Prevenzione secondaria con antiaggreganti: quale ruolo oggi per l'ASA?

M. Carnovali

Prevenzione secondaria: quale!

Prevenzione secondaria

- Quale farmaco

Prevenzione secondaria

- Quale farmaco

  Farmaco o farmaci

Prevenzione secondaria

- Quale farmaco

  Farmaco o farmaci

- Quali pazienti

Farmaci Antiaggreganti nella prevenzione cardiovascolare

Prevenzione secondaria con antiaggreganti: quale ruolo oggi per l'ASA?

Farmaci Antiaggreganti nella prevenzione cardiovascolare

Felix Hoffmann, era un giovane chimico dell'industria chimica tedesca Bayer di Leverkusen, in Renania. Il padre di Felix, affetto da una grave forma di malattia reumatica, assumeva il salicilato di sodio.

Nel tentativo di migliorare la qualità di vita del padre, Felix Hoffmann iniziò a condurre indagini sistematiche alla ricerca di un derivato efficace e meglio tollerato, alternativo al salicilato di sodio e nel **1897** riuscì nel suo intento mediante l'acetilazione, cioè attraverso la combinazione di acido salicilico con acido acetico.

Farmaci Antiaggreganti nella prevenzione cardiovascolare

- L'utilizzo dell'ASA per prevenire la trombosi coronarica è stato inizialmente proposto nel 1948 da un MMG che osservò una riduzione del rischio negli uomini che assumevano cronicamente ASA [1]

CV, cardiovascular; GP, general practitioner; LD-ASA, low-dose acetylsalicylic acid; MI, myocardial infarction.

1. Craven L. Ann West Med Surg 1950;4:95.
2. Antiplatelet Trialists' Collaboration. BMJ 1988;296:320–31.

Farmaci Antiaggreganti nella prevenzione cardiovascolare

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- Dal 1960 studi clinici in numero progressivamente crescente hanno valutato la capacità di ASA e di altri antiaggreganti nel prevenire la mortalità cardiovascolare in soggetti che avevano già avuto un evento (prevenzione secondaria)[2]

CV, cardiovascular; GP, general practitioner; LD-ASA, low-dose acetylsalicylic acid; MI, myocardial infarction.

1. Craven L. Ann West Med Surg 1950;4:95.
2. Antiplatelet Trialists' Collaboration. BMJ 1988;296:320–31.

Farmaci Antiaggreganti nella prevenzione cardiovascolare

Meta-analisi	Numero di pazienti	Numero di studi completati
APTC (1994)[1]	~100,000	174

AP, antiplatelet; APTC, Antiplatelet Trialists' Collaboration; ATTC, Antithrombotic Trialists' Collaboration.

1. Antiplatelet Trialists' Collaboration. BMJ 1994;308:81–106.

Farmaci Antiaggreganti nella prevenzione cardiovascolare

Criteri di inclusione	Riduzione del rischio relativo di morte CV, % (SD)
Pregresso stroke/TIA	14 (7)*
Pregresso MI	15 (5)*
Tutti i pazienti	17 (3)*

*p<0.00001.
APTC, Antiplatelet Trialists' Collaboration; MI, myocardial infarction; SD, standard deviation; TIA, transient ischemic attack.
Antiplatelet Trialists' Collaboration. BMJ 1994;308:81–106.

Farmaci Antiaggreganti nella prevenzione cardiovascolare

Meta-analisi	Numero di pazienti	Numero di studi completati
APTC (1994)[1]	~100,000	174
ATTC (2002)[2]	212,000 (135,000 AP vs controllo, 77,000 AP vs AP)	287

AP, antiplatelet; APTC, Antiplatelet Trialists' Collaboration; ATTC, Antithrombotic Trialists' Collaboration.

1. Antiplatelet Trialists' Collaboration. BMJ 1994;308:81–106.
2. Antithrombotic Trialists' Collaboration. BMJ 2002;324:71–86.

Farmaci Antiaggreganti nella prevenzione cardiovascolare

Tipo di pazienti	Morti prevenute per 1,000 trattati	p vs controllo
Pregresso IMA	14	p=0.0006
IMA acuto*	23	p<0.0001
Pregresso stroke/TIA	7	p=0.04
Stroke acuto*	5	p=0.05
Totale	**15% riduzione**	**p<0.0001**

*Acute data are recorded within ~30 days of a CV event.
ATTC, Antithrombotic Trialists' Collaboration; CV, cardiovascular; MI, myocardial infarction; TIA, transient ischemic attack.
Antithrombotic Trialists' Collaboration. BMJ 2002;324:71–86.

Farmaci Antiaggreganti nella prevenzione cardiovascolare

Conclusioni degli Antithrombotic Trialists' Collaboration:

- ASA è l'antiaggregante più ampiamente utilizzato e documentato
- non vi sono ragioni per utilizzare posologie superiori a 325 mg/die;
- la dose con miglior rapporto beneficio/rischio è 75-150 mg/die;
- l'efficacia di dosi inferiori a <75 mg/die sembra essere minore

Farmaci Antiaggreganti nella prevenzione cardiovascolare

Lancet 2009; 373: 1849–60

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

*Antithrombotic Trialists' (ATT) Collaboration**

Farmaci Antiaggreganti nella prevenzione cardiovascolare

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

*Antithrombotic Trialists' (ATT) Collaboration**

Methods We undertook meta-analyses of serious vascular events (myocardial infarction, stroke, or vascular death) and major bleeds in six primary prevention trials (95 000 individuals at low average risk, 660 000 person-years, 3554 serious vascular events) and 16 secondary prevention trials (17 000 individuals at high average risk, 43 000 person-years, 3306 serious vascular events) that compared long-term aspirin versus control. We report intention-to-treat analyses of first events during the scheduled treatment period.

Lancet 2009; 373: 1849–60

Farmaci Antiaggreganti nella prevenzione cardiovascolare

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

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	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**

Lancet 2009; 373: 1849–60

Farmaci Antiaggreganti nella prevenzione cardiovascolare

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

*Antithrombotic Trialists' (ATT) Collaboration**

Interpretation In primary prevention without previous disease, aspirin is of uncertain net value as the reduction in occlusive events needs to be weighed against any increase in major bleeds. Further trials are in progress.

In the secondary prevention trials, aspirin allocation yielded a greater absolute reduction in serious vascular events (6·7% *vs* 8·2% per year, p<0.0001), with a non-significant increase in haemorrhagic stroke but reductions of about a fifth in total stroke (2·08% *vs* 2·54% per year, p=0·002) and in coronary events (4·3% *vs* 5·3% per year, p<0·0001).

Lancet 2009; 373: 1849–60

Prevenzione secondaria

Quale farmaco

Farmaci Antiaggreganti nella prevenzione cardiovascolare

Meccanismi di attivazione piastrinica

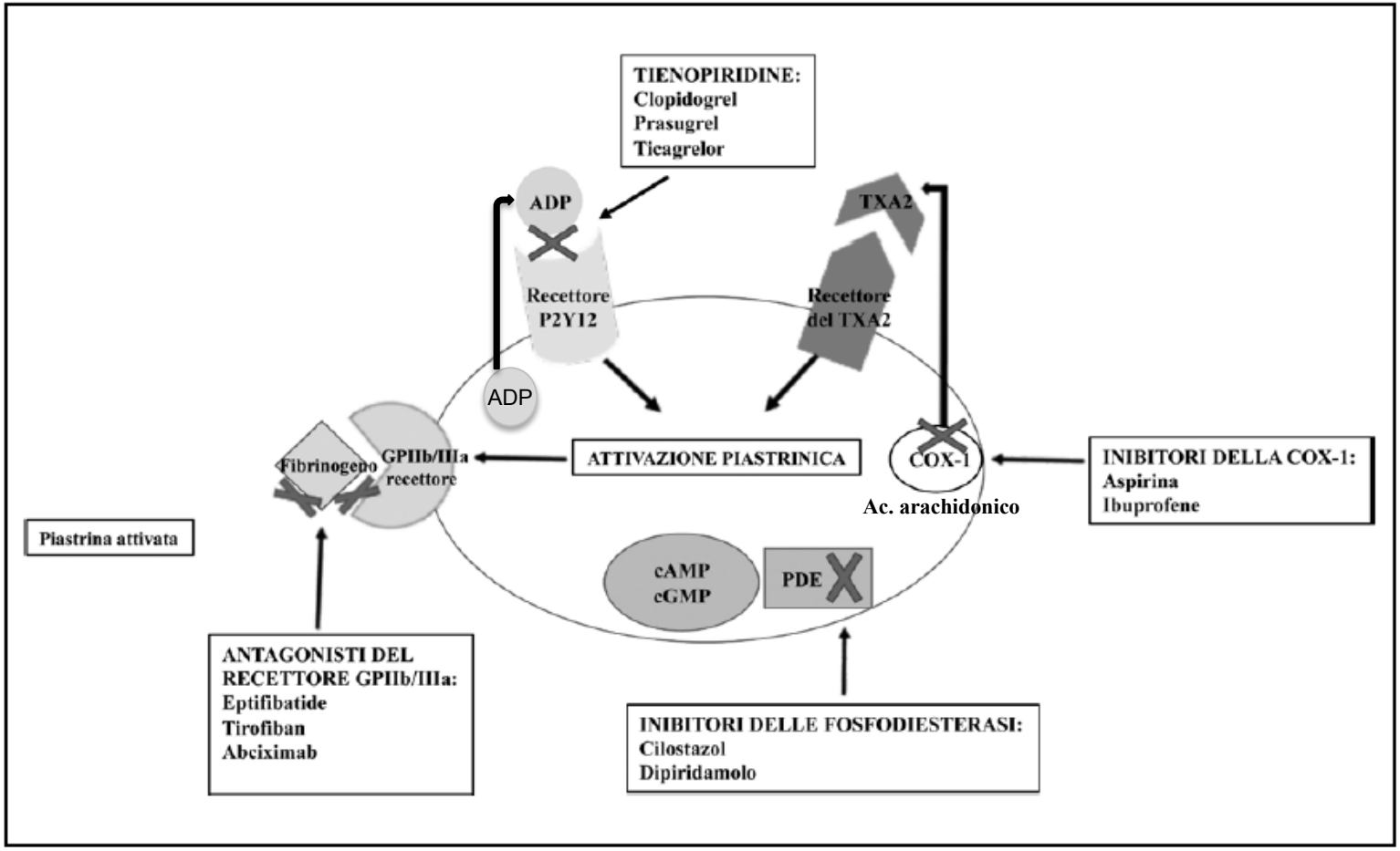

Figura 2. Meccanismo di azione dei farmaci antipiastrinici.
TxA2= TrombossanoA2; COX-1=Ciclossigenasi1; PDE=Fosfodiesterasi; ADP= Adenosina difosfato; cAMP= Adenosina monofosfato ciclico; cGMP= Guanosina monofosfato ciclico

Farmaci Antiaggreganti nella prevenzione cardiovascolare

CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE).
Lancet 1996 Nov 16; 348: 1329-39

Lancet 1996 Nov 16; 348: 1329-39

Farmaci Antiaggreganti nella prevenzione cardiovascolare

CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE).

Outcome (no. of events in recipients of clopidogrel/aspirin)[a]	Relative risk reduction (%)[b]	p value
Primary end-point: IS, MI, vascular death (939/1021)	8.7	0.043
For each outcome		
IS[c] (509/546)	5.2	0.42
MI[c] (308/376)	19.2	0.008
Vascular death (350/378)	7.6	0.29
Combined outcomes of vascular events		
IS,MI (817/922)	10.9	0.025
TIA, hospitalisation due to angina[d]	7.5	0.089
IS, MI, TIA, hospitalisation due to angina[d]	7.9	0.016
Combined outcomes of major vascular events		
Any stroke (IS or HS), vascular/haemorrhagic death (net benefit cluster)[d]	9.5	0.024
Any stroke, MI, death from any cause[d]	7.0	0.081

a Number of events occurring in 19 185 patients during the entire study as reported by the CAPRIE steering committee.[75]

b Relative risk reduction in the number of events/year.

c Includes nonfatal and fatal events.

d The number of events was not reported in the poster.[83]

CAPRIE = Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events; **HS** = haemorrhagic stroke; **IS** = ischaemic stroke; **MI** = myocardial infarction; **TIA** = transient ischaemic attack.

Lancet 1996 Nov 16; 348: 1329-39

UNIVERSITY of York
Centre for Reviews and Dissemination

Clopidogrel versus aspirin in patients with atherothrombosis: CAPRIE-based calculation of cost-effectiveness for Germany

Berger K, Hessel F, Kreuzer J, Smala A, Diener H C

Results

In a hypothetical cohort of 1,000 patients, the number of LYs saved, due to vascular deaths avoided, using clopidogrel compared with aspirin was 86.35 in scenario one (using Framingham database survival data) and 66.07 in scenario two (using Saskatchewan database survival data). The incremental two-year cost of clopidogrel over aspirin was EUR 1,241,440. Thus, the incremental cost per LY saved with clopidogrel over aspirin was EUR 14,380 in scenario one and EUR 18,790 in scenario two.

Farmaci Antiaggreganti nella prevenzione cardiovascolare

Farmaci Antiaggreganti nella prevenzione cardiovascolare

L'uso dei Farmaci in Italia

Rapporto Nazionale. Anno 2017

Tabella 3.2.6a. Antiaggreganti e anticoagulanti, consumo (DDD/1000 ab die) per categoria terapeutica e per sostanza: confronto 2013-2017

Sottogruppi e sostanze	2013	2014	2015	2016	2017	Δ % 17-16
Antiaggreganti e anticoagulanti	**89,0**	**86,9**	**89,2**	**90,7**	**92,3**	**1,7**
enoxaparina sodica	7,1	7,5	7,6	7,7	7,3	-4,6
apixaban	0,0	0,2	0,8	1,6	2,3	43,7
rivaroxaban	0,1	0,6	1,5	2,3	2,8	21,7
dabigatran	0,2	0,8	1,1	1,4	1,8	26,5
acido acetilsalicilico 2.700.000	47,0	43,6	44,4	44,5	45,0	1,3
clopidogrel 540.000	5,9	7,1	8,1	8,8	9,3	5,2
nadroparina calcica	1,6	1,4	1,4	1,2	1,2	3,6
ticagrelor	0,3	0,5	0,6	0,7	0,8	12,7
treprostinil	0,0	0,0	0,0	0,0	0,0	6,2
edoxaban	-	-	-	0,0	0,4	>100

€ 1.620.000.000

Farmaci Antiaggreganti nella prevenzione cardiovascolare

Farmaci Antiaggreganti nella prevenzione cardiovascolare

Sezione 4

Consumi e spesa per classe terapeutica

Categoria terapeutica		Spesa lorda pro capite	% *	Δ % 18-17	DDD/1000 ab die	% *
B – Sangue e organi emopoietici		**7,91**		**-2,2**	**87,1**	
enoxaparina		1,78	22,5	-13,2	1,9	2,2
acido acetilsalicilico	**2.616.000**	1,15	14,5	0,2	43,6	50,1
clopidogrel	**294.000**	1,02	12,9	4,6	4,9	5,6
nadroparina calcica		0,55	7,0	-17,0	0,5	0,6
acido folico		0,47	5,9	7,3	5,7	6,6
edoxaban		0,31	3,9	>100	0,2	0,2
ferroso solfato		0,25	3,2	2,1	2,2	2,5
clopidogrel/acido acetilsalicilico		0,24	3,0	0,6	0,7	0,9
ticlopidina		0,23	2,9	-14,0	2,5	2,9

Farmaci Antiaggreganti nella prevenzione cardiovascolare

Tabella 4.10. Primi trenta principi attivi per consumo in regime di assistenza convenzionata di classe A-SSN: confronto 2018-2017

ATC	Principio attivo	DDD/1000 ab die	%*	Rango 2018	Rango 2017
C	ramipril	61,8	6,3	1	1
C	atorvastatina	44,1	4,5	2	3
B	acido acetilsalicilico	43,6	4,5	3	2
C	amlodipina	26,5	2,7	4	4
C	furosemide	24,5	2,5	5	5
A	metformina	21,6	2,2	6	6
A	pantoprazolo	21,5	2,2	7	7
H	levotiroxina	20,3	2,1	8	8
A	omeprazolo	16,5	1,7	9	9
C	nebivololo	15,0	1,5	10	11
A	lansoprazolo	14,5	1,5	11	10
C	simvastatina	13,8	1,4	12	13
C	valsartan	13,3	1,4	13	12
A	esomeprazolo	12,7	1,3	14	14
A	colecalciferolo	12,3	1,3	15	16
C	rosuvastatina	12,2	1,2	16	15
C	bisoprololo	10,5	1,1	17	18
C	olmesartan	10,2	1,0	18	24
G	tamsulosina	10,0	1,0	19	20
C	enalapril	9,3	0,9	20	19
C	lercanidipina	9,3	0,9	21	21
C	valsartan/idroclorotiazide	9,0	0,9	22	17
C	telmisartan	8,7	0,9	23	23
C	atenololo	8,4	0,9	24	22
B	cianocobalamina	8,3	0,9	25	30
G	alfuzosina	8,3	0,8	26	27
C	candesartan	8,2	0,8	27	26
C	irbesartan	8,2	0,8	28	25
C	olmesartan/idroclorotiazide	8,1	0,8	29	35
G	dutasteride	7,8	0,8	30	34

Farmaci Antiaggreganti nella prevenzione cardiovascolare

ESC European Society of Cardiology
European Heart Journal (2018) **39**, 119–177
doi:10.1093/eurheartj/ehx393

ESC GUIDELINES

2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation

The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC)

Maintenance antithrombotic strategy after ST-elevation myocardial infarction

Recommendations	Class[a]	Level[b]
Antiplatelet therapy with low-dose aspirin (75–100 mg) is indicated.[329]	I	A

Lancet 1996 Nov 16; 348: 1329-39

Farmaci Antiaggreganti nella prevenzione cardiovascolare

Farmaci Antiaggreganti nella prevenzione cardiovascolare

forward 20 1997/2017

ISO

SPREAD

Stroke Prevention And Educational Awareness Diffusion

Raccomandazione 11.1.b	Forte a favore	Grado A

Nei pazienti con TIA e ictus ischemico non cardioembolico è raccomandato il trattamento antiaggregante con ASA 100-325 mg/die rispetto a nessuna terapia*.

*GPP

Per il trattamento prolungato, il gruppo ISO-SPREAD suggerisce 100 mg/die.

Farmaci Antiaggreganti nella prevenzione cardiovascolare

Neurol Sci (2016) 37:181–189
DOI 10.1007/s10072-015-2412-x

REVIEW ARTICLE

Aspirin resistance and other aspirin-related concerns

Gaoyu Cai[1] · Weijun Zhou[2] · Ya Lu[3] · Peili Chen[2] · Zhongjiao Lu[1] · Yi Fu[1]

Farmaci Antiaggreganti nella prevenzione cardiovascolare

Neurol Sci (2016) 37:181–189
DOI 10.1007/s10072-015-2412-x

REVIEW ARTICLE

Aspirin resistance and other aspirin-related concerns

The resistance and gene polymorphisms of aspirin

A recent study of the resistance mechanisms for aspirin revealed that genetic polymorphisms are closely related to aspirin resistance. Mutations in the nucleotide level may affect the sensitivity of various sites to aspirin, which causes aspirin resistance.

Cox-1 is one of the key enzymes in the production of TXA_2 from arachidonic acid. Its polymorphism may affect COX-1 activity and thus affect the antiplatelet effect of aspirin. The polymorphisms of C50T, -A842G and -A1676G on COX-1 are considered to be related to aspirin resistance

Neurol Sci (2016) 37:181–189

Farmaci Antiaggreganti nella prevenzione cardiovascolare

Journal of Thrombosis and Haemostasis, **10**: 1220–1230 DOI: 10.1111/j.1538-7836.2012.04723.x

IN FOCUS

The recovery of platelet cyclooxygenase activity explains interindividual variability in responsiveness to low-dose aspirin in patients with and without diabetes

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J Thromb Haemost 2012; **10**: 1220–30.

Farmaci Antiaggreganti nella prevenzione cardiovascolare

Journal of Thrombosis and Haemostasis, **10**: 1220–1230 DOI: 10.1111/j.1538-7836.2012.04723.x

IN FOCUS

The recovery of platelet cyclooxygenase activity explains interindividual variability in responsiveness to low-dose aspirin in patients with and without diabetes

Results and Conclusions. Platelet TXB_2 production was profoundly suppressed at 12 h in both groups. Serum TXB_2 recovered linearly, with a large interindividual variability in slope. Diabetic patients in the third tertile of recovery slopes (≥ 0.10 ng mL^{-1} h^{-1}) showed significantly higher mean platelet volume and body mass index, and younger age. Higher body weight was the only independent predictor of a faster recovery in non-diabetics. Aspirin 100 mg twice daily completely reversed the abnormal TXB_2 recovery in both groups.

J Thromb Haemost 2012; **10**: 1220–30.

ASA nella prevenzione primaria

Lancet 2018; 392: 387–99

Effects of aspirin on risks of vascular events and cancer according to bodyweight and dose: analysis of individual patient data from randomised trials

Peter M Rothwell, Nancy R Cook, J Michael Gaziano, Jacqueline F Price, Jill F F Belch, Maria Carla Roncaglioni, Takeshi Morimoto, Ziyah Mehta

Lancet 2018; 392: 387–99

ASA nella prevenzione primaria

	Bodyweight <70 kg				Bodyweight ≥70 kg				All			
	Aspirin	Control	HR (95% CI)	p value	Aspirin	Control	HR (95% CI)	p value	Aspirin	Control	HR (95% CI)	p value
Stroke												
All	198	279	0·71 (0·59–0·85)	0·0002	302	302	1·00 (0·86–1·18)	0·97	500	581	0·86 (0·76–0·97)	0·014
Women	161	218	0·74 (0·60–0·90)	..	147	172	0·86 (0·69–1·08)	..	308	390	0·79 (0·68–0·92)	..
Men	37	61	0·62 (0·41–0·93)	..	155	130	1·18 (0·94–1·49)	..	192	191	1·00 (0·82–1·22)	..
With diabetes	45	73	0·60 (0·41–0·87)	..	63	75	0·84 (0·60–1·18)	..	108	148	0·72 (0·56–0·93)	..
Smokers	59	77	0·74 (0·53–1·04)	..	86	56	1·57 (1·12–2·19)	..	145	133	1·09 (0·86–1·37)	..
Age ≥70 years	64	83	0·70 (0·51–0·97)	..	54	60	0·91 (0·63–1·32)	..	118	143	0·79 (0·62–1·01)	..
Myocardial infarction												
All	165	199	0·81 (0·66–1·00)	0·046	381	426	0·90 (0·78–1·03)	0·14	546	625	0·87 (0·78–0·98)	0·019
Women	120	131	0·91 (0·71–1·16)	..	152	143	1·08 (0·86–1·36)	..	272	274	1·00 (0·84–1·18)	..
Men	45	68	0·64 (0·44–0·93)	..	229	283	0·81 (0·68–0·96)	..	274	351	0·77 (0·66–0·90)	..
With diabetes	35	47	0·70 (0·45–1·09)	..	114	97	1·21 (0·92–1·58)	..	149	144	1·03 (0·82–1·30)	..
Smokers	68	63	1·05 (0·75–1·48)	..	145	138	1·06 (0·84–1·34)	..	213	201	1·06 (0·87–1·28)	..
Age ≥70 years	35	46	0·64 (0·41–1·00)	..	43	37	1·25 (0·80–1·94)	..	78	83	0·90 (0·66–1·23)	..
Vascular death												
All	128	160	0·79 (0·63–1·00)	0·048	296	274	1·09 (0·93–1·29)	0·30	424	434	0·98 (0·86–1·12)	0·76
Women	90	114	0·78 (0·59–1·03)	..	107	100	1·09 (0·83–1·43)	..	197	214	0·92 (0·76–1·12)	..
Men	38	46	0·85 (0·55–1·30)	..	189	174	1·09 (0·88–1·33)	..	227	220	1·03 (0·86–1·24)	..
With diabetes	26	42	0·59 (0·36–0·97)	..	76	68	1·14 (0·82–1·58)	..	102	110	0·92 (0·71–1·21)	..
Smokers	41	51	0·78 (0·52–1·18)	..	89	88	1·02 (0·76–1·38)	..	130	139	0·93 (0·74–1·19)	..
Age ≥70 years	51	67	0·67 (0·47–0·97)	..	72	54	1·38 (0·97–1·97)	..	123	121	0·99 (0·77–1·27)	..
All cardiovascular events												
All	419	537	0·77 (0·68–0·87)	<0·0001	791	840	0·95 (0·86–1·04)	0·24	1210	1377	0·88 (0·81–0·95)	0·0008
Women	322	400	0·80 (0·69–0·92)	..	346	362	0·97 (0·83–1·12)	..	668	762	0·88 (0·79–0·97)	..
Men	97	137	0·70 (0·54–0·91)	..	445	478	0·92 (0·81–1·05)	..	542	615	0·87 (0·77–0·98)	..
With diabetes	91	125	0·69 (0·53–0·91)	..	196	183	1·08 (0·88–1·32)	..	287	308	0·92 (0·78–1·08)	..
Smokers	143	158	0·88 (0·70–1·10)	..	259	222	1·19 (0·99–1·42)	..	402	380	1·05 (0·92–1·21)	..
Age ≥70 years	125	159	0·70 (0·55–0·88)	..	135	119	1·16 (0·91–1·49)	..	260	278	0·90 (0·76–1·07)	..

HR=hazard ratio.

Table 1: Pooled analysis of the effect of low-dose aspirin versus control in primary prevention of vascular events according to bodyweight, age, sex, presence of diabetes, and current smoking

Lancet 2018; 392: 387–99

ASA nella prevenzione primaria

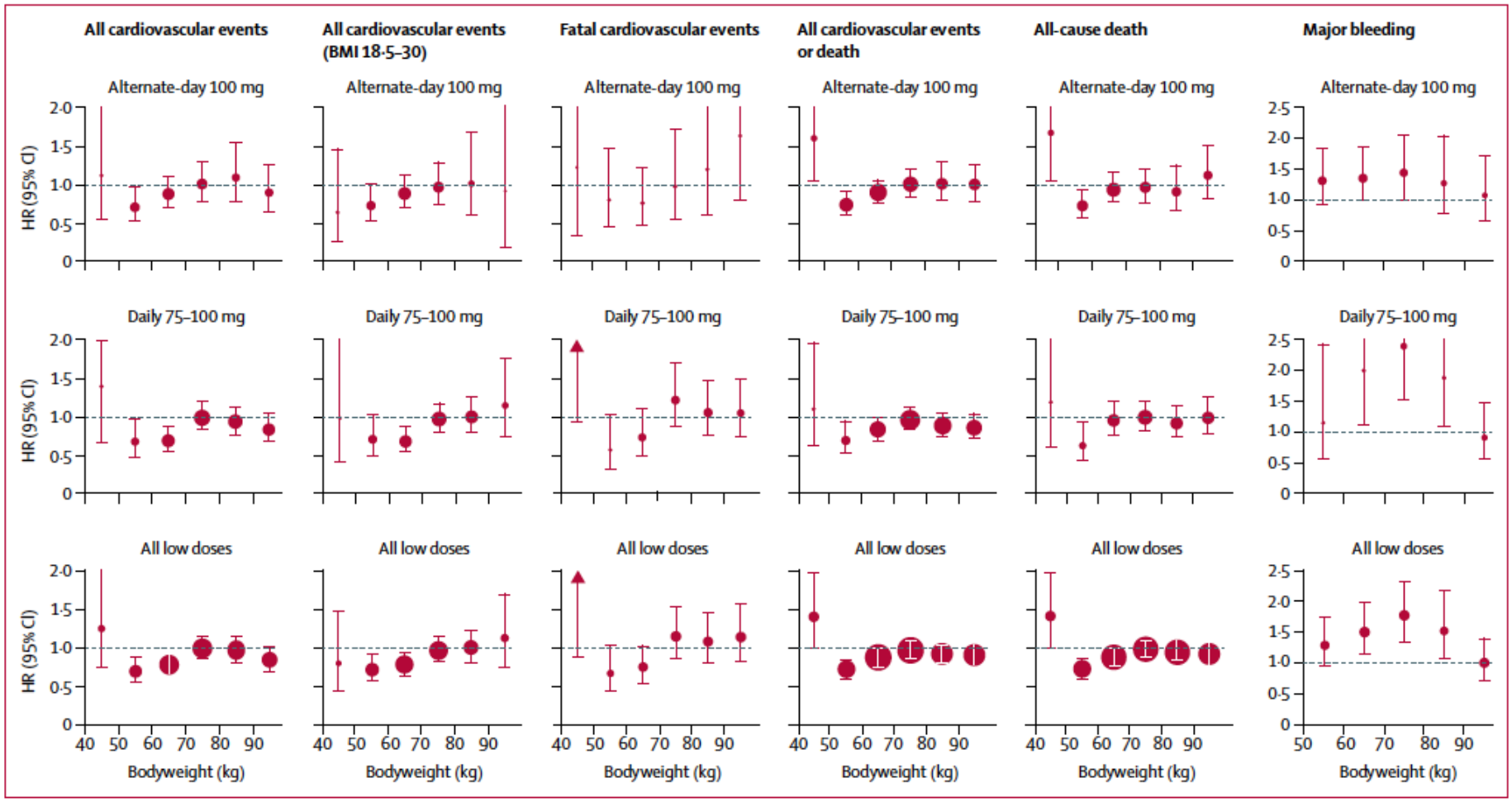


Figure 1: **Effect of low-dose aspirin versus control on risks of cardiovascular events, death, and major bleeding according to bodyweight in trials of aspirin in primary prevention**
The size of the circles representing the point estimates of the HRs is proportional to the inverse of the variance of the estimate. BMI=body-mass index. HR=hazard ratio.

Lancet 2018; 392: 387–99

ASA nella prevenzione primaria

Effects of aspirin on risks of vascular events and cancer according to bodyweight and dose: analysis of individual patient data from randomised trials

Peter M Rothwell, Nancy R Cook, J Michael Gaziano, Jacqueline F Price, Jill F F Belch, Maria Carla Roncaglioni, Takeshi Morimoto, Ziyah Mehta

Interpretation Low doses of aspirin (75–100 mg) were only effective in preventing vascular events in patients weighing less than 70 kg, and had no benefit in the 80% of men and nearly 50% of all women weighing 70 kg or more. By contrast, higher doses of aspirin were only effective in patients weighing 70 kg or more. Given that aspirin's effects on other outcomes, including cancer, also showed interactions with body size, a one-dose-fits-all approach to aspirin is unlikely to be optimal, and a more tailored strategy is required.

Lancet 2018; 392: 387–99

Farmaci Antiaggreganti nella prevenzione cardiovascolare

forward 20 1997/2017

SPREAD
Stroke Prevention And Educational Awareness Diffusion

Sintesi 11.1.k

La complessità delle numerose analisi statistiche derivate dagli studi pubblicati sui farmaci antiaggreganti piastrinici, impiegati sia da soli sia in associazione, fa rilevare come, a fronte delle diverse situazioni cliniche presentate dal paziente, sempre più il medico debba individualizzare le scelte. Sebbene l'ASA rimanga il farmaco più usato nella prevenzione secondaria degli eventi cerebrovascolari, è doveroso prendere in considerazione la terapia con clopidogrel in pazienti con intolleranza o documentata resistenza all'ASA, e che abbiano comunque presentato un nuovo evento in corso di trattamento con ASA o con l'associazione tra dipiridamolo ed ASA.

Possibile ASA 100 mg x 2 al dì ?

Farmaci Antiaggreganti nella prevenzione cardiovascolare

Prevenzione secondaria

- Quale farmaco
  Farmaco o farmaci

- Quali pazienti

Prevenzione secondaria nei

Pazienti stabili
con ictus o TIA pregresso

Farmaci Antiaggreganti nella prevenzione cardiovascolare

Lancet 2004; 364: 331–37

Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial

Hans-Christoph Diener, Julien Bogousslavsky, Lawrence M Brass, Claudio Cimminiello, Laszlo Csiba, Markku Kaste, Didier Leys, Jordi Matias-Guiu, Hans-Jürgen Rupprecht, on behalf of the MATCH investigators*

Farmaci Antiaggreganti nella prevenzione cardiovascolare

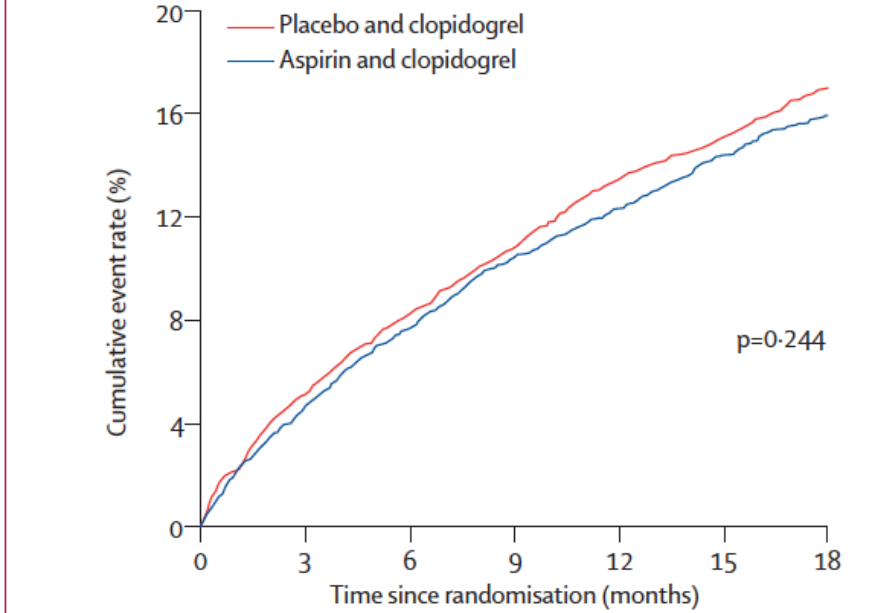
Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial

Methods We did a randomised, double-blind, placebo-controlled trial to compare aspirin (75 mg/day) with placebo in 7599 high-risk patients with recent ischaemic stroke or transient ischaemic attack and at least one additional vascular risk factor who were already receiving clopidogrel 75 mg/day.

Lancet 2004; 364: 331–37

Farmaci Antiaggreganti nella prevenzione cardiovascolare

Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial



Patients at risk

Aspirin and clopidogrel	3797	3576	3440	3321	3229	3130	2441
Placebo and clopidogrel	3802	3576	3439	3326	3200	3119	2446

Figure 2: **Kaplan-Meier curves for cumulative rates of primary endpoint events**

Lancet 2004; 364: 331–37

Farmaci Antiaggreganti nella prevenzione cardiovascolare

Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial

Interpretation Adding aspirin to clopidogrel in high-risk patients with recent ischaemic stroke or transient ischaemic attack is associated with a non-significant difference in reducing major vascular events. However, the risk of life-threatening or major bleeding is increased by the addition of aspirin.

Lancet 2004; 364: 331–37

Farmaci Antiaggreganti nella prevenzione cardiovascolare

The NEW ENGLAND JOURNAL of MEDICINE

N Engl J Med 2006;354:1706-17.

ORIGINAL ARTICLE

Clopidogrel and Aspirin versus Aspirin Alone for the Prevention of Atherothrombotic Events

Deepak L. Bhatt, M.D., Keith A.A. Fox, M.B., Ch.B., Werner Hacke, M.D., Peter B. Berger, M.D., Henry R. Black, M.D., William E. Boden, M.D., Patrice Cacoub, M.D., Eric A. Cohen, M.D., Mark A. Creager, M.D., J. Donald Easton, M.D., Marcus D. Flather, M.D., Steven M. Haffner, M.D., Christian W. Hamm, M.D., Graeme J. Hankey, M.D., S. Claiborne Johnston, M.D., Koon-Hou Mak, M.D., Jean-Louis Mas, M.D., Gilles Montalescot, M.D., Ph.D., Thomas A. Pearson, M.D., P. Gabriel Steg, M.D., Steven R. Steinhubl, M.D., Michael A. Weber, M.D., Danielle M. Brennan, M.S., Liz Fabry-Ribaudo, M.S.N., R.N., Joan Booth, R.N., and Eric J. Topol, M.D., for the CHARISMA Investigators*

Farmaci Antiaggreganti nella prevenzione cardiovascolare

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Clopidogrel and Aspirin versus Aspirin Alone for the Prevention of Atherothrombotic Events

METHODS

We randomly assigned 15,603 patients with either clinically evident cardiovascular disease or multiple risk factors to receive clopidogrel (75 mg per day) plus low-dose aspirin (75 to 162 mg per day) or placebo plus low-dose aspirin and followed them for a median of 28 months. The primary efficacy end point was a composite of myocardial infarction, stroke, or death from cardiovascular causes.

N Engl J Med 2006;354:1706-17.

Farmaci Antiaggreganti nella prevenzione cardiovascolare

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Clopidogrel and Aspirin versus Aspirin Alone for the Prevention of Atherothrombotic Events

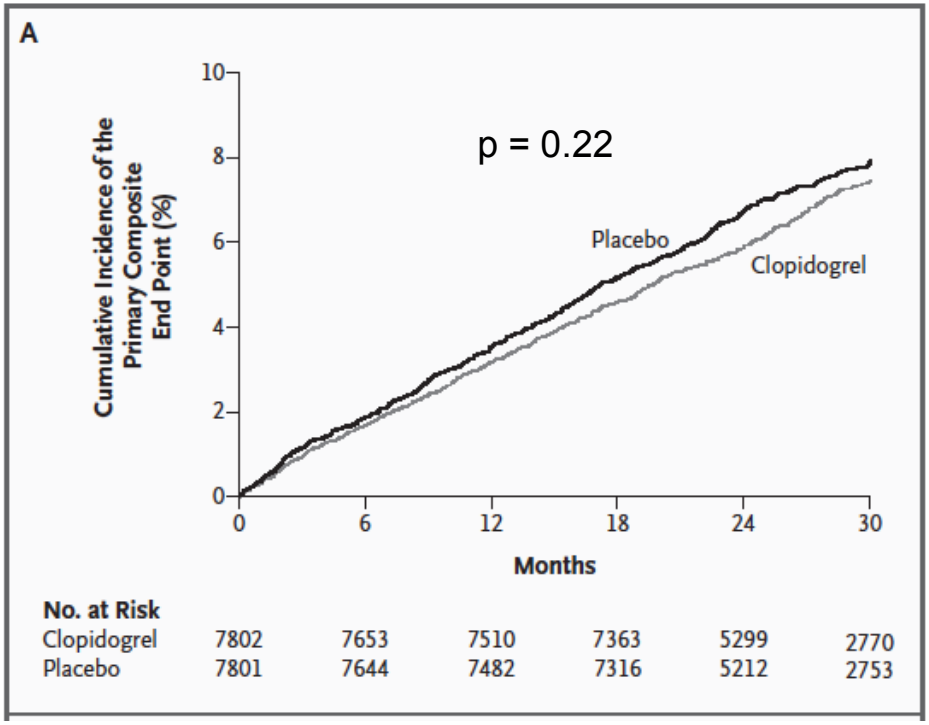


Figure 1. Cumulative Incidence of the Primary End Point (Panel A)

N Engl J Med 2006;354:1706-17.

Farmaci Antiaggreganti nella prevenzione cardiovascolare

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Clopidogrel and Aspirin versus Aspirin Alone for the Prevention of Atherothrombotic Events

CONCLUSIONS

In this trial, there was a suggestion of benefit with clopidogrel treatment in patients with symptomatic atherothrombosis and a suggestion of harm in patients with multiple risk factors. Overall, clopidogrel plus aspirin was not significantly more effective than aspirin alone in reducing the rate of myocardial infarction, stroke, or death from cardiovascular causes. (ClinicalTrials.gov number, NCT00050817.)

N Engl J Med 2006;354:1706-17.

Prevenzione secondaria nei

Pazienti acuti con ictus o TIA in atto

C'è qualcosa di meglio dell'ASA ?

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.

Farmaci Antiaggreganti nella prevenzione cardiovascolare

ORIGINAL ARTICLE

Ticagrelor versus Aspirin in Acute Stroke or Transient Ischemic Attack

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.

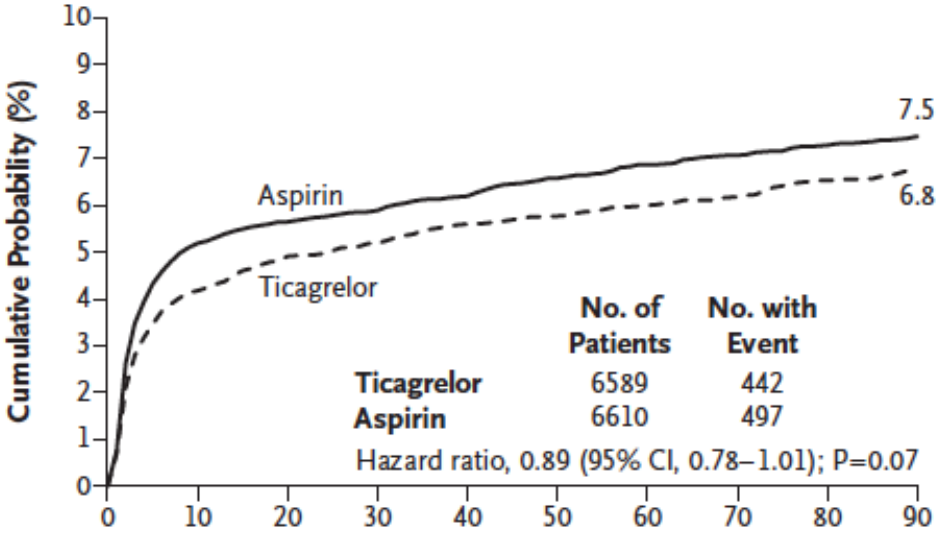
N Engl J Med 2016;375:35-43.

Farmaci Antiaggreganti nella prevenzione cardiovascolare

ORIGINAL ARTICLE

Ticagrelor versus Aspirin in Acute Stroke or Transient Ischemic Attack

A Primary End Point: Stroke, Myocardial Infarction, or Death



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

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

Farmaci Antiaggreganti nella prevenzione cardiovascolare

ORIGINAL ARTICLE

Ticagrelor versus Aspirin in Acute Stroke or Transient Ischemic Attack

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.)

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

Prevenzione secondaria nei

Pazienti acuti
con ictus o TIA in atto

E' utile associare qualcosa all'ASA ?

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 19, 2018 VOL. 379 NO. 3

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*

N Engl J Med 2018;379:215-25

Farmaci Antiaggreganti nella prevenzione cardiovascolare

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*

METHODS

In a randomized trial, we assigned patients with minor ischemic stroke or high-risk TIA to receive either clopidogrel at a loading dose of 600 mg on day 1, followed by 75 mg per day, plus aspirin (at a dose of 50 to 325 mg per day) or the same range of doses of aspirin alone. The dose of aspirin in each group was selected by the site investigator. The primary efficacy outcome in a time-to-event analysis was the risk of a composite of major ischemic events, which was defined as ischemic stroke, myocardial infarction, or death from an ischemic vascular event, at 90 days.

N Engl J Med 2018;379:215-25

Farmaci Antiaggreganti nella prevenzione cardiovascolare

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

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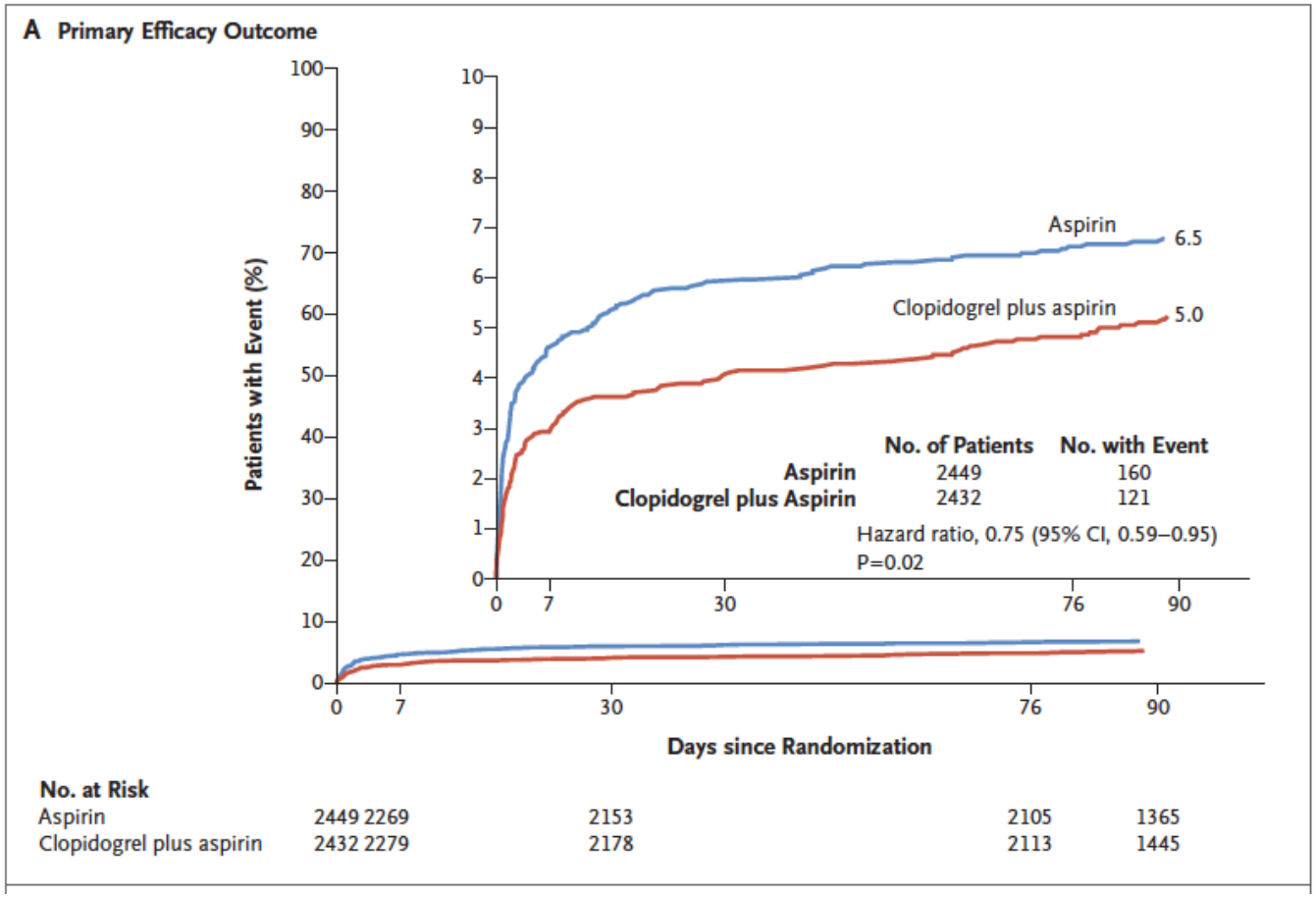

N Engl J Med 2018;379:215-25

Farmaci Antiaggreganti nella prevenzione cardiovascolare

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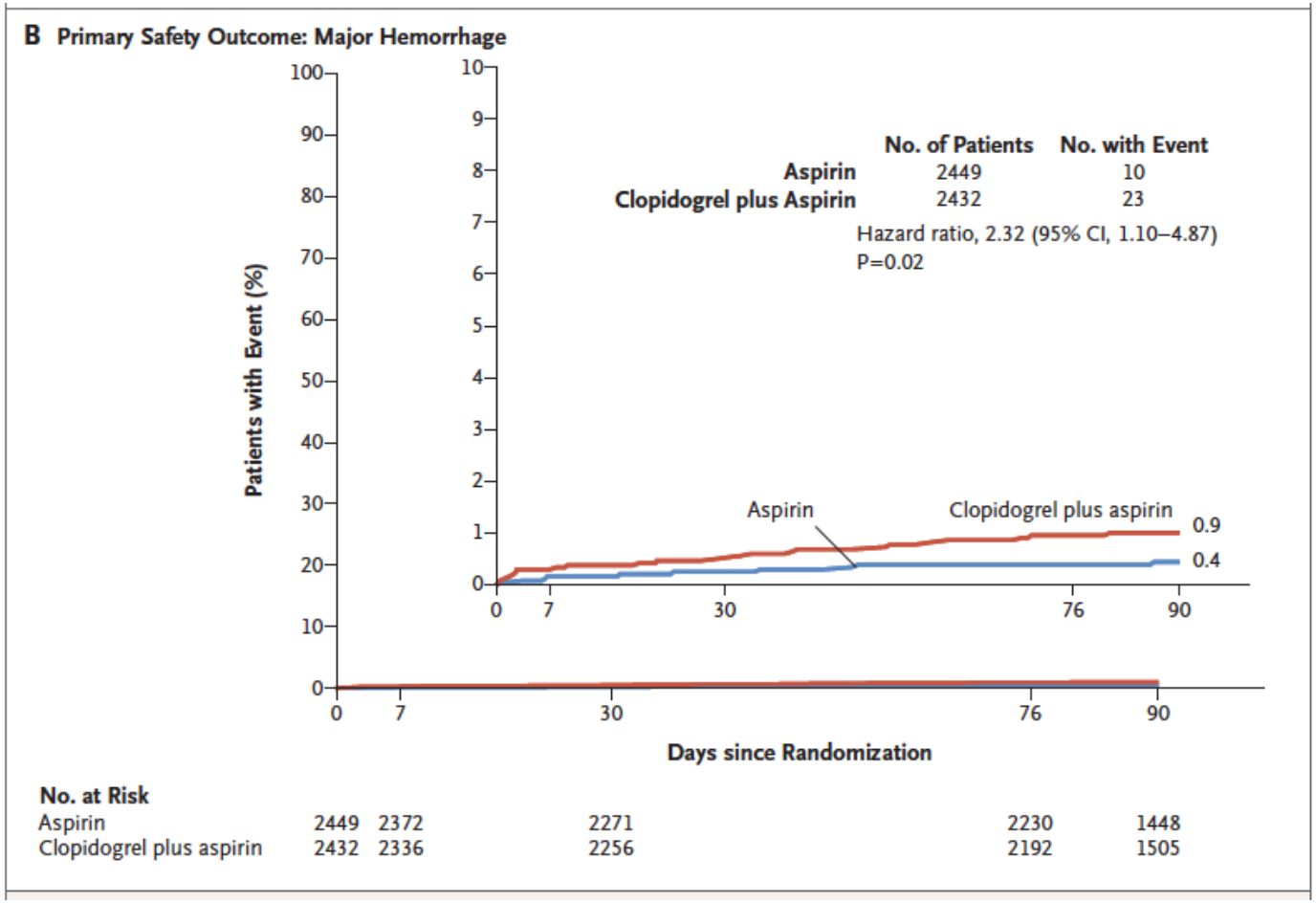

N Engl J Med 2018;379:215-25

Farmaci Antiaggreganti nella prevenzione cardiovascolare

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

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CONCLUSIONS

In patients with minor ischemic stroke or high-risk TIA, those who received a combination of clopidogrel and aspirin had a lower risk of major ischemic events but a higher risk of major hemorrhage at 90 days than those who received aspirin alone.

N Engl J Med 2018;379:215-25

Farmaci Antiaggreganti nella prevenzione cardiovascolare

Articles

Lancet 2018; 391: 850–59

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

*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**

Farmaci Antiaggreganti nella prevenzione cardiovascolare

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

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Methods We did an international, prospective, randomised, open-label, blinded-endpoint trial in adult participants with ischaemic stroke or transient ischaemic attack (TIA) within 48 h of onset. Participants were assigned in a 1:1 ratio using computer randomisation to receive loading doses and then 30 days of intensive antiplatelet therapy (combined aspirin 75 mg, clopidogrel 75 mg, and dipyridamole 200 mg twice daily) or guideline-based therapy (comprising either clopidogrel alone or combined aspirin and dipyridamole).

Lancet 2018; 391: 850–59

Farmaci Antiaggreganti nella prevenzione cardiovascolare

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

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	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%)	..	..

Lancet 2018; 391: 850–59

Farmaci Antiaggreganti nella prevenzione cardiovascolare

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

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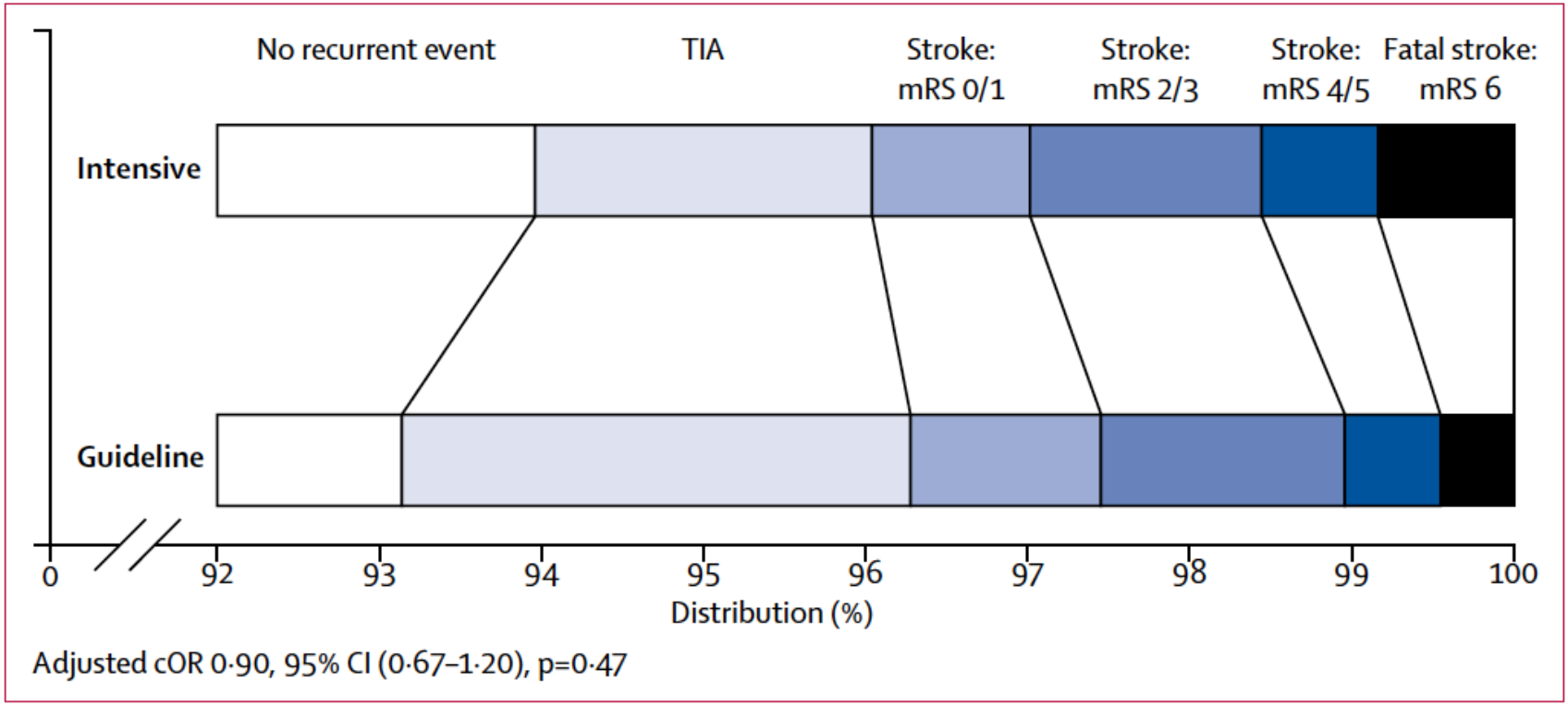

Figure 2: **Distribution of recurrent stroke and TIA by severity**

Lancet 2018; 391: 850–59

Farmaci Antiaggreganti nella prevenzione cardiovascolare

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

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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)				
Fatal or major[20]	39/1540 (3%)	17/1530 (1%)	2·23 (1·25–3·96)	0·0063
Intracranial bleeding	16/1540 (1%)	5/1530 (<1%)	3·14 (1·14–8·61)	0·026
Intracerebral	13/1540 (1%)	4/1530 (<1%)	3·26 (1·05–10·06)	0·040
Subdural or extradural	2/1540 (<1%)	0	..	NC
Fatal	6/1540 (<1%)	3/1530 (<1%)	2·43 (0·59–10·01)	0·22
Major	9/1540 (1%)	1/1530 (<1%)	8·79 (1·10–69·95)	0·040
Fatal or major	15/1540 (1%)	4/1530 (<1%)	3·84 (1·26–11·63)	0·018
Extracranial bleeding	293/1541 (19%)	135/1531 (9%)	2·37 (1·93–2·91)	<0·0001
Gastrointestinal	48/1540 (3%)	34/1530 (2%)	1·39 (0·89–2·16)	0·15
Other	255/1541 (17%)	104/1531 (7%)	2·70 (2·14–3·39)	<0·0001

Lancet 2018; 391: 850–59

Farmaci Antiaggreganti nella prevenzione cardiovascolare

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

*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**

Interpretation Among patients with recent cerebral ischaemia, intensive antiplatelet therapy did not reduce the incidence and severity of recurrent stroke or TIA, but did significantly increase the risk of major bleeding. Triple antiplatelet therapy should not be used in routine clinical practice.

Lancet 2018; 391: 850–59

Farmaci Antiaggreganti nella prevenzione cardiovascolare

forward 20 1997/2017

SPREAD
Stroke Prevention And Educational Awareness Diffusion

Raccomandazione 11.1.e **Debole a favore**

In pazienti con TIA o ictus minore di origine aterotrombotica, giudicati ad alto rischio di recidive (ad esempio per la presenza di microemboli derivanti da placca carotidea alla monitorizzazione con doppler transcranico, o per la presenza di documentata stenosi intracranica), è indicato il trattamento per 1-3 mesi con la doppia antiaggregazione ASA 100 mg + clopidogrel 75 mg.

Prevenzione secondaria nei

Pazienti acuti
con SCA o IMA

E' utile associare qualcosa all'ASA ?

Farmaci Antiaggreganti nella prevenzione cardiovascolare

Am J Cardiol 2008;101:960–966

Meta-Analysis of the Efficacy and Safety of *Clopidogrel* Plus *Aspirin* as Compared to Antiplatelet Monotherapy for the Prevention of Vascular Events

Ashna D.K. Bowry, MBChB, M. Alan Brookhart, PhD, and Niteesh K. Choudhry, MD, PhD*

Farmaci Antiaggreganti nella prevenzione cardiovascolare

Meta-Analysis of the Efficacy and Safety of *Clopidogrel* Plus *Aspirin* as Compared to Antiplatelet Monotherapy for the Prevention of Vascular Events

Ashna D.K. Bowry, MBChB, M. Alan Brookhart, PhD, and Niteesh K. Choudhry, MD, PhD*

Table 1
Characteristics of included trials

Characteristic	ACS			PCI			Other	
	CURE	COMMIT	CLARITY	PCI-CURE	CREDO	PCI-CLARITY	MATCH	CHARISMA
Publication year	2001	2005	2005	2001	2002	2005	2004	2006
Patients	Unstable angina/ NSTEMI	STEMI	STEMI	PCI substudy of CURE	CAD with symptoms of ischemia referred for PCI	PCI substudy of CLARITY	Recent ischemic stroke/TIA and cardiac risk factors	Established vascular disease or multiple risk factors
Intervention	Clopidogrel + aspirin vs aspirin alone	Clopidogrel + aspirin vs aspirin alone	Clopidogrel + aspirin vs aspirin alone	Clopidogrel + aspirin vs aspirin alone*	Clopidogrel + aspirin vs aspirin alone	Clopidogrel + aspirin vs aspirin alone and fibrinolytic†	Clopidogrel + aspirin vs clopidogrel alone	Clopidogrel + aspirin vs aspirin alone
No. of patients	12,562	45,852	2,658	1,863	2,116	19,185	7,599	15,603
Follow up, maximum (mean)	12 mo (9 mo)	28 days or discharge	30 days	12 mo (8 mo)	12 mo	30 days	18 mo	— (28 mo)‡
Patient characteristics								
Age (yrs)	64.2 ± 64.2	61.3 ± 61.4	57.7 ± 57.2	61.6 ± 61.4	61.5 ± 61.8	57.7 ± 56.9	66.5 ± 66.1	64.0 ± 64.0
Men	3,839/3,887	16,595/16,498	914/940	757/765	744/766	6,903/6,911	2,382/2,396	5,486/5,473
Previous MI	2,029/2,015	1,972/1,846	359/349	82/71	353/366	16/17	174/189	2,672/2,725
Hypertension	3,750/3,642	9,935/9,903	—	365/399	710/740	52/51	2,972/2,973	5,719/5,764
Previous TIA/stroke	274/232	—	—	—	67/74	19/19	1,727/1,696	1,942/1,895
Hypercholesterolemia	—	—	—	344/328	780/800	41/41	2,126/2,154	5,748/5,787
Diabetes mellitus	1,405/1,435	—	289/286	249/255	290/270	133/149	2,598/2,599	1,360/1,295
Smoker	3,790/3,841	—	887/865	406/396	339/313	480/469	1,825/1,772	284/271
Previous PCI	1,107/113§	—	84/85	176/185	902/916	54/48	—	398/434
Previous CABG	—	—	—	157/175	41/42	—	—	736/733
ST-segment depression	2,642/2,646	1,579/1,590	—	567/571	—	—	—	—
β-blocker use	664/696	—	—	—	—	1,554/1,559	1,457/1,533	3,678/3,690
Fibrinolysis	427/396	—	933/930	—	—	1,748/1,733	11,407/11,387	4,522/4,605

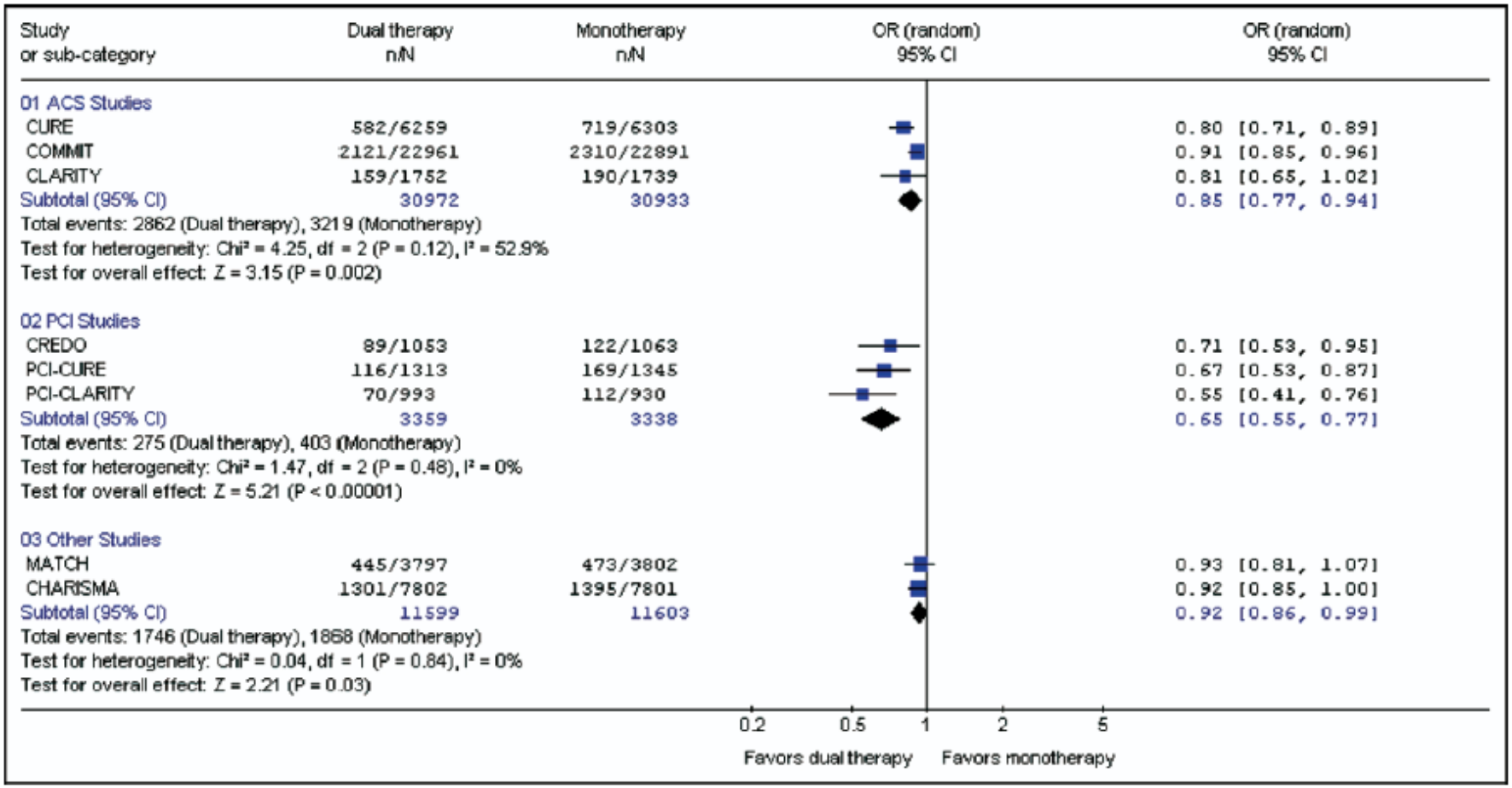
CABG = coronary artery bypass graft; CAD = coronary artery disease; NSTEMI = non-ST-segment elevation MI; STEMI = ST-segment elevation MI; TIA = transient ischemic attack.
* After PCI, patients received open-label clopidogrel or ticlopidine and aspirin for 2 to 4 weeks.
† Patients who underwent stenting received open-label clopidogrel after diagnostic angiography.
‡ Median follow-up time.
§ This includes prior PCI or CABG.

Am J Cardiol 2008;101:960–966

Farmaci Antiaggreganti nella prevenzione cardiovascolare

Meta-Analysis of the Efficacy and Safety of *Clopidogrel* Plus *Aspirin* as Compared to Antiplatelet Monotherapy for the Prevention of Vascular Events

Ashna D.K. Bowry, MBChB, M. Alan Brookhart, PhD, and Niteesh K. Choudhry, MD, PhD*



Plotted ORs and 95% CIs for major coronary events.

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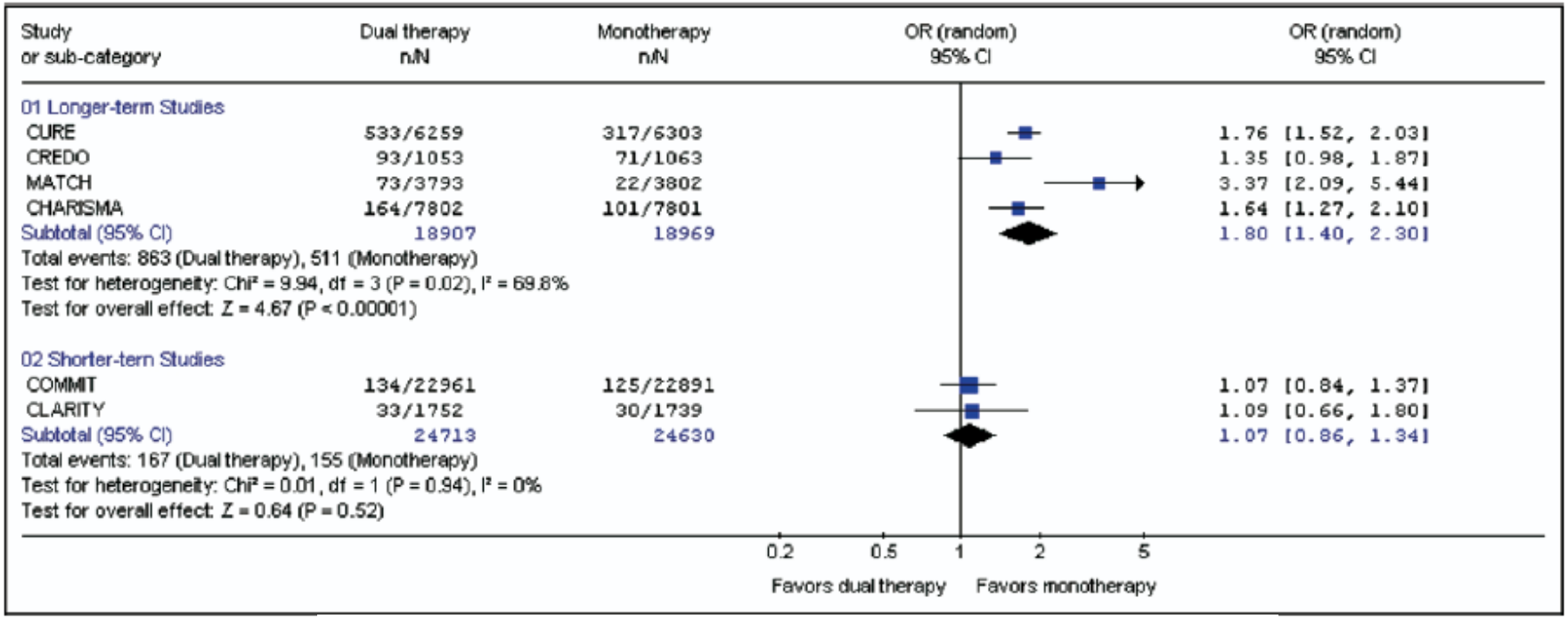

Plotted ORs and 95% CIs for major bleeding.

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Farmaci Antiaggreganti nella prevenzione cardiovascolare

Meta-Analysis of the Efficacy and Safety of *Clopidogrel* Plus *Aspirin* as Compared to Antiplatelet Monotherapy for the Prevention of Vascular Events

Ashna D.K. Bowry, MBChB, M. Alan Brookhart, PhD, and Niteesh K. Choudhry, MD, PhD*

Net clinical benefit from combined clopidogrel and aspirin therapy compared with aspirin monotherapy

Patient Subgroup	No. Needed to Treat (to Prevent 1 Major Coronary Event)*	No. Needed to Harm (to Cause 1 Major Bleeding Event)†	Net Clinical Benefit‡
ACS	67§	293	−227
PCI	9‖	114	−105

Am J Cardiol 2008;101:960–966

Farmaci Antiaggreganti nella prevenzione cardiovascolare

ESC European Society of Cardiology
European Heart Journal (2018) **39**, 213–254
doi:10.1093/eurheartj/ehx419

ESC GUIDELINES

2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS

The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS)

2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation

The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC)

2018 ESC/EACTS Guidelines on myocardial revascularization

The Task Force on myocardial revascularization of the European Society of Cardiology (ESC) and European Association for Cardio-Thoracic Surgery (EACTS)

Developed with the special contribution of the European Association for Percutaneous Cardiovascular Interventions (EAPCI)

e in prevenzione secondaria: quale!

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Farmaci Antiaggreganti nella prevenzione cardiovascolare

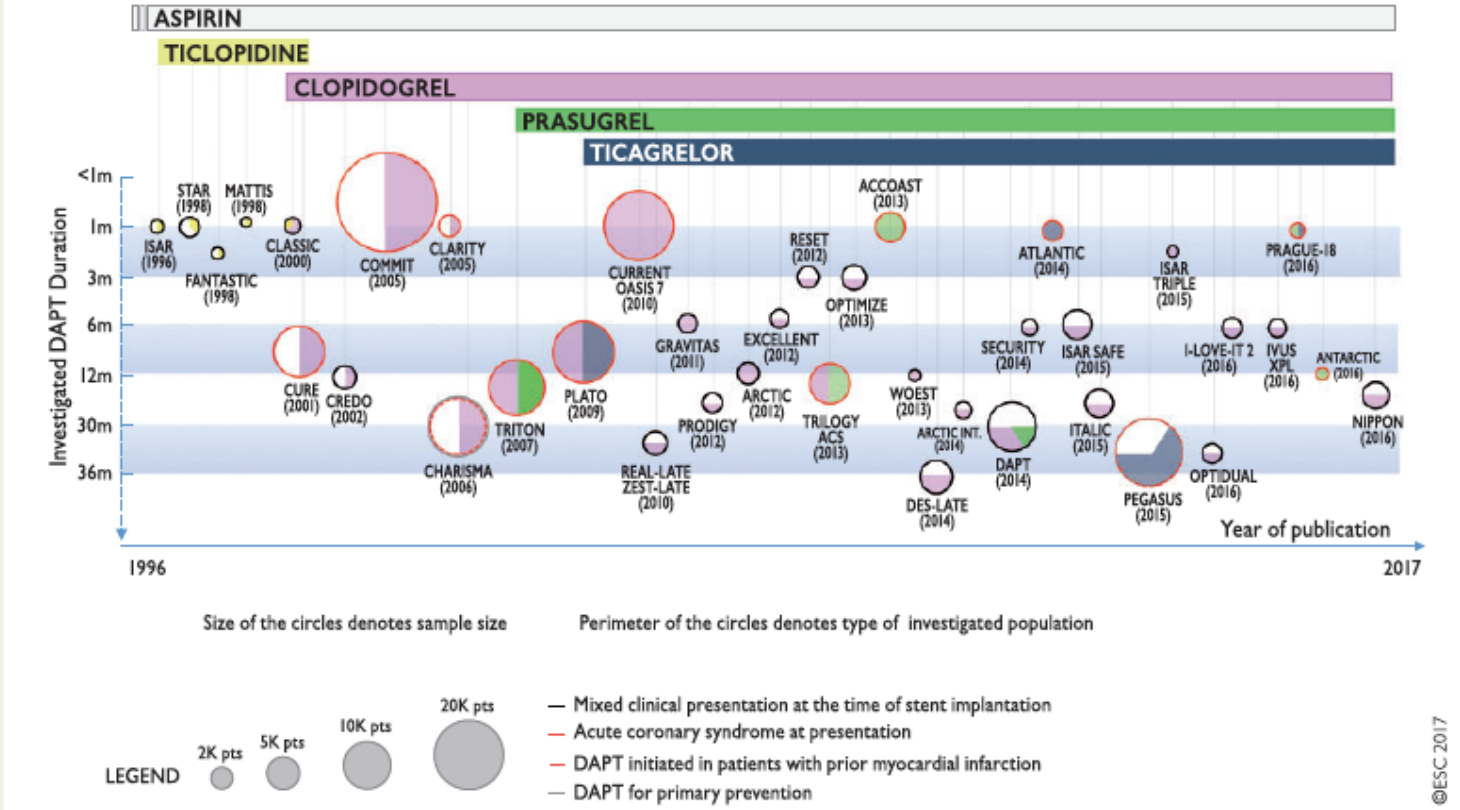

Figure 1 History of dual antiplatelet therapy (DAPT) in patients with coronary artery disease. The size of the circles denotes sample size. The colours of perimeters identify the type of included patient populations within each study. The colours within each circle identify the antiplatelet agent(s) investigated. Head-to-head studies comparing similar durations of two different antiplatelet strategies are shown with a vertical line, whereas those investigating different treatment durations are shown with a horizontal line. Studies investigating different treatment strategies or regimens and not

European Heart Journal (2018) **39**, 213–254

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Table 3 Risk scores validated for dual antiplatelet therapy duration decision-making

	PRECISE-DAPT score[18]	DAPT score[15]
Time of use	At the time of coronary stenting	After 12 months of uneventful DAPT
DAPT duration strategies assessed	Short DAPT (3–6 months) vs. Standard/long DAPT (12–24 months)	Standard DAPT (12 months) vs. Long DAPT (30 months)
Score calculation[a]	HB ≥12 11-5 11 10-5 ≤10 WBC ≤5 8 10 12 14 16 18 ≥20 Age ≤50 60 70 80 ≥90 CrCl ≥100 80 60 40 20 0 Prior Bleeding No Yes Score Points 0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30	Age ≥75 –2 pt 65 to <75 –1 pt <65 0 pt Cigarette smoking +1 pt Diabetes mellitus +1 pt MI at presentation +1 pt Prior PCI or prior MI +1 pt Paclitaxel-eluting stent +1 pt Stent diameter <3 mm +1 pt CHF or LVEF <30% +2 pt Vein graft stent +2 pt
Score range	0 to 100 points	–2 to 10 points
Decision making cut-off suggested	Score ≥25 → Short DAPT Score <25 → Standard/long DAPT	Score ≥2 → Long DAPT Score <2 → Standard DAPT
Calculator	www.precisedaptscore.com	www.daptstudy.org

CHF = congestive heart failure; CrCl = creatinine clearance; DAPT = dual antiplatelet therapy; Hb = haemoglobin; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PCI = percutaneous coronary intervention; PRECISE-DAPT = PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent Dual Anti Platelet Therapy; WBC = white blood cell count.

European Heart Journal (2018) **39**, 213–254

Farmaci Antiaggreganti nella prevenzione cardiovascolare

Use of risk scores as guidance for the duration of dual antiplatelet therapy

Recommendations	Class[a]	Level[b]
The use of risk scores designed to evaluate the benefits and risks of different DAPT durations[c] may be considered.[15,18]	IIb	A

DAPT = dual antiplatelet therapy.
[a]Class of recommendation.
[b]Level of evidence.
[c]The DAPT and PRECISE-DAPT scores are those currently fulfilling these requirements.

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Farmaci Antiaggreganti nella prevenzione cardiovascolare

Measures to minimize bleeding while on dual antiplatelet therapy

Recommendations	Class[a]	Level[b]
Radial over femoral access is recommended for coronary angiography and PCI if performed by an expert radial operator.[43,44]	I	A
In patients treated with DAPT, a daily aspirin dose of 75 - 100 mg is recommended.[45–47,51,52]	I	A
A PPI in combination with DAPT[c] is recommended.[70,79,80,86,87]	I	B
Routine platelet function testing to adjust antiplatelet therapy before or after elective stenting is not recommended.[58–60]	III	A

DAPT = dual antiplatelet therapy; PCI = percutaneous coronary intervention; PPI proton pump inhibitor.
[a]Class of recommendation.
[b]Level of evidence.
[c]While the evidence that a PPI does not increase the risk of cardiovascular events was generated with omeprazole, based on drug–drug interaction studies, omeprazole and esomeprazole would appear to have the highest propensity for clinically relevant interactions, while pantoprazole and rabeprazole have the lowest.

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Farmaci Antiaggreganti nella prevenzione cardiovascolare

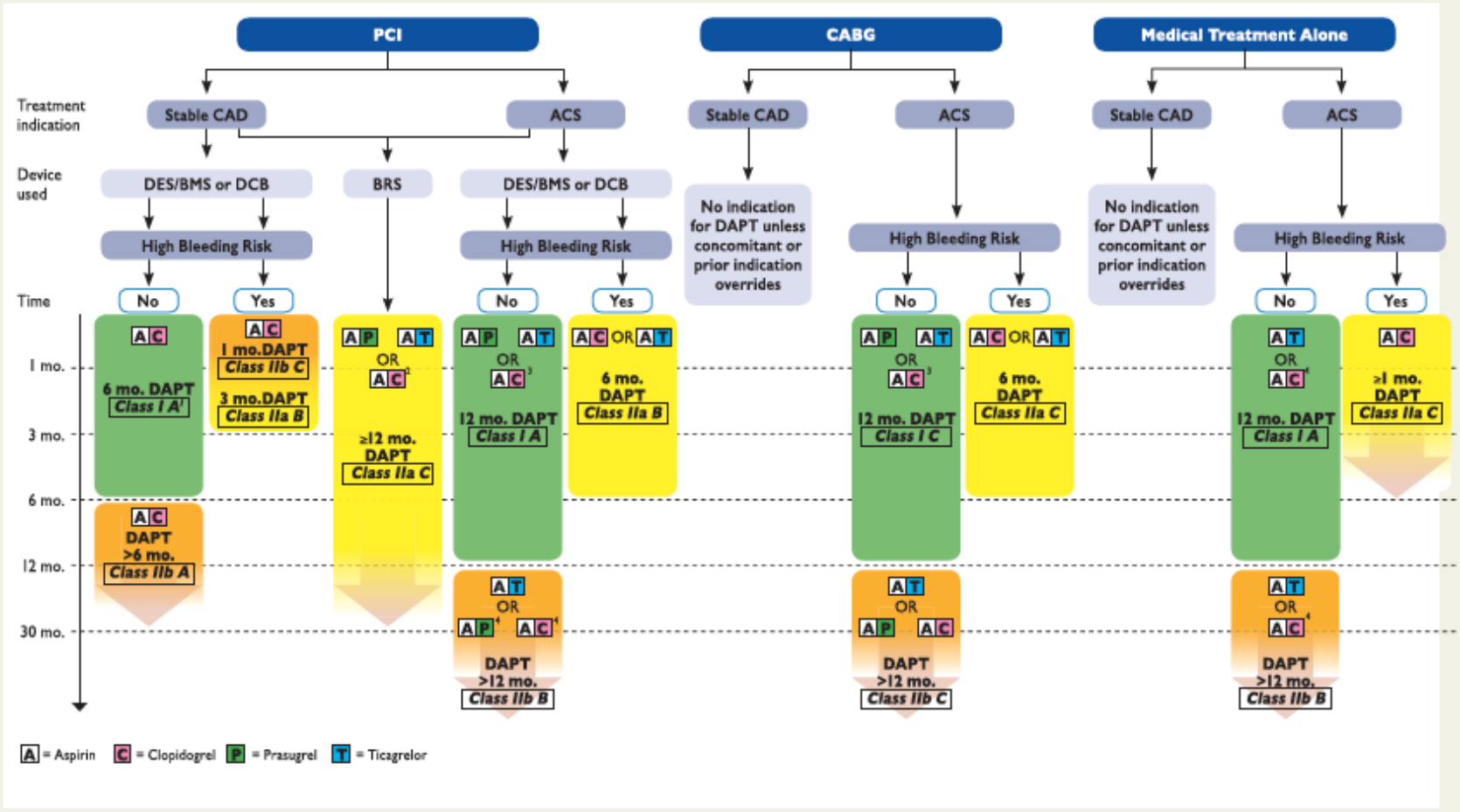

Figure 3 Algorithm for DAPT in patients with coronary artery disease. ACS = acute coronary syndrome, BMS = bare-metal stent; BRS = bioresorbable vascular scaffold; CABG = Coronary artery bypass graft; DCB = drug-coated balloon; DES: drug-eluting stent; PCI = percutaneous coronary intervention; Stable CAD = stable coronary artery disease.
High bleeding risk is considered as an increased risk of spontaneous bleeding during DAPT (e.g. PRECISE-DAPT score ≥25).
Colour-coding refers to the ESC Classes of Recommendations (green = Class I; yellow = Class IIa; orange = Class IIb).

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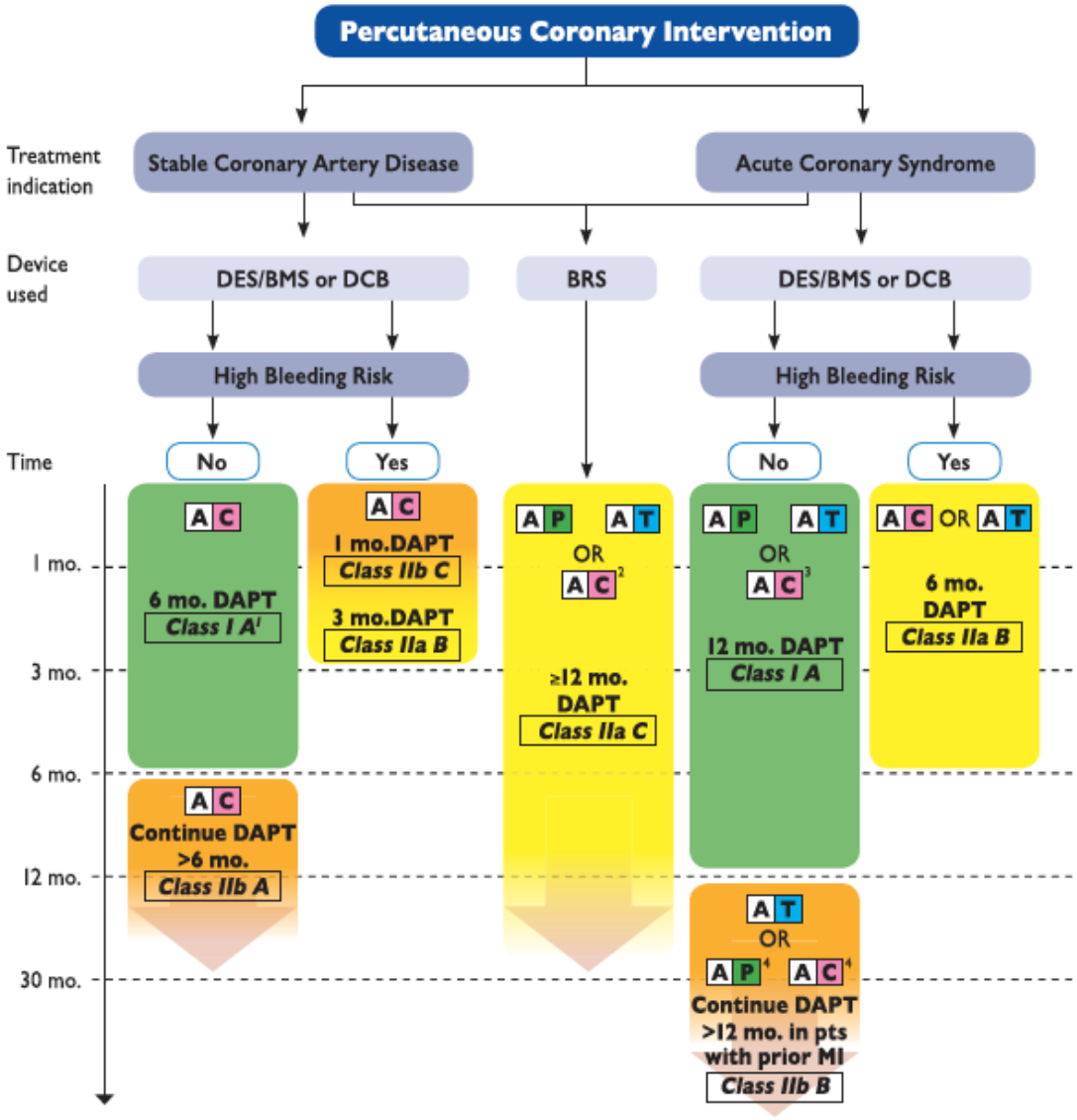

European Heart Journal (2018) **39**, 213–254 A = Aspirin C = Clopidogrel P = Prasugrel T = Ticagrelor

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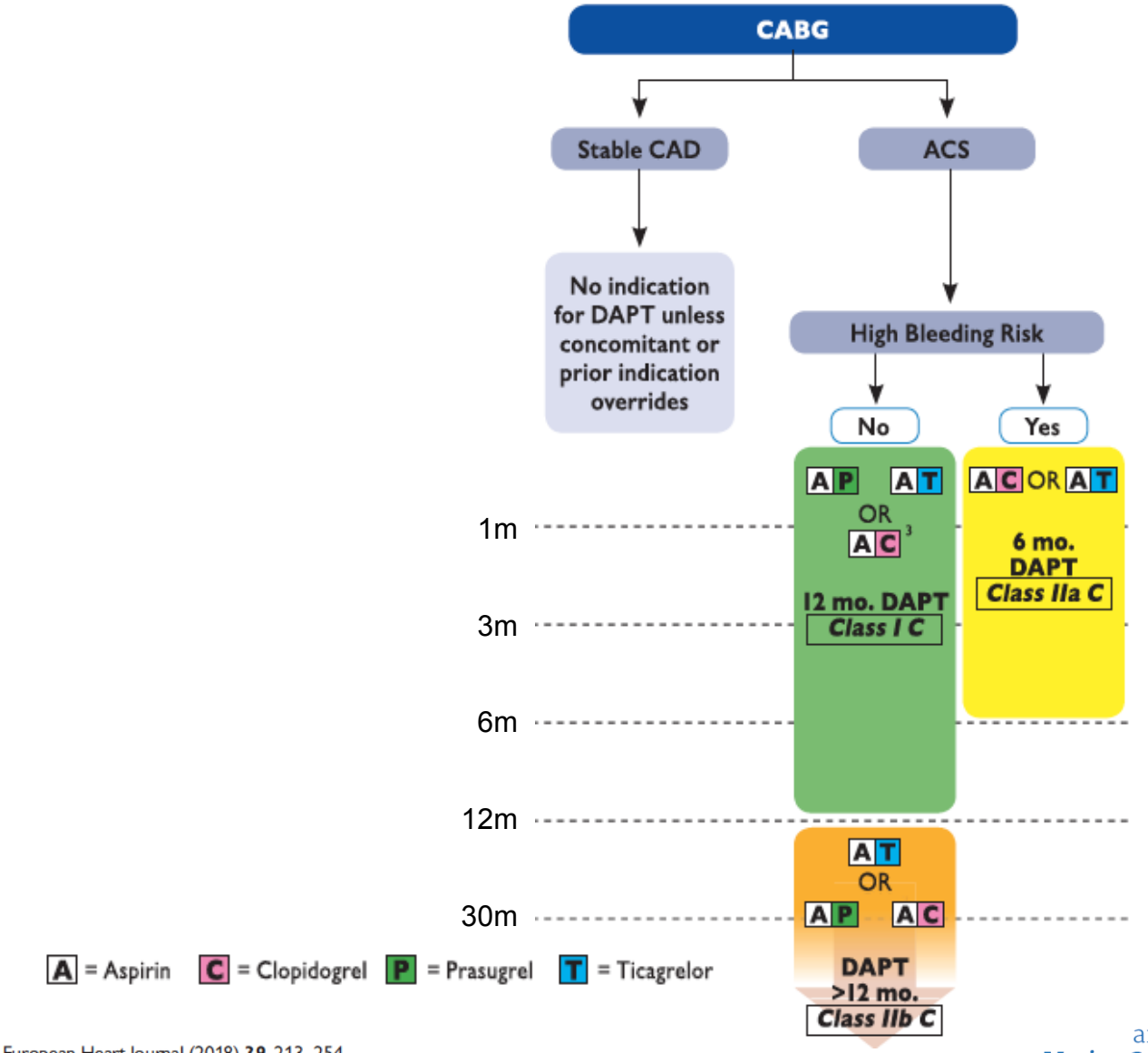

European Heart Journal (2018) **39**, 213–254

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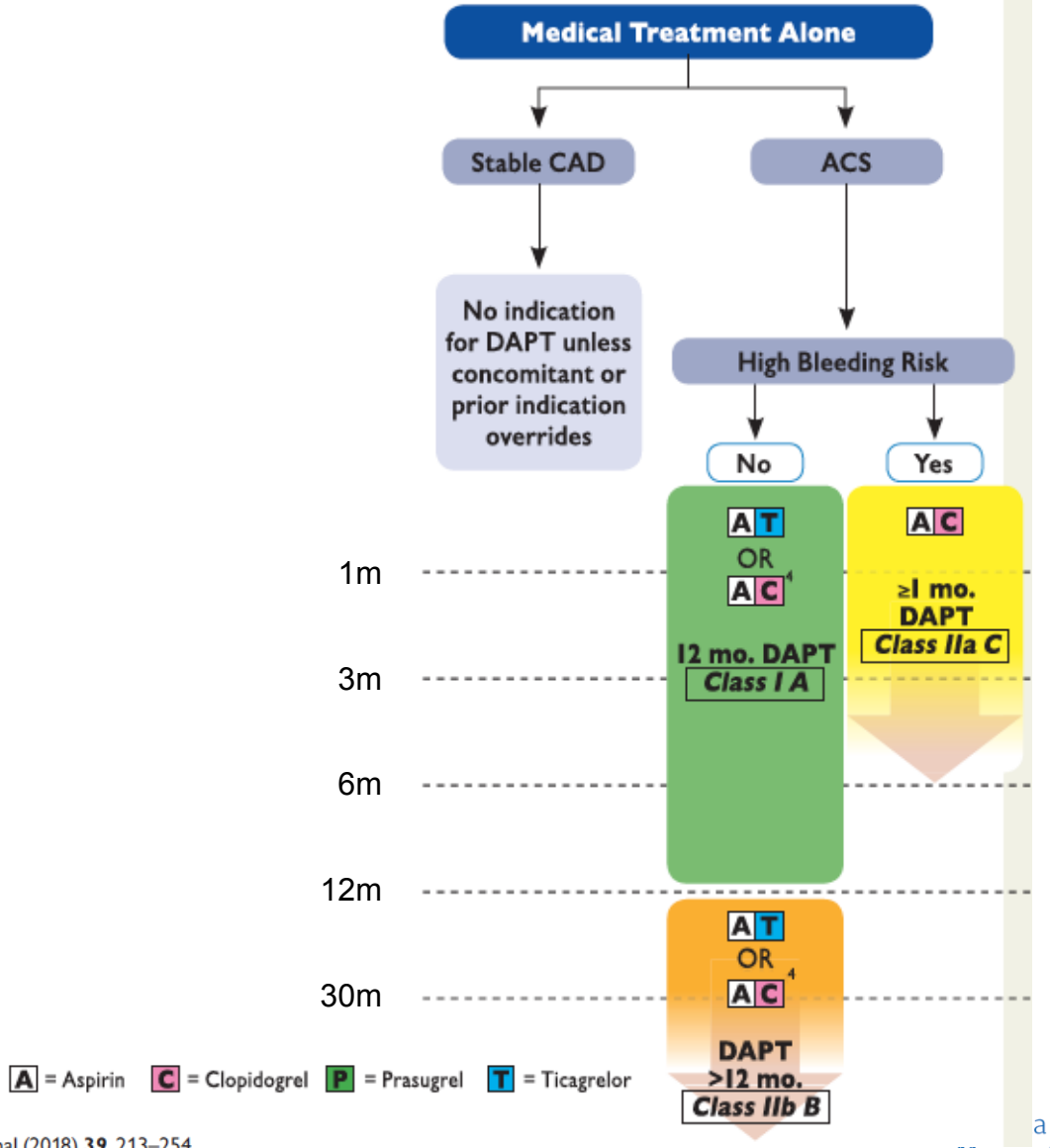

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a antiaggregante in prevenzione secondaria: quale!

Marino Carnovali

Farmaci Antiaggreganti nella prevenzione cardiovascolare

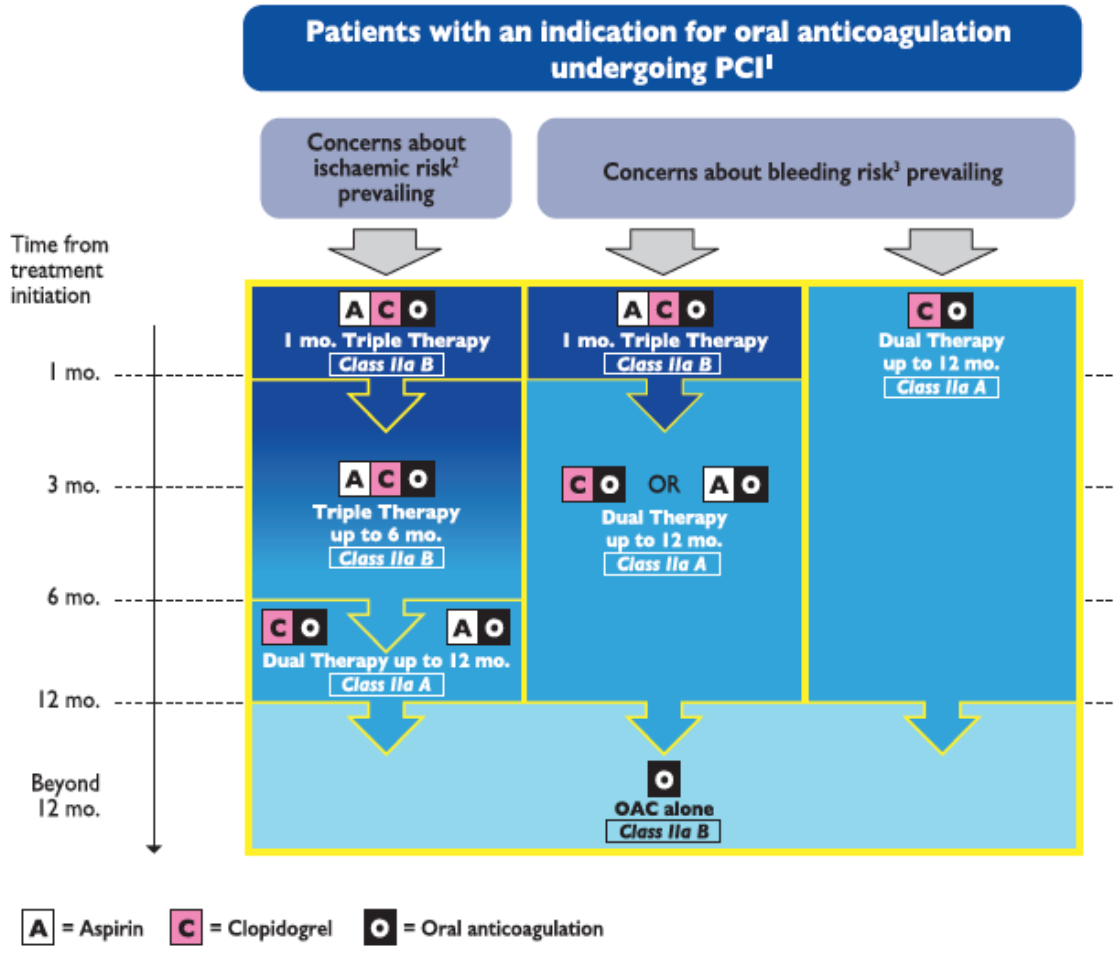

Figure 7 Algorithm for dual antiplatelet therapy (DAPT) in patients with an indication for oral anticoagulation undergoing percutaneous coronary intervention (PCI). Colour-coding refers to the number of concomitant antithrombotic medication(s). Triple therapy denotes treatment with DAPT plus oral anticoagulant (OAC). Dual therapy denotes treatment with a single antiplatelet agent (aspirin or clopidogrel) plus OAC.

zione secondaria: quale!

European Heart Journal (2018) **39**, 213–254

Farmaci Antiaggreganti nella prevenzione cardiovascolare

Table 4 Strategies to avoid bleeding complications in patients treated with oral anticoagulant

• Assess ischaemic and bleeding risks using validated risk predictors (e.g. CHA_2DS_2-VASc, ABC, HAS-BLED) with a focus on modifiable risk factors.
• Keep triple therapy duration as short as possible; dual therapy after PCI (oral anticoagulant and clopidogrel) to be considered instead of triple therapy.
• Consider the use of NOACs instead of VKA.
• Consider a target INR in the lower part of the recommended target range and maximize time in therapeutic range (i.e. > 65–70%) when VKA is used.
• Consider the lower NOAC regimen tested in approval studies and apply other NOAC regimens based on drug-specific criteria for drug accumulation.[a]
• Clopidogrel is the $P2Y_{12}$ inhibitor of choice.
• Use low-dose (≤ 100 mg daily) aspirin.
• Routine use of PPIs.

European Heart Journal (2018) **39**, 213–254

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Farmaci Antiaggreganti nella prevenzione cardiovascolare

Table 6 Unfavourable patient profile for a combination of oral anticoagulant and antiplatelet therapy

• Short life expectancy
• Ongoing malignancy
• Poor expected adherence
• Poor mental status
• End stage renal failure
• Advanced age
• Prior major bleeding/prior haemorrhagic stroke
• Chronic alcohol abuse
• Anaemia
• Clinically significant bleeding on dual antithrombotic therapy

European Heart Journal (2018) **39**, 213–254

Farmaci Antiaggreganti nella prevenzione cardiovascolare

Comportamento in caso di chirurgia elettiva

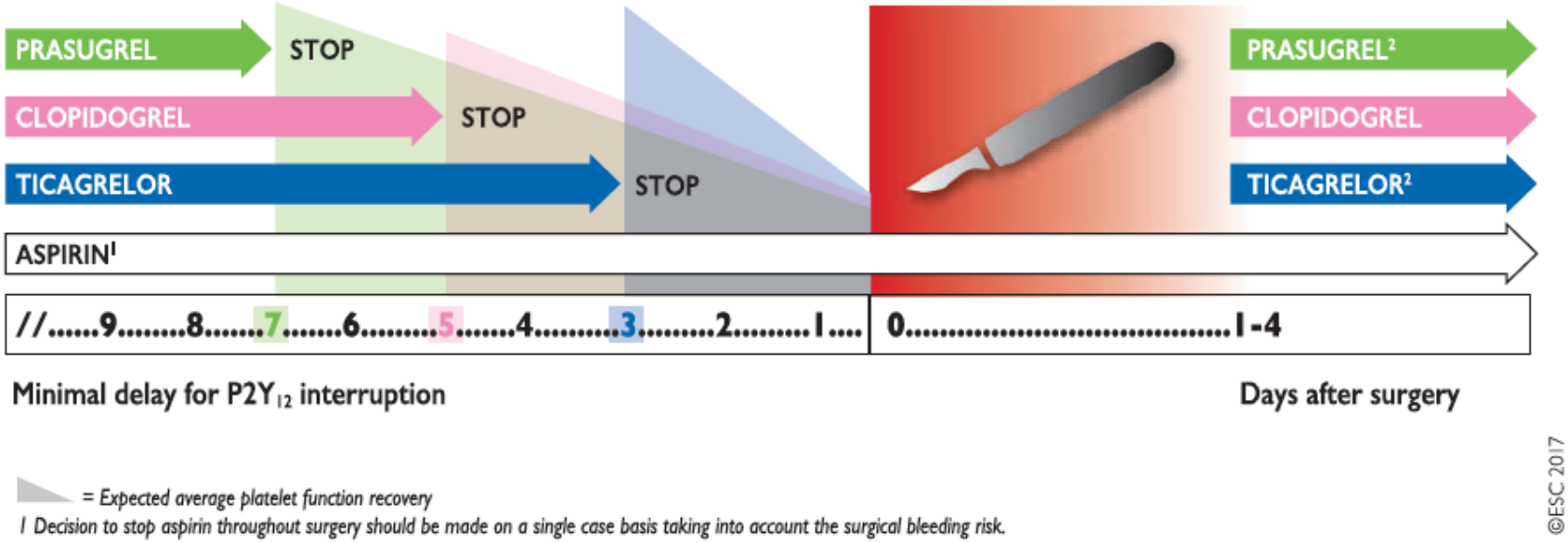

Figure 9 Minimal discontinuation and re-implementation time frames of dual antiplatelet therapy (DAPT) for patients undergoing elective surgery
OAC = oral anticoagulant.

European Heart Journal (2018) **39**, 213–254

Farmaci Antiaggreganti nella prevenzione cardiovascolare

Timing in caso di chirurgia elettiva

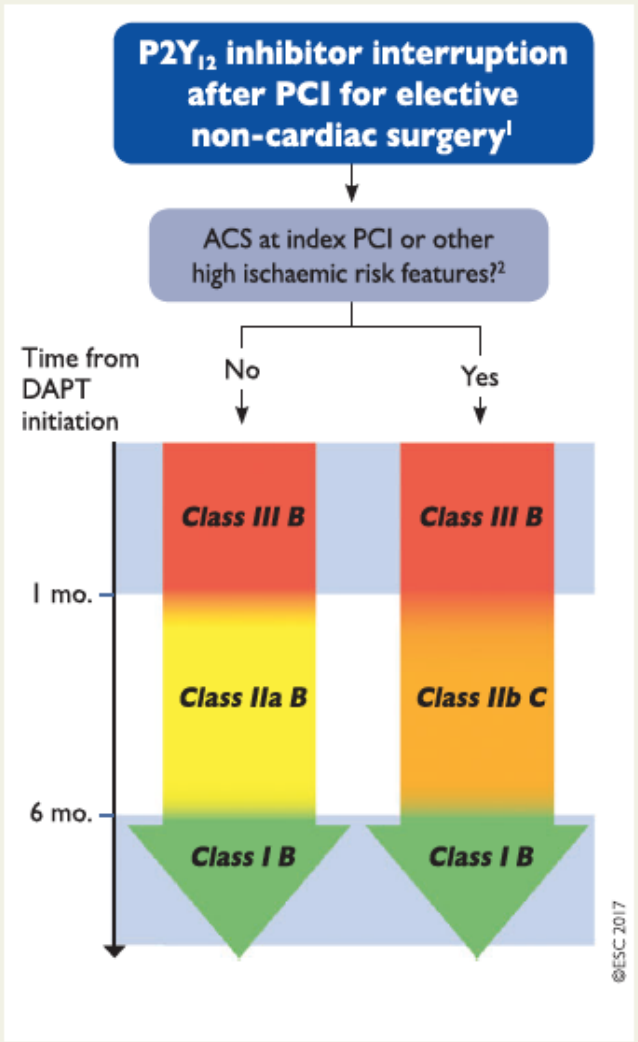

Figure 8 Timing for elective non-cardiac surgery in patients treated with dual antiplatelet therapy (DAPT) after percutaneous coronary intervention (PCI). Colour-coding refers to the ESC

European Heart Journal (2018) **39**, 213–254

Cosa fare al termine della fase di doppia antiaggregazione ?

2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation

The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC)

7.2 Antithrombotic therapy

7.2.1 Aspirin

Aspirin is recommended indefinitely in all patients with STEMI.[329,330]

For long-term prevention, low aspirin doses (75–100 mg) are indicated due to similar anti-ischaemic and less adverse events than higher doses, as demonstrated in the CURRENT-OASIS 7 trial.[330]

Prevenzione secondaria nei

Pazienti con malattia cardiovascolare stabile

Nuove opportunità per i pazienti in monoterapia antiaggregante ?

Farmaci Antiaggreganti nella prevenzione cardiovascolare

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*

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Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease

Exclusion criteria were a high bleeding risk; a recent stroke or previous hemorrhagic or lacunar stroke; severe heart failure; advanced stable kidney disease (estimated GFR <15 ml per minute); the use of dual antiplatelet therapy, anticoagulation

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Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease

Table 1. (Continued.)

Characteristic	Rivaroxaban plus Aspirin (N=9152)	Rivaroxaban Alone (N=9117)	Aspirin Alone (N=9126)
Coronary artery disease — no. (%)‡	8313 (90.8)	8250 (90.5)	8261 (90.5)
Peripheral arterial disease — no. (%)§	2492 (27.2)	2474 (27.1)	2504 (27.4)
Estimated GFR — no. (%)¶			
<30 ml/min	77 (0.8)	80 (0.9)	86 (0.9)
30 to <60 ml/min	1977 (21.6)	2028 (22.2)	2028 (22.2)
≥60 ml/min	7094 (77.5)	7005 (76.8)	7012 (76.8)

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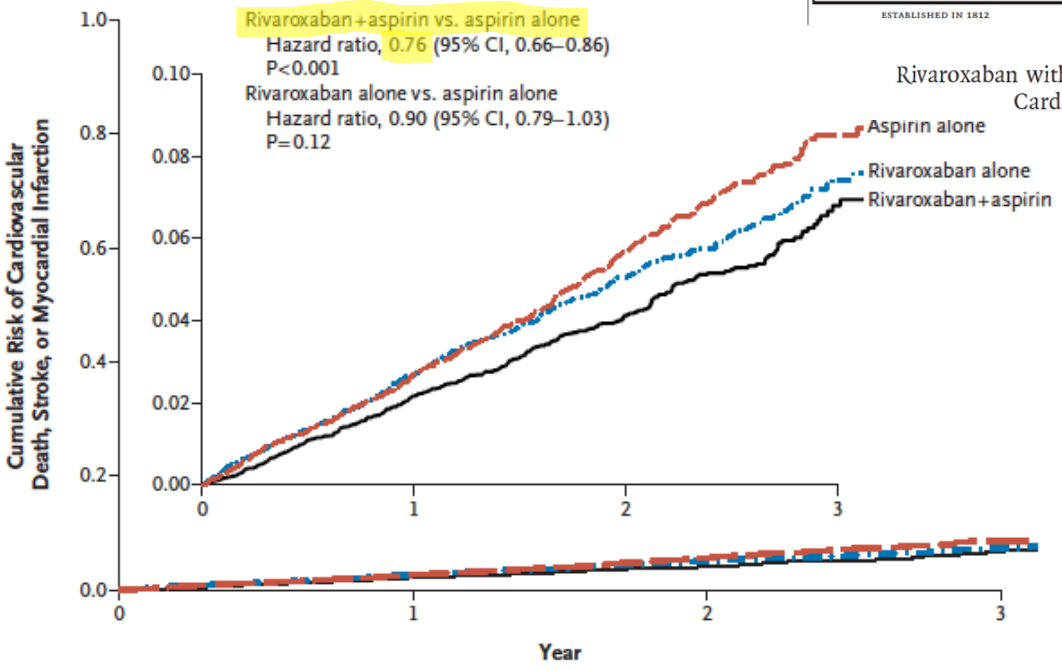

No. at Risk				
Aspirin alone	9126	7808	3860	669
Rivaroxaban alone	9117	7824	3862	670
Rivaroxaban+aspirin	9152	7904	3912	658

Figure 1. Cumulative Incidence of the Primary Efficacy Outcome among Participants Receiving Rivaroxaban plus Aspirin, Rivaroxaban Alone, or Aspirin Alone.

Participants in the rivaroxaban-plus-aspirin group received 2.5 mg of rivaroxaban twice daily and 100 mg of aspirin once daily. Participants in the rivaroxaban-alone group received 5 mg of rivaroxaban twice daily and an aspirin-matched placebo once daily. Participants in the aspirin-alone group received 100 mg of aspirin once daily and a rivaroxaban-matched placebo twice daily. The inset shows the same data on an expanded y axis.

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DISCUSSION

Among patients with stable atherosclerotic vascular disease, a high proportion of whom were receiving proven secondary prevention therapies, the rate of the primary outcome (a composite of cardiovascular death, stroke, or myocardial infarction) was lower by 24% with rivaroxaban (2.5 mg twice daily) plus aspirin than with aspirin alone (4.1% vs. 5.4%), but the rate of major bleeding was higher by 70% (3.1% vs. 1.9%). The rate of the net-clinical-benefit outcome was lower by 20% with rivaroxaban plus aspirin than with aspirin alone (4.7% vs. 5.9%). The com-

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Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease

CONCLUSIONS

Among patients with stable atherosclerotic vascular disease, those assigned to rivaroxaban (2.5 mg twice daily) plus aspirin had better cardiovascular outcomes and more major bleeding events than those assigned to aspirin alone. Rivaroxaban (5 mg twice daily) alone did not result in better cardiovascular outcomes than aspirin alone and resulted in more major bleeding events. (Funded by Bayer; COMPASS ClinicalTrials.gov number, NCT01776424.)

Farmaci Antiaggreganti nella prevenzione cardiovascolare

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 73, NO. 25, 2019

Rivaroxaban Plus Aspirin Versus Aspirin in Relation to Vascular Risk in the COMPASS Trial

Sonia S. Anand, MD, PhD,[a] John W. Eikelboom, MBBS, MSc,[a] Leanne Dyal, MSc,[b] Jackie Bosch, MSc, PhD,[c] Christoph Neumann, PhD,[d] Petr Widimsky, MD, DSc,[e] Alvaro A. Avezum, MD, PhD,[f] Jeffrey Probstfield, MD,[g] Nancy Cook Bruns, MD,[d] Keith A.A. Fox, MBChB, BSc,[h] Deepak L. Bhatt, MD, MPH,[i] Stuart J. Connolly, MD,[a] Salim Yusuf, MBBS, DPhil,[a] for the COMPASS Trial Investigators

Anand, S.S. et al. J Am Coll Cardiol. 2019;73(25):3271-80.

Farmaci Antiaggreganti nella prevenzione cardiovascolare

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 1

Rivaroxaban Plus Aspirin Versus Aspirin in Relation to Vascular Risk in the COMPASS Trial

BACKGROUND The COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies) trial showed that the combination of low-dose rivaroxaban and aspirin reduced major vascular events in patients with stable vascular disease.

OBJECTIVES The purpose of this study was to identify subsets of patients at higher risk of recurrent vascular events, which may help focus the use of rivaroxaban and aspirin therapy.

METHODS COMPASS patients with vascular disease were risk stratified using 2 methods: the REACH (REduction of Atherothrombosis for Continued Health) atherothrombosis risk score and CART (Classification and Regression Tree) analysis. The absolute risk differences for rivaroxaban with aspirin were compared to aspirin alone over 30 months for the composite of cardiovascular death, myocardial infarction, stroke, acute limb ischemia, or vascular amputation; for severe bleeding; and for the net clinical benefit.

Anand, S.S. et al. J Am Coll Cardiol. 2019;73(25):3271-80.

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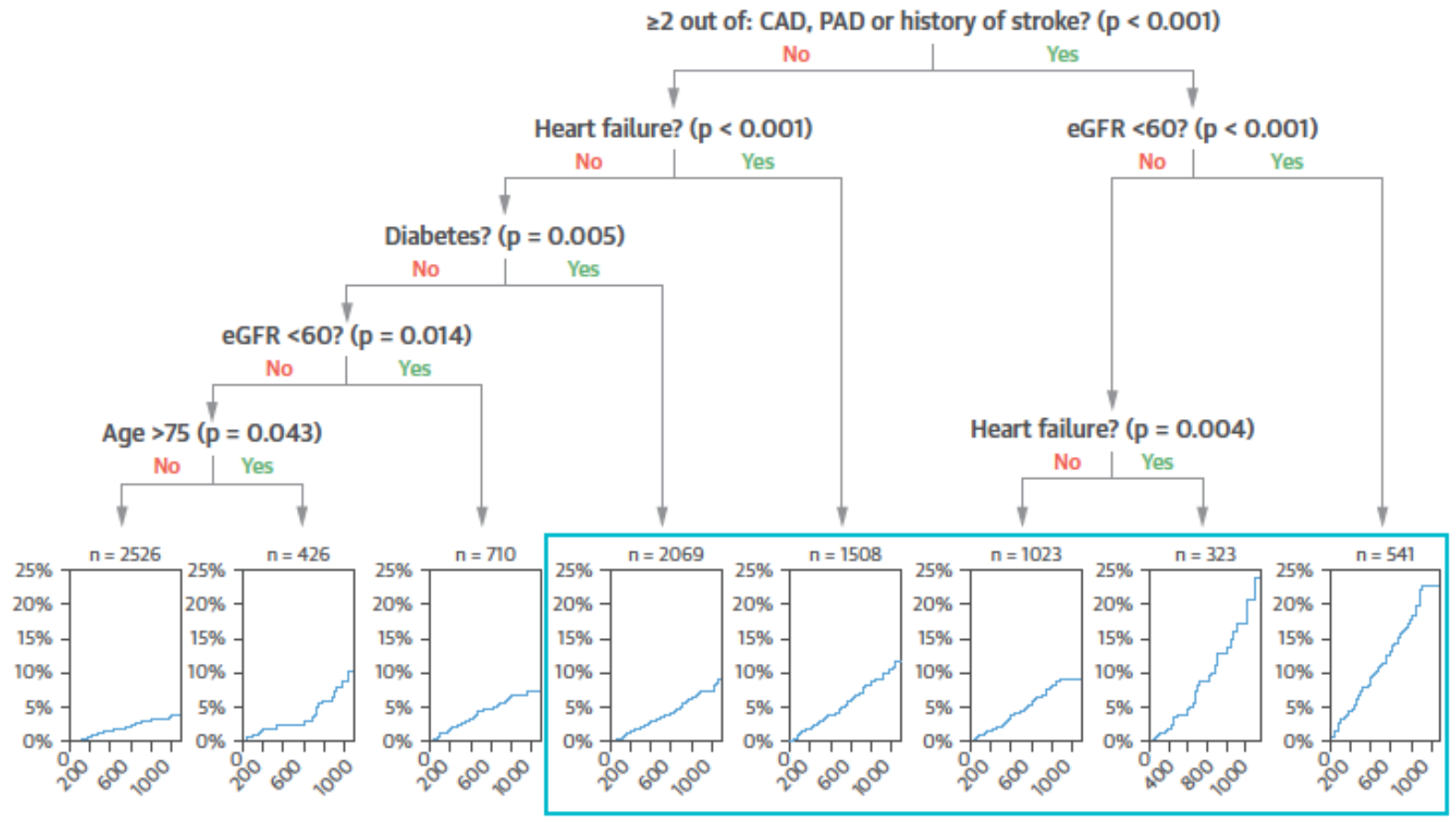
FIGURE 1 Classification and Regression Tree Analysis



This CART (Classification and Regression Tree) analysis shows the independent groups, outlined in **blue**, at highest risk for major vascular events. CAD = coronary artery disease; eGFR = estimated glomerular filtration rate; PAD = peripheral artery disease.

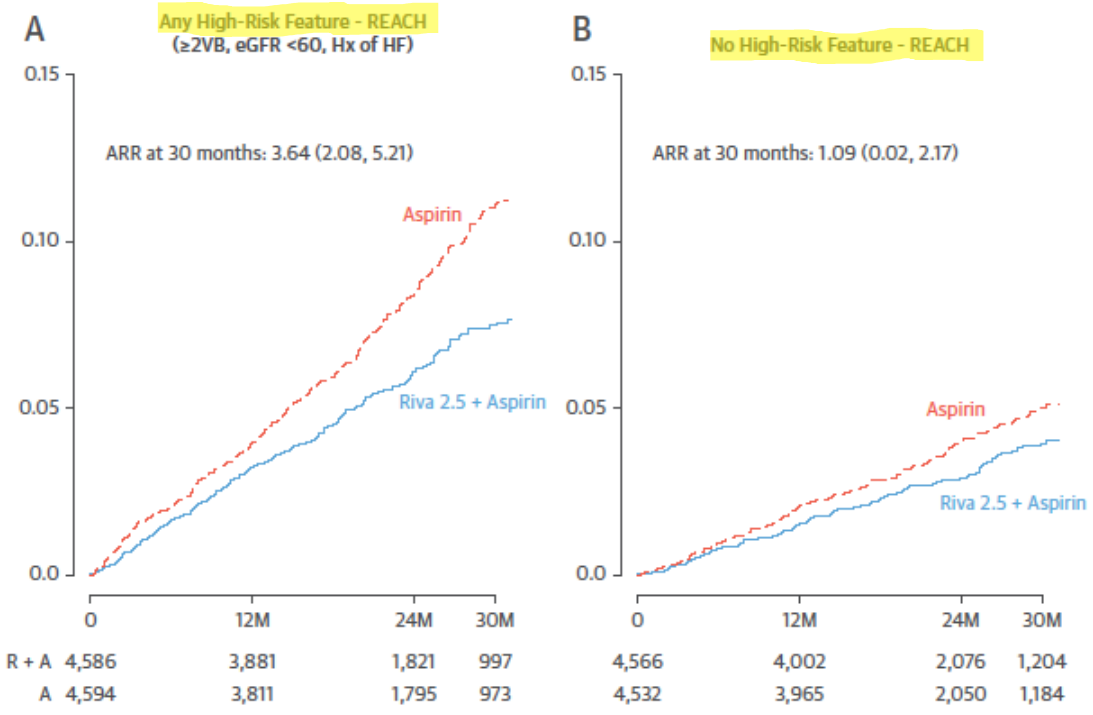
Anand, S.S. et al. J Am Coll Cardiol. 2019;73(25):3271-80.

Farmaci Antiaggreganti nella prevenzione cardiovascolare

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 1

Rivaroxaban Plus Aspirin Versus Aspirin in Relation to Vascular Risk in the COMPASS Trial

FIGURE 2 Incidence Risk for Vascular Events Comparing Patients With Any High-Risk Feature to Those With No High-Risk Features by REACH Score Classification



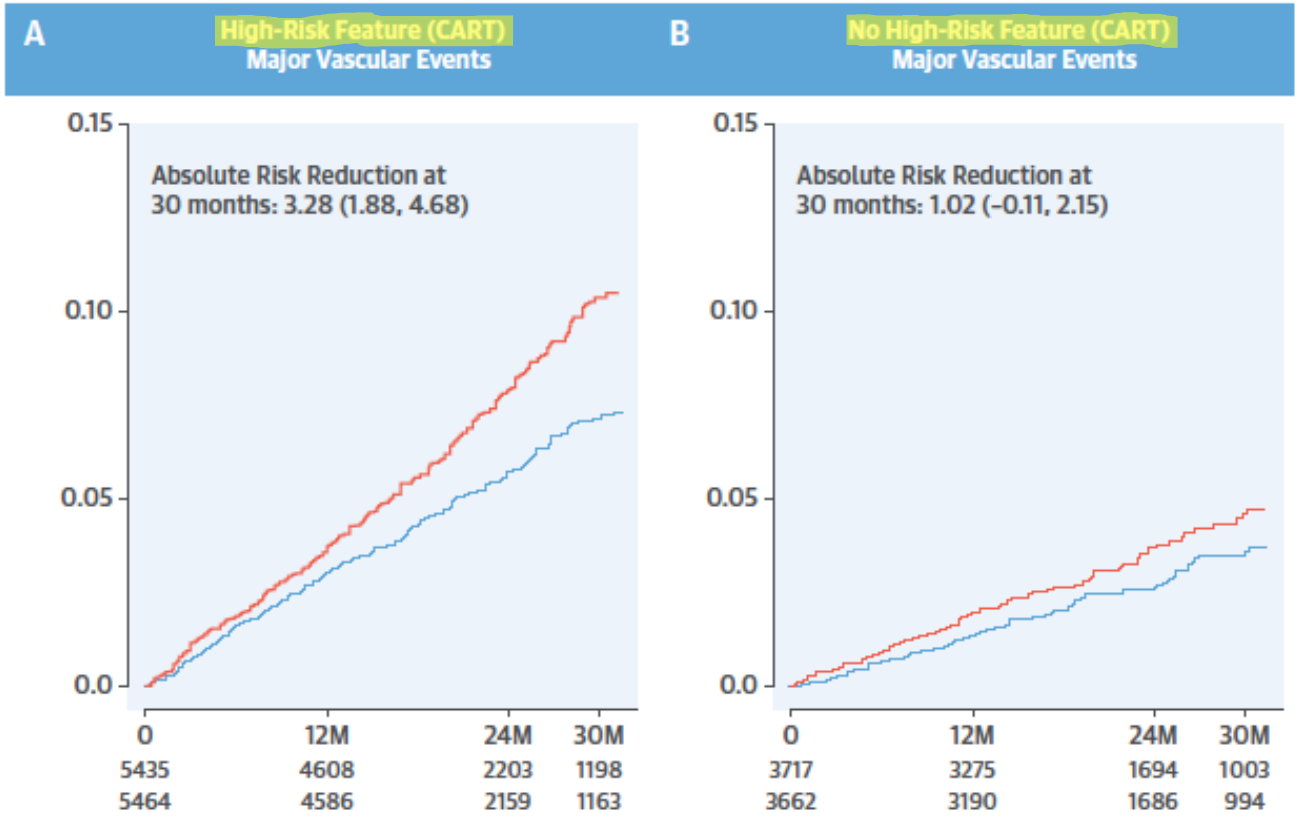
(A) The residual risk of cardiovascular (CV) events in patients with a high-risk feature by REACH (REduction of Atherothrombosis for Continued Health) who received aspirin **(red line)**, and the absolute risk reduction of 3% in patients who received rivaroxaban and aspirin combination **(blue line)**. **(B)** Even among patients without a high-risk feature, the cumulative incidence of CV events in the aspirin-treated patients remains considerable, and a treatment benefit with rivaroxaban and aspirin is observed. ARR = absolute risk reduction; eGFR = estimated glomerular filtration rate; HF = heart failure; Hx = history; VB = vascular bed.

Anand, S.S. et al. J Am Coll Cardiol. 2019;73(25):3271-80.

Farmaci Antiaggreganti nella prevenzione cardiovascolare

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 1

Rivaroxaban Plus Aspirin Versus Aspirin in Relation to Vascular Risk in the COMPASS Trial



Anand, S.S. et al. J Am Coll Cardiol. 2019;73(25):3271-80.

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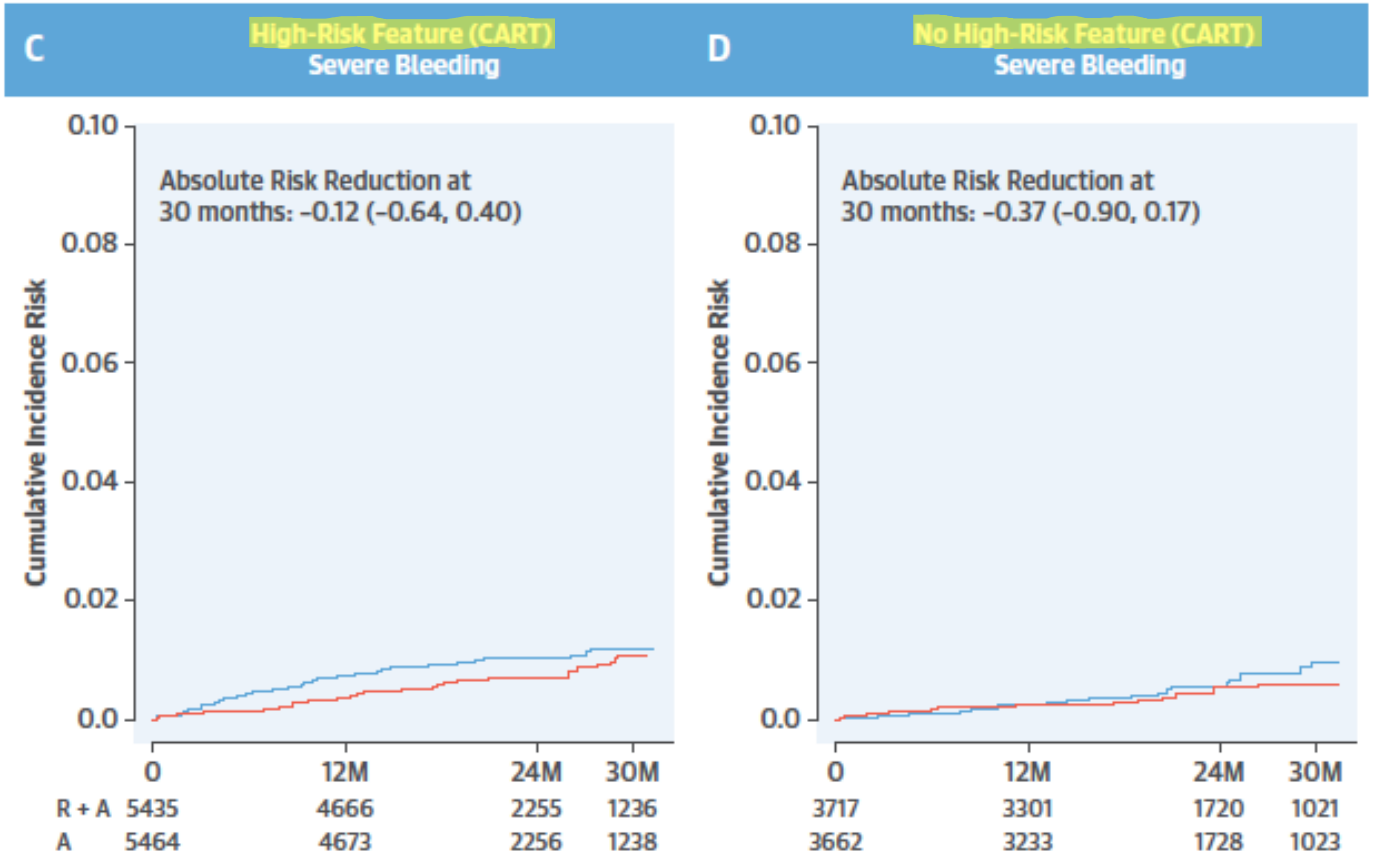

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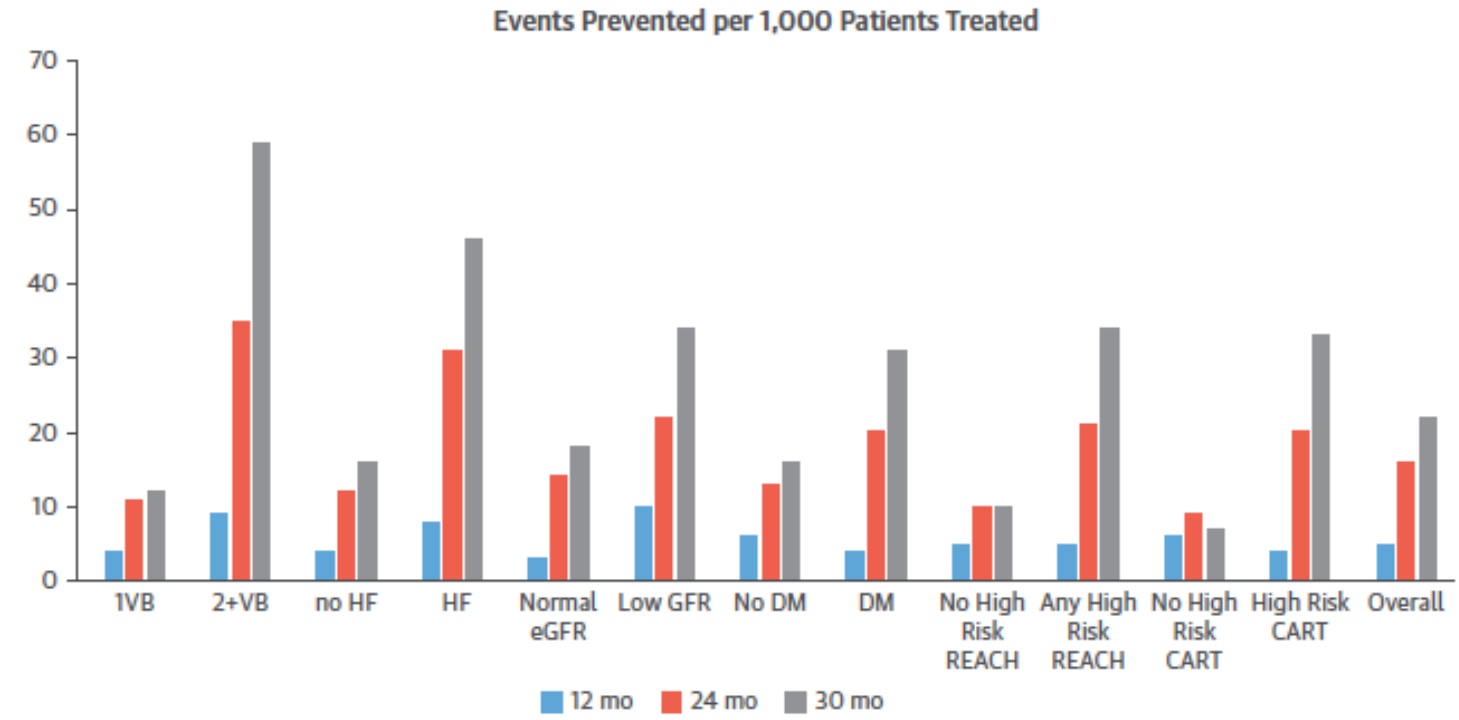
FIGURE 3 Net Clinical Benefit per 1,000 Patients Treated With Rivaroxaban and Aspirin to Aspirin Alone in High-Risk Subsets Over 12, 24, and 30 Months



Compared with aspirin alone, dual pathway inhibition with a Factor Xa inhibitor and aspirin significantly reduce cardiovascular events including CV death, myocardial infarction, stroke, acute limb ischemia, and vascular amputation, with incremental benefits accruing over time. High-risk groups derive the greatest net clinical benefit, shown in the figure as events prevented per 1,000 patients treated. The events prevented per 1,000 patients treated were similar within the 2+ vascular bed group for patients with CAD and PAD irrespective of whether PAD is PAD of lower extremities or carotid artery disease. GFR = glomerular filtration rate; PAD = peripheral artery disease; VB = vascular bed; other abbreviations as in Figures 1 and 2.

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CONCLUSIONS

In high-risk patients with vascular disease, further risk stratification can identify higher-risk patients (2 or more vascular beds affected, HF, renal insufficiency, or diabetes) in whom the benefits are substantial. However, even the lower-risk patient subsets have appreciable residual risk and benefit from more intensive treatment. The absolute risk of severe bleeding is low, and the net clinical benefit remains favorable for most patients treated with rivaroxaban and aspirin compared with aspirin alone.

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AGENZIA ITALIANA DEL FARMACO

1. DENOMINAZIONE DEL MEDICINALE

Xarelto 2,5 mg compresse rivestite con film

4. INFORMAZIONI CLINICHE

4.1 Indicazioni terapeutiche

Xarelto, somministrato insieme con il solo acido acetilsalicilico (*acetylsalicylic acid*, ASA) o con ASA e clopidogrel o ticlopidina, è indicato per la prevenzione di eventi aterotrombotici in pazienti adulti dopo una sindrome coronarica acuta (SCA) con biomarcatori cardiaci elevati (vedere paragrafi 4.3, 4.4 e 5.1).

Xarelto, somministrato insieme con acido acetilsalicilico (ASA), è indicato per la prevenzione di eventi aterotrombotici in pazienti adulti, ad alto rischio di eventi ischemici, che presentano coronaropatia (*coronary artery disease*, CAD) o arteriopatia periferica (*peripheral artery disease*, PAD) sintomatica.

Documento reso disponibile da AIFA il 02/08/2019

CONCLUSIONI

L'ASA riveste un ruolo di protagonista assoluto per la prevenzione cardiovascolare, indicazione relativamente alla quale, per efficacia, sicurezza e costo, è raccomandato in tutto il mondo come farmaco di prima scelta.

Grazie per l'attenzione

Quanto deve durare la prevenzione secondaria ?

Quanto deve durare la prevenzione secondaria ?

Prolungamento senza limiti nel tempo della terapia,
in assenza di problemi di tollerabilità.

Durata del trattamento per la prevenzione secondaria

BMJ

BMJ 2011;343:d4094 doi: 10.1136/bmj.d4094 Page 1 of 10

RESEARCH

Discontinuation of low dose aspirin and risk of myocardial infarction: case-control study in UK primary care

Luis A García Rodríguez *director*[1], Lucía Cea-Soriano *epidemiologist*[1], Elisa Martín-Merino *epidemiologist*[1], Saga Johansson *senior principal scientist/associate professor*[2 3]

[1]Spanish Centre for Pharmacoepidemiologic Research (CEIFE), Madrid 28004, Spain; [2]AstraZeneca Research and Development, Mölndal, Sweden; [3]Institute of Medicine, Sahlgrenska Academy, Gothenburg University, Gothenburg, Sweden

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What this study adds

Discontinuation of low dose aspirin increases the risk of non-fatal myocardial infarction or death from coronary heart disease by almost 50% in patients in primary care who have a history of ischaemic events

L’entità del vantaggio è costante nel tempo?

Lancet 2016; 388: 365–75

Effects of aspirin on risk and severity of early recurrent stroke after transient ischaemic attack and ischaemic stroke: time-course analysis of randomised trials

Peter M Rothwell, Ale Algra, Zhengming Chen, Hans-Christoph Diener, Bo Norrving, Ziyah Mehta

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Peter M Rothwell, Ale Algra, Zhengming Chen, Hans-Christoph Diener, Bo Norrving, Ziyah Mehta

Methods Pooling the individual patient data from all randomised trials of aspirin versus control in secondary prevention after TIA or ischaemic stroke, we studied the effects of aspirin on the risk and severity of recurrent stroke, stratified by the following time periods: less than 6 weeks, 6–12 weeks, and more than 12 weeks after randomisation.

Findings We pooled data for 15778 participants from 12 trials of aspirin versus control in secondary prevention.

Lancet 2016; 388: 365–75

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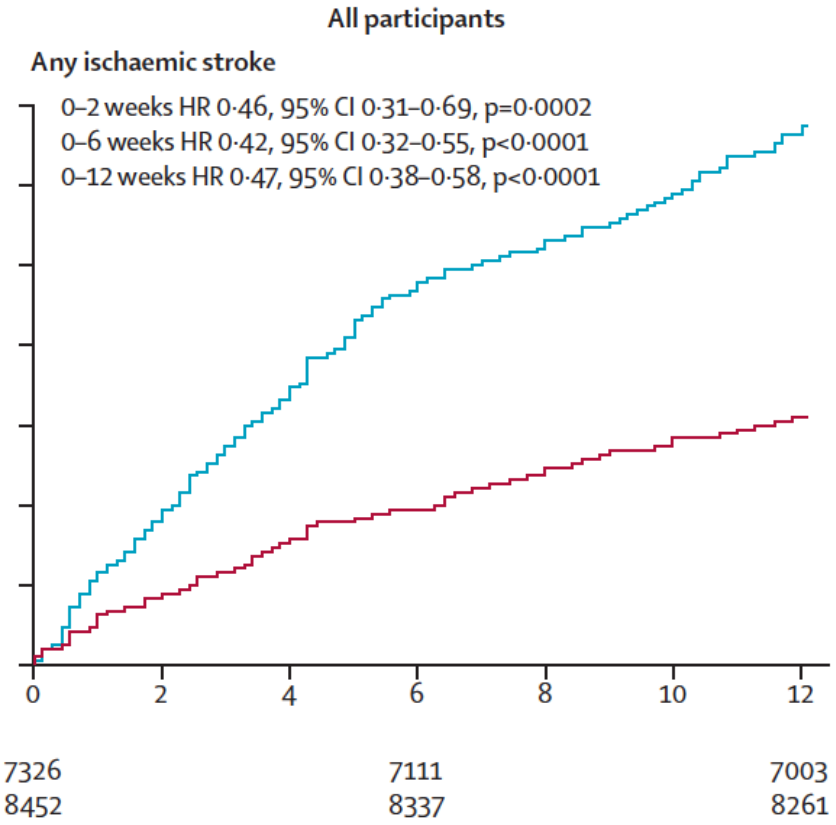

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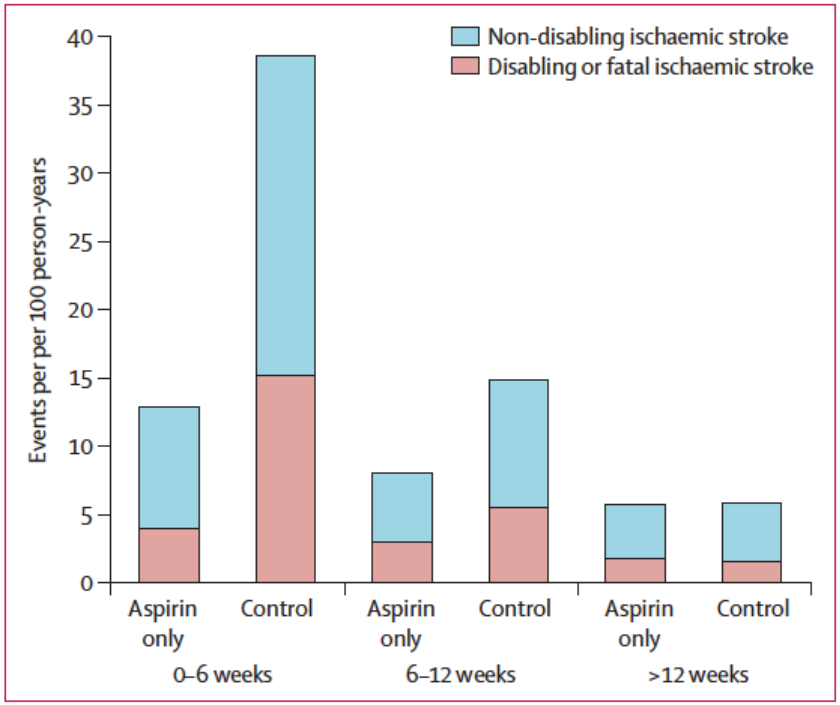

***Figure 2*: Pooled analysis of the effect of aspirin only versus control in secondary prevention after transient ischaemic attack and ischaemic stroke on the absolute risk of recurrent ischaemic stroke**
Time course of treatment effect interaction: $p_{interaction}<0{\cdot}0001$ for both outcomes.

Lancet 2016; 388: 365–75

L'entità del vantaggio è costante nel tempo?

Per la prevenzione secondaria in occasione di TIA o Stroke ischemico sono fondamentali le prime 12 settimane di trattamento

Farmaci Antiaggreganti nella prevenzione cardiovascolare

Gender considerations and special populations

Recommendations	Class[a]	Level[b]
Similar type and duration of DAPT are recommended in male and female patients.[26,240]	I	A
It is recommended to reassess the type, dose, and duration of DAPT in patients with actionable bleeding complications while on treatment.	I	C
Similar type and duration of DAPT should be considered in patients with and without diabetes mellitus.[145,242]	IIa	B

European Heart Journal (2018) **39**, 213–254