



GIOVEDÌ 29

Controversia in cardiologia: clopidogrel o acido acetilsalicilico nel trattamento delle sindromi coronariche croniche?

Laura Gatto, *Roma*



Antiplatelet Therapy for Secondary Prevention of CAD

- ✓ Long term antiplatelet therapy is a cornerstone of secondary prevention in patients with established atherosclerosis
- ✓ After PCI guidelines recommend an initial 6-12 months of dual antiplatelet therapy on the basis of various factors, including clinical presentation (ACS vs CCS) and balancing ischemic/bleeding risk
- ✓ After DAPT period, indefinite maintenance of single antiplatelet therapy is indicated for secondary prevention of atherosclerotic cardiovascular events and traditionally aspirin is the antiplatelet agent of choice

Antithrombotic Trialists' (ATT) Collaboration Meta-analysis

Secondary prevention of vascular disease by prolonged antiplatelet treatment

ANTIPLATELET TRIALISTS' COLLABORATION

**Collaborative overview of randomised trials of antiplatelet therapy—
I: Prevention of death, myocardial infarction, and stroke by
prolonged antiplatelet therapy in various categories of patients**

Antiplatelet Trialists' Collaboration

Collaborative meta-analysis of randomised trials of
antiplatelet therapy for prevention of death, myocardial
infarction, and stroke in high risk patients

Antithrombotic Trialists' Collaboration

Aspirin in the primary and secondary prevention of vascular
disease: collaborative meta-analysis of individual participant
data from randomised trials

*Antithrombotic Trialists' (ATT) Collaboration**

BMJ 1988

BMJ 1994

BMJ 2002

Lancet 2009

Aspirin in the secondary prevention of vascular disease

	Number of events (aspirin vs control)		Rate ratio (95% CI) (aspirin vs control)			Yearly absolute difference (% per year)	
	Primary prevention (660 000 person-years)	Secondary prevention (43 000 person-years)	Primary prevention	Secondary prevention	p value for heterogeneity	Primary prevention	Secondary prevention
Major coronary event	934 vs 1115	995 vs 1214	0.82 (0.75–0.90)	0.80 (0.73–0.88)	0.7	–0.06	–1.00*
Non-fatal MI	596 vs 756	357 vs 505	0.77 (0.69–0.86)	0.69 (0.60–0.80)	0.5	–0.05	–0.66
CHD mortality	372 vs 393	614 vs 696	0.95 (0.82–1.10)	0.87 (0.78–0.98)	0.4	–0.01	–0.34
Stroke	655 vs 682	480 vs 580	0.95 (0.85–1.06)	0.81 (0.71–0.92)	0.1	–0.01	–0.46*
Haemorrhagic	116 vs 89	36 vs 19	1.32 (1.00–1.75)	1.67 (0.97–2.90)	0.4	0.01	..†
Ischaemic	317 vs 367	140 vs 176	0.86 (0.74–1.00)	0.78 (0.61–0.99)	0.5	–0.02	..†
Unknown cause	222 vs 226	304 vs 385	0.97 (0.80–1.18)	0.77 (0.66–0.91)	0.1	–0.001	..†
Vascular death	619 vs 637	825 vs 896	0.97 (0.87–1.09)	0.91 (0.82–1.00)	0.4	–0.01	–0.29
Any serious vascular event	1671 vs 1883 (0.51% vs 0.57% per year)	1505 vs 1801 (6.69% vs 8.19% per year)	0.88 (0.82–0.94)	0.81 (0.75–0.87)	0.1	–0.07	–1.49*
Major extracranial bleed	335 vs 219	23 vs 6	1.54 (1.30–1.82)	2.69 (1.25–5.76)	0.2	0.03	..†

MI=myocardial infarction. CHD=coronary heart disease. Non-fatal MI definitions vary; see methods. *Major coronary event rates (percent per year, aspirin vs control) 6.0 vs 7.4 in post-MI trials and 2.4 vs 3.0 in post-cerebral vascular disease trials; corresponding rates of stroke (mainly of unknown cause) 0.6 vs 0.8 in post-MI trials and 3.9 vs 4.7 in post-cerebral vascular disease trials (webappendix pp 14–18). †Stroke causes, and extracranial bleeds, very incompletely reported.

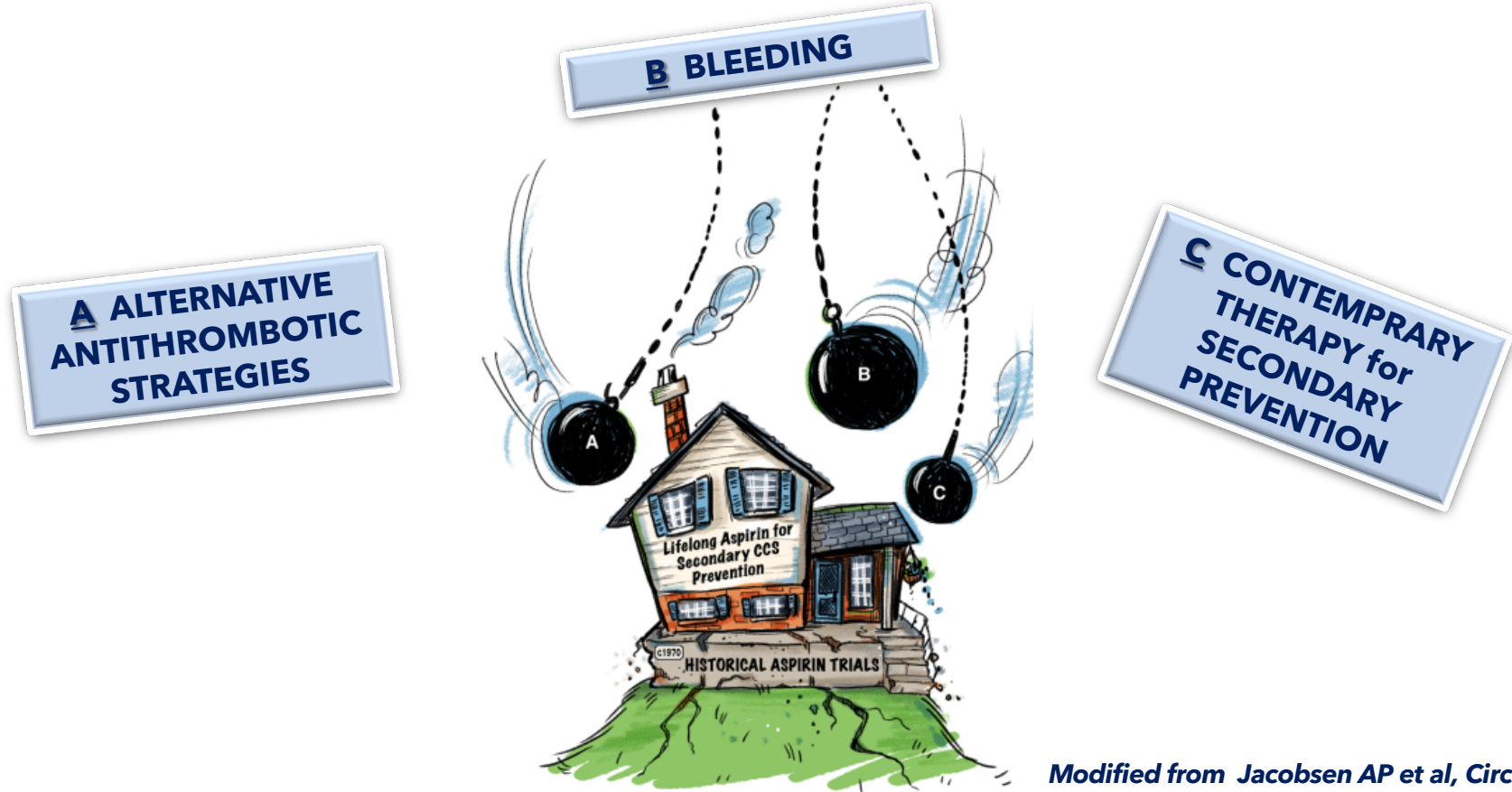
Table 2: Comparison of proportional and absolute effects of aspirin in primary and secondary prevention trials

Secondary Prevention Trials of Aspirin versus Control

Trial Name	Starting Year	Publication Year	Aspirin Daily Dose, mg	No. of Patients	Study Duration	Age	Male, %	Htn, %	Diabetes Mellitus, %	β -Blocker, %	Time From MI to Enrollment	Revascularization (PCI/CABG), %
Prior MI												
Cardiff I	1971	1974	300	1239	13 mo	55	100	NA	NA	NA	10 wk	0
Cardiff II	NA	1979	900	1725	12 mo	56	85	NA	0.5	NA	95% <7 days	0
PARIS I*	1975	1980	972	1216	41 mo	56	87	NA	10	15.4	8 wk to 60 mo	0
AMIS	1975	1980	1000	4524	38 mo	55	89	NA	11	12	8 wk to 60 mo	0
CDP-A†	1972	1976	972	1529	22 mo	56	100	NA	14	NA	75% >60 mo	0
GAMIS‡	1970	1980	1500	626*	24 mo	59	78	19	20	NA	30–42 days	0
Micristin	NA	1979	1500	1340	24 mo	NA	NA	NA	NA	NA	NA	NA
Acute MI												
ISIS-pilot§	1983	1987	162.5	619	1 mo	60	80	22	5	40	<24 h	0
ISIS-2	1985	1988	162.5	17187	35 days	NA	NA	NA	NA	NA	<24 h	0
Dutch-aspirin	NA	1990	100	100	3	62.5	74	NA	NA	32	<12 h	Rare, none within 1 wk
Huddinge	NA	1988	167 (500 every 3 days)	20	1 mo (12 mo)	63	80	NA	NA	20	<24 h	10
Frankfurt	NA	1976	1320	39	14 days	NA	NA	NA	NA	NA	NA	NA
APRICOT¶	NA	1993	325	192	3 mo	57	81	NA	NA	43	48 h	10.4
Unstable angina												
VA-pilot	1974	1986	324	50	3 mo	NA	100	NA	NA	NA	NA	NA
VA-main	1974	1983	324	1266	3 mo	56	100	41	17	74	48 h	3.5
RISC	1985	1990	75	796	12 mo	58	100	30	8	88	72 h	3.9
ALDUSA-pilot#	NA	1987	324–340	84	12 mo	NA	NA	NA	NA	NA	NA	NA
Thèroux**	1986	1988	650	479	6 days (3 mo)	58	71	38	13	96	<24 h	48
ATACS-pilot††	1987	1990	325–380	93	3 mo	62	60	49	37	39	<48 h	50
Coronary angioplasty												
Perth‡‡	1986	1991	100	212	6 mo	55	84	34	4	58	–	100% PCI for stable CAD
M-HEART III	NA	1995	325	503	6 mo	58	83	50	18	NA	–	100% PCI for stable CAD
Stable CAD												
SAPAT¶¶	1985	1992	75	2035	50	67	52	41	7	100	–	3.9
VA bypass IV-B#	1983	1989	325	502	24	58	100	46	NA	NA	–	100% enrolled after CABG

- Studies conducted several decades ago
- Young and Male Pts
- ASA different dosage
- Low rate of coronary revascularization
- No statin

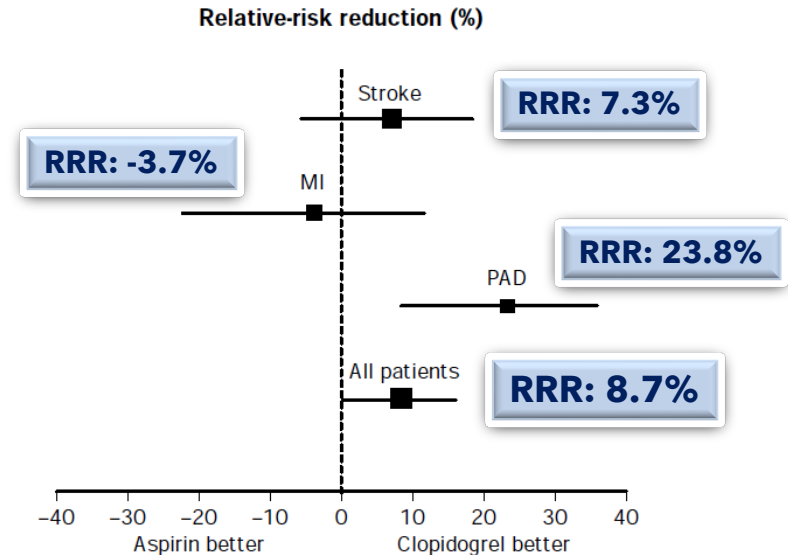
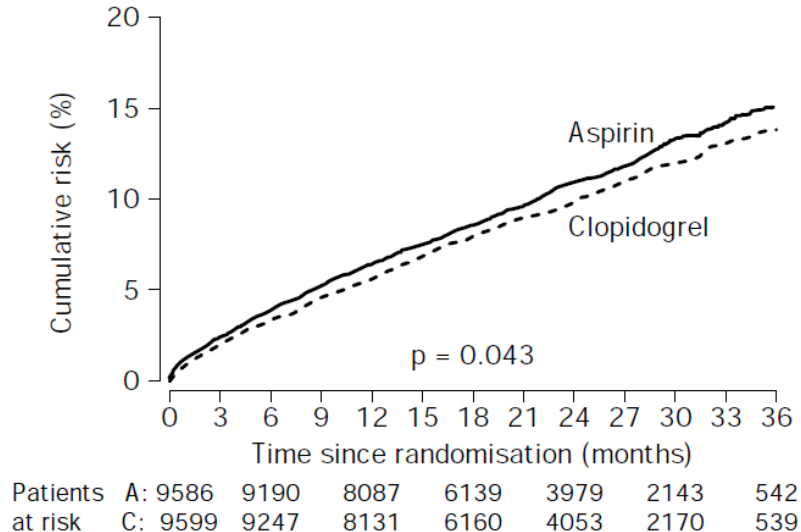
Lifelong Aspirin for all patient with Chronic Coronary Syndrome Still sacrosanct or is reappraisal warranted?



Modified from Jacobsen AP et al, Circulation 2020

CAPRIE: Clopidogrel vs ASA in pts at risk of ischemic events

- 19185 pts with atherosclerotic vascular disease (recent MI, recent stroke or symptomatic PAD) randomized to clopidogrel (75 mg/die) or aspirin (325 mg/die)
- Follow-up 2 years
- Endpoint: ischemic stroke, MI and vascular death



Secondary Prevention in Atherosclerosis

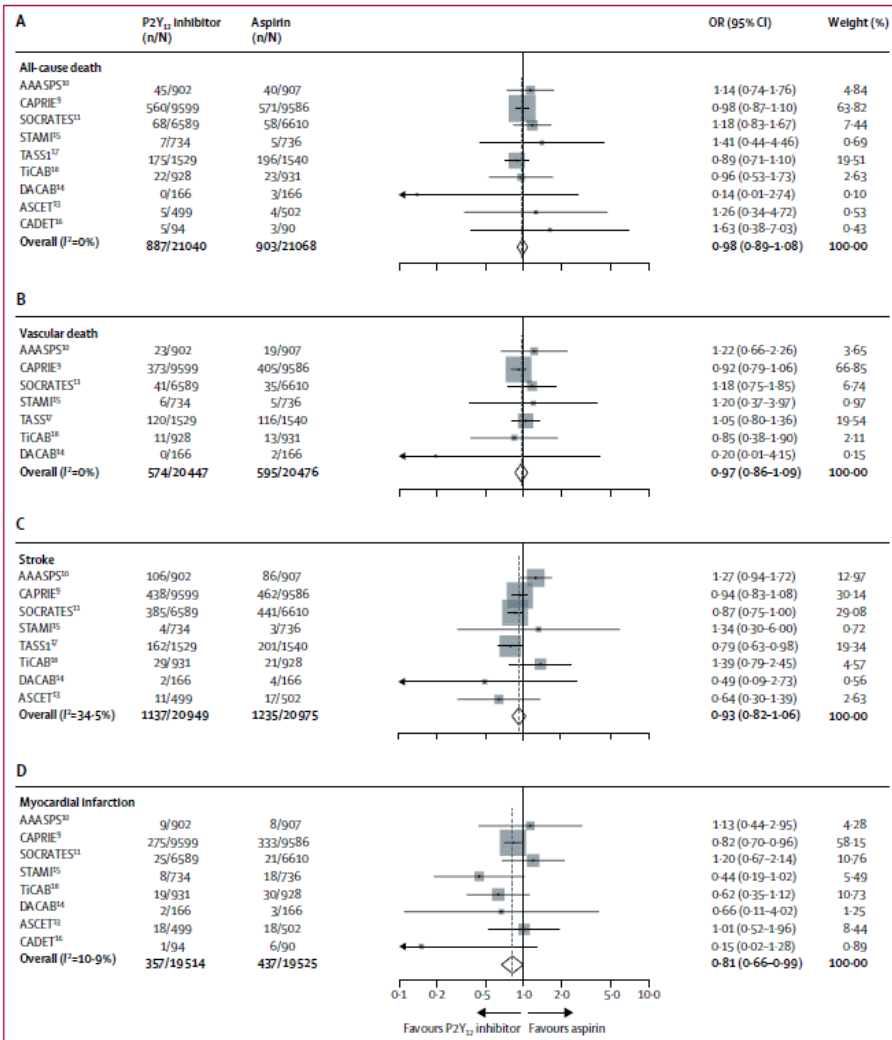
Monotherapy with Aspirin or P2Y₁₂ inhibitor?

	Qualifying event	Year of publication	Number of patients			P2Y ₁₂ inhibitor	P2Y ₁₂ inhibitor dosage	Aspirin dosage	Multicentre	Follow-up
			Overall	P2Y ₁₂ inhibitor	Aspirin					
TASS ¹⁷	Cerebrovascular disease	1989	3069	1529	1540	Ticlopidine	250 mg twice daily	650 mg twice daily	Yes	36 months
CAPRIE ⁹	Cerebrovascular, coronary, and peripheral artery disease	1996	19185	9599	9586	Clopidogrel	75 mg once daily	325 mg once daily	Yes	36 months
STAMI ¹⁵	Coronary artery disease	2001	1470	734	736	Ticlopidine	250 mg twice daily	80 mg twice daily	Yes	6 months
AAASPS ¹⁰	Cerebrovascular disease	2003	1809	902	907	Ticlopidine	250 mg twice daily	325 mg twice daily	Yes	24 months
CADET ¹⁶	Coronary artery disease	2004	184	94	90	Clopidogrel	75 mg once daily	75 mg once daily	Yes	6 months
ASCET ¹³	Coronary artery disease	2012	1001	499	502	Clopidogrel	75 mg once daily	75 mg once daily	No	24 months
SOCRATES ¹¹	Cerebrovascular disease	2016	13199	6589	6610	Ticagrelor	90 mg twice daily	100 mg once daily	Yes	3 months
DACAB ¹⁴	Coronary artery disease	2018	332	166	166	Ticagrelor	90 mg twice daily	100 mg once daily	Yes	12 months
TICAB ¹⁸	Coronary artery disease	2019	1859	931	928	Ticagrelor	90 mg twice daily	100 mg once daily	Yes	12 months

Table 1: Key study features

	Mean age (years)	Female (%)	Male (%)	Diabetes (%)	Hypertension (%)	Dyslipidaemia (%)	Prior cerebrovascular accident (%)	Prior myocardial infarction (%)	Chronic coronary syndromes (%)	Peripheral artery disease (%)
TASS ¹⁷	62.9	35.3%	64.7%	19.4%	39.2%	36.5%	100%	16.7%	18.0%	14.6%
CAPRIE ⁹	62.5	28.1%	71.9%	20.0%	51.5%	41.0%	40.0%	44.0%	14.0%	38.0%
STAMI ¹⁵	59.2	16.2%	83.8%	14.9%	33.6%	36.0%	2.1%	100%	33.6%	5.9%
AAASPS ¹⁰	61.3	53.5%	46.5%	40.7%	85%	38.5%	100%	9.6%	10.6%	4.0%
CADET ¹⁶	62.6	19.1%	80.9%	..	..	..	..	100%	..	..
ASCET ¹³	62.4	21.8%	78.2%	19.9%	55.4%	..	..	43.7%	100%	5.4%
SOCRATES ¹¹	65.8	41.6%	58.4%	24.3%	73.7%	38.0%	100%	4.1%	8.6%	..
DACAB ¹⁴	63.6	17.2%	82.8%	42.7%	72.8%	73.1%	10.5%	31.0%	34.0%	16.9%
TICAB ¹⁸	66.7	15.1%	84.9%	35.9%	89.9%	81.7%	8.9%	22.7%	69.2%	9.1%
Overall	63.6	32.6%	67.4%	22.9%	60.4%	40.6%	36.3%	28.4%	21.5%	28.6%

Table 2: Baseline clinical characteristics of patients included in our analyses



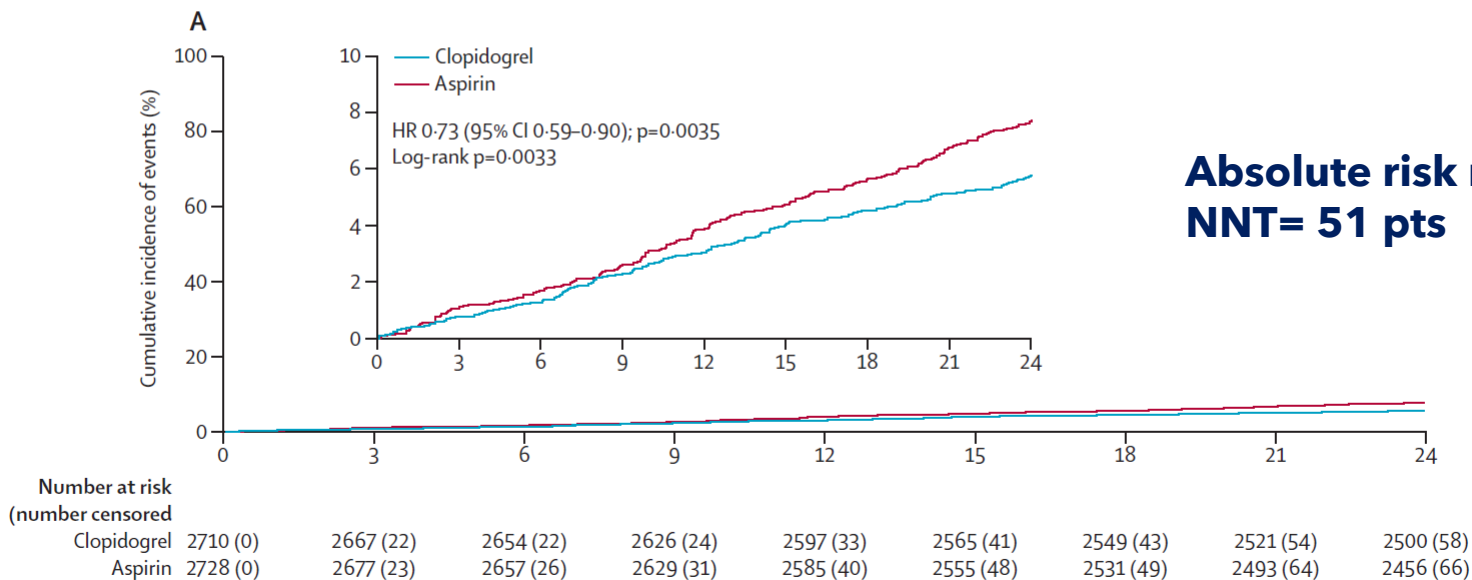
Secondary Prevention in Atherosclerosis Monotherapy with Aspirin or P2Y₁₂ inhibitor?

- Any bleeding (OR 1.08 [95% CI 0.91-1.29])
- Major bleeding (OR 0.90 [95% CI 0.74-1.10])
- Gastrointestinal bleeding lower in P2Y₁₂ inhibitor group

differ between patients receiving a P2Y₁₂ inhibitor and those receiving aspirin; (2) the risk of myocardial infarction is marginally lower in patients receiving a P2Y₁₂ inhibitor compared with those receiving aspirin, with a number needed to treat of 244 patients to prevent one myocardial infarction; and (3) findings are consistent irrespective of the type of P2Y₁₂ inhibitor used.

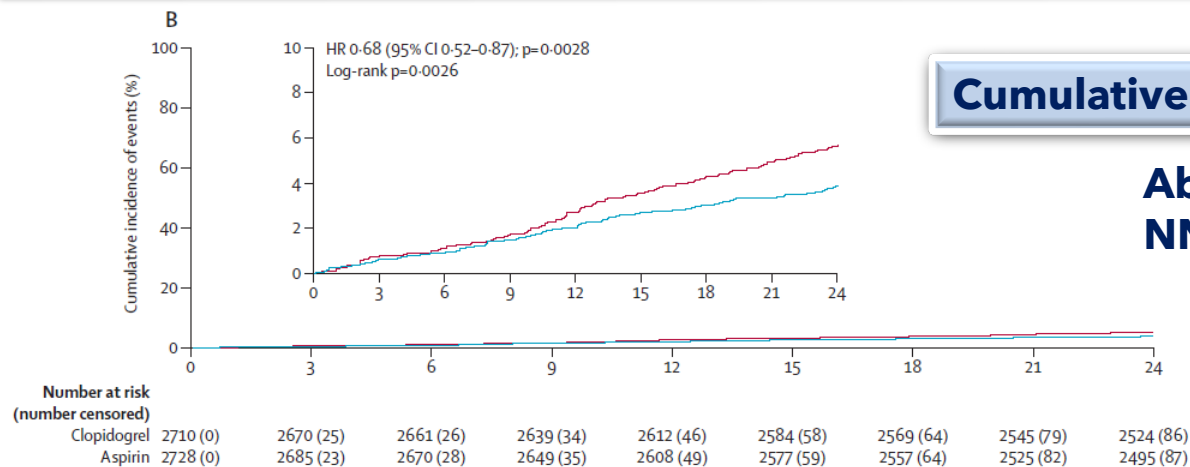
HOST-EXAM: Aspirin vs Clopidogrel for chronic monotherapy after PCI

- ✓ Prospective, randomised, **open-label**, multicentre trial done at 37 study sites in **South Korea**
- ✓ 5438 pts underwent DES-PCI and maintained DAPT without any clinical events within 6–18 months after PCI. Pts with any ischemic and major bleeding complications were excluded
- ✓ **Primary endpoint:** composite of all cause of death, non fatal myocardial infarction, stroke, readmission to ACS and bleeding BARC 3



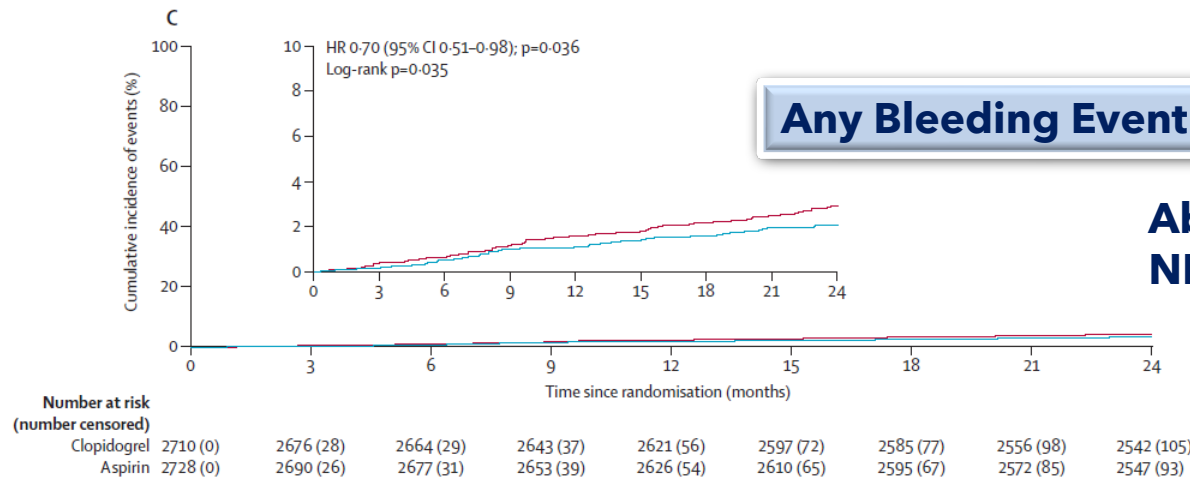
Absolute risk reduction of 2.0%
NNT= 51 pts

HOST-EXAM: Aspirin vs Clopidogrel for chronic monotherapy after PCI



Cumulative Thrombotic Endpoint

Absolute risk reduction of 1.7%
NNT= 59 pts



Any Bleeding Event

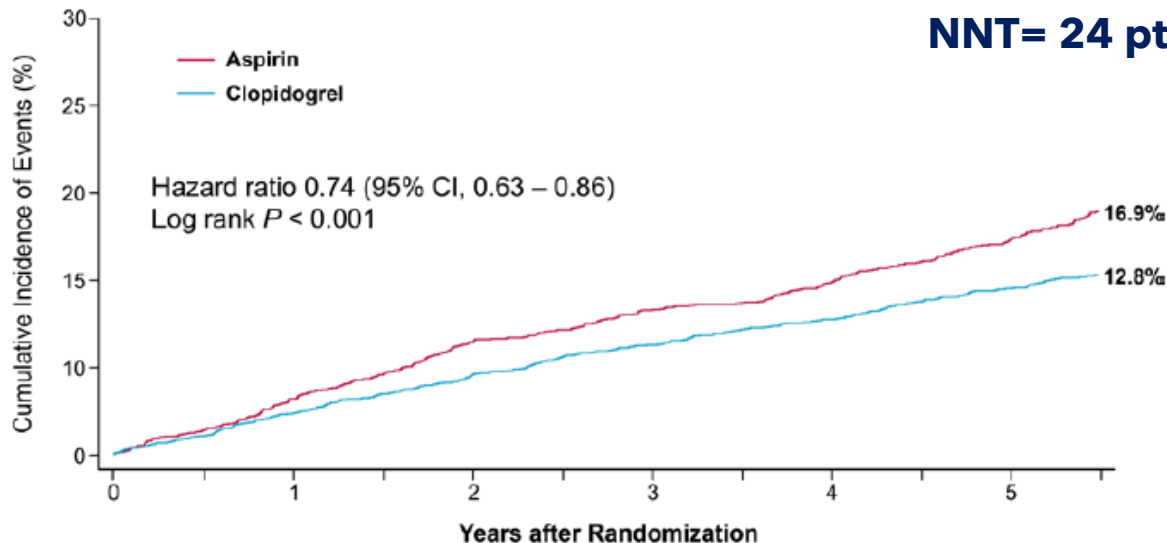
Absolute risk reduction of 0.9%
NNT= 111 pts

HOST-EXAM EXTENDED STUDY: follow-up 5.8 years

- 4717 pts of initial HOST-EXAM population
- The **discontinuation rate** was significantly higher in the aspirin group vs clopidogrel group (8.0% versus 13.5% $P < 0.001$)

A

Absolute risk reduction of 4.1%
NNT= 24 pts

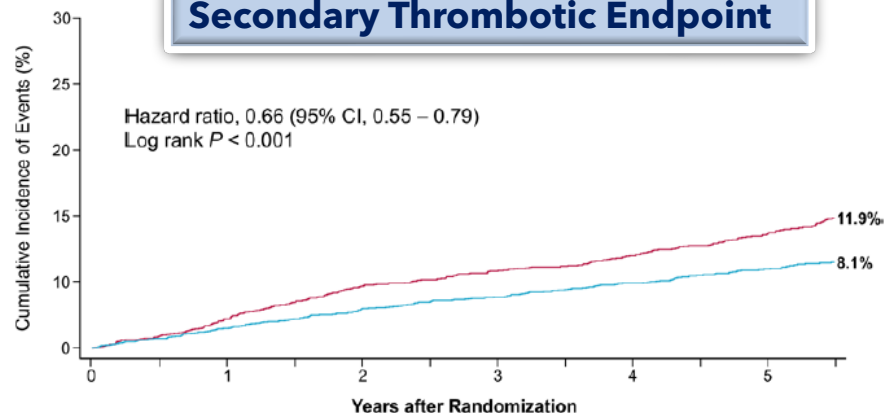


Number at Risk

Aspirin	2286	2189	2086	2014	1777	1287	1007
Clopidogrel	2431	2355	2280	2214	1964	1462	1181

B

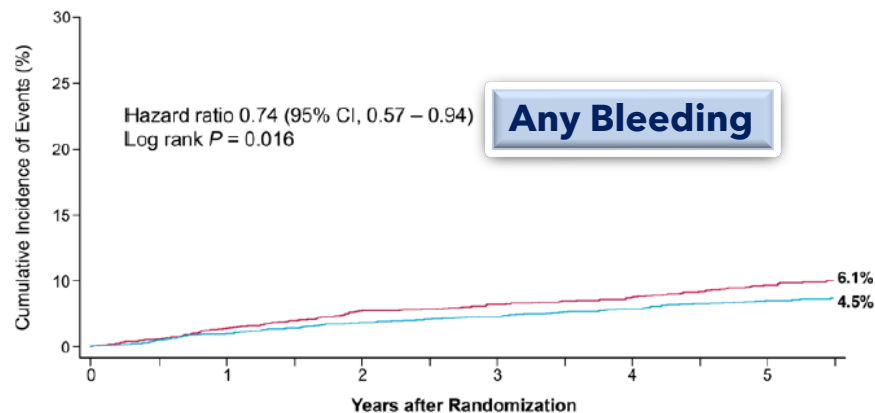
Secondary Thrombotic Endpoint



Number at Risk

Aspirin	2286	2208	2120	2053	1819	1322	1040
Clopidogrel	2431	2371	2304	2245	1992	1489	1202

C

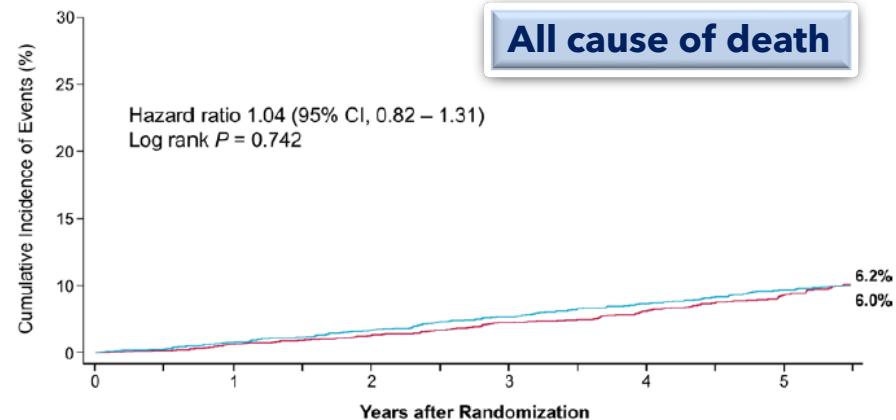


Number at Risk

Aspirin	2286	2229	2175	2123	1888	1395	1104
Clopidogrel	2431	2375	2323	2271	2028	1525	1238

D

All cause of death



Number at Risk

Aspirin	2286	2267	2244	2198	1971	1471	1165
Clopidogrel	2431	2405	2374	2330	2088	1579	1285

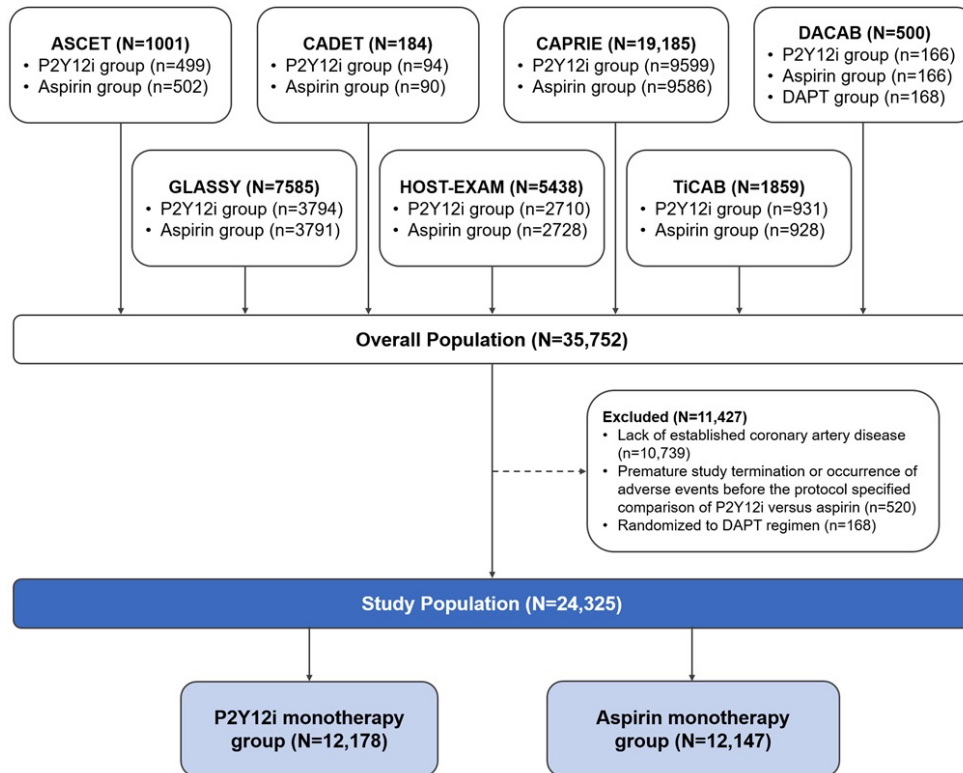
PANTHER: P2Y₁₂ Inhibitor or Aspirin Monotherapy for Secondary Prevention of Coronary Events

Individual patient-level meta-analysis of RCT evaluating the effect of P2Y₁₂ inhibitor monotherapy vs aspirin monotherapy on ischemic and bleeding outcomes in patients with established CAD

TABLE 1 Main Characteristics of Trials and Patient Populations Included in the PANTHER Meta-Analysis

	Year of Publication	Definition of CAD	Overall Population	P2Y ₁₂ Inhibitor Group	Aspirin Group	P2Y ₁₂ Inhibitor	P2Y ₁₂ Inhibitor Dose	Aspirin Dose	Initial DAPT Phase	Follow-Up (mo)
ASCET	2012	Stable CAD documented by coronary angiography (with or without PCI)	1,001	499	502	Clopidogrel	75 mg once daily	160 mg once daily	When clinically indicated (ie, PCI)	24
CADET	2004	Recent myocardial infarction (within 3-7 d)	184	94	90	Clopidogrel	75 mg once daily	75 mg once daily	No	6
CAPRIE ^a	1996	Previous myocardial infarction (at any time)	8,446	4,242	4,204	Clopidogrel	75 mg once daily	325 mg once daily	No	36
DACAB	2018	Post-CABG patients (within 24 h after surgery)	322	166	166	Ticagrelor	90 mg twice daily	100 mg once daily	No	12
GLASSY ^b	2019	Post-PCI patients (12 mo after index PCI)	7,065	3,536	3,529	Ticagrelor	90 mg twice daily	75-100 mg once daily	Yes	12
HOST-EXAM	2021	Post-PCI patients (6-18 mo after PCI)	5,438	2,710	2,728	Clopidogrel	75 mg once daily	100 mg once daily	Yes	24
TiCAB	2019	Post-CABG patients (within 24 h after surgery)	1,859	931	928	Ticagrelor	90 mg twice daily	100 mg once daily	No	12

PANTHER: Study Flow Chart and Endpoints



Median Follow-up 557 days

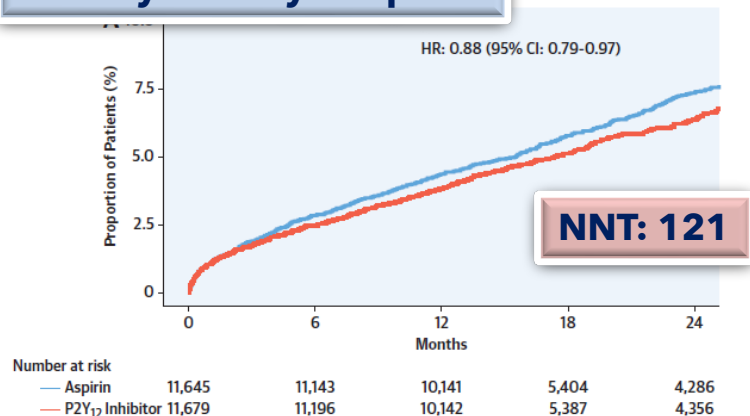
Primary efficacy endpoint: CV death, MI and stroke

Prespecified key secondary: Major bleeding and NACE (the composite of the primary outcome and major bleeding)

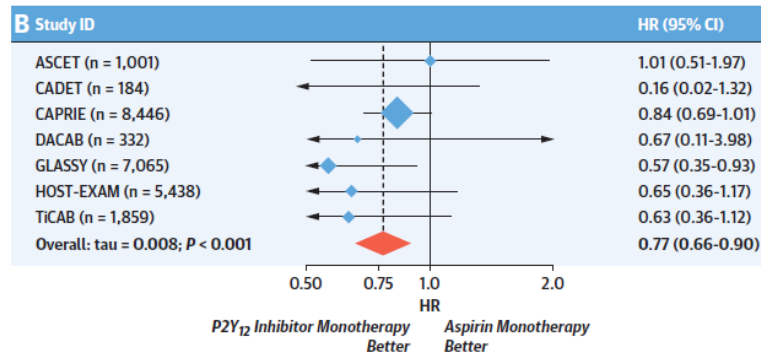
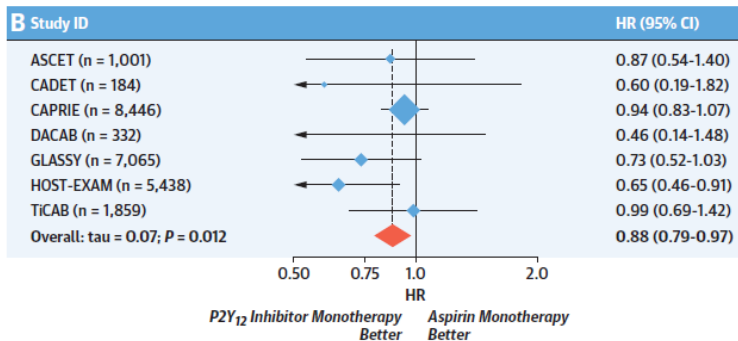
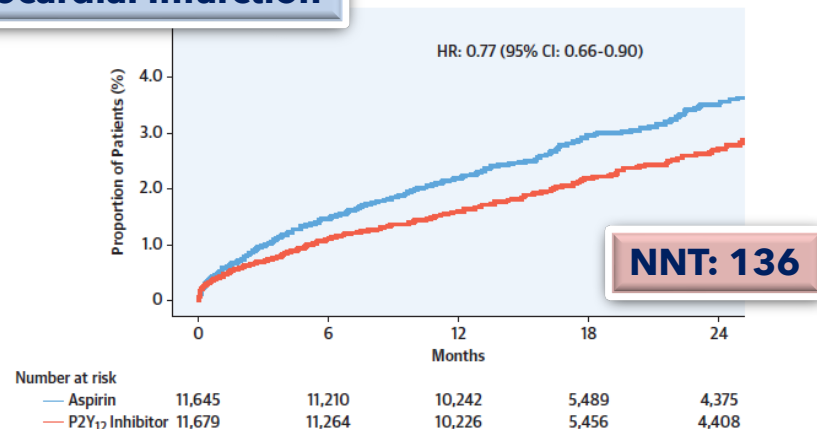
Other secondary endpoints: individual components of the primary outcome, death, definite/probable ST, ischemic or hemorrhagic stroke, any bleeding, ICH and GI bleeding

PANTHER: MAIN RESULTS

Primary Efficacy Endpoint

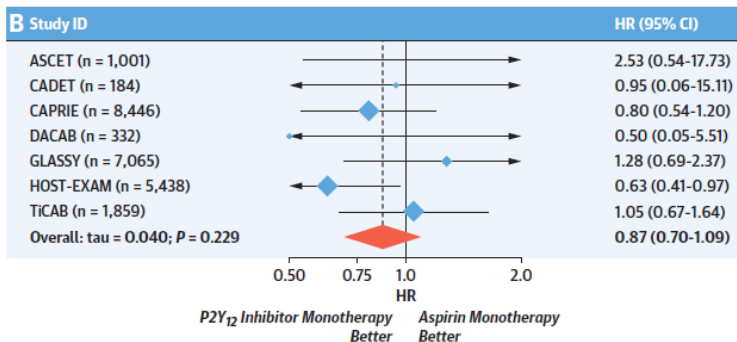
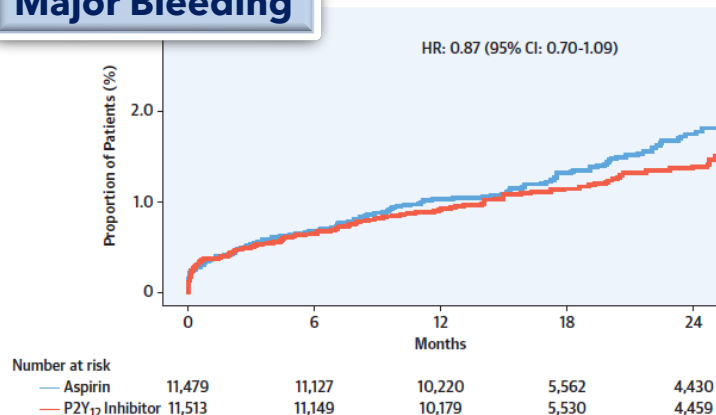


Myocardial Infarction

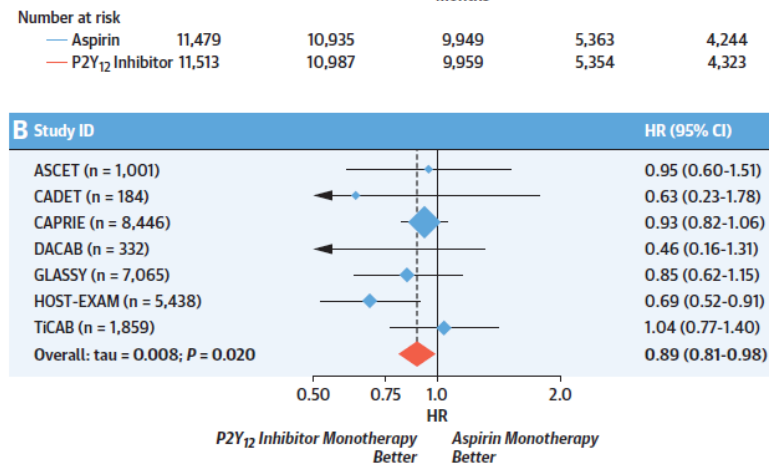
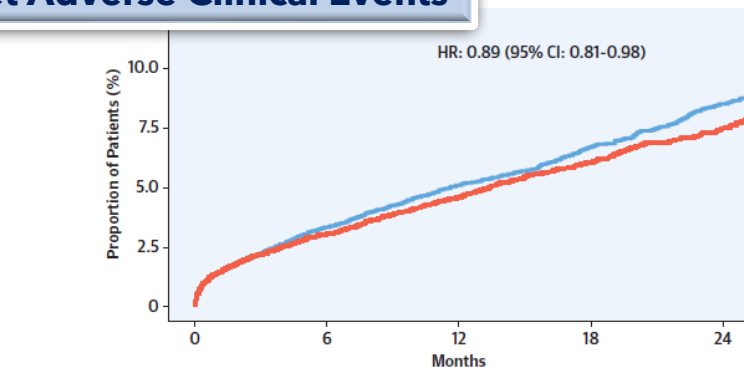


PANTHER: MAIN RESULTS

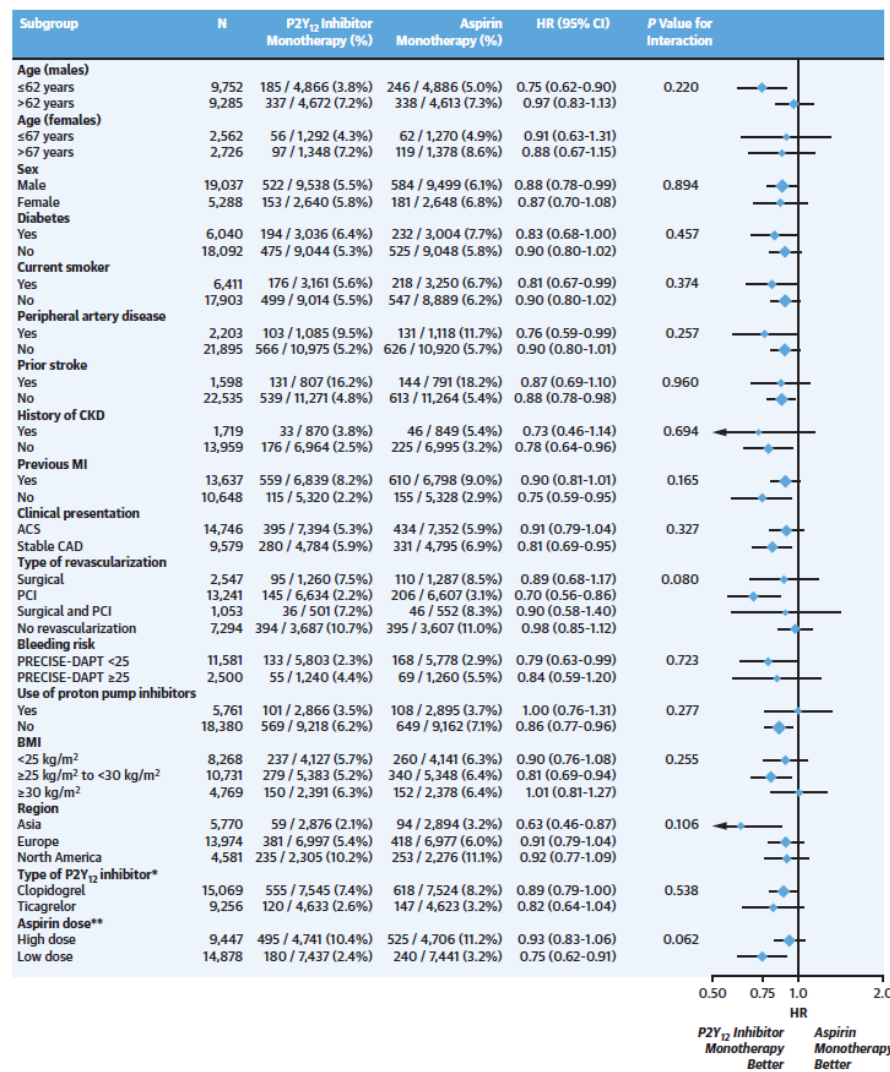
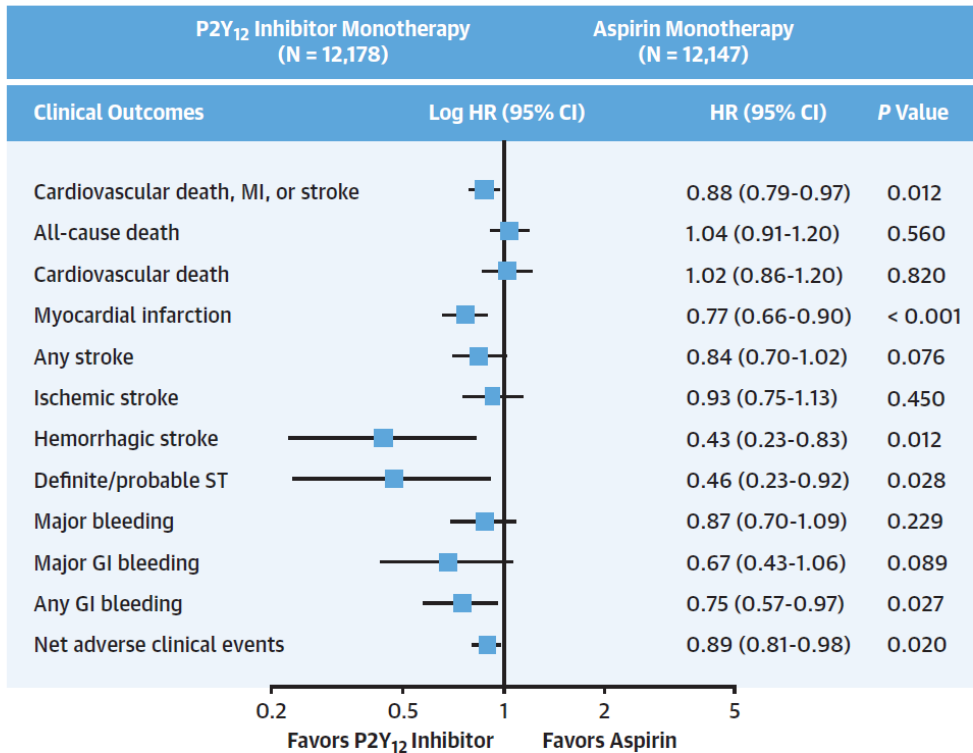
Major Bleeding



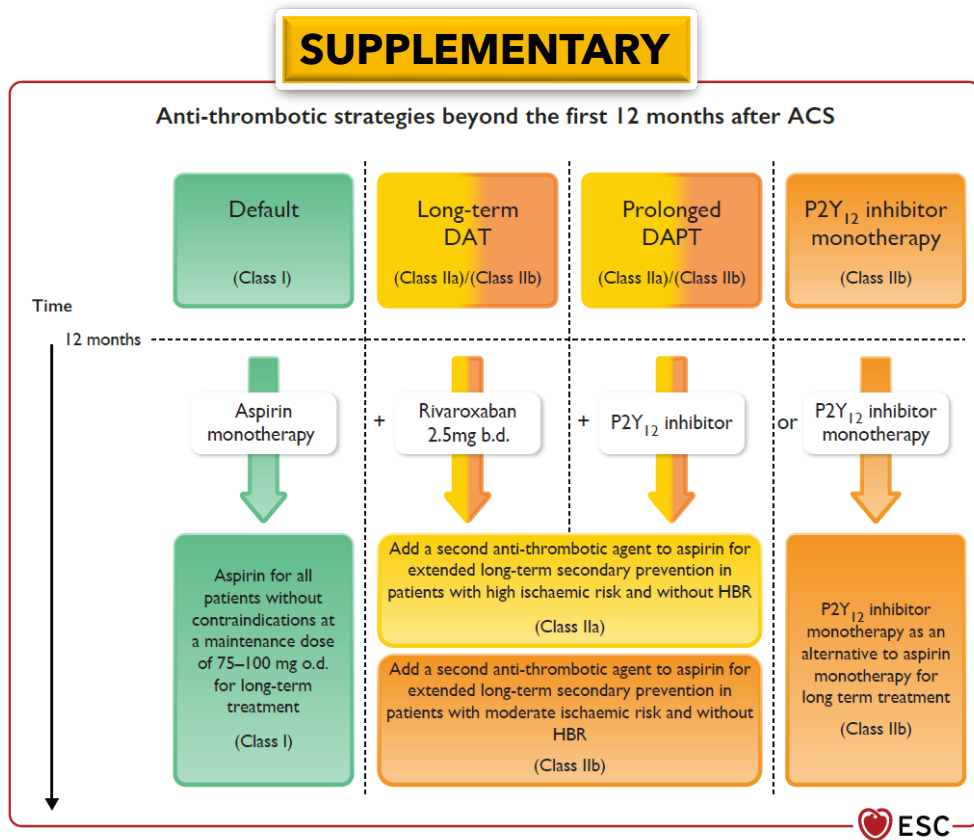
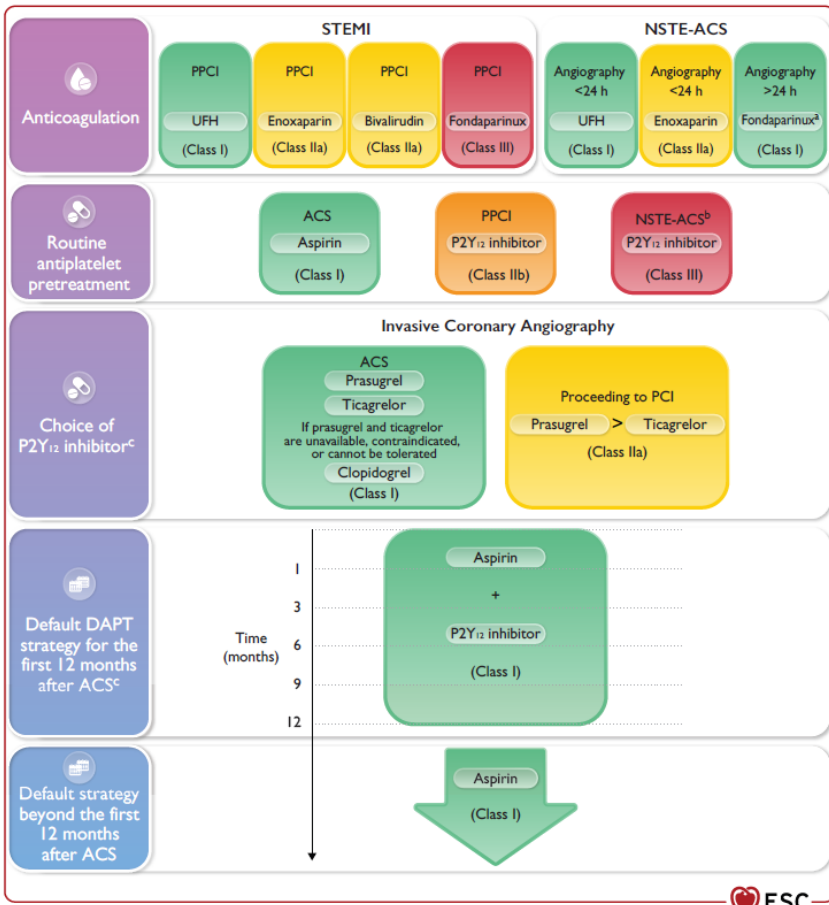
Net Adverse Clinical Events



PANTHER: OTHER RESULTS



2023 ACUTE CORONARY SYNDROMES GUIDELINES



TAKE HOME MESSAGE

- ✓ Long term antiplatelet therapy is a cornerstone of secondary prevention in patients with CCC and aspirin has been the standard of care for years
- ✓ The pivotal studies of aspirin were performed several decades ago, and it remains uncertain whether these results would be replicated nowadays
- ✓ CAPRIE was the first randomized trial to show that clopidogrel reduces events compared with aspirin in patients with atherosclerosis, but not in post-MI patients
- ✓ Recent studies and meta-analyses demonstrated that clopidogrel monotherapy represent a valid alternative to ASA in CCS pts
- ✓ However, last update ESC guidelines continue to consider Aspirin as the first choice probably waiting for other more robust evidences

