Optimal antiplatelet strategy for ASCVD prevention in DM patients

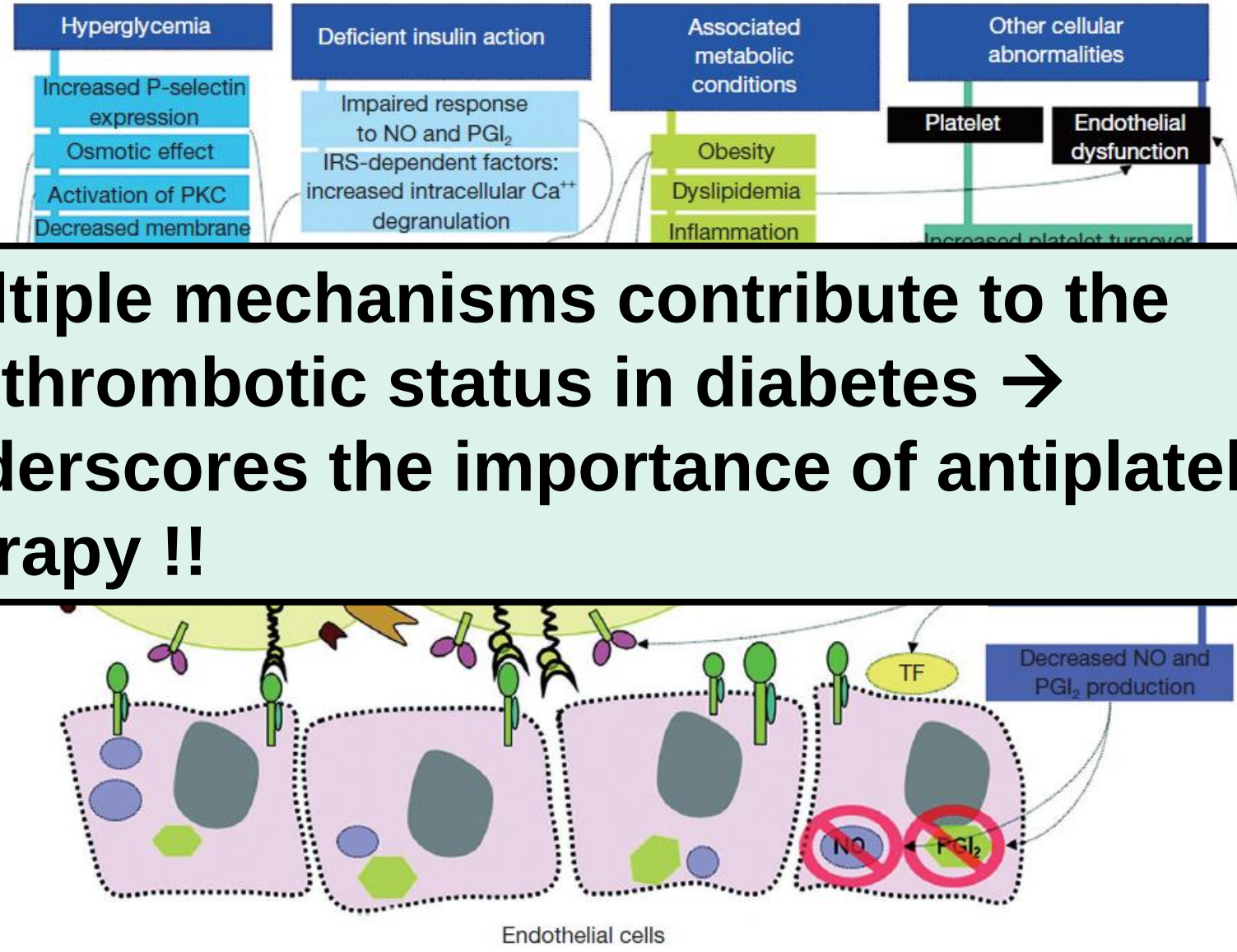
Jung Rae Cho, MD, PhD

Cardiovascular Division, Department of Internal Medicine

Kangnam Sacred Heart Hospital, Hallym University Medical Center, Seoul, Korea

HALLYM UNIVERSITY MEDICAL CENTER
KANGNAM SACRED HEART HOSPITAL

Diabetes and Platelet



Multiple mechanisms contribute to the prothrombotic status in diabetes → underscores the importance of antiplatelet therapy !!

Rivas Rios JR et al. Cardiovasc Diagn Ther 2018;8(5):594-609

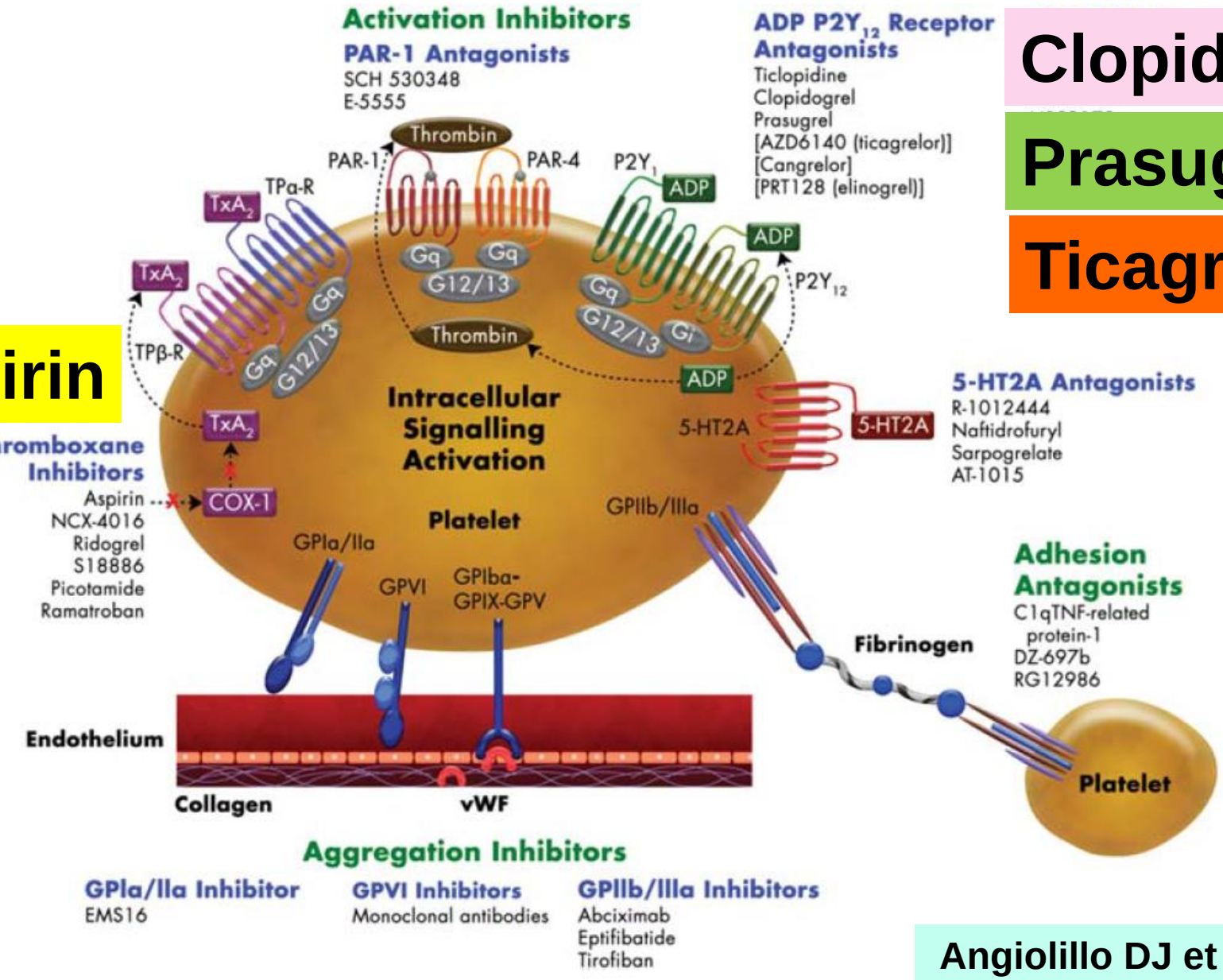
Binding sites of antiplatelet agents

Clopidogrel

Prasugrel

Ticagrelor

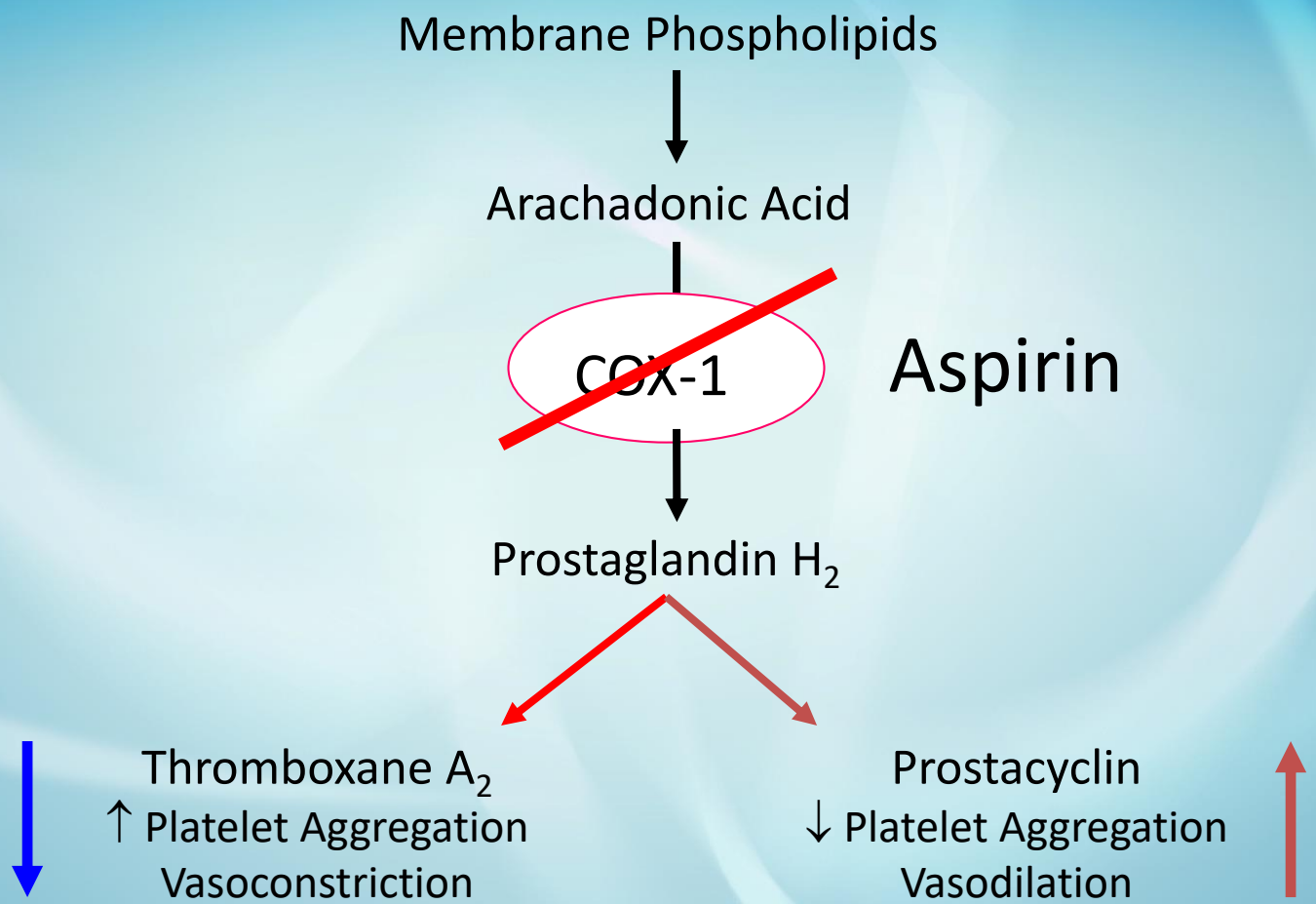
Aspirin



Angiolillo DJ et al. EHJ 2010

Aspirin: Mechanism of Action

- **Irreversible inhibition of cyclooxygenase enzyme (COX-1) via acetylation.**
- **Small dose inhibits thromboxane (TXA2) synthesis in platelets <u>But</u> not prostacyclin (PGI_2) synthesis in endothelium (larger dose).**



ASPECT study (demonstrated over-estimation of aspirin resistance)

TABLE 5. Platelet Function in Healthy Volunteers and Patients

	Healthy Volunteers	CAD Patients		
	No ASA (n=10)	81 mg ASA (n=120)	162 mg ASA (n=120)	325 mg ASA (n=120)
LTA, % aggregation				
5 μmol/L ADP	70±10	58±13*	58±10*	58±10*
TEG, % aggregation				
1 mmol/L AA	95±9	12±18*	11±16*	9±8*
VerifyNow, ARU	627±39	454±58*	434±44*	428±45*
PFA-100 closure time, secs	142±39	222±73*	257±63*	240±68*
Urinary thromboxane, pg 11-dh-TxB_2/mg Cr	614±108	378±182*	321±129*	291±13*

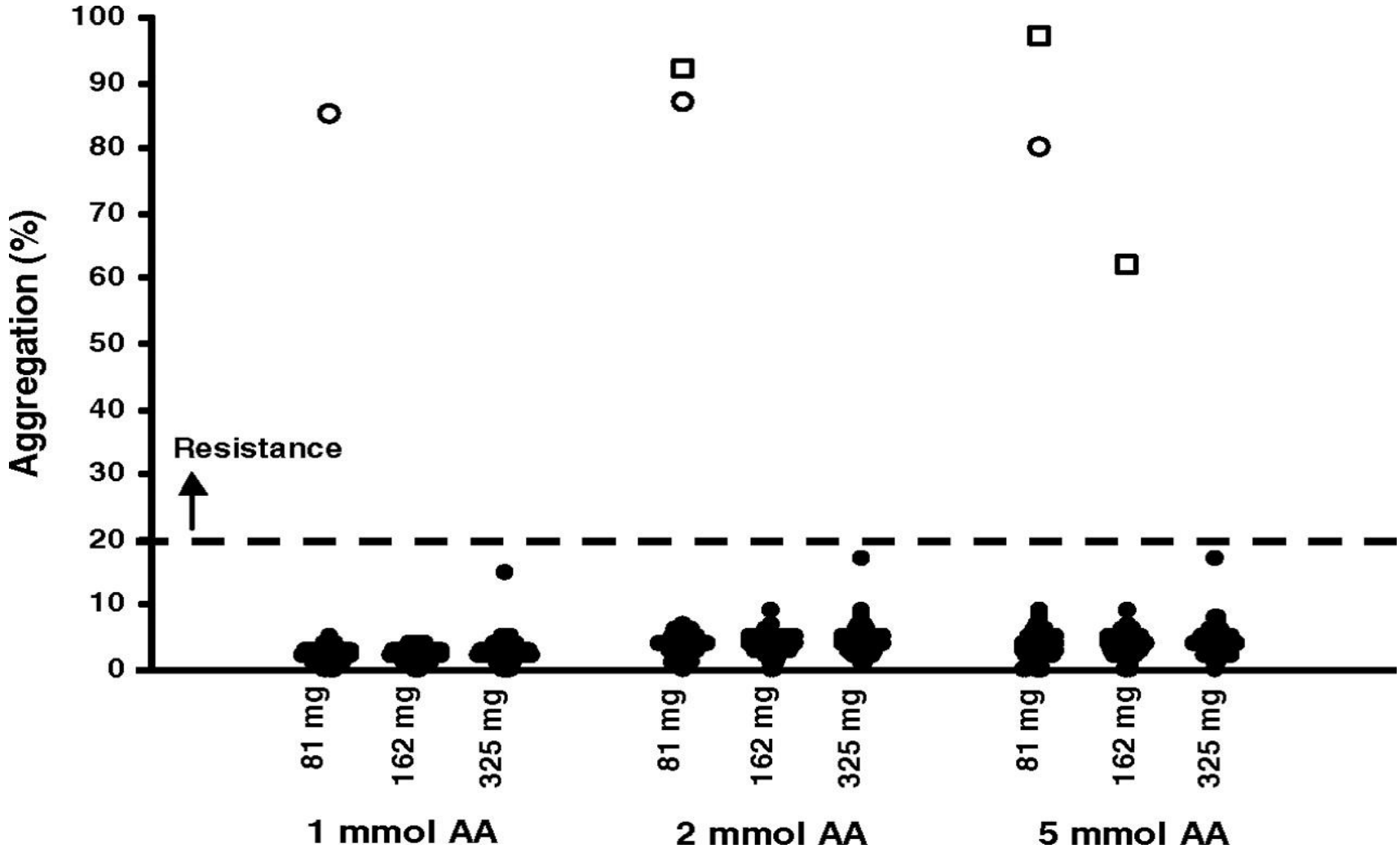
Data are expressed as mean±SD. ASA indicates aspirin.
*$P \leq 0.005$ for healthy volunteers compared to CAD patients.

Assays using AA as stimulants

The degree of inhibition of AA-induced platelet aggregation was not different across different aspirin dose.

Paul A. Gurbel et al. Circulation. 2007;115:3156-3164

Figure 1. Individual platelet aggregation data measured after stimulation by 3 concentrations of AA by LTA at 3 different doses of aspirin.



Paul A. Gurbel et al. Circulation. 2007;115:3156-3164

ASA Dose Comparison
Primary Outcome and Bleeding

	ASA 75-100 mg	ASA 300-325 mg	HR	95% CI	P
CV Death/MI/Stroke					
PCI (2N=17,232)	4.2	4.1	0.98	0.84-1.13	0.76
No PCI (2N=7855)	4.7	4.4	0.92	0.75-1.14	0.44
Overall (2N=25,087)	4.4	4.2	0.96	0.85-1.08	0.47
Stent Thrombosis	2.1	1.9	0.91	0.73-1.12	0.37
TIMI Major Bleed	1.03	0.97	0.94	0.73-1.21	0.71
CURRENT Major Bleed	2.3	2.3	0.99	0.84-1.17	0.90
CURRENT Severe Bleed	1.7	1.7	1.00	0.83-1.21	1.00

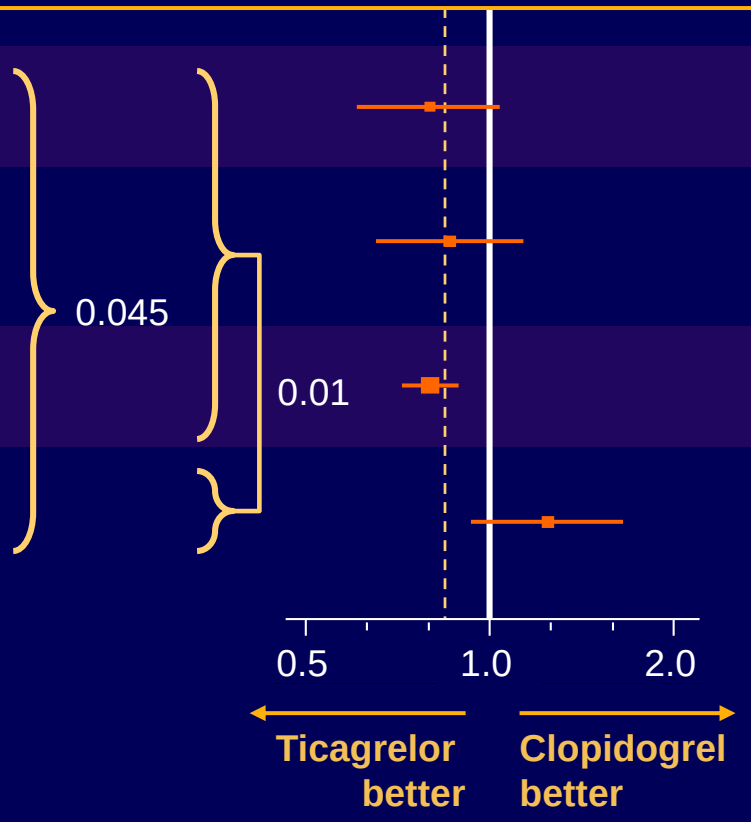
GI Bleeds: 30 (0.24%) v 47 (0.38%), P=0.051

No other significant differences between ASA dose groups

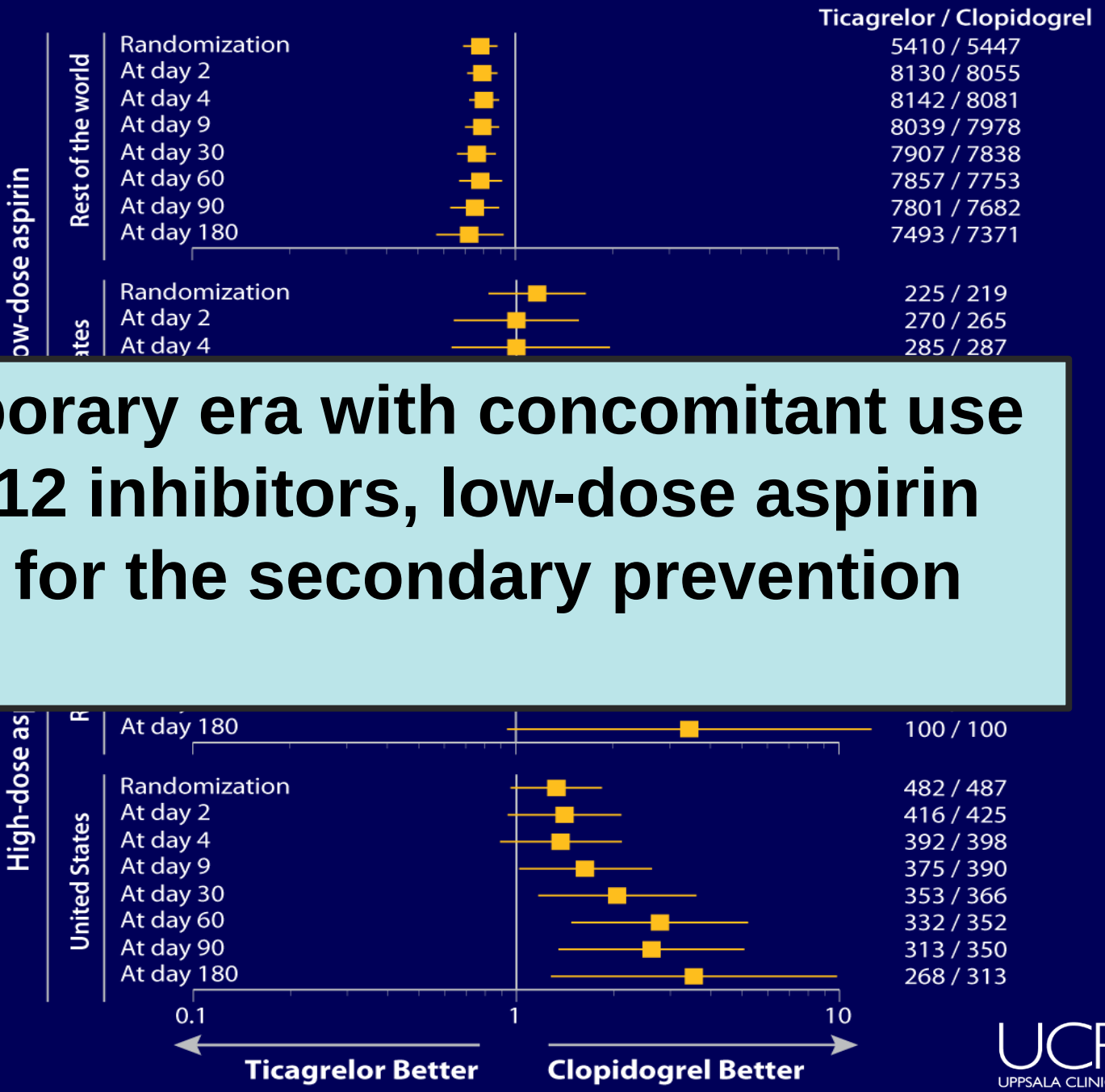
Geographic Regions
CV Death, MI, Stroke

PLATO

Geographic region	Total patients	KM at month 12 Tic	KM at month 12 Clop	HR (95% CI)	Interaction p-values
Asia / Australia	1714	11.4	14.8	0.80 (0.61, 1.04)	
Central America / South America	1237	15.2	17.9	0.86 (0.65, 1.13)	
Europe / Middle East / Africa	13859	8.8	11.0	0.80 (0.72, 0.90)	
North America	1814	11.9	9.6	1.25 (0.93, 1.67)	



Landmark Analyses
Region and ASA Dose



In the contemporary era with concomitant use of diverse P2Y12 inhibitors, low-dose aspirin is good as it is for the secondary prevention purpose.

PLATO

ASA:
<300 mg is low-dose;
≥300 mg is high-dose.

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Trials of Aspirin for Primary Cardiovascular Protection

Study	Year	Patients	Aspirin Dose	DM*	Mean or Median Follow-Up	Study Population	Primary Outcome Measure	Significant Efficacy
BDT[30]	1988	5139	300–500 mg/d	2%	5.6 y	Healthy men	CV death	No
PHS[31]	1989	22 071	325 mg every other day	4%	5 y	Healthy men	CV death	No
ETDRS[32]	1992	3711	650 mg/d	100%	5 y	DM†	All-cause mortality	No
ACBS[33]	1995	372	325 mg/d	19%	2.4 y	Carotid stenosis	Death, MI, stroke, TIA, stroke, MI, UA	No
HOT[34]	1998	18 790	75 mg/d	8%	3.8 y	Hypertension	CV death, MI, stroke	Yes
TPT[35]	1998	5085	75 mg/d	NR	6.7 y	CV risk factors	Coronary death and MI	Yes
PPP[36]	2001	4495	100 mg/d	17%	3.7 y	CV risk factors	CV death, nonfatal MI, stroke	No
ECLAP[37]	2004	518	100 mg/d	5%	3 y	Polycythemia vera	CV death, nonfatal MI, stroke, PE, VT	Yes
WHS[38]	2005	39 876	100 mg every other day	3%	10.1 y	Healthy women	CV death, nonfatal MI, stroke	No
CLIPS[39]	2007	366	100 mg/d	78%	2 y	PAD	CV death, MI, stroke	Yes
APLASA[40]	2007	98	81 mg/d	8%	2.3 y	AA syndrome	Acute thrombosis	No
POPADAD[41]	2008	1276	100 mg/d	100%	6.7 y	Diabetes, PAD	CV death, nonfatal MI, stroke, CLI	No
JPAD[42]	2008	2539	81–100 mg/d	100%	4.4 y	DM	Ischemic heart disease, stroke, PAD	No
AAA[43]	2010	3350	100 mg/d	3%	8.2 yr	PAD	CV death, MI, stroke, revascularization	No
JPPP[44]	2014	14 464	100 mg/d	34%	5.0 yr	CV risk factors	CV death, nonfatal MI, stroke	No

Angiolillo D, Capodanno D. Circulation 2016

Trials of Aspirin for Primary Cardiovascular Protection

Study Characteristic	ATT[45]	Bartolucci[46]	Raju[47]	Berger[48]	Seshasai[49]	Xie[50]	Raju[51]	Guirguis-Blake[52,53]
Publication date	2009	2011	2011	2011	2012	2014	2015	2016
Type	Patient level	Study level	Study level	Study level	Study level	Study level	Study level	Study level
Pooled patients	95 000	100 038	100 076	102 621	102 621	107 686	114 734	118 445
Summary measure	RaR (95% CI)	OR (95% CI)	RR (95% CI)	RR (95% CI)	OR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
Studies included	6	9	9	9	9	14	10	11
BDT[30]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
PHS[31]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
POPADAD[41]	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
JPAD[42]	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
AAA[43]	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
JPPP[44]	No	No	No	No	No	No	Yes	Yes
Follow-up	330,000 PY	NR	3.8–10.1 yr	710,053 PY	≈700,000 PY	734,170 PY	NR	3.6–10.1 y
Serious vascular events	0.88 (0.82–0.94)*	0.87 (0.80–0.93)*	0.88 (0.83–0.94)*	0.90 (0.85–0.96)*	0.90 (0.85–0.96)*	0.90 (0.85–0.95)*	0.89 (0.82–0.97)*	NR

In meta-analyses, treatment with aspirin significantly reduced the serious vascular events(composite of MI, stroke, or death from vascular cause) by 10-13%.

Angiolillo D, Capodanno D. Circulation 2016

Trials of Aspirin for Primary Cardiovascular Protection

Study Characteristic	ATT[45]	Bartolucci[46]	Raju[47]	Berger[48]	Seshasai[49]	Xie[50]	Raju[51]	Guirguis-Blake[52,53]
Any MI	NR	NR	0.83 (0.69–1.00)*	0.86 (0.74–1.00)*	NR	0.86 (0.75–0.98)*	0.78 (0.65–0.94)*	NR
Fatal MI	NR	NR	NR	NR	1.06 (0.83–1.37)	NR	NR	NR
Nonfatal MI	0.77 (0.69–0.86)*	0.81 (0.67–0.99)*	NR	NR	0.80 (0.67–0.96)*	NR	0.80 (0.64–0.99)*	0.78 (0.71–0.87)*
All-cause death	NR	0.95 (0.88–1.01)	0.94 (0.88–1.00)*	0.94 (0.89–1.00)	0.94 (0.88–1.00)	0.94 (0.89–0.99)*	0.94 (0.89–1.00)	0.94 (0.89–0.99)*
Cardiovascular	0.97 (0.87–1.09)	0.96 (0.80–1.14)	0.96 (0.84–1.09)	0.99 (0.85–1.14)	0.99 (0.85–1.15)	1.04 (0.86–1.25)	0.95 (0.84–1.07)	0.94 (0.86–1.03)
Any stroke	0.95 (0.85–1.06)	0.92 (0.83–1.02)	NR	0.94 (0.84–1.06)	0.94 (0.84–1.06)	0.95 (0.87–1.05)	0.94 (0.84–1.06)	0.95 (0.85–1.06)
Hemorrhagic	1.32 (1.00–1.75)*	NR	1.36 (1.01–1.82)*	1.35 (1.01–1.81)*	NR	1.34 (1.01–1.79)*	1.43 (1.10–1.86)*	1.33 (1.03–1.71)*
Ischemic	0.86 (0.74–1.00)*	NR	0.86 (0.75–0.98)*	0.87 (0.73–1.02)	NR	0.86 (0.75–0.98)*	NR	NR
Major bleeding	1.54 (1.30–1.82)*	NR	1.66 (1.41–1.95)*	1.62 (1.31–2.00)*	NR	1.55 (1.35–1.78)*	1.69 (1.43–1.98)*	NR
Gastrointestinal	NR	NR	1.37 (1.15–1.62)*	1.29 (1.24–1.47)*	NR	NR	1.64 (1.30–2.07)*	1.59 (1.32–1.91)*

Angiolillo D, Capodanno D. Circulation 2016

Relative Risk Estimates for ASCVD Risk Reduction

Therapy	Estimated RR for ASCVD Events (95% CI)	Quality of Evidence*	Comment
Aspirin	0.90 (0.85-0.96)	High	Increased risk for major bleeding (RR, 1.54; 95% CI, 1.30-1.82)
Blood pressure-lowering†	CHD: 0.84 (0.79-0.90) overall; 0.79 (0.72-0.86) per 10 mm Hg reduction in SBP	High High	Adverse effects poorly reported
	Stroke: 0.64 (0.56-0.73) overall; 0.54 (0.45-0.65) per 10 mm Hg reduction in SBP	High	
Cholesterol-lowering (statin)	0.75 (0.70-0.81) overall; 0.75 (0.70-0.80) per 1 mmol/L (38.7 mg/dL) reduction in LDL-cholesterol	High	No increased risk for adverse effects overall (RR, 1.00; 95% CI, 0.97-1.03)
Smoking cessation‡	0.73 overall; 0.85 at 1 y (>6-18 mo follow up); 0.73 at 2 y (>18-30 mo); 0.62 at 3 y (>30-42 mo); 0.53 at 4 y (>42 mo)	Not graded	Adverse effects poorly reported

JACC 2017;12:1617–36.

Courtesy by Dr. Yongwhi Park

Guidelines on the Use of Aspirin in Primary Prevention

Organization (yr)	Recommendation	Class (LoE)
ESC (2016)	Not recommended in individuals without CVD due to the increased risk of major bleeding.	III (B)
ADA (2018)	May be considered as a primary prevention strategy in those with type 1 or type 2 diabetes who are at increased CV risk. age >50 years who have at least one additional major risk factor (family history of premature ASCVD, HTN, dyslipidemia, smoking, or albuminuria) and are not at increased risk of bleeding.	C
USPSTF (2016)	Initiate in adults 50 to 59 years of age with a ≥10% 10-year CVD risk	B
	Individual judgment in adults 60 to 69 years of age with a ≥10% 10-year CVD risk	C
	No recommendation in adults <50 years or ≥70 years of age	I

EHJ 2016;37:2315–81.
Diabetes Care 2018;41(Supplement 1):S86-S104.

ASCEND in patients with DM

- **Men and women ≥ 40 years.**
- **Diabetes mellitus without CV disease.**
- **15,480 UK patients.**
- **Follow-up: Mean 7.4 years.**
- **Serious vascular events: nonfatal MI, nonfatal stroke (excluding confirmed intracranial hemorrhage) or TIA, or death from any vascular cause (excluding confirmed intracranial hemorrhage).**
- **Major bleeding: intracranial hemorrhage, sight-threatening bleeding event in the eye, GI bleeding, or any other serious bleeding (i.e., a bleeding event that resulted in hospitalization or transfusion or that was fatal).**

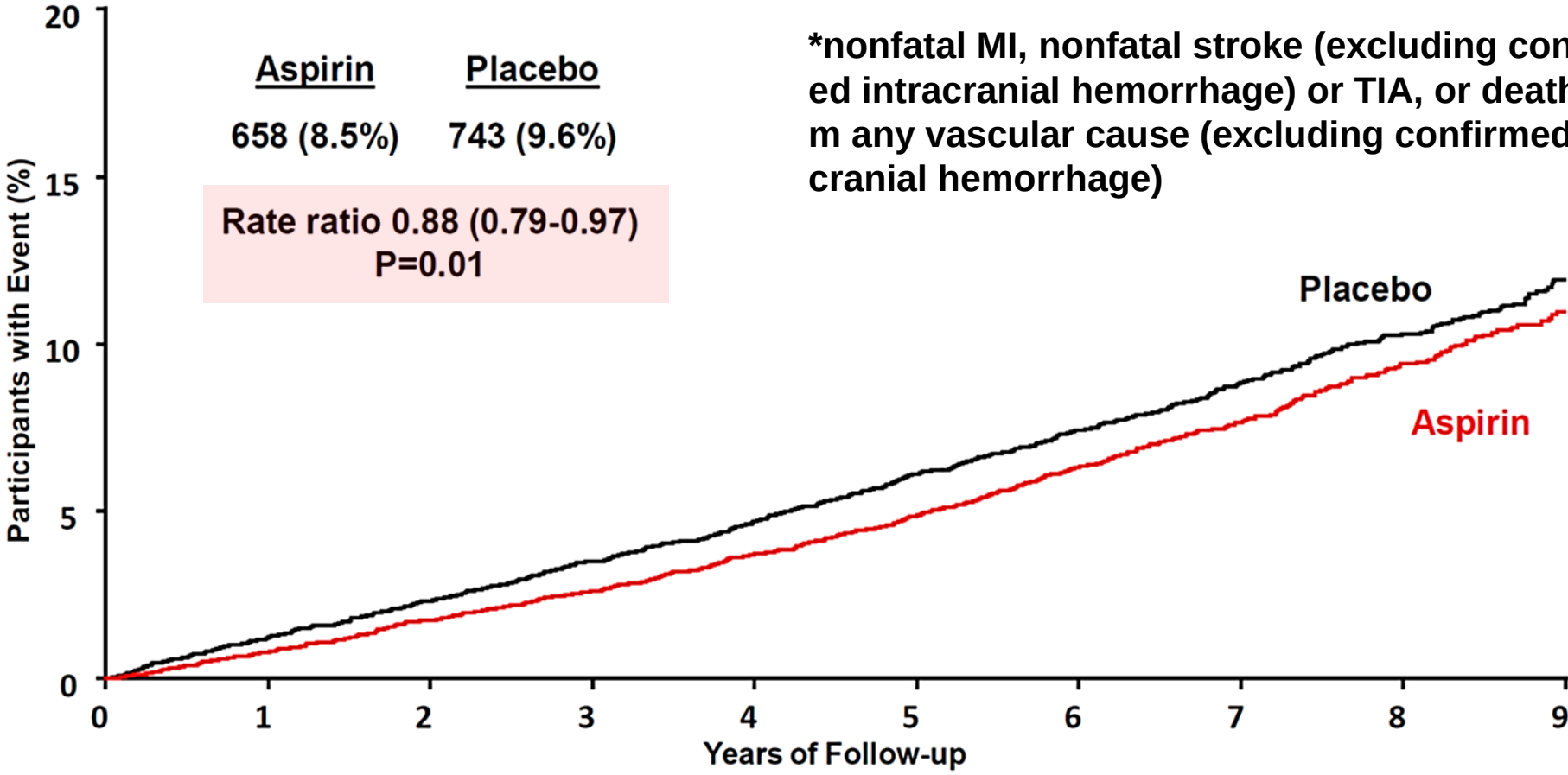
Bowman et al. NEJM 2018

Baseline Characteristics of ASCEND Participants

Table 1. Key Characteristics of the Participants at Baseline.*

Characteristic	Aspirin Group (N=7740)	Placebo Group (N=7740)
Age		
Mean — yr	63.2±9.2	63.3±9.2
Distribution — no. (%)		
<60 yr	2795 (36.1)	2795 (36.1)
60 to <70 yr	3123 (40.3)	3124 (40.4)
≥70 yr	1822 (23.5)	1821 (23.5)
Male sex — no. (%)	4843 (62.6)	4841 (62.5)
White race — no. (%)†	7467 (96.5)	7468 (96.5)
Body-mass index‡		
Mean	30.8±6.2	30.6±6.3
Distribution — no. (%)		
<25	1080 (14.0)	1169 (15.1)
25 to <30	2753 (35.6)	2776 (35.9)
≥30	3665 (47.4)	3536 (45.7)
Unknown	242 (3.1)	259 (3.3)
Smoking status — no. (%)		
Current smoker	639 (8.3)	640 (8.3)
Former smoker	3526 (45.6)	3525 (45.5)
Never smoked	3489 (45.1)	3488 (45.1)
Unknown	86 (1.1)	87 (1.1)
Participant-reported hypertension — no. (%)	4766 (61.6)	4767 (61.6)
Aspirin use before screening — no. (%)	2740 (35.4)	2768 (35.8)
Statin use — no. (%)	5854 (75.6)	5799 (74.9)
Type 2 diabetes — no. (%)§	7282 (94.1)	7287 (94.1)
Duration of diabetes		
Median (interquartile range) — yr	7 (3–13)	7 (3–13)
Distribution — no. (%)		
<9 yr	4337 (56.0)	4322 (55.8)
≥9 yr	2976 (38.4)	2989 (38.6)
Unknown	427 (5.5)	429 (5.5)
Systolic blood pressure		
Mean — mm Hg	136.1±15.2	136.2±15.3
Distribution — no. (%)		
<130 mm Hg	1694 (21.9)	1700 (22.0)
≥130 to <140 mm Hg	1550 (20.0)	1541 (19.9)
≥140 mm Hg	2263 (29.2)	2292 (29.6)
Unknown	2233 (28.9)	2207 (28.5)
Vascular risk score — no. (%)¶		
Low	3128 (40.4)	3136 (40.5)
Moderate	3294 (42.6)	3254 (42.0)
High	1318 (17.0)	1350 (17.4)

Effect of aspirin on Serious Vascular Events*



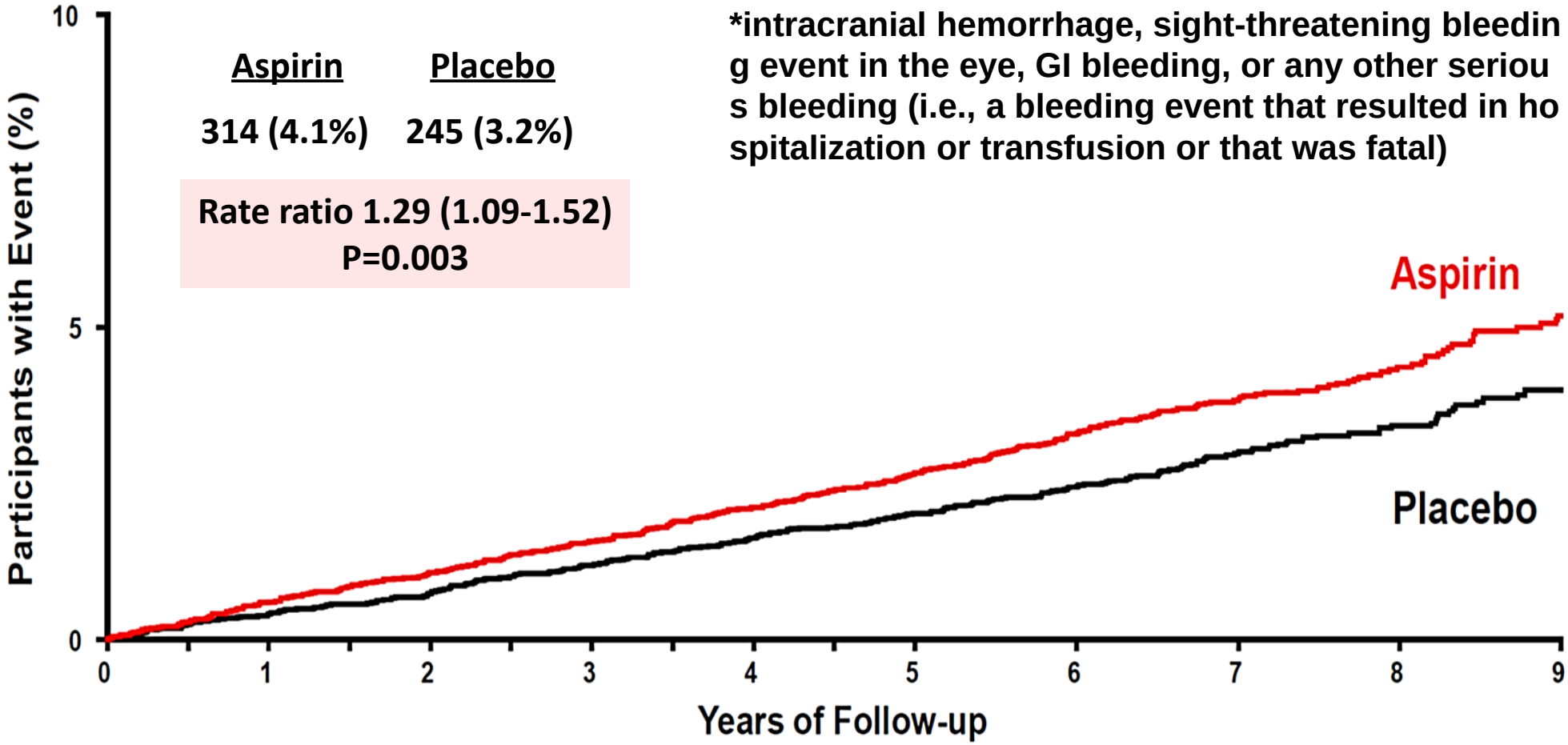
*nonfatal MI, nonfatal stroke (excluding confirmed intracranial hemorrhage) or TIA, or death from any vascular cause (excluding confirmed intracranial hemorrhage)

Effect of aspirin on major bleed*

Aspirin	Placebo
314 (4.1%)	245 (3.2%)

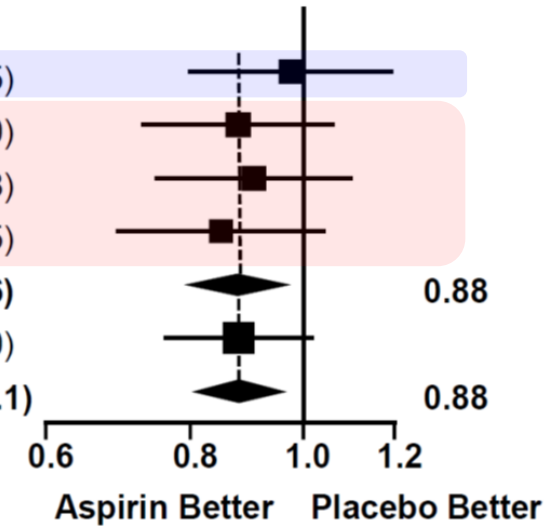
Rate ratio 1.29 (1.09-1.52)
P=0.003

*intracranial hemorrhage, sight-threatening bleeding event in the eye, GI bleeding, or any other serious bleeding (i.e., a bleeding event that resulted in hospitalization or transfusion or that was fatal)



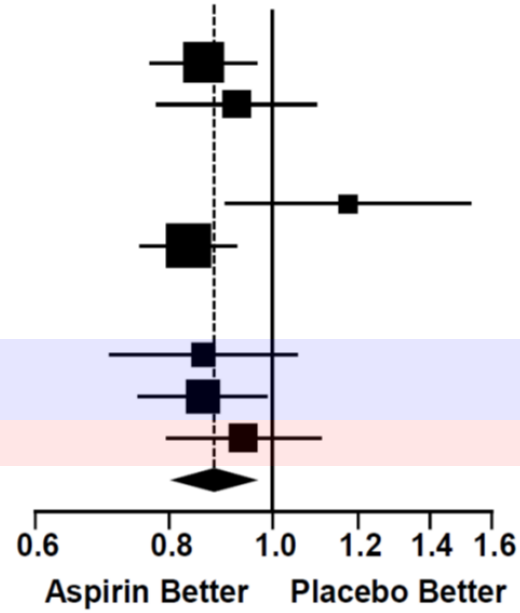
Components of the efficacy outcome + revascularization

Type of Event	Aspirin (N=7740) no. of participants with events (%)	Placebo (N=7740) no. of participants with events (%)	Rate Ratio (95% CI)
Vascular outcomes			
Non-fatal myocardial infarction	191 (2.5)	195 (2.5)	
Non-fatal presumed ischaemic stroke	202 (2.6)	229 (3.0)	
Vascular death excl. intracranial haemorrhage	197 (2.5)	217 (2.8)	
Transient ischaemic attack (TIA)	168 (2.2)	197 (2.5)	
Any serious vascular event	**658 (8.5)**	**743 (9.6)**	**0.88 (0.79–0.97) P = 0.01**
Any arterial revascularization	340 (4.4)	384 (5.0)	
Any serious vascular event or revascularization	**833 (10.8)**	**936 (12.1)**	**0.88 (0.80–0.97) P = 0.01**



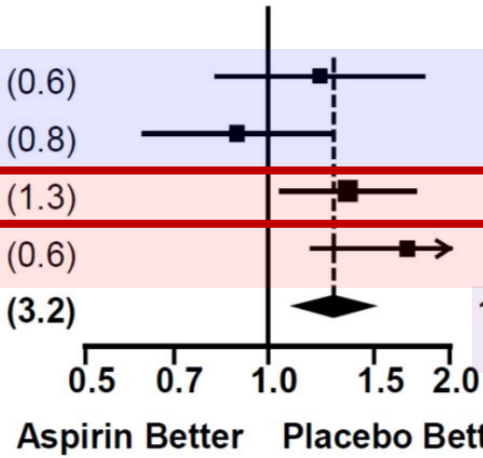
Effects of ASA in different types of participants

Baseline Characteristic	Aspirin (N=7740) no. of participants with events (%)	Placebo (N=7740) no. of participants with events (%)	Rate Ratio (95% CI)	
Sex				
Men	573 (11.8)	658 (13.6)	0.86	(0.77–0.96)
Women	260 (9.0)	278 (9.6)	0.92	(0.78–1.09)
Weight at randomization (kg)				
<70	118 (13.1)	108 (11.4)	1.17	(0.90–1.52)
≥70	694 (10.4)	812 (12.3)	0.83	(0.75–0.92)
5-year vascular risk				
<5%	179 (5.7)	208 (6.6)	0.86	(0.71–1.05)
≥5% <10%	384 (11.7)	431 (13.2)	0.86	(0.75–0.99)
≥10%	270 (20.5)	297 (22.0)	0.94	(0.80–1.11)
All	**833 (10.8)**	**936 (12.1)**	**0.88**	**(0.80–0.97)**



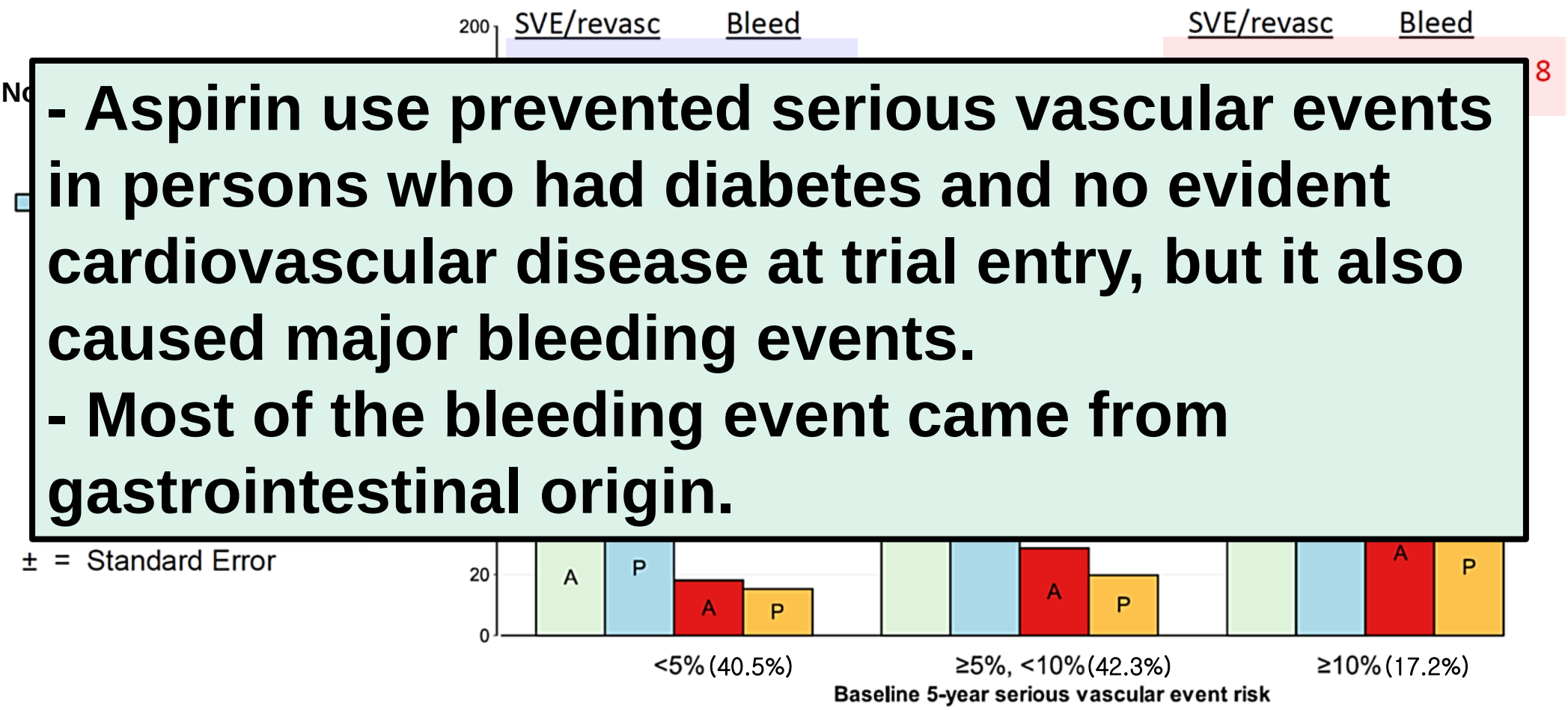
Effect of aspirin on major bleed

Type of Event	Aspirin (N=7740) no. of participants with events (%)	Placebo (N=7740) no. of participants with events (%)	Rate Ratio (95% CI)	Absolute Difference (%)
Major bleed				
Intracranial hemorrhage	55 (0.7)	45 (0.6)		0.1
Sight threatening eye bleed	57 (0.7)	64 (0.8)		-0.1
Serious gastrointestinal hemorrhage	137 (1.8)	101 (1.3)		0.5
Other major bleed	74 (1.0)	43 (0.6)		0.4
Any major bleed	**314 (4.1)**	**245 (3.2)**	**1.29 (1.09–1.52) P = 0.003**	**0.9**

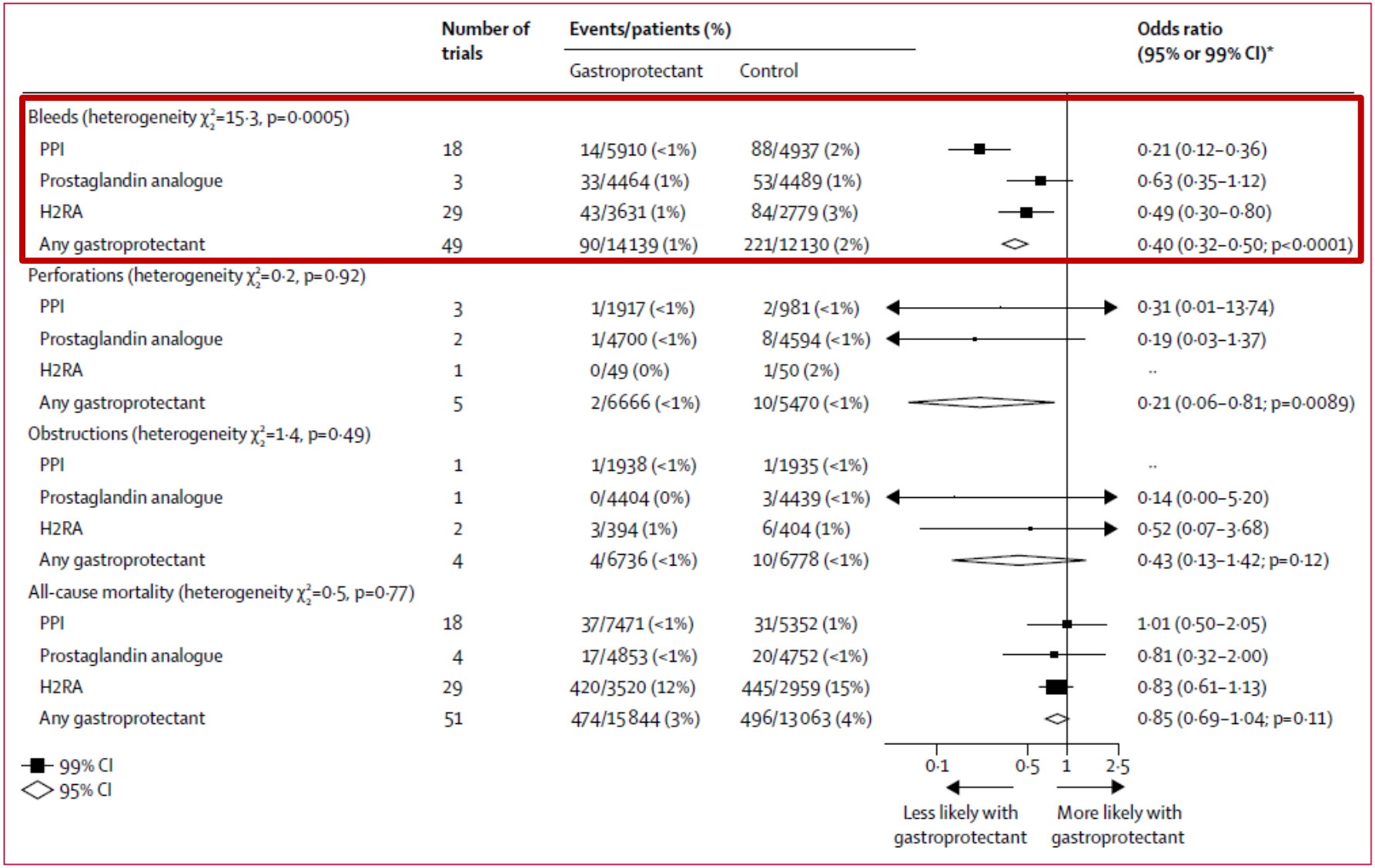


Absolute effects of ASA according to vascular risk*

- Aspirin use prevented serious vascular events in persons who had diabetes and no evident cardiovascular disease at trial entry, but it also caused major bleeding events.
- Most of the bleeding event came from gastrointestinal origin.



Prevention of GI bleeding by PPI in Patients taking NSAID (including Aspirin) – Meta-analysis of 142,485 patients



	Number of trials	Events/patients (%)		Odds ratio (95% or 99% CI)*
		Gastroprotectant	Control	
Bleeds (heterogeneity χ^2_2=15·3, p=0·0005)				
PPI	18	14/5910 (<1%)	88/4937 (2%)	0·21 (0·12–0·36)
Prostaglandin analogue	3	33/4464 (1%)	53/4489 (1%)	0·63 (0·35–1·12)
H2RA	29	43/3631 (1%)	84/2779 (3%)	0·49 (0·30–0·80)
Any gastroprotectant	49	90/14139 (1%)	221/12130 (2%)	0·40 (0·32–0·50; p<0·0001)
Perforations (heterogeneity χ^2_2=0·2, p=0·92)				
PPI	3	1/1917 (<1%)	2/981 (<1%)	0·31 (0·01–13·74)
Prostaglandin analogue	2	1/4700 (<1%)	8/4594 (<1%)	0·19 (0·03–1·37)
H2RA	1	0/49 (0%)	1/50 (2%)	..
Any gastroprotectant	5	2/6666 (<1%)	10/5470 (<1%)	0·21 (0·06–0·81; p=0·0089)
Obstructions (heterogeneity χ^2_2=1·4, p=0·49)				
PPI	1	1/1938 (<1%)	1/1935 (<1%)	..
Prostaglandin analogue	1	0/4404 (0%)	3/4439 (<1%)	0·14 (0·00–5·20)
H2RA	2	3/394 (1%)	6/404 (1%)	0·52 (0·07–3·68)
Any gastroprotectant	4	4/6736 (<1%)	10/6778 (<1%)	0·43 (0·13–1·42; p=0·12)
All-cause mortality (heterogeneity χ^2_2=0·5, p=0·77)				
PPI	18	37/7471 (<1%)	31/5352 (1%)	1·01 (0·50–2·05)
Prostaglandin analogue	4	17/4853 (<1%)	20/4752 (<1%)	0·81 (0·32–2·00)
H2RA	29	420/3520 (12%)	445/2959 (15%)	0·83 (0·61–1·13)
Any gastroprotectant	51	474/15844 (3%)	496/13063 (4%)	0·85 (0·69–1·04; p=0·11)

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Table 7 Cardiovascular risk categories in patients with diabetes[a]

Very high risk	Patients with DM **and** established CVD **or** other target organ damage[b] **or** three or more major risk factors[c] **or** early onset T1DM of long duration (>20 years)
High risk	Patients with DM duration ≥10 years without target organ damage plus any other additional risk factor
Moderate risk	Young patients (T1DM aged <35 years or T2DM aged <50 years) with DM duration <10 years, without other risk factors

CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

[a]Modified from the 2016 European Guidelines on cardiovascular disease prevention in clinical practice.[27]

[b]Proteinuria, renal impairment defined as eGFR ≥30 mL/min/1.73 m^2, left ventricular hypertrophy, or retinopathy.

[c]Age, hypertension, dyslipidemia, smoking, obesity.

ESC Guideline 2018

Recommendations for the use of antiplatelet therapy in primary prevention in patients with diabetes

Recommendations	Class[a]	Level[b]
In patients with DM at high/very high risk,[c] aspirin (75 - 100 mg/day) may be considered in primary prevention in the absence of clear contraindications.[d] [231]	IIb	A
In patients with DM at moderate CV risk,[c] aspirin for primary prevention is not recommended.	III	B
Gastric protection		
When low-dose aspirin is used, proton pump inhibitors should be considered to prevent gastrointestinal bleeding.[232,235]	IIa	A

CV = cardiovascular; DM = diabetes mellitus.
[a]Class of recommendation.
[b]Level of evidence.
[c]See *Table 7*.
[d]Gastrointestinal bleeding, peptic ulceration within the previous 6 months, active hepatic disease, or history of aspirin allergy.

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Summary

- **Diabetes mellitus is a metabolic disorder associated with accelerated atherogenesis and an increased risk of atherothrombotic complications.**
- **Low-dose aspirin could effectively inhibit platelet activation associated with thromboxane pathway, which was also in line with the clinical trial results.**
- **In meta-analyses, treatment with aspirin significantly reduced the serious vascular events(composite of MI, stroke, or death from vascular cause) at the expense of increased bleeding.**
- **Recent large-scale RCT(ASCEND study) shown the similar results, but the most bleeding events came from gastrointestinal origin.**
- **Summarizing the available evidences, 2018 ESC guideline recommends the use of aspirin as a primary prevention in diabetes patients for those who are at very high/high risk(class IIb), with preferably concommittant use of PPI as gastroprotectant(class IIa).**

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