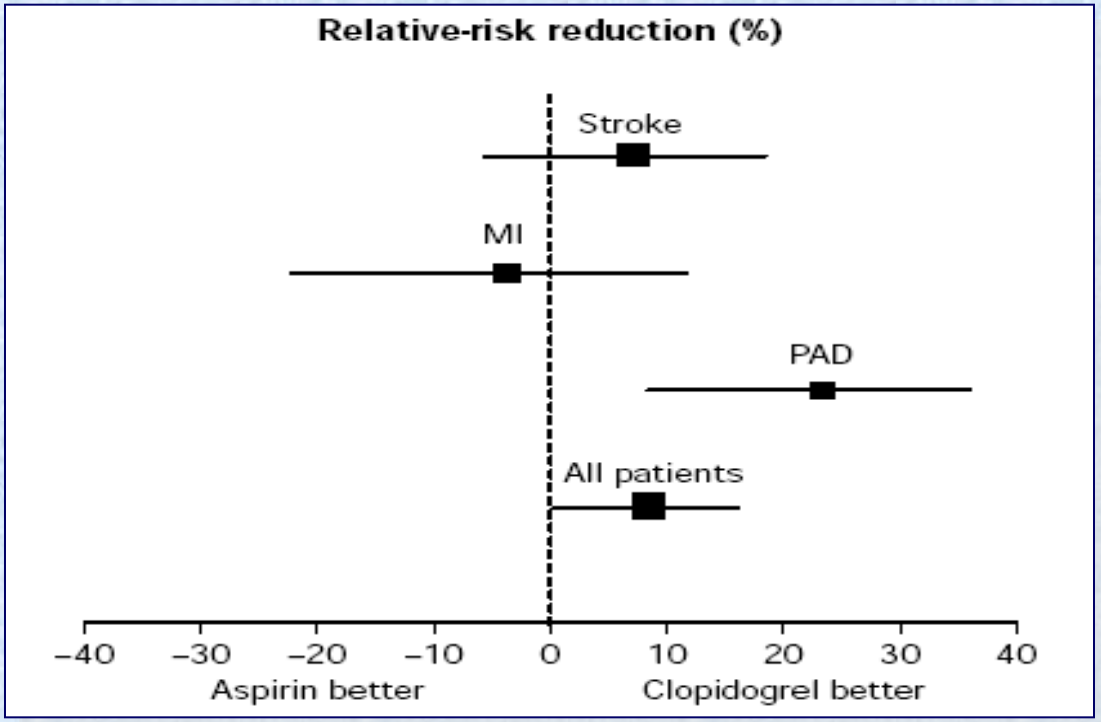
(95% Confidence Interval: 0.3%, 16.5%)

CAPRIE Steering Committee. Lancet 1996;348:1329-1339.

Clopidogrel

- Clopidogrel is slightly but significantly more effective than medium-dose aspirin (RRR 8.7%, ARR 0.5%) in preventing vascular events in patients with previous stroke, MI or PAD.

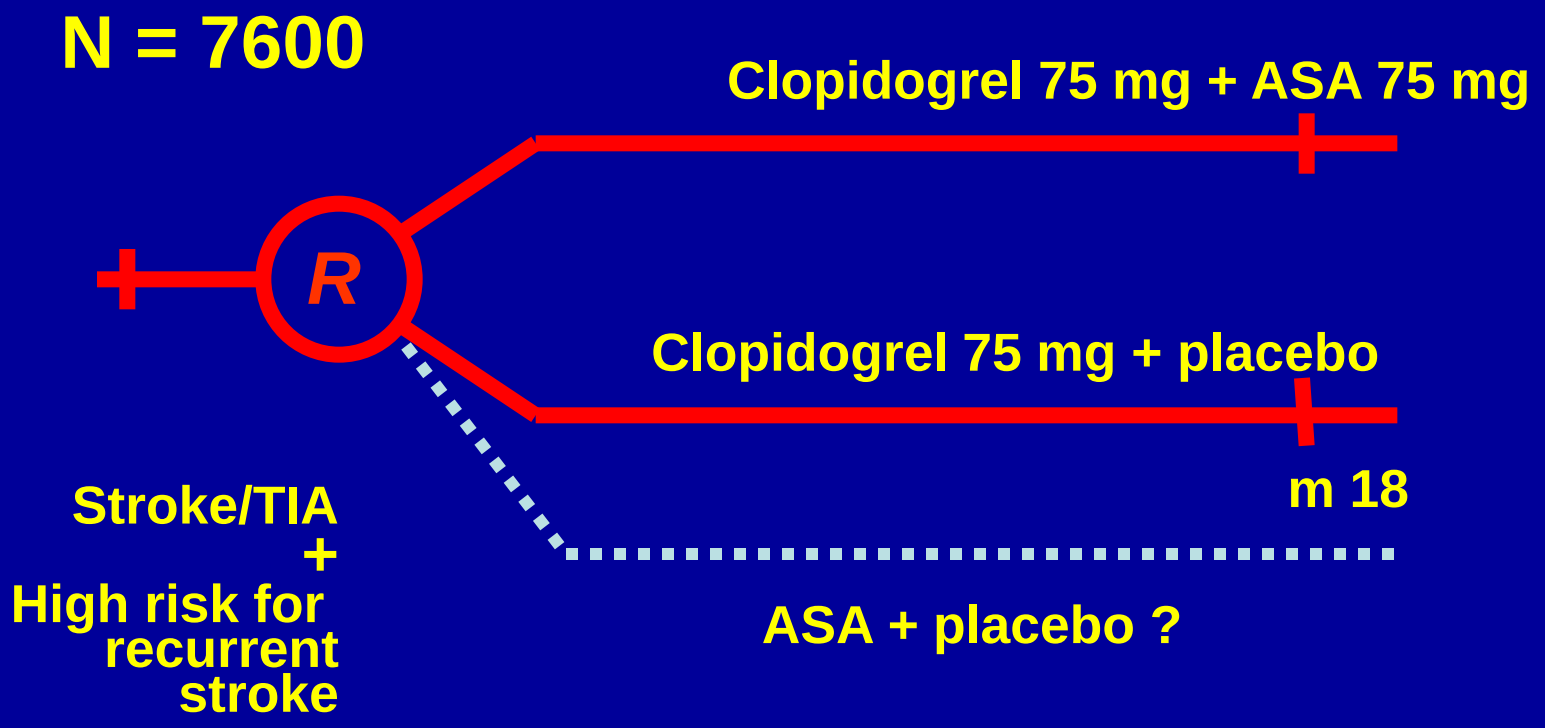
NNT= 200



CAPRIE Steering Committee: Lancet (1996) 348:1329-1339

Clopidogrel + Aspirin

Management of ATherothrombosis with Clopidogrel in High-risk patients

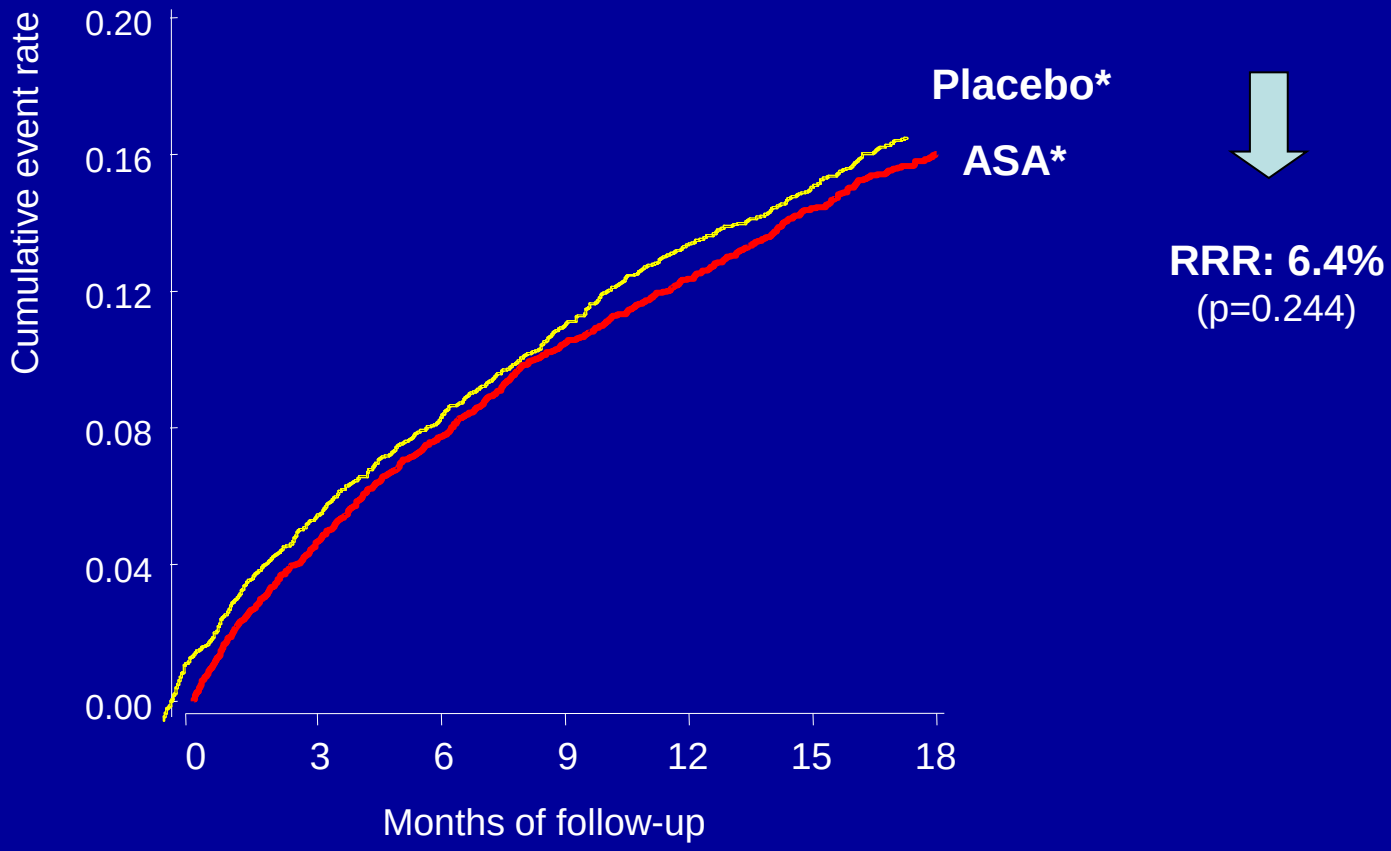


MATCH Steering Committee, 2000

ASA showed a non significant trend for the reduction in major vascular events of in specific high risk cerebrovascular patients*

Primary Endpoint (ITT)

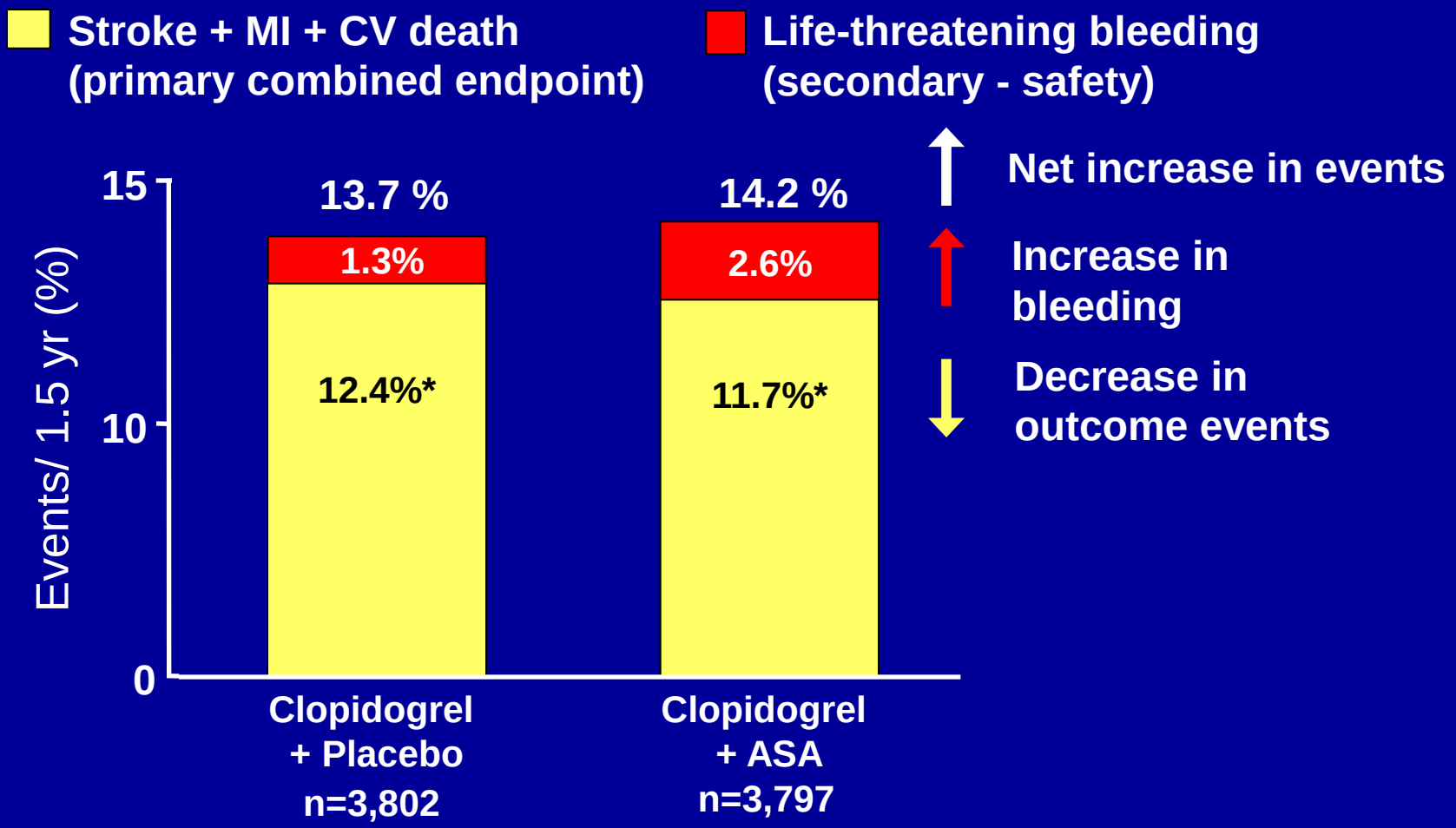
IS, MI, VD, rehospitalization for acute ischemic event



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

MATCH: Net Benefit

5 additional events/1000 treated/1.5 yr (-3/yr)



*First event counted; does not include rehospitalization unless associated with an endpoint

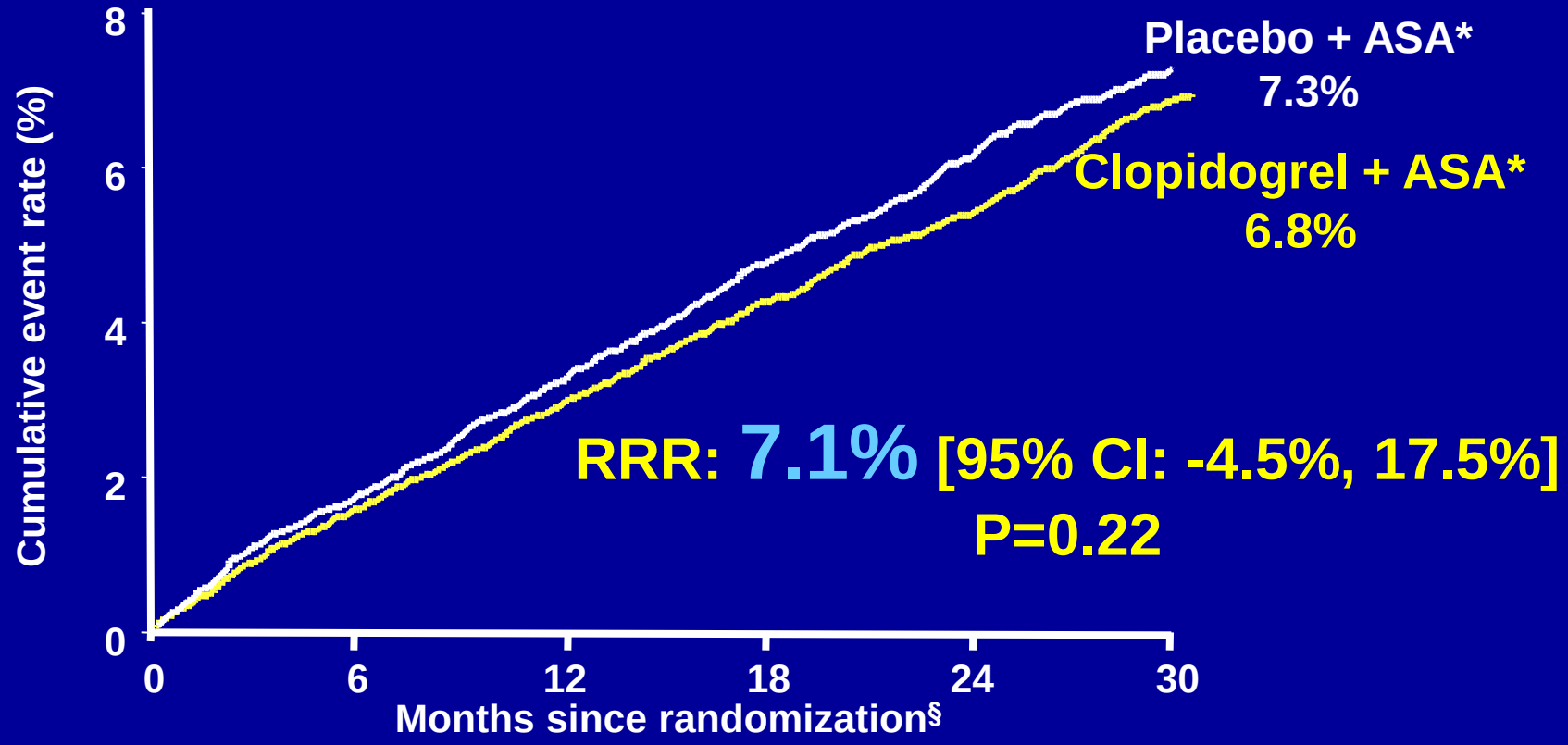
Diener HC, et al. *Lancet.* 2004;364:331337.

CHARISMA: Clopidogrel and Aspirin vs. Aspirin Alone for the Prevention of Atherothrombotic Events

Study design	768 clinical centers in 32 countries; randomized, blinded
Study population	**15,603 patients** > 45 yr (median age 64 yr) with cardiovascular disease or multiple risk factors
Study drugs	Clopidogrel (75 mg/day)+ low dose ASA (75-162 mg/day) vs low-dose aspirin
Primary endpoint	Composite outcome cluster of ischemic stroke, MI, vascular death
Treatment duration	Average patient follow-up 28 months

Bhatt DL et al. *N Engl J Med* 2006

Overall Population: Primary Efficacy Outcome (MI, Stroke, or CV Death)†



† First Occurrence of MI (fatal or non-fatal), stroke (fatal or non-fatal), or cardiovascular death

*All patients received ASA 75-162 mg/day

§The number of patients followed beyond 30 months decreases rapidly to zero and there are only 21 primary efficacy events that occurred beyond this time (13 clopidogrel and 8 placebo)

Bhatt DL, Fox KA, Hacke W, et al. 2006 NEJM:354

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ORIGINAL ARTICLE

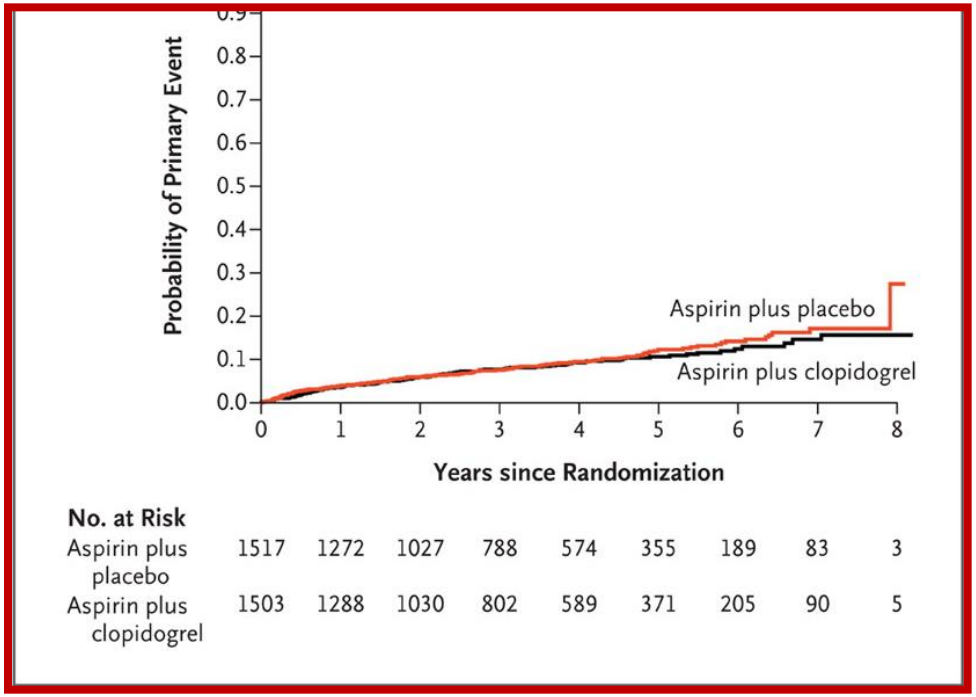
Effects of Clopidogrel Added to Aspirin in Patients with Recent Lacunar Stroke

The SPS3 Investigators*

N Engl J Med. 2012 Aug 30;367(9):817-25.

Long-term DAPT

Clopidogrel added to aspirin after lacunar stroke- SPS3 Trial



AHA/ASA secondary prevention guidelines 2014

The combination of aspirin and clopidogrel, when initiated days to years after a minor stroke or TIA and continued for 2 to 3 years, increases the risk of hemorrhage relative to either agent alone and is not recommended for routine long-term secondary prevention after ischemic stroke or TIA *(Class III; Level of Evidence A)*.

Outcome	Aspirin plus Placebo (N=1503)		Aspirin plus Clopidogrel (N=1517)		Hazard Ratio (95% CI)	P Value
	no.	*rate (%/yr)*	*no.*	*rate (%/yr)*		
All major hemorrhages	56	1.1	105	2.1	1.97 (1.41–2.71)	<0.001

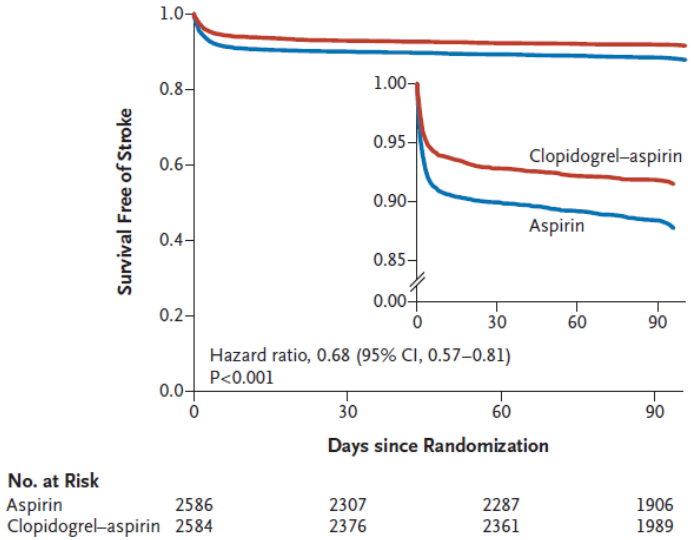
N Engl J Med 2012;367:817-25.

Short-term DAPT after high-risk TIA/minor stroke?

ORIGINAL ARTICLE

Clopidogrel with Aspirin in Acute Minor Stroke or Transient Ischemic Attack

CHANCE



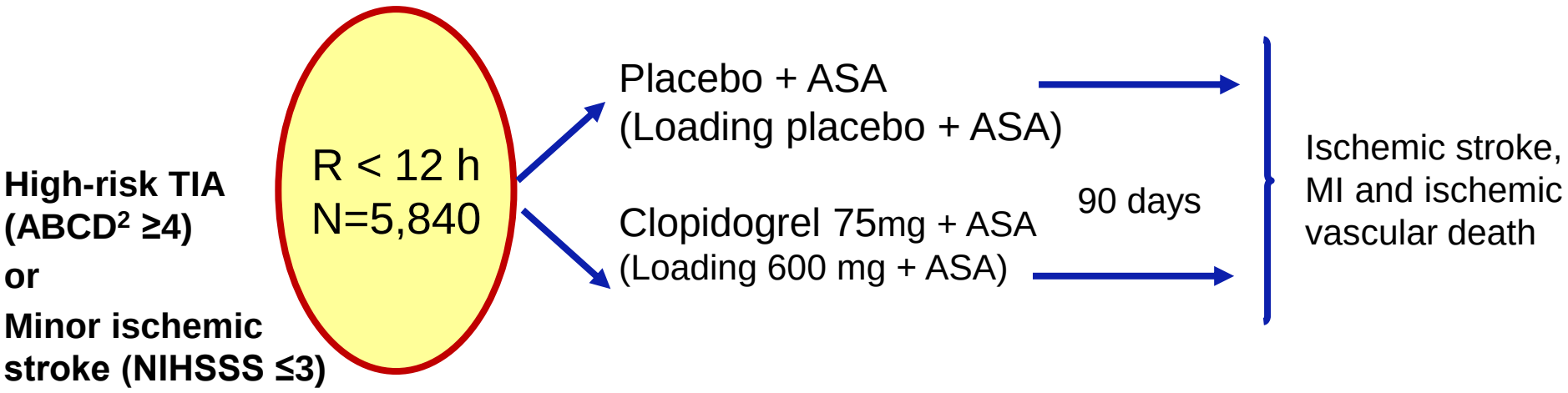
No. at Risk				
Aspirin	2586	2307	2287	1906
Clopidogrel–aspirin	2584	2376	2361	1989

Hazard ratio, 0.68 (95% CI, 0.57–0.81)
P<0.001

Clopidogrel 300 mg loading followed by 75 mg daily for 90 days + aspirin at a dose of 75 mg daily for the first 21 days **VS.** aspirin only in a Chinese population

N Engl J Med 2013;369:11-19.

Platelet-Oriented Inhibition in New TIA and minor ischemic stroke



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The POINT trial

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ORIGINAL ARTICLE

Clopidogrel and Aspirin in Acute Ischemic Stroke and High-Risk TIA

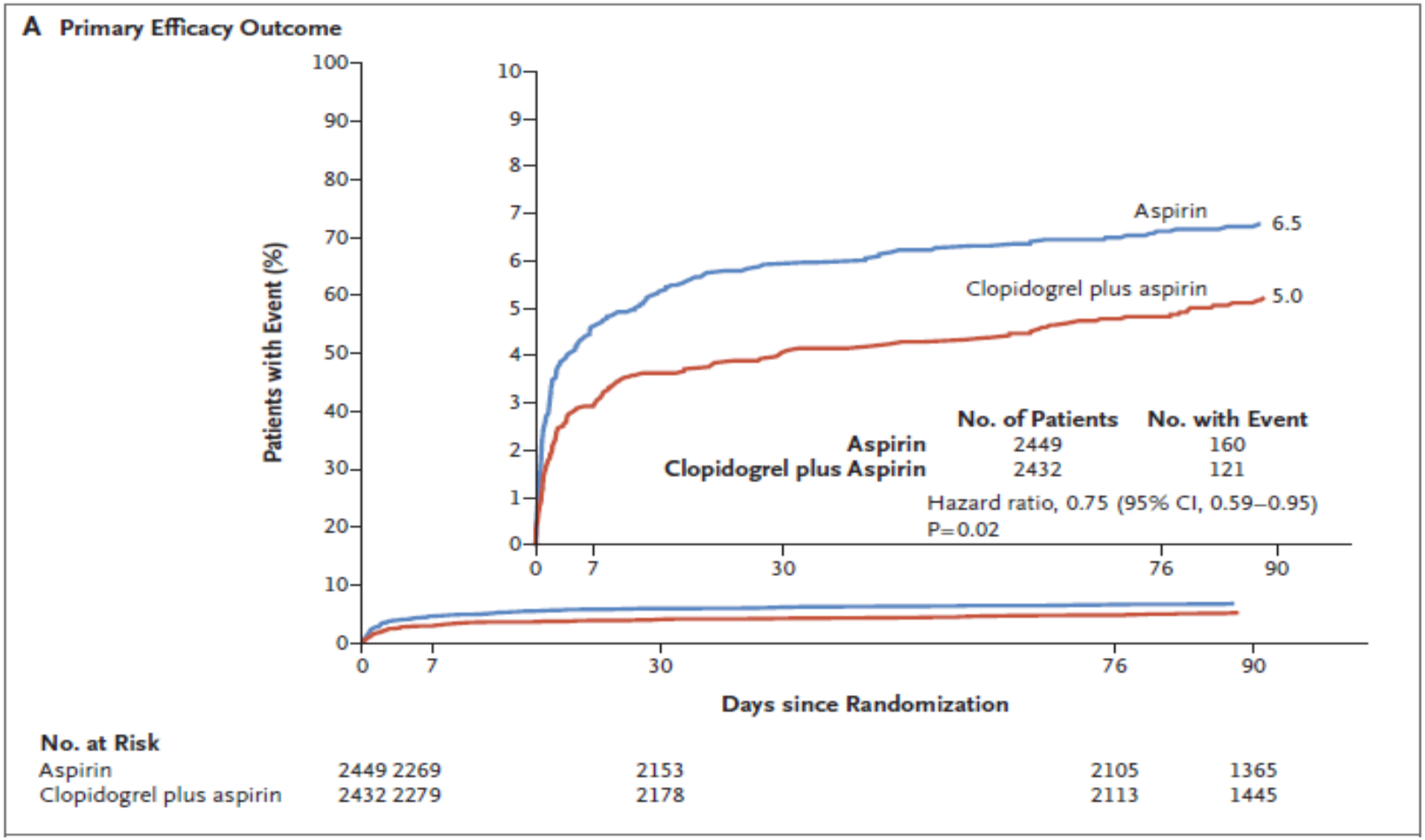
S. Claiborne Johnston, M.D., Ph.D., J. Donald Easton, M.D., Mary Farrant, M.B.A., William Barsan, M.D., Robin A. Conwit, M.D., Jordan J. Elm, Ph.D., Anthony S. Kim, M.D., Anne S. Lindblad, Ph.D., and Yuko Y. Palesch, Ph.D., for the Clinical Research Collaboration, Neurological Emergencies Treatment Trials Network, and the POINT Investigators*

Table 1. Characteristics of the Patients at Baseline. *

Characteristic	Clopidogrel plus Aspirin (N=2432)	Aspirin (N=2449)
Median age (IQR) — yr	65.0 (55.0–74.0)	65.0 (56.0–74.0)
Female sex — no. (%)	1097 (45.1)	1098 (44.8)
Qualifying event — no. (%)		
TIA	1056 (43.4)	1052 (43.0)
Ischemic stroke	1376 (56.6)	1397 (57.0)

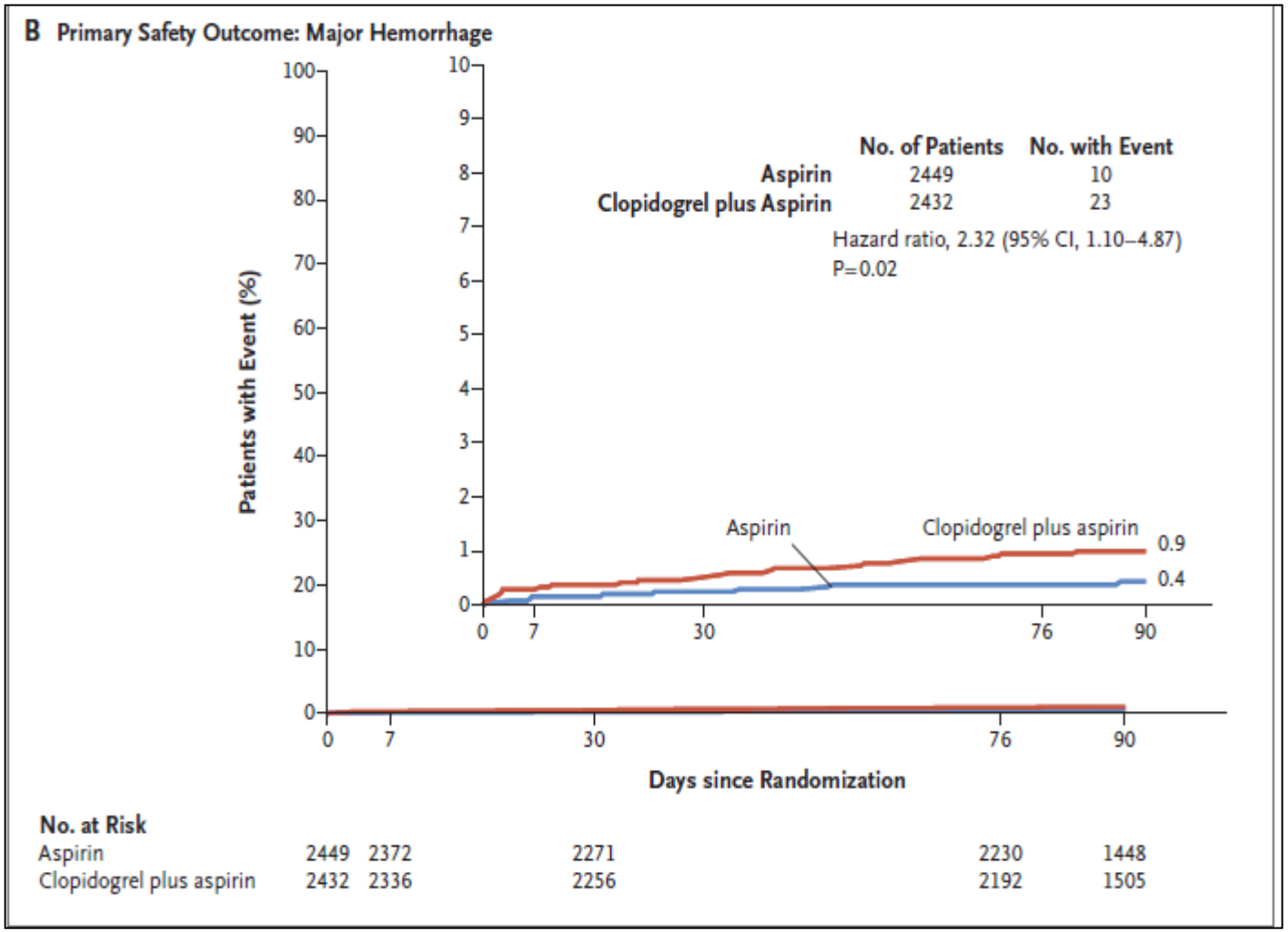
Aspirin plus clopidogrel versus aspirin in mild stroke or high risk TIA

The POINT trial



Significant benefit for ischemic stroke, MI and vascular death

The POINT trial



Increased risk of major bleeding

Antiplatelet therapy: triple therapy

Antiplatelet therapy with aspirin, clopidogrel, and dipyridamole versus clopidogrel alone or aspirin and dipyridamole in patients with acute cerebral ischaemia (TARDIS): a randomised, open-label, phase 3 superiority trial

- Randomized open study with 3096 Patienten and TIA or ischemic stroke
- Gruppe 1: Aspirin plus Clopidogrel plus Dipyridamol
- Gruppe 2: Clopidogrel or Aspirin plus Dipyridamol
- Treatment for 30 days
- Primary endpoint: stroke or TIA in 90 days

Study terminated by DSMB

*Philip M Bath, Lisa J Woodhouse, Jason P Appleton, Maia Beridze, Hanne Christensen, Robert A Dineen, Lelia Duley, Timothy J England, Katie Flaherty, Diane Havard, Stan Heptinstall, Marilyn James, Kailash Krishnan, Hugh S Markus, Alan A Montgomery, Stuart J Pocock, Marc Randall, Annemarei Ranta, Thompson G Robinson, Polly Scutt, Graham S Venables, Nikola Sprigg, for the TARDIS Investigators**

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S0140-6736(17)32849-0

Antiplatelet therapy: triple therapy

Antiplatelet therapy with aspirin, clopidogrel, and dipyridamole versus clopidogrel alone or aspirin and dipyridamole in patients with acute cerebral ischaemia (TARDIS): a randomised, open-label, phase 3 superiority trial

	Intensive antiplatelet therapy (n=1556)	Guideline antiplatelet therapy (n=1540)	Adjusted cOR or HR (95% CI)	p value
Primary outcome				
Number of patients	1540	1530	..	..
Ordinal stroke or TIA	93 (6%)	105 (7%)	0·90 (0·67–1·20)	0·47
Death (mRS 6)	13 (1%)	7 (<1%)	1·92 (0·76–4·84)	0·17
mRS 4–5	11 (1%)	9 (1%)	..	..
mRS 2–3	22 (1%)	23 (2%)	..	..
mRS 0–1	15 (1%)	18 (1%)	..	..
TIA	32 (2%)	48 (3%)	..	..
No stroke or TIA	1447 (94%)	1425 (93%)	..	..

No benefit in the prevention of vascular events

*Philip M Bath, Lisa J Woodhouse, Jason P Appleton, Maia Beridze, Hanne Christensen, Robert A Dineen, Lelia Duley, Timothy J England, Katie Flaherty, Diane Havard, Stan Heptinstall, Marilyn James, Kailash Krishnan, Hugh S Markus, Alan A Montgomery, Stuart J Pocock, Marc Randall, Annemarei Ranta, Thompson G Robinson, Polly Scutt, Graham S Venables, Nikola Sprigg, for the TARDIS Investigators**

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Antiplatelet therapy: triple therapy

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	Intensive antiplatelet therapy (n=1556)	Guideline antiplatelet therapy (n=1540)	Adjusted cOR or HR (95% CI)	p value
Bleeding (safety analysis)				
Ordinal bleeding (cOR)	305/1541 (20%)	139/1531 (9%)	2·54 (2·05–3·16)	<0·0001
Fatal[20]	8/1541 (1%)	3/1531 (<1%)	3·48 (0·89–13·63)	0·074
Major	31/1541 (2%)	14/1531 (1%)	..	..
Moderate	25/1541 (2%)	13/1531 (1%)	..	..
Mild	241/1541 (16%)	109/1531 (7%)	..	..
None	1236/1541 (80%)	1392/1531 (91%)	..	..

Significant increase in bleeding complications

*Philip M Bath, Lisa J Woodhouse, Jason P Appleton, Maia Beridze, Hanne Christensen, Robert A Dineen, Lelia Duley, Timothy J England, Katie Flaherty, Diane Havard, Stan Heptinstall, Marilyn James, Kailash Krishnan, Hugh S Markus, Alan A Montgomery, Stuart J Pocock, Marc Randall, Annemarei Ranta, Thompson G Robinson, Polly Scutt, Graham S Venables, Nikola Sprigg, for the TARDIS Investigators**

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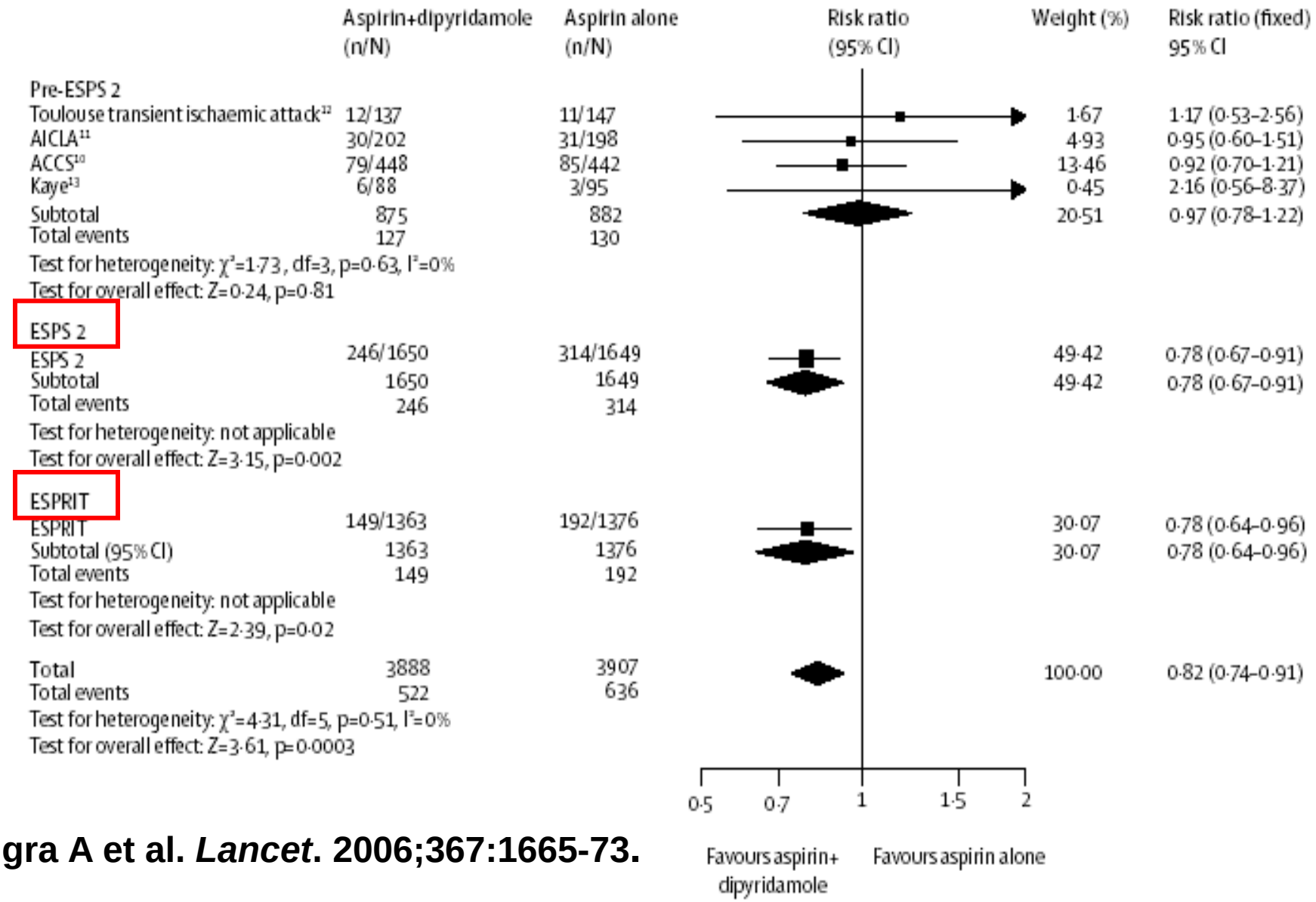
S0140-6736(17)32849-0

5. In patients presenting with minor stroke, treatment for 21 days with dual antiplatelet therapy (aspirin and clopidogrel) begun within 24 hours can be beneficial for early secondary stroke prevention for a period of up to 90 days from symptom onset.	**IIa**	**B-R**	New recommendation.
The CHANCE trial (Clopidogrel in High-Risk Patients With Acute Nondisabling Cerebrovascular Events) was a randomized, double-blind, placebo-controlled trial conducted in China to study the efficacy of short-term dual antiplatelet therapy begun within 24 hours, clopidogrel plus aspirin for 21 days followed by clopidogrel alone to 90 days, in patients with minor stroke (NIHSS score ≤3) or high-risk TIA (ABCD^2 [Age, Blood Pressure, Clinical Features, Duration, Diabetes] score ≥4). The primary outcome of recurrent stroke at 90 days (ischemic or hemorrhagic) favored dual antiplatelet therapy over aspirin alone (hazard ratio [HR], 0.68; 95% CI, 0.57–0.81; P<0.001).[193] A subsequent report of 1-year outcomes found a durable treatment effect, but the HR for secondary stroke prevention was only significantly beneficial in the first 90 days.[194] The generalizability of this intervention in non-Asian populations remains to be established, and a large phase III multicenter trial in the United States, Canada, Europe, and Australia is ongoing.[195]			See Table XLV in online Data Supplement 1.

Dipyridamole + Aspirin

Meta-Analysis: Composite of Vascular Death, Non-fatal Stroke, Non-fatal MI



Algra A et al. *Lancet*. 2006;367:1665-73.

ASA+ ER DP

- Risk reduction of stroke is significantly greater (RR 0.82; 95%CI 0.71-0.91) than with aspirin alone[1,2]
- ARR 1.0% per year
- **NNT = 100[3]**

1. Diener HC et al.: J Neurol Sci (1996) 143:1-13
2. Halkes P et al.: Lancet (2006) 367:1665-1673
3. JNNP, 2008.

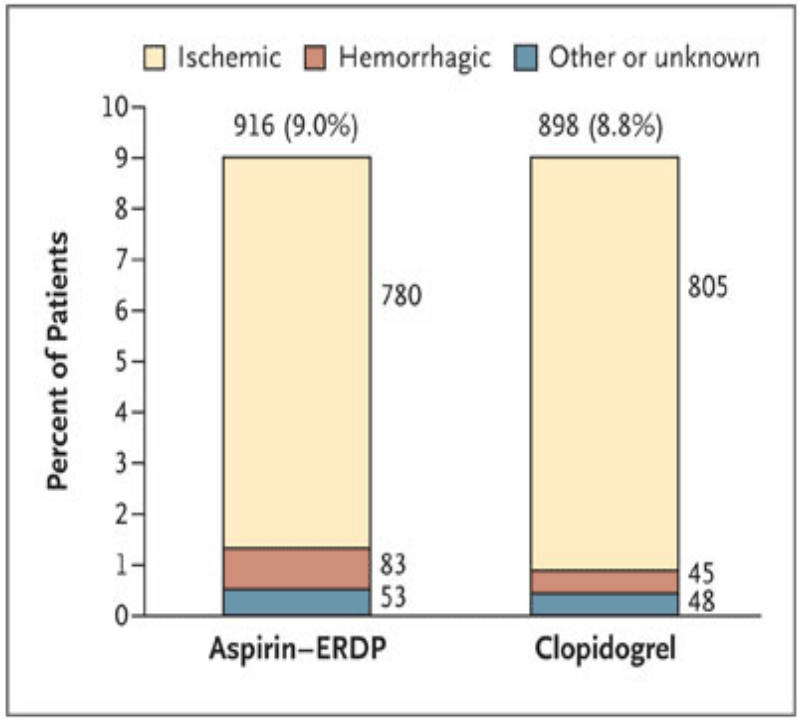
Aspirin and Extended-Release Dipyridamole versus Clopidogrel for Recurrent Stroke

Ralph L. Sacco, M.D., Hans-Christoph Diener, M.D., Ph.D.,
Salim Yusuf, M.B., B.S., D.Phil., Daniel Cotton, M.S., Stephanie ıunpuu, Ph.D.,
William A. Lawton, B.A., Yuko Palesch, Ph.D., Reneˈ H. Martin, Ph.D.,
Gregory W. Albers, M.D., Philip Bath, F.R.C.P., Natan Bornstein, M.D.,
Bernard P.L. Chan, M.D., Sien-Tsong Chen, M.D., Luis Cunha, M.D., Ph.D.,
Bjɤrn Dahlɤf, M.D., Ph.D., Jacques De Keyser, M.D., Ph.D.,
Geoffrey A. Donnan, M.D., Conrado Estol, M.D., Ph.D., Philip Gorelick, M.D.,
Vivian Gu, M.D., Karin Hermansson, D.M.Sc., Lutz Hilbrich, M.D.,
Markku Kaste, M.D., Ph.D., Chuanzhen Lu, M.D., Thomas Machnig, M.D.,
Prem Pais, M.D., Robin Roberts, M.Tech., Veronika Skvortsova, M.D.,
Philip Teal, M.D., Danilo Toni, M.D., Cam VanderMaelen, Ph.D.,
Thor Voigt, M.D., Michael Weber, M.D., and Byung-Woo Yoon, M.D., Ph.D.,
for the PRoFESS Study Group*

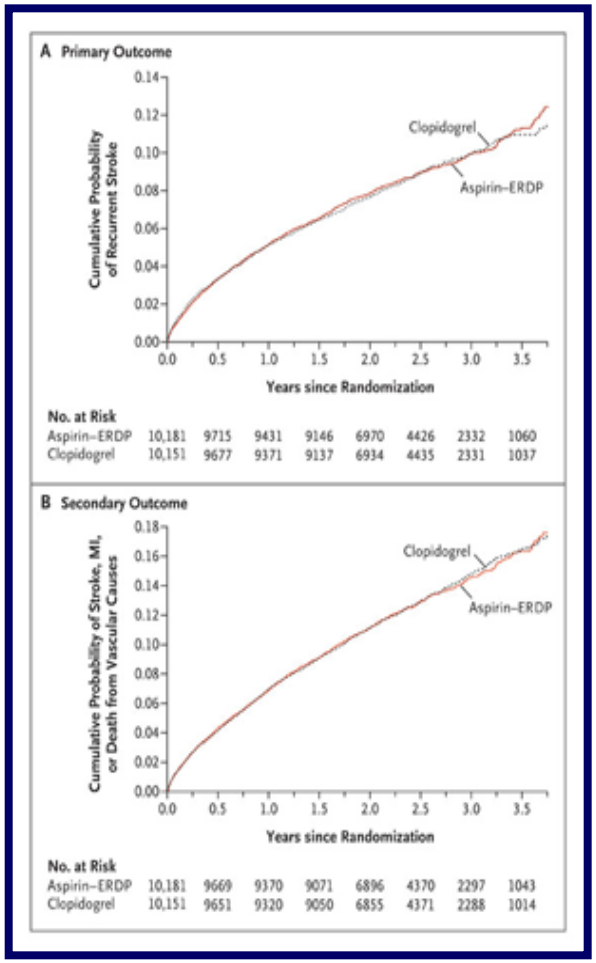
N Engl J Med 2008;359:1238-51. *2008*.

PROFESS

Aspirin and extended-release dipyridamole versus clopidogrel for recurrent stroke.



20 332 patients (mean age 66 years)



Sacco et al, NEJM 2008;359:1838

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 5, 2017 VOL. 377 NO. 14

Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease

J.W. Eikelboom, S.J. Connolly, J. Bosch, G.R. Dagenais, R.G. Hart, O. Shestakovska, R. Diaz, M. Alings, E.M. Lonn, S.S. Anand, P. Widimsky, M. Hori, A. Avezum, L.S. Piegas, K.R.H. Branch, J. Probstfield, D.L. Bhatt, J. Zhu, Y. Liang, A.P. Maggioni, P. Lopez-Jaramillo, M. O'Donnell, A.K. Kakkar, K.A.A. Fox, A.N. Parkhomenko, G. Ertl, S. Störk, M. Keltai, L. Ryden, N. Pogosova, A.L. Dans, F. Lanas, P.J. Commerford, C. Torp-Pedersen, T.J. Guzik, P.B. Verhamme, D. Vinereanu, J.-H. Kim, A.M. Tonkin, B.S. Lewis, C. Felix, K. Yusoff, P.G. Steg, K.P. Metsarinne, N. Cook Bruns, F. Misselwitz, E. Chen, D. Leong, and S. Yusuf, for the COMPASS Investigators*

Rivaroxaban and vascular disease: COMPASS - Study

Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease: an international, randomised, double-blind, placebo-controlled trial

- Multi-centre, double-blind, randomized study
- 27.395 patients with atherosclerotic disease
- Treatment arm 1: 2 x 2,5 mg rivaroxaban plus aspirin
- Treatment arm 2: 2 x 5 mg rivaroxaban
- Treatment arm 3: aspirin 100 mg
- Endpoint: stroke, MI, vascular death

Study terminated due to superior efficacy of rivaroxaban plus aspirin

*Sonia S Anand, Jackie Bosch, John W Eikelboom, Stuart J Connolly, Rafael Diaz, Peter Widimsky, Victor Aboyans, Marco Alings, Ajay K Kakkar, Katalin Keltai, Aldo P Maggioni , Basil S Lewis, Stefan Störk, Jun Zhu, Patricio Lopez-Jaramillo, Martin O'Donnell, Patrick J Commerford, Dragos Vinereanu, Nana Pogosova, Lars Ryden, Keith A A Fox, Deepak L Bhatt, Frank Misselwitz, John D Varigos, Thomas Vanassche, Alvaro A Avezum, Edmond Chen, Kelley Branch, Darryl P Leong, Shrikant I Bangdiwala, Robert G Hart, Salim Yusuf; on behalf of the COMPASS Investigators**

Rivaroxaban and carotid stenosis: COMPASS - Study

Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease: an international, randomised, double-blind, placebo-controlled trial

	Low-dose rivaroxaban plus aspirin (n=2492)	Rivaroxaban alone (n=2474)	Aspirin alone (n=2504)
Mean age, years	67·9 (8·45)	67·8 (8·49)	67·8 (8·47)
Sex			
Female	718 (29%)	674 (27%)	717 (29%)
Male	1774 (71%)	1800 (73%)	1787 (71%)
Carotid artery disease†	617 (24·8)	622 (25·1)	680 (27·2)

Small subgroup with asymptomatic carotid stenosis

*Sonia S Anand, Jackie Bosch, John W Eikelboom, Stuart J Connolly, Rafael Diaz, Peter Widimsky, Victor Aboyans, Marco Alings, Ajay K Kakkar, Katalin Keltai, Aldo P Maggioni, Basil S Lewis, Stefan Störk, Jun Zhu, Patricio Lopez-Jaramillo, Martin O'Donnell, Patrick J Commerford, Dragos Vinereanu, Nana Pogosova, Lars Ryden, Keith A A Fox, Deepak L Bhatt, Frank Misselwitz, John D Varigos, Thomas Vanassche, Alvaro A Avezum, Edmond Chen, Kelley Branch, Darryl P Leong, Shrikant I Bangdiwala, Robert G Hart, Salim Yusuf; on behalf of the COMPASS Investigators**

Rivaroxaban and carotid stenosis: COMPASS - Study

	Low-dose rivaroxaban plus aspirin (n=2492)	Rivaroxaban alone (n=2474)	Aspirin alone (n=2504)	Low-dose rivaroxaban plus aspirin versus aspirin alone		Rivaroxaban alone versus aspirin alone	
				HR (95% CI)	p value	HR (95% CI)	p value
Primary and secondary outcomes							
Cardiovascular death, stroke, myocardial infarction*	126 (5%)	149 (6%)	174 (7%)	0·72 (0·57–0·90)	0·0047	0·86 (0·69–1·08)	0·19
Coronary heart disease death, myocardial infarction, ischaemic stroke, acute limb ischaemia†	115 (5%)	147 (6%)	169 (7%)	0·68 (0·53–0·86)	0·0011	0·88 (0·70–1·10)	0·25
Cardiovascular death, myocardial infarction, ischaemic stroke, acute limb ischaemia†	142 (6%)	168 (7%)	198 (8%)	0·71 (0·57–0·88)	0·0019	0·86 (0·70–1·05)	0·14
Myocardial infarction	51 (2%)	56 (2%)	67 (3%)	0·76 (0·53–1·09)	..	0·84 (0·59–1·20)	..
Stroke	25 (1%)	43 (2%)	47 (2%)	0·54 (0·33–0·87)	..	0·93 (0·61–1·40)	..
Cardiovascular death	64 (3%)	66 (3%)	78 (3%)	0·82 (0·59–1·14)	..	0·86 (0·62–1·19)	..
Death	129 (5%)	134 (5%)	142 (6%)	0·91 (0·72–1·16)	..	0·95 (0·75–1·20)	..

Rivaroxaban plus aspirin more effective compared to rivaroxaban or aspirin

Rivaroxaban and carotid stenosis: COMPASS - Study

Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease: an international, randomised, double-blind, placebo-controlled trial

	Low-dose rivaroxaban plus aspirin group (n=2492)	Rivaroxaban alone group (n=2474)	Aspirin alone group (n=2504)	Low-dose rivaroxaban plus aspirin versus aspirin alone		Rivaroxaban alone versus asprin alone	
				HR (95% CI)	p value	HR (95% CI)	p value
Major bleeding*	77 (3%)	79 (3%)	48 (2%)	1·61 (1·12–2·31)	0·0089	1·68 (1·17–2·40)	0·0043
Fatal bleeding	4 (<1%)	5 (<1%)	3 (<1%)	..	..	..	..
Non-fatal symptomatic intracranial haemorrhage	4 (<1%)	3 (<1%)	8 (<1%)	..	..	..	..
Non-fatal, non-intracranial haemorrhage symptomatic bleeding into a critical organ	13 (1%)	18 (1%)	8 (<1%)	1·55 (0·64–3·74)	0·33	2·15 (0·94–4·96)	0·065
Other major bleeding (surgical site bleeding requiring reoperation or bleeding leading to hospitalisation	56 (2%)	53 (2%)	29 (1%)	1·94 (1·24–3·04)	0·0031	1·86 (1·18–2·92)	0·0064
Fatal or symptomatic bleeding into a critical organ	21 (1%)	26 (1%)	19 (1%)	1·10 (0·59–2·05)	..	1·39 (0·89–3·09)	..
Fatal or symptomatic bleeding into a critical organ or surgical site bleeding leading to re-operation	25 (1%)	29 (1%)	22 (1%)	1·13 (0·64–2·01)	..	1·34 (0·77–2·52)	..
ISTH major bleeding	64 (3%)	53 (2%)	40 (2%)	1·61 (1·08–2·39)	..	1·34 (0·89–2·02)	..

Rivaroxaban plus aspirin has a higher rate of bleeding

ESO recomendation - 2008

- **Patients are recommended to take antithrombotic therapy (Class I, Level A) .**

- **Those not requiring anticoagulation are recommended to take antiplatelet therapy (Class I, Level A). Where possible, combined aspirin and dipyridamole, or clopidogrel alone, should be taken. Alternatively, aspirin alone, or triflusal alone, may be used (Class I, Level A)**

- **The combination of aspirin and clopidogrel is not recommended in patients with recent ischemic stroke except in patients with specific indications, e.g. unstable angina or non-Q-wave MI during the last 12 months, or recent stenting; treatment should be given for up to 9 months after the event (Class I, Level A)**
- **Patient who have a stroke on antiplatelet therapy should be re-evaluated for pathophysiology and risk factors (Class IV, GCP)**

Antiplatelets

- Aspirin offers **15%** relative risk reduction for stroke after TIA or stroke
- Most widely studied dosages of aspirin are 50-150mg
- Aspirin, ASA+Dipyridamole, Clopidogrel are all acceptable initial therapy.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 10, 2009 VOL. 361 NO. 11

Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes

Lars Wallentin, M.D., Ph.D., Richard C. Becker, M.D., Andrzej Budaj, M.D., Ph.D., Christopher P. Cannon, M.D., Håkan Emanuelsson, M.D., Ph.D., Claes Held, M.D., Ph.D., Jay Horrow, M.D., Steen Husted, M.D., D.Sc., Stefan James, M.D., Ph.D., Hugo Katus, M.D., Kenneth W. Mahaffey, M.D., Benjamin M. Scirica, M.D., M.P.H., Allan Skene, Ph.D., Philippe Gabriel Steg, M.D., Robert F. Storey, M.D., D.M., and Robert A. Harrington, M.D., for the PLATO Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIALS

Ticagrelor — Is There Need for a New Player in the Antiplatelet-Therapy Field?

Albert Schömig, M.D.

N Engl J Med 361:1108, September 10, 2009 *Editorial*

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIALS

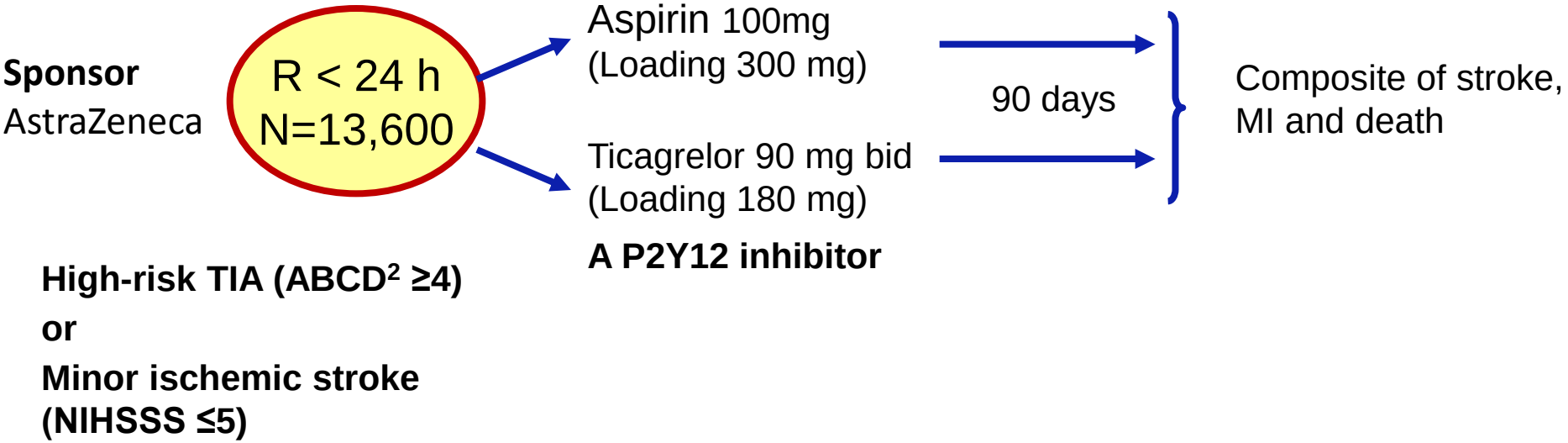
Ticagrelor — Is There Need for a New Player in the Antiplatelet-Therapy Field?

Albert Schömig, M.D.

N Engl J Med 361:1108, September 10, 2009 *Editorial*

SOCRATES

Acute Stroke Or Transient IsChaemic Attack TReated With Aspirin or Ticagrelor and Patient OutcomES



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ticagrelor versus Aspirin in Acute Stroke or Transient Ischemic Attack

S. Claiborne Johnston, M.D., Ph.D., Pierre Amarenco, M.D., Gregory W. Albers, M.D., Hans Denison, M.D., Ph.D., J. Donald Easton, M.D., Scott R. Evans, Ph.D., Peter Held, M.D., Ph.D., Jenny Jonasson, Ph.D., Kazuo Minematsu, M.D., Ph.D., Carlos A. Molina, M.D., Yongjun Wang, M.D., and K.S. Lawrence Wong, M.D., for the SOCRATES Steering Committee and Investigators*

N Engl J Med 2016;375:35-43.

BACKGROUND

Ticagrelor may be a more effective antiplatelet therapy than aspirin for the prevention of recurrent stroke and cardiovascular events in patients with acute cerebral ischemia.

METHODS

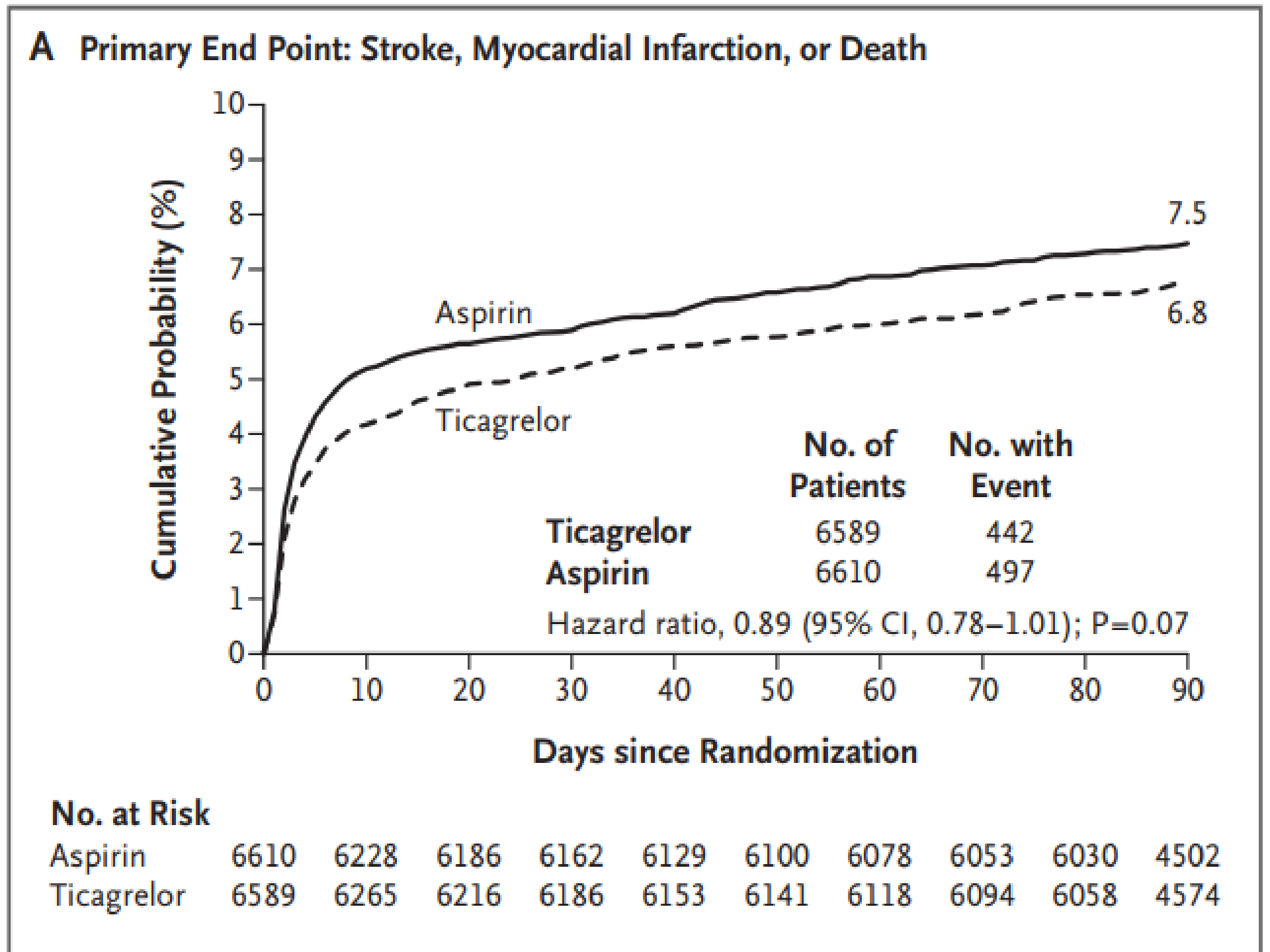
We conducted an international double-blind, controlled trial in 674 centers in 33 countries, in which 13,199 patients with a nonsevere ischemic stroke or high-risk transient ischemic attack who had not received intravenous or intraarterial thrombolysis and were not considered to have had a cardioembolic stroke were randomly assigned within 24 hours after symptom onset, in a 1:1 ratio, to receive either ticagrelor (180 mg loading dose on day 1 followed by 90 mg twice daily for days 2 through 90) or aspirin (300 mg on day 1 followed by 100 mg daily for days 2 through 90). The primary end point was the time to the occurrence of stroke, myocardial infarction, or death within 90 days.

RESULTS

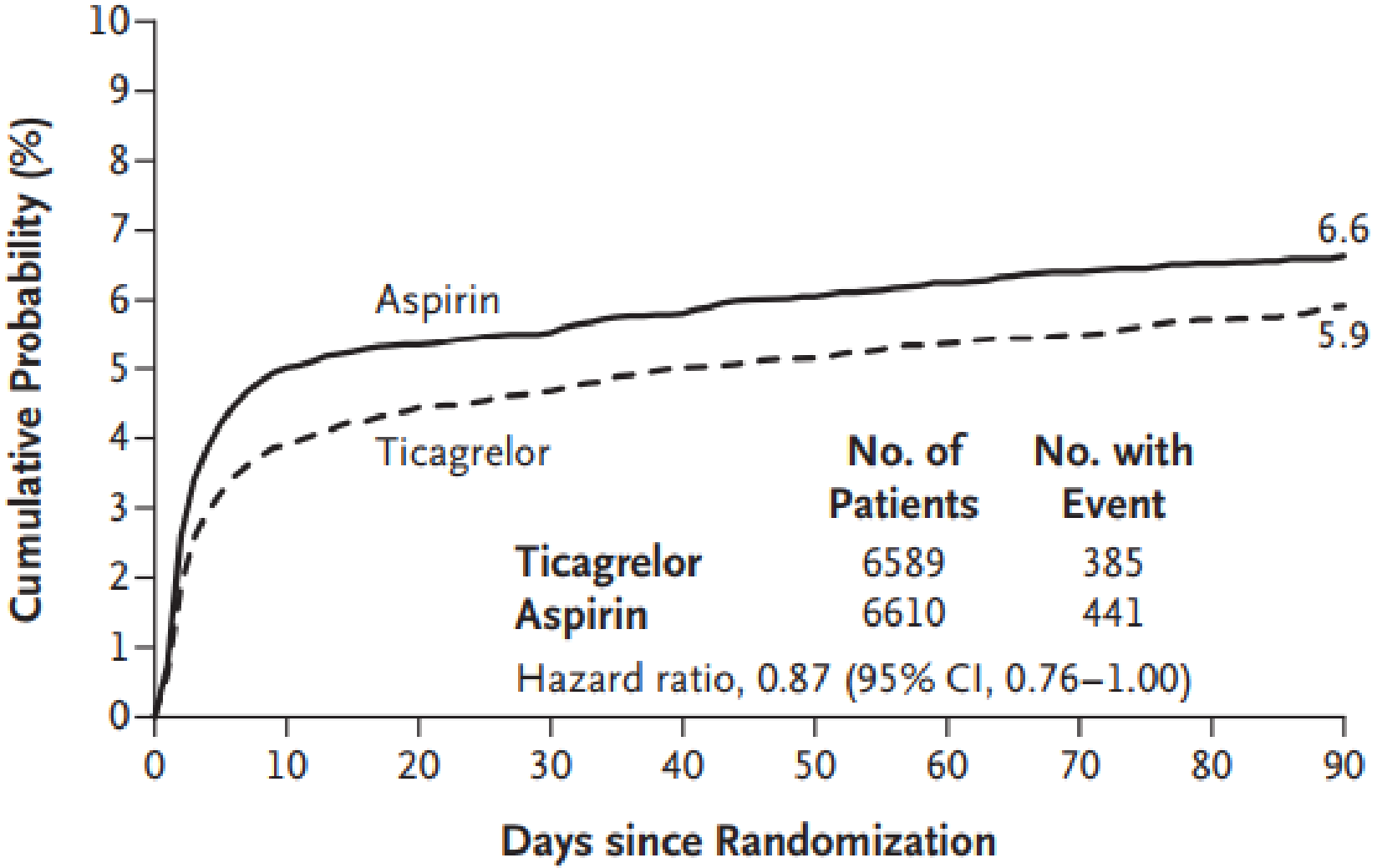
During the 90 days of treatment, a primary end-point event occurred in 442 of the 6589 patients (6.7%) treated with ticagrelor, versus 497 of the 6610 patients (7.5%) treated with aspirin (hazard ratio, 0.89; 95% confidence interval [CI], 0.78 to 1.01; P=0.07). Ischemic stroke occurred in 385 patients (5.8%) treated with ticagrelor and in 441 patients (6.7%) treated with aspirin (hazard ratio, 0.87; 95% CI, 0.76 to 1.00). Major bleeding occurred in 0.5% of patients treated with ticagrelor and in 0.6% of patients treated with aspirin, intracranial hemorrhage in 0.2% and 0.3%, respectively, and fatal bleeding in 0.1% and 0.1%.

CONCLUSIONS

In our trial involving patients with acute ischemic stroke or transient ischemic attack, ticagrelor was not found to be superior to aspirin in reducing the rate of stroke, myocardial infarction, or death at 90 days. (Funded by AstraZeneca; ClinicalTrials.gov number, NCT01994720.)


A Primary End Point: Stroke, Myocardial Infarction, or Death
Cumulative Probability (%)
10
9
8
7
6
5
4
3
2
1
0
7.5
6.8
Aspirin
Ticagrelor
No. of Patients
No. with Event
Ticagrelor 6589 442
Aspirin 6610 497
Hazard ratio, 0.89 (95% CI, 0.78–1.01); P=0.07
0 10 20 30 40 50 60 70 80 90
Days since Randomization
No. at Risk
Aspirin 6610 6228 6186 6162 6129 6100 6078 6053 6030 4502
Ticagrelor 6589 6265 6216 6186 6153 6141 6118 6094 6058 4574

B **Ischemic Stroke**



No. at Risk

Aspirin	6610	6230	6193	6169	6134	6112	6092	6065	6046	4518
Ticagrelor	6589	6272	6230	6204	6169	6157	6133	6102	6073	4587

Efficacy and safety of ticagrelor versus aspirin in acute stroke or transient ischaemic attack of atherosclerotic origin: a subgroup analysis of SOCRATES, a randomised, double-blind, controlled trial

Pierre Amarenco, Gregory W Albers, Hans Denison, J Donald Easton, Scott R Evans, Peter Held, Michael D Hill, Jenny Jonasson, Scott E Kasner, Per Ladenvall, Kazuo Minematsu, Carlos A Molina, Yongjun Wang, K S Lawrence Wong, S Claiborne Johnston, for the SOCRATES Steering Committee and Investigators

Summary

Background Ticagrelor is an effective antiplatelet therapy for patients with coronary atherosclerotic disease and might be more effective than aspirin in preventing recurrent stroke and cardiovascular events in patients with acute cerebral ischaemia of atherosclerotic origin. Our aim was to test for a treatment-by-ipsilateral atherosclerotic stenosis interaction in a subgroup analysis of patients in the Acute Stroke or Transient Ischaemic Attack Treated with Aspirin or Ticagrelor and Patient Outcomes (SOCRATES) trial.

Methods SOCRATES was a randomised, double-blind, controlled trial of ticagrelor versus aspirin in patients aged 40 years or older with a non-cardioembolic, non-severe acute ischaemic stroke, or high-risk transient ischaemic attack from 674 hospitals in 33 countries. We randomly allocated patients (1:1) to ticagrelor (180 mg loading dose on day 1 followed by 90 mg twice daily for days 2–90, given orally) or aspirin (300 mg on day 1 followed by 100 mg daily for days 2–90, given orally) within 24 h of symptom onset. Investigators classified all patients into atherosclerotic and non-atherosclerotic groups for the prespecified, exploratory analysis reported in this study. The primary endpoint was the time to occurrence of stroke, myocardial infarction, or death within 90 days. Efficacy analysis was by intention to treat. The SOCRATES trial is registered with ClinicalTrials.gov, number NCT01994720.

Findings Between Jan 7, 2014, and Oct 29, 2015, we randomly allocated 13 199 patients (6589 [50%] to ticagrelor and 6610 [50%] to aspirin). Potentially symptomatic ipsilateral atherosclerotic stenosis was reported in 3081 (23%) of 13 199 patients. We found a treatment-by-atherosclerotic stenosis interaction (p=0·017). 103 (6·7%) of 1542 patients with ipsilateral stenosis in the ticagrelor group and 147 (9·6%) of 1539 patients with ipsilateral stenosis in the aspirin group had an occurrence of stroke, myocardial infarction, or death within 90 days (hazard ratio 0·68 [95% CI 0·53–0·88]; p=0·003). In 10 118 patients with no ipsilateral stenosis, 339 (6·7%) of 5047 patients in the ticagrelor group had an occurrence of stroke, myocardial infarction, or death within 90 days compared with 350 (6·9%) of 5071 in the aspirin group (0·97 [0·84–1·13]; p=0·72). There were no significant differences in the proportion of life-threatening bleeding or major or minor bleeding events in patients with ipsilateral stenosis in the ticagrelor group compared with the aspirin group.

Interpretation In this prespecified exploratory analysis, ticagrelor was superior to aspirin at preventing stroke, myocardial infarction, or death at 90 days in patients with acute ischaemic stroke or transient ischaemic attack when associated with ipsilateral atherosclerotic stenosis. An understanding of stroke mechanisms and causes is important to deliver safe and efficacious treatments for early stroke prevention.

Lancet Neurol 2017

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6. Ticagrelor is not recommended (over aspirin) in the acute treatment of patients with minor stroke.	**III: No Benefit**	**B-R**	New recommendation.
The recently completed SOCRATES trial (Acute Stroke or Transient Ischaemic Attack Treated With Aspirin or Ticagrelor and Patient Outcomes) was a randomized, double-blind, placebo-controlled trial of ticagrelor versus aspirin begun within 24 hours in patients with minor stroke (NIHSS score ≤5) or TIA (ABCD^2 [Age, Blood Pressure, Clinical Features, Duration, Diabetes] score ≥4). With a primary outcome of time to the composite end point of stroke, myocardial infarction (MI), or death up to 90 days, ticagrelor was not found to be superior to aspirin (HR, 0.89; 95% CI, 0.78–1.01; *P*=0.07).[196] However, because there were no significant safety differences in the 2 groups, ticagrelor may be a reasonable alternative in stroke patients who have a contraindication to aspirin.			See Table XLV in online Data Supplement 1.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Antibody-Based Ticagrelor Reversal Agent in Healthy Volunteers

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ABSTRACT

BACKGROUND

Ticagrelor is an oral $P2Y_{12}$ inhibitor that is used with aspirin to reduce the risk of ischemic events among patients with acute coronary syndromes or previous myocardial infarction. Spontaneous major bleeding and bleeding associated with urgent invasive procedures are concerns with ticagrelor, as with other antiplatelet drugs. The antiplatelet effects of ticagrelor cannot be reversed with platelet transfusion. A rapid-acting reversal agent would be useful.

METHODS

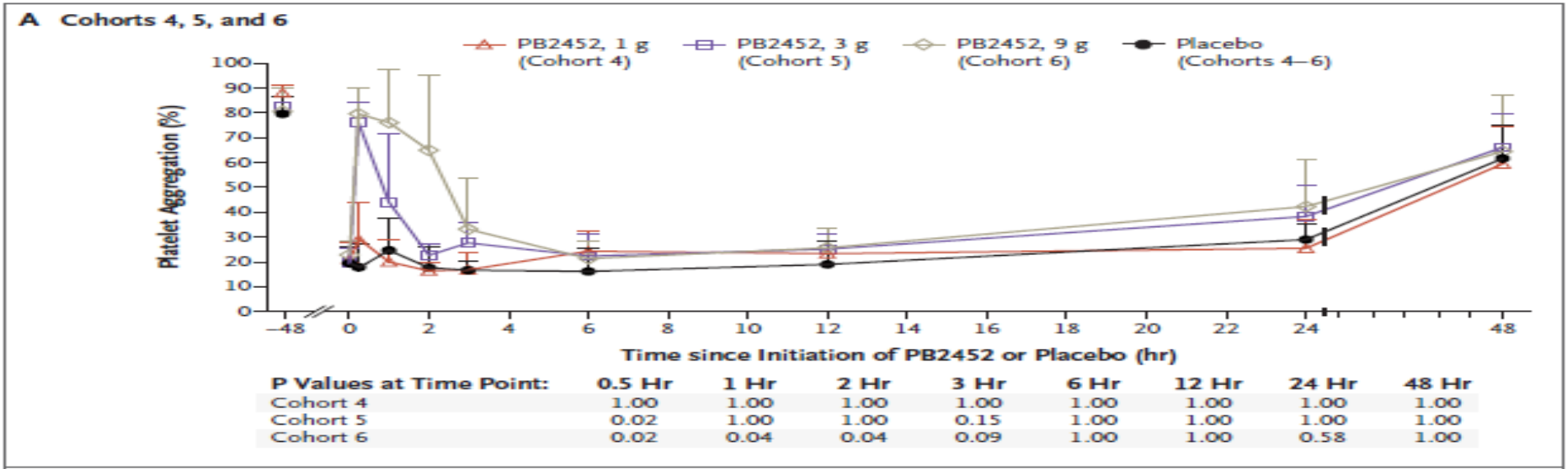
In this randomized, double-blind, placebo-controlled, phase 1 trial, we evaluated intravenous PB2452, a monoclonal antibody fragment that binds ticagrelor with high affinity, as a ticagrelor reversal agent. We assessed platelet function in healthy volunteers before and after 48 hours of ticagrelor pretreatment and again after the administration of PB2452 or placebo. Platelet function was assessed with the use of light transmission aggregometry, a point-of-care $P2Y_{12}$ platelet-reactivity test, and a vasodilator-stimulated phosphoprotein assay.

RESULTS

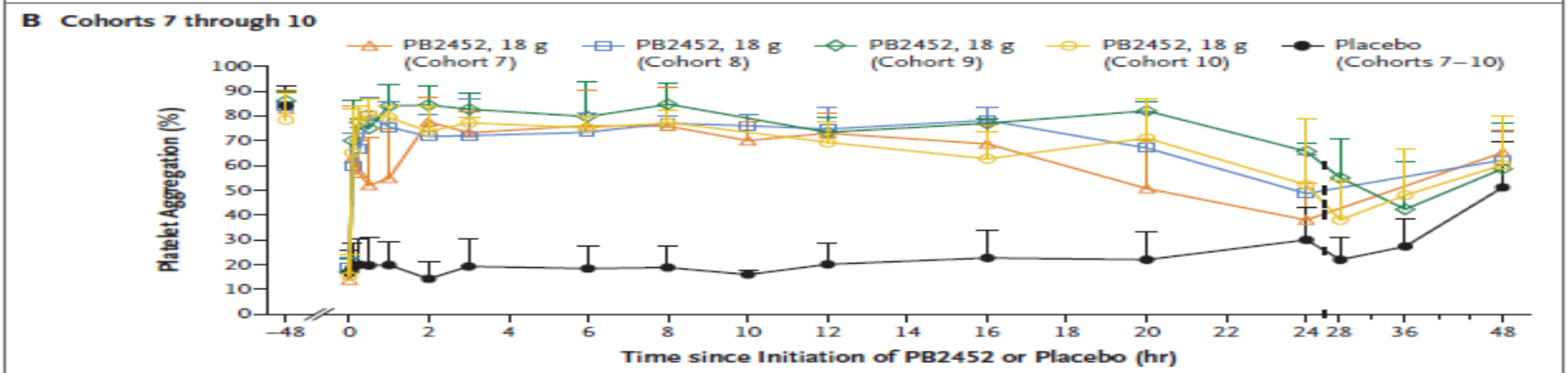
Of the 64 volunteers who underwent randomization, 48 were assigned to receive PB2452 and 16 to receive placebo. After 48 hours of ticagrelor pretreatment, platelet aggregation was suppressed by approximately 80%. PB2452 administered as an initial intravenous bolus followed by a prolonged infusion (8, 12, or 16 hours) was associated with a significantly greater increase in platelet function than placebo, as measured by multiple assays. Ticagrelor reversal occurred within 5 minutes after the initiation of PB2452 and was sustained for more than 20 hours ($P<0.001$ after Bonferroni adjustment across all time points for all assays). There was no evidence of a rebound in platelet activity after drug cessation. Adverse events related to the trial drug were limited mainly to issues involving the infusion site.

CONCLUSIONS

In healthy volunteers, the administration of PB2452, a specific reversal agent for ticagrelor, provided immediate and sustained reversal of the antiplatelet effects of ticagrelor, as measured by multiple assays. (Funded by PhaseBio Pharmaceuticals; ClinicalTrials.gov number, NCT03492385.)



P Values at Time Point:	0.5 Hr	1 Hr	2 Hr	3 Hr	6 Hr	12 Hr	24 Hr	48 Hr
Cohort 4	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Cohort 5	0.02	1.00	1.00	0.15	1.00	1.00	1.00	1.00
Cohort 6	0.02	0.04	0.04	0.09	1.00	1.00	0.58	1.00



P Values at Time Point:	5 Min	0.25 Hr	0.5 Hr	1 Hr	2 Hr	3 Hr	6 Hr	8 Hr	10 Hr	12 Hr	16 Hr	20 Hr
Cohort 7	0.04	0.04	0.13	0.04	0.40	0.02	0.02	0.02	0.15	0.02	0.02	0.22
Cohort 8	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.15	0.02	0.02	0.02
Cohort 10	0.04	0.02	0.02	0.02	0.02	0.02	0.02	0.02	NA	0.02	0.02	0.02

Figure 1. Onset and Duration of Ticagrelor Reversal.

Ticagrelor reversal is shown as an increase in mean platelet aggregation after ticagrelor pretreatment, as assessed with the use of light transmission aggregometry. Shown are the onset and duration of ticagrelor reversal among volunteers in cohorts 4, 5, and 6, who were randomly assigned to receive either a 30-minute infusion of PB2452 at a dose of 1 g, 3 g, and 9 g, respectively, or placebo (Panel A), as well as among volunteers in cohorts 7, 8, 9, and 10, who were randomly assigned to receive an 18-g fixed dose of PB2452 with an infusion duration of 8 hours, 12 hours, 16 hours, and 16 hours, respectively, or placebo (Panel B). Mean platelet aggregation at baseline (before the administration of ticagrelor) is shown at −48 hours. P values are for the comparison of PB2452 with placebo. Statistical testing was not performed in cohort 9 because only three volunteers in that cohort received PB2452. I bars indicate the standard deviation. NA denotes not available.

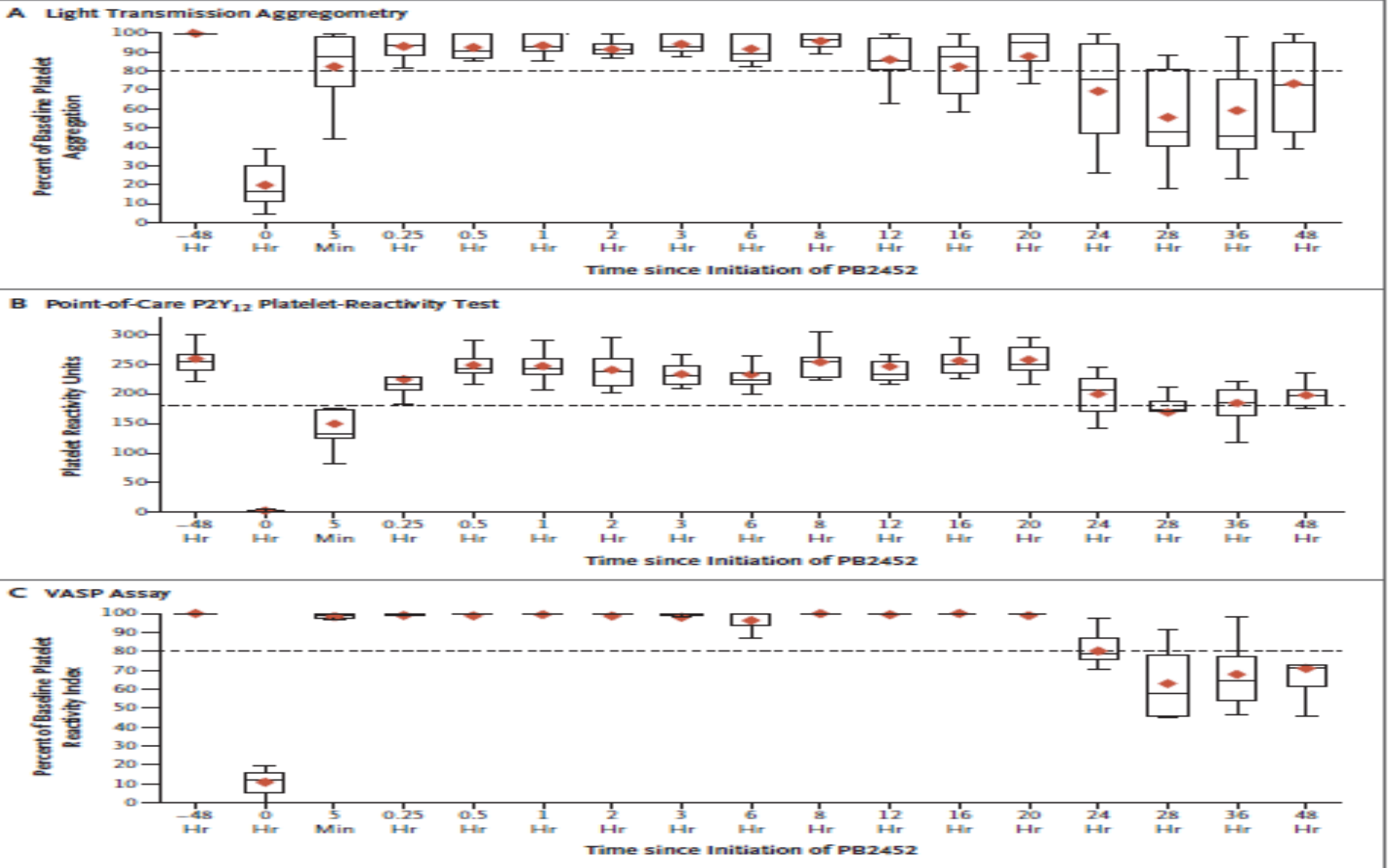


Figure 2. Normalization of Platelet Function after Ticagrelor Reversal.

Normalization of platelet function is shown as an increase in platelet function to within the normal range after ticagrelor pretreatment and subsequent initiation of PB2452. Shown are data from cohorts 9 and 10 (pooled). On light transmission aggregometry (Panel A), a normal level of platelet aggregation is at least 80% of the baseline value (dashed line). On the point-of-care $P2Y_{12}$ platelet-reactivity test (Panel B), a normal level of platelet reactivity units is at least 180 (dashed line). On assessment of $P2Y_{12}$ receptor signaling with the vasodilator-stimulated phosphoprotein (VASP) assay (Panel C), a normal platelet reactivity index is at least 80% of the baseline value (dashed line). Red diamonds indicate the mean, horizontal lines the median, and I bars the range. The tops and bottoms of the boxes indicate the third and first quartiles, respectively.

Age-specific risks, severity, time course, and outcome of bleeding on long-term antiplatelet treatment after vascular events: a population-based cohort study

Linxin Li, Olivia C Geraghty*, Ziyah Mehta, Peter M Rothwell, on behalf of the Oxford Vascular Study*

Summary

Background Lifelong antiplatelet treatment is recommended after ischaemic vascular events, on the basis of trials done mainly in patients younger than 75 years. Upper gastrointestinal bleeding is a serious complication, but had low case fatality in trials of aspirin and is not generally thought to cause long-term disability. Consequently, although co-prescription of proton-pump inhibitors (PPIs) reduces upper gastrointestinal bleeds by 70–90%, uptake is low and guidelines are conflicting. We aimed to assess the risk, time course, and outcomes of bleeding on antiplatelet treatment for secondary prevention in patients of all ages.

Methods We did a prospective population-based cohort study in patients with a first transient ischaemic attack, ischaemic stroke, or myocardial infarction treated with antiplatelet drugs (mainly aspirin based, without routine PPI use) after the event in the Oxford Vascular Study from 2002 to 2012, with follow-up until 2013. We determined type, severity, outcome (disability or death), and time course of bleeding requiring medical attention by face-to-face follow-up for 10 years. We estimated age-specific numbers needed to treat (NNT) to prevent upper gastrointestinal bleeding with routine PPI co-prescription on the basis of Kaplan–Meier risk estimates and relative risk reduction estimates from previous trials.

Findings 3166 patients (1582 [50%] aged ≥75 years) had 405 first bleeding events (n=218 gastrointestinal, n=45 intracranial, and n=142 other) during 13 509 patient-years of follow-up. Of the 314 patients (78%) with bleeds admitted to hospital, 117 (37%) were missed by administrative coding. Risk of non-major bleeding was unrelated to age, but major bleeding increased steeply with age (≥75 years hazard ratio [HR] 3·10, 95% CI 2·27–4·24; p<0·0001), particularly for fatal bleeds (5·53, 2·65–11·54; p<0·0001), and was sustained during long-term follow-up. The same was true of major upper gastrointestinal bleeds (≥75 years HR 4·13, 2·60–6·57; p<0·0001), particularly if disabling or fatal (10·26, 4·37–24·13; p<0·0001). At age 75 years or older, major upper gastrointestinal bleeds were mostly disabling or fatal (45 [62%] of 73 patients *vs* 101 [47%] of 213 patients with recurrent ischaemic stroke), and outnumbered disabling or fatal intracerebral haemorrhage (n=45 *vs* n=18), with an absolute risk of 9·15 (95% CI 6·67–12·24) per 1000 patient-years. The estimated NNT for routine PPI use to prevent one disabling or fatal upper gastrointestinal bleed over 5 years fell from 338 for individuals younger than 65 years, to 25 for individuals aged 85 years or older.

Interpretation In patients receiving aspirin-based antiplatelet treatment without routine PPI use, the long-term risk of major bleeding is higher and more sustained in older patients in practice than in the younger patients in previous trials, with a substantial risk of disabling or fatal upper gastrointestinal bleeding. Given that half of the major bleeds in patients aged 75 years or older were upper gastrointestinal, the estimated NNT for routine PPI use to prevent such bleeds is low, and co-prescription should be encouraged.

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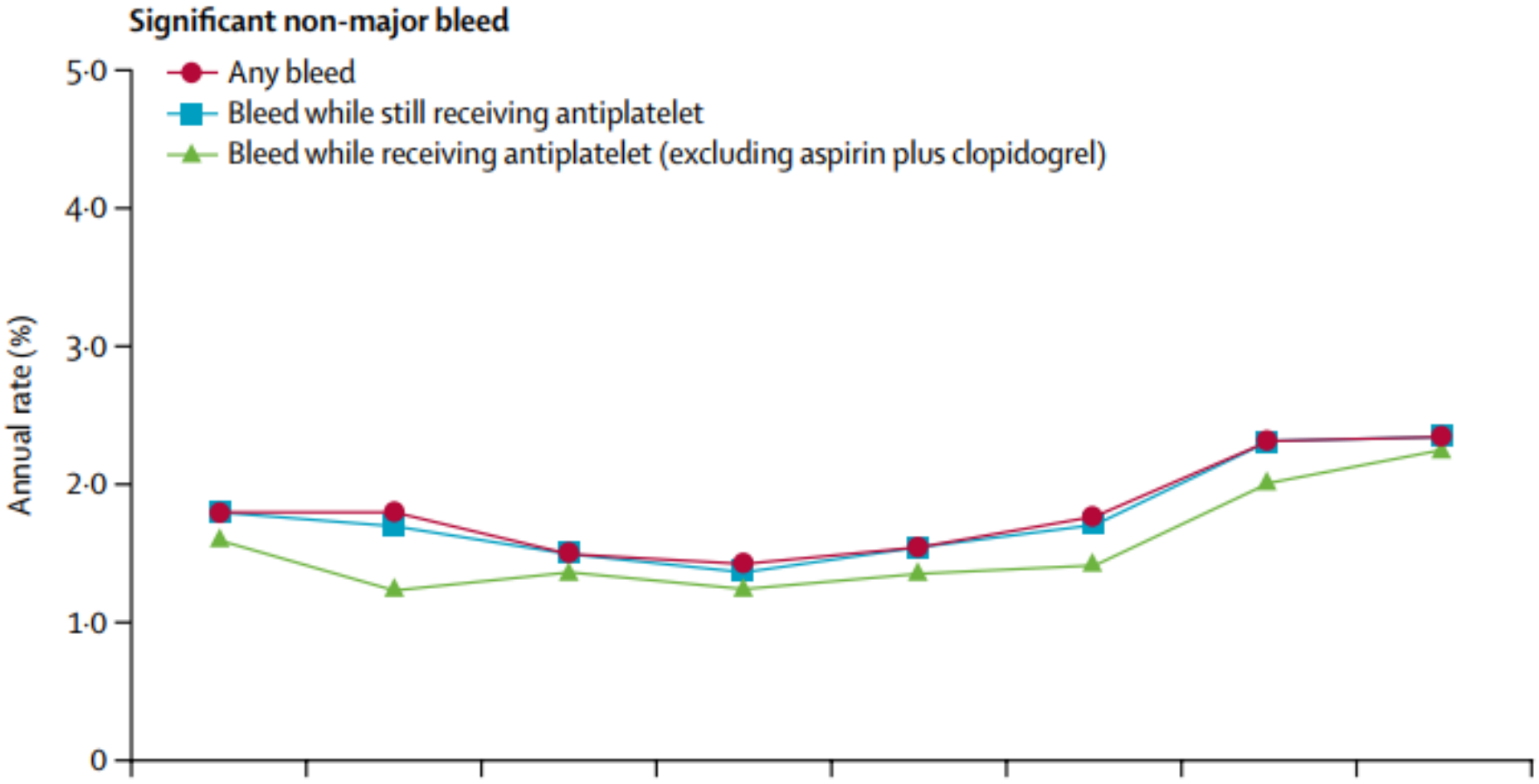
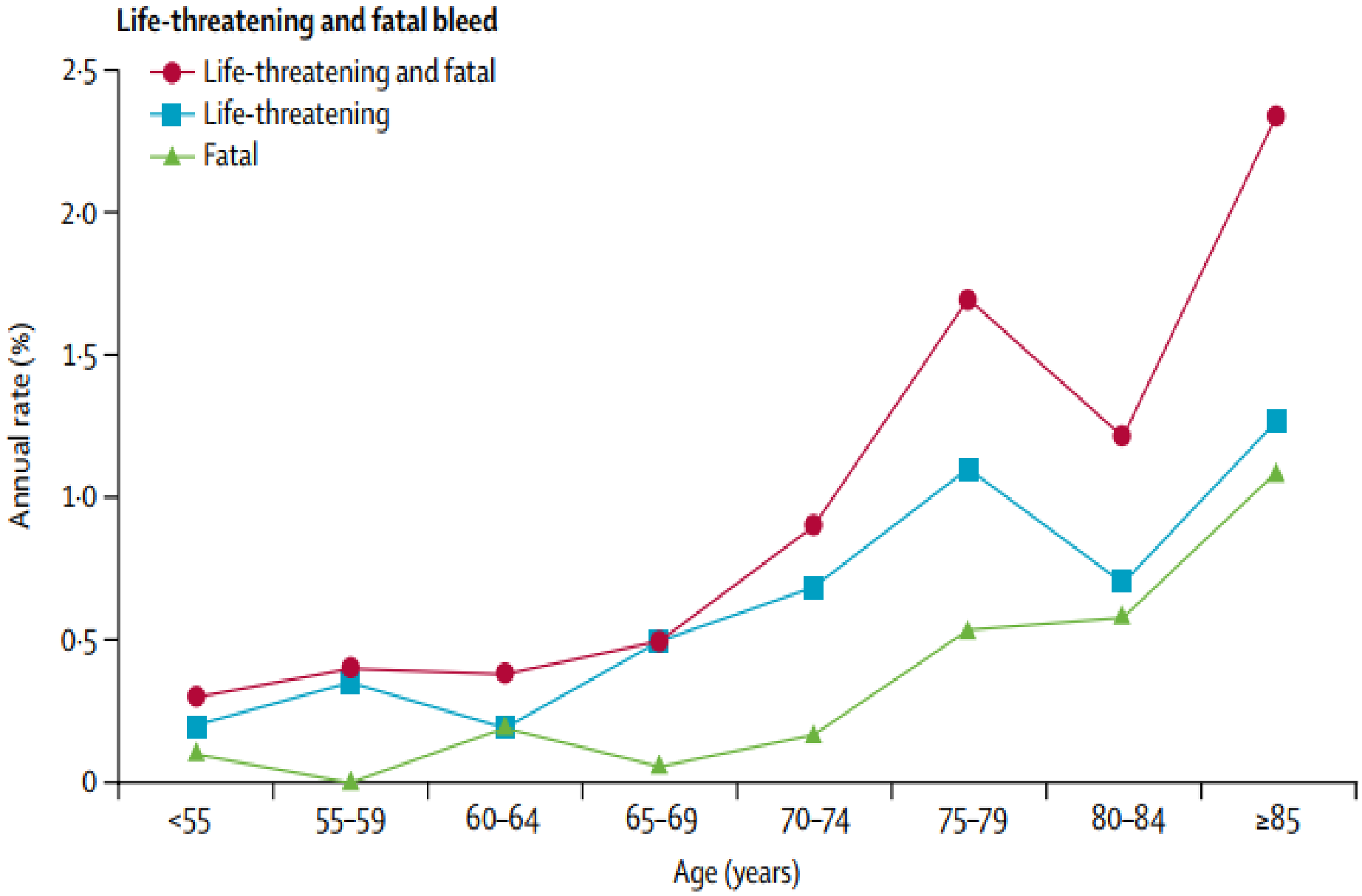
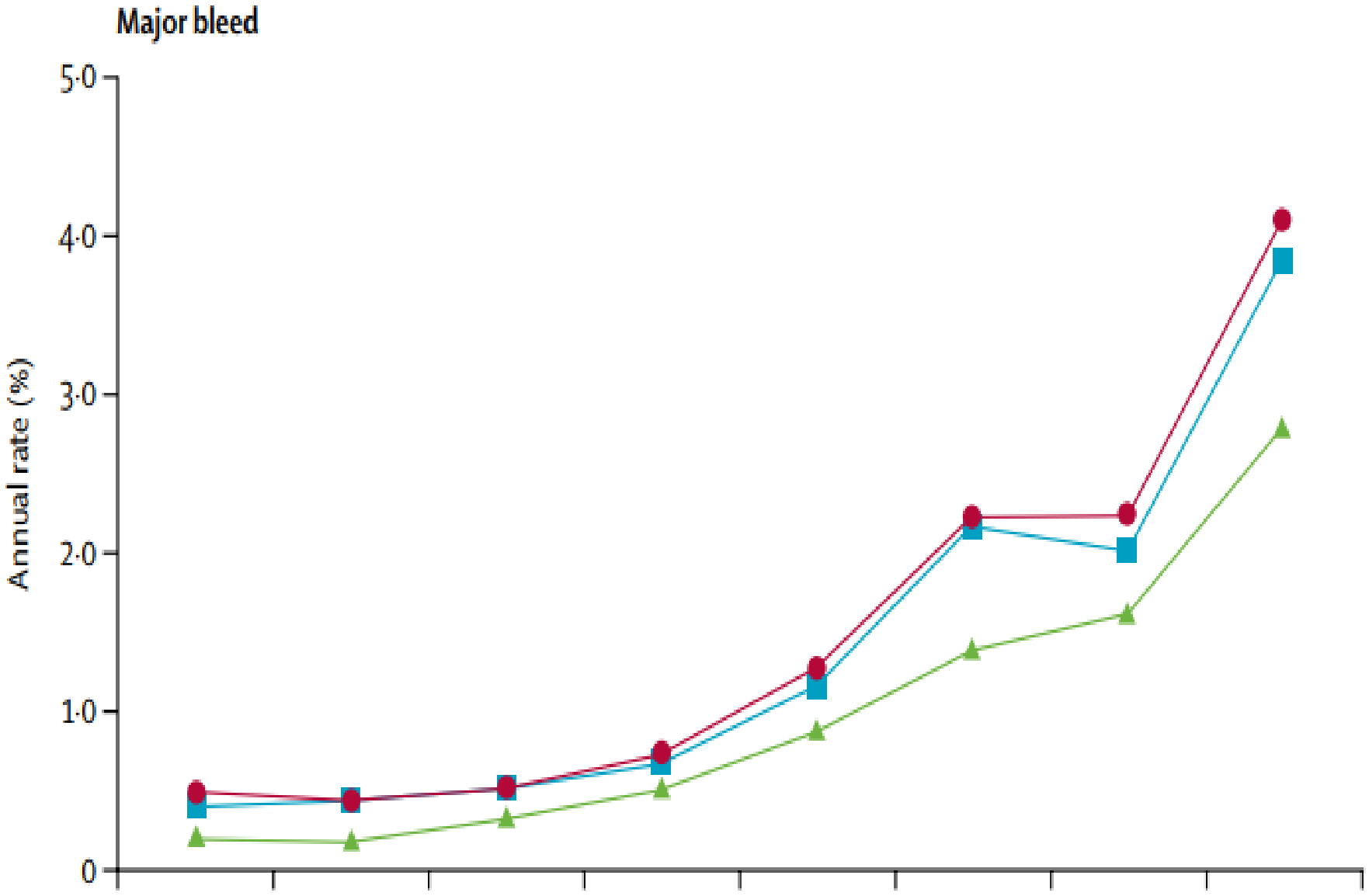


Figure 2: **Age-specific annual rate of bleeding events requiring medical attention**
Stratified by severity and by antiplatelet treatment immediately before the event. Annual rate derived as number per 100 patient-years. We used Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) criteria to define bleeding events as major (substantially disabling with persistent sequelae, intraocular bleeding leading to significant loss of vision, or bleeding requiring transfusion of ≥2 units of blood) and life-threatening or fatal (symptomatic intracranial haemorrhage, fall in haemoglobin of ≥5 g/dL, hypotension requiring intravenous inotropes, or required surgical intervention or transfusion of ≥4 units of blood).


Life-threatening and fatal bleed
Life-threatening and fatal
Life-threatening
Fatal
2·5
2·0
1·5
1·0
0·5
0
Annual rate (%)
<55
55–59
60–64
65–69
70–74
75–79
80–84
≥85
Age (years)


Major bleed
Annual rate (%)
5·0
4·0
3·0
2·0
1·0
0

Antiplatelets

- Aspirin offers **15%** relative risk reduction for stroke after TIA or stroke
- Most widely studied dosages of aspirin are 50-150mg
- Aspirin, ASA+Dipyridamole, Clopidogrel are all acceptable initial therapy.

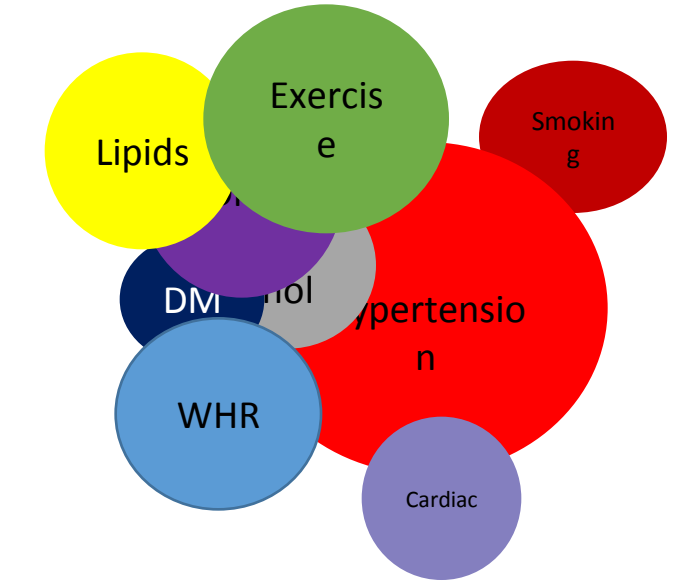
Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case-control study

	Overall (n=13 447)	Western Europe, North America, Australia (n=1917)	Eastern and central Europe, Middle East (n=1394)	South America (n=1471)	China (n=3987)	South Asia (n=2850)	Southeast Asia (n=855)	Africa (n=973)
Age, years	62·2 (13·6)	66·7 (13·4)	63·9 (13·4)	65·8 (14·3)	61·9 (12·5)	59·6 (12·9)	56·6 (13·0)	58·7 (15·2)
Age ≤45 years	1582 (11·8%)	141 (7·4%)	143 (10·3%)	123 (8·4%)	364 (9·1%)	451 (15·8%)	156 (18·3%)	204 (21·0%)
Women	5434 (40·4%)	781 (40·7%)	556 (39·9%)	652 (44·3%)	1606 (40·3%)	1017 (35·7%)	352 (41·2%)	470 (48·3%)
Intracerebral haemorrhage	3059 (22·7%)	128 (6·7%)	117 (8·4%)	348 (23·7%)	1102 (27·6%)	785 (27·5%)	285 (33·3%)	294 (30·2%)
Ischaemic stroke	10 388 (77·3%)	1789 (93·3%)	1277 (91·6%)	1123 (76·3%)	2885 (72·4%)	2065 (72·5%)	570 (66·7%)	679 (69·7%)

Case-Control Study: 13.477 cases

*Martin J O'Donnell, Siu Lim Chin, Sumathy Rangarajan, Denis Xavier, Lisheng Liu, Hongye Zhang, Purnima Rao-Melacini, Xiaohe Zhang, Prem Pais, Steven Agapay, Patricio Lopez-Jaramillo, Albertino Damasceno, Peter Langhorne, Matthew J McQueen, Annika Rosengren, Mahshid Dehghan, Graeme J Hankey, Antonio L Dans, Ahmed Elsayed, Alvaro Avezum, Charles Mondo, Hans-Christoph Diener, Danuta Ryglewicz, Anna Czlonkowska, Nana Pogosova, Christian Weimar, Romaina Iqbal, Rafael Diaz, Khalid Yusoff, Afzalhussein Yusufali, Aytekin Oguz, Xingyu Wang, Ernesto Penaherrera, Fernando Lanas, Okechukwu S Ogah, Adesola Ogunniyi, Helle K Iversen, German Malaga, Zvonko Rumboldt, Shahram Oveisgharan, Fawaz Al Hussain, Daliwonga Magazi, Yongchai Nilanont, John Ferguson, Guillaume Pare, Salim Yusuf; on behalf of the INTERSTROKE investigators**

INTERSTROKE: POPULATION ATTRIBUTABLE RISK



Collective PAR (99%CI)	
All Stroke	**90.7% (88.7-92.4)**
Ischemic Stroke	**91.5% (89.4-93.2)**
ICH	**87.1% (82.2-90.8)**

HTN Cardiac Exercise Smoking Lipids Diet WHR Alcohol DM

Summary

- Stroke is largely a preventable disease.
- Aggressive risk factor management is important.
- All antiplatelets have almost similar efficacy with marginal benefit of clopidogrel or ASA+DP over aspirin
- “Polypill concept” is yet to be proven for routine use.