Aspirin in Primary and Secondary Cardiovascular Disease Prevention. Still Four Questions: About Enteric-Coated, Indicated Doses, Use in Diabetes, Use in PVD

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I received consultant and speakers fees from Amgen, AstraZeneca, Bayer and GlaxoSmithKline

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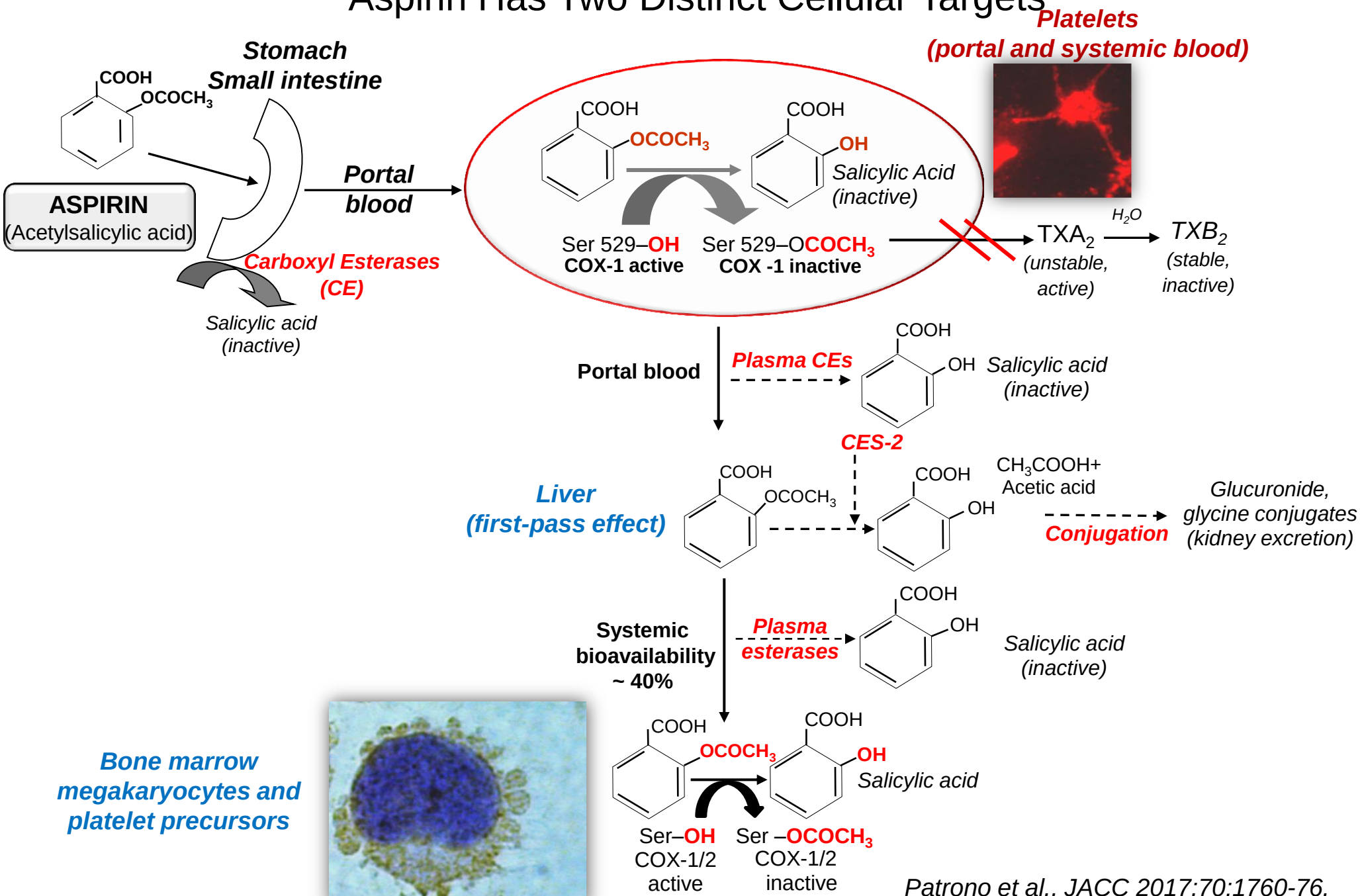
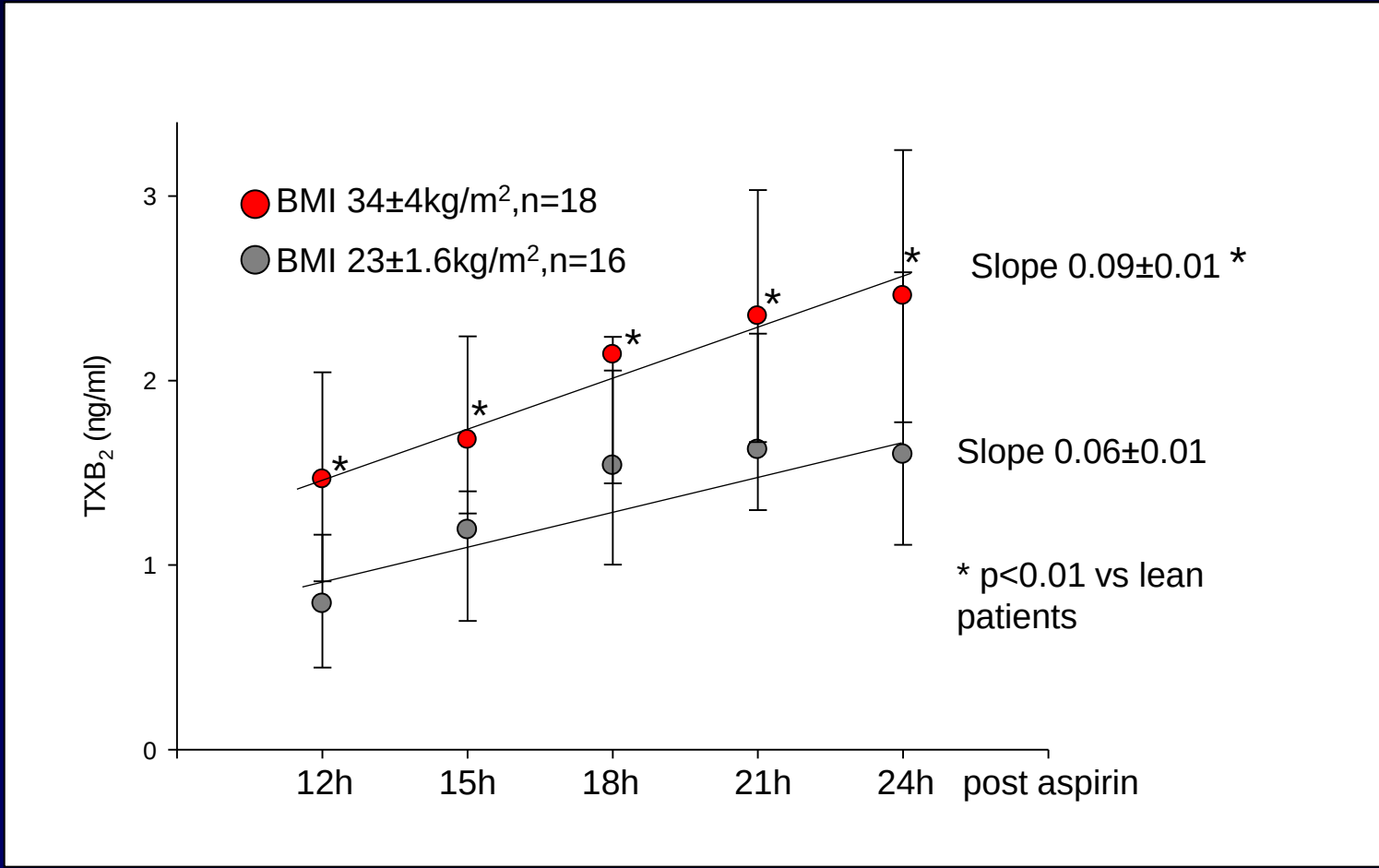
- Bayer AG

Aspirin Has Two Distinct Cellular Targets



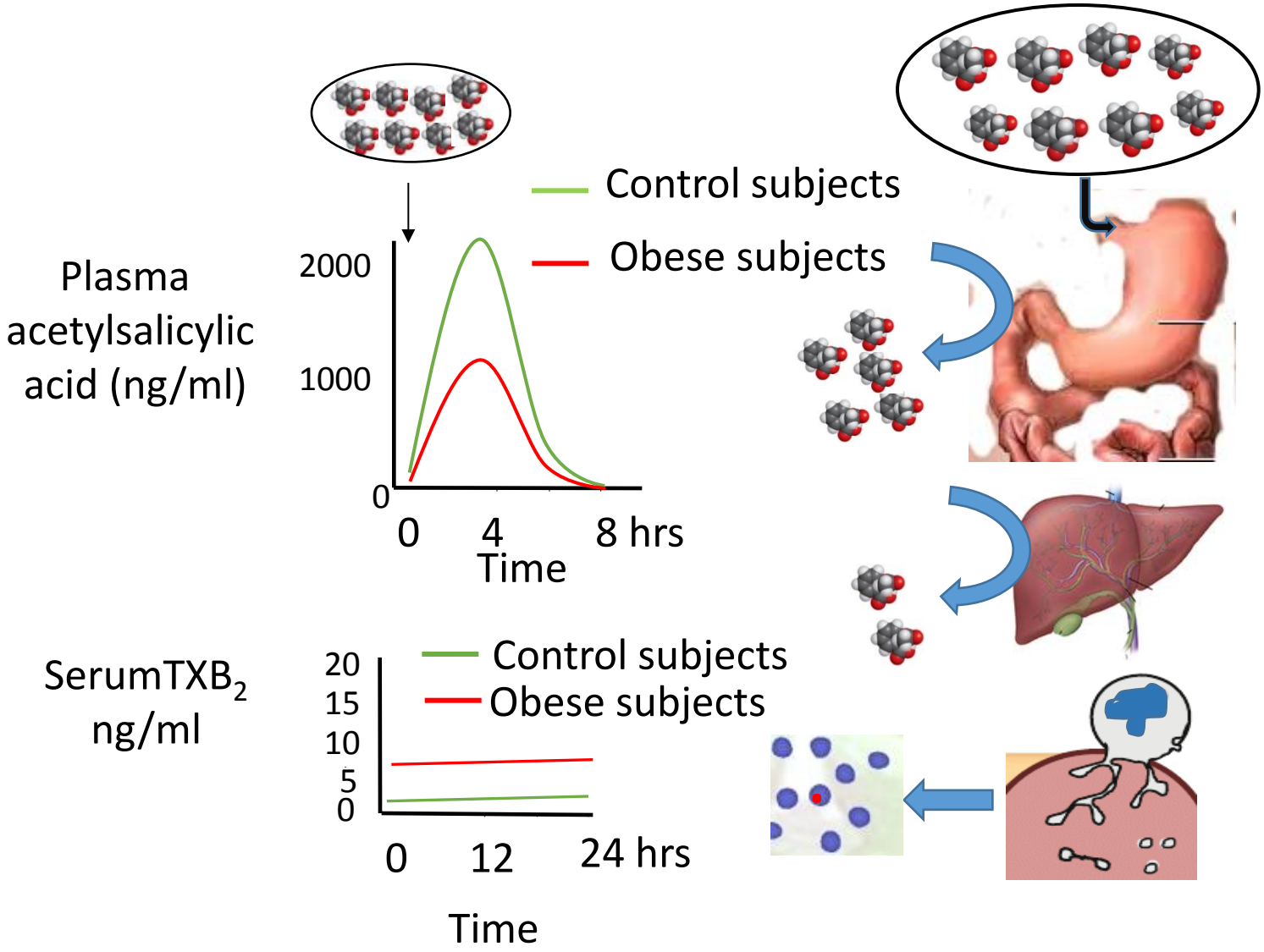
Patrono et al., JACC 2017;70:1760-76.

Serum TXB_2 Levels are Significantly Higher in EC Aspirin-Treated Obese *vs* Lean Non-Diabetic Patients Over the 12-24h Dosing Interval



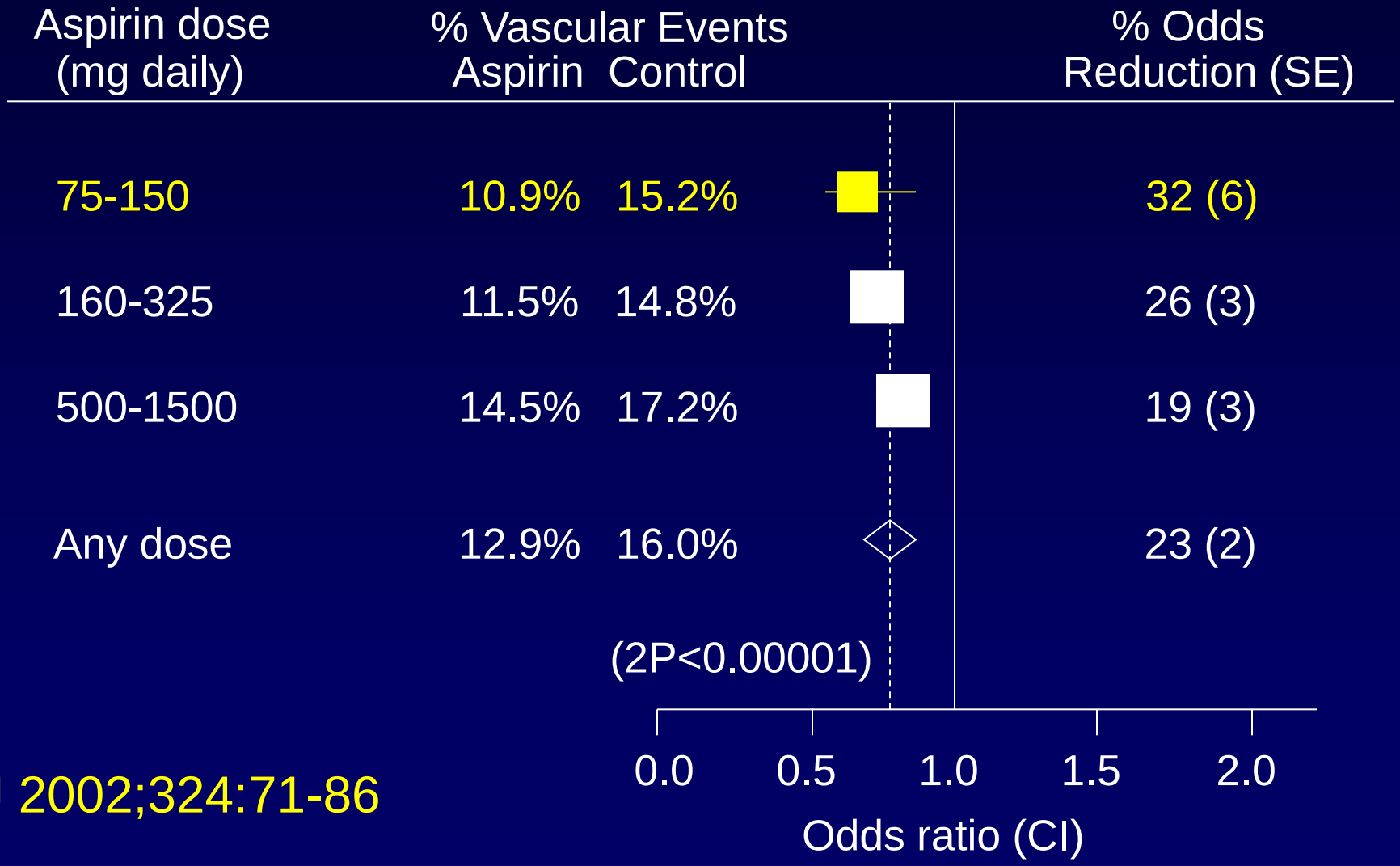
Rocca, et al., J Thormb Haemost 2012;10:1220-30.

Obesity and Aspirin PK



Patrono & Rocca JACC 2017,69:613-15

Antithrombotic Trialists' Collaboration
Meta-Analysis of Aspirin Trials in High-Risk Patients



BMJ 2002;324:71-86

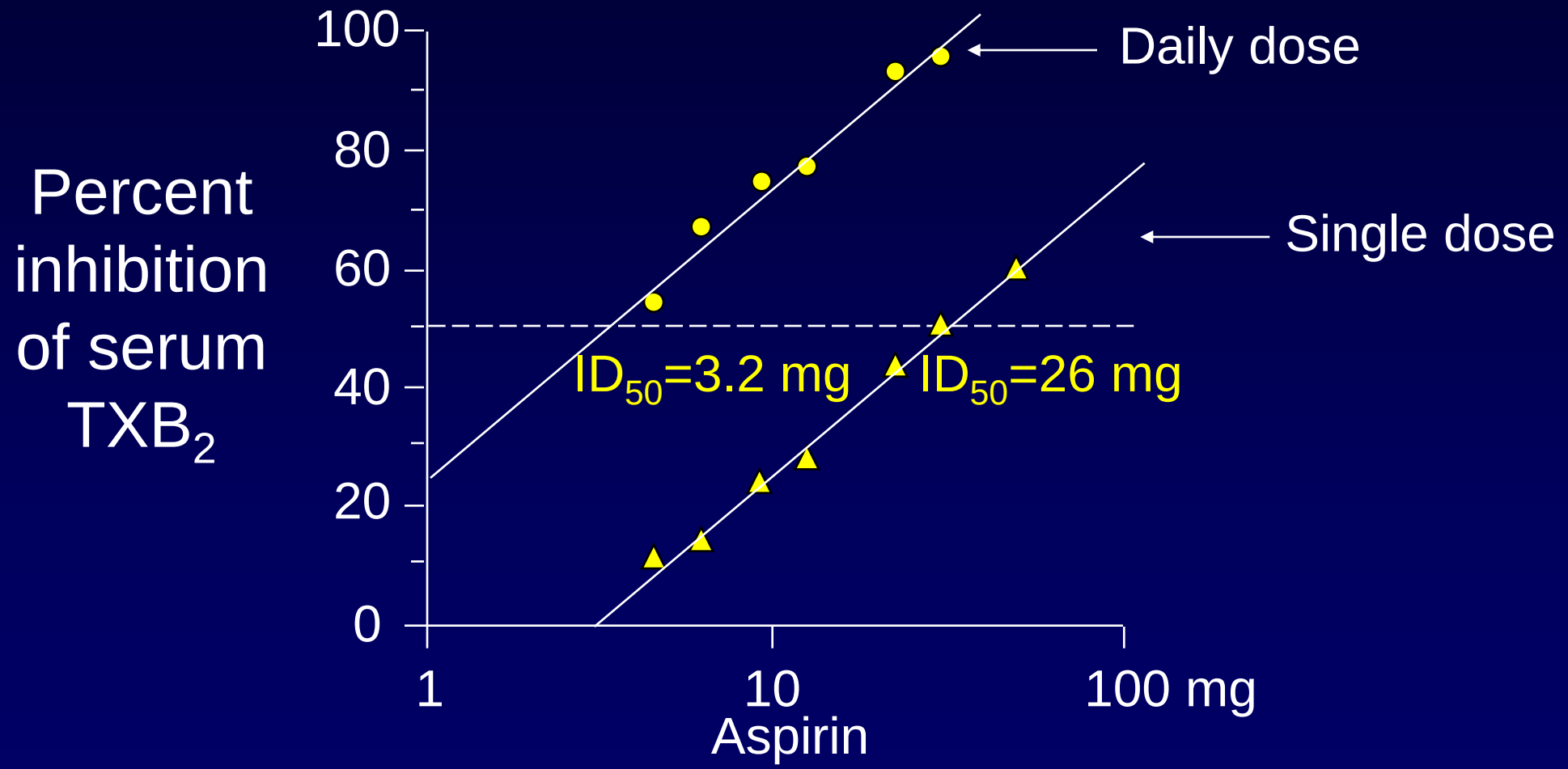
Does One Size Fit All?

Probably yes, because:

a) Inactivation of platelet COX-1 and suppression of thromboxane production are cumulative upon repeated daily dosing, and saturable at doses as low as 30-40 mg daily.

b) There is no evidence that higher doses (e.g., 300-325 mg) are more effective than lower doses (i.e., 75-100 mg), and the opposite may be true.

Cumulative Inhibition of Platelet COX-1 by Low Doses of Aspirin Shifts the Dose-Response Curve by a Factor Equivalent to the Daily Platelet Turnover

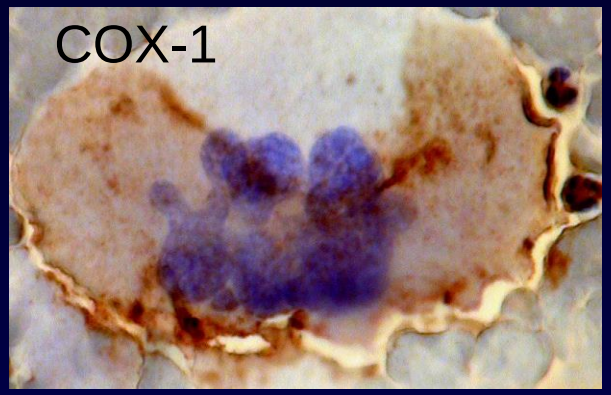


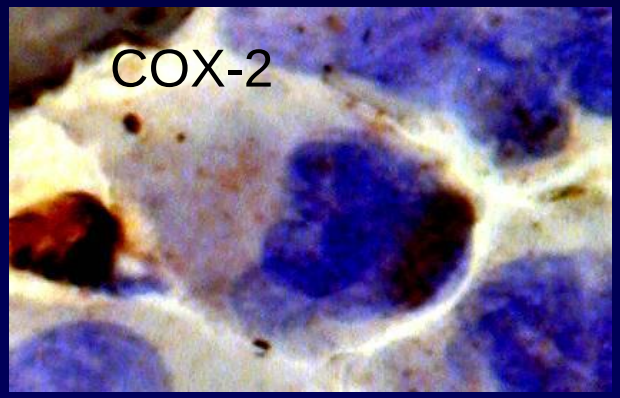
Patrono et al., Circulation 1985; 72:1177-84

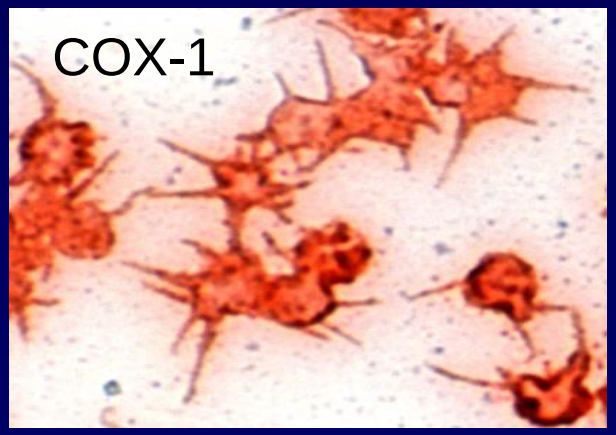
Does One Dosing Regimen Fit All?

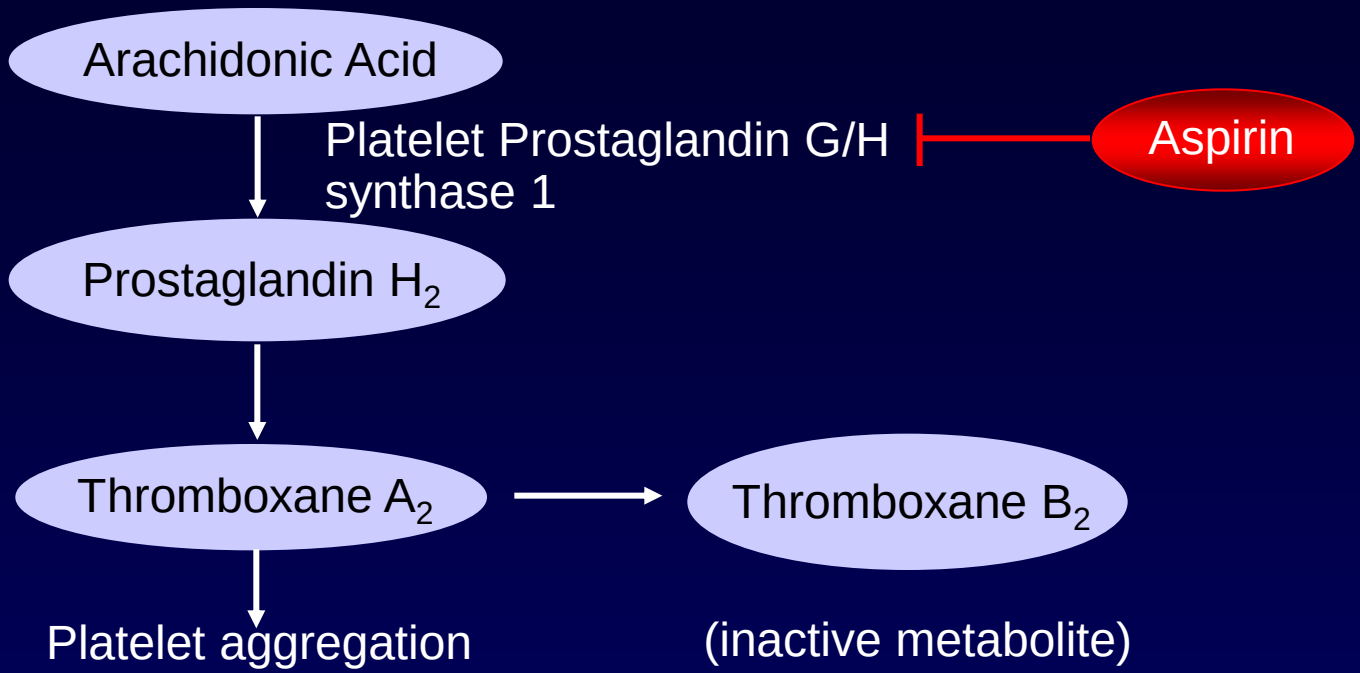
Maybe not, because there is substantial interindividual variability in the rate of recovery of platelet COX-1 activity during the 24-hour dosing interval, perhaps requiring more frequent dosing (e.g., bid) in patients with accelerated renewal of the drug target.

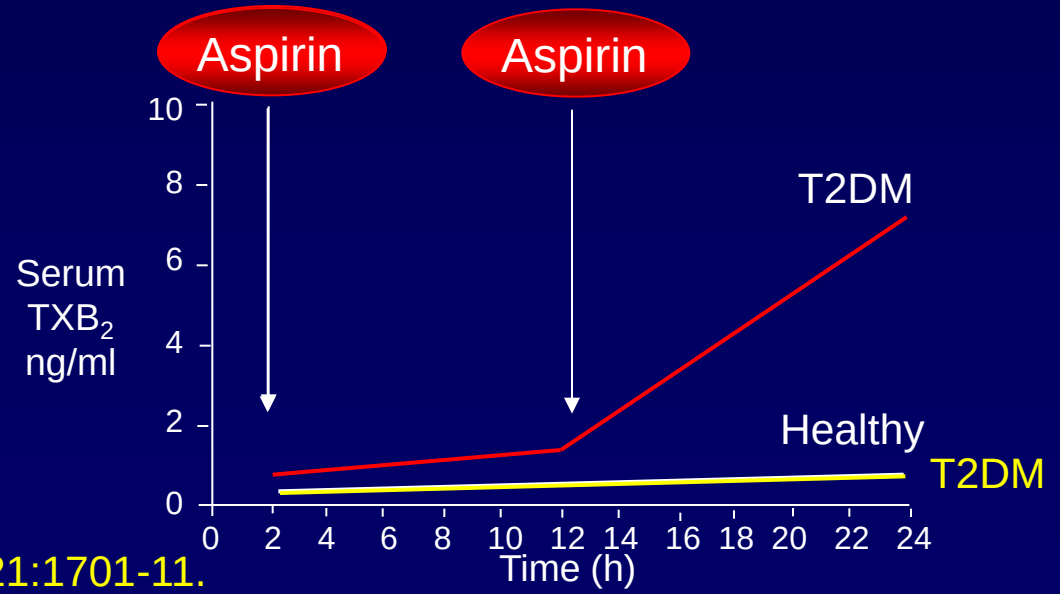
Altered Pharmacodynamics of Low-Dose Aspirin in Type 2 Diabetes





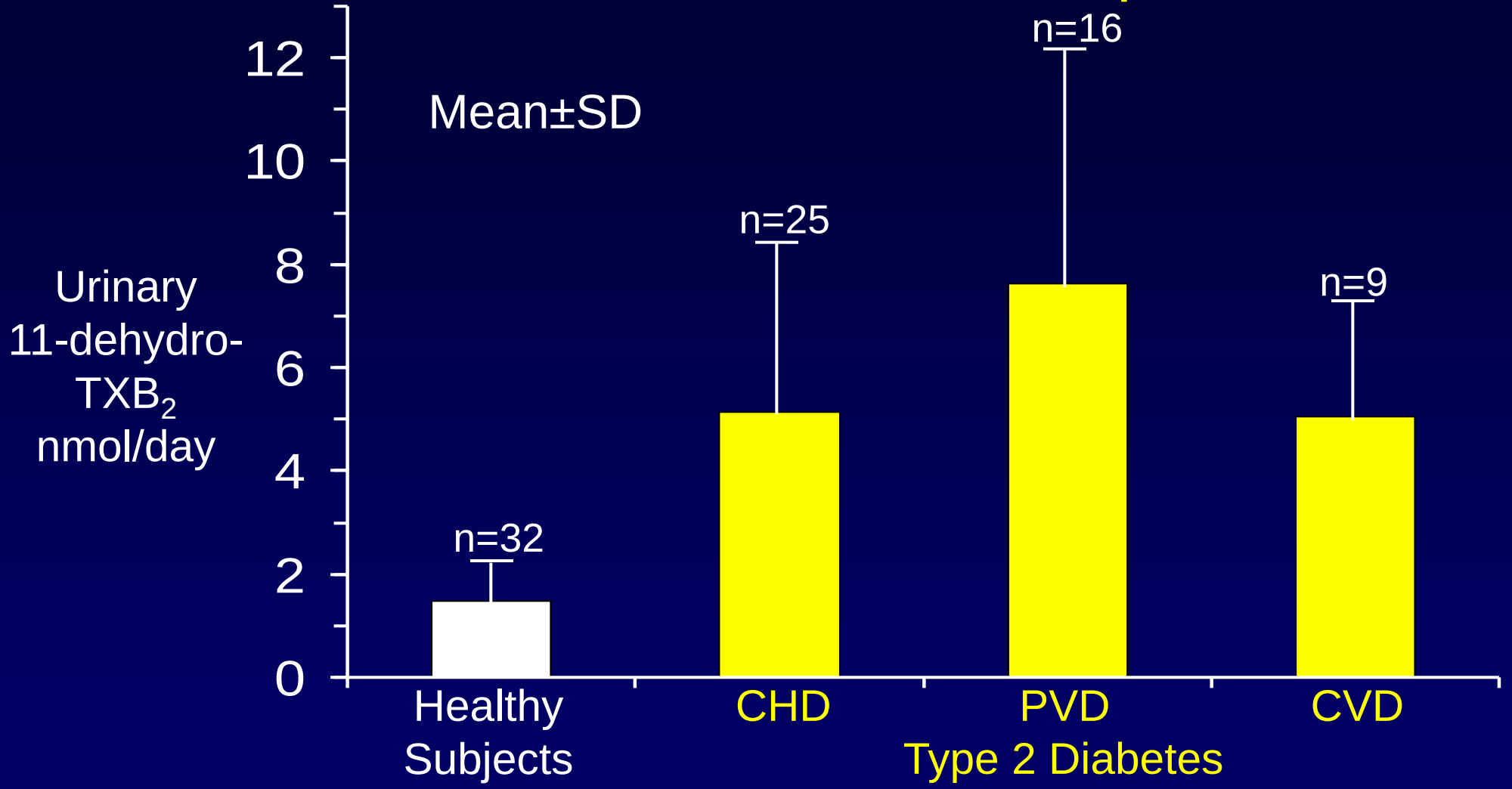






Patrono, Rocca, De Stefano Blood 2013;121:1701-11.

Thromboxane Biosynthesis is Enhanced in Type 2 Diabetes with Macrovascular Complications



Davì et al, N Engl J Med 1990;322:1769-74

Aspirin for Primary Prevention of CVD in Diabetes: Current Guidelines

ADA/AHA[1]	1) Low-dose aspirin (75-162 mg/day) is reasonable among those with a 10-year CVD risk of at least 10% and without an increased risk of bleeding. 2) Low-dose aspirin is reasonable in adults with diabetes mellitus at intermediate risk (10-year CVD risk, 5-10%)
ESC-EASD[2]	Antiplatelet therapy for primary prevention may be considered in high-risk patients with DM on an individual basis
IDF[3]	Recommended in people at high risk
AACE[4]	Recommended
Canadian Diabetes Associaton[5]	No evidence, use left to individual clinical judgment

1. Circulation 2015;132:691-718
2. Eur Heart J 2013;34:3035-87
3. Diabet Med 2006;23:579-593
4. Endocr Pract. 2007;13(Suppl 1)
5. CMAJ 2008;179:920-926

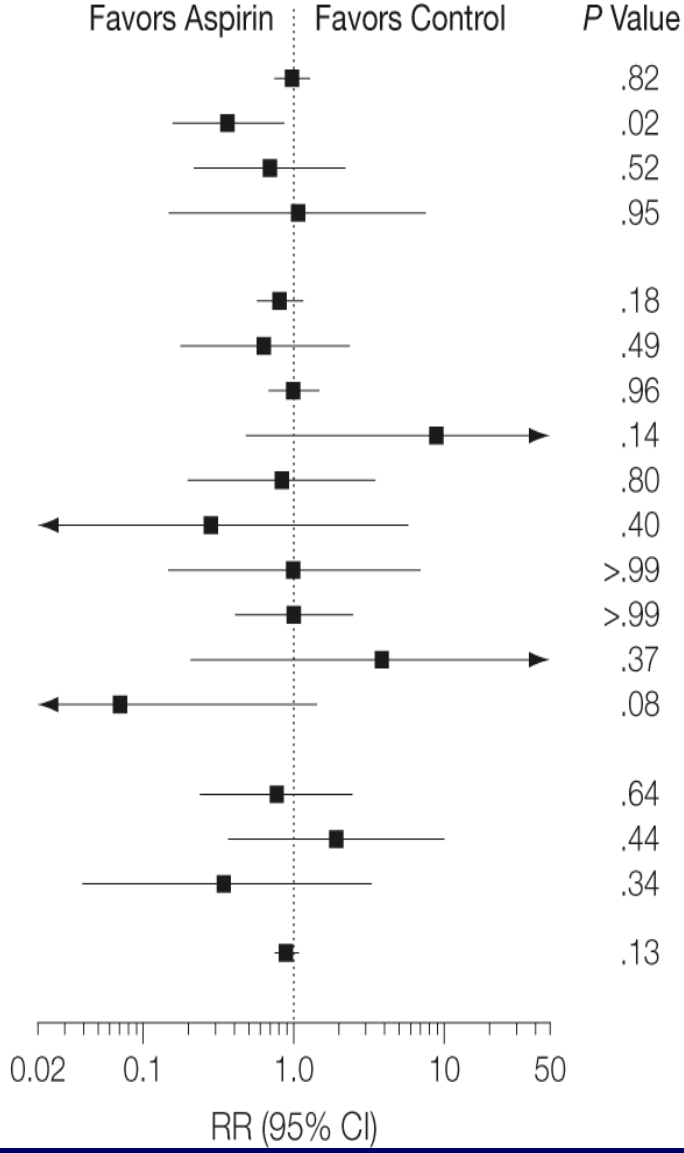
Ongoing Randomized Trials of Aspirin vs Placebo: High-Risk Individuals

Study	Regimen(s)	Treatment duration	N	Eligibility	Primary endpoint	End date
ARRIVE	EC Aspirin 100 mg vs Placebo	5y	~12,000	10-20% estimated 10y risk of CHD	MI, stroke, CV death, unstable angina, TIA	2018
ASPREE	EC Aspirin 100 mg vs Placebo	5 y	~ 19,000	Elderly, no diabetes or CVD	Death, dementia or significant disability	2018
ASCEND	EC Aspirin 100 mg vs Placebo (ω3FA vs P)	7.5 y	~ 15,000	Diabetes, no CVD	MI, stroke or TIA, or CV death	2018

Patrono, JACC 2015;66:74-85

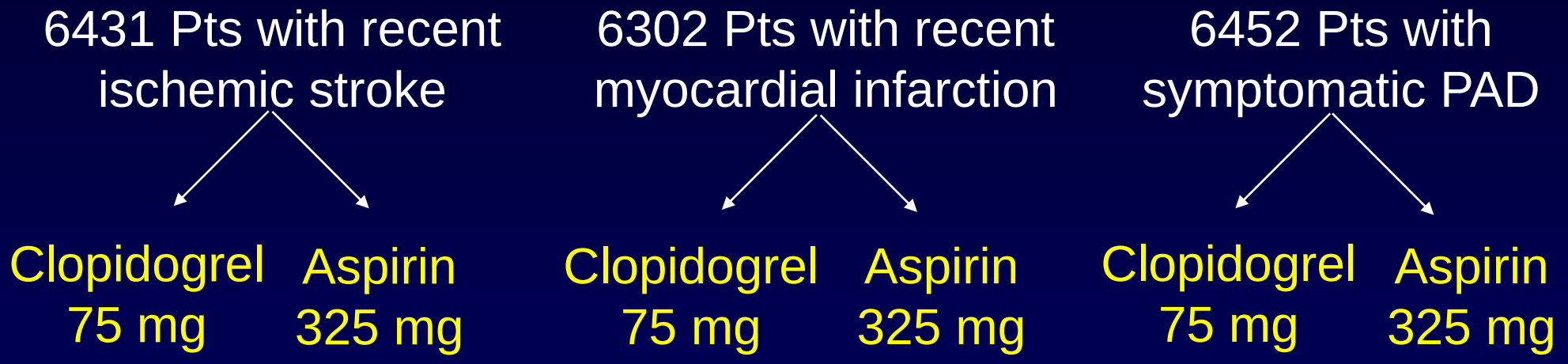
Effect of Aspirin on Major Vascular Events in PAD Trials

Source	No. of Cardiovascular Events/ Total No. of Patients: Aspirin	Control	Weight, %	RR (95% CI)[a]	*P* Value
Belch et al, 2008	105/638	108/638	41.3	0.97 (0.76-1.24)	.82
Catalono et al, 2007	7/185	19/181	3.5	0.36 (0.16-0.84)	.02
BMFT-II, 1998	5/170	7/164	2.0	0.69 (0.22-2.13)	.52
Study group on pharmacological treatment after PTA, 1994	2/108	2/115	0.7	1.06 (0.15-7.43)	.95
McCollum et al, 1991	53/286	61/263	23.1	0.80 (0.58-1.11)	.18
Heiss et al, 1990	5/132	4/67	1.5	0.63 (0.18-2.29)	.49
Colwell et al, 1989	36/110	40/121	18.3	0.99 (0.68-1.43)	.96
Donaldson et al, 1985	4/33	0/32	0.3	8.74 (0.49-155.97)	.14
Hess et al, 1985	5/160	3/80	1.3	0.83 (0.20-3.40)	.80
Goldman and McCollum, 1984	0/22	2/31	0.3	0.28 (0.01-5.53)	.40
Kohler et al, 1984	2/50	2/50	0.7	1.00 (0.15-6.82)	>.99
Schoop and Levy, 1984	14/200	7/100	3.2	1.00 (0.42-2.40)	>.99
Green et al, 1982	3/32	0/17	0.3	3.82 (0.21-69.88)	.37
Harjola et al, 1981	0/200	3/100	0.3	0.07 (0.00-1.38)	.08
Ehresmann et al, 1977	0/215	0/213	0.0		
Hess and Keil-Kuri, 1975	5/92	6/84	1.9	0.76 (0.24-2.40)	.64
Hess and Keil-Kuri, 1975	4/42	2/40	0.9	1.90 (0.37-9.83)	.44
Zekert, 1975	1/148	3/150	0.5	0.34 (0.04-3.21)	.34
Total	251/2823	269/2446		0.88 (0.76-1.04)	.13



Berger et al, JAMA 2009;301:1909-19.

Clopidogrel vs Aspirin in Patients at Risk of Ischemic Events (CAPRIE)



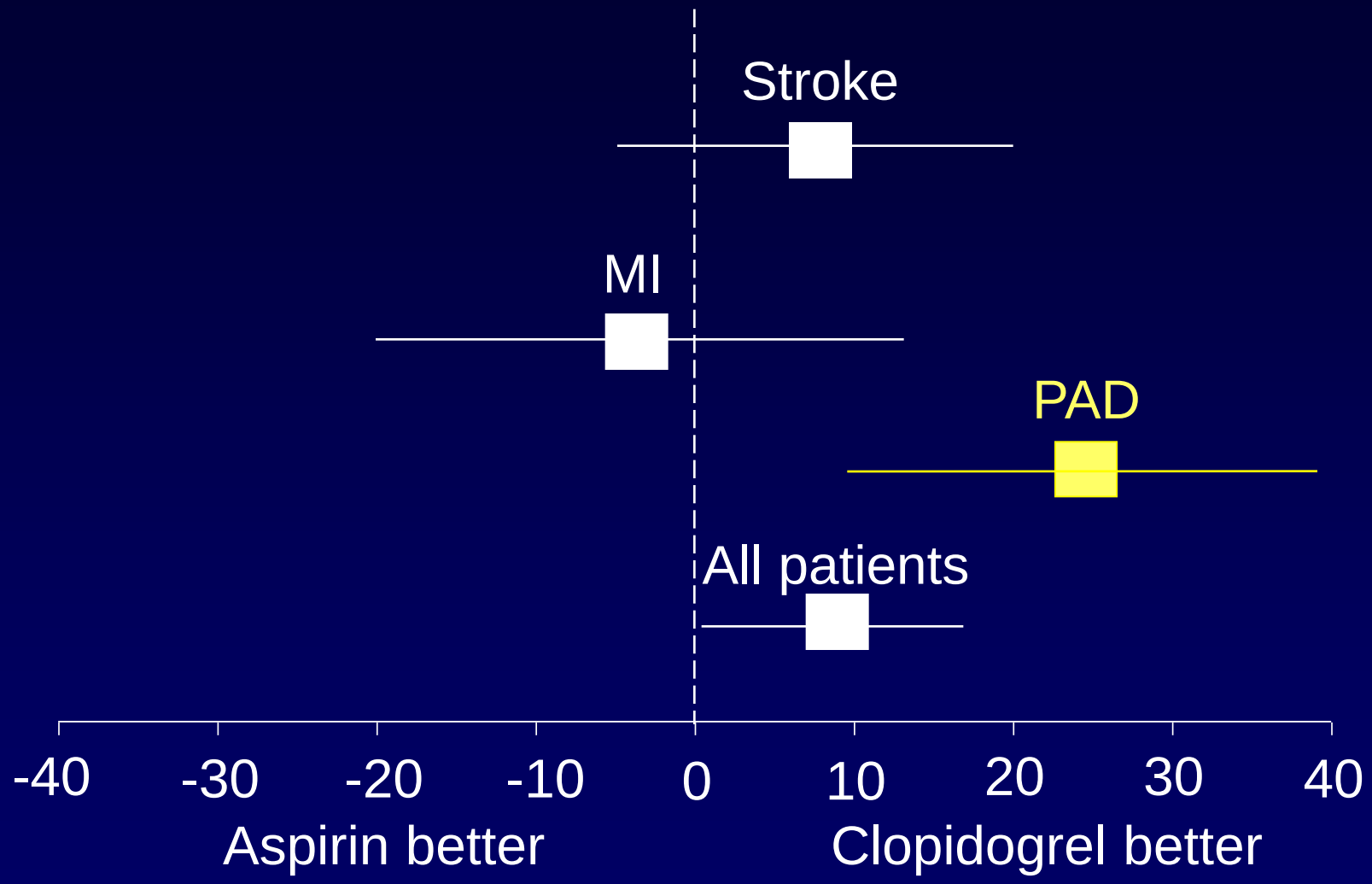
Follow-up: 1.91 yr (1-3yr)

Primary end-point: cluster of ischemic stroke, MI, or vascular death

Primary analysis: intention-to-treat comparison for the entire patient population and for each of the clinical categories

Lancet 1996;348:1329-39.

Relative Risk Reduction and 95% CI



Lancet 1996;348:1329-39.

The NEW ENGLAND JOURNAL of MEDICINE

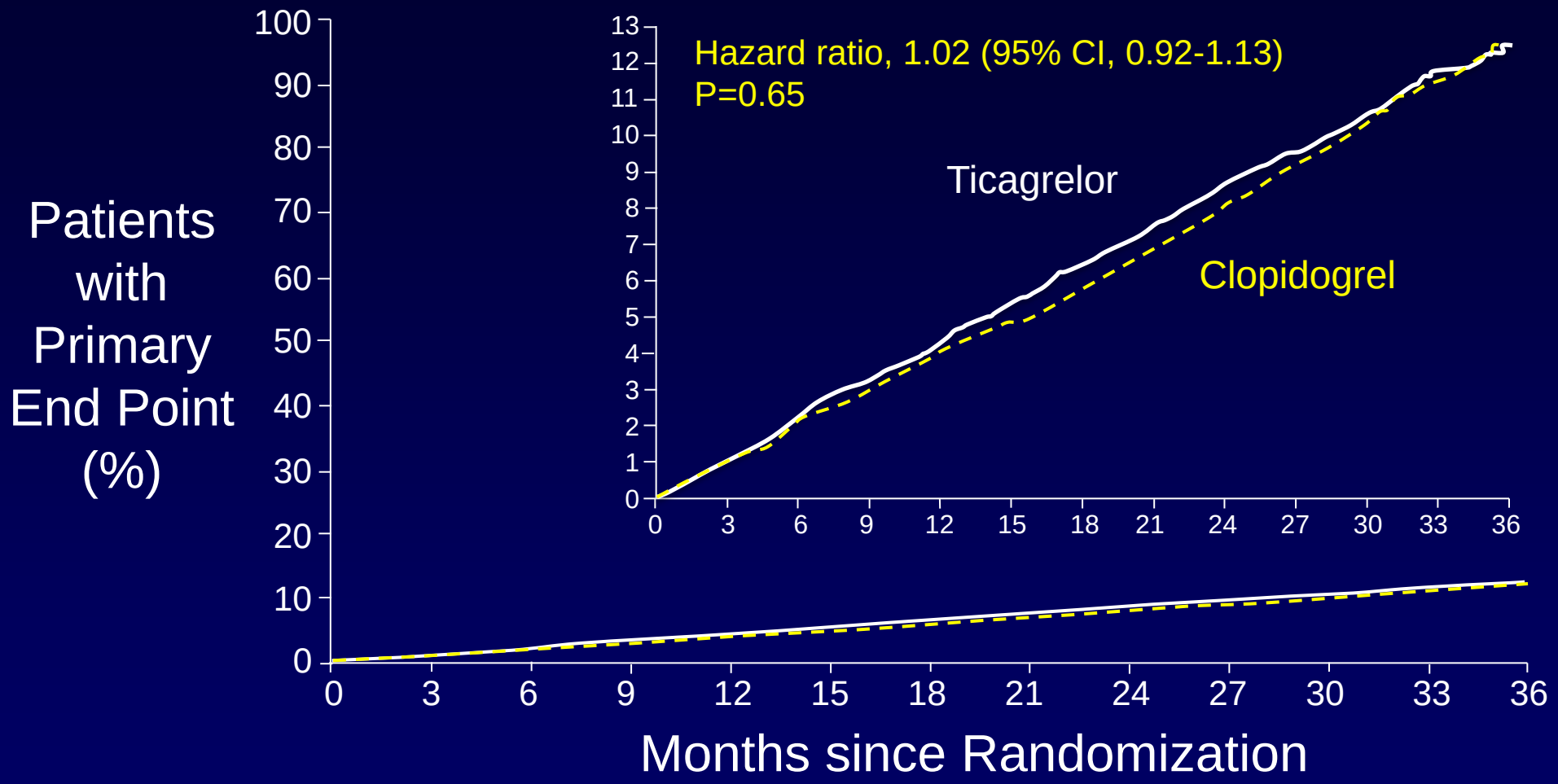
ORIGINAL ARTICLE

Ticagrelor versus Clopidogrel in Symptomatic Peripheral Artery Disease

William R. Hiatt, M.D., F. Gerry R. Fowkes, M.D., Gretchen Heizer, M.S., Jeffrey S. Berger, M.D., Iris Baumgartner, M.D., Peter Held, M.D., Ph.D., Brian G. Katona, Pharm.D., Kenneth W. Mahaffey, M.D., Lars Norgren, M.D., Ph.D., W. Schuyler Jones, M.D., Juuso Blomster, M.D., Marcus Millegård, M.Sc., Craig Reist, Ph.D., and Manesh R. Patel, M.D., for the EUCLID Trial Steering Committee and Investigators*

N Engl J Med 2017;376:32-40.

Kaplan–Meier Analysis of the Primary End Point



No. At Risk													
Ticagrelor	6930	6792	6679	6583	6474	6360	6248	6143	6036	5802	3830	2089	865
Clopidogrel	6955	6830	6744	6639	6538	6455	6353	6237	6111	5835	3834	2055	852

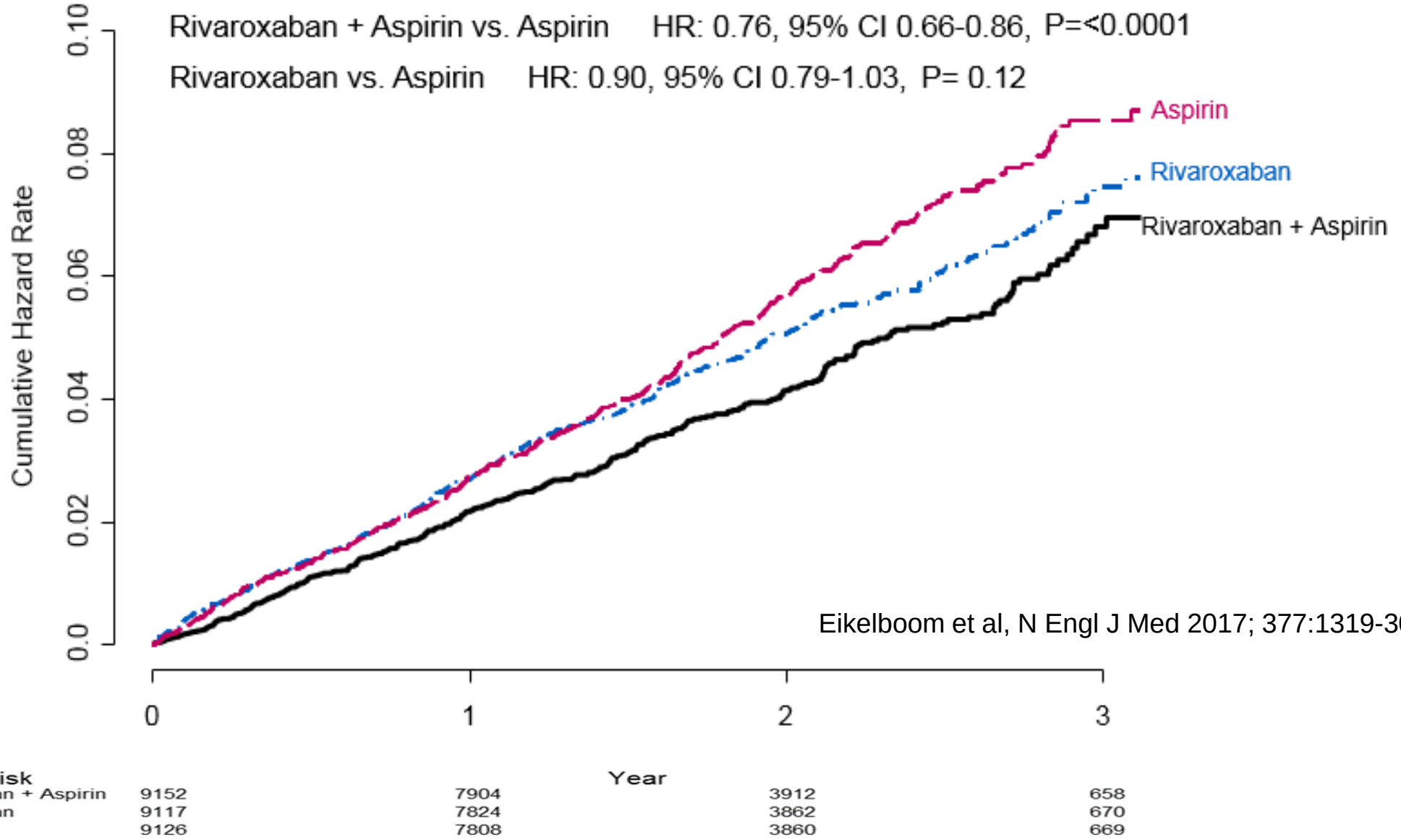
Hiatt WR et al. N Engl J Med 2017;376:32-40

2016 AHA/ACC Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease

COR	LOE	Recommendations
I	A	Antiplatelet therapy with aspirin alone (range 75-325 mg per day) or clopidogrel alone (75 mg per day) is recommended to reduce MI, stroke, and vascular death in patients with symptomatic PAD.
IIa	C-EO	In asymptomatic patients with PAD (ABI ≤0.90), antiplatelet therapy is reasonable to reduce the risk of MI, stroke, or vascular death.
IIb	B-R	In asymptomatic patients with borderline ABI (0.91–0.99), the usefulness of antiplatelet therapy to reduce the risk of MI, stroke, or vascular death is uncertain.
IIb	B-R	The effectiveness of dual antiplatelet therapy (DAPT) (aspirin and clopidogrel) to reduce the risk of cardiovascular ischemic events in patients with symptomatic PAD is not well established.
IIb	C-LD	DAPT (aspirin and clopidogrel) may be reasonable to reduce the risk of limb-related events in patients with symptomatic PAD after lower extremity revascularization.
IIb	B-R	The overall clinical benefit of vorapaxar added to existing antiplatelet therapy in patients with symptomatic PAD is uncertain.

Gerhard-Hermann et al. Circulation 2017;135:e726–79.

COMPASS: Aspirin, Rivaroxaban, or Both in Stable CAD and PAD



Eikelboom et al, N Engl J Med 2017; 377:1319-30.

COMPASS: CAD and PAD Subgroups for Primary Outcome

Outcome	R + A N=9,152	A N=9,126	Rivaroxaban + Aspirin vs. Aspirin
	N (%)	N (%)	HR (95% CI)
CAD	347 (4.2%)	460 (5.6%)	0.74 (0.65-0.86)
PAD	126 (5.1%)	174 (6.9%)	0.72 (0.57-0.90)

COMPASS Investigators, Lancet Nov 10, 2017 (Epub ahead of print)

Conclusions

1. Obesity and diabetes are independent and possibly additive determinants of poor aspirin responsiveness, limiting the extent and/or duration of platelet inhibition, and possibly requiring different dosing strategies, well beyond the uncertain effect of enteric coating.
2. Except for a loading dose in the setting of ACS or acute ischemic stroke, prescribing aspirin 325 mg daily for long-term treatment would not produce any additional benefit above and beyond 75-100 mg, while exposing the patient to unnecessary GI damage and undue bleeding complications, as well as to potential negative interactions with ACE-inhibitors and ticagrelor.

Conclusions

3. Use of aspirin for primary CV prevention in diabetes is not uniformly recommended because of inadequate evidence. The results of the ASCEND trial should clarify its benefit/risk profile in this setting.
4. Use of aspirin in PAD is controversial and is associated with high residual CV risk. Combination of aspirin with a factor Xa inhibitor may improve clinical outcomes in this setting.