Paolo Cerrato

Stroke Unit

Molinette

- Donna 72 anni di età
- Ipertesa da 10 anni in terapia con Losartan + idroclorotiazide
- Un anno prima TIA (transitoria afasia) con riscontro di FA→ da allora in terapia con warfarin (INR 2-3)

- Alle ore 9 comparsa acuta di emiplegia FBC dx e afasia globale

- Inviata in PS con 118
- TC cranio normale (ad 1 ora dall'esordio)
    - Creat 1.5 INR=1.8
    - PA 170/90 mmHg
    - Sat 96% in AA
    - FA con Fc 88/min

- EON
    - Afasia globale
    - Emiplegia FBC dx
    - NIHSS=23

- Quale terapia in acuto?
  - Trombolisi ev
  - Trombolisi IA
  - Eparina sodica
  - Ebpm a dosi scoagulanti
  - Aspirina 300 mg/die
  - Warfarin

- Quale terapia in acuto?
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  - Trombolisi IA
  - Eparina sodica
  - Ebpm a dosi scoagulanti
  - Aspirina 300 mg/die
  - Warfarin

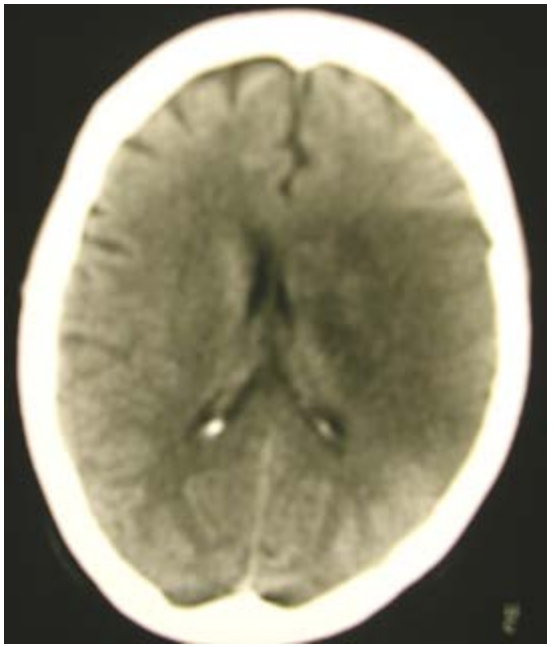
- Eseguita angiografia con riscontro di occlusione AC media sin→eseguita trombolisi IA con trombectomia meccanica con parziale ricanalizzazione (persiste occlusione ramo di divisione anteriore)
- Scarso recupero del deficit neurologico (NIHSS=20) a 3 ore

Il giorno dopo:

- EON plegia FB dx, afasia espressiva, migliorata la comprensione)
- NIHSS= 16

- Ecocardio TT→ dilatazione atriale sin, FE 62% (no trombi intracavitari)
- Eco-TSA: placche su ICA senza stenosi significativa
- INR 1.4
- Creat 1.4

- Tc cranio: estesa ipodensità nel territorio dell'ACM di sin



Quale prevenzione a breve termine?

- ASA
- Clopidodrel
- Ebpm a dosi 100U Kg x 2/die
- Eparina a dosi profilattiche (50-60 U /Kg/die)
- Eparina sodica PTT 2-2.5
- Warfarin INR 2-3

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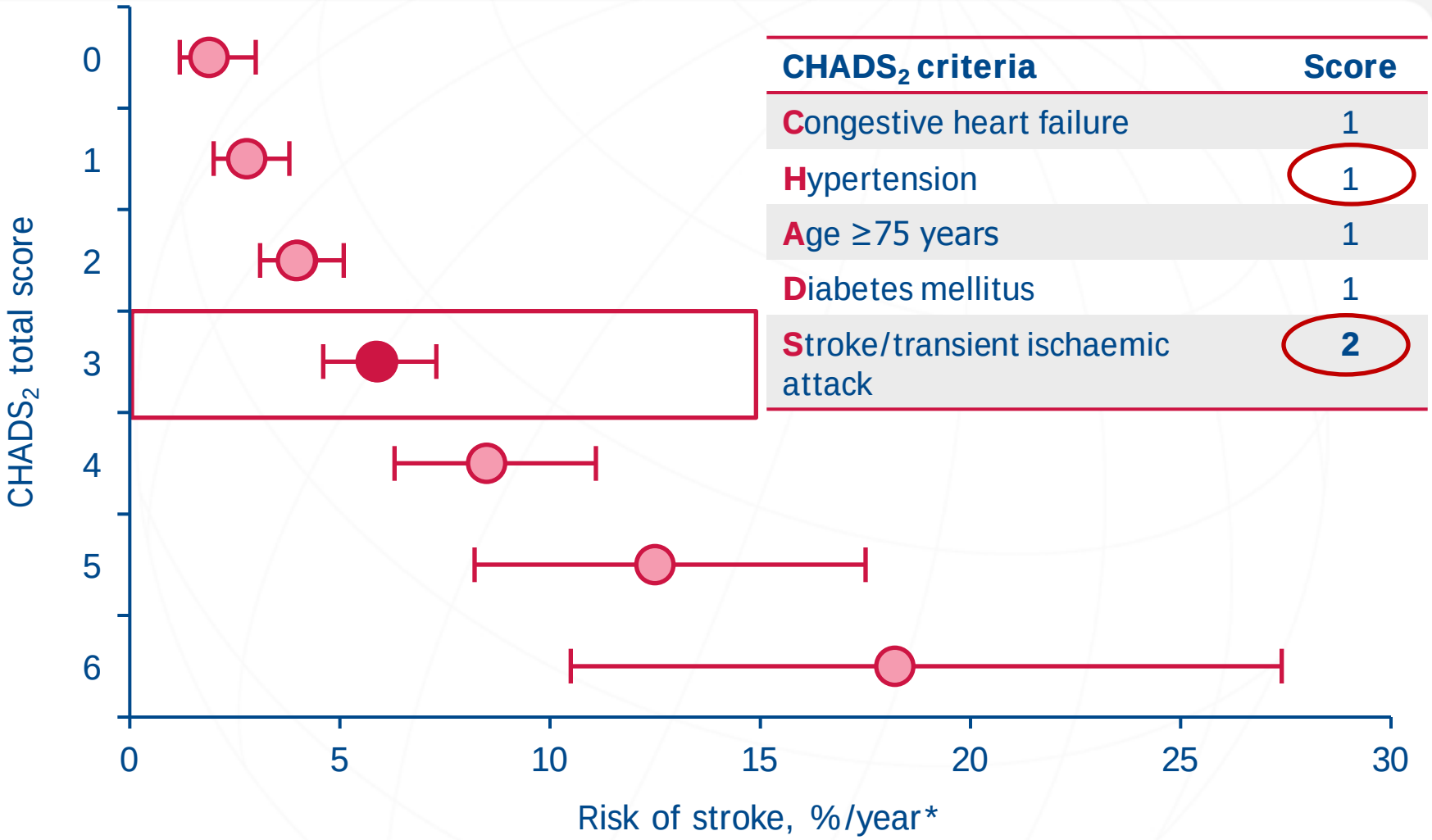
Quale prevenzione a lungo termine?

- ASA
- Clopidogrel
- ASA + Clopidogrel
- Warfarin INR 2-3
- Nuovi anticoagulanti orali

CHADS2=3
CHADS-Vasc= 6
HAS-BLED= 4

Risk of stroke according to $CHADS_2$



$CHADS_2$ criteria	Score
Congestive heart failure	1
Hypertension	1
Age ≥75 years	1
Diabetes mellitus	1
Stroke/transient ischaemic attack	**2**

Error bars = 95% confidence intervals; *Theoretical rates without therapy
ACC/AHA/ESC guidelines: Fuster V et al. Circulation 2006;114:e257–354 & Eur Heart J 2006;27:1979–2030; Gage BF et al. JAMA 2001;285:2864–70

Risk of stroke according to CHA_2DS_2-VASc

CHA_2DS_2-VASc criteria	Score
Congestive heart failure/ left ventricular dysfunction	1
Hypertension	1
Age ≥75 years	**2**
Diabetes mellitus	1
Stroke/transient ischaemic attack/TE	**2**
Vascular disease (prior myocardial infarction, peripheral artery disease or aortic plaque)	1
Age 65–74 years	1
Sex **c**ategory (i.e. female gender)	1

Total score	N	Adjusted stroke rate (% / year)*
0	1	0.0
1	422	1.3
2	1230	2.2
3	1730	3.2
4	1718	4.0
5	1159	6.7
6	679	9.8
7	294	9.6
8	82	6.7
9	14	15.2

*Adjusted for warfarin use. Theoretical rates without therapy; assuming that warfarin provides a 64% reduction in stroke risk, based on Hart RG et al. 2007.

TE = thromboembolism

Lip G et al. Chest 2010;137:263–72; Lip G et al. Stroke 2010;41:2731–8; ESC guidelines: Camm J et al. Eur Heart J 2010;31:2369–429; Hart RG et al. Ann Intern Med 2007;146:857–67

Risk of bleeding according to HAS-BLED

HAS-BLED risk criteria	Score
Hypertension (SBP >160 mmHg)	1
Abnormal renal or liver function (1 point each)	1 or 2
Stroke	1
Bleeding (history or predisposition)	1
Labile INRs	1
Elderly (e.g. age >65 years)	1
Drugs† or alcohol (1 point each)	1 or 2

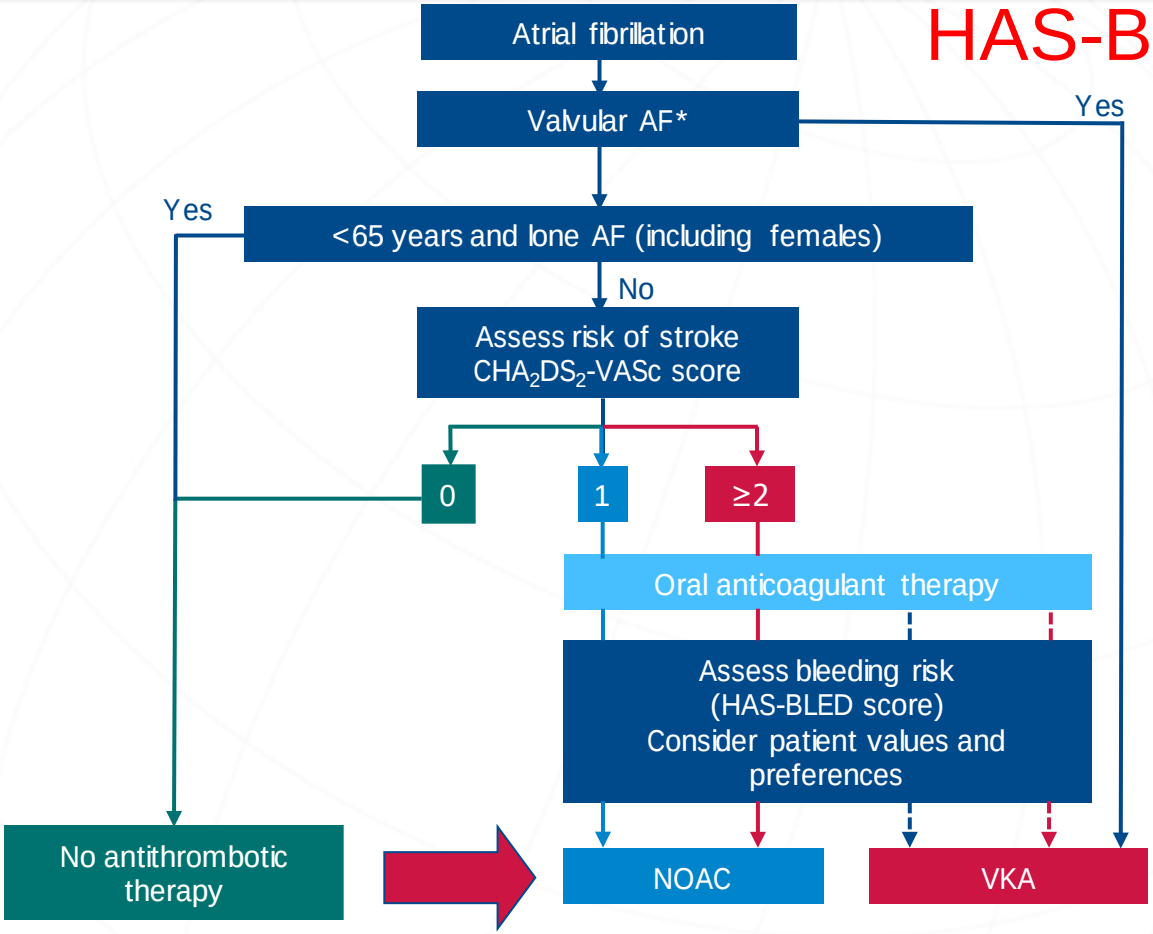
HAS-BLED total score	N	Number of bleeds	Bleeds per 100 patient-years*
0	798	9	1.13
1	1286	13	1.02
2	744	14	1.88
3	187	7	3.74
4	46	4	8.70
5	8	1	12.5
6	2	0	0.0
7	0	–	–
8	0	–	–
9	0	–	–

*P value for trend = 0.007; †Antiplatelets and non-steroidal anti-inflammatories; INR = international normalized ratio; SBP = systolic blood pressure

Pisters R et al. Chest 2010;138:1093–100; ESC guidelines: Camm J et al. Eur Heart J 2010;31:2369–429

Choice of anticoagulant

CHADS2=3
CHADS-Vasc= 6
HAS-BLED= 4



Antiplatelet therapy with ASA plus clopidogrel or – less effectively – ASA only, should be considered in patients who refuse any OAC or cannot tolerate anticoagulation for reasons unrelated to bleeding. If there are contraindications to OAC or antiplatelet therapy, left atrial appendage occlusion, closure or excision may be considered

Colour CHA_2DS_2-VASc: green = 0, blue = 1, red ≥2; line: solid = best option; dashed = alternative option

*Includes rheumatic valvular disease and prosthetic valves; ASA = acetylsalicylic acid; NOAC = novel oral anticoagulant; VKA = vitamin K antagonist

Camm AJ et al. Eur Heart J doi:10.1093/eurheartj/ehs253

Prior stroke subgroup analysis: stroke or systemic embolism

- Higher rate of stroke/systemic embolism in patients with prior stroke/TIA vs those without across treatment groups (2.38% vs 1.22%/yr; P<0.001)
- No significant interaction between previous stroke/TIA and treatment effects on primary outcome

	Dabigatran 110 mg BID	Dabigatran 150 mg BID	Warfarin
Prior stroke/TIA			
Annual rate, %	2.32	2.07	2.78
RR (95% CI) vs warfarin	0.84 (0.58–1.20)	0.75 (0.52–1.08)	
No prior stroke/TIA			
Annual rate, %	1.34	0.87	1.45
RR (95% CI) vs warfarin	0.93 (0.73–1.18)	0.60 (0.45–0.78)	
P value for interaction	0.62	0.34	

BID = twice daily; RR = relative risk; TIA = transient ischaemic attack

Diener HC et al. Lancet Neurol 2010;9:1157–63

Disclaimer: Dabigatran etexilate is now approved for clinical use in stroke prevention in atrial fibrillation in certain countries. Please check local prescribing information for further details

Prior stroke subgroup analysis: ischaemic (or unknown) stroke

- No significant difference in rate of ischaemic stroke between dabigatran and warfarin in patients with prior stroke/TIA

	Dabigatran 110 mg BID	Dabigatran 150 mg BID	Warfarin
Prior stroke/TIA			
Annual rate, %	2.19	1.75	1.75
RR (95% CI) vs warfarin	1.26 (0.84–1.90)	1.00 (0.65–1.54)	
No prior stroke/TIA			
Annual rate, %	1.12	0.71	1.08
RR (95% CI) vs warfarin	1.04 (0.80–1.37)	0.66 (0.48–0.89)	
P value for interaction	0.46	0.12	

BID = twice daily; TIA = transient ischaemic attack

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Prior stroke subgroup analysis: major bleeding

	Dabigatran 110 mg BID	Dabigatran 150 mg BID	Warfarin
Prior stroke/TIA			
Annual rate, %	2.74	4.15	4.15
RR (95% CI) vs warfarin	0.66 (0.48–0.90)	1.01 (0.77–1.34)	
No prior stroke/TIA			
Annual rate, %	2.91	3.10	3.43
RR (95% CI) vs warfarin	0.85 (0.72–0.99)	0.91 (0.77–1.06)	
P value for interaction	0.15	0.51	

BID = twice daily; TIA = transient ischaemic attack

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Prior stroke subgroup analysis: intracranial bleeding

	Dabigatran 110 mg BID	Dabigatran 150 mg BID	Warfarin
Prior stroke/TIA			
Annual rate, %	0.25	0.53	1.28
RR (95% CI) vs warfarin	0.20 (0.08–0.47)	0.41 (0.21–0.79)	
No prior stroke/TIA			
Annual rate, %	0.22	0.27	0.63
RR (95% CI) vs warfarin	0.35 (0.21–0.57)	0.43 (0.27–0.68)	
P value for interaction	0.26	0.91	

BID = twice daily; TIA = transient ischaemic attack

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Prior stroke subgroup analysis: haemorrhagic stroke

- Lower stroke risk in patients with prior stroke/TIA receiving dabigatran vs warfarin mainly due to decrease in haemorrhagic stroke

	Dabigatran 110 mg BID	Dabigatran 150 mg BID	Warfarin
Prior stroke/TIA			
Annual rate, %	0.08	0.20	0.77
RR (95% CI) vs warfarin	0.11 (0.03–0.47)	0.27 (0.10–0.72)	
No prior stroke/TIA			
Annual rate, %	0.13	0.07	0.29
RR (95% CI) vs warfarin	0.44 (0.22–0.86)	0.25 (0.11–0.59)	
P value for interaction	0.09	0.97	

BID = twice daily; TIA = transient ischaemic attack

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General recommendations (2)

Recommendation	Class	Level
In patients with CHA_2DS_2-VASc score ≥2, OAC therapy with: •a dose-adjusted VKA (INR 2–3); or •a direct thrombin inhibitor (**dabigatran**); or •an oral Factor Xa inhibitor (e.g. rivaroxaban, apixaban*) … **is recommended** unless contraindicated	I	A
In patients with CHA_2DS_2-VASc score 1, OAC therapy with: •a dose-adjusted VKA (INR 2–3); or •a direct thrombin inhibitor (**dabigatran**); or •an oral Factor Xa inhibitor (e.g. rivaroxaban, apixaban*) … **should be considered**, based upon an assessment of the risk of bleeding complications and patient preferences	IIa	A

*Pending approval; INR = international normalized ratio; OAC = oral anticoagulation; VKA = vitamin K antagonist

Camm AJ et al. Eur Heart J doi:10.1093/eurheartj/ehs253

NOAC-specific recommendations (2)

Recommendation	Class	Level
When dabigatran is prescribed, a dose of **150 mg BID should be considered for most patients** in preference to 110 mg BID, with the latter dose recommended in: •elderly patients, age ≥80 years •concomitant use of interacting drugs (e.g. verapamil) •**high bleeding risk (HAS-BLED score ≥3)** •moderate renal impairment (CrCl 30–49 mL/min)	IIa	B

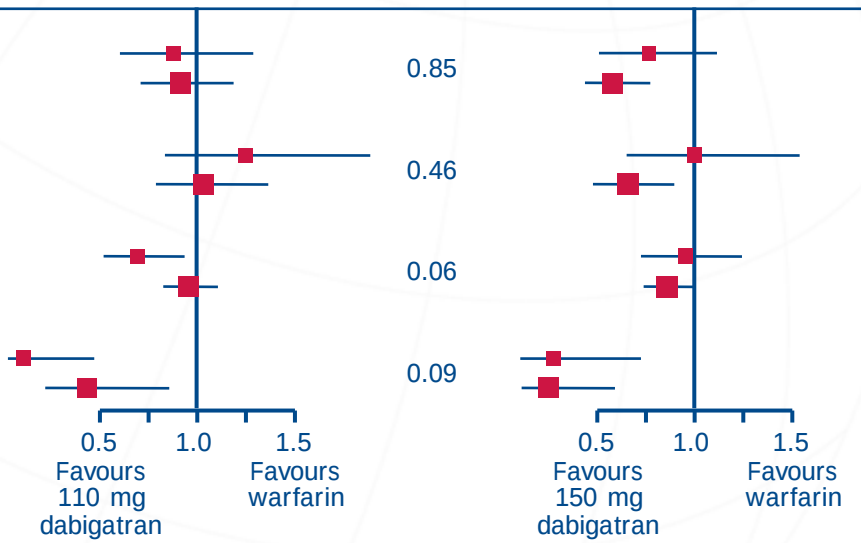
BID = twice daily; CrCl = creatinine clearance; OD = once daily

Camm AJ et al. Eur Heart J doi:10.1093/eurheartj/ehs253

Prior stroke subgroup analysis: major clinical outcomes in patients with or without previous stroke or TIA (1)

- No significant interactions between primary and secondary outcomes in patients with and without a history of prior stroke

	Rate (% per year)				
	Dabigatran		Warfarin	Interaction P	Interaction P
	110 mg	150 mg			
Stroke					
Previous stroke or TIA	2.23	1.91	2.53	0.85	0.28
No previous stroke or TIA	1.24	0.78	1.34		
Ischaemic or unknown stroke					
Previous stroke or TIA	2.19	1.75	1.75	0.46	0.12
No previous stroke or TIA	1.12	0.71	1.08		
Death from any cause					
Previous stroke or TIA	3.24	4.39	4.58	0.06	0.50
No previous stroke or TIA	3.87	3.45	4.02		
Haemorrhagic stroke					
Previous stroke or TIA	0.08	0.20	0.77	0.09	0.97
No previous stroke or TIA	0.13	0.07	0.29		



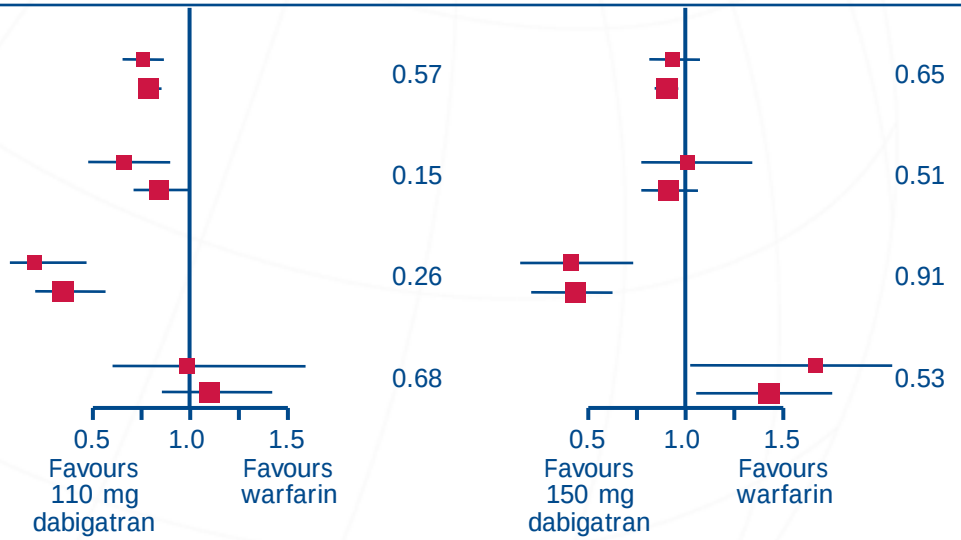
TIA = transient ischaemic attack

Diener HC et al. Lancet Neurol 2010;9:1157–63

Prior stroke subgroup analysis: major clinical outcomes in patients with or without previous stroke or TIA (2)

- No significant interactions between primary and secondary outcomes in patients with and without a history of prior stroke

	Rate (% per year)			Interaction P	Interaction P
	Dabigatran 110 mg	Dabigatran 150 mg	Warfarin		
Total bleeding					
Previous stroke or TIA	14.49	16.90	18.53	0.57	0.65
No previous stroke or TIA	14.71	16.33	18.15		
Major bleeding					
Previous stroke or TIA	2.74	4.15	4.15	0.15	0.51
No previous stroke or TIA	2.91	3.10	3.43		
Intracranial bleeding					
Previous stroke or TIA	0.25	0.53	1.28	0.26	0.91
No previous stroke or TIA	0.22	0.27	0.63		
Gastrointestinal major bleed					
Previous stroke or TIA	1.39	2.32	1.41	0.68	0.53
No previous stroke or TIA	1.35	1.73	1.23		



TIA = transient ischaemic attack

Diener HC et al. Lancet Neurol 2010;9:1157–63

Prior stroke subgroup analysis: major clinical outcomes in patients with or without previous stroke or TIA

	Rate (% per year)			Interaction P	Interaction P
	D110 mg	D150 mg	Warfarin		
Stroke					
Previous stroke or TIA	2.23	1.91	2.53	0.85	0.28
No previous stroke or TIA	1.24	0.78	1.34		
Ischaemic or unknown stroke					
Previous stroke or TIA	2.19	1.75	1.75	0.46	0.12
No previous stroke or TIA	1.12	0.71	1.08		
Death from any cause					
Previous stroke or TIA	3.24	4.39	4.58	0.06	0.50
No previous stroke or TIA	3.87	3.45	4.02		
Haemorrhagic stroke					
Previous stroke or TIA	0.08	0.20	0.77	0.09	0.97
No previous stroke or TIA	0.13	0.07	0.29		
Total bleeding					
Previous stroke or TIA	14.49	16.90	18.53	0.57	0.65
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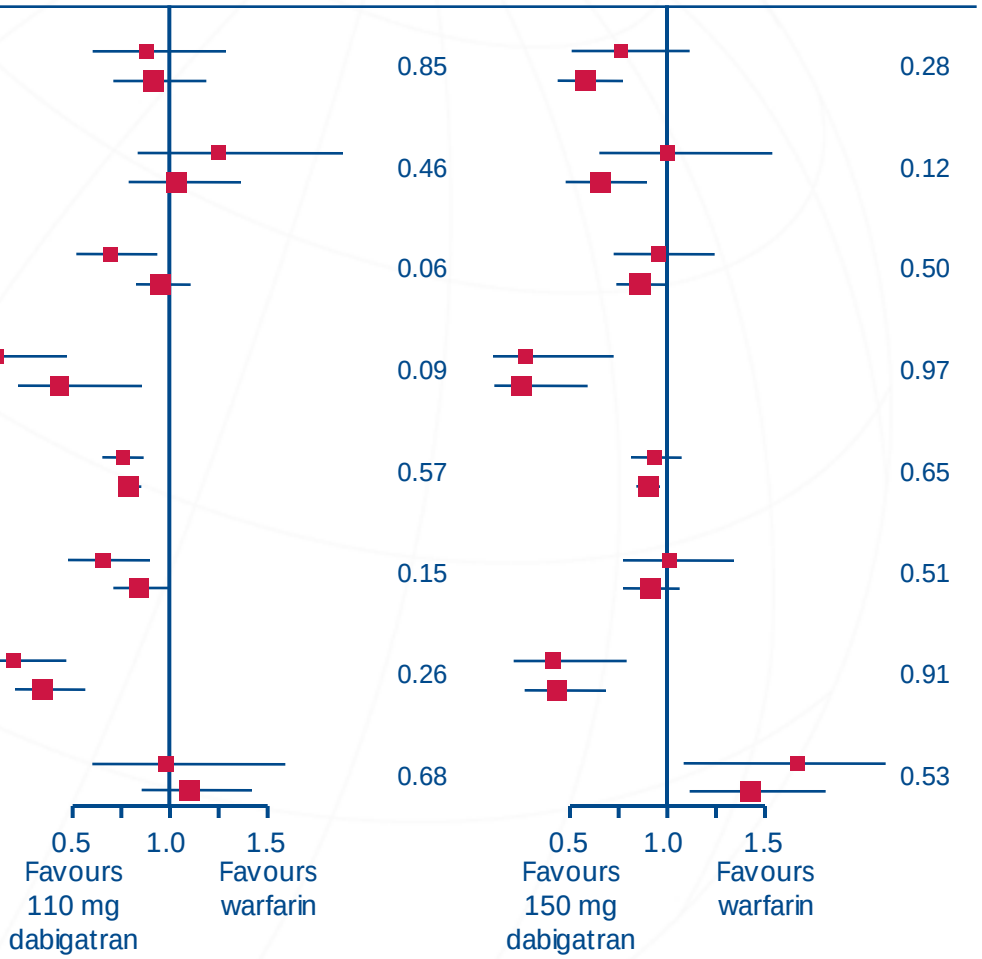
Major bleeding					
Previous stroke or TIA	2.74	4.15	4.15	0.15	0.51
No previous stroke or TIA	2.91	3.10	3.43		
Intracranial bleeding					
Previous stroke or TIA	0.25	0.53	1.28	0.26	0.91
No previous stroke or TIA	0.22	0.27	0.63		
Gastrointestinal major bleed					
Previous stroke or TIA	1.39	2.32	1.41	0.68	0.53
No previous stroke or TIA	1.35	1.73	1.23		



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Prior stroke subgroup analysis: vascular death

- Vascular death the only outcome significantly different between patients with or without a prior stroke/TIA

	Dabigatran 110 mg BID	Dabigatran 150 mg BID	Warfarin
Prior stroke/TIA			
Annual rate (%)	1.90	2.97	3.00
RR (95% CI) vs warfarin	0.63 (0.43–0.92)	0.98 (0.70–1.36)	
No prior stroke/TIA			
Annual rate (%)	2.56	2.10	2.61
RR (95% CI) vs warfarin	0.98 (0.82–1.17)	0.80 (0.67–0.97)	
P value for interaction	0.04	0.29	

BID = twice daily; RR = relative risk; TIA = transient ischaemic attack

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General recommendations (2)

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In patients with CHA_2DS_2-VASc score 1, OAC therapy with: •a dose-adjusted VKA (INR 2–3); or •a direct thrombin inhibitor (**dabigatran**); or •an oral Factor Xa inhibitor (e.g. rivaroxaban, apixaban*) … **should be considered**, based upon an assessment of the risk of bleeding complications and patient preferences	IIa	A

*Pending approval; INR = international normalized ratio; OAC = oral anticoagulation; VKA = vitamin K antagonist

Camm AJ et al. Eur Heart J doi:10.1093/eurheartj/ehs253

General recommendations (3)

Recommendation	Class	Level
Female patients who are aged <65 years and have lone AF (but still have a CHA_2DS_2-VASc score of 1 by virtue of their gender) are low risk and no antithrombotic therapy should be considered	IIa	B
When patients refuse the use of any OAC (whether VKA or NOACs), antiplatelet therapy should be considered, using combination therapy with ASA 75–100 mg plus clopidogrel 75 mg daily (where there is a low risk of bleeding) or – less effectively – ASA 75–325 mg daily	IIa	B

ASA = acetylsalicylic acid; NOAC = novel oral anticoagulant; OAC = oral anticoagulation; VKA = vitamin K antagonist; Camm AJ et al. Eur Heart J doi:10.1093/eurheartj/ehs253

NOAC-specific recommendations (2)

Recommendation	Class	Level
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BID = twice daily; CrCl = creatinine clearance; OD = once daily

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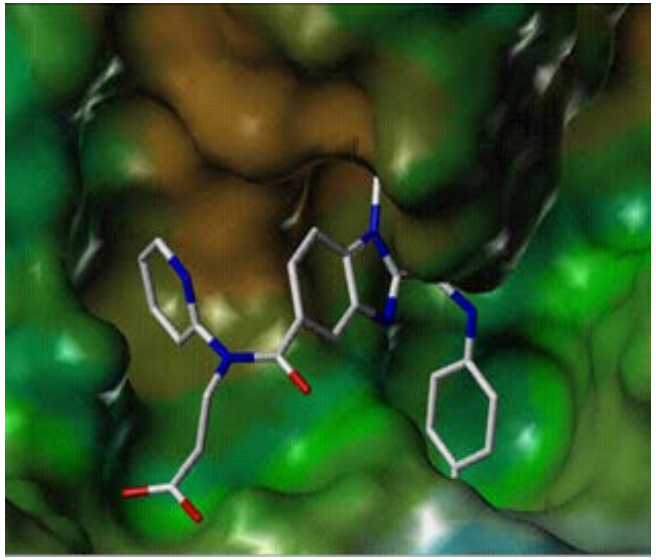
Dabigatran and stroke prevention

- Dabigatran 150 mg twice daily[1,2]
  - Superior efficacy to well-controlled warfarin with a similar risk of major bleeding
- Dabigatran 110 mg twice daily[1,2]
  - Similar efficacy to well-controlled warfarin with a lower risk of major bleeding
- Low potential for drug–drug interactions[3]
- Predictable and consistent pharmacodynamic effects[4,5]
- No requirement for routine anticoagulation monitoring[6]



1. Connolly SJ et al. N Engl J Med 2009;361:1139–51; **2.** Connolly SJ et al. N Engl J Med 2010;363:1875–6;
3. Blech S et al. Drug Metab Dispos 2008;36:386–99; **4.** Stangier J et al. Clin Pharmacokinet 2008;28:47–59;
5. Stangier J. Clin Pharmacokinet 2008;47:285–95; **6.** Stangier J et al. Br J Pharmacol 2007;64:292–303