MARTEDI' DELL'ORDINE

21 Gennaio 2014

L A CHIUSURA PERCUTANEA
DELL'AURICOLA SINISTRA
NELLA PREVENZIONE
DELL'EMBOLIA CARDIOGENA

LA CHIUSURA DELL'AURICOLA: l'opinione dell'esperto del Centro Emostasi

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Numero stimato e prevalenza di paz. in trattamento con AVK in Italia

ANNO 2008		ANNO 2011	
n.paz.	911.269	n.paz.	1.050.000
Prevalenza	1,58	Prevalenza	1,70

Fonte: FCSA (Federazione Centri per la diagnosi della trombosi e la Sorveglianza delle terapie Antitrombotiche)

Fibrillazione atriale: le stime di prevalenza/incidenza in RER

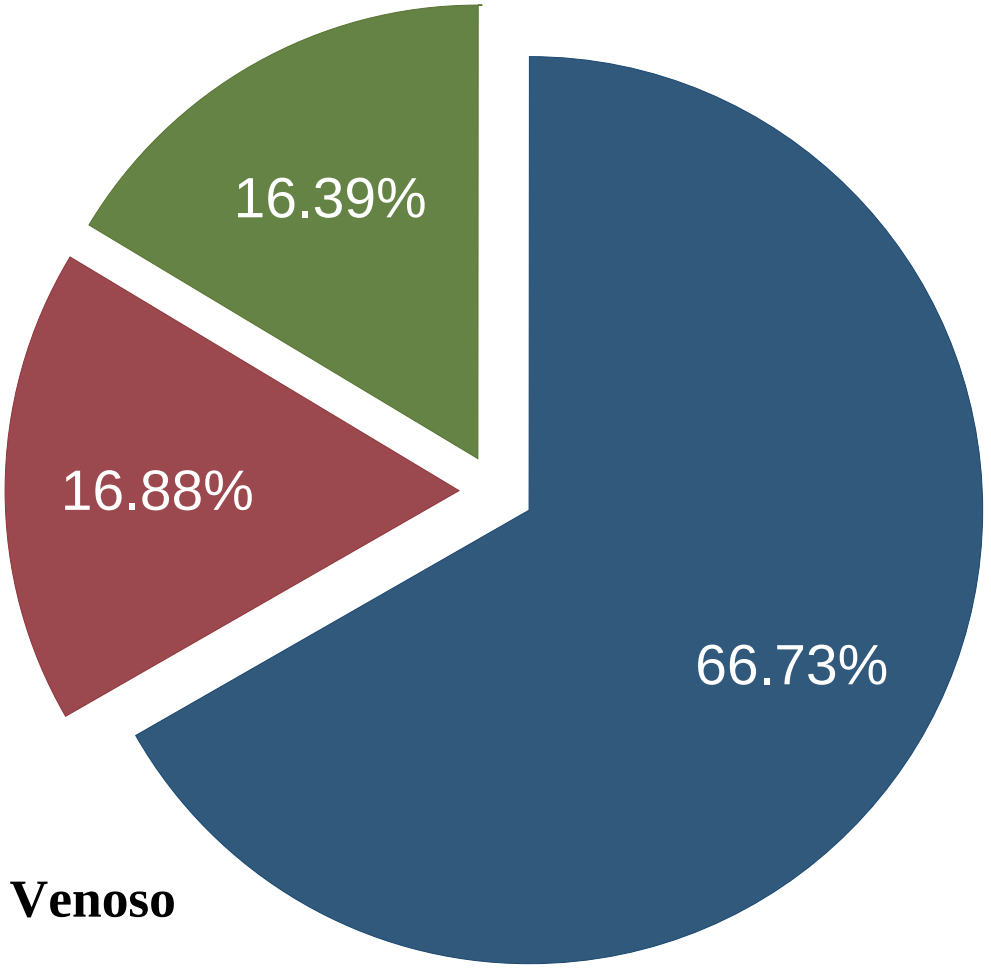
Al 2010 la **popolazione in RER**: **4.430.000**
Prevalenza della FA 1,7%: **75.310 paz. In FA**

Si possono approssimare a:
60.000 i paz. con Fibrillazione Atriale Non Valvolare (FANV) nella RER

Incidenza di **3 casi per 1.000 anni/persona**: circa **13.000 nuovi casi /anno**

Nel 2012 i **paz. che hanno assunto anticoagulanti anti vit. K (AVK)** nella RER sono stati **circa 86.000**
I 60.000 con FANV sono quindi circa i 2/3 dei trattati con AVK

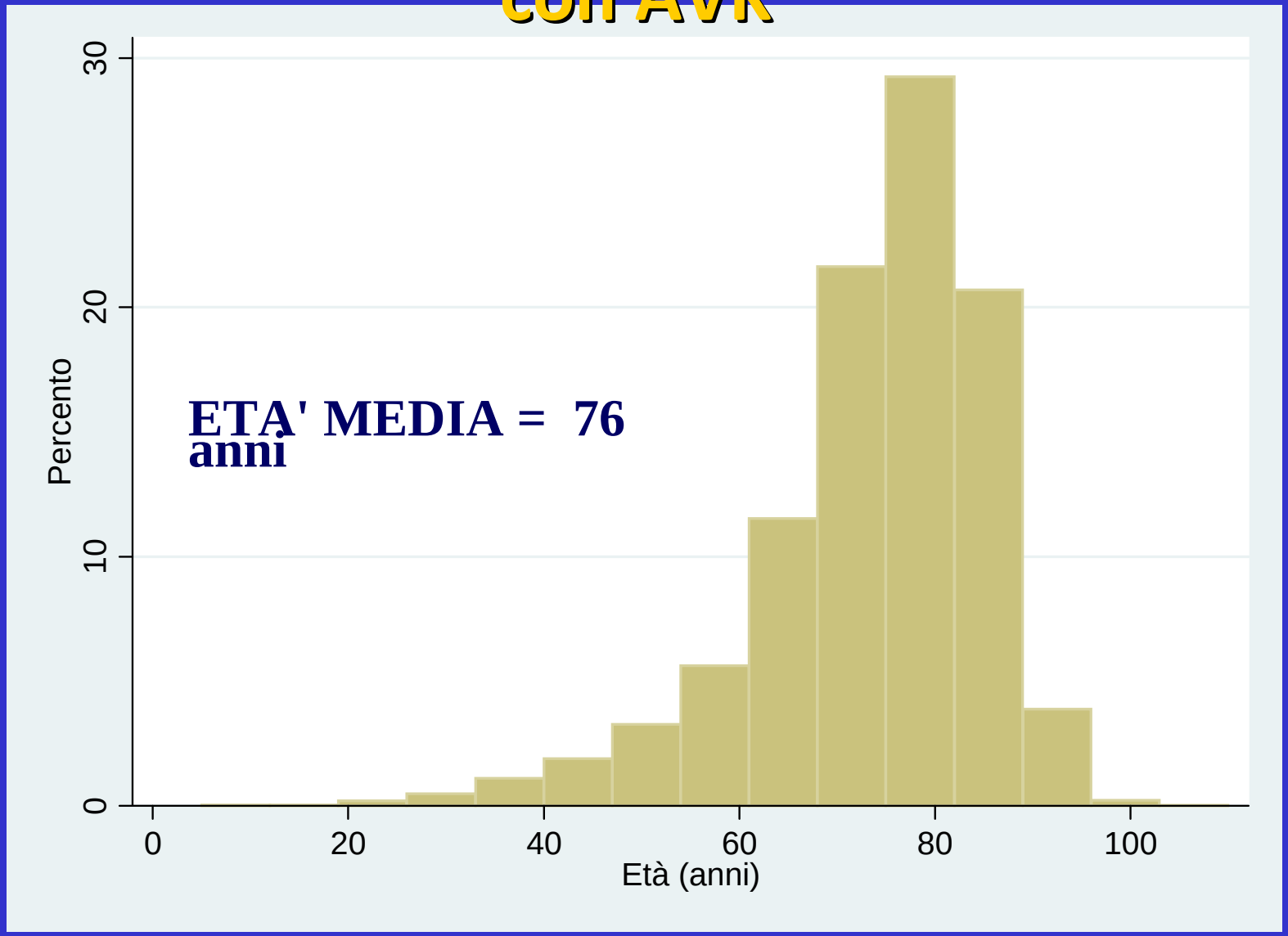
indicazioni per l'utilizzo degli AVK



FA = Fibrillazione Atriale
VTE = Trombo embolismo Venoso
PVM = Protesi Valvolari Meccaniche

Dati FCSA, 2010

Distribuzione per età dei paz. in trattamento con AVK

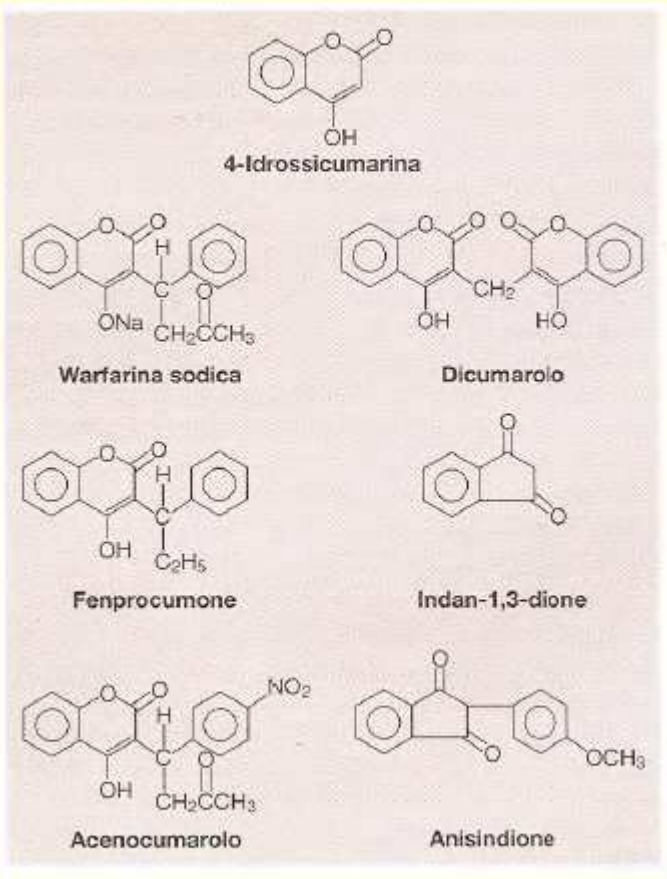


Dati FCSA, 2010

VECCHI (?) ANTICOAGULANTI ORALI

ANTI-VITAMINA K

ANTICOAGULANTI ORALI



Il dicumarolo è stato identificato come principio attivo emorragico del trifoglio dolce nel 1939

La warfarina è stata commercializzata nel 1948 come topicida

Dagli anni 50 sono largamente utilizzati come farmaci anticoagulanti

La warfarina è il più frequentemente prescritto

Il nome deriva dall'istituzione dove lavoravano gli scopritori:

Wisconsin Alumni Research Foundation

ANTICOAGULANTI ORALI

Meccanismo di azione

La warfarina inibisce pertanto la sintesi dei fattori Vit. K-dipendenti:

- Fattore II → (50 ore)
- Fattore VII → (6 ore)
- Fattore IX → (24 ore)
- Fattore X → (36 ore)

(emivita)

L'effetto anticoagulante della warfarina si instaura dopo alcuni giorni di somministrazione

	Contr.	N paz	ACO dose piena INR	Aspirina	ACO+aspir	ACO Bassa dose
AFASAK	Si	1007	2.8 – 4.2	75	-	-
SPAF1	Si	1330	2.0 – 4.5	325	-	-
BAATAF	Si	420	1.5 – 2.7	-	-	-
CAFA	Si	383	2.0 – 3.0	-	-	-
SPINAF	Si	525	1.4 – 2.8	-	-	-
EAFT	Si	1007	2.5 – 4.0	300	-	-
SPAF2	-	1100	2.0 – 4.5	325	-	-
SPAF3A.R.	-	1044	2.0 – 3.0	-	Aspirina 325 + INR 1.2 – 1.5	-
SPAF3 B.R.	-	892		325		-
AFASAK2	-	677	2.0 – 3.0	300	Aspirina 300+ Warf.1.25 mg	Warfarin 1.25mg
ESPS2	Si	429		50	-	-
SIFA	-	916	2.0 – 3.0	400	-	-
POSADA	Si	285		125	-	-
PENGO	-	303	2.0 – 3.0	-	-	Warfarin 1.25mg
HELLEMONS	-	729	2.5 – 3.5	150	-	INR 1.1 – 1.6

Trials clinici randomizzati con TAO nella FA non valvolare (anni di pubblicazione 1989-1992)

Studio	Range INR	Riduzione Stroke/TE
AFASAK	2.8 – 4.2	- 53%
SPAF	2.0 – 3.5	- 67%
BAATAF	1.5 – 2.7	- 86%
CAFA	2.3 – 3.0	- 45%
SPINAF	1.4 – 2.8	- 79%

La metanalisi dei 5 trial randomizzati e controllati con placebo, per un totale di 3.665 pazienti con FA non valvolare, ha mostrato che la terapia con Warfarin (INR compreso tra 1.8 e 4.2) è in grado di ridurre l'incidenza di stroke ed embolie sistemiche dal 4.5% all'1.4% per anno (riduzione RR del 69%, range 50-79%), ovvero riduzione di 31 eventi per 1.000 pazienti trattati per 1 anno.

(Arch Intern Med 1994; 154: 1449-1457)

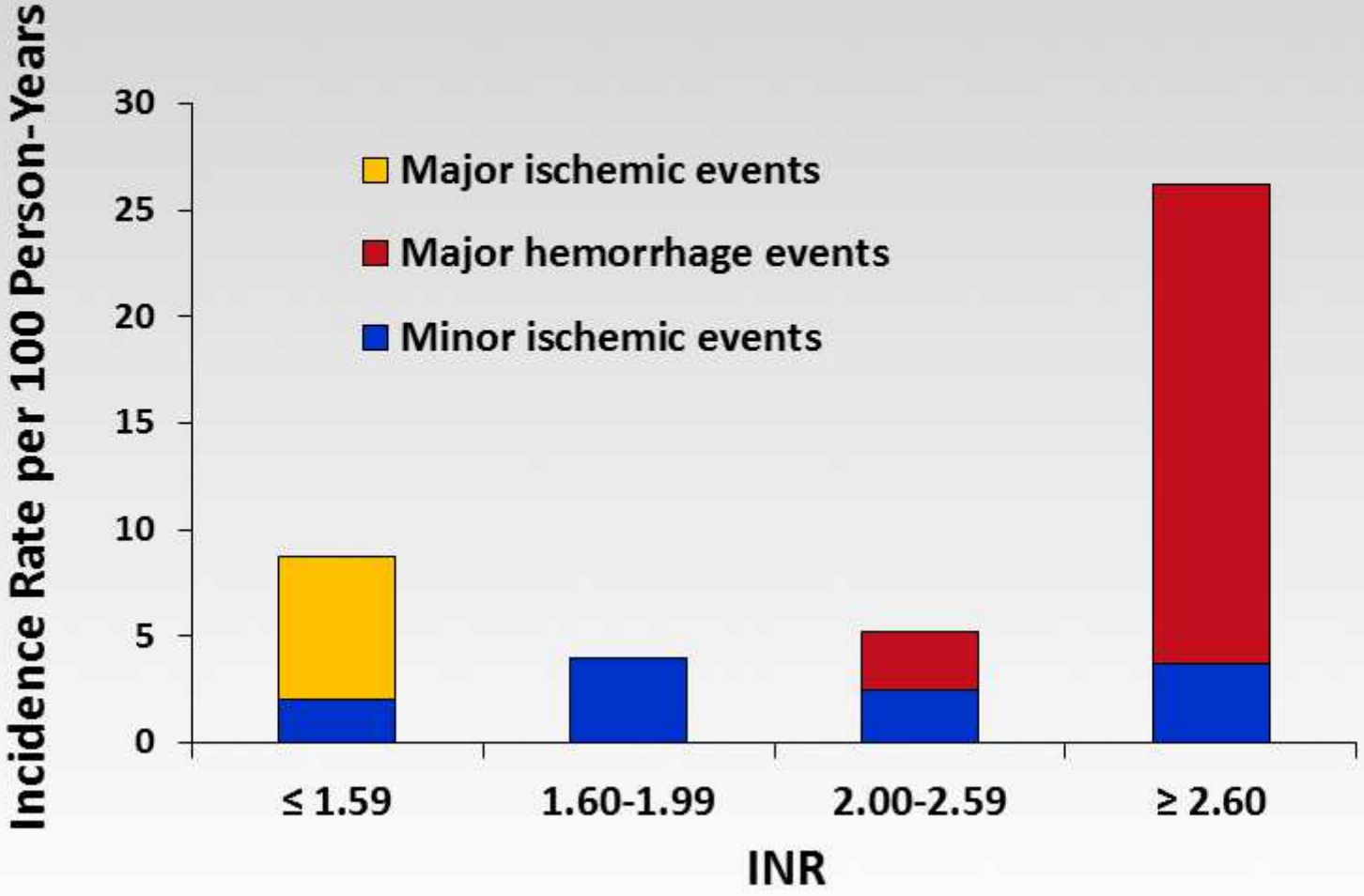
I risultati di questi studi randomizzati non hanno dimostrato un significativo aumento di emorragie maggiori nei pazienti in TAO (eventi emorragici 7.6% per anno di cui 0.25% fatali – 1.1% maggiori -6.2% minori)

La sicurezza di utilizzo degli ACO dipende dalla collaborazione da parte del paziente e da un sistema di monitoraggio che consenta di mantenere i valori di INR nel range definito (2.0-3.0)

Limiti della terapia anticoagulante attuale

- Antagonisti della vitamina K (VKA)
  - Azione iniziale lenta
  - Finestra terapeutica ristretta / monitoraggio frequente
  - Interazione con farmaci / alimenti
  - Scarsa compliance
  - Elevato rischio di emorragie (3.4% per anno)
- Eparina
  - Uso parenterale
- Obbiettivo dello sviluppo clinico
  - Farmaco “ideale”

Intensity of Anticoagulation and Incidence of Ischemic and Hemorrhagic Events



Arrhythmia & EP

Yasaka M, et al. *Intern Med*. 2001;40(12):1183-1188.

theheart.org from WebMD

Medscape EDUCATION

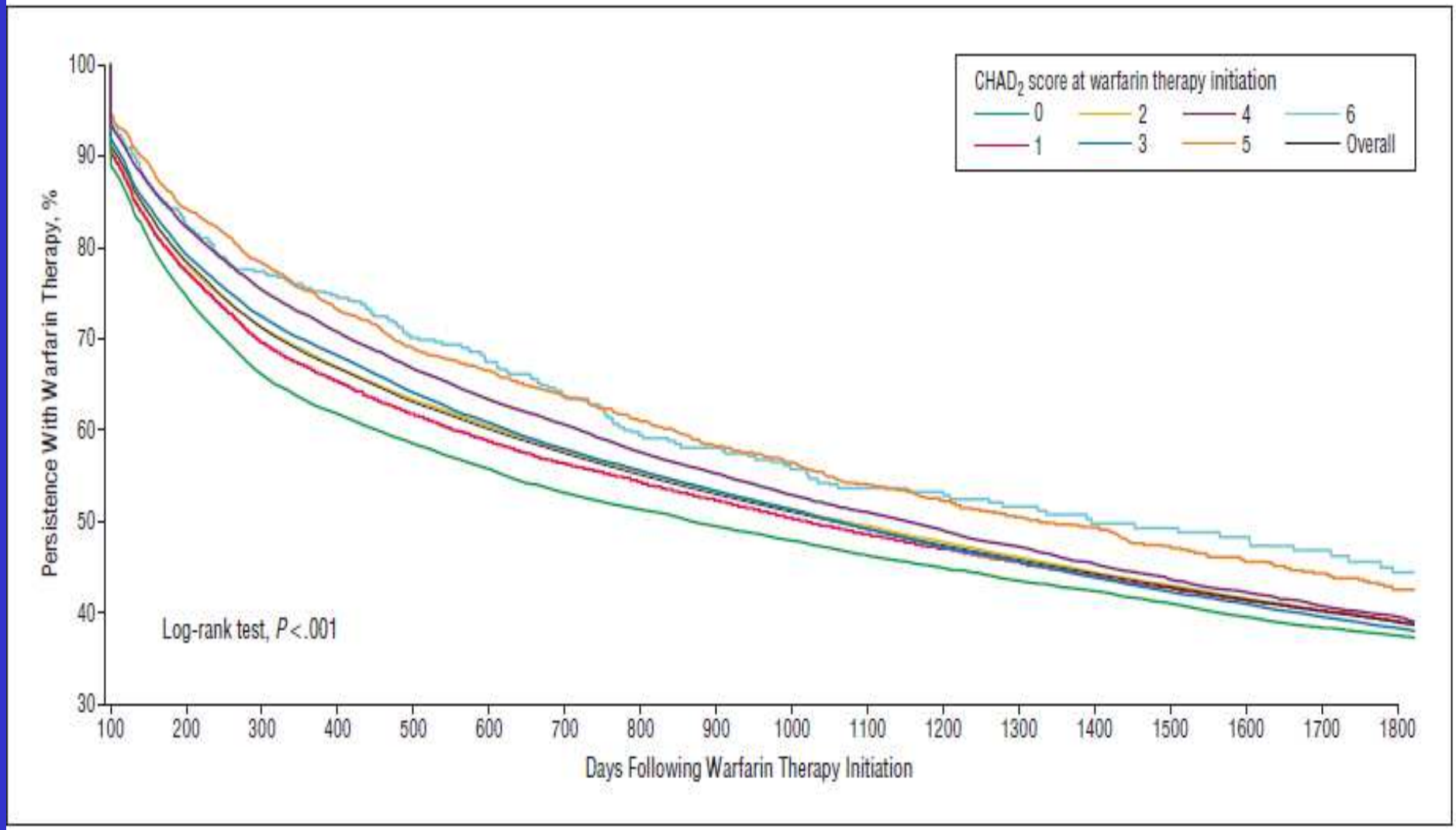


Figure. Persistence with warfarin therapy among patients with atrial fibrillation newly treated with warfarin, overall and stratified by $CHADS_2$ category. Survival curves for warfarin therapy discontinuation, from start of treatment among Ontario, Canada, residents 66 years and older with a past diagnosis of atrial fibrillation. $CHADS_2$ indicates congestive heart failure, hypertension, age 75 years or older, diabetes mellitus, and prior stroke or transient ischemic attack.

European Heart Journal
doi:10.1093/eurheartj/eht499

CLINICAL RESEARCH

Initiation of warfarin in patients with atrial fibrillation: early effects on ischaemic strokes

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Aims An increased risk of stroke was observed in two atrial fibrillation (AF) trials of oral factor Xa inhibitors, when patients were transitioned to open label warfarin at the end of the study. The objective of this study is to determine whether initiation of warfarin is associated with an increased risk of stroke in patients with AF.

Methods and results Using the UK Clinical Practice Research Datalink, a nested case–control analysis was conducted within a cohort of 70 766 patients with AF between 1993 and 2008. Stroke cases were randomly matched with up to 10 controls on age, sex, date of AF diagnosis, and time since AF diagnosis. Conditional logistic regression was used to estimate adjusted rate ratios (RRs) with 95% confidence intervals (CIs) of stroke associated with current warfarin use classified according to time since initiation of treatment (<30 days, 31–90 days, and >90 days), when compared with non-use. A total of 5519 patients experienced a stroke during follow-up. Warfarin was associated with a 71% increased risk of stroke in the first 30 days of use (RR: 1.71, 95% CI: 1.39–2.12), while decreased risks were observed with initiation >30 days before the event (31–90 days: RR: 0.50, 95% CI: 0.34–0.75 and >90 days: RR: 0.55, 95% CI: 0.50–0.61, respectively).

Conclusion Patients initiating warfarin may be at an increased risk of stroke during the first 30 days of treatment, supporting the biological plausibility of a transient hypercoagulable state at the start of the treatment, although additional studies are needed to confirm these findings.

accepted 14 November 2013

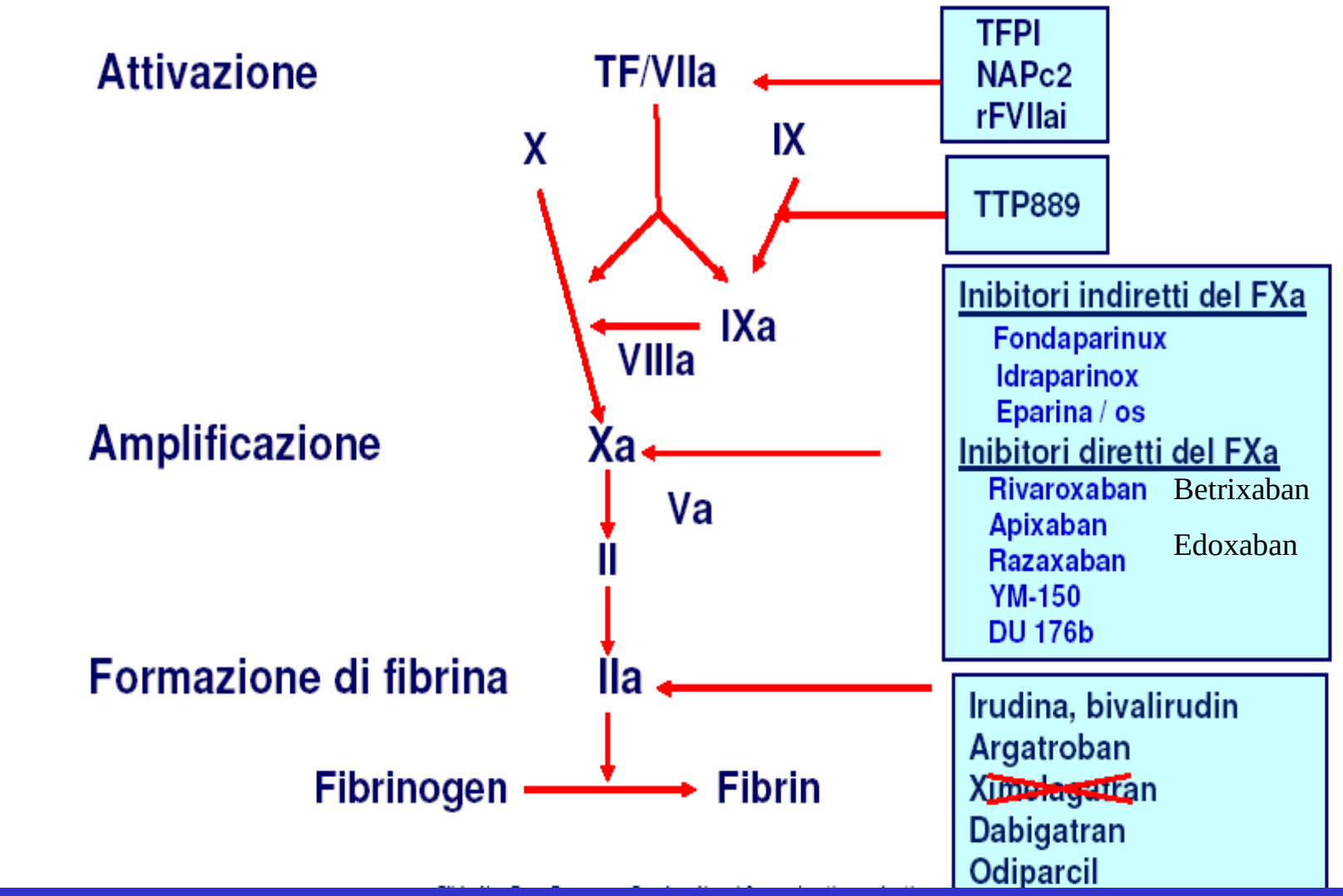
I NUOVI ANTICOAGULANTI ORALI

(anti-IIa ; anti-Xa)

Characteristics of an 'ideal anticoagulant' (adapted from Bauer, 2006; Haas, 2008; Bounameaux, 2009; Laux et al., 2009).

Characteristics required for an 'ideal anticoagulant'
Oral administration
No requirement for routine coagulation monitoring and dose adjustment
Wide therapeutic window
Rapid onset of action
Predictable pharmacokinetics and pharmacodynamics
Minimal interactions with foods and other drugs
Ability to inhibit free and clot-bound coagulation factors
Low non-specific binding
Availability of an antidote
No unexpected toxicities
Acceptable costs

Fasi della coagulazione



	Warfarin	Dabigatran	Rivaroxaban	Apixaban
Target	VKOR and factors II,VII,IX,X	Factor IIa (thrombin)	Factor Xa	Factor Xa
Time to peak concentration	72–96 h	1.5–3 h	2–4 h	1–3 h
Vol. of dist.		60–70 l	50 l	Reported as low
Half-life	40 h	12–14 h	9–13 h	9–14 h
Metabolism	Liver-CYP2C9	Conjugation	Liver-CYP3A4 and CYP2J2	Partially through CYP3A4
Elimination	Bile and urine	80% renal, 20% faecal	66% faecal, 33% renal	75% faecal, 25% renal
Administration	Once daily	Once or twice daily	Once daily	Twice daily
Monitoring	INR	Not needed	Not needed	Not needed
Antidote or potential therapy for bleeding	Vitamin K, FFP, PCC or rFVIIa	FFP, PCC or rFVIIa	FFP, PCC or rFVIIa	FFP, PCC or rFVIIa
Assay	PT/INR	Experimental	Experimental	Experimental
Drug interactions	CYP 2C9	PPIs decrease absorption and potent P-gp inhibitors	Potent CYP 3A4 inhibitors and P-gp inhibitors	Potent CYP 3A4 inhibitors

VKOR, vitamin K oxidase reductase; CYP, cytochrome P450; PCC, prothrombin complex concentrates; PPIs, proton pump inhibitors; P-gp, P-glycoprotein; h, hour.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 17, 2009 VOL. 361 NO. 12

Dabigatran versus Warfarin in Patients with Atrial Fibrillation

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CONCLUSIONS

In patients with atrial fibrillation, dabigatran given at a dose of 110 mg was associated with rates of stroke and systemic embolism that were similar to those associated with warfarin, as well as lower rates of major hemorrhage. Dabigatran administered at a dose of 150 mg, as compared with warfarin, was associated with lower rates of stroke and systemic embolism but similar rates of major hemorrhage. (ClinicalTrials.gov number, NCT00262600.)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 8, 2011 VOL. 365 NO. 10

Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation

Manesh R. Patel, M.D., Kenneth W. Mahaffey, M.D., Jyotsna Garg, M.S., Guohua Pan, Ph.D., Daniel E. Singer, M.D., Werner Hacke, M.D., Ph.D., Günter Breithardt, M.D., Jonathan L. Halperin, M.D., Graeme J. Hankey, M.D., Jonathan P. Piccini, M.D., Richard C. Becker, M.D., Christopher C. Nessel, M.D., John F. Paolini, M.D., Ph.D., Scott D. Berkowitz, M.D., Keith A.A. Fox, M.B., Ch.B., Robert M. Califf, M.D., and the ROCKET AF Steering Committee, for the ROCKET AF Investigators*

CONCLUSIONS

In patients with atrial fibrillation, rivaroxaban was noninferior to warfarin for the prevention of stroke or systemic embolism. There was no significant between-group difference in the risk of major bleeding, although intracranial and fatal bleeding occurred less frequently in the rivaroxaban group. (Funded by Johnson & Johnson and Bayer; ROCKET AF ClinicalTrials.gov number, NCT00403767.)

The NEW ENGLAND JOURNAL of MEDICINE

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Apixaban versus Warfarin in Patients with Atrial Fibrillation

Christopher B. Granger, M.D., John H. Alexander, M.D., M.H.S., John J.V. McMurray, M.D., Renato D. Lopes, M.D., Ph.D., Elaine M. Hylek, M.D., M.P.H., Michael Hanna, M.D., Hussein R. Al-Khalidi, Ph.D., Jack Ansell, M.D., Dan Atar, M.D., Alvaro Avezum, M.D., Ph.D., M. Cecilia Bahit, M.D., Rafael Diaz, M.D., J. Donald Easton, M.D., Justin A. Ezekowitz, M.B., B.Ch., Greg Flaker, M.D., David Garcia, M.D., Margarida Geraldes, Ph.D., Bernard J. Gersh, M.D., Sergey Golitsyn, M.D., Ph.D., Shinya Goto, M.D., Antonio G. Hermosillo, M.D., Stefan H. Hohnloser, M.D., John Horowitz, M.D., Puneet Mohan, M.D., Ph.D., Petr Jansky, M.D., Basil S. Lewis, M.D., Jose Luis Lopez-Sendon, M.D., Prem Pais, M.D., Alexander Parkhomenko, M.D., Freek W.A. Verheugt, M.D., Ph.D., Jun Zhu, M.D., and Lars Wallentin, M.D., Ph.D., for the ARISTOTLE Committees and Investigators*

CONCLUSIONS

In patients with atrial fibrillation, apixaban was superior to warfarin in preventing stroke or systemic embolism, caused less bleeding, and resulted in lower mortality. (Funded by Bristol-Myers Squibb and Pfizer; ARISTOTLE ClinicalTrials.gov number, NCT00412984.)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Edoxaban versus Warfarin in Patients with Atrial Fibrillation

Robert P. Giugliano, M.D., Christian T. Ruff, M.D., M.P.H., Eugene Braunwald, M.D., Sabina A. Murphy, M.P.H., Stephen D. Wiviott, M.D., Jonathan L. Halperin, M.D., Albert L. Waldo, M.D., Michael D. Ezekowitz, M.D., D.Phil., Jeffrey I. Weitz, M.D., Jindřich Špinar, M.D., Witold Ruzyllo, M.D., Mikhail Ruda, M.D., Yukihiro Koretsune, M.D., Joshua Betcher, Ph.D., Minggao Shi, Ph.D., Laura T. Grip, A.B., Shirali P. Patel, B.S., Indravadan Patel, M.D., James J. Hanyok, Pharm.D., Michele Mercuri, M.D., and Elliott M. Antman, M.D., for the ENGAGE AF-TIMI 48 Investigators*

CONCLUSIONS

Both once-daily regimens of edoxaban were noninferior to warfarin with respect to the prevention of stroke or systemic embolism and were associated with significantly lower rates of bleeding and death from cardiovascular causes. (Funded by Daiichi Sankyo Pharma Development; ENGAGE AF-TIMI 48 ClinicalTrials.gov number, NCT00781391.)

SONO MEGLIO I NUOVI ANTICOAGULANTI DEGLI ANTICOAGULANTI ANTI-VITAMINA K?

Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials

Christian T Ruff, Robert P Giugliano, Eugene Braunwald, Elaine B Hoffman, Naveen Deenadayalu, Michael D Ezekowitz, A John Camm, Jeffrey I Weitz, Basil S Lewis, Alexander Parkhomenko, Takeshi Yamashita, Elliott M Antman

Summary

Background Four new oral anticoagulants compare favourably with warfarin for stroke prevention in patients with atrial fibrillation; however, the balance between efficacy and safety in subgroups needs better definition. We aimed to assess the relative benefit of new oral anticoagulants in key subgroups, and the effects on important secondary outcomes.

Methods We searched Medline from Jan 1, 2009, to Nov 19, 2013, limiting searches to phase 3, randomised trials of patients with atrial fibrillation who were randomised to receive new oral anticoagulants or warfarin, and trials in which both efficacy and safety outcomes were reported. We did a prespecified meta-analysis of all 71 683 participants included in the RE-LY, ROCKET AF, ARISTOTLE, and ENGAGE AF–TIMI 48 trials. The main outcomes were stroke and systemic embolic events, ischaemic stroke, haemorrhagic stroke, all-cause mortality, myocardial infarction, major bleeding, intracranial haemorrhage, and gastrointestinal bleeding. We calculated relative risks (RRs) and 95% CIs for each outcome. We did subgroup analyses to assess whether differences in patient and trial characteristics affected outcomes. We used a random-effects model to compare pooled outcomes and tested for heterogeneity.

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Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA (C T Ruff MD, R P Giugliano MD, Prof E Braunwald MD, E B Hoffman PhD, N Deenadayalu MPH, Prof E M Antman MD); **Jefferson Medical College, Philadelphia, PA, and Cardiovascular Research Foundation,**

Findings 42 411 participants received a new oral anticoagulant and 29 272 participants received warfarin. New oral anticoagulants significantly reduced stroke or systemic embolic events by 19% compared with warfarin (RR 0·81, 95% CI 0·73–0·91; p<0·0001), mainly driven by a reduction in haemorrhagic stroke (0·49, 0·38–0·64; p<0·0001). New oral anticoagulants also significantly reduced all-cause mortality (0·90, 0·85–0·95; p=0·0003) and intracranial haemorrhage (0·48, 0·39–0·59; p<0·0001), but increased gastrointestinal bleeding (1·25, 1·01–1·55; p=0·04). We noted no heterogeneity for stroke or systemic embolic events in important subgroups, but there was a greater relative reduction in major bleeding with new oral anticoagulants when the centre-based time in therapeutic range was less than 66% than when it was 66% or more (0·69, 0·59–0·81 *vs* 0·93, 0·76–1·13; p for interaction 0·022). Low-dose new oral anticoagulant regimens showed similar overall reductions in stroke or systemic embolic events to warfarin (1·03, 0·84–1·27; p=0·74), and a more favourable bleeding profile (0·65, 0·43–1·00; p=0·05), but significantly more ischaemic strokes (1·28, 1·02–1·60; p=0·045).

Interpretation This meta-analysis is the first to include data for all four new oral anticoagulants studied in the pivotal phase 3 clinical trials for stroke prevention or systemic embolic events in patients with atrial fibrillation. New oral anticoagulants had a favourable risk–benefit profile, with significant reductions in stroke, intracranial haemorrhage, and mortality, and with similar major bleeding as for warfarin, but increased gastrointestinal bleeding. The relative efficacy and safety of new oral anticoagulants was consistent across a wide range of patients. Our findings offer clinicians a more comprehensive picture of the new oral anticoagulants as a therapeutic option to reduce the risk of stroke in this patient population.

Research Foundation, New York, NY, USA (Prof M D Ezekowitz MBChB); St George's University, London, UK (Prof A J Camm MD); McMaster University and the Thrombosis and Atherosclerosis Research Institute, Hamilton, ON, Canada (Prof J I Weitz MD); Lady Davis Carmel Medical Center, Haifa, Israel (Prof B S Lewis MD); Institute of Cardiology, Kiev, Ukraine (Prof A Parkhomenko MD); and The Cardiovascular Institute, Tokyo, Japan (Prof T Yamashita MD)

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	RE-LY[5]			ROCKET-AF[6]		ARISTOTLE[7]		ENGAGE AF-TIMI 48[8]			Combined	
	Dabigatran 150 mg (n=6076)	Dabigatran 110 mg (n=6015)	Warfarin (n=6022)	Rivaroxaban (n=7131)	Warfarin (n=7133)	Apixaban (n=9120)	Warfarin (n=9081)	Edoxaban 60 mg (n=7035)	Edoxaban 30 mg (n=7034)	Warfarin (n=7036)	NOAC (n=42 411)	Warfarin (n=29 272)
Age (years)	71·5 (8·8)	71·4 (8·6)	71·6 (8·6)	73 (65–78)	73 (65–78)	70 (63–76)	70 (63–76)	72 (64–68)	72 (64–78)	72 (64–78)	71·6	71·5
≥75 years	40%	38%	39%	43%	43%	31%	31%	41%	40%	40%	38%	38%
Women	37%	36%	37%	40%	40%	36%	35%	39%	39%	38%	38%	37%
Atrial fibrillation type												
Persistent or permanent	67%	68%	66%	81%	81%	85%	84%	75%	74%	75%	76%	77%
Paroxysmal	33%	32%	34%	18%	18%	15%	16%	25%	26%	25%	24%	22%
CHADS2*	2·2 (1·2)	2·1 (1·1)	2·1 (1·1)	3·5 (0·94)	3·5 (0·95)	2·1 (1·1)	2·1 (1·1)	2·8 (0·97)	2·8 (0·97)	2·8 (0·98)	2·6 (1·0)	2·6 (1·0)
0–1	32%	33%	31%	0	0	34%	34%	<1%	<1%	<1%	17%	17%
2	35%	35%	37%	13%	13%	36%	36%	46%	47%	47%	35%	33%
3–6	33%	33%	32%	87%	87%	30%	30%	54%	53%	53%	48%	50%
Previous stroke or TIA*	20%	20%	20%	55%	55%	19%	18%	28%	29%	28%	29%	30%
Heart failure†	32%	32%	32%	63%	62%	36%	35%	58%	57%	58%	46%	47%
Diabetes	23%	23%	23%	40%	40%	25%	25%	36%	36%	36%	31%	31%
Hypertension	79%	79%	79%	90%	91%	87%	88%	94%	94%	94%	88%	88%
Prior myocardial infarction	17%	17%	16%	17%	18%	15%	14%	11%	12%	12%	15%	15%
Creatinine clearance‡												
<50 mL/min	19%	19%	19%	21%	21%	17%	17%	20%	19%	19%	19%	19%
50–80 mL/min	48%	49%	49%	47%	48%	42%	42%	43%	44%	44%	45%	45%
>80 mL/min	32%	32%	32%	32%	31%	41%	41%	38%	38%	37%	36%	36%
Previous VKA use§	50%	50%	49%	62%	63%	57%	57%	59%	59%	59%	57%	57%
Aspirin at baseline	39%	40%	41%	36%	37%	31%	31%	29%	29%	30%	34%	34%
Median follow-up (years)¶	2·0	2·0	2·0	1·9	1·9	1·8	1·8	2·8	2·8	2·8	2·2	2·2
Individual median TTR	NA	NA	67 (54–78)	NA	58 (43–71)	NA	66 (52–77)	NA	NA	68 (57–77)	NA	65 (51–76)

Data are mean (SD), median (IQR), or percent, unless otherwise indicated. NOAC=new oral anticoagulant. $CHADS_2$=stroke risk factor scoring system in which one point is given for history of congestive heart failure, hypertension, age ≥75 years, and diabetes, and two points are given for history of stroke or transient ischaemic attack. TIA=transient ischaemic attack. VKA=vitamin K antagonist. TTR=time in therapeutic range. NA=not available. *ROCKET-AF and ARISTOTLE included patients with systemic embolism. †ROCKET-AF included patients with left ventricular ejection fraction <35%; ARISTOTLE included those with left ventricular ejection fraction<40%. ‡RE-LY <50 mL/min, 50–79 mL/min, ≥80 mL/min; ARISTOTLE ≤50 mL/min, >50–80 mL/min, >80 mL/min. §RE-LY, ARISTOTLE, and ENGAGE AF-TIMI 48 patients who used VKAs for ≥61 days; ROCKET AF patients who used VKAs for ≥6 weeks at time of screening. ¶IQRs not available.

Table: **Baseline characteristics of the intention-to-treat populations of the included trials**

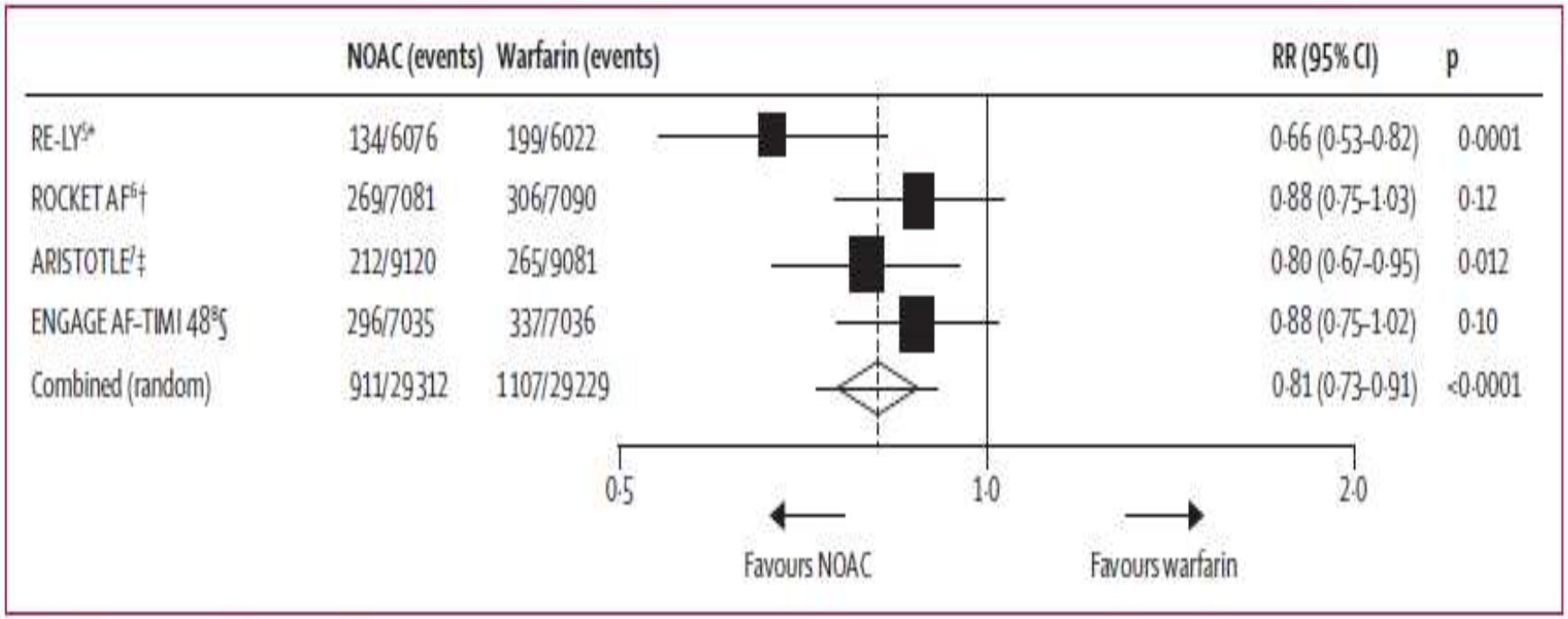

Figure 1: **Stroke or systemic embolic events**

Data are n/N, unless otherwise indicated. Heterogeneity: I^2=47%; p=0·13. NOAC=new oral anticoagulant. RR=risk ratio. *Dabigatran 150 mg twice daily. †Rivaroxaban 20 mg once daily. ‡Apixaban 5 mg twice daily. §Edoxaban 60 mg once daily.

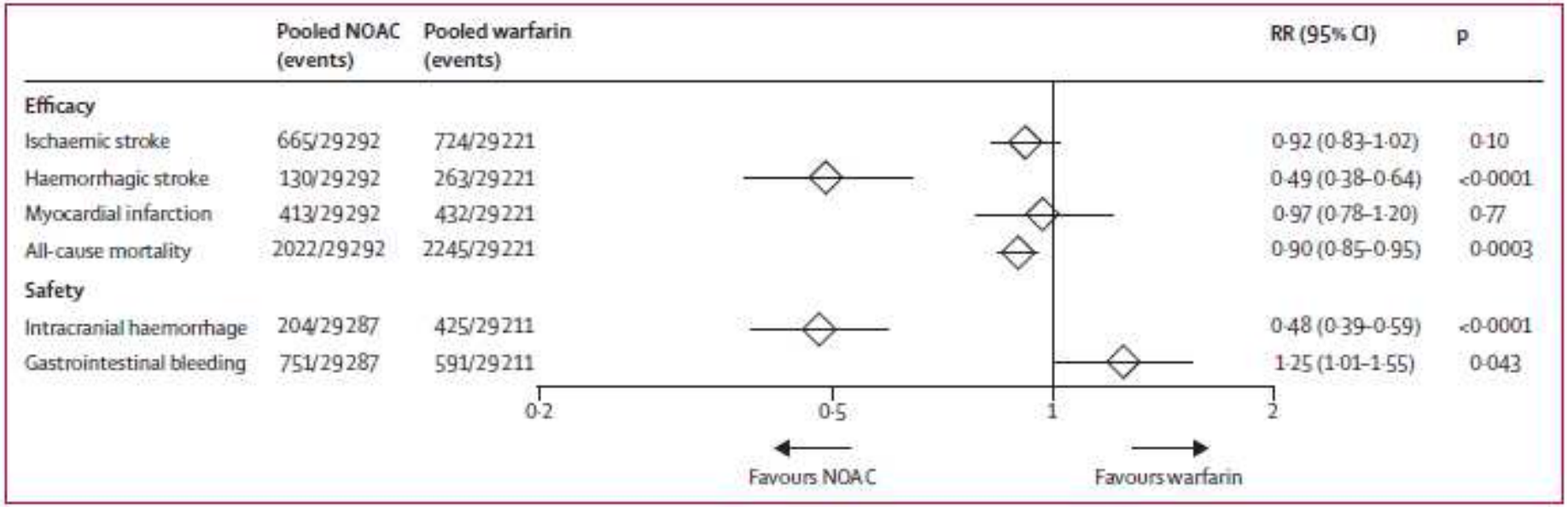

Figure 2: Secondary efficacy and safety outcomes

Data are n/N, unless otherwise indicated. Heterogeneity: ischaemic stroke I^2=32%, p=0·22; haemorrhagic stroke I^2=34%, p=0·21; myocardial infarction I^2=48%, p=0·13; all-cause mortality I^2=0%, p=0·81; intracranial haemorrhage I^2=32%, p=0·22; gastrointestinal bleeding I^2=74%, p=0·009. NOAC=new oral anticoagulant. RR=risk ratio.

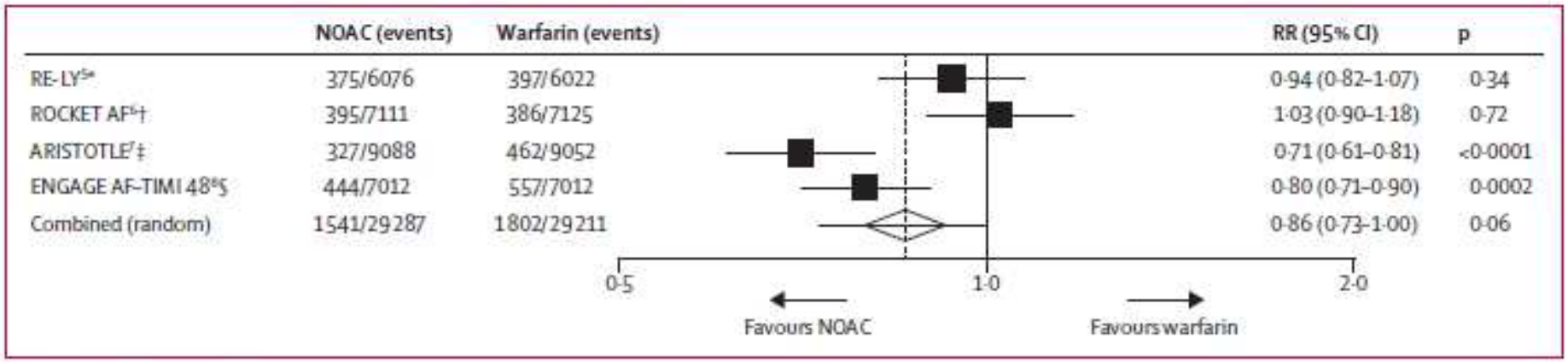

Figure 3: Major bleeding

Data are n/N, unless otherwise indicated. Heterogeneity: I^2=83%; p=0·001. NOAC=new oral anticoagulant. RR=risk ratio. *Dabigatran 150 mg twice daily. †Rivaroxaban 20 mg once daily. ‡Apixaban 5 mg twice daily. §Edoxaban 60 mg once daily.

QUALE NUOVO ANTICOAGULANTE ORALE E’ MEGLIO?

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Antithrombotic Therapy

Indirect Comparisons of New Oral Anticoagulant Drugs for Efficacy and Safety When Used for Stroke Prevention in Atrial Fibrillation

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Table 1 Summary of the Main Clinical Trials Involving Novel Anticoagulants for Stroke Prevention in Nonvalvular AF

	Dabigatran (RE-LY)	Rivaroxaban (ROCKET-AF)	Apixaban (ARISTOTLE)
Drug characteristics			
Mechanism	Oral direct thrombin inhibitor	Oral direct factor Xa inhibitor	Oral direct factor Xa inhibitor
Bioavailability, %	6	60–80	50
Time to peak levels, h	3	3	3
Half-life, h	12–17	5–9	9–14
Excretion	80% renal	2/3 liver, 1/3 renal	25% renal, 75% fecal
Dose	150 mg BID	20 mg OD	5 mg BID
Dose in renal impairment	110 mg BID	15 mg OD (if creatinine clearance 30–49 ml/min)	2.5 mg BID
Special considerations	Intestinal absorption is pH dependent and is reduced in patients taking proton pump inhibitors.	Higher levels expected in patients with renal or hepatic failure. Activity lower in fasted patients, so should be taken after food.	
Study characteristics			
Study design	Randomized open label	Multicenter, randomized, double-blind, double-dummy	Randomized control, double-blind, parallel arm
Number of patients	18,113	14,264	18,201
Follow-up period, months	24	40	40
Randomized groups	Dose-adjusted warfarin vs. blinded doses of dabigatran (150 mg BID, 110 mg BID)	Dose-adjusted warfarin vs. rivaroxaban 20 mg OD	Dose-adjusted warfarin vs. apixaban 5 mg BID

ARISTOTLE = Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; BID = twice daily; OD = once daily; RE-LY = Randomized Evaluation of Long-Term Anticoagulant Therapy; ROCKET-AF = Rivaroxaban Once Daily Oral Direct Factor Xa Inhibitor Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation.

Table 2 Risk Differences and Confidence Intervals, in Relation to Differences in the Study Populations at Baseline

Baseline Characteristics	RE-LY (N = 18,113)	ROCKET-AF (N = 14,264)	ARISTOTLE (N = 18,201)	RE-LY vs. ROCKET-AF	RE-LY vs. ARISTOTLE Percent Point (% Study 1; % Study 2)	ROCKET-AF vs. ARISTOTLE Percent Point (% Study 1; % Study 2)
Age, yrs*	71.5 ± 8.7	73 [65-78]	70 [63-76]	—	—	—
Female, %	36.4	39.7	35.2	−3.3 (−4.3; −2.2)	1.1 (0.2; 2.2)	4.5 (3.3; 5.5)
$CHADS_2$, mean	2.2	3.5	2.1	−1.26 (−1.28; −1.23)	0.1 (0.08; 0.12)	1.36 (1.34; 1.38)
$CHADS_2$ 3-6, %	32.5	87.0	30.2	−54.5 (−55.3; −53.6)	2.2 (1.3; 3.2)	56.7 (55.9; 57.6)
Paroxysmal AF, %	32.8	17.6	15.3	15.2 (14.3; 16.1)	17.5 (16.6; 18.4)	2.3 (1.5; 3.1)
Prior stroke, TIA, or systemic embolism, %	20.0	54.8	19.4	−34.8 (−35.8; −33.8)	0.6 (−0.03; 1.4)	35.3 (43.3; 36.3)
Heart failure, %	32.0	62.5	35.4	−30.5 (−31.5; −29.4)	−3.5 (−4.4; −2.5)	27.0 (26.0; 28.1)
Prior myocardial infarction, %	16.6	17.3	14.2	−0.7 (−1.5; 0.1)	2.4 (1.6; 3.1)	3.1 (2.3; 3.9)
Diabetes, %	23.3	40.0	25.0	−16.6 (−17.6; −15.6)	−1.7 (−2.6; −0.8)	14.9 (13.9;16.0)
Hypertension, %	78.9	90.5	87.5	−11.7 (−12.4; −10.9)	−8.6 (−9.4; −7.8)	3.1 (2.9; 3.7)
Medication						
Aspirin, %	39.8	36.5	30.9	3.3 (2.2; 4.3)	8.8 (7.8; 9.8)	5.5 (4.5; 6.6)
Vitamin K antagonist, %	49.6	62.4	57.2	−12.8 (−13.9; −11.7)	−7.5 (−8.5; −6.5)	5.3 (4.2; 6.3)

*Values for RE-LY: mean ± SD; for ROCKET-AF and ARISTOTLE: median [interquartile range].

AF = atrial fibrillation; TIA = transient ischemic attack; other abbreviations as in Table 1.

Table 4 Indirect Comparison Using Warfarin as Single Common Comparator, on the Basis of the RE-LY, ROCKET-AF, and ARISTOTLE Trials

	Apixaban ← → Dabigatran 110		Apixaban ← → Dabigatran 150		Apixaban ← → Rivaroxaban		Dabigatran 110 ← → Rivaroxaban		Dabigatran 150 ← → Rivaroxaban	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Efficacy endpoints										
Stroke or systemic embolism	0.88	(0.67–1.15)	1.22	(0.91–1.62)	0.90	(0.71–1.13)	1.02	(0.79–1.32)	**0.74**	**(0.56–0.97)**
Stroke	0.86	(0.65–1.14)	1.23	(0.92–1.66)	0.93	(0.71–1.22)	1.08	(0.81–1.44)	0.75	(0.56–1.02)
Ischemic or uncertain type of stroke	0.83	(0.61–1.13)	1.21	(0.88–1.67)	0.98	(0.72–1.33)	1.18	(0.86–1.62)	0.81	(0.58–1.13)
Hemorrhagic stroke	1.65	(0.81–3.34)	1.96	(0.94–4.08)	0.86	(0.48–1.57)	0.53	(0.25–1.12)	**0.44**	**(0.20–0.96)**
Systemic embolism	NA		NA		**3.78**	**(1.16–12.31)**	NA		NA	
Nondisabling stroke	NA		NA		NA		0.83	(0.53–1.32)	**0.60**	**(0.37–0.97)**
Mortality endpoints										
Death from any cause	0.98	(0.83–1.16)	1.01	(0.85–1.20)	1.05	(0.84–1.30)	1.07	(0.85–1.34)	1.04	(0.82–1.30)
Death from vascular causes	NA		NA		NA		1.01	(0.78–1.31)	0.96	(0.74–1.24)
Other endpoints										
Myocardial infarction	0.68	(0.45–1.03)	0.69	(0.46–1.05)	1.09	(0.74–1.60)	**1.59**	**(1.07–2.37)**	**1.57**	**(1.05–2.33)**
Pulmonary embolism	0.62	(0.17–2.20)	0.48	(0.14–1.68)	NA		NA		NA	
Bleeding endpoints										
Major bleeding	0.86	(0.7–1.06)	**0.74**	**(0.61–0.91)**	**0.66**	**(0.54–0.81)**	**0.77**	**(0.63–0.94)**	0.89	(0.73–1.09)
Major or clinically relevant nonmajor bleeding	NA		NA		**0.66**	**(0.58–0.75)**	NA		NA	
Life-threatening bleeding	NA		NA		NA		1.36	(0.82–2.27)	1.62	(0.97–2.70)
Intracranial bleeding	1.35	(0.79–2.32)	1.05	(0.63–1.76)	0.63	(0.39–1.01)	**0.46**	**(0.27–0.80)**	0.60	(0.35–1.01)
Gastrointestinal bleeding	0.81	(0.57–1.15)	**0.59**	**(0.42–0.83)**	NA		NA		NA	
Extracranial or unclassified bleeding	0.84	(0.67–1.05)	**0.74**	**(0.59–0.92)**	NA		NA		NA	

See Online Table 1 for availability and endpoint definition in original study. How to read: Drug A ←→ Drug B, HR <1.00 means hazard risk of Drug A is smaller than hazard risk of Drug B, indirectly compared via 1 common comparator, warfarin (A ←→ warfarin ←→ B). Comparisons with HR = 1.00 outside 95% confidence interval are in boldface. The **bold** values indicate significant values.

NA = not available; other abbreviations as in Table 2.

Results

There was a significantly lower risk of stroke and systemic embolism (by 26%) for dabigatran (150 mg BID) compared with rivaroxaban, as well as hemorrhagic stroke and nondisabling stroke. There were no significant differences for apixaban versus dabigatran (both doses) or rivaroxaban; or rivaroxaban versus dabigatran 110 mg BID in preventing stroke and systemic embolism. For ischemic stroke, there were no significant differences between the new OACs. Major bleeding was significantly lower with apixaban compared with dabigatran 150 mg BID (by 26%) and rivaroxaban (by 34%), but not significantly different from dabigatran 110 mg BID. There were no significant differences between apixaban and dabigatran 110 mg BID in safety endpoints. Apixaban also had lower major or clinically relevant bleeding (by 34%) compared with rivaroxaban. When compared with rivaroxaban, dabigatran 110 mg BID was associated with less major bleeding (by 23%) and intracranial bleeding (by 54%). There were no significant differences in myocardial infarction events between the dabigatran (both doses) and apixaban.

Conclusions

Notwithstanding the limitations of an indirect comparison study, we found no profound significant differences in efficacy between apixaban and dabigatran etexilate (both doses) or rivaroxaban. Dabigatran 150 mg BID was superior to rivaroxaban for some efficacy endpoints, whereas major bleeding was significantly lower with dabigatran 110 mg BID or apixaban. Only a head-to-head direct comparison of the different new OACs would fully answer the question of efficacy/safety differences between the new drugs for stroke prevention in AF. (J Am Coll Cardiol 2012;60:738–46) © 2012 by the American College of Cardiology Foundation

Limiti dello studio

1) Differenze nella popolazione arruolata
2) Differenze nella definizione delle emorragie maggiori
3) Differenze nel disegno dello studio (confronto in aperto/cieco/doppio cieco)
4) Analisi non tiene conto delle caratteristiche demografiche e del rischio di stroke della popolazione arruolata
5) Analisi non può considerare le differenze nel controllo del warfarin (TTR)

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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

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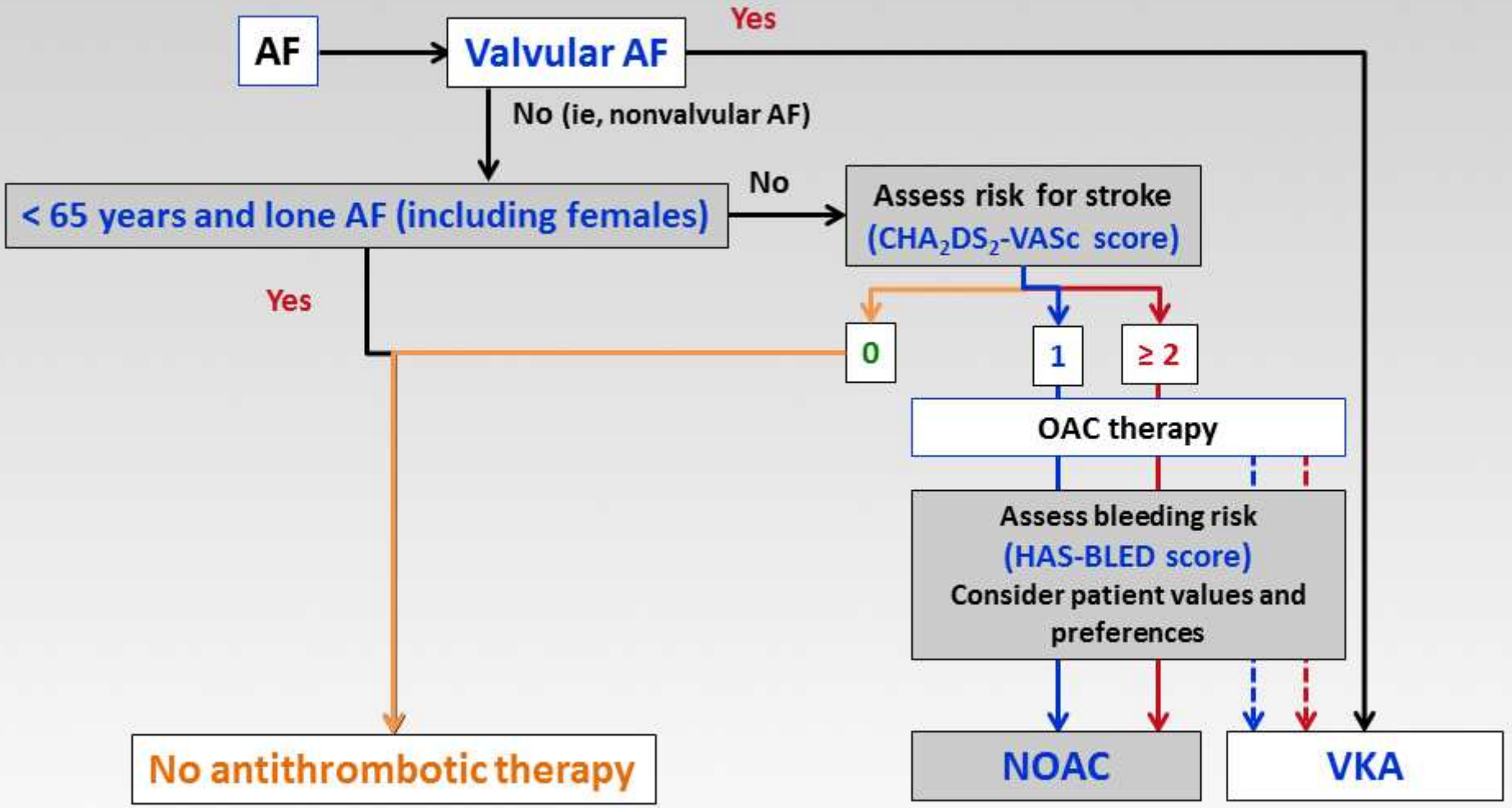
Recommendations	Class[a]	Level[b]	Ref[c]
Recommendations for prevention of thromboembolism in non-valvular AF—general			
Antithrombotic therapy to prevent thromboembolism is recommended for all patients with AF, except in those patients (both male and female) who are at low risk (aged <65 years and lone AF), or with contraindications.	I	A	21, 63, 104, 105, 106
The choice of antithrombotic therapy should be based upon the absolute risks of stroke/thromboembolism and bleeding and the net clinical benefit for a given patient.	I	A	21, 63, 105
The CHA_2DS_2-VASc score is recommended as a means of assessing stroke risk in non-valvular AF.	I	A	25, 36 ,39
In patients with a CHA_2DS_2-VASc score of 0 (i.e., aged <65 years with lone AF) who are at low risk, with none of the risk factors, no antithrombotic therapy is recommended.	I	B	21, 36, 82
In patients with a CHA_2DS_2-VASc score ≥2, OAC therapy with: • adjusted-dose VKA (INR 2–3); or • a direct thrombin inhibitor (dabigatran); or • an oral factor Xa inhibitor (e.g. rivaroxaban, apixaban)[d] … is recommended, unless contraindicated.	I	A	3, 4, 70, 82
In patients with a CHA_2DS_2-VASc score of 1, OAC therapy with • adjusted-dose VKA (INR 2–3); or • a direct thrombin inhibitor (dabigatran); or • an oral factor Xa inhibitor (e.g. rivaroxaban, apixaban)[d] …. should be considered, based upon an assessment of the risk of bleeding complications and patient preferences.	IIa	A	33, 44
Female patients who are aged <65 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	33, 44
When patients refuse the use of any OAC (whether VKAs or NOACs), antiplatelet therapy should be considered, using combination therapy with aspirin 75–100 mg plus clopidogrel 75 mg daily (where there is a low risk of bleeding) or—less effectively—aspirin 75–325 mg daily.	IIa	B	21, 26, 51, 109

Recommendations for prevention of thromboembolism in non-valvular AF—NOACs			
When adjusted-dose VKA (INR 2–3) cannot be used in a patient with AF where an OAC is recommended, due to difficulties in keeping within therapeutic anticoagulation, experiencing side effects of VKAs, or inability to attend or undertake INR monitoring, one of the NOACs, either: • a direct thrombin inhibitor (dabigatran); or • an oral factor Xa inhibitor (e.g. rivaroxaban, apixaban)[c] … is recommended.	I	B	2, 28, 65, 107
Where OAC is recommended, one of the NOACs, either: • a direct thrombin inhibitor (dabigatran); or • an oral factor Xa inhibitor (e.g. rivaroxaban, apixaban)[c] … should be considered rather than adjusted-dose VKA (INR 2–3) for most patients with non-valvular AF, based on their net clinical benefit.	IIa	A	3, 4, 70, 82
Where dabigatran is prescribed, a dose of 150 mg b.i.d. should be considered for most patients in preference to 110 mg b.i.d., with the latter dose recommended in: • elderly patients, age ≥ 80 • 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	85, 96
Where rivaroxaban is being considered, a dose of 20 mg o.d. should be considered for most patients in preference to 15 mg o.d., with the latter dose recommended in: • high bleeding risk (HAS-BLED score ≥3) • moderate renal impairment (CrCl 30–49 mL/min).	IIa	C	3, 108
Baseline and subsequent regular assessment of renal function (by CrCl) is recommended in patients following initiation of any NOAC, which should be done annually but more frequently in those with moderate renal impairment where CrCl should be assessed 2–3 times per year.	IIa	B	85
NOACs (dabigatran, rivaroxaban, and apixaban) are not recommended in patients with severe renal impairment (CrCl <30 mL/min).	III	A	3, 24, 70

Clinical Flowchart for OAC¶



NOAC = novel oral anticoagulation; HAS-BLED = hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly
Note: Aspirin no longer included in flowchart due to weak evidence for its effectiveness

Arrhythmia & EP

Adapted from Camm AJ, et al. *Eur Heart J.* 2012;33(21):2719-2747.

theheart.org from WebMD

Medscape EDUCATION

COME POSSIAMO DECIDERE CHE ANTICOAGULANTE ORALE USARE NEL SINGOLO PAZIENTE?

CHEST

Original Research

CARDIOVASCULAR DISEASE

Factors Affecting Quality of Anticoagulation Control Among Patients With Atrial Fibrillation on Warfarin

The SAMe-TT_2R_2 Score

Stavros Apostolakis, MD, PhD; Renee M. Sullivan, MD; Brian Olshansky, MD; and Gregory Y. H. Lip, MD

Conclusion: **Common clinical and demographic factors can influence the quality of oral anticoagulation. We incorporated these factors into a simple score (SAMe-TT2R2) that can predict poor INR control and aid decision-making by identifying those patients with AF who would do well on VKA (SAMe-TT 2 R 2 score = 0-1), or conversely, those who require additional interventions to achieve acceptable anticoagulation control (SAMe-TT 2 R 2 score ≥ 2).** ***CHEST 2013; 144(5):1555–1563***

	Definitions	Points
S	Sex (female)	1
A	Age (<60 years)	1
M	Medical history*	1
e	..	..
T	Treatment (interacting Rx†)	1
T	Tobacco use (within 2 years)	2
R	Race (non-white)	2
Maximum points	..	8

SAMe-TT_2R_2=Sex female, Age less than 60, Medical history, Treatment strategy (rhythm control), Tobacco use (doubled), Race (doubled). *Two of the following: hypertension, diabetes, coronary artery disease, myocardial infarction, peripheral artery disease, congestive heart failure, previous stroke, pulmonary disease, hepatic or renal disease. †Eg, amiodarone for rhythm control.

***Table*: Definition of the SAMe-TT_2R_2 score**

In caso di emorragia cerebrale (EC):

a) EC in TAO con INR> range
b) EC in TAO in range
c) EC in ASA o clopidogrel
d) EC spontanea

In tutti i casi è indicata la chiusura dell’auricola?

FA- Cosa fare se

1) Recidiva di ictus o embolia sistemica in TAO ben condotta : + ASA?
2) Recidiva in TAO + ASA : cambiare Asa con Clopidogrel?
3) Recidiva in TAO + Clopidogrel: associare ASA?

SE LA CHIUSURA DELL'AURICOLA FOSSE LA SOLUZIONE?