Prevenzione del cardioembolismo nella Fibrillazione Atriale: antiaggreganti o anticoagulanti?

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Occurrence of Hemispheric and Retinal Ischemia in Atrial Fibrillation Compared With Carotid Stenosis

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TABLE 2. Number of Outcome Events by Territory, Type, and Odds of Occurrence*

	SPAF, Aspirin Treated (n=2012)	NASCET, 50% to 99% Symptomatic ICA (n=759)	NASCET, 50% to 99% Asymptomatic ICA (n=324)
Hemispheric, n	127	253	48
TIA[†]	36 [4]	173 [1]	24
Stroke[†]	91 [5]	80 [4]	24 [2]
Vertebrobasilar, n	33	37	22
TIA[†]	11	27	15
Stroke[†]	22	10 [1]	7
Retinal, n	5	124	22
TIA[†]	4 [2]	113 [1]	19 [1]
Stroke	1	11	3
H:R odds	25:1	2:1	2:1
B:R odds	32:1	2:1	3:1

*The following additional events occurred in multiple/unknown territories: SPAF patients, 4 TIAs and 7 strokes; NASCET patients, 0.

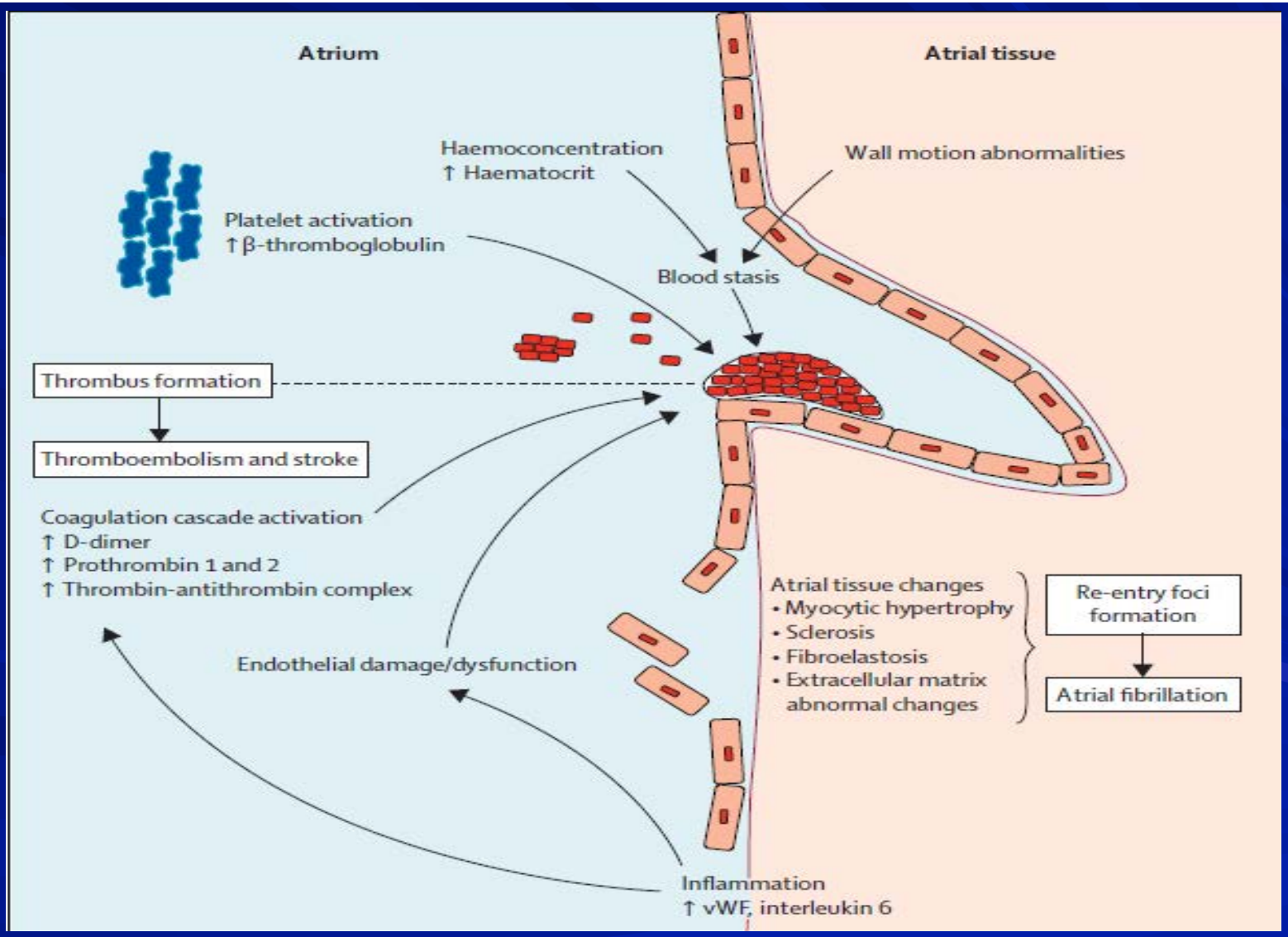
[†]Events with both atrial fibrillation and relevant carotid stenosis.

(*Stroke*. 2002;33:1963-1968.)

Mechanisms of thrombogenesis in atrial fibrillation: Virchow's triad revisited

Timothy Watson, Eduard Shantsila, Gregory Y H Lip

Lancet 2009; 373: 155–66



Anticoagulanti
o
Antiaggreganti Piastrinici?

Annals of Internal Medicine | REVIEW

Meta-analysis: Antithrombotic Therapy to Prevent Stroke in Patients Who Have Nonvalvular Atrial Fibrillation

Robert G. Hart, MD; Lesly A. Pearce, MS; and Maria I. Aguilar, MD

Background: Atrial fibrillation is a strong independent risk factor for stroke.

Purpose: To characterize the efficacy and safety of antithrombotic agents for stroke prevention in patients who have atrial fibrillation, adding 13 recent randomized trials to a previous meta-analysis.

Data Sources: Randomized trials identified by using the Cochrane Stroke Group search strategy, 1966 to March 2007, unrestricted by language.

Study Selection: All published randomized trials with a mean follow-up of 3 months or longer that tested antithrombotic agents in patients who have nonvalvular atrial fibrillation.

Data Extraction: Two coauthors independently extracted information regarding interventions; participants; and occurrences of ischemic and hemorrhagic stroke, major extracranial bleeding, and death.

Data Synthesis: Twenty-nine trials included 28 044 participants (mean age, 71 years; mean follow-up, 1.5 years). Compared with the control, adjusted-dose warfarin (6 trials, 2900 participants) and antiplatelet agents (8 trials, 4876 participants) reduced stroke by 64% (95% CI, 49% to 74%) and 22% (CI, 6% to 35%), respectively. Adjusted-dose warfarin was substantially more efficacious than antiplatelet therapy (relative risk reduction, 39% [CI, 22% to 52%]) (12 trials, 12 963 participants). Other randomized comparisons were inconclusive. Absolute increases in major extracranial hemorrhage were small (≤0.3% per year) on the basis of meta-analysis.

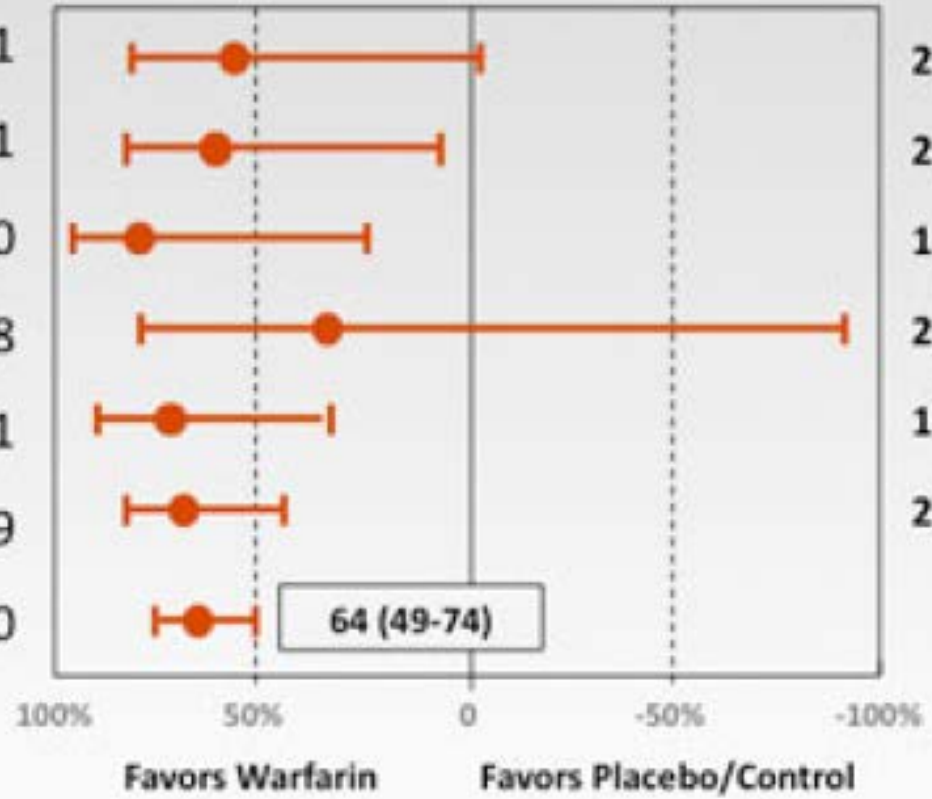
Limitation: Methodological features and quality varied substantially and often were incompletely reported.

Conclusions: Adjusted-dose warfarin and antiplatelet agents reduce stroke by approximately 60% and by approximately 20%, respectively, in patients who have atrial fibrillation. Warfarin is substantially more efficacious (by approximately 40%) than antiplatelet therapy. Absolute increases in major extracranial hemorrhage associated with antithrombotic therapy in participants from the trials included in this meta-analysis were less than the absolute reductions in stroke. Judicious use of antithrombotic therapy importantly reduces stroke for most patients who have atrial fibrillation.

Ann Intern Med. 2007;146:857-867. www.annals.org

For author affiliations, see end of text.

Stroke: Adjusted-Dose Warfarin vs Placebo/Control



Study	N	Target INR	Warfarin %	Control %
AFASAK I	671	2.8-4.2	2.7	5.7
SPAF I	421	2.0-4.5	3.8	9.0
BAATAF	420	1.5-2.7	1.4	6.3**
CAFA	378	2.0-3.0	3.2	4.7
SPINAF	571	1.4-2.8	2.5	7.9
EAFT	439	2.5-4.0	8.9*	23.4
Total	2900		3.7	9.2

*Several oral vitamin K antagonists used
**46% of exposure ASA in control group

Anticoagulanti Orali vs Placebo

- 64% RRR
- 67% RRR per stroke ischemico
- NNT=40 (p. primaria)
- NNT=14 (p. secondaria)
- Efficace su major/minor stroke
- 26% RRR mortalità (tutte le cause)
- “The risk of intracranial haemorrhage was small”
  - 1,8%-anno in p.>75 anni (SPAF II)
  - 2,5%-anno in p.>65 anni (Hylek, 2007)

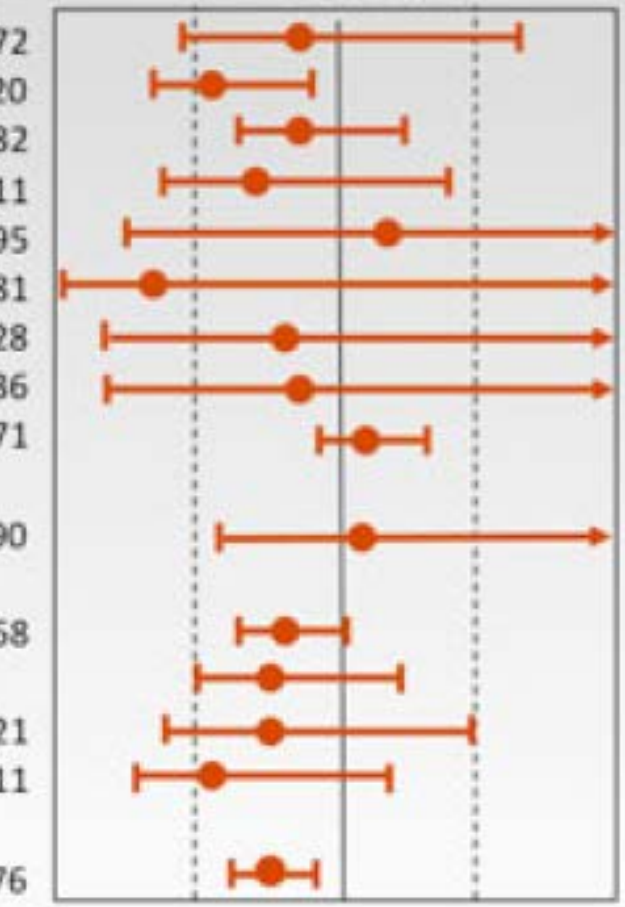
Anticoagulanti Orali vs Placebo

Table 5. Safety Outcomes for Major Antithrombotic Comparisons*

Variable	Adjusted-Dose Warfarin vs. Control or Placebo
Trials (references), *n*	6 (3–8)
Patients, *n*	2900
Intracranial hemorrhage‡	
Events, *n*	6 vs. 3
Relative risk reduction (95% CI), %	NC
Absolute risk reduction, %/*y*	NC
Major extracranial hemorrhage	
Events, *n*	31 vs. 17§
Relative risk reduction (95% CI), %	−66 (−235 to 18)
Absolute risk reduction, %/*y*	−0.3
All-cause mortality	
Deaths, *n*	110 vs. 143
Relative risk reduction (95% CI), %	26 (3 to 43)
Absolute risk reduction, %/*y*	1.6

Stroke: Antiplatelet Agents vs Placebo/Control

Study		N	Antiplatelet	Control
AFASAK I		672	4.8	5.7
SPAF I		1120	4.5	7.7
EAFT		782	21.8	23.8
ESPS II		211	16.3	21.5
LASAF	Daily	195	3.8	3.3
	Alternate day	181	1.1	3.3
UK-TIA	300 mg daily	28	23.1	26.7
	1200 mg daily	36	23.8	26.7
JAST		871	4.7	4.3
Total - Aspirin Trials		3990	8.7	10.2
SAFT		668	9.6	12.3
ESPS II				
Dipyridamole		221	17.5	21.5
Combination		211	13.5	21.5
Total – Antiplatelet Trials		4876	9.4	11.4



29% secondary prevention

Antiaggreganti vs Placebo

- 22% RRR
- NNT=111 (p. primaria)
- NNT=34 (p. secondaria)
- Effetto prevalente sugli stroke meno severi

- Nei 7 studi con ASA
  - NNT 125 (p. primaria)
  - NNT 40 (p. secondaria)

Stroke Prevention in Atrial Fibrillation Study

Final Results

(*Circulation* 1991;84:527–539)

Stroke Prevention in Atrial Fibrillation Investigators*

- aspirin 325 mg vs. placebo
- 42% stroke risk reduction
- Internal heterogeneity, with inconsistencies for the aspirin effect between the results for the warfarin-eligible (RR reduction 94%) and warfarin-ineligible (RR reduction 8%) arms of the trial.
- Aspirin had less effect in people older than 75 years and did not prevent severe or recurrent strokes.

Low-Dose Aspirin for Prevention of Stroke in Low-Risk Patients With Atrial Fibrillation

Japan Atrial Fibrillation Stroke Trial

Background and Purpose—Although the efficacy of anticoagulant therapy for primary prevention of stroke in patients with nonvalvular atrial fibrillation (NVAF) has been established, efficacy of antiplatelet therapy for low-risk patients is disputable in Japanese patients because of the frequent hemorrhagic complications. We examined the efficacy and safety of aspirin therapy in Japanese patients with NVAF in a prospective randomized multicenter trial.

Methods—Patients with NVAF were randomized to an aspirin group (aspirin at 150 to 200 mg per day) or a control group without antiplatelet or anticoagulant therapy. Primary end points included cardiovascular death, symptomatic brain infarction, or transient ischemic attack.

Results—A total of 426 patients were randomized to aspirin group and 445 to no treatment. The trial was stopped earlier because there were 27 primary end point events (3.1% per year; 95% CI, 2.1% to 4.6% per year) in the aspirin group versus 23 (2.4% per year; 95% CI, 1.5% to 3.5% per year) in the control group, suggesting a low possibility of superiority of the aspirin treatment for prevention of the primary end point. In addition, treatment with aspirin caused a marginally increased risk of major bleeding (7 patients; 1.6%) compared with the control group (2 patients; 0.4%; Fisher exact test $P=0.101$).

Conclusions—For prevention of stroke in patients with NVAF, aspirin at 150 to 200 mg per day does not seem to be either effective or safe. Further prospective studies are needed to determine the best preventive therapy for cerebrovascular events in Japanese patients with NVAF. (*Stroke*. **2006;37:447-451.**)

ASA e Rischio emorragico

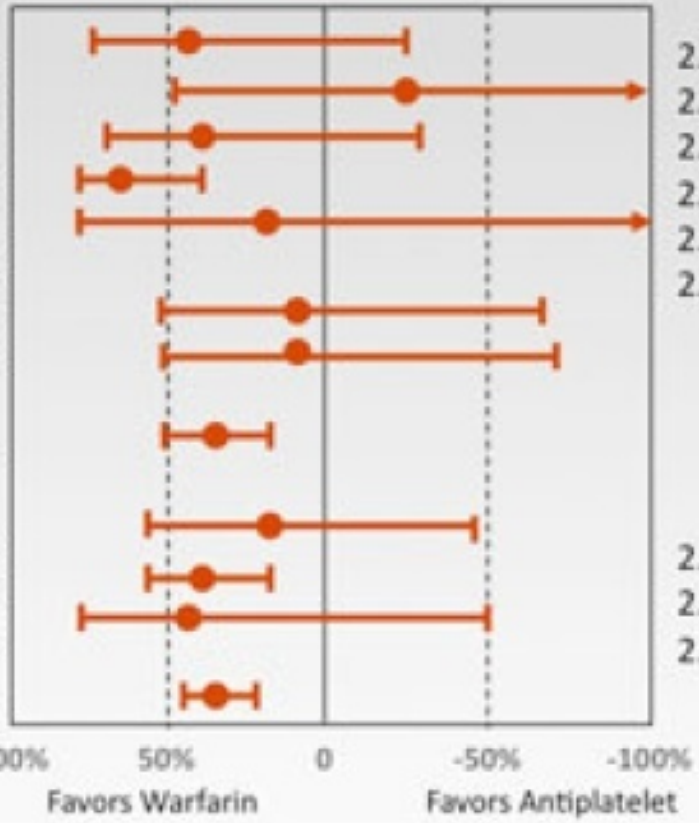
- 50-60% incremento del RR per emorragia maggiore extracranica

- *Baigent C , Blackwell L , Collins R , et al ; Antithrombotic Trialists' (ATT) Collaboration . Aspirin in the primary andsecondary prevention of vascular disease: collaborative metaanalysis of individual participant data from randomised trials . Lancet . 2009 ; 373 (9678): 1849 - 1860 .*
  - *6 RCT; 95,000 soggetti*

- *Antithrombotic Trialists' Collaboration; Baigent C, Blackwell L, Collins R, et al. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients . BMJ . 2002 ; 324 (7329): 71 - 86 .*
  - *60 trials; 94,000pazienti*

Stroke: Adjusted-Dose Warfarin vs Antiplatelet Rx

Study	N	Target INR	Warfarin %	Antiplatelet %
AFASAK I	671	2.8-4.2	2.7	4.8
AFASAK II	339	2.0-3.0	6.5	5.3
Chinese ATAFS	704	2.0-3.0	2.7	4.6
EAFT	455	2.5-4.0	8.9	22.6
PATAF	272	2.5-3.5	2.3	2.8
SPAF II	1100	2.0-4.5		
Age ≤ 75 years	715		5.3	5.9
Age > 75 years	385		10.2	11.2
Total - Aspirin Trials*	3647		5.0	7.7
SIFA (indobufen)	916	2.0-3.5	4.0	5.0
ACTIVE-W (clop. + asp.)	6706	2.0-3.0	1.9	3.2
NASPEAF (triflusal)	479	2.0-3.0	2.5	4.5
Total - Antiplatelet Trials*	11748		3.1	4.8



22% secondary prevention

*Includes 2 small trials (n = 106) with only 2 strokes; does not include SPAF III (n = 1044) and part of AFASAK II (n = 341) where antiplatelet groups also received warfarin

Warfarin vs Antiaggreganti

- RRR 39%
- NNT 81 (p primaria)
- NNT 24 (p. secondaria)

- ICH: incremento 0.2%-anno

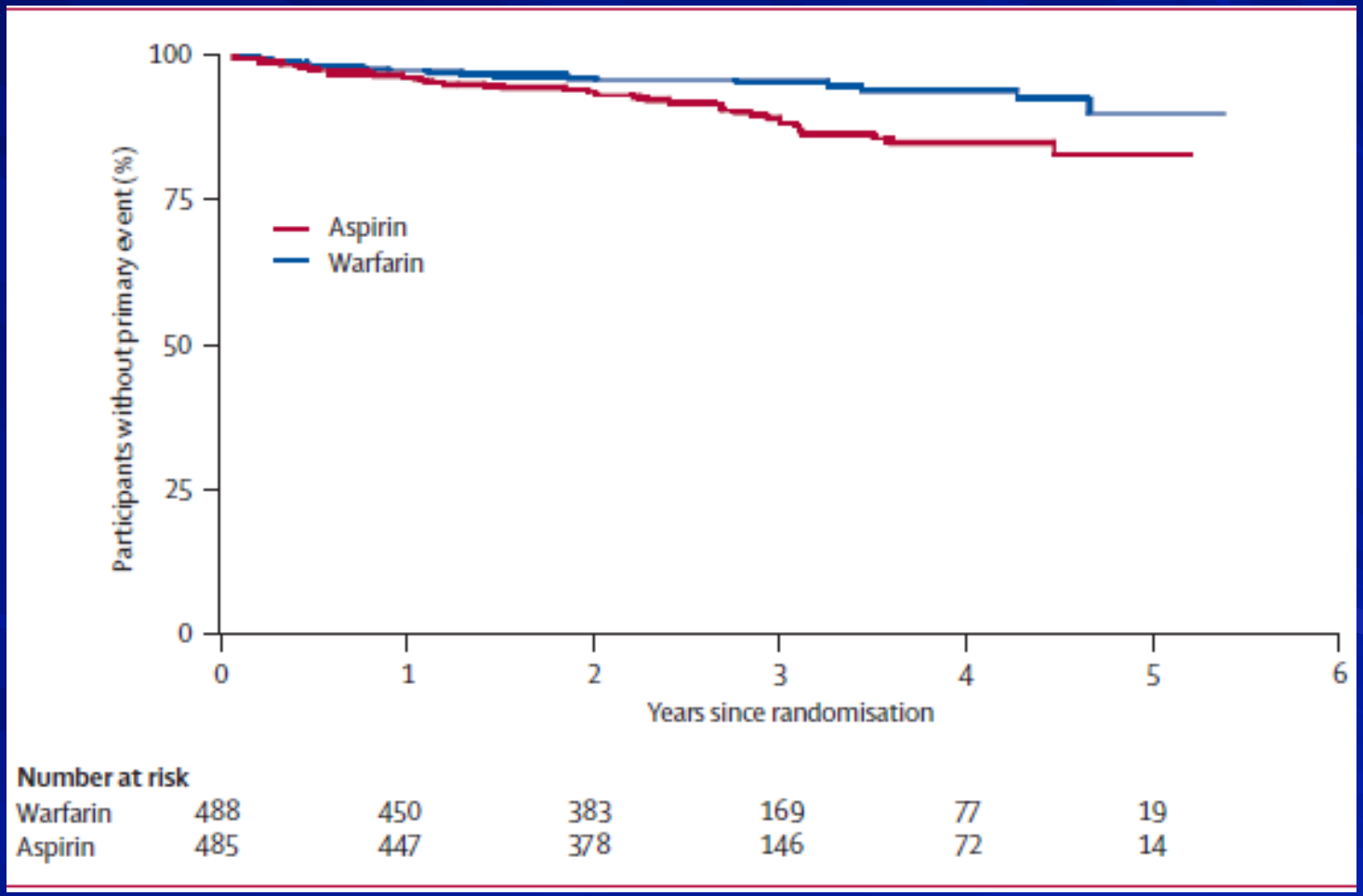
Anticoagulanti Orali vs ASA

Table 5. Safety Outcomes for Major Antithrombotic Comparisons*

Variable	Adjusted-Dose Warfarin vs. Aspirin
Trials (references), *n*	8 (3, 8, 10, 14, 16, 27, 30, 31
Patients, *n*	3647
Intracranial hemorrhage‡	
Events, *n*	20 vs. 7
Relative risk reduction (95% CI), %	−128 (−399 to −4)
Absolute risk reduction, %/y	−0.2
Major extracranial hemorrhage	
Events, *n*	40 vs. 22
Relative risk reduction (95% CI), %	−70 (−234 to 14)
Absolute risk reduction, %/y	−0.2
All-cause mortality	
Deaths, *n*	117 vs. 128‖
Relative risk reduction (95% CI), %	9 (−19 to 30)
Absolute risk reduction, %/y	0.5

Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial

Jonathan Mant, FD Richard Hobbs, Kate Fletcher, Andrea Roalfe, David Fitzmaurice, Gregory YH Lip, Ellen Murray, on behalf of the BAFTA investigators and the Midland Research Practices Network (MidReC)**



Number at risk						
Warfarin	488	450	383	169	77	19
Aspirin	485	447	378	146	72	14

Lancet 2007; 370: 493–503

	Warfarin (n=488)		Aspirin (n=485)		Warfarin *vs* aspirin	
	n	Risk per year	n	Risk per year	RR (95% CI)	p
Stroke	21	1·6%	44	3·4%	0·46 (0·26–0·79)	0·003
By severity						
Fatal	13	1·0%	21	1·6%	0·59 (0·27–1·24)	0·14
Disabling non-fatal	8	0·6%	23	1·8%	0·33 (0·13–0·77)	0·005
Type of stroke*						
Ischaemic	10	0·8%	32	2·5%	0·30 (0·13–0·63)	0·0004
Haemorrhagic	6	0·5%	5	0·4%	1·15 (0·29–4·77)	0·83
Unknown	5	0·4%	7	0·5%	0·69 (0·17–2·51)	0·53
Other intracranial haemorrhage†	2	0·2%	1	0·1%	1·92 (0·10–113·3)	0·65
Systemic embolism‡	1	0·1%	3	0·2%	0·32 (0·01–3·99)	0·36
Total number of events	24	1·8%	48	3·8%	0·48 (0·28–0·80)	0·0027

RR=relative risk. *Type of stroke was determined by the endpoint committee on the basis of brain imaging or post-mortem findings. If neither of these was available, the stroke was classified as unknown. †The three other intracranial haemorrhages were subdural; two of these were fatal (one in each treatment group). ‡Two of the systemic emboli were fatal (one in each treatment group).

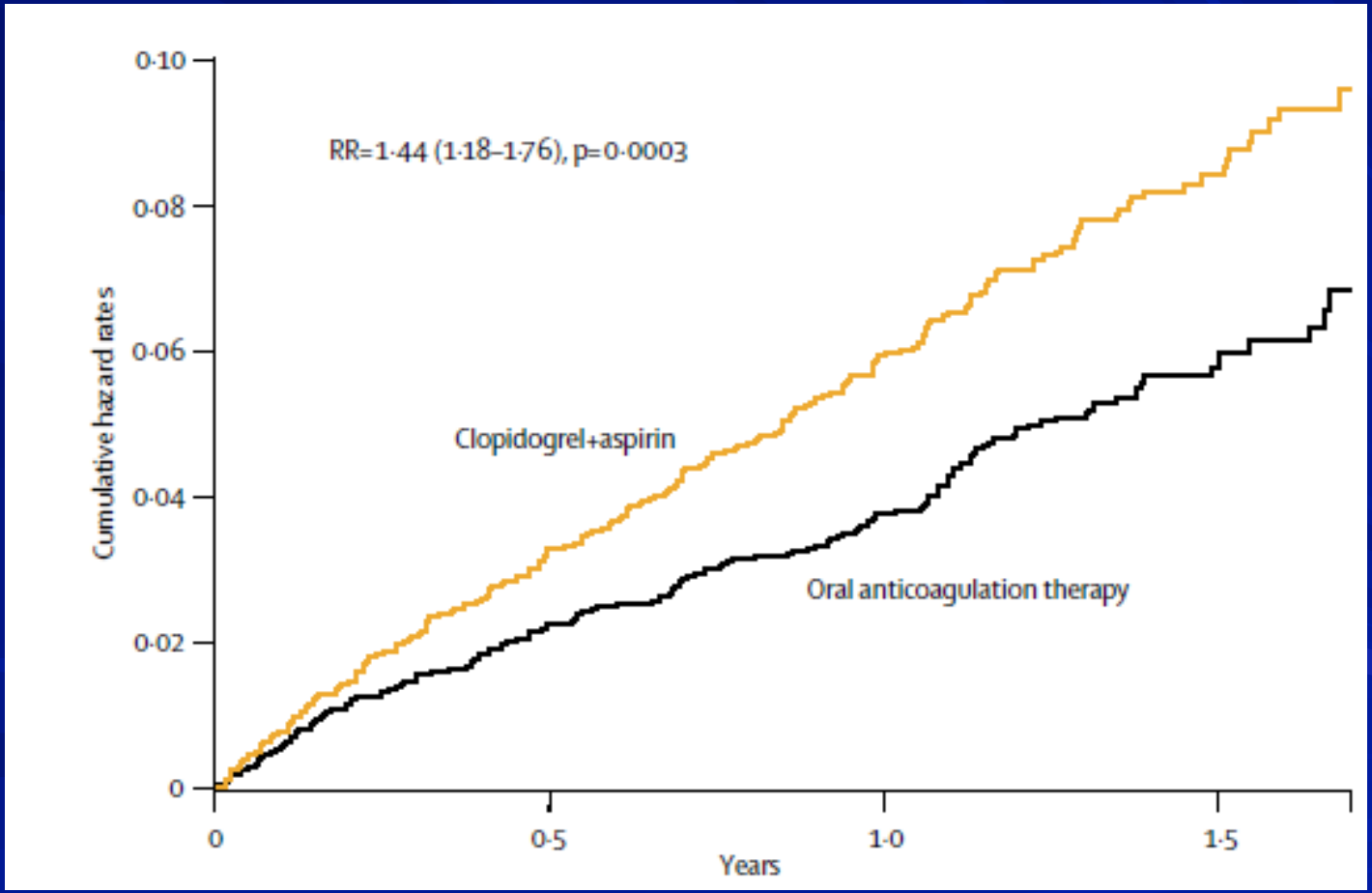
Table 3: **Nature of primary events**

Lancet 2007; 370: 493–503

ASA + Clopidogrel?

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

*The ACTIVE Writing Group on behalf of the ACTIVE Investigators**



Lancet 2006; 367: 1903–12

Effect of Clopidogrel Added to Aspirin in Patients with Atrial Fibrillation

The ACTIVE Investigators*

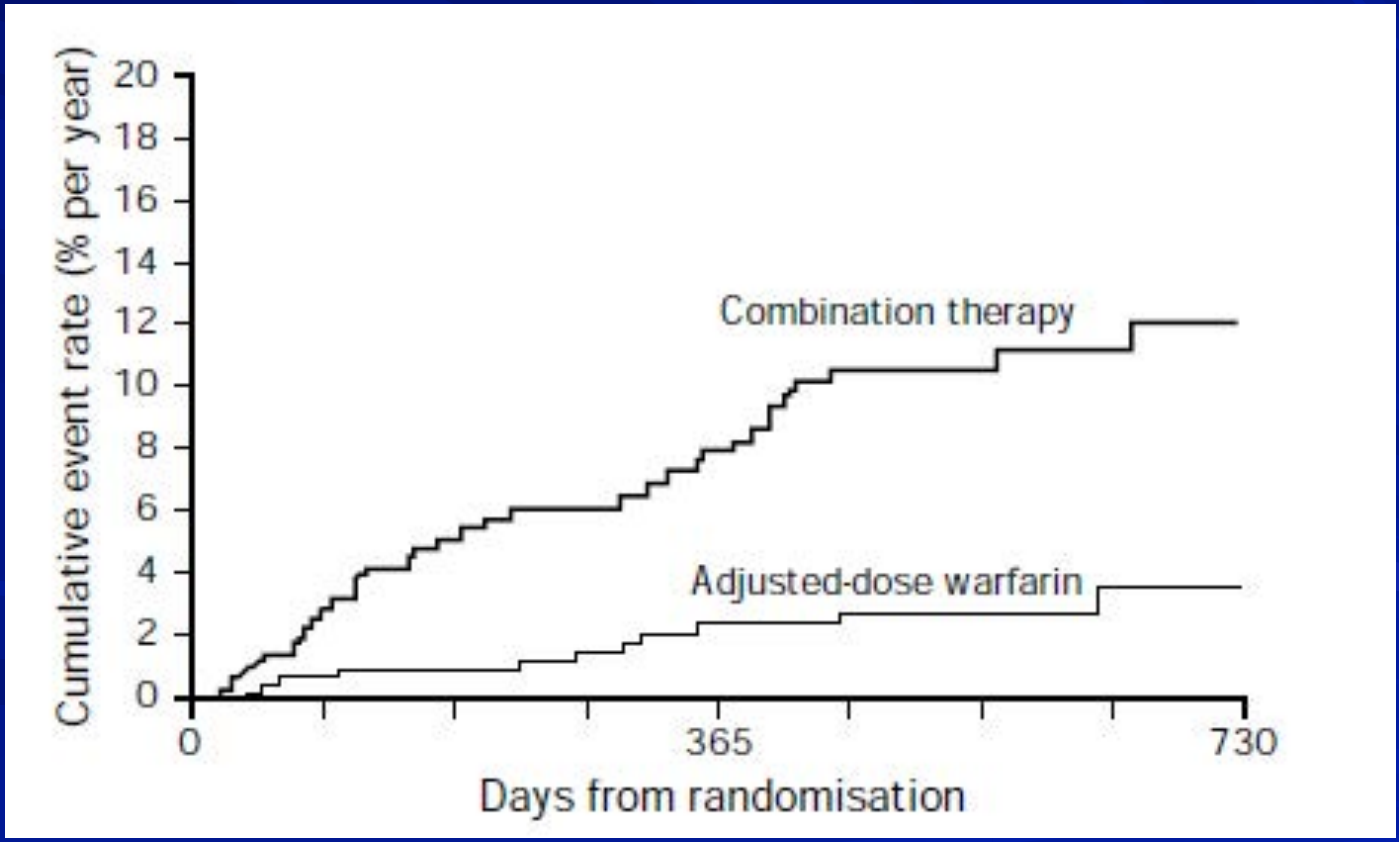
CONCLUSIONS

In patients with atrial fibrillation for whom vitamin K–antagonist therapy was unsuitable, the addition of clopidogrel to aspirin reduced the risk of major vascular events, especially stroke, and increased the risk of major hemorrhage. (ClinicalTrials.gov number, NCT00249873.)

ASA + Low-Dose-Warfarin?

Adjusted-dose warfarin versus low-intensity, fixed-dose warfarin plus aspirin for high-risk patients with atrial fibrillation: Stroke Prevention in Atrial Fibrillation III randomised clinical trial

*Stroke Prevention in Atrial Fibrillation Investigators**

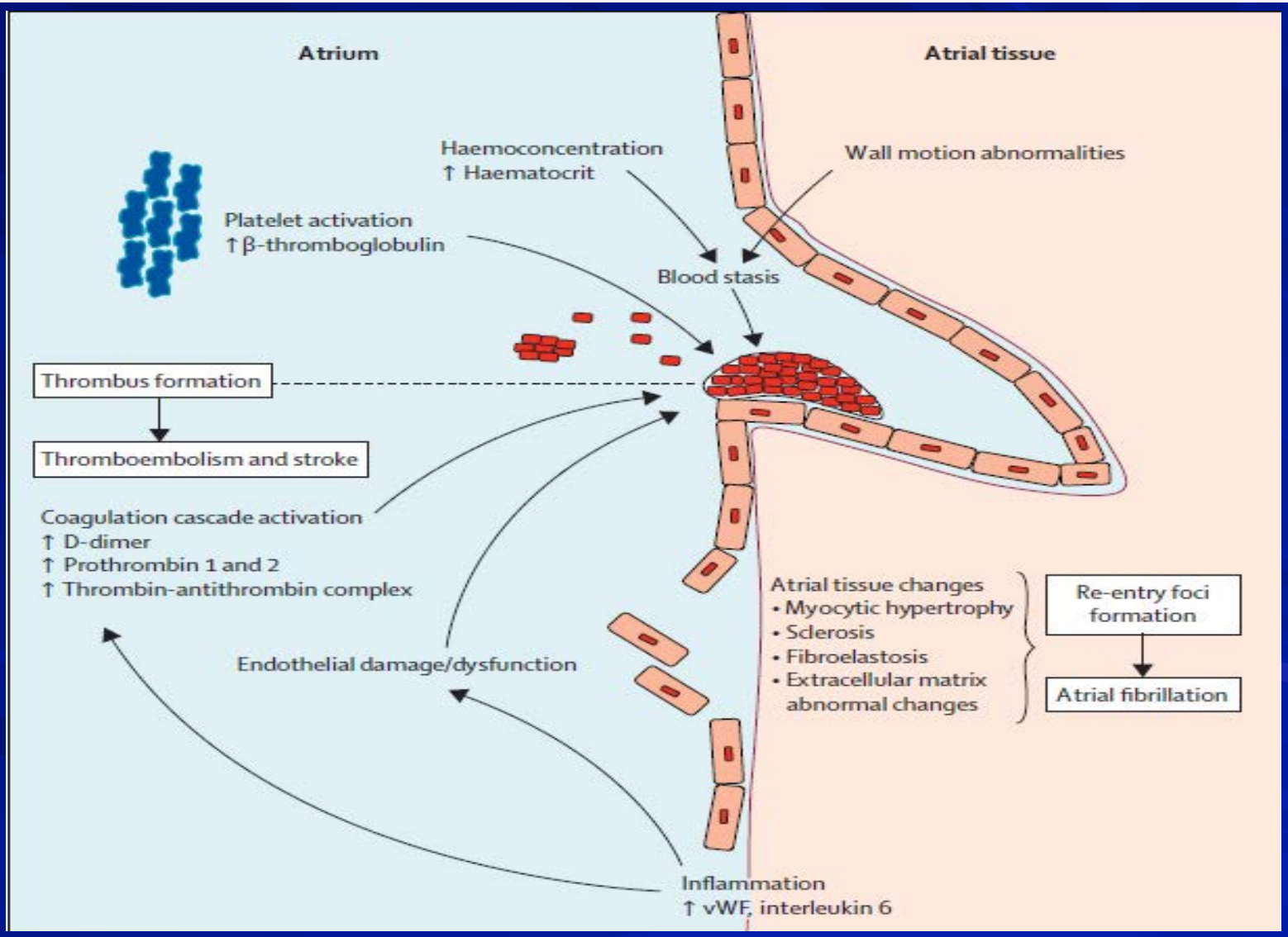


Lancet 1996; **348:** 633–38

Mechanisms of thrombogenesis in atrial fibrillation: Virchow's triad revisited

Timothy Watson, Eduard Shantsila, Gregory Y H Lip

Lancet 2009; 373: 155–66



Effects of Fixed Low-Dose Warfarin, Aspirin-Warfarin Combination Therapy, and Dose-Adjusted Warfarin on Thrombogenesis in Chronic Atrial Fibrillation

(*Stroke*. 2000;31:828-833.)

Foo Leong Li-Saw-Hee, MRCP; Andrew D. Blann, PhD, MRCPath; Gregory Y.H. Lip, MD, FRCPE

TABLE 4. Effects of Treatment on Hemostatic Markers in Patients With Chronic AF

		After Treatment		
	Before Treatment	2 wk	8 wk	*P*
2 mg warfarin				
Fibrinogen, g/L	3.0±0.9	2.8±1.0	2.4±0.9	0.240
von Willebrand factor, IU/dL	144±36	141±40	148±40	0.836
Plasminogen activator inhibitor-1, IU/dL	6.3 (3.9–10.5)	7.0 (4.2–9.5)	7.0 (5.7–12.6)	0.477
Fibrin D-dimer, ng/mL	280 (160–700)	290 (150–630)	191 (76–534)	0.055
INR	1.1 (1.0–1.2)	1.1 (1.025–1.4)	1.2 (1.1–1.4)	0.257
1 mg warfarin plus 300 mg aspirin				
Fibrinogen, g/L	3.0±0.9	3.0±0.7	2.5±0.8	0.134
von Willebrand factor, IU/dL	135±33	136±37	138±36	0.980
Plasminogen activator inhibitor-1, IU/dL	7.5 (4.2–11.1)	9.6 (4.3–20)	10 (5.6–23)	0.358
Fibrin D-dimer, ng/mL	210 (72–510)	169 (80–223)	142 (55–169)	0.168
INR	1.0 (1.0–1.1)	1.1 (1.0–1.1)	1.1 (1.0–1.2)	0.126
2 mg warfarin plus 300 mg aspirin				
Fibrinogen, g/L	2.8±0.7	2.9±0.9	2.9±0.8	0.917
von Willebrand factor, IU/dL	148±42	154±46	151±33	0.901
Plasminogen activator inhibitor-1, IU/dL	6.0 (3.2–10)	7.5 (4.6–13.1)	7.8 (4.9–15.9)	0.024
Fibrin D-dimer, ng/mL	100 (94–420)	125 (74–505)	119 (67–286)	0.708
INR	1.0 (1.0–1.125)	1.1 (1.0–1.2)	1.1 (1.0–1.1)	0.697

TABLE 5. Effect of Dose-Adjusted Warfarin (Achieving Target INR of 2.0–3.0) on Hemostatic Markers in Patients With Chronic AF

	Before Treatment	INR 2.0–3.0	*P*
Fibrinogen, g/L	2.9±0.9	2.4±0.7	0.023
von Willebrand factor, IU/dL	143±37	134±34	0.33
Plasminogen activator inhibitor-1, IU/dL	6.3 (3.9–10.4)	7.4 (5.9–14.5)	0.198
Fibrin D-dimer, ng/mL	212 (98–515)	130 (61–175)	0.0067
INR	1.05 (1.125)	2.48 (2.1–2.7)	<0.00001

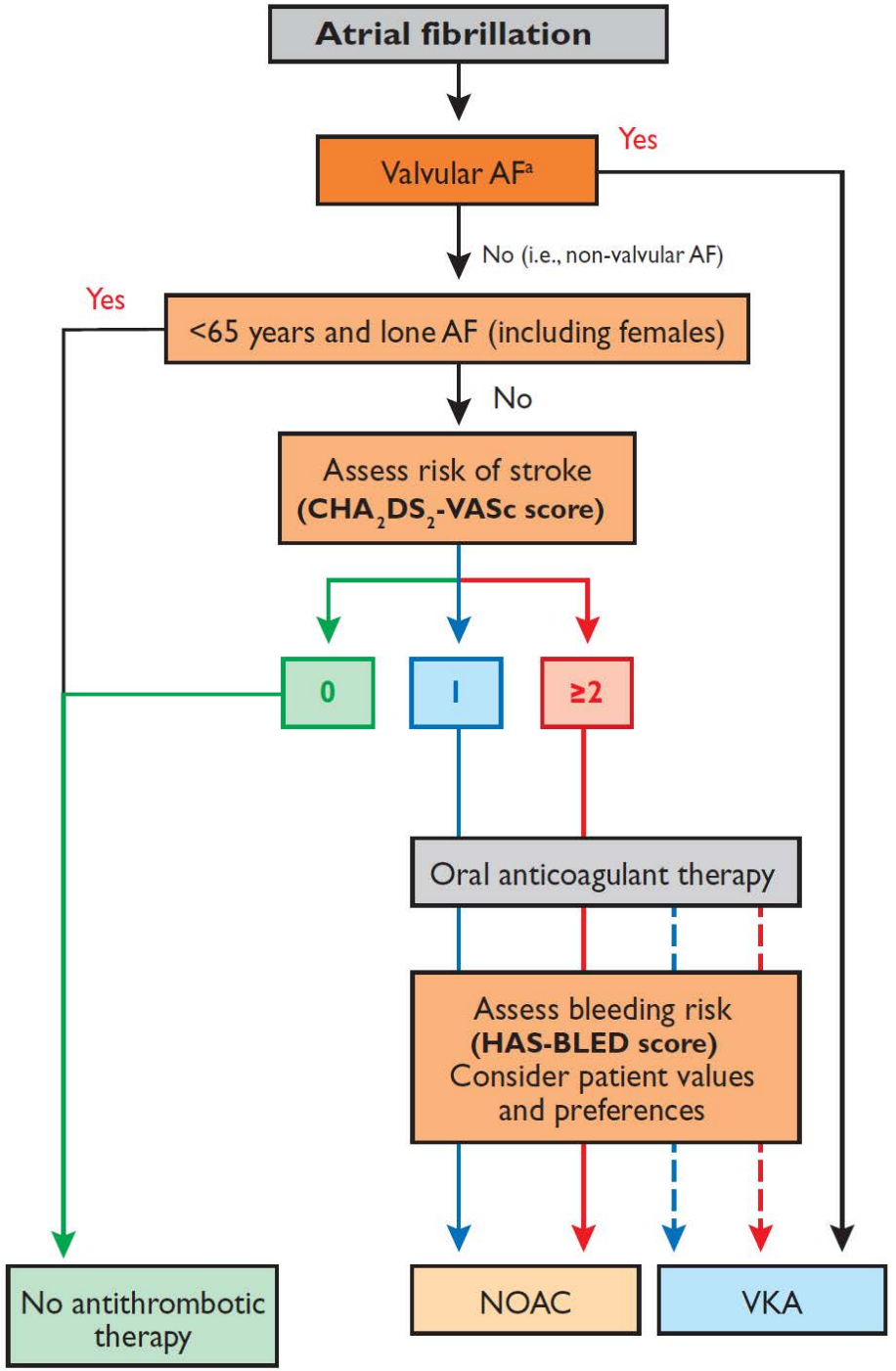
(*Stroke*. 2000;31:828-833.)

European Heart Journal
doi:10.1093/eurheartj/ehs253

ESC GUIDELINES

2012 focused update of the ESC Guidelines for the management of atrial fibrillation

An update of the 2010 ESC Guidelines for the management of atrial fibrillation
Developed with the special contribution of the European Heart Rhythm Association



Colour: CHA_2DS_2-VASc; green = 0, blue = 1, red ≥2.
Line: solid = best option; dashed = alternative option.
AF = atrial fibrillation; CHA_2DS_2-VASc = see text; HAS-BLED
NOAC = novel oral anticoagulant; OAC = oral anticoagulant;
VKA = vitamin K antagonist.

Camm JA et al. European Heart Journal 2012
doi:10.1093/eurheartj/ehs253

Substantial unmet need remains for antithrombotic agents that are more efficacious than aspirin and that are safer or more easily administered than adjusted-dose warfarin.

(Hart, 2007)

- FA: fisiopatologia
- Quali farmaci/combinazioni
- TAO vs placebo
  - Hart, 2007
- Antiaggreganti vs placebo
  - SPAF II
- TAO vs ASA

- TAO vs ASA/Clop
  - ACTIVE-W/A
- TAO vs LD/ ASA
  - SPAF III/AFASAK II

- Four of these trials were placebo controlled;
- of the two that were double blind with regard to anticoagulation, one was stopped early because of external evidence that OAC with VKA was superior to placebo, and the other included no female subjects.
- In three of the trials, VKA dosing was regulated according to the prothrombin time ratio, while two trials used INR target ranges of 2.5–4.0 and 2.0–3.0.

- This reduction was similar for both primary and secondary prevention and for both disabling and nondisabling strokes.
- Of note, many strokes occurring in the VKAtreated patients occurred when patients were not taking therapy or were subtherapeutically anticoagulated.
- All-cause mortality was significantly reduced (26%) by adjusted-dose VKA vs control.
- The risk of intracranial haemorrhage was small

- When aspirin alone was compared with placebo or no treatment in seven trials, treatment with aspirin was associated with a nonsignificant 19% (95% CI –1% to –35%) reduction in the incidence of stroke.
- There was an absolute risk reduction of 0.8% per year for primary prevention trials and 2.5% per year for secondary prevention by using aspirin.
- Aspirin was also associated with a 13% (95% CI –18% to –36%) reduction in disabling strokes and a 29% (95% CI –6% to –53%) reduction in non-disabling strokes.
- When only strokes classified as ischaemic were considered, aspirin resulted in a 21% (95% CI –1% to –38%) reduction in strokes.
- When data from all comparisons of antiplatelet agents and placebo or control groups were included in the meta-analysis, antiplatelet therapy reduced stroke by 22% (95% CI 6–35).

JAST

- In the Japan Atrial Fibrillation Stroke Trial,55 patients with lone AF were randomized to an aspirin group (aspirin at 150–200 mg/day) or a control group without antiplatelet or anticoagulant therapy.

- The primary outcomes (3.1% per year) in the aspirin group were worse than those in the control group (2.4% per year), and treatment with aspirin caused a non-significant increased risk of major bleeding (1.6%) compared with control (0.4%).