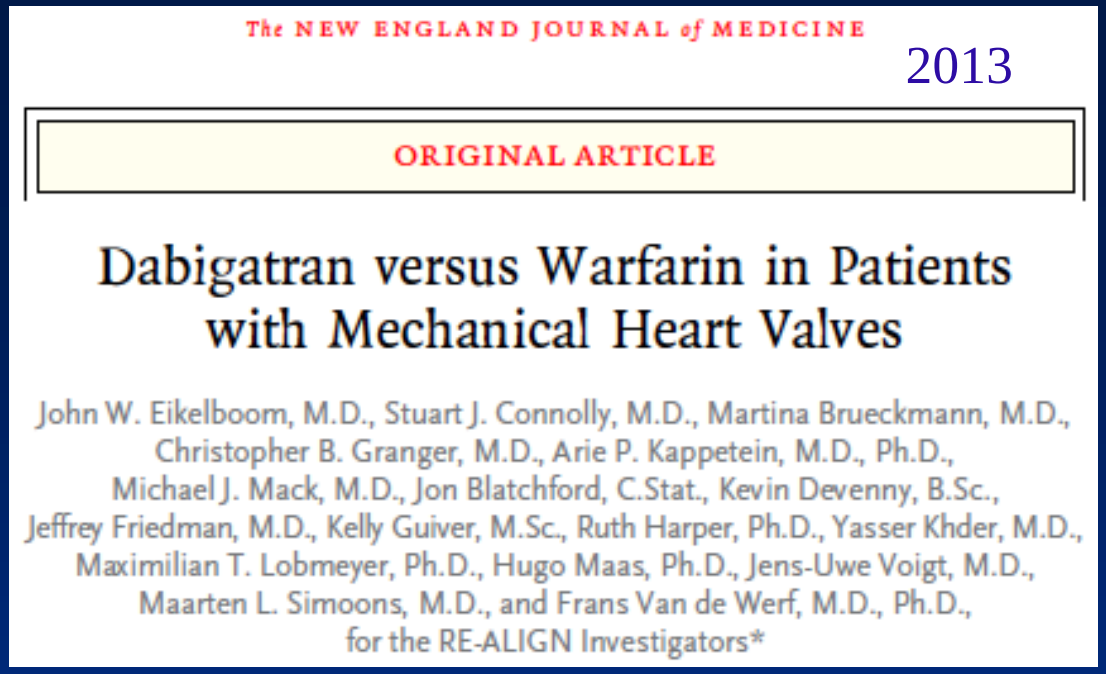
Terzo Meeting di Ematologia Non-Oncologica
Firenze 26-27 Gennaio 2017

A chi ancora i dicumarolici oggi?

Prof. Gualtiero Palareti
Malattie Cardiovascolari
Università di Bologna

Non indicazione per NAO



The NEW ENGLAND JOURNAL of MEDICINE

2013

ORIGINAL ARTICLE

Dabigatran versus Warfarin in Patients with Mechanical Heart Valves

John W. Eikelboom, M.D., Stuart J. Connolly, M.D., Martina Brueckmann, M.D., Christopher B. Granger, M.D., Arie P. Kappetein, M.D., Ph.D., Michael J. Mack, M.D., Jon Blatchford, C.Stat., Kevin Devenny, B.Sc., Jeffrey Friedman, M.D., Kelly Guiver, M.Sc., Ruth Harper, Ph.D., Yasser Khder, M.D., Maximilian T. Lobmeyer, Ph.D., Hugo Maas, Ph.D., Jens-Uwe Voigt, M.D., Maarten L. Simoons, M.D., and Frans Van de Werf, M.D., Ph.D., for the RE-ALIGN Investigators*

RE-ALIGN trial

- In a phase 2 trial, patients with mechanical heart valves were randomly assigned to receive either dabigatran or warfarin for anticoagulation.
- Dabigatran was associated with higher rates of ischemic stroke (5%, vs. 0% with warfarin) and major bleeding (4% vs. 2%).

Patients Requiring Dose Escalation or Discontinuation of Dabigatran and Mean Percentage of Time above the Target Trough Plasma Level of Dabigatran.

Table 2. Patients Requiring Dose Escalation or Discontinuation of Dabigatran and Mean Percentage of Time above the Target Trough Plasma Level of Dabigatran.*

Dabigatran Dose	Population A (N=127)		Population B (N=35)		All Patients (N=162)	
	Patients Requiring Dose Escalation or Discontinuation†	Percent of Time above Target Level‡	Patients Requiring Dose Escalation or Discontinuation†	Percent of Time above Target Level‡	Patients Requiring Dose Escalation or Discontinuation†	Percent of Time above Target Level‡
	no./total no. (%)		*no./total no. (%)*		*no./total no. (%)*	
All doses	47/127 (37)	84	5/35 (14)	96	52/162 (32)	86
150 mg twice daily	4 /11 (36)	99	2/13 (15)	98	6/24 (25)	98
220 mg twice daily	32/71 (45)	84	1/16 (6)	100	33 /87 (38)	87
300 mg twice daily	11/45 (24)	79	2/6 (33)	83	13/51 (25)	79

* Shown are the numbers of all patients who received at least one dose of dabigatran who required a dose escalation or discontinuation, divided by the total number of patients receiving the initial dose level. The target trough plasma level of dabigatran was 50 ng per milliliter or more. Data are from the initial 12-week treatment period.

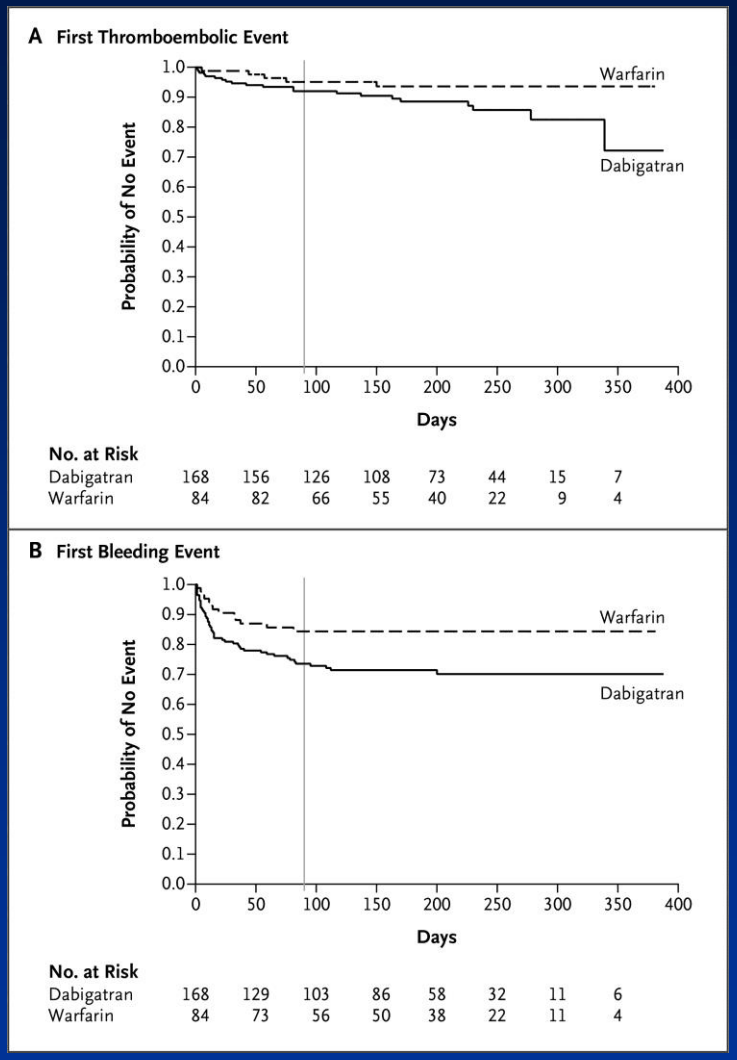
† Doses were increased from 150 mg twice daily to 220 mg twice daily and from 220 mg twice daily to 300 mg twice daily if the steady-state trough level of dabigatran was less than 50 ng per milliliter. Among patients receiving an initial dose of 300 mg twice daily, dabigatran was discontinued if repeated measurement of the trough level was less than 50 ng per milliliter.

‡ The percentage of time above the target level was calculated with the use of the Rosendaal method on the basis of trough levels of dabigatran, as measured on high-performance liquid chromatography–tandem mass spectrometry. Excluded from this calculation were three patients for whom no measurements were available during the initial study period.

Eikelboom JW et al. N Engl J Med 2013;369:1206-1214

The NEW ENGLAND JOURNAL of MEDICINE

Kaplan–Meier Analysis of Event-free Survival.



Eikelboom JW et al. N Engl J Med 2013;369:1206-1214

The NEW ENGLAND JOURNAL of MEDICINE

Adjudicated Efficacy and Safety Outcomes in the Initial and Extended Trials in the Intention-to-Treat Population.

Table 4. Adjudicated Efficacy and Safety Outcomes in the Initial and Extended Trials in the Intention-to-Treat Population.*

Outcome	Population A		Population B		All Patients		Hazard Ratio (95% CI)†	P Value‡
	Dabigatran (N=133)	Warfarin (N=66)	Dabigatran (N=35)	Warfarin (N=18)	Dabigatran (N=168)	Warfarin (N=84)		
	number of patients (percent)							
Death, stroke, transient ischemic attack, systemic embolism, or myocardial infarction	12 (9)	4 (6)	3 (9)	0	15 (9)	4 (5)	1.94 (0.64–5.86)	0.24
Valve thrombosis without symptoms	2 (2)	0	3 (9)	0	5 (3)	0	NA	NA
Bleeding								
Any	35 (26)	8 (12)	10 (29)	2 (11)	45 (27)	10 (12)	2.45 (1.23–4.86)	0.01
Major	7 (5)	2 (3)	0	0	7 (4)	2 (2)	1.76 (0.37–8.46)	0.48
Major with pericardial location	7 (5)	2 (3)	0	0	7 (4)	2 (2)	1.76 (0.36–8.45)	0.48

Eikelboom JW et al. N Engl J Med 2013;369:1206-1214

Fibrillazione atriale non-valvolare per i NAO?

Apixaban in Comparison With Warfarin in Patients With Atrial Fibrillation and Valvular Heart Disease

Findings From the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) Trial

Alvaro Avezum, MD, PhD; Renato D. Lopes, MD, PhD, MHS; Phillip J. Schulte, PhD; Fernando Lanas, MD; Bernard J. Gersh, MB, ChB, DPhil; Michael Hanna, MD; Prem Pais, MD; Cetin Erol, MD; Rafael Diaz, MD; M. Cecilia Bahit, MD; Jozef Bartunek, MD, PhD; Raffaele De Caterina, MD, PhD; Shinya Goto, MD, PhD; Witold Ruzyllo, MD, PhD; Jun Zhu, MD; Christopher B. Granger, MD; John H. Alexander, MD, MHS

(ARISTOTLE) trial included a substantial number of patients with valvular heart disease and only excluded patients with clinically significant mitral stenosis or mechanical prosthetic heart valves.

Circulation 2015

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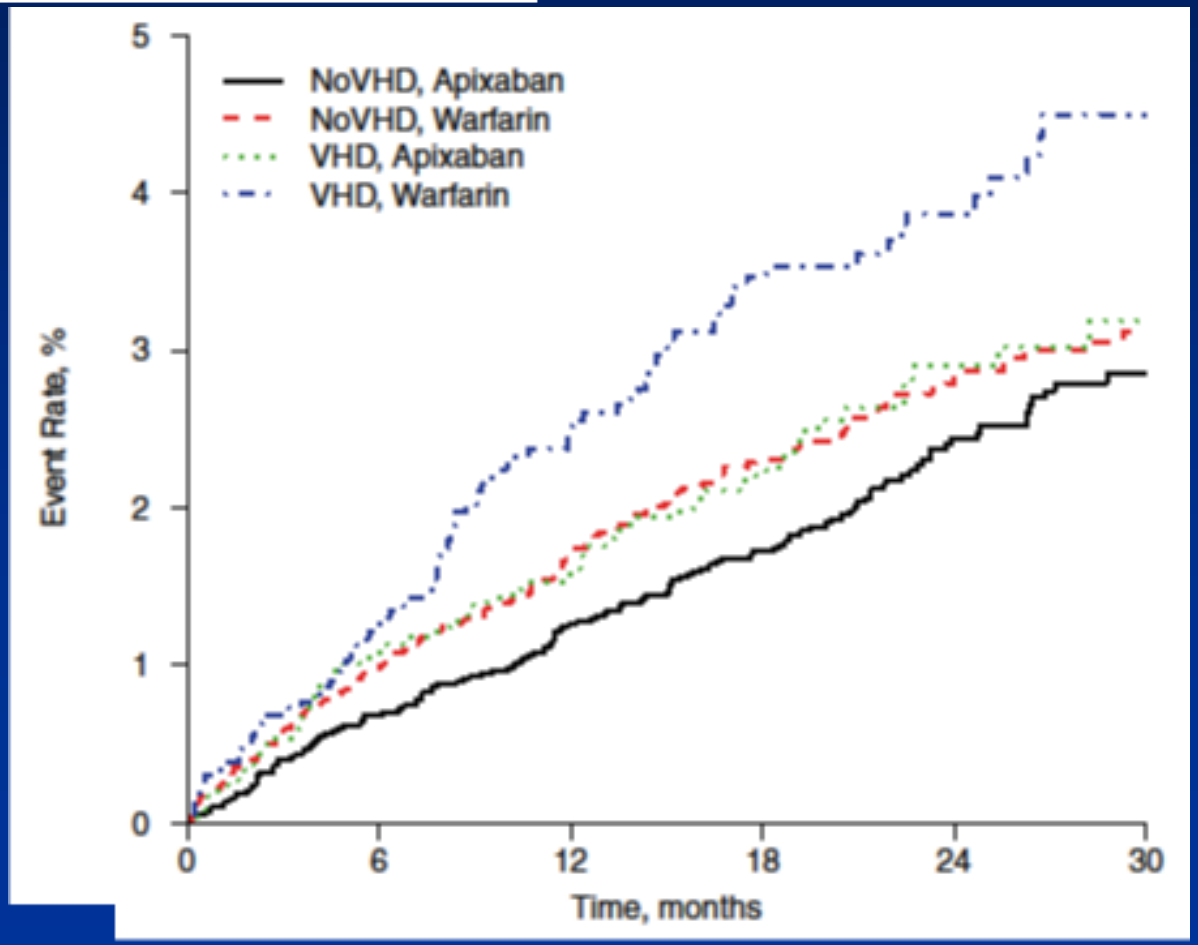
Circulation
2015

Stroke and
systemic embolism



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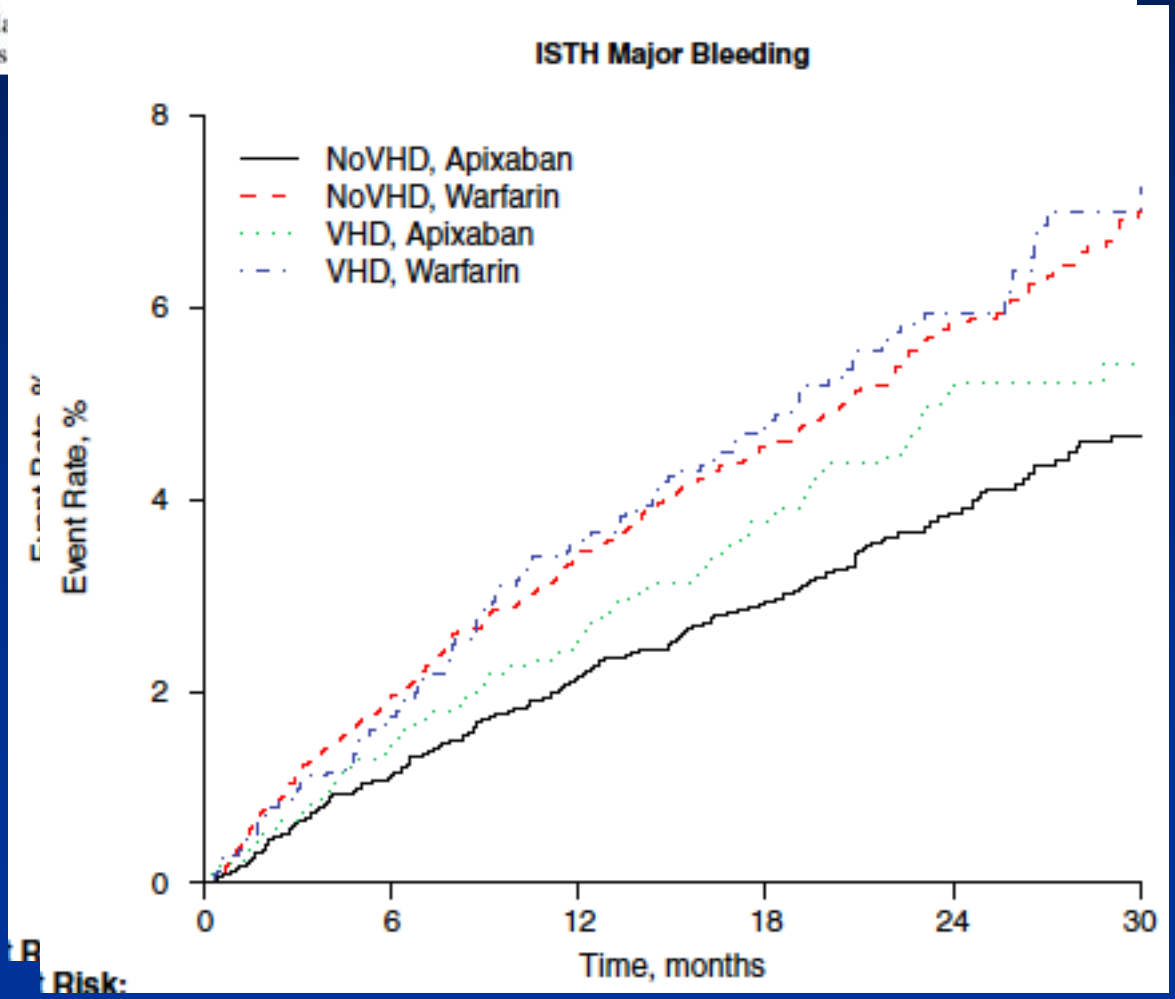

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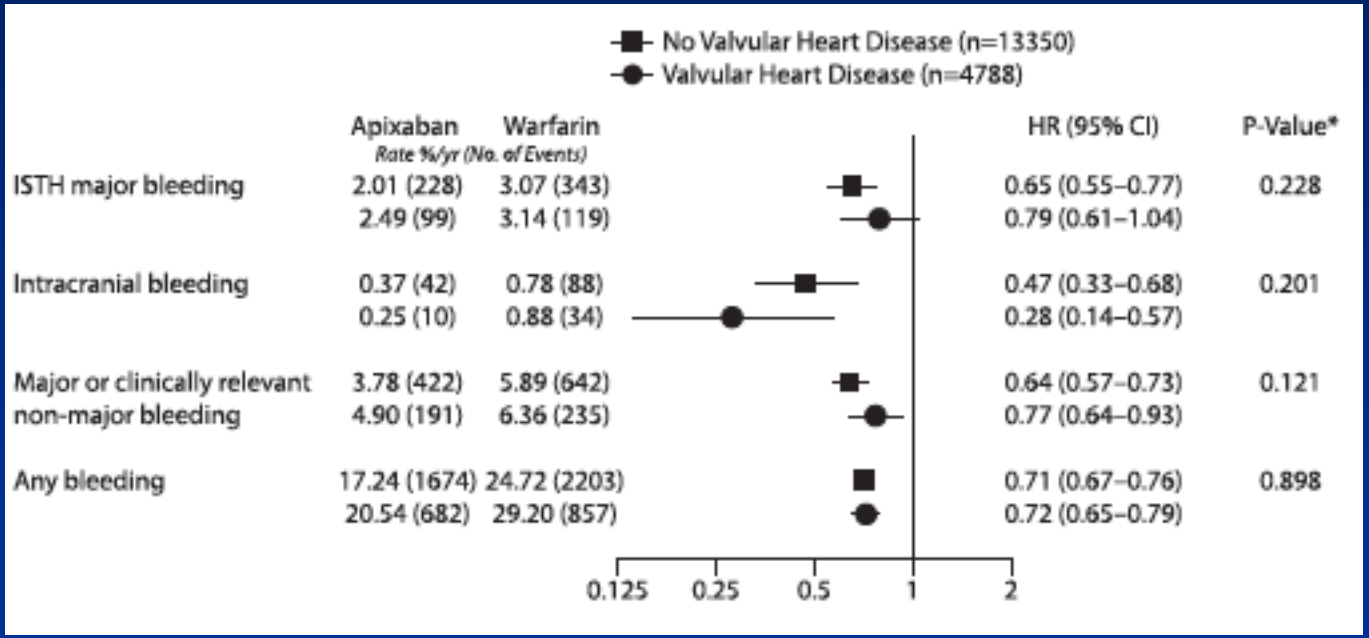

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Circulation 2015

Table 3. Apixaban Versus Warfarin in Patients With Mitral and Aortic Valvular Heart Disease

	Rate %/y (No. of Events)		
	Apixaban	Warfarin	HR (95% CI)*
Mitral VHD	(n=1801)	(n=1777)	
Stroke or SE	1.32 (43)	1.89 (61)	0.70 (0.47–1.04)
ISTH major bleeding	2.12 (63)	2.94 (84)	0.72 (0.52–1.00)
Aortic VHD	(n=604)	(n=546)	
Stroke or SE	1.57 (17)	2.88 (27)	0.55 (0.30–1.01)
ISTH major bleeding	2.98 (29)	4.21 (34)	0.72 (0.44–1.18)

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Circulation 2015

Conclusions—More than a quarter of the patients in ARISTOTLE with NVAF had moderate or severe valvular heart disease.
No evidence of a differential effect of apixaban over warfarin on stroke or systemic embolism, bleeding, death in patients with and without valvular heart disease.

Table I **Valvular indications and contra-indications for NOAC therapy in atrial fibrillation patients**

	Eligible	Contra-indicated
Mechanical prosthetic valve		✓
Moderate-to-severe mitral stenosis (usually of rheumatic origin)		✓
Mild-to-moderate other native valvular disease	✓	
Severe aortic stenosis	✓ Limited data Most will undergo intervention	
Bioprosthetic valve[a]	✓ (except for the first 3 months post-operatively)	
Mitral valve repair[a]	✓ (except for the first 3–6 months post-operatively)	
PTAV and TAVI	✓ (but no prospective data; may require combination with single or double antiplatelets: consider bleeding risk)[10]	
Hypertrophic cardiomyopathy	✓ (but no prospective data)	

PTAV, percutaneous transluminal aortic valvuloplasty; TAVI, transcatheter aortic valve implantation.
[a]American guidelines do not recommend NOAC in patients with biological heart valves or after valve repair.[12]

Heidbuchel et al., EHJ 2016

Controindicazioni ai NAO

Controindicazioni: specifiche popolazioni

- Gravidanza (tutti)
- Allattamento (tutti)
- Insuff. Ren. Grave (tutti); Cl.Creat. <30ml/min Pradaxa; <15 Xarelto
- Insuff. Epatica (Xarelto: Child-Pugh B e C)
- Diatesi emorragica

Esclusi dai trial

Pazienti < 18 anni

Cosa fare?

Thrombin generation and other coagulation parameters in a patient with homozygous congenital protein S deficiency on treatment with rivaroxaban
(a 6-year-old girl)

Tripodi et al. Int J Hematol 2015

Phamacokinetics of rivaroxaban in adolescents

Beyer-Westendorf & Gehrisch, Hamostaseologie 2014

CONCLUSION:

"Our data indicate that adolescents may exhibit lower peak and trough levels after rivaroxaban intake compared to adult patients, ……..we strongly discourage the routine use of rivaroxaban in non-adult patients, until data from phase II and III trials are available."

Journal of Thrombosis and Haemostasis, 11: 177–179 DOI: 10.1111/jth.12038

OFFICIAL COMMUNICATION OF THE SSC

Selection and assessment of patients treated with the novel oral anticoagulant drugs: a recommendation from the Subcommittee on Control of Anticoagulation of the Scientific and Standardisation Committee of the International Society on Thrombosis and Haemostasis

W. AGENO,* M. CROWTHER,† T. BAGLIN,‡ A. FALANGA,§ H. BULLER¶ and G. PALARETI**

2013

Conditions requiring special attention:

- advanced age
- impaired renal or liver function
- low body weight
- presence of multiple co-morbidities
- need for concomitant therapies

Such conditions commonly co-exist, in particular in elderly patients

Continuare gli AVK

- Se INR ben controllato e stabile
- Controllo facile da effettuare (qualità di vita)
- Disfunzione renale severa (moderata?)
- Epatopatia (?)
- Storia di ulcera peptica o GI emorragia
- Non complianti

L’aderenza e la persistenza con i DOAC sono un vero problema?

Adherence to dabigatran therapy and longitudinal patient outcomes: Insights from the Veterans Health Administration

Shore et al. Am Heart J 2014

A cohort of 5,376 patients with NVAF, initiated on dabigatran at all Veterans Affairs hospitals.

Adherence = proportion of days covered (PDC)

27.8% of patients < 80% PDC, classified as non-adherent

Low adherence associated with > risk for combined = all-cause mortality and stroke

= HR 1.13 (07–1.19 per 10% decrease in PDC)

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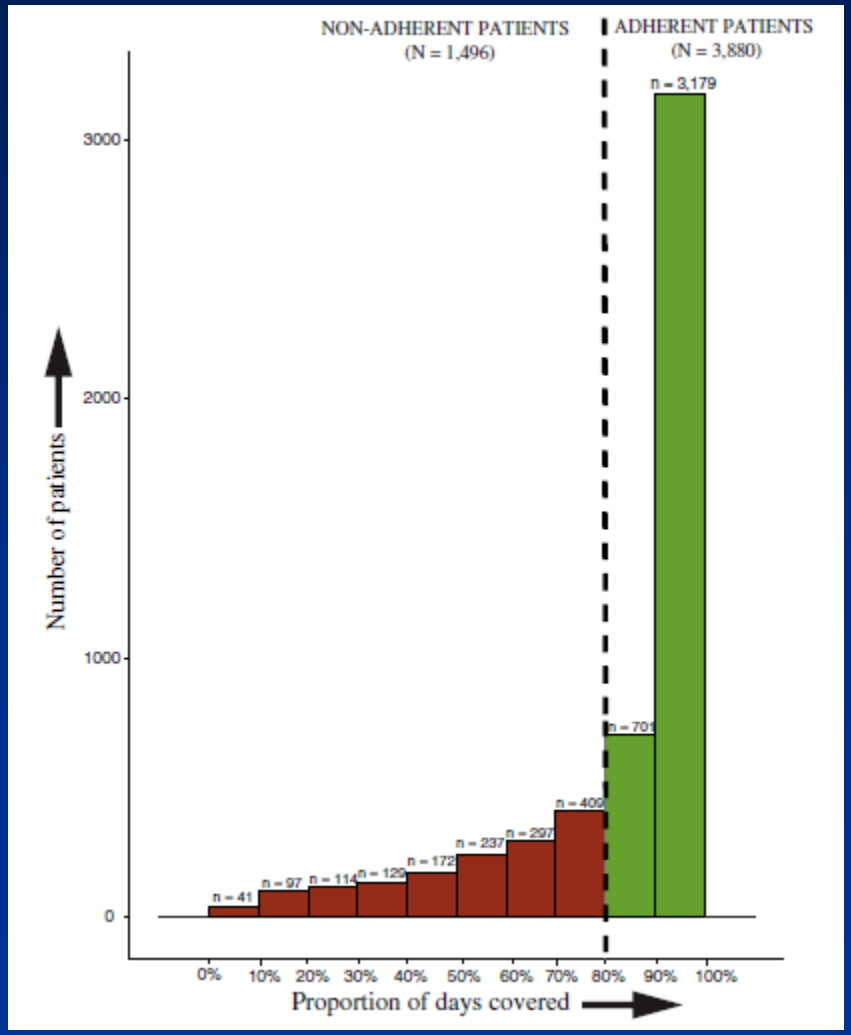

Effect of Adherence to Oral Anticoagulants on Risk of Stroke and Major Bleeding Among Patients With Atrial Fibrillation

Xiaoxi Yao, PhD; Neena S. Abraham, MD, MSCE; G. Caleb Alexander, MD, MS; William Crown, PhD; Victor M. Montori, MD, MSc; Lindsey R. Sangaralingham, MPH; Bernard J. Gersh, MB, ChB, DPhil, FRCP; Nilay D. Shah, PhD; Peter A. Noseworthy, MD

J Am Heart Assoc 2016

Mayo Clinic, Rochester, US; retrospettivo, database assicurativi
64.661 pazienti con FA:
Warfarin: 59,1%; dabigatran 15,8%; rivaroxaban 19,1%; apixaban 6.0%

Aderenza idonea (>80%) durante 1,1 anni (mediana):
47,5% dei pazienti con DOACs
40,2% con warfarin ($p<0.001$).

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J Am Heart Assoc 2016

Rischio di ictus rispetto ai pazienti con ottima aderenza:

Se CHA2DS2-VASc => 4

- 1 mese senza terapia 1,96 HR
- 3-6 mesi senza terapia 2,64 HR
- > 6 mesi senza terapia 3,66 HR (tutti $p < 0.001$)

Se CHA2DS2-VASc 2 o 3

- > 6 mesi senza terapia 2,73 HR

Se CHA2DS2-VASc di 0 o 1

non risultavano a rischio di ictus con bassa aderenza, ma minor rischio emorragico.

Adherence

Adherence is facilitated when patients understand their diagnosis, believe in their therapy, and trust their clinician

(Gladstone et al. Ann Intern Med 2015)

OPEN ACCESS Freely available online

PLOS ONE

Educational Intervention Improves Anticoagulation Control in Atrial Fibrillation Patients: The TREAT Randomised Trial

Danielle E. Clarkesmith[1,2], Helen M. Pattison[2], Gregory Y. H. Lip[1,2], Deirdre A. Lane[1*]

2013

An intervention using patient interviews and focus groups, utilising an "expert-patient" DVD, educational booklet, self-monitoring diary and worksheet, was compared in a randomised controlled trial against usual care

The intervention significantly improved TTR in AF patients initiating warfarin during the first 6-months.

Grazie