anti-platelet agents in the treatment of ischemic stroke

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thrombotic stroke

1. acute intervention
2. secondary prevention following a signal ischemic event
   - TIA
   - completed stroke
   - PFO
3. primary prevention
   - non-valvular atrial fibrillation
   - rheumatic valvular disease
   - thrombophilic states
4. microvascular disease
   - lacunes
   - neuropsychiatric lupus

anti-thrombotic therapy for stroke

1.0 acute intervention in ischemic stroke or TIA

ASA (160 – 325 mg/d) within 48 hours over no ASA (1A)

ASA (160 – 325 mg/d) within 48 hours over parenteral anticoagulation (1A)

ACCP Guidelines Chest *141* (2_suppl): (2012)

anti-thrombotic therapy for stroke

2.0 secondary prevention of noncardioembolic stroke

long-term treatment with ASA (75 – 100 mg/d), clopidogrel (75 mg/d). ASA/ERDP (20mg/200 mg x 2/d), or cilostazol (100 mg x 2/d) over no anti-platelet treatment (1A), oral anticoagulation (1B), clopidogrel + ASA (1B), or triflusal (2B)

of the above regimens, this panel favors clopidogrel or ASA/ERDP over ASA alone (2B) or cilostazol (2C)

ACCP Guidelines Chest *141* (2_suppl): (2012)

anti-thrombotic therapy for stroke

3.0 secondary prevention of cardioembolic stroke

patients with a history of ischemic stroke or TIA and atrial fibrillation (AF), including PAF

oral anticoagulation over no anti-thrombotic treatment (1A), ASA (1B), or ASA + clopidogrel (1B)

patients who choose not to take or are unsuitable to take oral anticoagulation

ASA + clopidogrel > ASA (1B)

ACCP Guidelines Chest *141* (2_suppl): (2012)

microvascular endothelial cell area

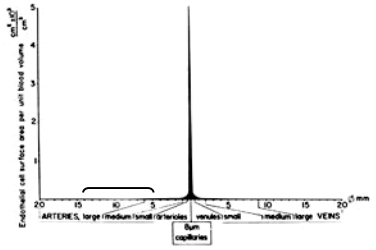

Fig. 1.2 The relationship of endothelial 'containers' surface to contained blood volume at different points in the vascular system. (Drawing courtesy of Dr Christer Busch, Department of Pathology, University of Uppsala, Sweden.)

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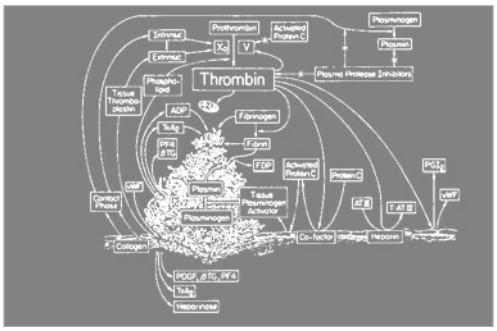
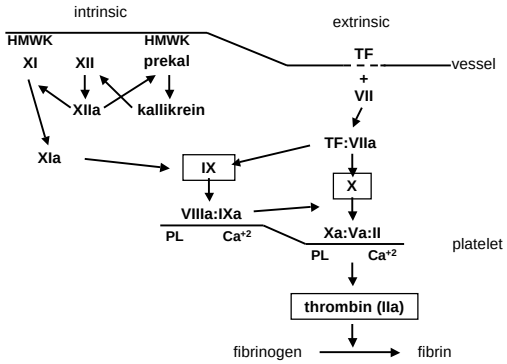
platelet aggregation and thrombosis

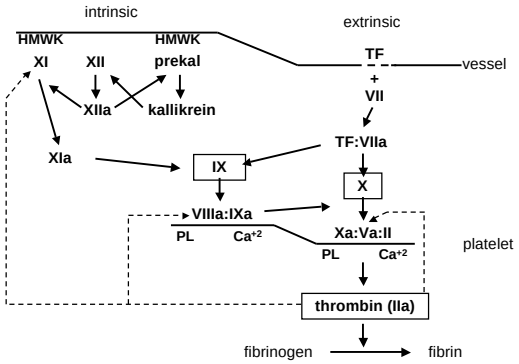


from l harker, 1986

coagulation system activation



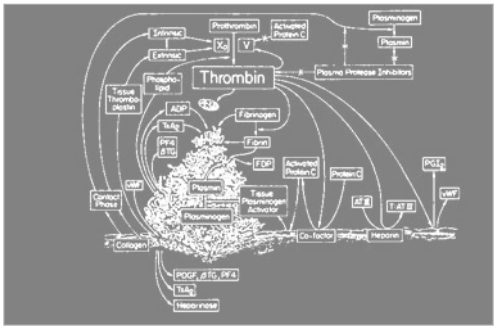
coagulation system activation



thrombin: multiple effects

- cleavage of fibrinogen (factor I)
- activation of factors V, VIII, and XI
- activation of factor XIII
- activation of resting platelets
- endothelial cell permeability
- activation of protein C (in presence of thrombomodulin)
- modulation of fibrinolysis (binding of plasminogen, t-PA, and α_2-AP)
- activation of inflammation

platelet aggregation and thrombosis



from l harker, 1986

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platelet activation associated with brain-supplying arteries

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platelet activation
ischemic stroke

source	(n)	groups	β-TG	PF4
Hoogendijk	186 176	stroke + TIA control	↑	~ ~
Cella	24 103	stroke (old) control	0	~
Fisher	24 20 40 15	stroke TIA control (younger) control (age-matched)	↑ ↑	↑ ↑
de Boer	36 31 80	stroke + heparin stroke + placebo control	0 0	~ ~ ~
Taomoto	70 80 117 136 39	stroke, acute stroke, chronic TIA + RIND cerebral atherosclerosis control	↑ ↑ ↑ ↑	~ ~ ~ ~
Lane	66 16	stroke control	↑	~ ~
Shah	13 10 11 10 14 20 15	stroke (thromboembolic) stroke (cardioembolic) TIA lacunes uncertain control (young) control (aged)	↑ ↑ 0 0 ↑	↑ 0 0 0 0

1979-1985

platelet activation
ischemic stroke

source	(n)	groups	β-TG	PF4
Landi	70 45	stroke control	↑	~ ~
Fisher	85 57 18 44	stroke + TIA, acute stroke + TIA, follow-up control, nonvascular control, normal	↑ ↑	↑ ↑
Feinberg	39 37	stroke , 2 weeks control	↑	↑
Iwamoto	56 31 62 7 30 25 25	atherothrombotic cardioembolic lacunar TIA Binswanger's disease control, non-stroke control, healthy	↑ ↑ ↑ 0 ↑ ~	~ ~ ~ ~ ~ ~ ~

1987-1995

del zoppo gj. Chapter 33: central nervous system ischemia *In* Platelets (ed a michelson) edition 3, elsevier - london, 2013; pp 669-697.

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anti-platelet agents

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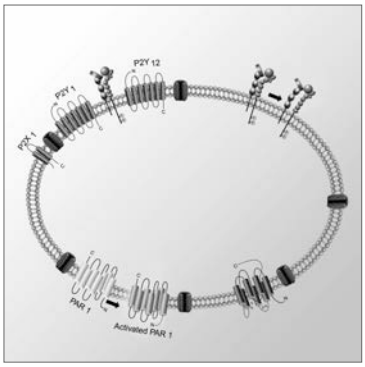
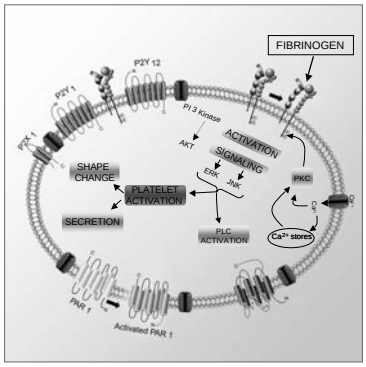
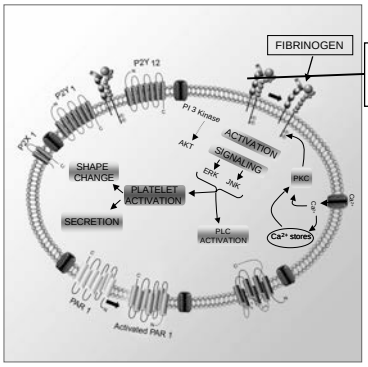
resting platelet



GP IIb/IIIa receptor



GP IIb/IIIa receptor



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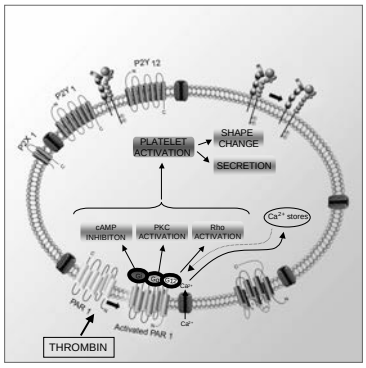
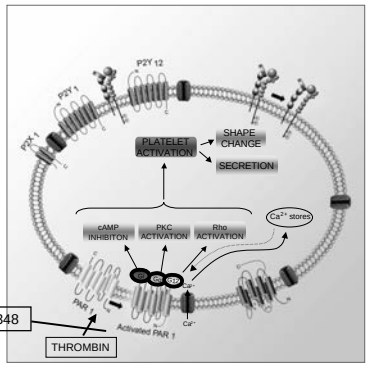
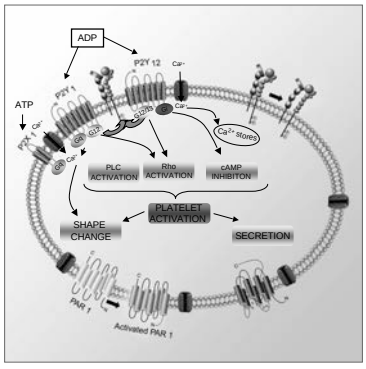
thrombin receptor



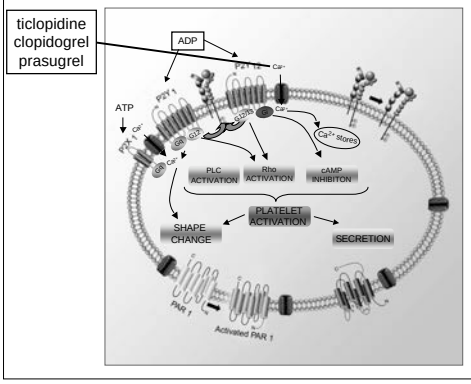
thrombin receptor



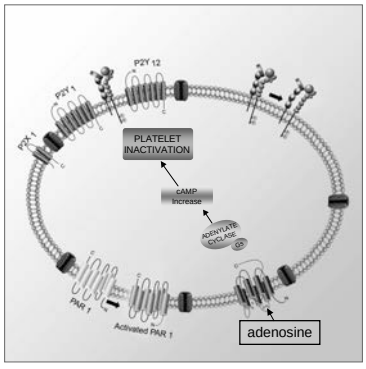
purine receptors



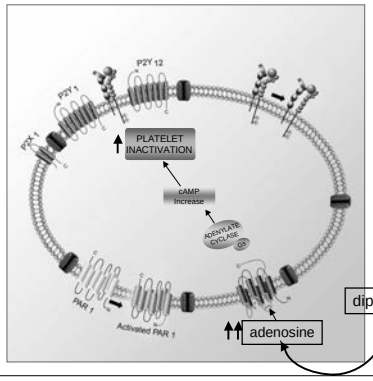
purine receptors



adenosine receptor



adenosine receptor



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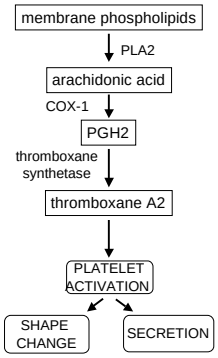
thromboxane A_2 activation pathway



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anti-platelet agents

ischemic stroke

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platelet aggregation inhibitors

aspirin (ASA)

prostacyclin (PGI2)

suloctidil

sulfinpyrazone

dipyridamole
ASA/dipyridamole
ASA/ERDP

thienopyridines

GP IIb/IIIa antagonists

thrombin inhibitors

platelet activation
focal cerebral ischemia

- platelet-thrombus formation on atheromata
- platelet accumulation within microvessels of ischemic regions
- normal platelet function required to prevent hemorrhage within ischemic regions
- potential vascular effects of platelet release products

platelet activation
focal cerebral ischemia

- contribution of microvessel obstruction to neurological outcome
- genetic manipulation of platelet adherence and CNS injury

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

antiplatelet trialists' collaboration. lancet 308: 81-106 (1994)

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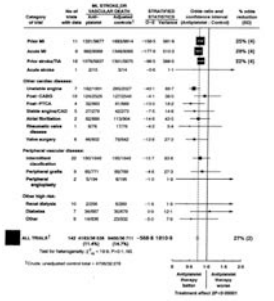
antiplatelet trialists' collaboration



antiplatelet trialists' collaboration. lancet 308: 81-106 (1994)

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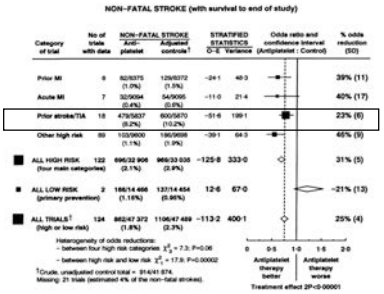

antiplatelet trialists' collaboration. lancet 308: 81-106 (1994)

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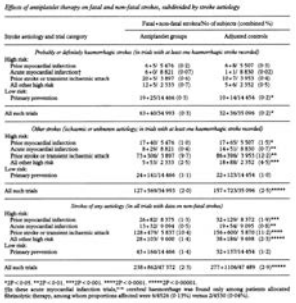

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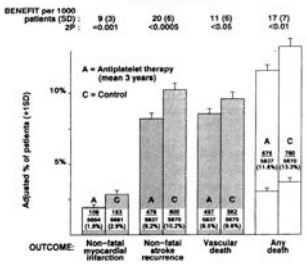

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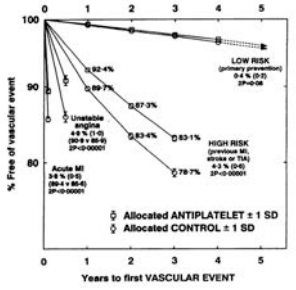

antiplatelet trialists' collaboration. lancet 308: 81-106 (1994)

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

Antithrombotic Trialists' Collaboration

antithrombotic trialists' collaboration. bmj 324: 71-86 (2002)

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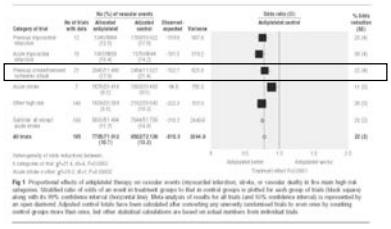
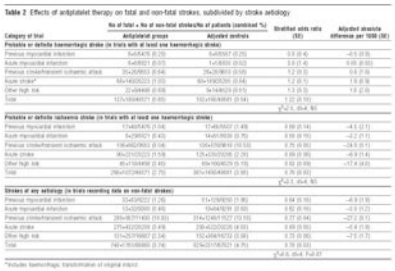
antithrombotic trialists' collaboration



antithrombotic trialists' collaboration. bmj 324: 71-86 (2002)

antithrombotic trialists' collaboration



antithrombotic trialists' collaboration. bmj 324: 71-86 (2002)

antithrombotic trialists' collaboration

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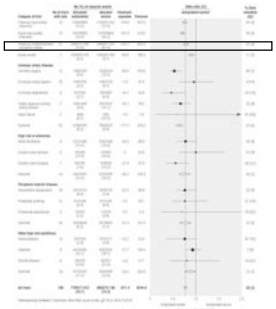

antithrombotic trialists' collaboration. bmj 324: 71-86 (2002)

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secondary prevention

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aspirin

study	year	agent	dose	n	f/u	stroke	mortality (v)
AITIA	1977	ASA placebo	1300	88 90	0.5	10 12	3 6
Canadian Cooperative study	1978	ASA/placebo 1 sulfinpyrazone/placebo 2 ASA/sulfinpyrazone placebo 1/placebo 2	1300 1300	144 156 146 139	2.2	22 29 14 20	4 6 4 8
Danish Cooperative study	1983	ASA placebo	1000	101 102	2.1	11 18	6 6
AICLA	1983	ASA/dipyridamole ASA placebo	990 990	202 198 204	3.0	18 17 31	5 5 4
UK-TIA study	1988	ASA ASA placebo	1200 300	815 806 814	4.0	66 68 88	84 84 86

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aspirin

study	year	agent	dose	n	f/u	stroke	mortality (v)
Dutch TIA trial	1991	ASA ASA	283 30	1576 1555	2.6	109 90	107 105
SALT	1991	ASA placebo	75 –	676 684	2.7	93 112	48 50
Swedish Cooperative study	*1987	ASA placebo	1500 –	253 252	2.0	32 32	27 25
ESPS-2	*1997	ERDP/ASA ERDP ASA placebo	400/5 0 400 50 –	1650 1654 1649 1649	2.0	157 211 206 250	105 118 109 117
IST	*1997	ASA no ASA	300 –	9720 9715	0.5	362 452	855 896
CAST	*1997	ASA no ASA	160 –	1055 4 1055 2	0.08	335 351	243 283

sulfinpyrazone

sulfinpyrazone/suloctidil

study	year	agent	dose	n	f/u	stroke	mortality (v)
Canadian Cooperative study	1978	ASA/placebo 1 sulfinpyrazone/placebo 2 ASA/sulfinpyrazone placebo 1/placebo 2	1300 1300 	144 156 146 139	2.2	22 29 14 20	4 6 4 8
Roden	1981	sulfinpyrazone placebo	800	39 39	0.3	1 3	1 1
Candelise	1982	sulfinpyrazone ASA	800 1000	62 63	2.0	2 2	1 0
Candelise	*1979	sulfinpyrazone placebo	800	145 145			
Gent	*1985	suloctidil placebo	600	218 220	1.7	29 28	4 14

clopidogrel

clopidogrel

study	year	agent	dose	n	f/u	stroke	mortality (v)
Hass	1989	ticlopidine ASA	500 1300	1529 1540	2.0 - 6.0	172 212	120 116
CATS	*1989	ticlopidine placebo	500 –	525 528	2.0	54 89	17 29
CAPRIE	*1996	clopidogrel ASA	75 325	3233 3198	1.9	315 338	102 102
Diener	*2004	ASA/clopidogrel placebo/clopidogrel	75/75 –/75	3420 3454	1.5	299 309	124 121
Bhatt	*2006	ASA/clopidogrel ASA/placebo	75-162/75 75-162/–	7802 7801	2.3	132 163	
Sacco	*2008	ASA/ERDP clopidogrel	50/400 75	1018 1 1015 1	2.5	916 898	435 459

C<u>l</u>opidogrel versus <u>A</u>spirin in <u>P</u>atients at <u>R</u>isk for <u>I</u>schaemic <u>E</u>vents (CAPRIE)

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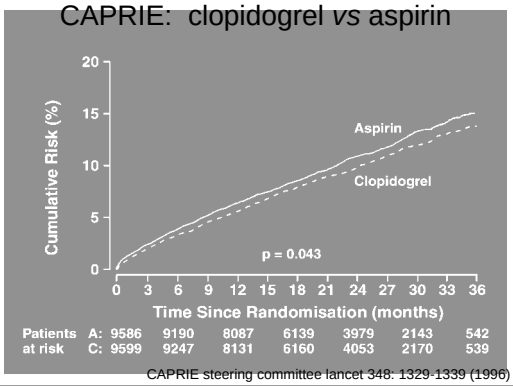
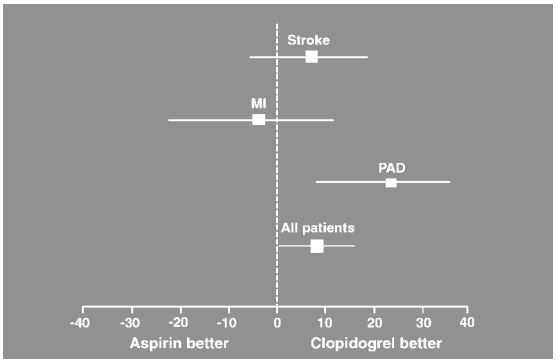
CAPRIE: clopidogrel *vs* aspirin



CAPRIE steering committee lancet 348: 1329-1339 (1996)

CAPRIE: relative-risk reduction (%)



EFFECTS OF CLOPIDOGREL IN ADDITION TO ASPIRIN IN PATIENTS WITH ACUTE CORONARY SYNDROMES WITHOUT ST-SEGMENT ELEVATION

THE CLOPIDOGREL IN UNSTABLE ANGINA TO PREVENT RECURRENT EVENTS TRIAL INVESTIGATORS*

CURE trial investigators n engl j med 345: 494-502 (2001)

CURE

hypothesis: clopidpgrel + ASA is superior to various doses of ASA in patients with acute coronary syndrome for vascular outcome(s)

design: prospective randomized blinded, six-arm study (12,562 patients)
clopidogrel (75 mg/d) + ASA (v) ASA (75 – 325 mg/d)

primary outcome: cardiovascular demise, MI, or stroke
results:

	primary outcome (ITT)	major hemorrhages
placebo + ASA	11.4%	2.7%
clopidogrel + ASA	9.3%	3.7%

conclusion: in ACS, clopidogrel added to ASA had greater benefit and increased hemorrhagic risk

CURE

TABLE 2. INCIDENCE OF THE MAIN STUDY OUTCOMES.*

OUTCOME	CLOPIDOGREL GROUP (N=6259)	PLACEBO GROUP (N=6303)	RELATIVE RISK (95% CI)	P VALUE
	no. (%)			
First primary outcome: nonfatal myocardial infarction, stroke, or death from cardiovascular causes	582 (9.3)	719 (11.4)	0.80 (0.72–0.90)	<0.001
Second primary outcome: first primary outcome or refractory ischemia	1035 (16.5)	1187 (18.8)	0.86 (0.79–0.94)	<0.001
Death from cardiovascular causes	318 (5.1)	345 (5.5)	0.93 (0.79–1.08)	
Myocardial infarction†	326 (5.2)	419 (6.7)	0.77 (0.67–0.89)	
Q wave	116 (1.9)	193 (3.1)	0.60 (0.48–0.76)	
Non–Q wave	216 (3.5)	242 (3.8)	0.89 (0.74–1.07)	
Stroke	75 (1.2)	87 (1.4)	0.86 (0.63–1.18)	
Refractory ischemia‡	544 (8.7)	587 (9.3)	0.93 (0.82–1.04)	
During initial hospitalization	86 (1.4)	126 (2.0)	0.68 (0.52–0.90)	
After discharge	469 (7.6)	461 (7.6)	0.99 (0.87–1.13)	
Death from noncardiovascular causes	41 (0.7)	45 (0.7)	0.91 (0.60–1.39)	

*The number of patients who died from cardiovascular causes or had a nonfatal myocardial infarction was 539 (8.6 percent) in the clopidogrel group and 660 (10.5 percent) in the placebo group ($P<0.001$, relative risk, 0.81; 95 percent confidence interval, 0.72 to 0.91). The corresponding numbers at 30 days were 241 (3.9 percent) and 305 (4.8 percent) (relative risk, 0.79; 95 percent confidence interval, 0.67 to 0.94; $P=0.007$). CI denotes confidence interval.

†Some patients had both a Q-wave and a non–Q-wave myocardial infarction.

‡Only the first ischemic event was counted for each patient.

CURE trial investigators n engl j med 345: 494-502 (2001)

CURE

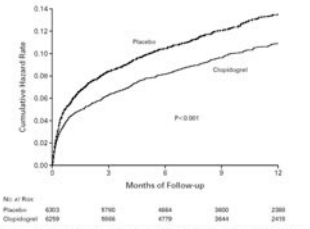


Figure 1. Cumulative Hazard Rates for the First Primary Outcome (Death from Cardiovascular Causes, Nonfatal Myocardial Infarction, or Stroke) during the 12 Months of the Study.
The results demonstrate the sustained effect of clopidogrel.

CURE trial investigators n engl j med 345: 494-502 (2001)

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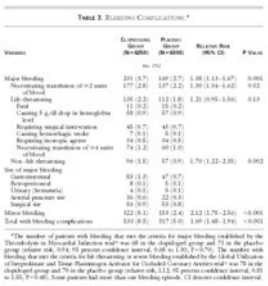
CURE



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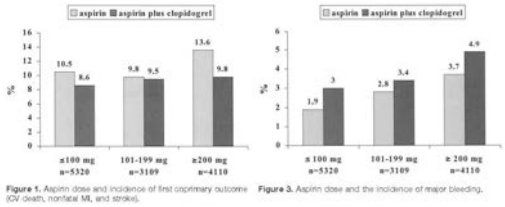


Figure 1. Aspirin dose and incidence of first coprimary outcome (CV death, nonfatal MI, and stroke).

Figure 3. Aspirin dose and the incidence of major bleeding.

peters rjg *et al* circulation 108: 1682-1687 (2003)

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

diener h-c *et al* lancet 364: 331-337 (2004)

MATCH

hypothesis: adding clopidogrel to ASA is superior to ASA alone for outcomes in high-risk patients with recent ischemic stroke or TIA

design: prospective randomized double-blinded, placebo-controlled two-arm study (7,599 patients)

clopidogrel (75 mg/d) + ASA (75 mg/d) clopidogrel (75 mg/d)

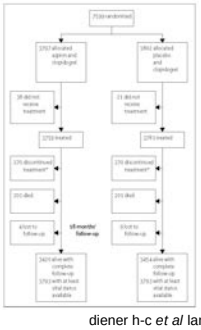
primary outcome: ischemic stroke, MI, vascular mortality, or rehospitalization

results:

	primary outcome (ITT)	life-threatening hemorrhages
clopidogrel	16.7%	1.3%
clopidogrel + ASA	15.7%	2.6%

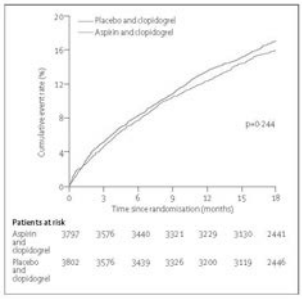
conclusion: combination not different from ASA alone

MATCH



diener h-c *et al* lancet 364: 331-337 (2004)

MATCH



diener h-c *et al* lancet 364: 331-337 (2004)

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MATCH

	Number (%) with event: Aspirin and clopidogrel (n=3797)	Placebo and clopidogrel (n=3802)	Absolute risk reduction (95% CI)	Relative risk reduction (95% CI)	p*
Myocardial infarction, ischaemic stroke, and vascular death	445 (12%)	473 (12%)	0·72% (−0·7 to 2·2)	5·9% (−7·1 to 17·3)	0·360
Myocardial infarction (fatal or not)	73 (2%)	68 (2%)	−0·12% (−0·7 to 0·5)	−7·7% (−49·8 to 22·6)	0·660
Ischaemic stroke (fatal or not)	359 (9%)	333 (9%)	0·62% (−0·6 to 1·9)	7·3% (−8·5 to 20·4)	0·353
Vascular death	124 (3%)	121 (3%)	−0·08% (−0·9 to 0·7)	−2·4% (−31·5 to 20·3)	0·854
Ischaemic stroke (fatal or not) and vascular death	401 (11%)	430 (11%)	0·75% (−0·7 to 2·2)	6·6% (−7·0 to 18·5)	0·324
Any stroke (ischaemic stroke, primary intracranial haemorrhage, or non-classifiable stroke [fatal or not])	339 (9%)	347 (9%)	0·20% (−1·1 to 1·5)	2·0% (−13·8 to 15·6)	0·790
Death (all cause)	201 (5%)	201 (5%)	−0·01% (−1·0 to 1·0)	−0·1% (−21·5 to 17·8)	0·992
Non-fatal myocardial infarction, non-fatal ischaemic stroke, rehospitalisation for acute ischaemic event	505 (13%)	546 (14%)	1·06% (−0·5 to 2·6)	7·6% (−4·3 to 18·2)	0·199

*First event counted (independently from the first outcome from the composite of the primary endpoint).

Table 3: Frequency of secondary endpoint events

diener h-c *et al* lancet 364: 331-337 (2004)

MATCH

	Number (%) with event: Aspirin and clopidogrel (n=3759)	Placebo and clopidogrel (n=3781)	Difference (%) between aspirin and placebo (95% CI)	p*
Life-threatening bleeding	96 (3%)	49 (1%)	1·26 (0·64 to 1·88)	<0·0001
Fatal bleeding	16 (<1%)	11 (<1%)	0·13 (−0·14 to 0·40)	
Non-fatal bleeding	81 (2%)	38 (1%)	1·15 (0·59 to 1·71)	
Symptomatic intracranial haemorrhage†	40 (1%)	25 (1%)	0·40 (−0·01 to 0·82)	
Primary intracranial haemorrhage	32 (1%)	17 (<1%)	0·40 (0·04 to 0·76)	
Major bleeding	73 (2%)	22 (1%)	1·36 (0·86 to 1·86)	<0·0001
Minor bleeding	120 (3%)	39 (1%)	2·16 (1·51 to 2·81)	<0·0001

*Pearson's χ^2 test. †All symptomatic (and thus primary) intracranial haemorrhages were life-threatening bleeds.

Table 4: Number (%) of patients with bleeding events

diener h-c *et al* lancet 364: 331-337 (2004)

MATCH

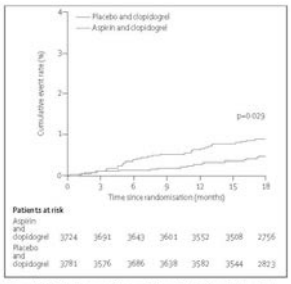

Figure 4: Kaplan-Meier curves for cumulative rates of primary intracranial haemorrhage

diener h-c *et al* lancet 364: 331-337 (2004)

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*

bhatt dl *et al* n engl j med 354: 1706-1717 (2006)

CHARISMA

hypothesis: clopidogrel and ASA are superior to ASA and placebo for clinically evident cardiovascular disease or multiple risk factors

design: prospective randomized double-blinded, placebo-controlled two-arm study (15,603 patients)
clopidogrel (75 mg/d) + ASA (v) ASA (75 – 162 mg/d)

primary outcome: MI, stroke, or cardiovascular mortality

results:

primary outcome (ITT)		severe hemorrhages	
placebo + ASA	7.3%	1.3%	clopidogrel + ASA 6.8%
	1.7%		

conclusion: combination not more effective than ASA in reducing cardiovascular and cerebrovascular events

CHARISMA

Table 4. Composite and Individual Primary and Secondary End Points.

End Point	Clopidogrel plus Aspirin (N = 7802)	Placebo plus Aspirin (N = 7801)	Relative Risk (95% CI)*	P Value
	no. (%)			
Efficacy end points				
Primary efficacy end point	534 (6.8)	575 (7.3)	0.93 (0.83–1.05)	0.22
Death from any cause	371 (4.8)	374 (4.8)	0.99 (0.86–1.14)	0.90
Death from cardiovascular causes	238 (3.1)	229 (2.9)	1.04 (0.87–1.25)	0.68
Myocardial infarction (nonfatal)	146 (1.9)	155 (2.0)	0.94 (0.75–1.18)	0.59
Ischemic stroke (nonfatal)	132 (1.7)	163 (2.1)	0.81 (0.64–1.02)	0.07
Stroke (nonfatal)	150 (1.9)	189 (2.4)	0.79 (0.64–0.98)	0.03
Secondary efficacy end point ‡	1301 (16.7)	1395 (17.9)	0.92 (0.86–0.995)	0.04
Hospitalization for unstable angina, transient ischemic attack, or revascularization	866 (11.1)	957 (12.3)	0.90 (0.82–0.98)	0.02
Safety end points				
Severe bleeding	130 (1.7)	104 (1.3)	1.25 (0.97–1.61)	0.09
Fatal bleeding	26 (0.3)	17 (0.2)	1.53 (0.83–2.82)	0.17
Primary intracranial hemorrhage	26 (0.3)	27 (0.3)	0.96 (0.56–1.65)	0.89
Moderate bleeding	164 (2.1)	101 (1.3)	1.62 (1.27–2.08)	<0.001

bhatt dl *et al* n engl j med 354: 1706-1717 (2006)

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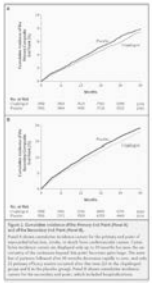
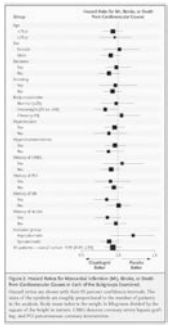
CHARISMA



bhatt dl *et al* n engl j med 354: 1706-1717 (2006)

CHARISMA



bhatt dl *et al* n engl j med 354: 1706-1717 (2006)

Clopidogrel with Aspirin in Acute Minor Stroke or Transient Ischemic Attack

Yongjun Wang, M.D., Yilong Wang, M.D., Ph.D., Xingquan Zhao, M.D., Ph.D., Liping Liu, M.D., Ph.D., David Wang, D.O., F.A.H.A., F.A.A.N., Chunxue Wang, M.D., Ph.D., Chen Wang, M.D., Hao Li, Ph.D., Xia Meng, M.D., Ph.D., Liying Cui, M.D., Ph.D., Jianping Jia, M.D., Ph.D., Qiang Dong, M.D., Ph.D., Anding Xu, M.D., Ph.D., Jinsheng Zeng, M.D., Ph.D., Yansheng Li, M.D., Ph.D., Zhimin Wang, M.D., Haiqin Xia, M.D., and S. Claiborne Johnston, M.D., Ph.D., for the CHANCE Investigators*

wang y *et al* n engl j med 369: 11-19 (2013)

CHANCE

hypothesis: clopidogrel and ASA are superior to ASA and placebo for TIA or minor stroke (within 24 hours)

design: prospective randomized double-blinded, placebo-controlled two-arm study (5,170 patients/China)

clopidogrel (75 mg/d) + ASA (75 mg) ASA (75 mg/d)

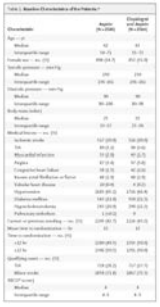
primary outcome: stroke (ischemic or hemorrhagic)

results:

	primary outcome (ITT)	severe hemorrhages
placebo + ASA	11.7%	0.2%
clopidogrel + ASA	8.2%	0.2%

conclusion: combination clopidogrel + ASA superior to ASA in decreasing stroke within 90 days in a Chinese population

CHANCE



wang y *et al* n engl j med 369: 11-19 (2013)

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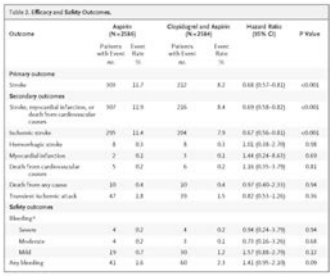

wang y *et al* n engl j med 369: 11-19 (2013)

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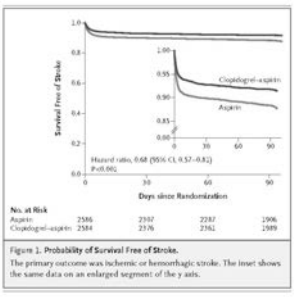
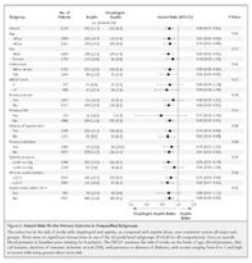


Figure 1. Probability of Survival Free of Stroke.
The primary outcome was ischemic or hemorrhagic stroke. The inset shows the same data on an enlarged segment of the y axis.

wang y *et al* n engl j med 369: 11-19 (2013)

CHANCE



wang y *et al* n engl j med 369: 11-19 (2013)

POINT

hypothesis: 90-day event-free survival higher with clopidogrel + ASA compared to placebo + ASA when patients treated within 12 hours of last known new ischemic symptoms

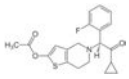
design: prospective randomized double-blinded, placebo-controlled two-arm study (North America)
clopidogrel (600mg + 75 mg/d) + ASA (50 – 325 mg/d)
placebo + ASA (50 – 325 mg/d)

primary outcome: ischemic stroke, MI, or ischemic vascular death within 90 days

results: in progress

conclusion: in progress

prasugrel



prasugrel

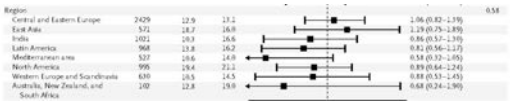
Prasugrel versus Clopidogrel for Acute Coronary Syndromes without Revascularization

Prasugrel versus clopidogrel for patients with unstable angina or non-ST-segment elevation myocardial infarction with or without angiography: a secondary, prespecified analysis of the TRILOGY ACS trial

Pretreatment with Prasugrel in Non–ST-Segment Elevation Acute Coronary Syndromes

roe mt *et al* n engl j med 367: 1297-1309 (2012)
wiviott sd *et al* lancet 382: 605-613 (2013)
montalescot g *et al* n engl j med 369: 999-1010 (2013)

prasugrel



roe mt *et al* n engl j med 367: 1297-1309 (2012)

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dipyridamole

dipyridamole

study	year	agent	dose	n	f/u	stroke	mortality (v)
Acheson	1969	dipyridamole placebo	400/800 –	85/69 84/70	2.1	5/7 7/4	– –
AICLA	1983	ASA/dipyridamole ASA placebo	990/225 990	202 198 204	3.0	18 17 31	5 5 4
ESPS	1987	ASA/dipyridamole placebo	975/225 –	1250 1250	2.0	114 184	69 100
A-C Cooperative study	1985	ASA/dipyridamole ASA	1300/300 1300	448 442	1.5	53 60	29 29
Mathius-Guiu	1987	ASA/dipyridamole dipyridamole	50/300 400	115 71	1.8	3 3	1 2
ESPS-2	*1997	ERDP/ASA ERDP ASA placebo	400/50 400 50 –	1650 1654 1649 1649	2.0	157 211 206 250	105 118 109 117
ESPRIT	2006	ASA/dipyridamole ASA	30-325/400 30-325	1363 1376	3.5	96 116	44 60

European Stroke Prevention Study 2
(ESPS 2)

Prevention Regimen for Effectively Avoiding
Second Strokes (PRoFESS)

European Stroke Prevention Study 2 (ESPS 2)

aim: compare the relative efficacy and safety of ASA (25 mg), ERDP (200 mg), ASA + ERDP, or placebo among 6,000 patients with recent ischemic stroke

design: multicenter, randomized, double-blind, placebo-controlled with a 2 x 2 factorial distribution

primary outcome: fatal/non-fatal stroke, any cause mortality, stroke and/or mortality

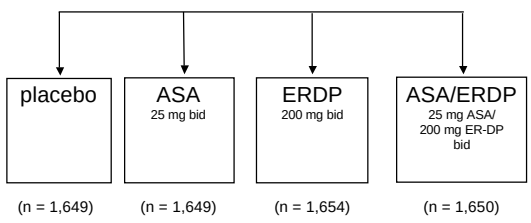
secondary outcome: TIA, MI, vascular events (APT definition), other vascular events

safety outcomes: major/minor hemorrhagic events, intracerebral hemorrhage

ESPS 2 group. j neurol sci 151:S1-S77 (1997)

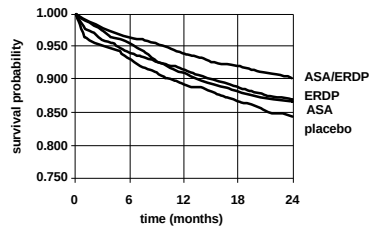
ESPS 2

n = 6,602



ESPS 2 group. j neurol sci 151:S1-S77 (1997)

ESPS 2
stroke survival



all patients

diener hc *et al* j neurol sci 143:1-13 (1996)

delZoJMEMppt1c101702pm

ESPS 2: safety
severe or fatal hemorrhage

placebo	ERDP	ASA	ERDP + ASA
7	6	20	27
(0.4%)	(0.4%)	(1.2%)	(1.6%)

n.s.

ESPS 2 group. j neurol sci 151:S1-S77 (1997)

Aspirin plus dipyridamole versus aspirin alone after cerebral ischaemia of arterial origin (ESPRIT): randomised controlled trial

The ESPRIT Study Group*

ESPRIT study group lancet 367:1665-1673 (2006)

ESPRIT

hypothesis: resolve uncertainty among trials of ASA + dipyridamole *vs* ASA for secondary prevention

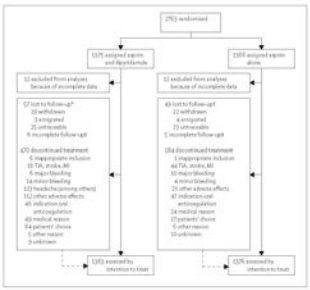
design: prospective randomized controlled trial (2,763 patients) ASA (30-325 mg/d) ASA (30-325 mg/d) + dipyridamole (200 mg x 2/d)

primary outcome: first of vascular mortality, stroke, MI, or major hemorrhage

results:
primary event rate (ITT) major hemorrhages ASA 16% ASA + dipyridamole 13%

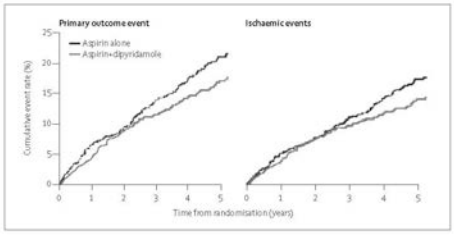
conclusion: prefer ASA/dipyridamole over ASA alone

ESPRIT



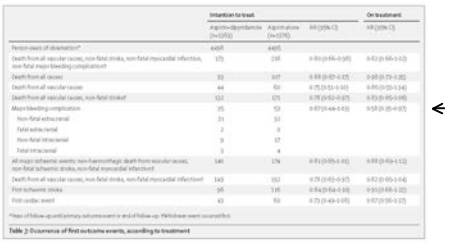
ESPRIT study group lancet 367:1665-1673 (2006)

ESPRIT



ESPRIT study group lancet 367:1665-1673 (2006)

ESPRIT



ESPRIT study group lancet 367:1665-1673 (2006)

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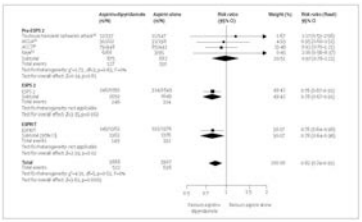
ESPRIT



ESPRIT study group lancet 367:1665-1673 (2006)

Aspirin and Extended-Release Dipyridamole versus Clopidogrel for Recurrent Stroke

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

sacco rl *et al* n engl j med 359: 1238-1251 (2008)

Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS)

aim: compare the relative efficacy and safety of ASA/ERDP with clopidogrel among patients with recent ischemic stroke

design: prospective 2 x 2 factorial randomized blinded placebo controlled trial

ASA (20 mg)/ERDP (200 mg) clopidogrel 75 mg daily

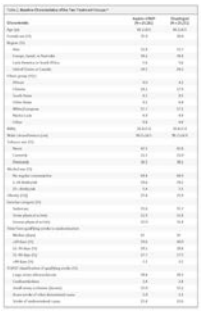
primary outcome: recurrent stroke of any type

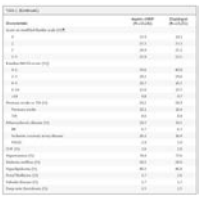
secondary outcome: composite of stroke, MI, mortality

safety outcomes: major/minor hemorrhagic events, intracerebral hemorrhage

sacco rl *et al* n engl j med 359: 1238-1251 (2008)

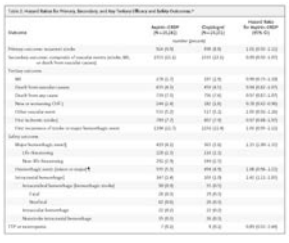
PRoFESS





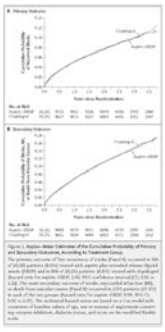
sacco rl *et al* n engl j med 359: 1238-1251 (2008)

PRoFESS



sacco rl *et al* n engl j med 359: 1238-1251 (2008)

PRoFESS



sacco rl *et al* n engl j med 359: 1238-1251 (2008)

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PRoFESS

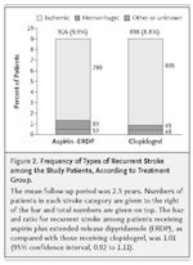

Figure 2. Frequency of Types of Recurrent Stroke among the Study Patients, According to Treatment Group.

The mean follow-up period was 2.5 years. Numbers of patients in each stroke category are given to the right of the bar and total numbers are given on top. The hazard ratio for recurrent stroke among patients receiving aspirin plus extended-release dipyridamole (ERDP), as compared with those receiving clopidogrel, was 1.01 (95% confidence interval, 0.92 to 1.11).

sacco rl *et al* n engl j med 359: 1238-1251 (2008)

PRoFESS

"The trial did not meet the predefined criteria for noninferiority but showed similar rates of recurrent stroke with ASA-ERDP and with clopidogrel. There is no evidence that either of the two treatments was superior to the other in the prevention of recurrent stroke."

sacco rl *et al* n engl j med 359: 1238-1251 (2008)

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primary prevention

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atrial fibrillation and stroke
l'aquila

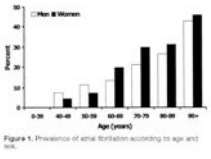

Figure 1. Prevalence of atrial fibrillation according to age and sex.

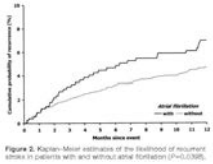

Figure 2. Kaplan-Meier estimates of the likelihood of recurrent stroke in patients with and without atrial fibrillation (P=0.038).

marini c, *et al*. stroke 36: 1115-1119 (2005)

atrial fibrillation and stroke
framingham

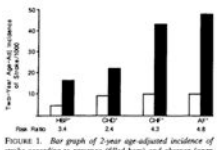

FIGURE 1. *Bar graph of 2-year age-adjusted incidence of stroke according to presence (filled bars) and absence (open bars) of cardiovascular condition. HBP, hypertension; CHD, coronary heart disease; CHF, cardiac failure; AF, atrial fibrillation. *p<0.001 different from unity.*

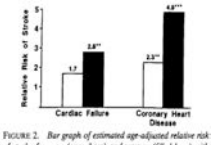

FIGURE 2. *Bar graph of estimated age-adjusted relative risk of stroke for men (open bars) and women (filled bars) with atrial fibrillation compared with those without atrial fibrillation in presence of cardiac failure or coronary heart disease. **p<0.01, ***p<0.001 significant excess of strokes.*

wolf pa *et al*. stroke 22: 983-988 (1991)

non-valvular atrial fibrillation
primary prevention studies

AFASAK *
SPAF *
BAATAF *
CAFA *
SPAF II
SPINAF
SPAF III

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non-valvular atrial fibrillation

study	agent	patients	stroke	mortality
AFASAK	warfarin	335	5(0)	~~
	ASA	336	17(3)	~~
	placebo	336	19(2)	~~
SPAF	warfarin/ASA	393	7(0)	14
	placebo	195	17(1)	8
	ASA	517	18(1)	31
	placebo	528	34(4)	39
BAATAF	warfarin	212	2(0)	11
	placebo	208	(0)	26
CAFA	warfarin	187	4(1)	7
	placebo	191	9(2)	6
SPAFII	warfarin	358	13(1)	36
	ASA	357	19(2)	41
	warfarin	197	13(1)	26
	ASA	188	18(0)	24
SPAFIII	warfarin INR 2.0-3.0	523	11(0)	35
	warfarin INR 1.2-1.5	521	43(1)	42

non-valvular atrial fibrillation

study	agent	patients	stroke	mortality
AFASAK	warfarin	335	5(0)	~~
	ASA	336	17(3)	~~
	placebo	336	19(2)	~~
SPAF	warfarin/ASA	393	7(0)	14
	placebo	195	17(1)	8
	ASA	517	18(1)	31
	placebo	528	34(4)	39
BAATAF	warfarin	212	2(0)	11
	placebo	208	(0)	26
CAFA	warfarin	187	4(1)	7
	placebo	191	9(2)	6
SPAFII	warfarin	358	13(1)	36
	ASA	357	19(2)	41
	warfarin	197	13(1)	26
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SPAFIII	warfarin INR 2.0-3.0	523	11(0)	35
	warfarin INR 1.2-1.5	521	43(1)	42

AF and anti-thrombotics
comparisons

comparison	n (trials)	relative risk	*p*
warfarin *vs* control/placebo	13	0.33 (0.24-0.45) 0.69 (0.53-0.89)	
ASA *vs* placebo	6	0.78 (0.62-0.98)	
warfarin *vs* ASA	5	0.65 (0.49-0.86)	0.003
warfarin *vs* ASA*		0.56 (0.41-0.76)	< 0.001

* ischemic strokes

lip gyh, boos cj heart 92: 155-161 (2006)

atrial fibrillation
anti-platelet agents *vs* warfarin ± irbesartan

- Atrial Fibrillation Clopidogrel Focal with Irbesartan for Prevention of Vascular Events trial

  ACTIVE – W clopidogrel/ASA *vs* warfarin

- Atrial Fibrillation Clopidogrel Focal with Irbesartan for Prevention of Vascular Events trial

  ACTIVE – A clopidogrel/ASA *vs* ASA

  ACTIVE – I irbesartan *vs* placebo

ACTIVE – W

Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial

Summary

Background Oral anticoagulation therapy reduces risk of vascular events in patients with atrial fibrillation. However, long-term monitoring is necessary and many patients cannot achieve optimum anticoagulation. We assessed whether clopidogrel plus aspirin was non-inferior to oral anticoagulation therapy for prevention of vascular events.

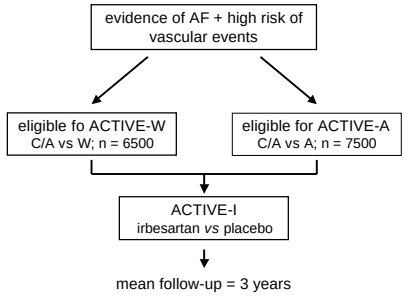
Methods Patients were enrolled if they had atrial fibrillation plus one or more risk factor for stroke, and were randomly allocated to receive oral anticoagulation therapy (target international normalised ratio of 2·0–3·0; n=1371) or clopidogrel (75 mg per day) plus aspirin (75–100 mg per day recommended; n=1331). Outcome events were adjudicated by a blinded committee. Primary outcome was first occurrence of stroke, non-CNS systemic embolus, myocardial infarction, or vascular death. Analyses were by intention-to-treat. This study is registered with ClinicalTrials.gov, number NCT00241176.

Results The study was stopped early because of clear evidence of superiority of oral anticoagulation therapy. There were 165 primary events in patients on oral anticoagulation therapy (annual risk 3·93%) and 214 in those on clopidogrel plus aspirin (annual risk 5·44%, relative risk 1·44 [1·18–1·76], p=0·0003). Patients on oral anticoagulation therapy who were already receiving this treatment at study entry had a trend towards a greater reduction in vascular events (relative risk 1·50, 95% CI 1·19–1·90) and a significantly (p=0·49 for interaction) lower risk of major bleeding with oral anticoagulation therapy (1·30 [0·94–1·79] than patients not on this treatment at study entry (1·27, 0·85–1·89 and 0·59, 0·32–1·08, respectively).

Conclusion Oral anticoagulation therapy is superior to clopidogrel plus aspirin for prevention of vascular events in patients with atrial fibrillation at high risk of stroke, especially in those already taking oral anticoagulation therapy.

the ACTIVE investigators. lancet 367: 1903-1912 (2006)

atrial fibrillation
anti-platelet agents *vs* warfarin ± irbesartan



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ACTIVE – W

hypothesis: the combination clopidogrel + aspirin is not inferior to well-controlled warfarin for prophylaxis against embolic events in non-valvular AF

design: prospective randomized, two-arm (6706 patients)

warfarin, INR 2.0-3.0 — clopidogrel 75 mg/day + ASA 75 – 100 mg/day

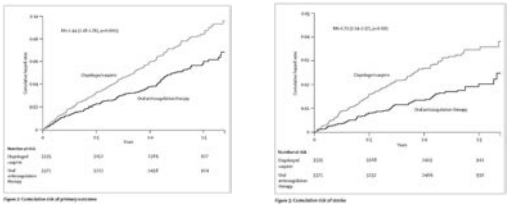
primary outcome: stroke, systemic embolism, MI, vascular mortality

results: terminated early

primary event rate (ITT)		major hemorrhage
warfarin	3.93%/year	2.2%/year
combination	5.64%/year	2.4%/year
	$p = 0.0002$	$p = 0.67$

the ACTIVE investigators. lancet 367: 1903-1912 (2006)

ACTIVE – W
outcomes



primary outcome — stroke

the ACTIVE investigators. lancet 367: 1903-1912 (2006)

atrial fibrillation
warfarin *vs* clopidogrel

phase III prospective trial terminated due to safety concerns

incidence of stroke increased 75% in clopidogrel arm over warfarin arm

report by Sanofi, late 2005

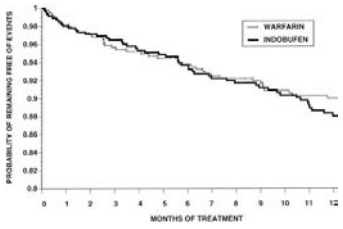
non-valvular atrial fibrillation
secondary prevention studies

- significant reduction in mortality from vascular disease, stroke, MI, or embolism with warfarin (group 1, INR 2.5 – 4.0) compared to ASA (group 2, 300 mg) *vs* respective placebo
  EAFT study group. lancet 342: 1255-1262 (1993)

non-valvular atrial fibrillation
secondary prevention studies

- significant reduction in mortality from vascular disease, stroke, MI, or embolism with warfarin (group 1, INR 2.5 – 4.0) compared to ASA (group 2, 300 mg) *vs* respective placebo
  EAFT study group. lancet 342: 1255-1262 (1993)
- no difference in non-fatal stroke, MI, or systemic/pulmonary embolism, or vascular death between warfarin (INR 2.0 – 3.5) and ibuprofen (200 mg x 2)
  morocutto c *et al* for the studio italiano fibrillazione atriale (SIFA) investigators. stroke 28: 1015-1021 (1997)

non-valvular atrial fibrillation
secondary prevention studies



morocutto c *et al* (SIFA) stroke 28: 1015-1021 (1997)

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acute intervention

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The Combined Approach to Lysis Utilizing Eptifibatide and rt-PA in Acute Ischemic Stroke
The CLEAR Stroke Trial

Arthur M. Pancioli, MD; Joseph Broderick, MD; Thomas Brott, MD; Thomas Tomsick, MD; Jane Khoury, PhD; Judy Bean, PhD; Gregory del Zoppo, MD; Dawn Kleindorfer, MD; Daniel Woo, MD; Pooja Khatri, MD; John Castaldo, MD; James Frey, MD; James Gebel, Jr. MD; Scott Kasner, MD; Chelsea Kidwell, MD; Thomas Kwiatkowski, MD; Richard Libman, MD; Richard Mackenzie, MD; Phillip Scott, MD; Sidney Starkman, MD; R. Jason Thurman, MD; for the CLEAR Trial Investigators

pancioli am *et al* stroke 39: 3268-3276 (2008)

CLEAR

hypothesis: eptifibatide and rt-PA (modified dose) is as safe as rt-PA (0.9 mg/kg) for acute treatment of ischemic stroke

design: prospective randomized double-blinded, dose-escalation safety phase II study (94 patients)
eptifibatide (0.75 µg/kg/min) + rt-PA rt-PA (0.9 mg/kg)
rt-PA (0.3 mg/kg) or rt-PA (0.45 mg/kg)

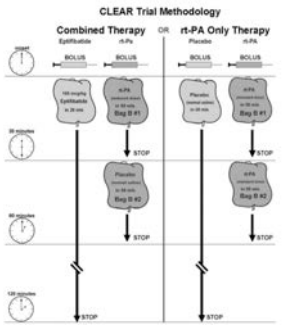
primary outcome: symptomatic intracerebral hemorrhage

results:

primary safety outcome			
tier 1 + tier 2	1.4%	rt-PA	8.0%

conclusion: safety of eptifibatide + rt-PA dose tiers shown

CLEAR



pancioli am *et al* stroke 39: 3268-3276 (2008)

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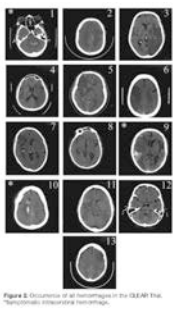

pancioli am *et al* stroke 39: 3268-3276 (2008)

CLEAR

Table 3. Clinical Outcomes at 3 Months for Tier 1, Tier 2, and the Overall Trial of Combination Treatment Versus rt-PA–Only Groups

	Tier 1			Tier 2			Overall		
	Combined	Control	*P* Value	Combined	Control	*P* Value	Combined	Control	*P* Value
n	29	11		40	14		69	25	
mRS score 0–1 or return to baseline*	9 (31%)	5 (45%)	0.47	12 (30%)	7 (50%)	0.25	21 (30%)	12 (48%)	0.14
Barthel index <95*	12 (41%)	8 (73%)	0.10	20 (50%)	10 (71%)	0.22	32 (46%)	18 (72%)	0.04
Glasgow outcome score 5*	13 (45%)	5 (45%)	1.0	15 (38%)	8 (57%)	0.25	28 (41%)	13 (52%)	0.35
Symptomatic ICH	1 (3%)	1 (9%)	0.48	0 (0%)	1 (7%)	0.26	1 (1%)	2 (8%)	0.17
Any ICH	5 (17%)	3 (27%)	0.66	3 (8%)	2 (14%)	0.60	8 (12%)	5 (20%)	0.32
Death at 90 days	8 (28%)	1 (9%)	0.40	7 (18%)	2 (14%)	1.0	15 (22%)	3 (12%)	0.38
Death at 7 days	4 (14%)	1 (9%)	1.0	5 (12%)	0 (0%)	0.31	9 (13%)	1 (4%)	0.28
NIHSS score decrease ≥4 in 24 hours	14 (48%)	6 (54%)	1.0	15 (38%)	5 (36%)	1.0	29 (42%)	11 (44%)	1.0
NIHSS score <2 at 24 hours	2 (7%)	1 (9%)	1.0	7 (18%)	4 (29%)	0.45	9 (13%)	5 (20%)	0.51

Data are expressed as n (%); comparisons were made with Fisher's exact test owing to small numbers.
*Deaths (n=19) and missing (n=4) patients were coded as "bad" outcome.

pancioli am *et al* stroke 39: 3268-3276 (2008)

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CLEAR

Table 6. Outcome Variables: CLEAR Trial Combination Pts Versus NINDS Stroke Trial rt-PA and Control Pts

	CLEAR	NINDS rt-PA	P Value	CLEAR	NINDS Control	P Value
n or N	69	115		69	151	
mRS score 0–1 or return to baseline*	21 (30%)	46 (40%)	0.19	21 (30%)	36 (24%)	0.30
Barthel index ≥95*	32 (46%)	53 (46%)	0.97	32 (46%)	57 (38%)	0.23
Glasgow outcome score=0*	28 (41%)	47 (41%)	0.97	28 (41%)	44 (29%)	0.09
Symptomatic ICH	1 (1%)	9 (8%)	0.08	1 (1%)	2 (1%)	1.0
Any ICH	8 (12%)	13 (11%)	0.95	8 (12%)	8 (5%)	0.10
Death at 90 days	15 (22%)	23 (20%)	0.56	15 (22%)	31 (20%)	0.84
Death at 7 days	9 (13%)	9 (8%)	0.25	9 (13%)	14 (9%)	0.40
NIHSS score decrease ≥4 in 24 hours*	29 (42%)	47 (41%)	0.88	29 (42%)	57 (38%)	0.55
NIHSS score ≤2 at 24 hours*	9 (13%)	15 (13%)	1.0	9 (13%)	8 (5%)	0.04

Data expressed as n (%).
*Deaths and missing patients were coded as "bad" outcome.

pancioli am *et al* stroke 39: 3268-3276 (2008)

Combined Approach to Lysis Utilizing Eptifibatide and Recombinant Tissue Plasminogen Activator in Acute Ischemic Stroke–Enhanced Regimen Stroke Trial

Arthur M. Pancioli, MD; Opeolu Adeoye, MD, MS; Pamela A. Schmit, RN, BSN; Jane Khoury, PhD; Steven R. Levine, MD; Thomas A. Tomsick, MD; Heidi Sucharew, PhD; Claudette E. Brooks, MD; Todd J. Crocco, MD; Laurie Gutmann, MD; Thomas M. Hemmen, MD, PhD; Scott E. Kasner, MD; Dawn Kleindorfer, MD; William A. Knight, MD; Sharyl Martini, MD, PhD; James S. McKinney, MD; William J. Meurer, MD, MS; Brett C. Meyer, MD; Alexander Schneider, MD; Phillip A. Scott, MD; Sidney Starkman, MD; Steven Warach, MD, PhD; Joseph P. Broderick, MD; for The CLEAR-ER Investigators

pancioli am *et al* stroke 44: 2381-2387 (2013)

CLEAR-ER

hypothesis: eptifibatide and rt-PA (modified dose) is as safe as rt-PA (0.9 mg/kg) for acute treatment of ischemic stroke

design: prospective randomized double-blinded, dose-escalation safety phase II study (94 patients)
eptifibatide (135 µg/0.75 µg/kg/min) + rt-PA (0.6 mg/kg)
rt-PA (0.9 mg/kg)

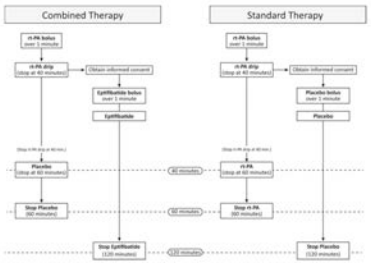
primary outcome: symptomatic intracerebral hemorrhage

results:

	primary efficacy outcome	ICH	
eptifibatide + rt-PA	49.5%	2.0%	rt-PA
	36.0%	12.0%	

conclusion: safety shown for combination

CLEAR-ER



pancioli am *et al* stroke 44: 2381-2387 (2013)

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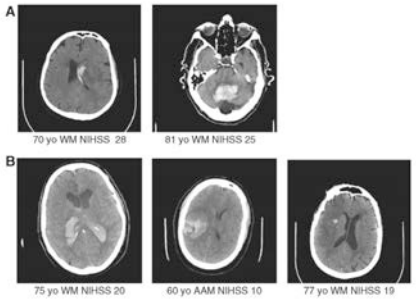

pancioli am *et al* stroke 44: 2381-2387 (2013)

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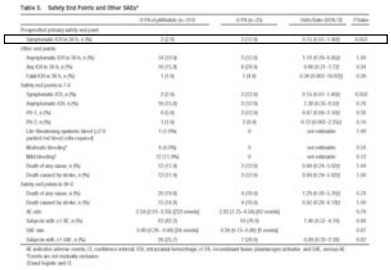

Table 3. Safety End Points and Other SAEs*

pancioli am *et al* stroke 44: 2381-2387 (2013)

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CLEAR-ER

Table 4. Ninety-Day Outcomes

	rt-PA-Left Behind (n=103)	rt-PA (n=75)	Unadjusted Odds Ratio (95% CI)	Adjusted* Odds Ratio (95% CI)	P Value Unadjusted	P Value Adjusted
Prespecified primary efficacy outcome measure						
mRS 0–1 at 90 days in Baseline, n (%)	59 (58.5)	9 (36.0)	1.24 (0.79–4.91)	1.37 (0.51–3.71)	0.006	0.006
Other efficacy end points						
mRS 0–1 only, n (%)	48 (45.6)	6 (24.0)	2.48 (0.96–6.66)	1.98 (0.67–5.85)	0.076	0.22
Barthel Index of ≥95, n (%)	55 (54.5)	11 (44.0)	1.52 (0.65–3.67)	1.19 (0.40–3.62)	0.35	0.85
Glasgow Outcome Scale of 1, n (%)	52 (51.5)	10 (40.0)	1.58 (0.65–3.98)	1.19 (0.44–3.24)	0.30	0.73
New stroke within 90 d, n (%)	1 (1.0)	0 (0.0)			1.00	

CI indicates confidence interval; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; and rt-PA, recombinant tissue plasminogen activator.
*Adjusted for age, baseline NIHSS and time to IV rt-PA.

pancioli am *et al* stroke 44: 2381-2387 (2013)

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interesting questions

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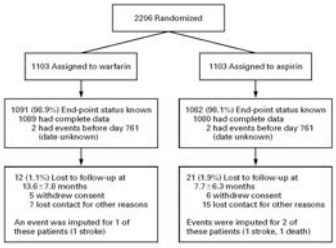
The New England Journal of Medicine

A COMPARISON OF WARFARIN AND ASPIRIN FOR THE PREVENTION OF RECURRENT ISCHEMIC STROKE

J.P. Mohr, M.D., J.L.P. Thompson, Ph.D., R.M. Lazar, Ph.D., B. Levin, M.D., R.L. Sacco, M.D., K.L. Furie, M.D., J.P. Kistler, M.D., G.W. Albers, M.D., L.C. Pettigrew, M.D., H.P. Adams, Jr., M.D., C.M. Jackson, M.D., and P. Pullicino, M.D., for the Warfarin–Aspirin Recurrent Stroke Study Group*

mohr jp *et al* n engl j med 345: 1444-1451 (2001)

WARSS



mohr jp *et al* n engl j med 345: 1444-1451 (2001)

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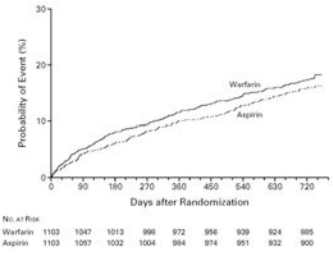

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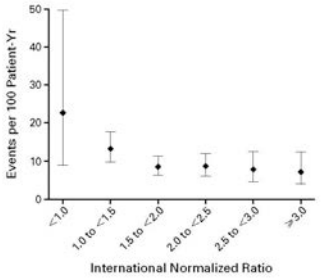

mohr jp *et al* n engl j med 345: 1444-1451 (2001)

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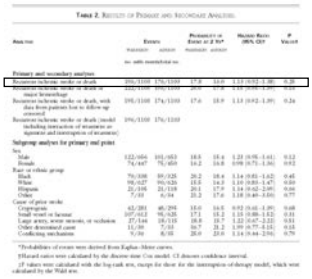
WARSS



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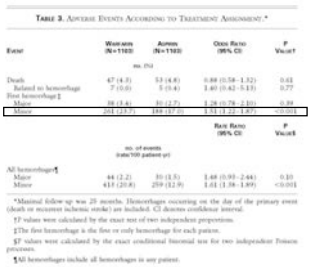

mohr jp *et al* n engl j med 345: 1444-1451 (2001)

warfarin-aspirin in reduced ejection fraction (WARCEF) study

study	EF	NYHA	stroke events per year	AF
SAVE	31%	1	1.5%	10%
SOLVD	27	2-3	1.8	0
V-Heft I	30	2-3	2.0	16
V-Heft II	29	2-3	1.9	13
Cioffi *et al*	23	2-3	2.0	16
Katz *et al*	27	2-3	1.7	13
CONSENSUS	~	4	2.4	42
CIBIS-II	28	3-4	~	~

oral anticoagulants and anti-platelet agents used

warfarin-aspirin in reduced ejection fraction (WARCEF) study

study	EF	NYHA	stroke events per year	AF
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CONSENSUS	~	4	2.4	42
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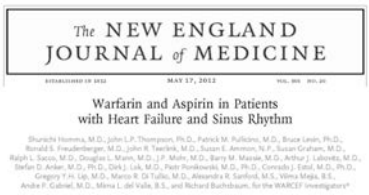
oral anticoagulants and anti-platelet agents used



The NEW ENGLAND JOURNAL of MEDICINE

MAY 17, 2012

Warfarin and Aspirin in Patients with Heart Failure and Sinus Rhythm

homma s *et al* n engl j med 366: 1859-1869 (2012)

WARCEF

hypothesis: randomized double-blind assessment of the effect of well-controlled warfarin vs ASA on the incidence of stroke in the setting of reduced ejection fraction (EF < 0.35)

design: prospective randomized blinded, two-arm
warfarin, INR 2.5 - 3.0 ASA 325 mg daily

primary outcome: all-cause mortality or stroke
primary null hypothesis = no difference in arms
assumption: AF rate = 2.5%/year; assigned permanent warfarin

results: equivalent outcome to 3 years

conclusion: advantage to warfarin after 4 years

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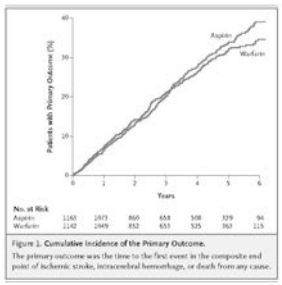

Figure 1. Cumulative Incidence of the Primary Outcome.
The primary outcome was the time to the first event in the composite end point of ischemic stroke, intracerebral hemorrhage, or death from any cause.

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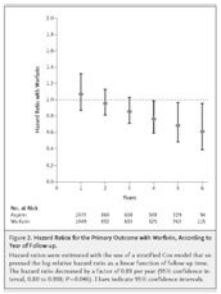

Figure 2. Hazard Ratios for the Primary Outcome with Warfarin, According to Year of Follow-up.
Hazard ratios were estimated with the use of a stratified Cox model that expressed the log relative hazard ratio as a linear function of follow-up time. The hazard ratio decreased by a factor of 0.89 per year (95% confidence interval, 0.80 to 0.98; P=0.046). I bars indicate 95% confidence intervals.

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Table 2. Primary, Safety, and Main Secondary Outcomes.*

Outcome	Warfarin (N=1142)		Aspirin (N=1165)		Hazard Ratio (95% CI)†	P Value
	no. of patients (%)	unadjusted rate of events/100 patient-yr	no. of patients (%)	unadjusted rate of events/100 patient-yr		
Primary outcome: death, ischemic stroke, or intracerebral hemorrhage						
Composite	102 (26.4)	7.47	120 (27.5)	7.93	0.93 (0.79–1.10)	0.40
Components						
Death	268 (23.5)	6.63	263 (22.6)	6.52	1.01 (0.85–1.20)	0.91
Ischemic stroke	29 (2.5)	0.72	55 (4.7)	1.36	0.52 (0.33–0.82)	0.005
Intracerebral hemorrhage	5 (0.4)	0.12	2 (0.2)	0.05	2.22 (0.45–11.04)	0.35
Safety outcome: death, ischemic stroke, intracerebral hemorrhage, or intracranial hemorrhage‡	307 (26.9)	7.61	321 (27.8)	8.02	0.94 (0.80–1.10)	0.44
Main secondary outcome: death, ischemic stroke, intracerebral hemorrhage, myocardial infarction, or hospitalization for heart failure						
Composite	447 (39.1)	12.70	435 (37.6)	12.15	1.07 (0.93–1.23)	0.33
Components§						
Death	156 (13.7)	4.43	158 (13.6)	4.61	1.01 (0.81–1.26)	0.93
Ischemic stroke	20 (1.8)	0.57	41 (3.5)	1.14	0.55 (0.32–0.96)	0.03
Intracerebral hemorrhage	4 (0.4)	0.11	2 (0.2)	0.06	1.77 (0.32–9.80)	0.51
Myocardial infarction	28 (2.5)	0.80	31 (2.7)	0.87	0.98 (0.58–1.64)	0.91
Hospitalization for heart failure	239 (20.9)	6.79	201 (17.3)	5.67	1.21 (0.998–1.47)	0.053

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Table 3. Rates of Hemorrhage and Death, According to Treatment Group.*

Event	Warfarin (N=1142)	Aspirin (N=1165)	Odds Ratio or Rate Ratio (95% CI)†	P Value‡
Death as part of primary outcome — no. of patients (%)				
From any cause	268 (23.5)	263 (22.6)	1.05 (0.86–1.27)	0.66
Related to hemorrhage§	7 (0.6)	4 (0.3)	1.84 (0.54–6.32)	0.38
Death after primary outcome — no. of patients (%)¶				
After ischemic stroke	5 (0.4)	7 (0.6)	0.71 (0.22–2.40)	0.77
After intracerebral hemorrhage	2 (0.2)	2 (0.2)	0.98 (0.13–9.18)	1.00
Major hemorrhage — no. of patients (%)‖	66 (5.8)	31 (2.7)	2.21 (1.42–3.47)	<0.001
Intracerebral	5 (0.4)	2 (0.2)	2.52 (0.52–17.9)	0.29
Intracranial**	5 (0.4)	7 (0.6)	0.72 (0.22–2.43)	0.77
Gastrointestinal	37 (3.2)	16 (1.4)	2.35 (1.30–4.38)	0.005
Other	21 (1.8)	7 (0.6)	3.06 (1.26–7.57)	0.008
Minor hemorrhage — no. of patients (%)	280 (24.5)	189 (16.3)	1.65 (1.34–2.05)	<0.001
All hemorrhages††				
Total no. of patient-yr	4044.7	4052.8		
Major hemorrhage — no. of events (no./100 patient-yr)	72 (1.78)	35 (0.87)	2.05 (1.36–3.12)	<0.001
Intracerebral	5 (0.12)	2 (0.05)	2.48 (0.52–17.6)	0.45
Intracranial**	6 (0.15)	7 (0.17)	0.86 (0.29–2.85)	1.00
Gastrointestinal	38 (0.94)	18 (0.45)	2.10 (1.23–3.70)	0.010
All other	23 (0.57)	8 (0.2)	2.88 (1.30–6.94)	0.01
Minor hemorrhage — no. of events (no./100 patient-yr)	468 (11.6)	296 (7.34)	1.56 (1.34–1.82)	<0.001

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some topics not covered

- cilostazol
- triflusal
- "ASA resistance"
- "clopidogrel resistance" and genotypic variability
- platelet polymorphisms and stroke
- matrix receptors and thrombosis
- ACTIVE A
- meta-analyses and heterogeneity
- anti-platelet agents and the new oral anticoagulants
- and others ….

some observations about the "art"

- safety of application
- hemorrhagic risk small, relatively important
- understand pathophysiology of ischemic event(s)
- anti-platelet agents effective in stroke risk reduction, dependent upon setting and etiology
- ASA is foundation of anti-platelet effects
- development of new agents with differing anti-platelet/hemorrhagic risk profiles

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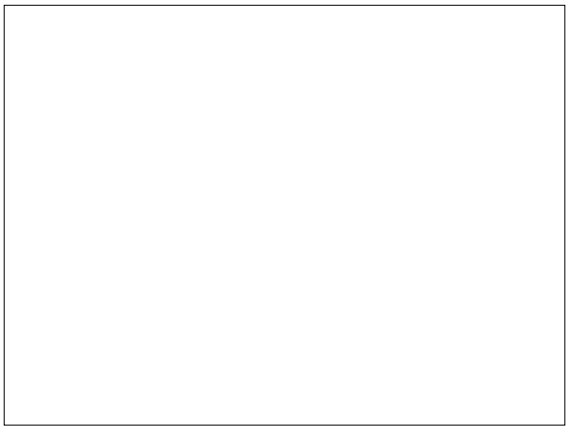

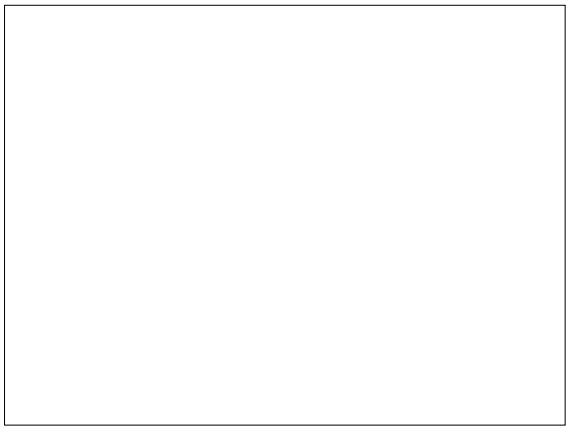

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