ADVANCES IN CARDIAC ARRHYTHMIAS
and GREAT INNOVATIONS IN CARDIOLOGY

Torino, 25 ottobre 2012

DABIGATRAN IN CLINICAL PRACTICE:

CASE SCENARIO

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- *Sett 2012: la paziente viene ricoverata presso la nostra Divisione per riferita lieve dispnea e elevati valori pressori domiciliari.*

- *M.F., **femmina, 73** anni, ex operatrice socio-sanitaria*
- *1982 isteroannessectomia*
- *1998 addominoplastica per laparocele*
- *1999 frattura post-traumatica di ulna e radio*
- ***Ipertensione** arteriosa essenziale postmenopausale*
- ***Epatosteatosi** lieve e **gastrite atrofica** del fondo gastrico*
- ***FA cronica***
- *Gozzo nodulare normofunzionante*
- *Anemia da carenza di vit.B12 e iperomocisteinemia in mutazione eterozigote MTHFR.*

- *Ultimo ricovero Nov. 2011 per astenia, durante il quale, in assenza di deficit neurologici, ha eseguito **TC cranio,** che ha evidenziato **ampio esito poromalacico** in sede temporo-parietale dx.*

- ***Terapia in atto:** Amlodipina 10 mg, Warfarin, Dobetin 5000 ogni 3 mesi, cicli di Folina, Lansoprazolo 20*

EO all'ingresso:

- *Condizioni generali buone; eupnoica a riposo e per sforzi lievi (NYHA II); cognitivamente in limiti, autonoma. Alt 1.68 kg 65*
- *EOCV: toni aritmici, soffio sistolico al meso da rigurgito mitralico, giugulare non distesa; PA 165/90; minima succulenza perimalleolare; assenti segni suggestivi di TVP; non apprezzabili soffi carotidei; polsi distali simmetrici.*
- *EOP: normoplessico, basi mobili, MV bilaterale, sat O2 98%*
- *EOA: trattabile, non dolente; fegato all'arcata, liscio, non dolente*

Principali ematochimici:

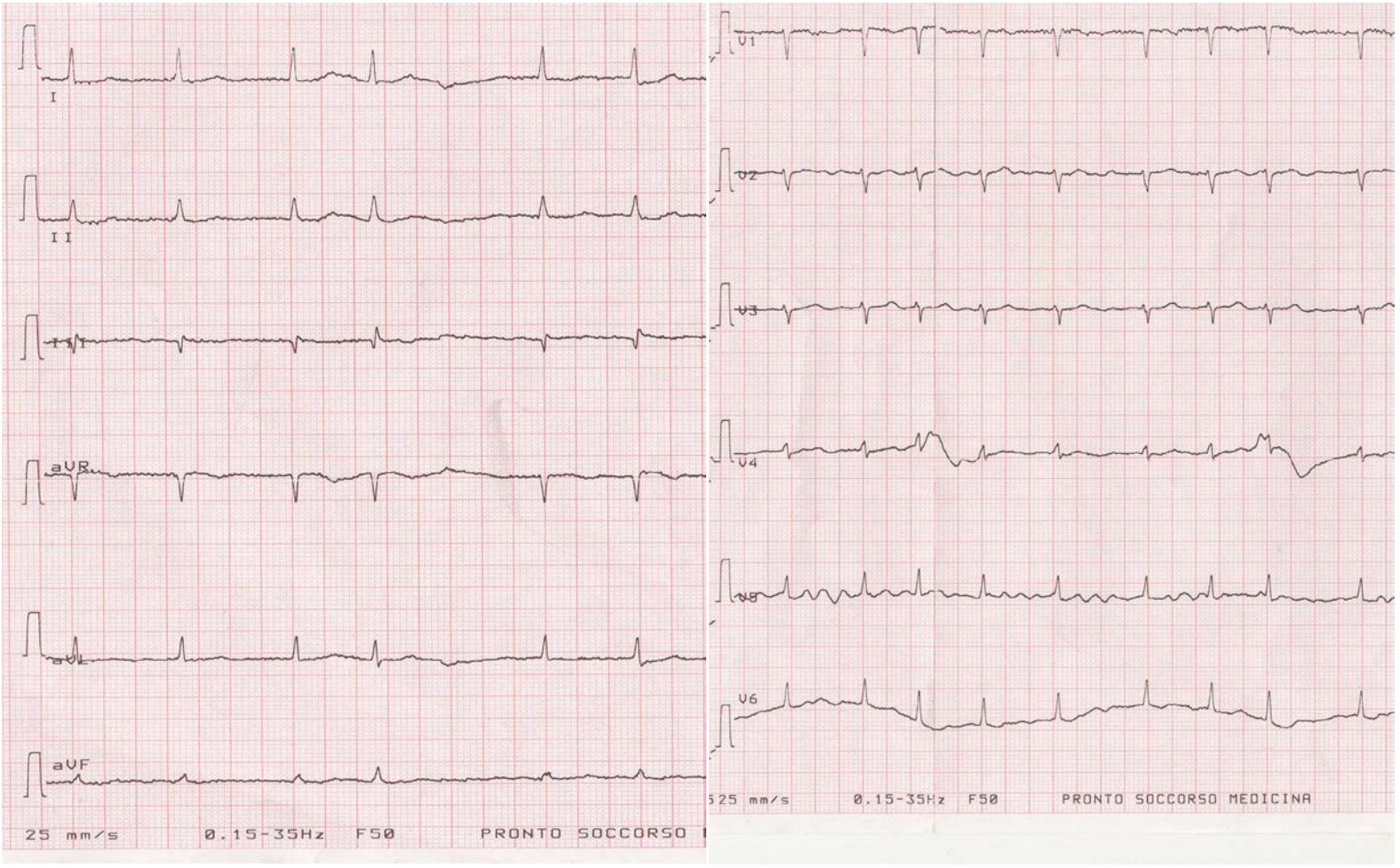
HGB 14.2 g/dL; MCV 99 fL; PLT 250.000/L; INR 1.85

TSH 1.170 mcUI/mL; Vitamina B12 135 pg/mL; Ac folico 4.9 ng/mL

AST e ALT nn; GGT 68; Creatinina 1.38 mg/dl (VFG 45,1 ml/min, formula CG)

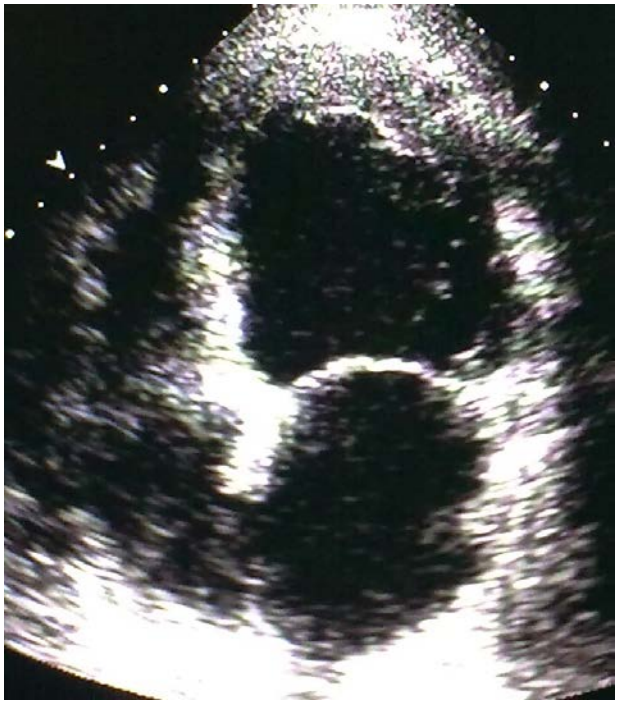
cTnT 0.012 NTproBNP 674

***RX Torace**: segni di enfisema con accentuazione del disegno vascolare polmonare e delle ombre ilari; ombra cardiaca ingrandita con prevalente aumento dei diametri relativi al ventricolo sx; aorta toracica allungata con calcificazioni lamellari in corrispondenza dell'arco.*



***TC encefalo basale**: in quadro di vasculopatia cerebrale cronica, due estese ipodensita' di natura ischemica pregressa, in regione temporoparietale dx ed occipitale sx con associata attrazione ex vacuo dei contigui corni ventricolari. Non altre alterazioni focali del parenchima cerebrale ne' segni di emorragie cerebro-meningei. Sistema ventricolare in asse di dimensioni nei limiti della norma.*

***Ecocardio**: Vsx ipertrofico, dimensioni TD ai limiti superiori, FE 55%, IM lieve; Asx 45 mm; PAPs 31 mmHg*



QUALI CONSIDERAZIONI CLINICHE?

1. *Cardiopatia ipertensiva, con minimo iniziale scompenso e valori pressori non adeguatamente controllati*
2. *Duplice episodio ischemico cerebrale, verosimilmente embolico, senza reliquati, in corso di TAO con warfarin. Scarsa aderenza terapeutica? Farmacoresistenza? Terapia non condotta in modo ottimale?*

***VALORI INR**:*

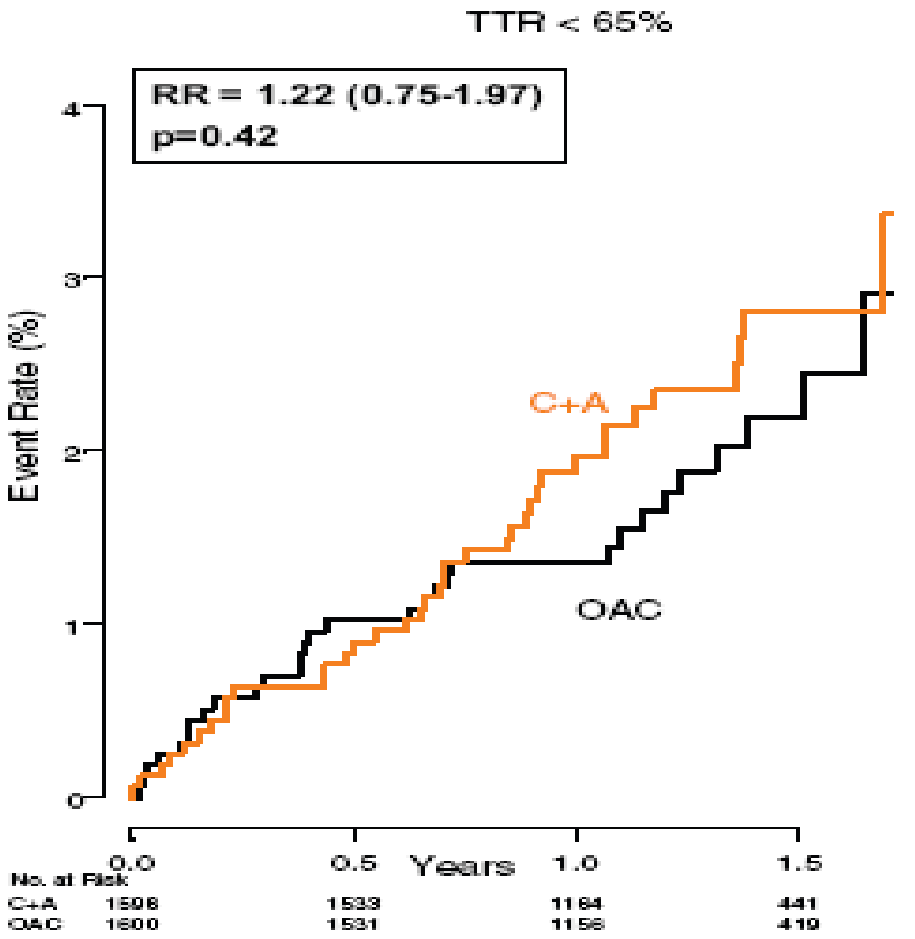
- *5/6/12: 1.71*
- *20/6/12: 1.98*
- *03/7/12: 2.87*
- *20/7/12: 2.11*
- *04/8/12: 1.84*
- *20/8/12: 3.99*
- *04/9/12: 1.77*

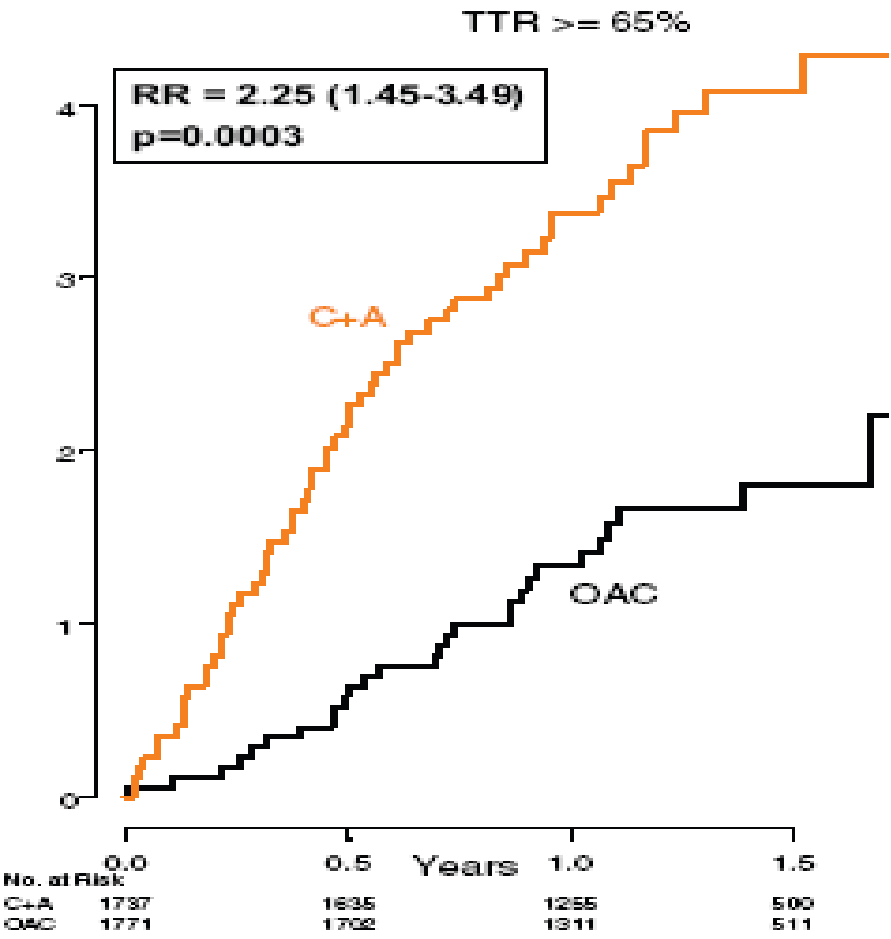
Criteri per una buona gestione della TAO nell'anziano

1. **Valutare attentamente il dato anamnestico di sanguinamenti pregressi** (spontanei, traumatici, in corso di TAO)
2. Nei limiti del possibile, **evitare interazioni farmacologiche a rischio** (FANS occasionali/abituali, statine, calcio-antagonisti, allopurinolo, macrolidi, ecc)
3. Mantenere **dieta congrua**
4. Utilizzare **dosi compatibili** con l'età del paziente
5. **Ottimizzare il controllo pressorio**
6. **Ottimizzare la gestione della terapia per mantenere un INR terapeutico** (INR 2.0-2.5, controlli ravvicinati, diario INR e posologia farmaco, sorveglianza medica, ecc)
7. **Intensificare la frequenza dei controlli o sospendere la terapia in occasione di eventi intercorrenti acuti**

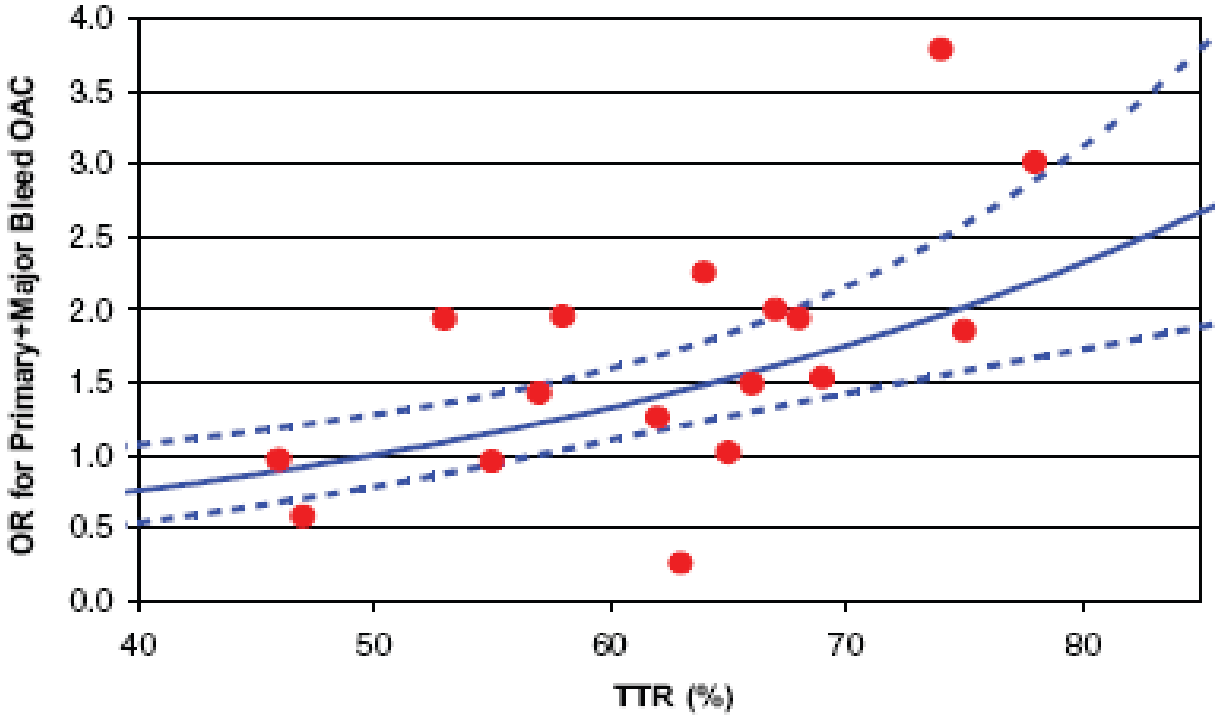
(*Circulation*. 2008;118:2029-2037.)

Benefit of Oral Anticoagulant Over Antiplatelet Therapy in Atrial Fibrillation Depends on the Quality of International Normalized Ratio Control Achieved by Centers and Countries as Measured by Time in Therapeutic Range





Rischio cumulativo di stroke in rapporto al TTR nei centri (<65% vs >=65%)



TTR > 60% soglia minima di beneficio durante TAO

Figure 3. Relationship between the odds ratio (OR) of stroke, myocardial infarction, systemic embolism, vascular death, or major hemorrhage and TTR using population-average logistic regression. The hatched lines show the 95% CI of the OR. The relationship is described by the following equation: log (OR)=−1.4+0.028×TTR. Each dot represents 1 country participating in ACTIVE, showing the relationship between the OR and TTR for that country (for all countries with ≥10 events). OR is for clopidogrel plus aspirin vs OAC.

Conclusions—A wide variation exists in international normalized ratio control, as measured by TTR, between clinical centers and between countries, which has a major impact on the treatment benefit of OAC therapy. For centers and countries, a target threshold TTR exists (estimated between 58% and 65%) below which there appears to be little benefit of OAC over antiplatelet therapy. (***Circulation*. 2008;118:2029-2037.**)

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Europace
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ESC GUIDELINES

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

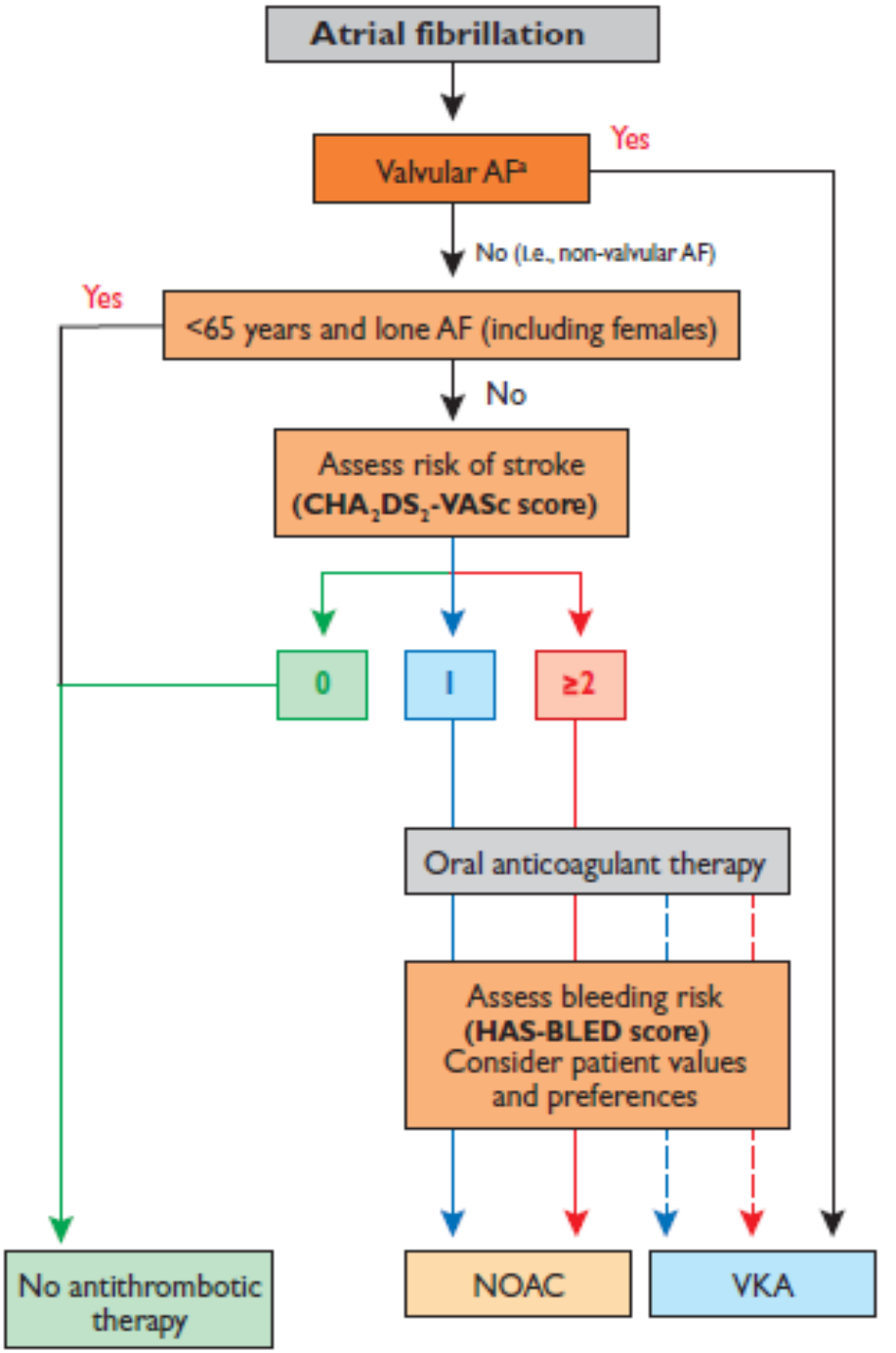
An update of the 2010 ESC Guidelines for the management of atrial fibrillation
Developed with the special contribution of the European Heart Rhythm Association

*The **evidence for effective stroke prevention with aspirin in AF is weak**, with a **potential for harm**… given the availability of NOACs, the use of antiplatelet therapy for stroke prevention in AF should be limited to the few patients who refuse any form of OAC.*

In patients with a CHA2DS2-VASc score ≥2, OAC therapy with:

- ***adjusted dose VKA, or***
- ***a direct thrombin inhibitor (dabigatran), or***
- ***an oral factor Xa inhibitor (eg rivaroxaban, apixaban)***

is recommended, unless contraindicated (Class I, Level A)



Age and Ageing 2010; **39:** 533–535
doi: 10.1093/ageing/afq059
Published electronically 26 May 2010

Simplifying stroke risk stratification in atrial fibrillation patients: implications of the CHA_2DS_2–VASc risk stratification scores

Table 1. Stroke risk stratification with the $CHADS_2$ and CHA_2DS_2–VASc schemas

$CHADS_2$ [6]	Score	CHA_2DS_2–VASc [20]	Score
Congestive heart failure	1	**C**ongestive heart failure/LV dysfunction	1
Hypertension	1	**H**ypertension	1
Aged ≥75 years	1	**A**ged ≥75 years	2
Diabetes mellitus	1	**D**iabetes mellitus	1
Stroke/TIA/TE	2	**S**troke/TIA/TE	2
		Vascular disease (prior MI, PAD or aortic plaque)	1
		Aged 65–74 years	1
		Sex category (i.e. female gender)	1
Maximum score	6	Maximum score	10

5

0: Low risk; 1: intermediate risk; >=2: high risk

Table 10 Clinical characteristics comprising the HAS-BLED bleeding risk score

Letter	Clinical characteristic[a]	Points awarded
H	Hypertension	1
A	Abnormal renal and liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly (e.g. age >65 years)	1
D	Drugs or alcohol (1 point each)	1 or 2
		Maximum 9 points

4

QUALI PROVVEDIMENTI TERAPEUTICI?

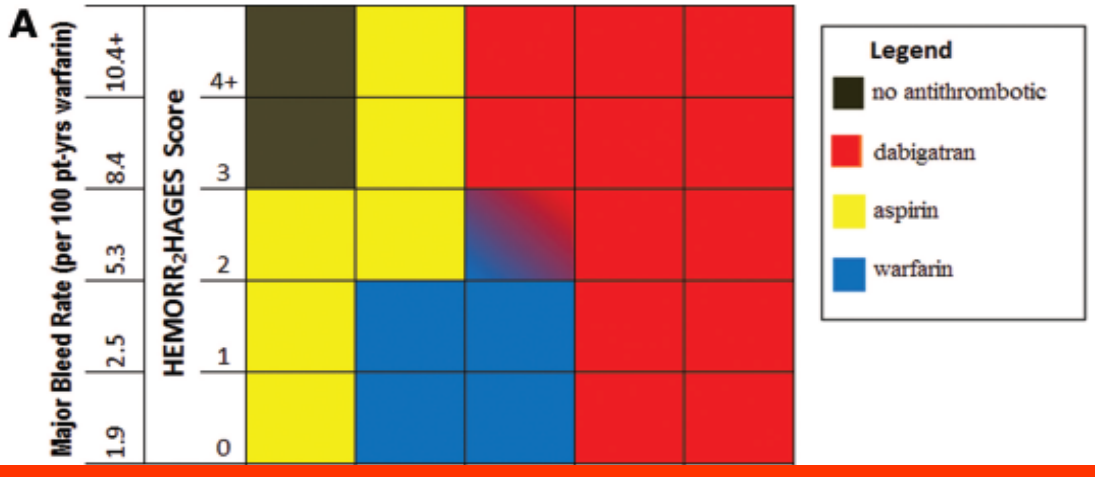
1. *Aggiunta di Telmisartan-Idroclorotiazide 80/25 mg*
2. *Intensificazione della terapia anticoagulante con warfarin? Passaggio ad un nuovo anticoagulante orale?*

Stroke

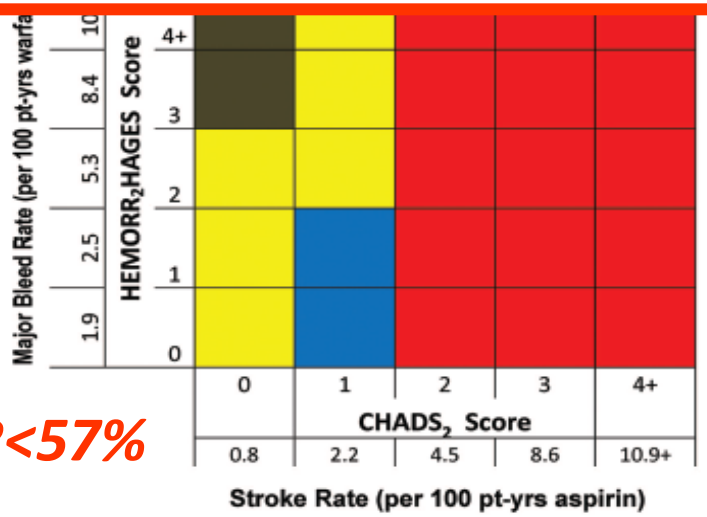
(*Circulation*. 2011;123:2562-2570.)

Cost-Effectiveness of Dabigatran for Stroke Prophylaxis in Atrial Fibrillation

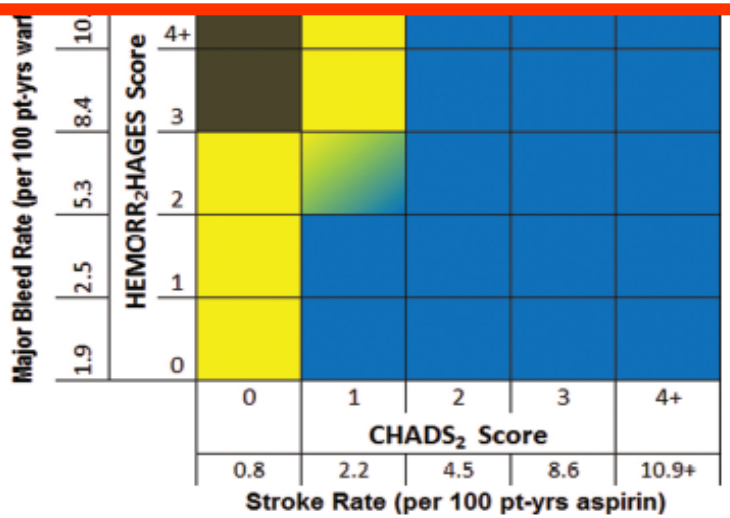
Base-Case scenario



Conclusions*-Dabigatran 150 bid was cost-effective in AF populations at high risk of hemorrhage or high risk of stroke unless INR control with warfarin was excellent.*



TTR<57%



TTR>72%

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

New Oral Anticoagulants for Atrial Fibrillation

(*Circulation*. 2012;126:133-137.)

American Heart Association

Recommendations for Converting Between Anticoagulants

From parenteral anticoagulation to dabigatran or rivaroxaban

- Heparin - Administer first dose at time heparin is discontinued
- LMWH - Administer first dose at time next dose is due

To parenteral anticoagulation from

- Dabigatran
  - For CrCl ≥30 mL/min wait 12 hours after last dose dabigatran
  - For CrCl <30 mL/min, wait 24 hours after last dose of dabigatran
- Rivaroxaban
  - At time of next scheduled rivaroxaban dose

From warfarin to

- Dabigatran - Start dabigatran when INR<2.0
- Rivaroxaban - Start rivaroxaban when INR<3.0

From dabigatran to warfarin

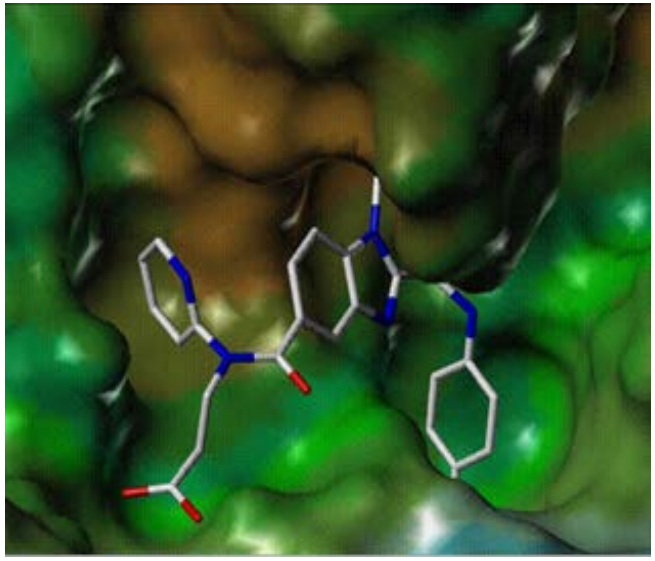
- For CrCl ≥50 mL/min - Start warfarin 3 d before discontinuing dabigatran
- For CrCl 30–50 mL/min - Start warfarin 2 d before discontinuing dabigatran
- For CrCl 15–30 mL/min - Start warfarin 1 d before discontinuing dabigatran

From rivaroxaban to warfarin

- Use parenteral anticoagulation bridge

Dabigatran and stroke prevention in RE-LY®

- Dabigatran 150 mg twice daily[1,2]
  - In RE-LY®: superior efficacy to well-controlled warfarin with a similar risk of major bleeding
- Dabigatran 110 mg twice daily[1,2]
  - In RE-LY®: 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

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.

Approval of dabigatran: Europe

- ***Europe:*** *prevention of stroke and systemic embolism in patients with nonvalvular AF and one or more risk factors*[1]
  - *Renal function should be assessed prior to initiation of treatment to exclude patients with severe renal impairment (CrCl <30 mL/min)*
  - *While on treatment, renal function should be assessed in clinical situations where a decline in renal function is suspected (e.g. hypovolaemia, dehydration, and with certain co-medications)*
  - *In patients >75 years or with renal impairment, renal function should be assessed at least yearly while on treatment*
  - *150 mg BID recommended for the majority of patients*
  - *110 mg BID in patients aged ≥80 years and with concomitant verapamil treatment; may also be considered if the risk of bleeding is high*

BID = twice daily; CrCl = creatinine clearance

1. *Pradaxa®: SmPC, 2011*

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.

Approval of dabigatran: Canada

- ***Canada:*** *prevention of stroke or systemic embolism in patients with AF in whom anticoagulation is appropriate*
  - *150 mg BID recommended for the majority of patients*
  - *110 mg BID in patients aged ≥80 years and those at high risk of bleeding*
  - *Updated guidance regarding renal function guidance, similar to Europe, is expected in early 2012*

BID = twice daily

1. *Pradaxa®: SmPC, 2011*

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The 2010 Canadian Cardiovascular Society guidelines and 2011 ACCF/AHA/HRS update guidelines recommend dabigatran

- *2010 Canadian Cardiovascular Society guidelines for patients with AF:*[1]
  - ***$CHADS_2$ score ≥2:*** *Warfarin (INR 2.0–3.0) or dabigatran (preferred option)*
  - ***$CHADS_2$ score = 1:*** *Warfarin (INR 2.0–3.0) or dabigatran (preferred option)*
  - ***$CHADS_2$ score = 0:*** *Aspirin (75–325 mg/day)*
- *2011 ACCF/AHA/HRS focused update guidelines recommend dabigatran as an alternative to warfarin in patients with paroxysmal to permanent AF*[2]

ACCF = American College of Cardiology Foundation; AHA = American Heart Association; HRS = Heart Rhythm Society; INR = international normalized ratio

1. *CCS guidelines: Cairns JA et al. Can J Cardiol 2011;27:74–90;*

2. *ACCF/AHA/HRS focused update guidelines: Wann LS et al. J Am Coll Cardiol 2011;57:1330–37*

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Approval of dabigatran: USA

- *Reduction of the risk of stroke and systemic embolism in patients with nonvalvular AF*[1]
  - *Renal function should be assessed:*
    - *prior to initiation of treatment*
    - *during treatment in clinical situations that may be associated with a decline in renal function*
    - *at least once a year during treatment in patients aged >75 years and in those with CrCl <50 mL/min*
  - *150 mg BID recommended in patients with a CrCl >30 mL/min*
  - *75 mg BID in patients with severe renal insufficiency (CrCl 15–30 mL/min)*
  - *75 mg BID may be considered in patients with moderate renal impairment (CrCl 30–50 mL/min) and concomitant use of dronedarone or systemic ketoconazole*
  - *110 mg BID not approved as no particular subgroups were identified for which the lower dose was considered more advantageous than dabigatran 150 mg BID*[2]

BID = twice daily; CrCl = creatinine clearance

1. *Pradaxa®: US Prescribing Information, 2011;* ***2.*** *Beasley LS et al. N Engl J Med 2011;364:1788–90*

Treatment guidelines recommend oral anticoagulation

- *2010 ESC guidelines:*[1]
  - *Oral anticoagulation in patients with AF and ≥1 risk factors for stroke*[1]
  - *New oral anticoagulants, which may be viable alternatives to vitamin K antagonists, may ultimately be considered (e.g. dabigatran)*
- *The 2010 Canadian Cardiovascular Society and 2011 ACCF/AHA/HRS focused update guidelines both recommend dabigatran*[2,3]
  - *Canadian Cardiovascular Society: dabigatran is the preferred treatment in patients with AF and a $CHADS_2$ score of ≥1*
  - *ACCF/AHA/HRS: dabigatran is recommended as an alternative to warfarin in patients with paroxysmal to permanent AF*

ACCF = American College of Cardiology Foundation; AHA = American Heart Association; ESC = European Society of Cardiology; HRS = Heart Rhythm Society

1. *ESC guidelines: Camm J et al. Eur Heart J 2010;31:2369–429;* ***2.*** *CCS guidelines: Cairns JA et al. Can J Cardiol 2011;27:74–90;* ***3.*** *ACCF/AHA/HRS focused update guidelines: Wann LS et al. J Am Coll Cardiol 2011;57:1330–37*

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Table 2. Potential Drug Interactions With New Oral Anticoagulants Dabigatran Etexilate and Rivaroxaban*[1,4,5]

CYP3A4†					
Inducer		Inhibitor		P-Glycoprotein (P-gp)	
Strong‡	Moderate	Strong	Moderate	Inducer	Inhibitor§
Carbamazepine	Bosentan	Clarithromycin‖	Amprenavir	Carbamazepine	Amiodarone
Phenytoin	Efavirenz	Conivaptan‖	Aprepitant	Phenytoin	Conivaptan‖
Rifampin	Etravirine	Grapefruit juice (high-dose, double strength)	Atazanavir	Rifampin	Clarithromycin‖
St. John's wort	Modafenil	Indinavir‖	Ciprofloxacin	Tiprinavir/Ritonavir	Cyclosporine
	Nafcillin	Itraconazole‖	Darunavir/ Ritonavir	St. John's wort	Dronedarone¶
		Ketoconazole‖	Diltiazem		Erythromycin
		Lopinivir/ Ritonavir‖	Erythromycin		Indinavir/Ritonavir‖
		Nefazadone	Fluconazole		Lopinavir/ Ritonavir‖
		Nelfinavir	Fosamprenavir		Itraconazole‖
		Posaconazole	Grapefruit juice (low-dose-single strength)		Ketoconazole‖¶
		Ritonavir‖	Imatinib		Quinidine
		Saquinavir	Verapamil		Ritonavir‖
		Telaprevir			Verapamil
		Telithromycin			
		Voriconazole			