Ordine provinciale dei Medici Chirurghi e Odontoiatri di Vicenza

Serate all' Ordine dei Medici

Vicenza 21 gennaio 2016

La prevenzione dell'ictus nella fibrillazione atriale: TAO e nuove prospettive terapeutiche con i NAO

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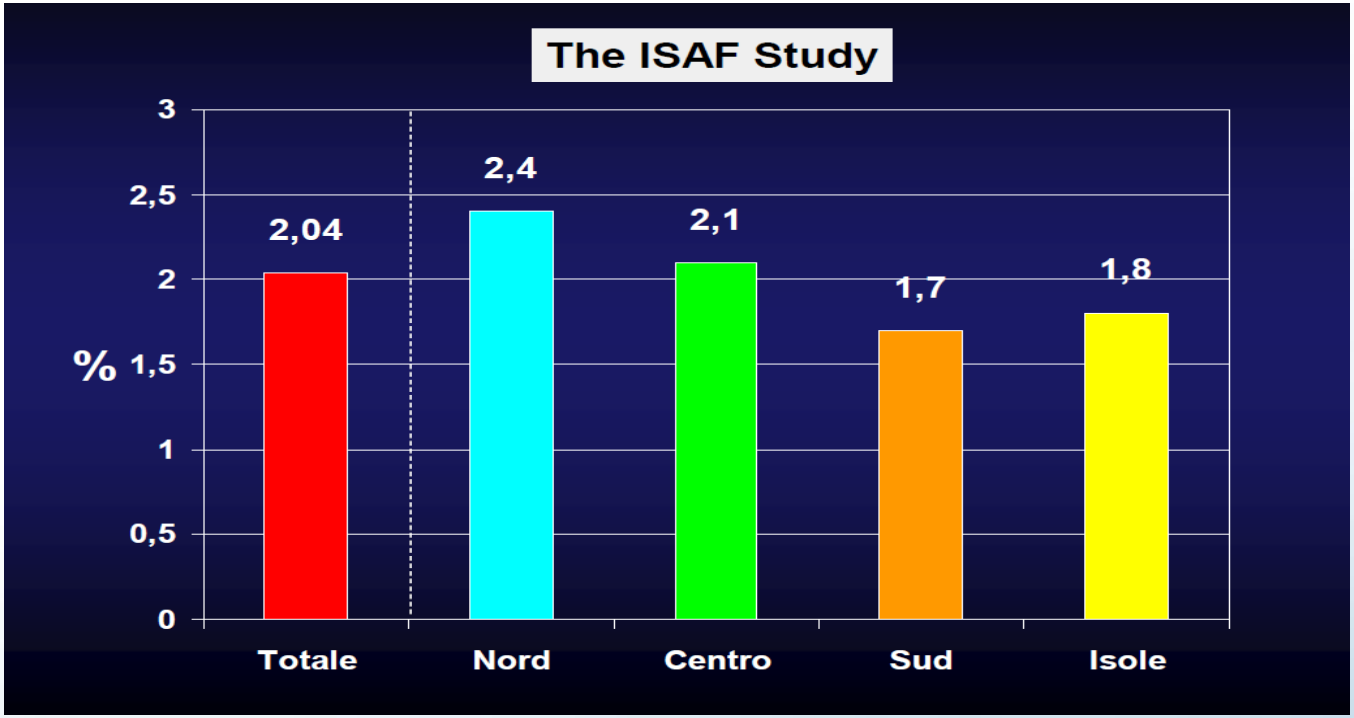
Epidemiologia della FA

- In Europa si stimano **6 milioni** gli individui con FA, di cui **600mila in Italia (ISAF Study)**

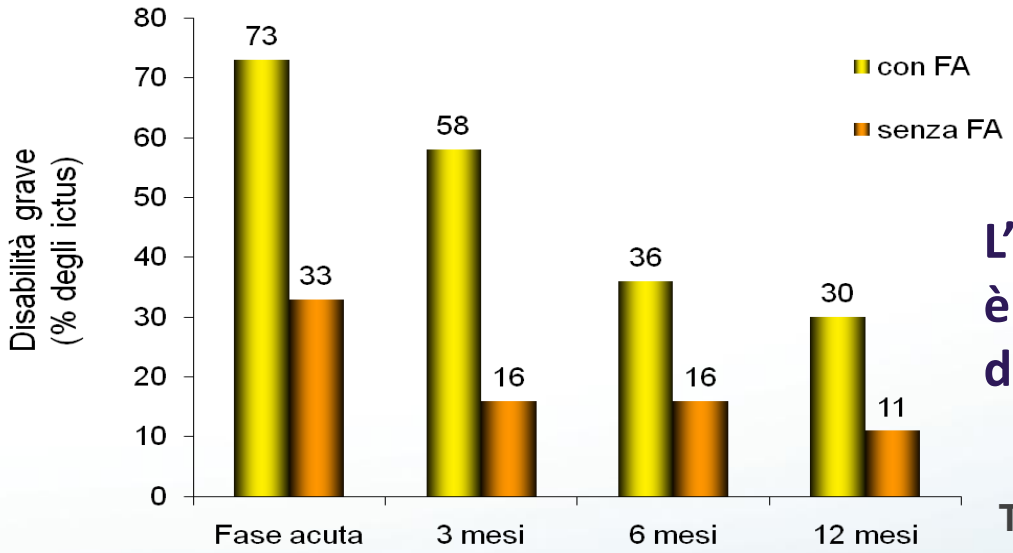


- **Ecco perché la FA è un impegno rilevante per il medico**

1) Prevalenza “pandemica” soprattutto nella popolazione senile del ‘west world’
2) Fattore di rischio per scompoenso infarto declino cognitivo mortalità “all-cause”
3) Eventi CV e tromboembolie frequenti nei soggetti, con “rischio crescente” (score)

Incidenza di ictus:

In Italia si verificano 200.000 episodi di ictus ogni anno, 660 casi al giorno: "cardioembolici" dal 15 al 25%, in base alla fascia di età



L'ictus embolico nella FA
è più grave di quello ischemico
da cerebrovasculopatia

Tempo dopo l'ictus

Limiti della pratica clinica:

il sottotrattamento nel mondo

Gran parte dei pazienti con FA e rischio intermedio o alto di ictus non è trattato in modo appropriato:

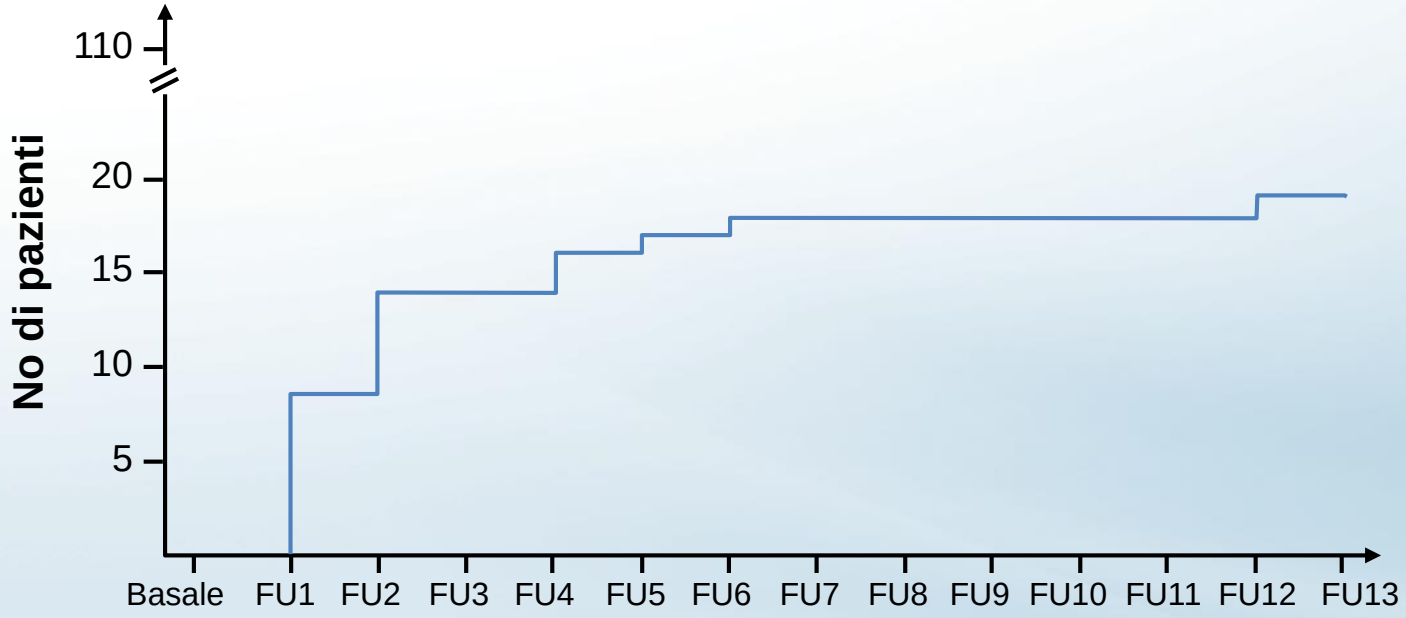
per scelta (TAO con AVK o ASA) e/o dose-INR

FA silente

- **La FA è spesso asintomatica** [2]

  In 110 pz con storia di FA sottoposti a monitoraggio ECG per 19±11 mesi
  - **45% avevano episodi di FA che duravano > 48 ore**
  - **di cui 38% erano asintomatici, senza FA ad ECG ambulatoriali**

Incidenza cumulativa di FA asintomatica ricorrente > 48 ore non rilevata da registrazioni ECG seriali durante il FU[1]



2. Israel *et al.;* J Am Coll Cardiol 2004; 43: 47–52

Il rischio trombotico è correlato principalmente al “fenotipo” del soggetto con FA (scores)

- Il rischio individuale di trombosi sistemica e cerebrale nei soggetti con FA è stato definito dopo l’analisi di ampi studi clinici controllati (SPAF I-II-III)

- I fattori di rischio identificati sono:
  - età elevata
  - sesso femminile
  - precedente ictus o TIA
  - ipertensione arteriosa
  - diabete mellito
  - scompenso cardiaco
  - cardiopatia ischemica

CHADS2 score

CHA2DS2-VASc score

Table 6. Comparison of the $CHADS_2$ and CHA_2DS_2-VASc Risk Stratification Scores for Subjects With Nonvalvular AF

Definition and Scores for $CHADS_2$ and CHA_2DS_2-VASc	Score
$CHADS_2$ acronym	
Congestive HF	1
Hypertension	1
Age ≥75 y	1
Diabetes mellitus	1
Stroke/TIA/TE	2
Maximum Score	6
CHA_2DS_2-VASc acronym	
Congestive HF	1
Hypertension	1

Stroke Risk Stratification With the $CHADS_2$ and CHA_2DS_2-VASc scores	Adjusted stroke rate (% per y)
$CHADS_2$ acronym‡	
0	1.9%
1	2.8%
2	4.0%
3	5.9%
4	8.5%
5	12.5%
6	18.2%
CHA_2DS_2-VASc acronym†	
0	0%

Sistema CHADS2

January, CT et al.
2014 AHA/ACC/HRS Atrial Fibrillation Guideline

Age ≥75 y	2
Diabetes mellitus	1
Stroke/TIA/TE	2
Vascular disease (prior MI, PAD, or aortic plaque)	1
Age 65–74 y	1
Sex category (i.e., female sex)	1
Maximum Score	9

1	1.3%
2	2.2%
3	3.2%
4	4.0%
5	6.7%
6	9.8%
7	9.6%
8	6.7%
9	15.20%

Sistema CHA2DS2-VAS

‡ These adjusted-stroke rates are based on data for hospitalized patients with AF and were published in 2001 (89). Because stroke rates are decreasing, actual stroke rates in contemporary nonhospitalized cohorts might vary from these estimates.
†Adjusted-stroke rate scores are based on data from Lip and colleagues (90). Actual rates of stroke in contemporary cohorts might vary from these estimates.

AF indicates atrial fibrillation; $CHADS_2$, Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Prior Stroke or TIA or Thromboembolism (doubled); CHA_2DS_2-VASc, Congestive heart failure, Hypertension, Age ≥75 years (doubled), Diabetes mellitus, Prior Stroke or TIA or thromboembolism (doubled), Vascular disease, Age 65–74 years, Sex category; HF, heart failure; LV, left ventricular; MI, myocardial infarction; PAD, peripheral artery disease; TE, thromboembolic; and TIA, transient ischemic attack (90, 91).

Definizione dello score di rischio

$CHADS_2$

C: Congestive heart failure — 1
H: Hypertension — 1
A: Age (**≥ 75 anni**) — 1
D: Diabetes mellitus — 1
S_2: **Stroke** — **2**

Punteggio massimo = 6

Score	Rischio
0	Basso
1	Moderato
≥ 2	**Alto**

Definizione dello score di rischio

CHA_2DS_2 – VAS

C: Congestive heart failure or left ventricular systolic disfunction

H: Hypertension

A: Age (età ≥ 75 anni)

D: Diabetes mellitus

S_2: Stroke or TIA

V: Vascular disease (es. IMA, placca aortica carotide)

A: Age 65-74

S: Sex category (genere femminile)

Punteggio massimo = 9

1
1
2
1
2
1
1
1

Score	Rischio
0	Basso
1-2	Moderato
> 2	**Alto**

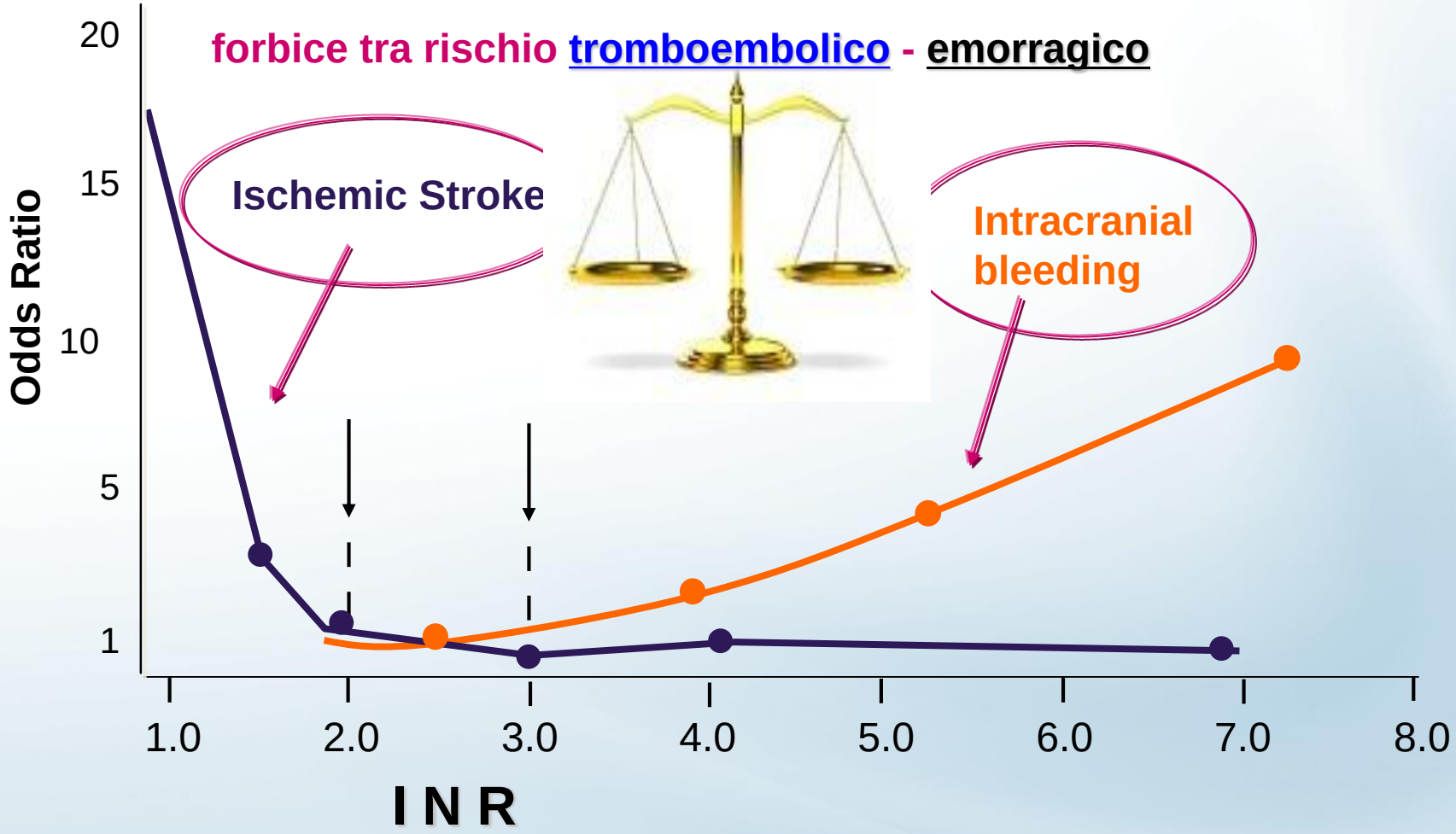
Rischio sanguinamento: HAS-BLED score

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

Un HAS-BLED score ≥ 3 indica un rischio elevato di sanguinamento e richiede qualche cautela e controlli regolari del paziente sia se in TAO con VKA che con ASA (ed anche ora coi NAO)

La TAO quando ben condotta riduce di 2/3 l'ictus e del 25% la mortalità da FA

Poco agevole la finestra terapeutica degli AVK: efficacia e sicurezza



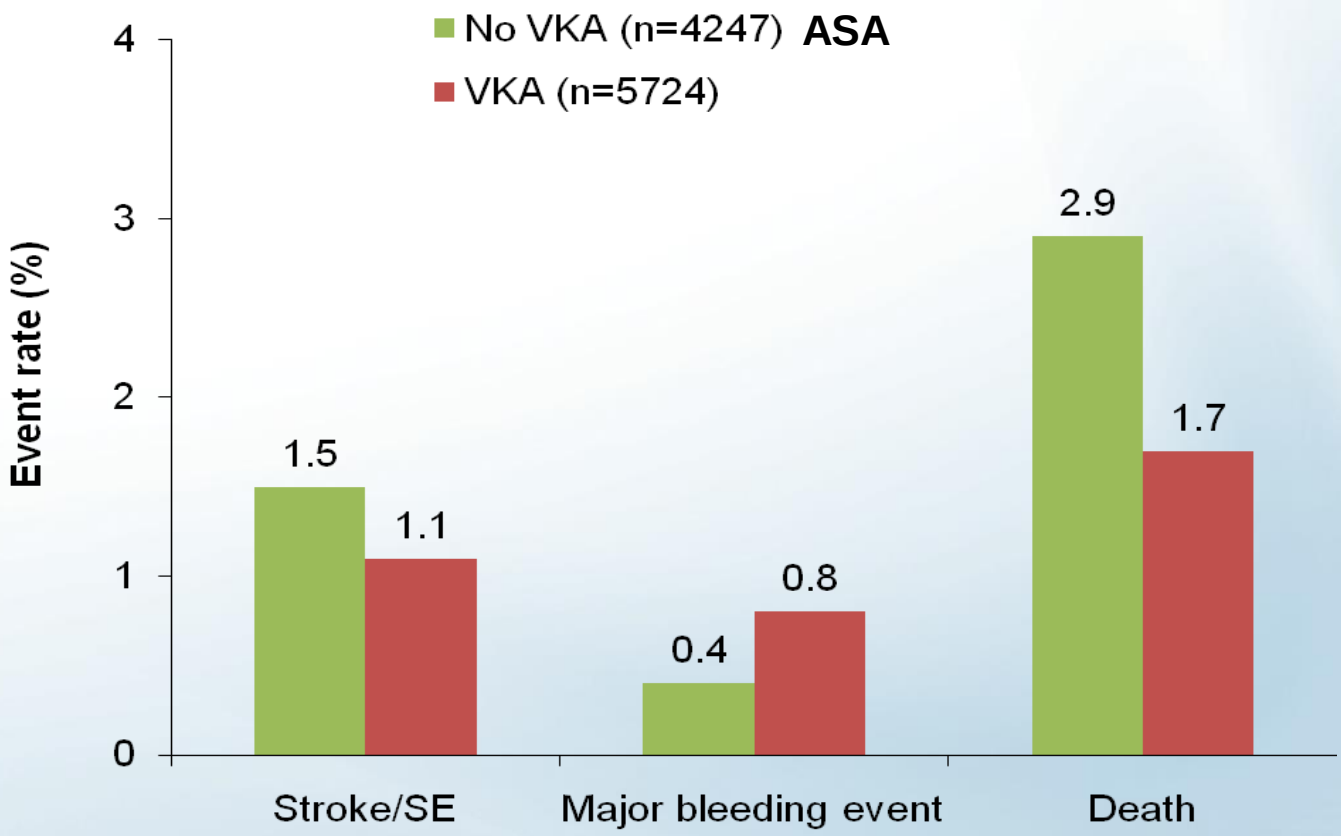
1. Fang M.C. *et al.*; Ann Intern Med 2004; 141: 745. 2. Hylek E.M. *et al.* ; N Engl J Med 1996; 335: 540.

Incidenza di eventi nel primo anno

"la differenza tra trattare e non i paz con TAO"

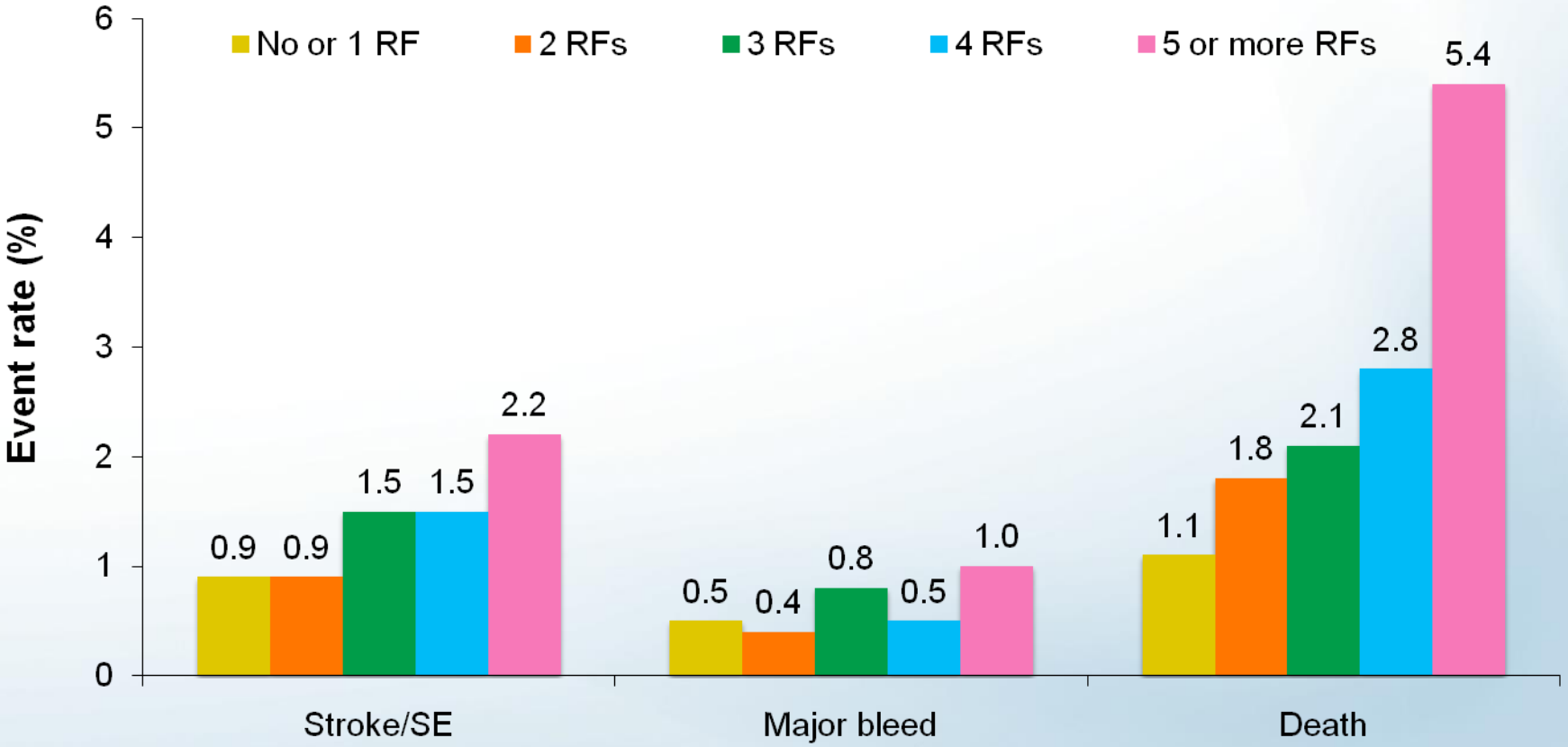
Incidenza eventi

- **Ictus/SE: 1,3%**
- **Evento di sanguinamento maggiore: 0,6%**
- **Decesso: 2,2%**



Kakkar *et al.* AHA 2012

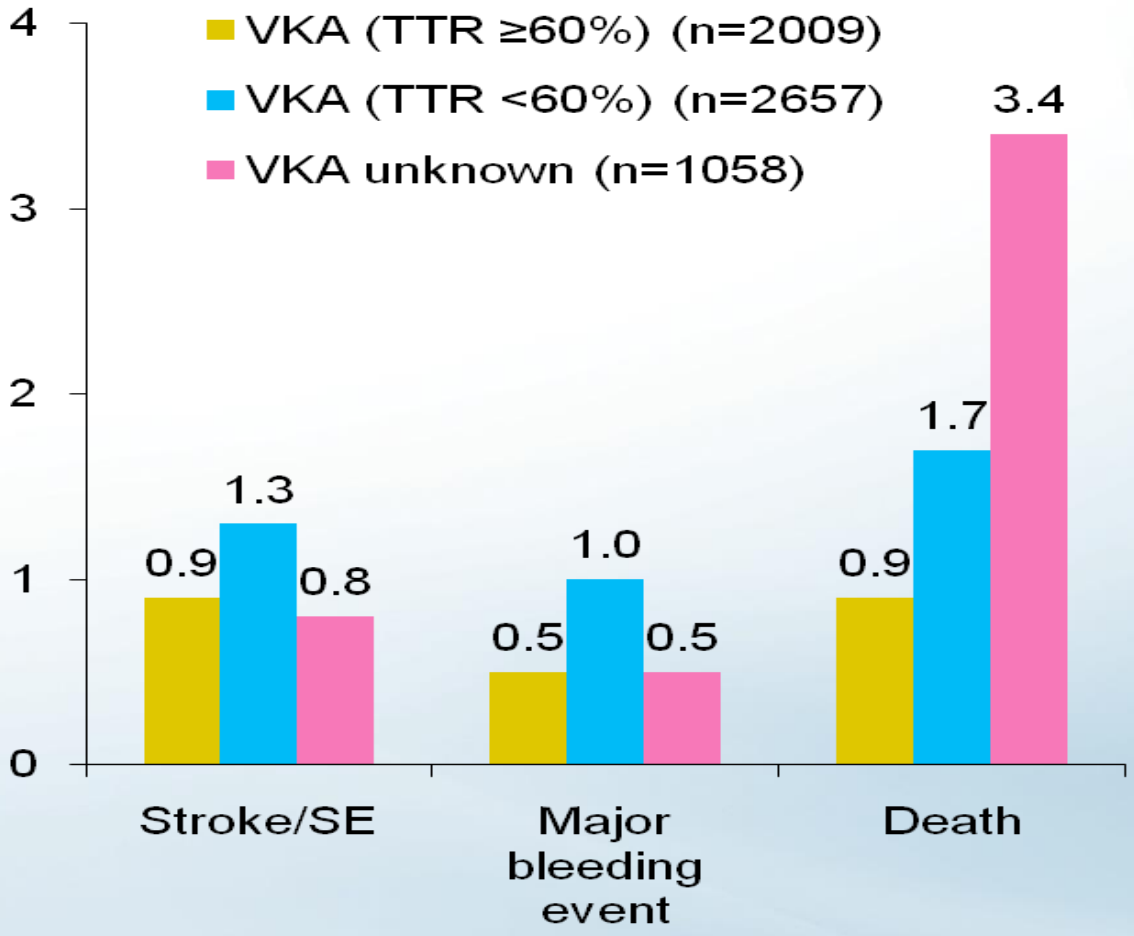
Incidenza di eventi nel primo anno in base al numero dei FR



RF: fattore di rischio (insufficienza cardiaca, LVEF < 40%, ipertensione, età ≥ 75 anni, diabete, ictus pregresso/TIA/SE, vasculopatia, età 65–74 anni, sesso femminile).

Kakkar *et al.*; AHA 2012

Incidenza di eventi in base all'impiego di VKA e sua adeguatezza



Kakkar *et al.*; AHA 2012

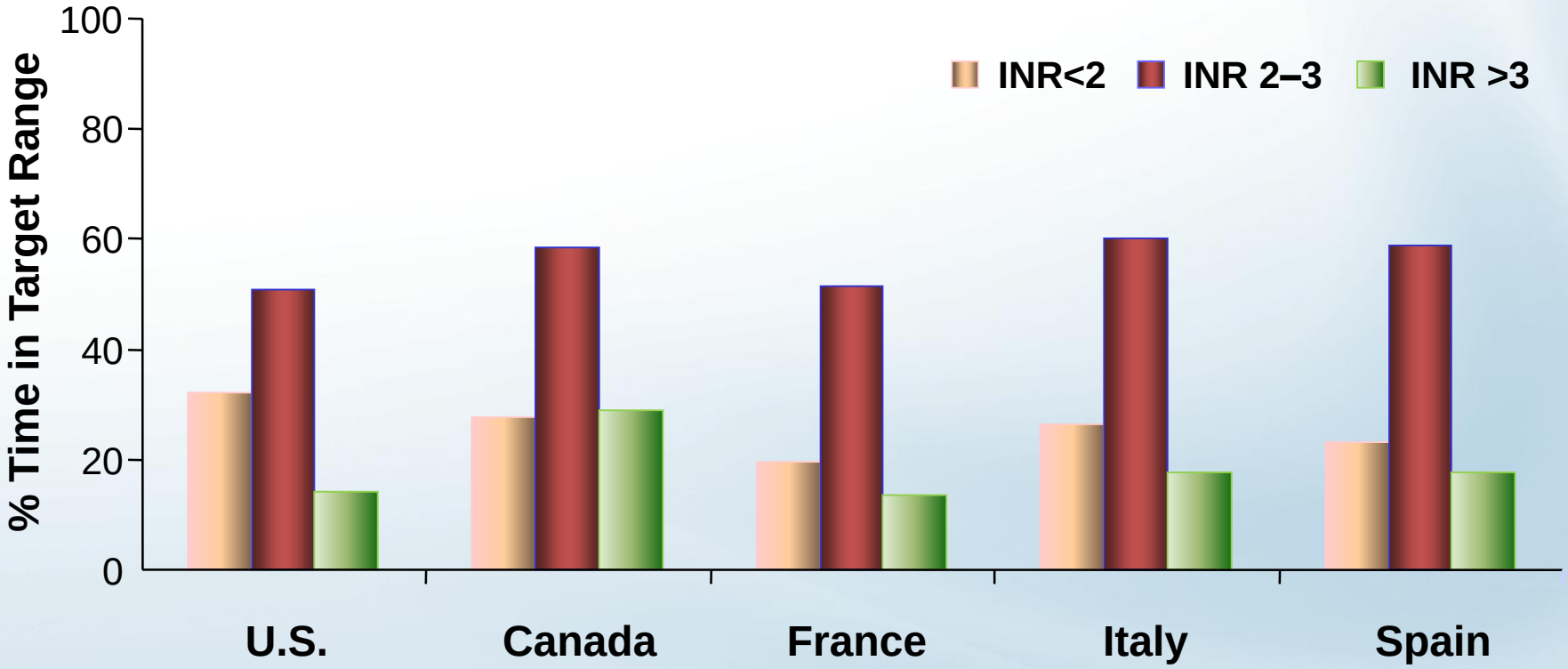
Correlazione fra gli outcome e il livello di controllo dell'INR

	TTR < 60%	TTR 60 – 75%	TTR > 75%
MORTALITY (%)	4.20	1.84	1.69
MAJOR BLEEDING (%)	3.85	1.96	1.58
STROKE / SYSTEMIC EMBOLISM (%)	2.10	1.07	0.02

White H.D. *et al*.; Arch Inten Med 2007; 167: 239-45

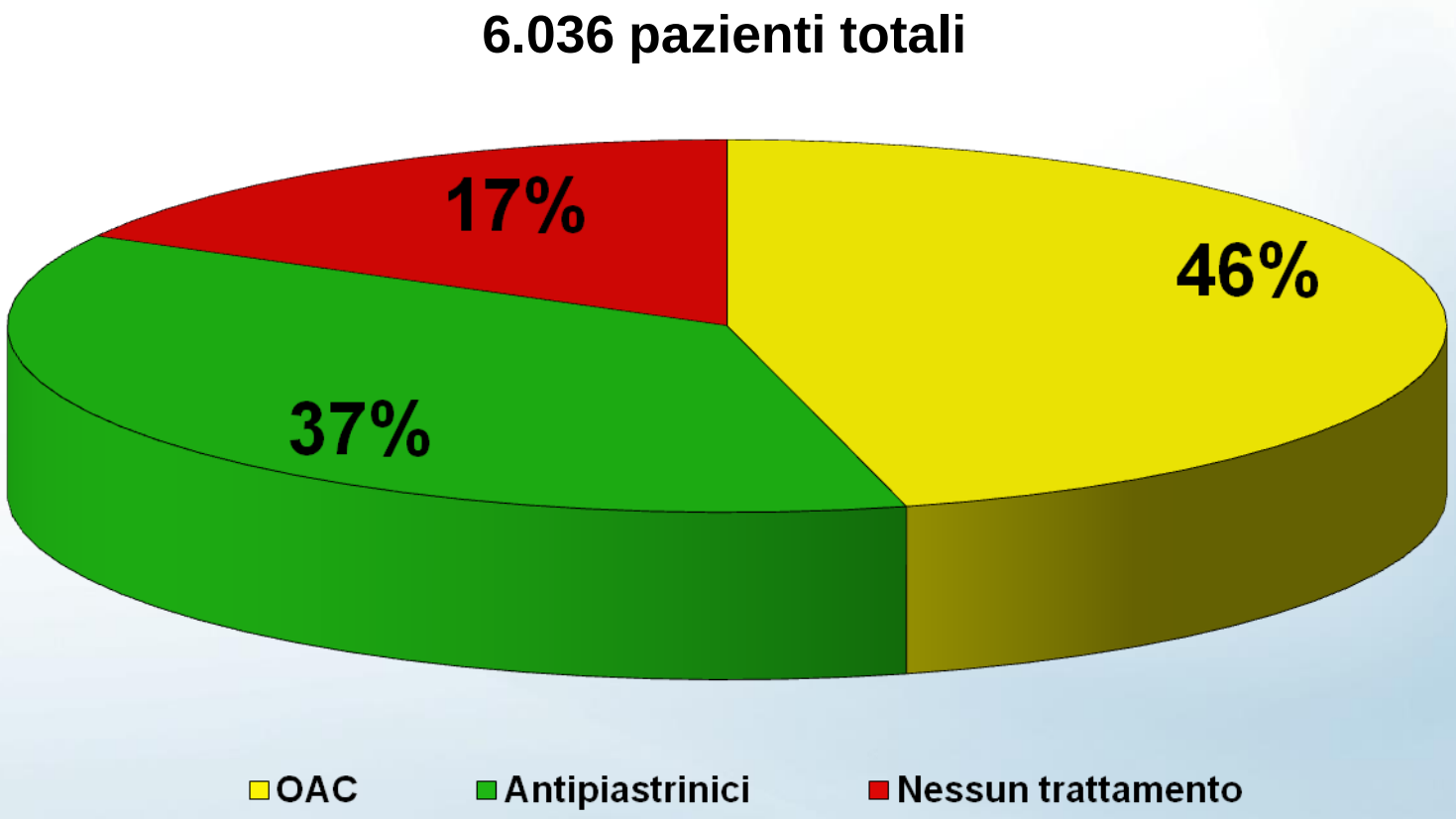
Anticoagulazione con warfarin: attività spesso esterna al range target

Studio internazionale sulla gestione dell'anticoagulazione



Ansell J. *et al*.; J Thromb Thrombolysis 2007; 23: 83-91.

Studio ISAF: trattamenti antitrombotici nella FA



Limiti della reale pratica clinica: il sottotrattamento in Italia

- **In Italia:**
  - Fino al 65% circa dei pazienti con FA non è trattato con AVK anche se raccomandato al trattamento secondo le Linee Guida internazionali.(1)
  - Il sottotrattamento risulta indipendente dal livello di rischio d'ictus e resta quindi rilevante anche nel caso di alto rischio.(1)
  - Il 35% circa dei pazienti a intermedio-alto rischio è trattato con antiaggreganti piastrinici(1) il cui impiego, secondo le nuove Linee Guida internazionali, è decisamente scoraggiato.

Dato *Health Search*

1. Mazzaglia G. *et al*.; Thromb Haemost 2010; 103 (5): 968-75

Limiti della reale pratica clinica: il sottotrattamento e il trattamento paradosso

- Da una recente revisione della letteratura risulta che: [1]
  - non riceve alcuna terapia:
    - fino al **47%** dei pazienti a rischio moderato di ictus
    - fino al **27%** dei pazienti a rischio elevato di ictus
  - è trattato con antiaggreganti piastrinici (**scarso effetto**):
    - fino al **49%** dei pazienti a rischio moderato
    - fino al **64%** dei pazienti a rischio elevato

1. Ogilvie I.M. *et al*.; Am J Cardiol 2011; 108: 151-161

Limiti dei dicumarolici :

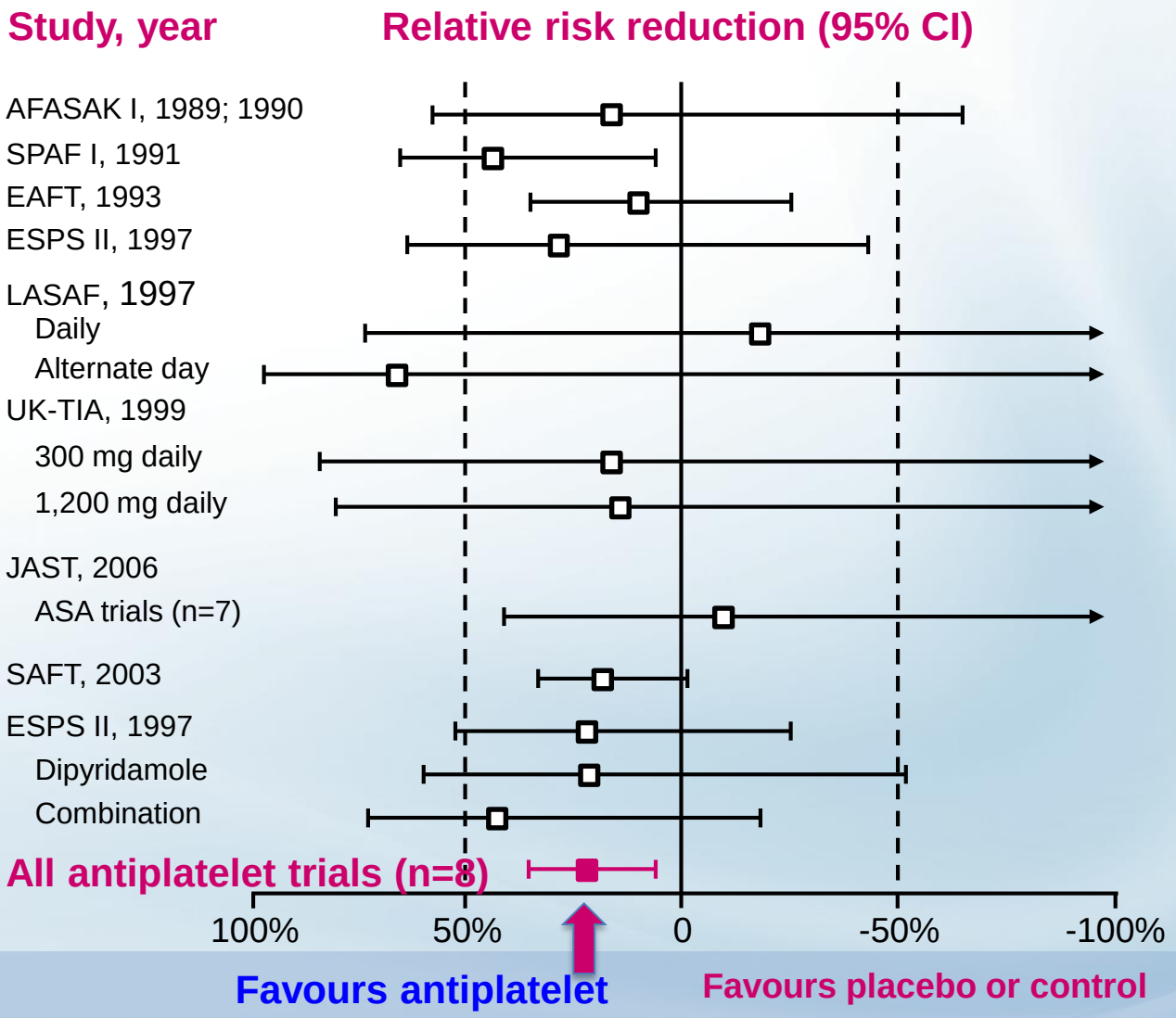
- **sottoprescrizione del medico (paradosso di % pz ad alto rischio CHADS)**
- **abbandono timoroso da parte del pz (sospensioni - irregolarità di assunzioni)**
- **Gestione mirata dell'INR: warfarin poco efficace fuori dal range (più trombosi! più emorragie!)**
- **difficile la gestione emorragie maggiori e la sospensione transitoria col "bridge" (farmaco ad azione prolungata, antidoto non sempre rapido)**

Terapia antiaggregante (ASA, ASA-Dip,Clopid, Ticlop, Ibupr): modesta efficacia (20%) nella prevenzione dell'ictus in FA

- Facile da utilizzare
- No monitoraggio

MA

- Efficacia modesta nella prevenzione dell'ictus e del tromboembolismo
- Bilanciata dal proporzionale rischio emorragico



Hart R.G. *et al.*; Ann Intern Med 2007;146: 857-867

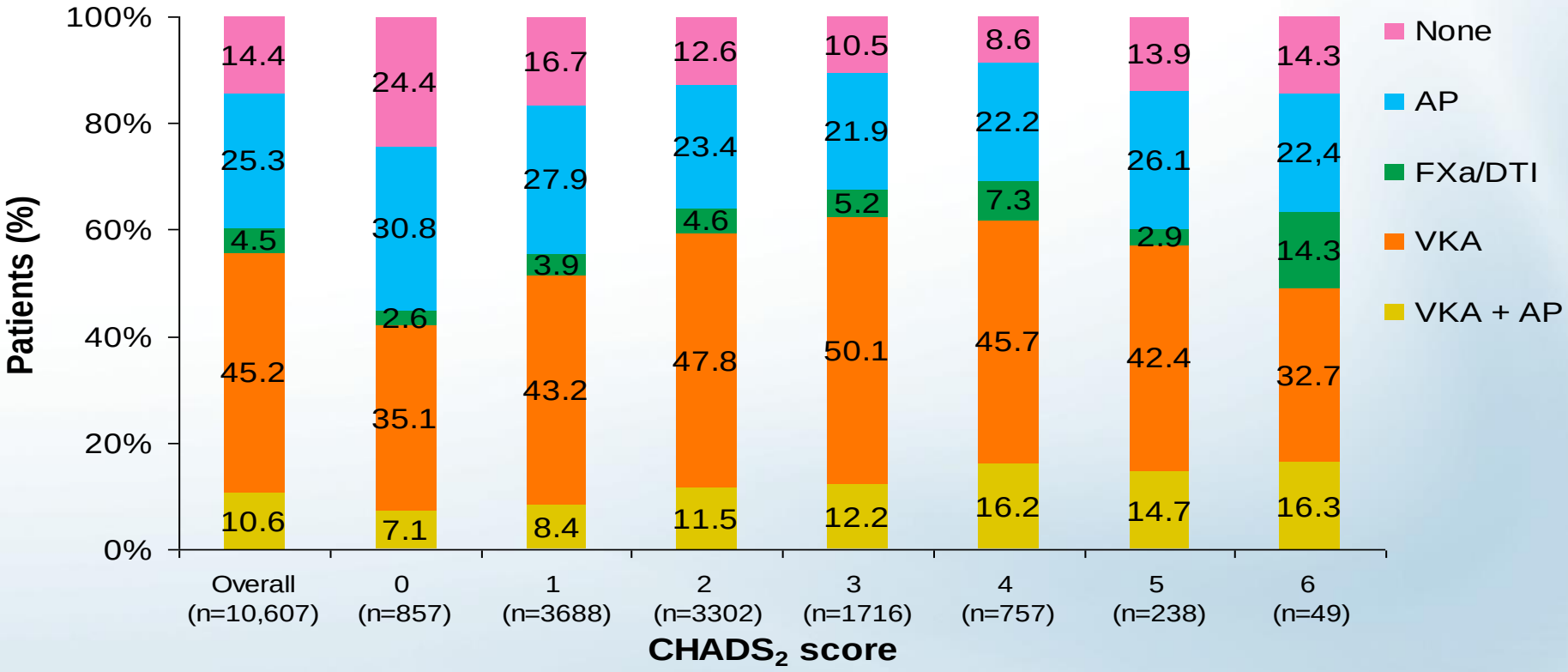
Le evidenze dai Registri Internazionali

- DANISH REGISTRY 5 milions entire nation citizens
- Societal Registries (ie ANMCO AIAC)
- Industries Registries (GLORIA,PREFER, GARFIELD, ORBIT I & II)
- MEDICARE REGISTRY 134-000 pts
- XANTUS e DRESDEN REGISTRY

Registro prospettico, multicentrico, internazionale di circa 30 mila pz con recente diagnosi di FANV

Garfield
global anticoagulant registry in the field

Coorte 1: utilizzo degli anticoagulanti in base al $CHADS_2$

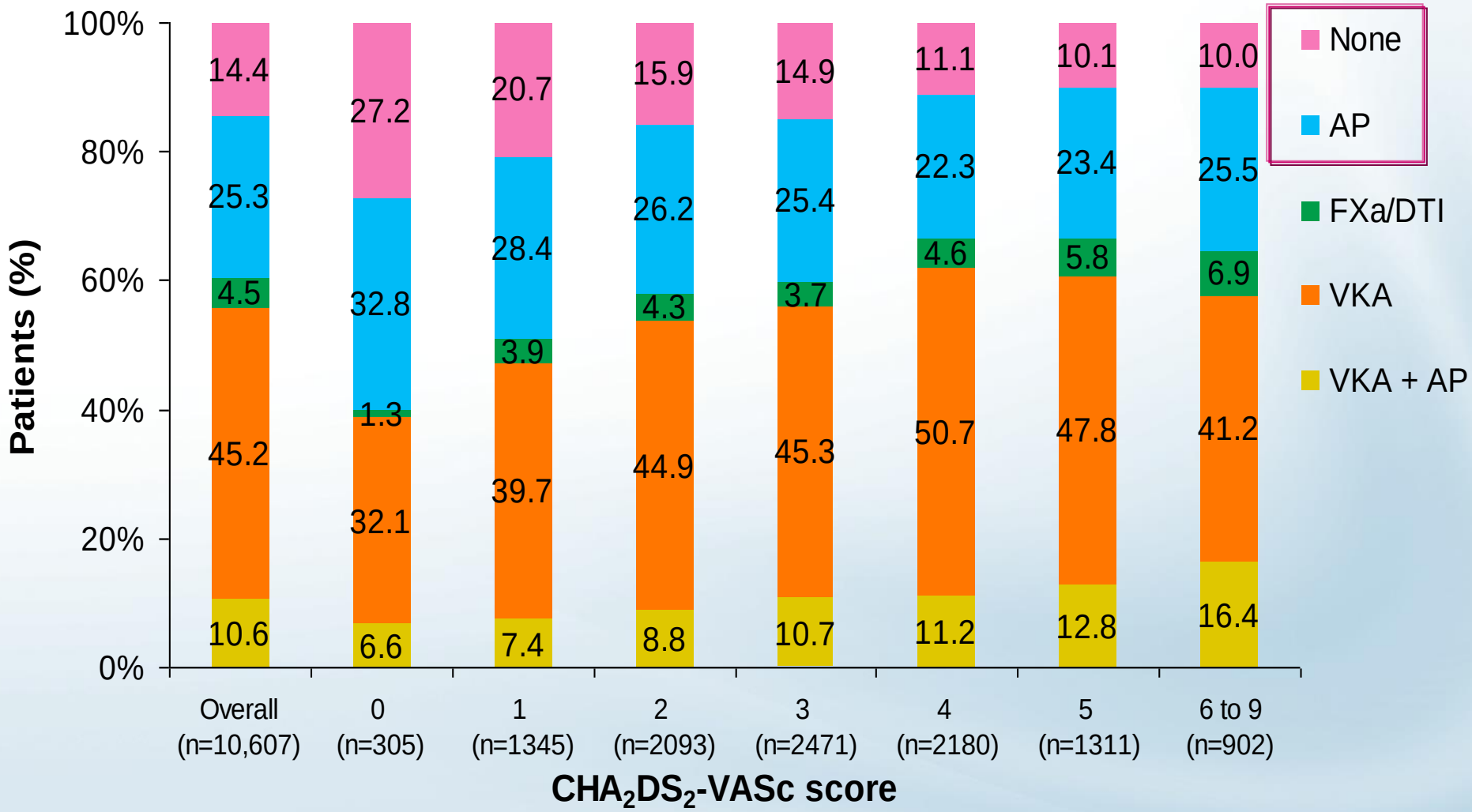


Gli anticoagulanti non sono stati prescritti nel 38% dei pazienti con punteggio $CHADS_2 \geq 2$

Kakkar *et al.*; PLoS One 2013; 8: e63479

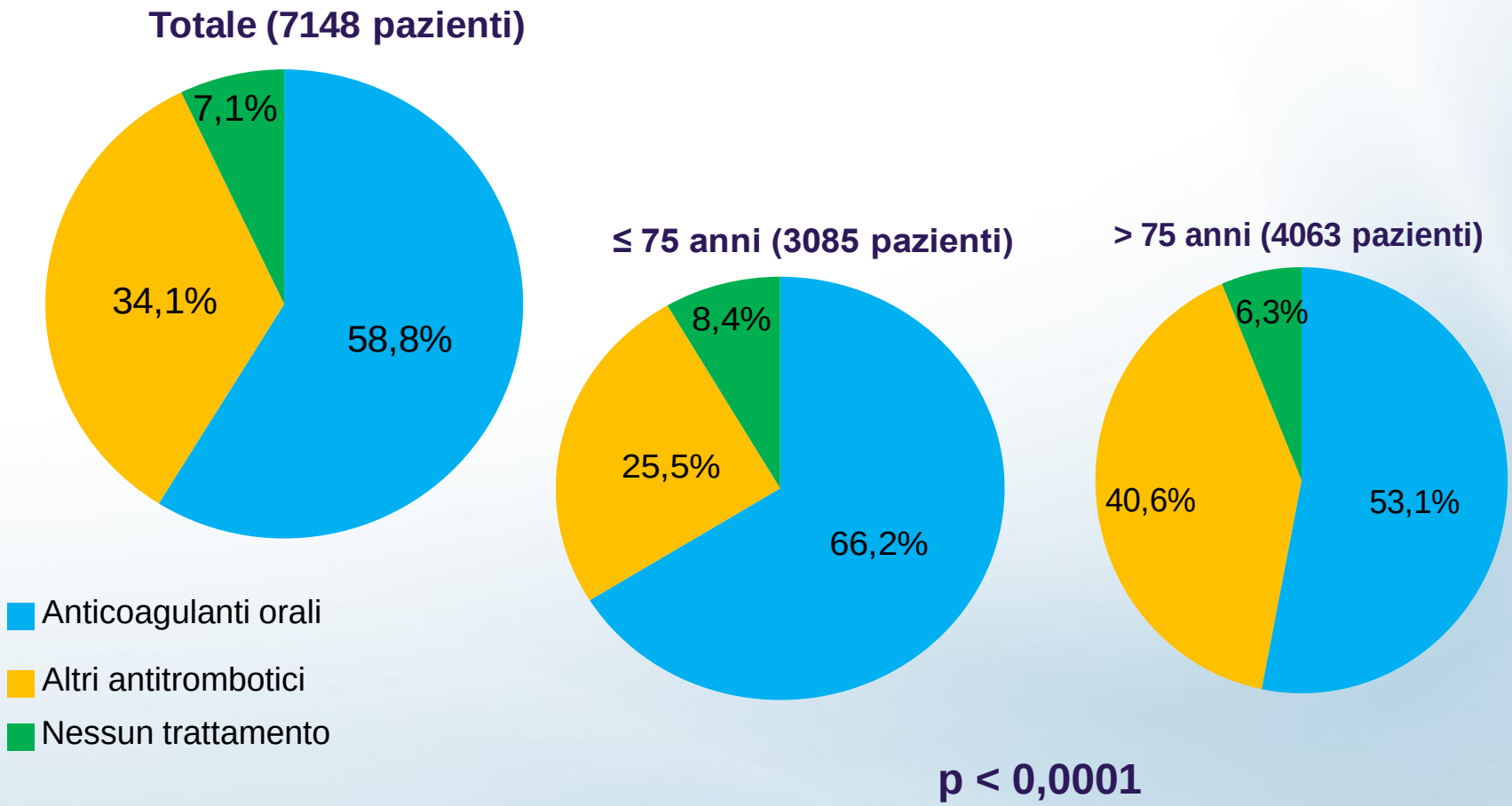
Utilizzo degli anticoagulanti in base al CHA_2DS_2-VASc

La TAO non è stata prescritta in circa il 40% dei pz con punteggio CHA_2DS_2-VASc ≥ 2



Kakkar *et al.*; PLoS One 2013; 8: e63479

Trattamenti antitrombotici in relazione all'età (il paradosso terapeutico)



p < 0,0001

La prescrizione della TAO è inversamente correlata all'età dei pazienti !!
Ma l'età è uno dei rischi CHADS2 score… e spesso essa si porta dietro altri FR!!

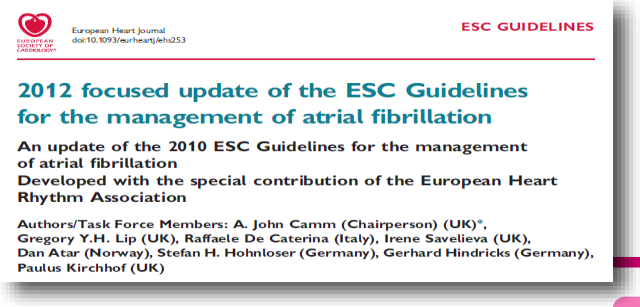
COMPORTAMENTO “PARADOSSALE” DELLA TAO PER FA E SUOI LIMITI

EURO HEART SURVEY

>> timore dei medici e pazienti:
maggiore per il *rischio emorragico*
rispetto al *rischio tromboembolico*

La % di pazienti in TAO non aumenta con l’aumentare del CHADS2 score, (anzi!) e spesso a favore di ASA

- **Con ASA il rischio ictus si riduce solo del 20%, quindi meno della metà rispetto alla TAO che lo riduce oltre il 65% (pur con lo stesso rischio emorragico dell’ASA !).**
- **Ciò spiega perché gli Autori delle LG hanno deciso di sconsigliare l’uso di ASA nel rischio basso**



Linee Guida ESC, ANMCO, AIAC

(Le Linee Guida ESC preferiscono i NAO)

NV AF

Valvular AF

Yes

lone AF < 65 years and including women

Stroke risk assessment using CHA_2DS_2-VASc

0

1

≥2

OACs

Assess bleeding risk (HAS-BLED score)
consider patient values/preferences

No AT therapy

NOACs
Rivaroxaban, Dabigatran Apixaban

Vitamin K antagonist

Slide line preferred; dotted line alternative

Camm A.J. *et al.*; Eur Heart Journ 2012; doi:10.1093/eurheartj/ehs253

Linee guida ESC 2012

Raccomandazioni Europee per la prescrizione dei NAO

	Classe	Livello
Quando è raccomandata la TAO, sono raccomandati i seguenti farmaci [al posto di VKA (INR 2-3)] sulla base del loro beneficio clinico netto: • **inibitore diretto della trombina (dabigatran)** • **inibitore orale del Fattore Xa (Rivaroxaban, Apixaban)**	**II a**	**A**

Modificato da Camm A.J. *et al*.; Eur Heart J 2012; 33: 2719-47.

Le raccomandazioni Italiane

(AIFA e Rimborsabilità)

ANMCO

Tra i pazienti con la **maggiore priorità** nell'utilizzare i NAO potrebbero essere compresi quelli :

- **con storia di emorragia intracranica e ad alto rischio di ictus**
- **con problemi logistici ad adeguato monitoraggio di INR**
- **che non assumono alcun anticoagulante se indicato**

(es. per un precedente rifiuto con warfarin)

- **considerati inadatti ai VKA e/o trattati finora con antiaggreganti**
- **che manifestano una preferenza a essere trattati con i NAO (? AIFA)**

It. Heart Journal 2013;14 (4): 295-322

Linee guida AIAC: aggiornamento 2013

Raccomandazioni per la TAO nella riduzione del rischio tromboembolico dei pazienti con FANV

	Terapia antitrombotica raccomandata	Classe	Livello
FA con CHA_2DS_2-VAS score = 0	Nessuna	I	B
FA con CHA_2DS_2-VAS score = 1[c]	Warfarin (INR 2,0-3,0) o dabigatran, rivaroxaban, apixaban	II b	B
FA con CHA_2DS_2-VAS score ≥ 2	¥ Warfarin (INR 2,0-3,0) o dabigatran, rivaroxaban, apixaban	I	A

[c] Nella categoria **CHA_2DS_2-VASc score 1** esistono **pazienti a basso rischio** per i quali
- non è raccomandata **alcuna terapia (sesso femminile di età < 65 anni)**
- oppure è raccomandato **ASA** (**malattia vascolare**).

¥ La presenza di **disfunzione renale** (clearance della creatinina **< 30** ml/min) identifica pazienti ad alto rischio per i quali **è invece indicata la terapia anticoagulante orale**.

Raviele A. *et al*.; Italian Heart Journal 2013;14 (3): 215-40

Le raccomandazioni AIAC

- Nei pazienti **warfarin-naïve,** i NAO sono da preferire ai VKA in:
  - **pregresso ictus ischemico;**
  - **difficoltà logistiche nell'effettuare il monitoraggio della TAO**
  - **pregressa emorragia intracranica;**
  - **giovane età;**
  - **paziente candidato a cardioversione elettrica** (**X-VERT Study**).
- Nei pazienti **warfarin-experienced** è proponibile lo switch ai NAO in:
  - **difficoltà logistiche nell'effettuare l'INR o labilità dell'INR**
  - **pregressa emorragia maggiore (escluse le gastrointestinali)**
  - **TAO subottimale (TTR:tempo all'interno del R.T. < 60%)**
  - **pregressa ICH e/o ictus/TIA in terapia con warfarin e INR in R.T.**
  - **impiego di farmaci interferenti con il warfarin e non con i NAO**
  - **impiego giornaliero di basse dosi di warfarin** (8-10 mg/settimana)

Raviele A. *et al*.; G Ital Cardiol 2013;14 (3): 215-40

Le promesse dei nuovi anticoagulanti orali
La risposta al 'medical need'

The NEW ENGLAND JOURNAL of MEDICINE

RE-LY

Dabigatran versus Warfarin in Patients with Atrial Fibrillation

ROCKET-AF

Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation

ARISTOTLE

Apixaban versus Warfarin in Patients with Atrial Fibrillation

Studi clinici di confronto tra i NAO e lo standard of care in pazienti con FA

Criteri e disegni degli studi: **DIFFERENTI PER TIPO PAZIENTI E DISEGNO STUDIO**

	RE-LY	ROCKET-AF	ARISTOTLE
Farmaco	**Dabigatran**	**Rivaroxaban**	**Apixaban**
Dose (mg)	**150 BID | 110 BID**	**20 (15) OD**	**5 (2,5) BID**
Numero di pazienti	**18.113** (3 bracci)	**14.266**	**18.206**
Disegno dello studio	**PROBE**	**Doppio cieco**	**Doppio cieco**
Periodo valutazione efficacia	Tutta la durata dello studio	**Tutta la durata dello studio + 30 giorni di follow-up**	Tutta la durata dello studio
Outcome sicurezza	Emorragie maggiori	**Emorragie maggiori e non-maggiori clinicamente rilevanti**	Emorragie maggiori

PROBE = Prospective, Randomized, Open-label, Blinded End point evaluation

Studi clinici di confronto tra i NAO e lo standard of care in pazienti con FA

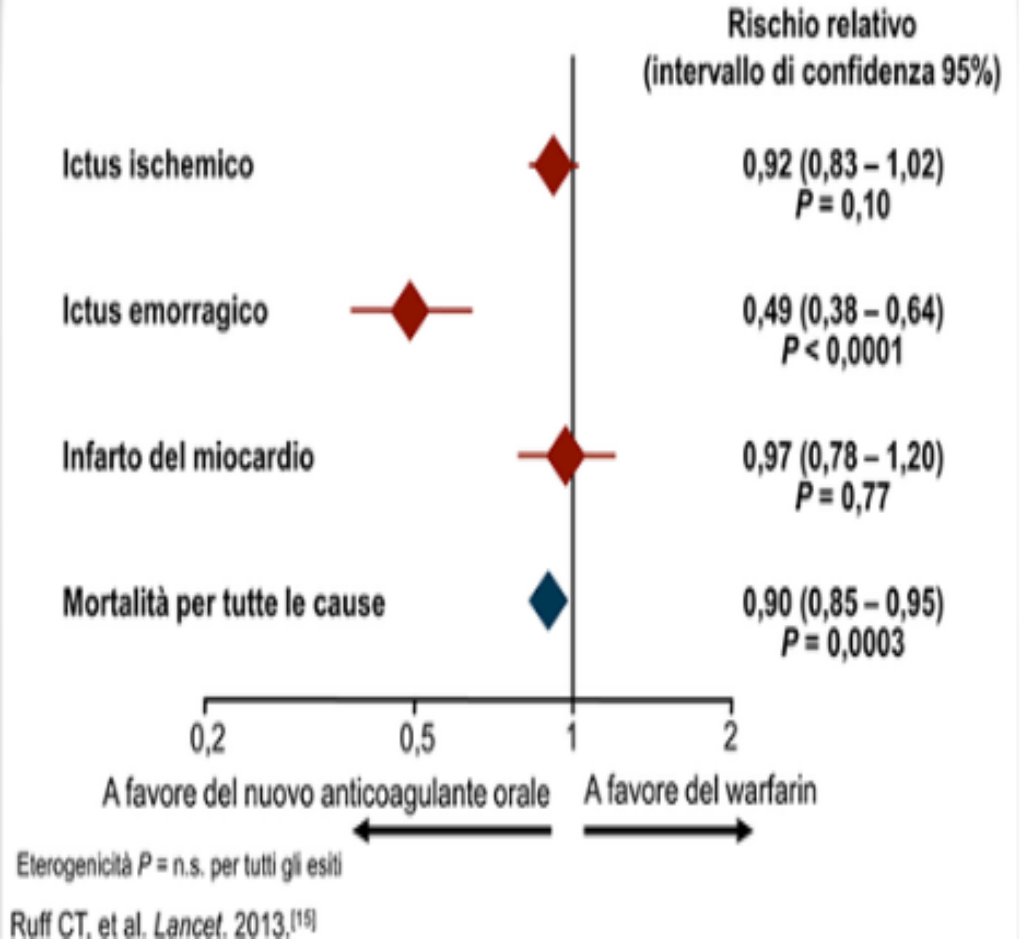
Caratteristiche dei pazienti al basale

	RE-LY	ROCKET-AF	ARISTOTLE
Dose (mg)	150 BID | 110 BID	**20 (15) OD**	5 (2,5) BID
$CHADS_2$ Medio	2,1	**3,5**	2,1
$CHADS_2$ = 0-1 (%)	32	**0**	34
$CHADS_2$ = 2 (%)	35	**13**	36
$CHADS_2 \geq 3$ (%)	33	**87**	30
Età >75 anni	40,1	**43,7**	31,2
Pregresso ictus/TIA/embolia (%)	20,3 | 19,9	**54,9**	19,2
Scompenso (%)	31,8 | 32,2	**62,6**	35,5
Diabete (%)	23,1 | 23,4	**40,4**	25
ClCr 30-49 mL/min (%)	19	**20,7**	16,6
Infarto del miocardio (%)	16,9 | 16,8	**16,6**	14,5
Tempo range terapeutico (TTR)	**64 (media)**	**55 (media)** **58 (mediana)**	**62** (media) 66 (mediana)

Pensiero del Relatore: **il ROCKET-AF si presenta come lo studio più vicino al real world**

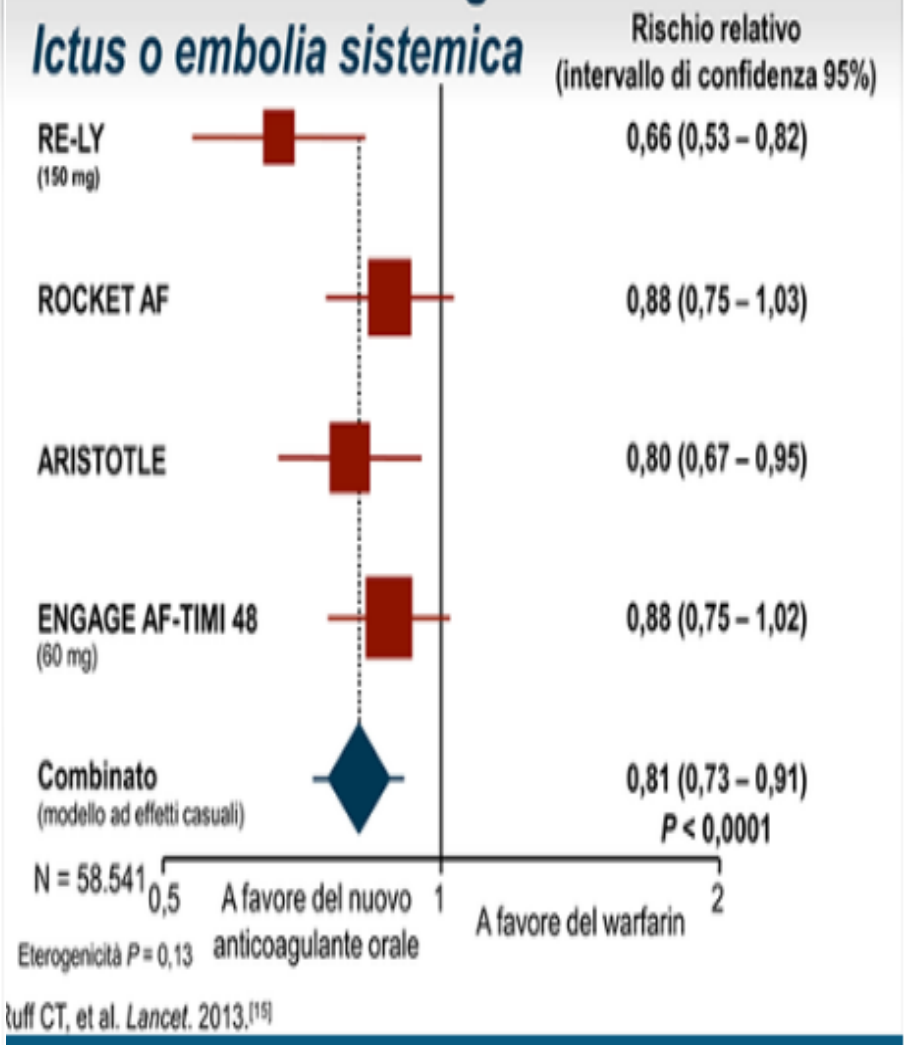
Efficacia dei NAO

Esiti di efficacia secondari



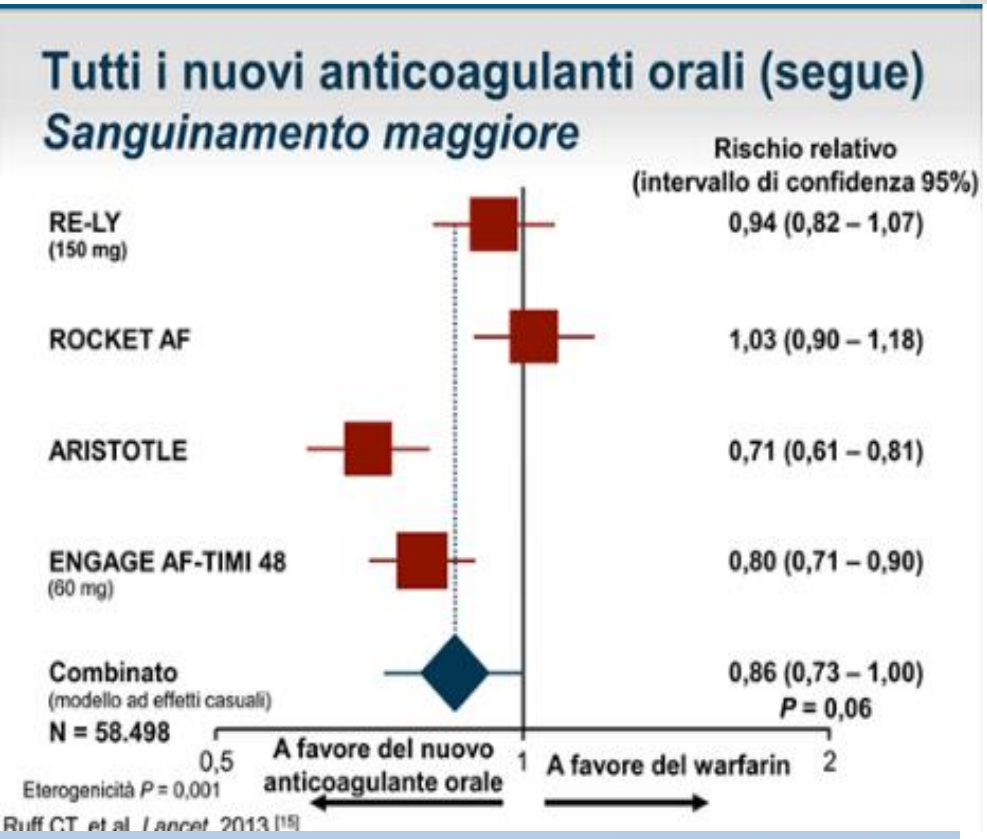
Ruff CT, et al. *Lancet*. 2013.[15]

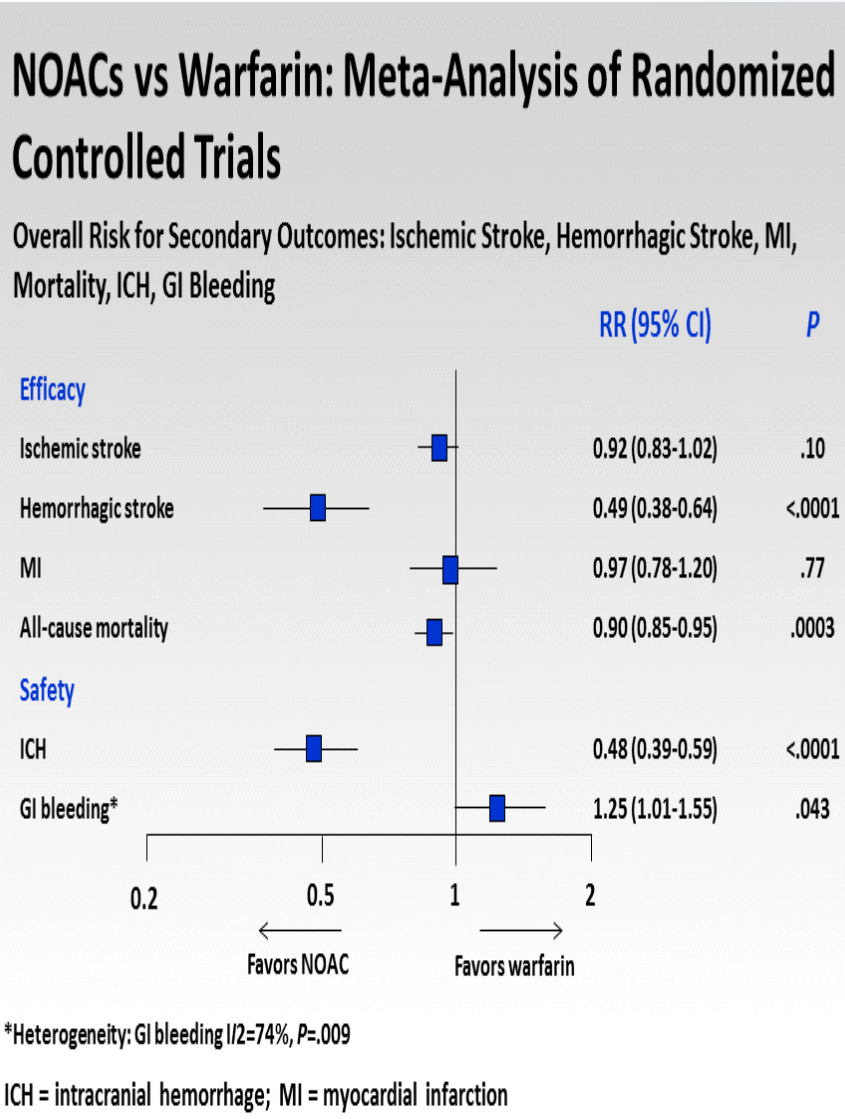
Tutti i nuovi anticoagulanti orali



Ruff CT, et al. *Lancet*. 2013.[15]

…e Sicurezza dei NAO





NOAC Stroke Reduction and Bleeding Risk vs Warfarin: Balance of Efficacy and Safety*

Efficacy (Reduction of Stroke or SE)	Safety (Major Bleeding)
Best	
Dabigatran 150 mg bid RR 0.66 (95% CI, 0.53-0.82)	Edoxaban 30 mg qd HR 0.47 (97.5% CI, 0.41-0.55)
Apixaban 5 mg bid HR 0.79 (95% CI, 0.66-0.95)	Apixaban 5 mg bid HR 0.69 (95% CI, 0.60-0.80)
Edoxaban 60 mg qd HR 0.87 (97.5% CI, 0.73-1.04)	Dabigatran 110 mg bid RR 0.80 (95% CI, 0.69-0.93)
Rivaroxaban 20 mg qd HR 0.88 (95% CI, 0.74-1.03)	Edoxaban 60 mg qd HR 0.80 (97.5% CI, 0.71-0.91)
Dabigatran 110 mg bid RR 0.91 (95% CI, 0.74-1.11)	Dabigatran 150 mg bid RR 0.93 (95% CI, 0.81-1.07)
Edoxaban 30 mg qd HR 1.13 (97.5% CI, 0.96-1.34)	Rivaroxaban 20 mg qd HR 1.04 (95% CI, 0.90-1.20)
Worst†	

*Study populations vary for each trial, and direct comparisons cannot be made between agents.
†Worst risk estimate is still noninferior to warfarin.

Arrhythmia & EP

Schulman S. *Thromb Haemost.* 2014;111(4):575-582

Medscape EDUCATION

- le evidenze cliniche -

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

European Heart Journal (2012) 33, 2719–2747
doi:10.1093/eurheartj/ehs253

Outcome	RE-LY Dabigatran 150 mg x 2 (P solo per significatività)	RE-LY Dabigatran 110 mg x 2 RR (P solo per significatività)	ROKET AF Rivaroxaban 20 mg RR (P solo per significatività)	ARISTOTLE Apixaban 5 mg x 2 RR (P solo per significatività)
troke/Systemic mbolism	**HR=0.66 (p<001 per superiorità)**	**HR=0.91 non inferiore**	**HR=0.88 non inferiore**	**HR=0.79 (p=0.01 per superiorità)**
chaemic stroke	*HR=0.76 Superiore (p=0.03)*	*HR=1.11 non inferiore*	*HR=0.94 non inferiore*	*HR=0.92 non inferiore*
aemorrhagic stroke	*HR=0.26 Superiore (p<0.001)*	*HR=0.31 Superiore (p<0.001)*	*HR=0.59 Superiore (p=0.024)*	*HR=0.51 Superiore (p<0.001)*
Major bleeding	**HR=0.93 non inferiore**	**HR=0.80 (p=0.03 per superiorità)**	**HR=1.04 non inferiore**	**HR=0.69 (p<0.001 per superiorità)**
tracranial bleeding	*HR=0.40 (p<0.001 per superiorità)*	*HR=0.31 (p<0.001 per superiorità)*	*HR=0.67 (p=0.02 per superiorità)*	*HR=0.42 (p<0.001 per superiorità)*
astrointestinal bleeding	*HR=1.48 INFERIORE (p<0.001)*	*HR=1.12 non inferiore*	*HR=1.49 INFERIORE (p<0.001)*	*HR=0.89 non inferiore*
Myocardial infarction	*HR=1.27 non inferiore*	*HR=1.29 non inferiore*	*HR=0.81 non inferiore*	*HR=0.88 non inferiore*
eath from any cause	**HR=0.88 non inferiore**	**HR=0.91 non inferiore**	**HR=0.85 non inferiore**	**HR=0.89 (p=0.047 per superiorità)**

NO NETWORK-METANALISI

I NAO hanno dimostrato di essere:

Efficaci nella prevenzione dell'ictus

- **Rivaroxaban, Dabigatran e Apixaban si sono dimostrati efficaci almeno quanto il warfarin …(e forse di più nella pratica clinica)**

Più sicuri del warfarin

- **riducendo in maniera significativa le emorragie, specie le emorragie intracraniche.**

Più accettati dai pazienti ("qualità di vita")

- dose orale fissa: OD o BID

- senza necessità di monitoraggio continuo

- bassa interazione con farmaci e alimenti

- la sospensione - quando serve (es atti chirurgici) o in caso di emorragie - toglie rapidamente il "rischio" emorragico senza attese lunghe e/o uso di antidoto

ESC 2012: non ci sono evidenze sufficienti per raccomandare un NAO rispetto a un altro

- Non esistono evidenze sufficienti per raccomandare un NAO rispetto a un altro, nonostante ci siano
  - “fenotipo” del paziente
  - Aderenza e compliance al farmaco
  - interazioni farmacologiche
  - tollerabilità
  - costi

Specifici
per ogni tipo di farmaco

E questi potrebbero essere considerati fattori sufficienti nella scelta del tipo di farmaco NAO.

Flow Chart TAO: VKA or NOACs

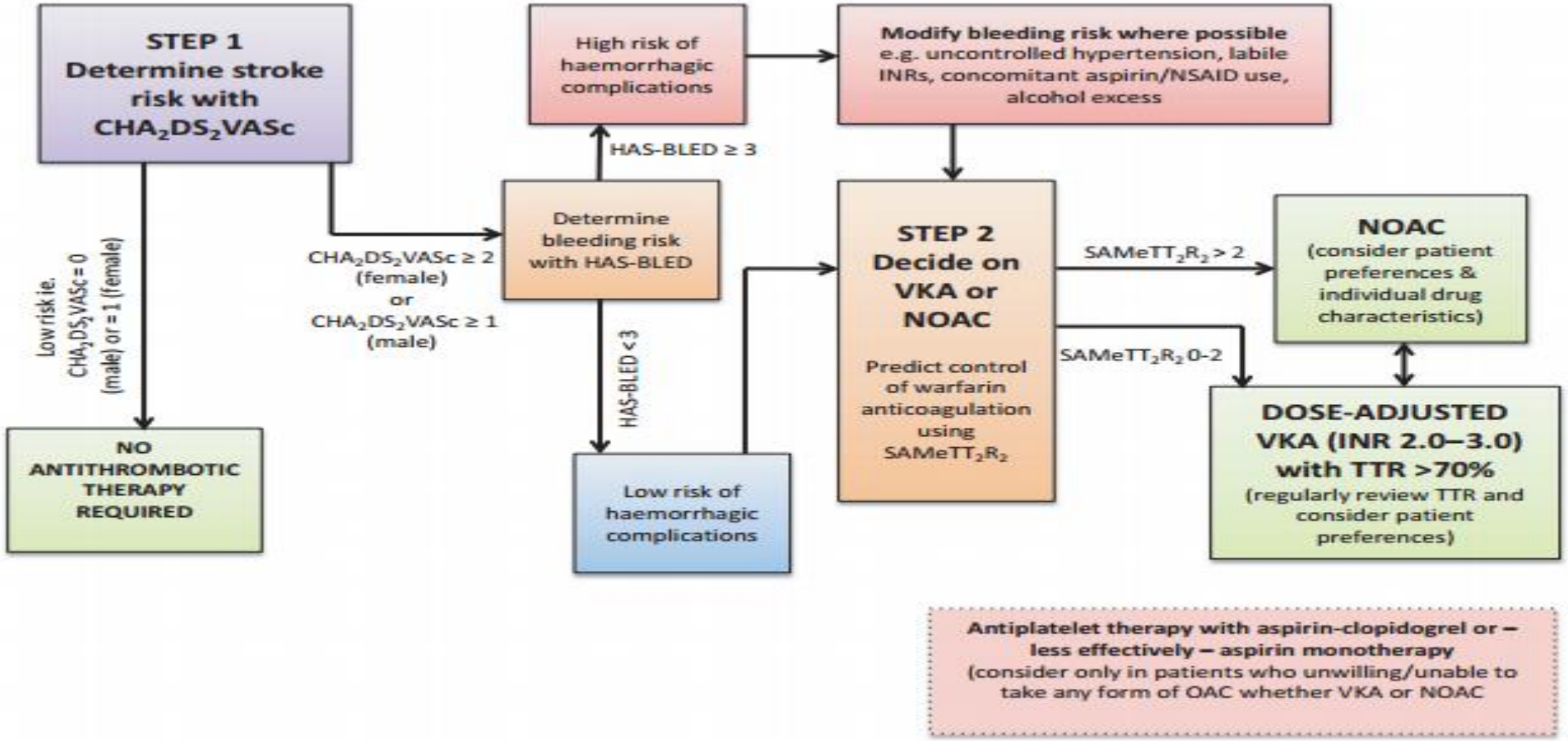


Fig. 1 *An algorithm for the risk assessment of atrial fibrillation (AF) patients about to start anticoagulation treatment. The assessment of risk of anticoagulation in patients with AF involves the use of the CHA_2DS_2VASc, HAS-BLED and $SAMeTT_2R$ scores to evaluate stroke risk, bleeding risk and likelihood of successful warfarin therapy, respectively. Non-vitamin K antagonist oral anticoagulants (NOACs) may be considered where the $SAMeTT_2R$ score predicts poor control of anticoagulation with warfarin. VKA, vitamin K antagonist; INR, international normalized ratio; NSAID, nonsteroidal anti-inflammatory drug; OAC, oral anticoagulant; TTR, time in therapeutic range.*

TAO: terapia personalizzabile?

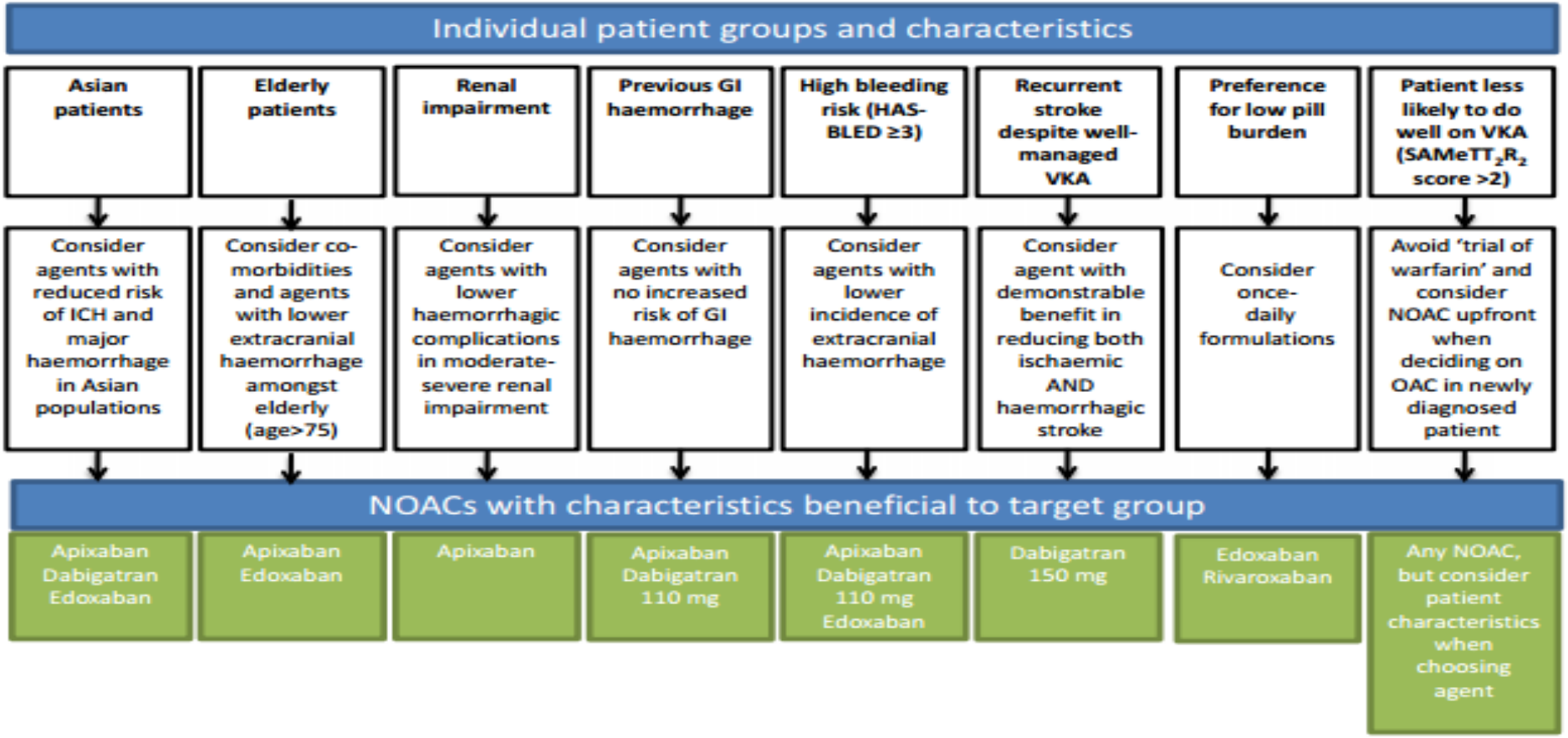


Fig. 2 *Suggested patient groups in which specific non-VKA oral anticoagulants (NOACs) may be relatively advantageous or disadvantageous. The NOACs are all individually noninferior to warfarin in terms of efficacy for stroke prevention in patients with nonvalvular atrial fibrillation (AF). The evidence that may favour the use of a particular NOAC in various subgroups of patients is summarized. ICH, intracranial haemorrhage; GI, gastrointestinal; OAC, oral anticoagulant; VKA, vitamin K antagonist.*

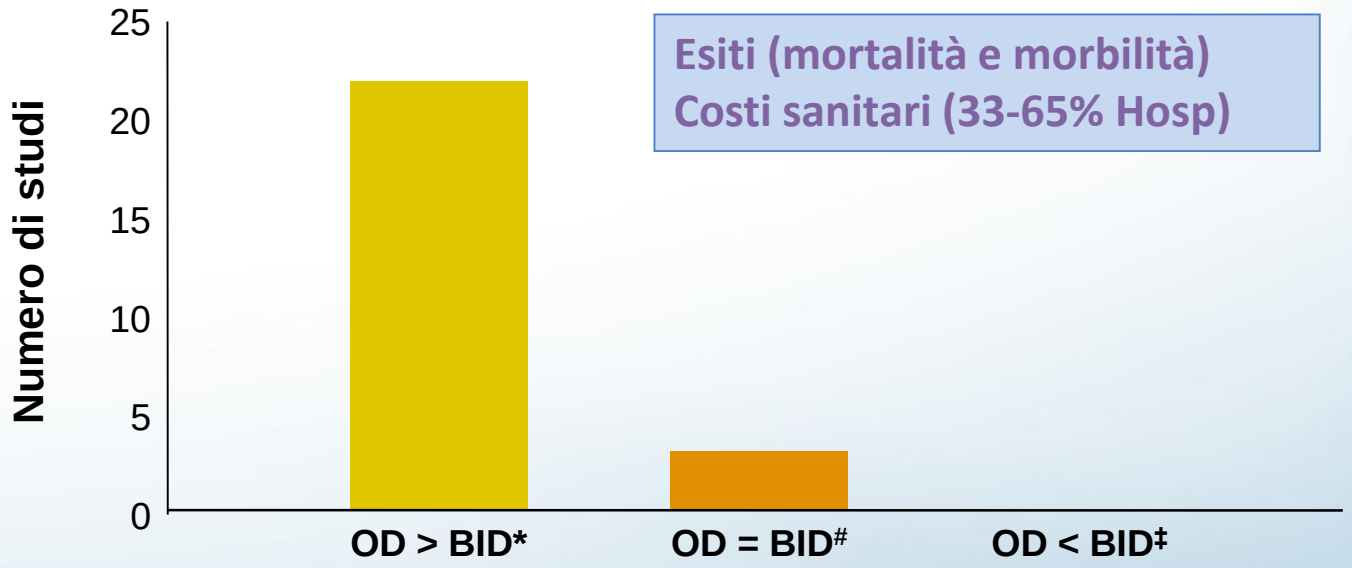
OD vs. BID

- La scelta del dosaggio e del regime posologico risulta cruciale nello sviluppo di un farmaco
- La scelta del dosaggio deve tenere conto di tutti gli elementi che massimizzano l'efficacia, preservando la sicurezza
- Viene selezionato in studi clinici di fase II, non sempre nella stessa popolazione di pazienti a cui poi potrebbe poi essere prescritto
- Deve essere presa in considerazione la comodità del paziente (es. OD) in quanto aumenta l'aderenza e la qualità di vita
- L'**aderenza** al dosaggio selezionato è uno dei fattori più importanti nella differenza fra lo studio clinico e l'utilizzo reale post-marketing del farmaco

La compliance del regime OD rispetto al regime BID è generalmente migliore in condizioni croniche (FANV)

Numero di studi che valutano direttamente la compliance

(10.000 NVAF – pts)



* La *compliance* del paziente (valutata nello studio) con regime OD è significativamente migliore rispetto al regime BID.
# Nessuna differenza significativa nella *compliance* del paziente (valutata nello studio) tra regime OD e BID.
‡ La *compliance* del paziente (valutata nello studio) con regime BID è significativamente migliore rispetto al regime OD.

Ricerca Pub Med, marzo 2001-2011.

La compliance al regime OD vs. BID risulta migliore nei pazienti con FA

Adv Ther (2012) 29(8):675–690.
DOI 10.1007/s12325-012-0040-x

ORIGINAL RESEARCH

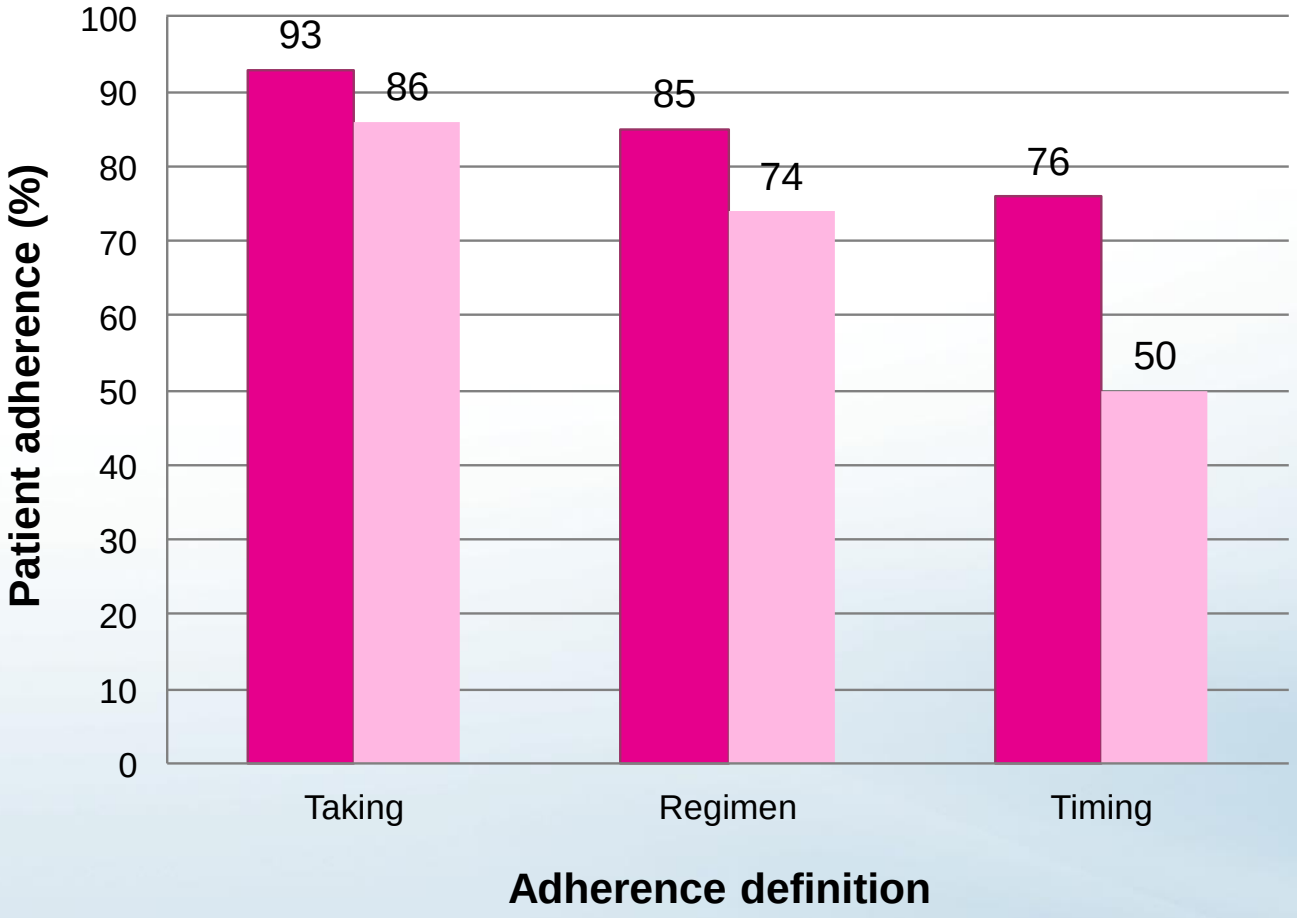
Impact of Daily Dosing Frequency on Adherence to Chronic Medications Among Nonvalvular Atrial Fibrillation Patients

François Laliberté · Winnie W. Nelson · Patrick Lefebvre · Jeff R. Schein · Jonathan Rondeau-Leclaire · Mei Sheng Duh

CONCLUSION

This large population-based study of >10,000 patients, based on real-world data, indicates that nonvalvular AF patients treated with q.d. dosing regimens for chronic medications were associated with approximately a 26% higher likelihood of adherence compared with subjects on b.i.d. regimens. The findings were consistent across two methods of determining medication adherence.

Aderenza al trattamento CV: OD vs. BID



Aderenza valutata mediante 3 misurazioni, in ordine crescente di importanza:

- Assunzione - Numero di aperture del tappo del flacone diviso per il numero di dosi prescritte.
- Regime - Percentuale di giorni in cui è stato assunto un numero appropriato di dosi.
- Tempo - Percentuale di intervalli fra le somministrazioni vicini alla frequenza di somministrazione ottimale

Coleman C.I. *et al.*; Curr Med Res Opin 2012; 28 (5):1–12

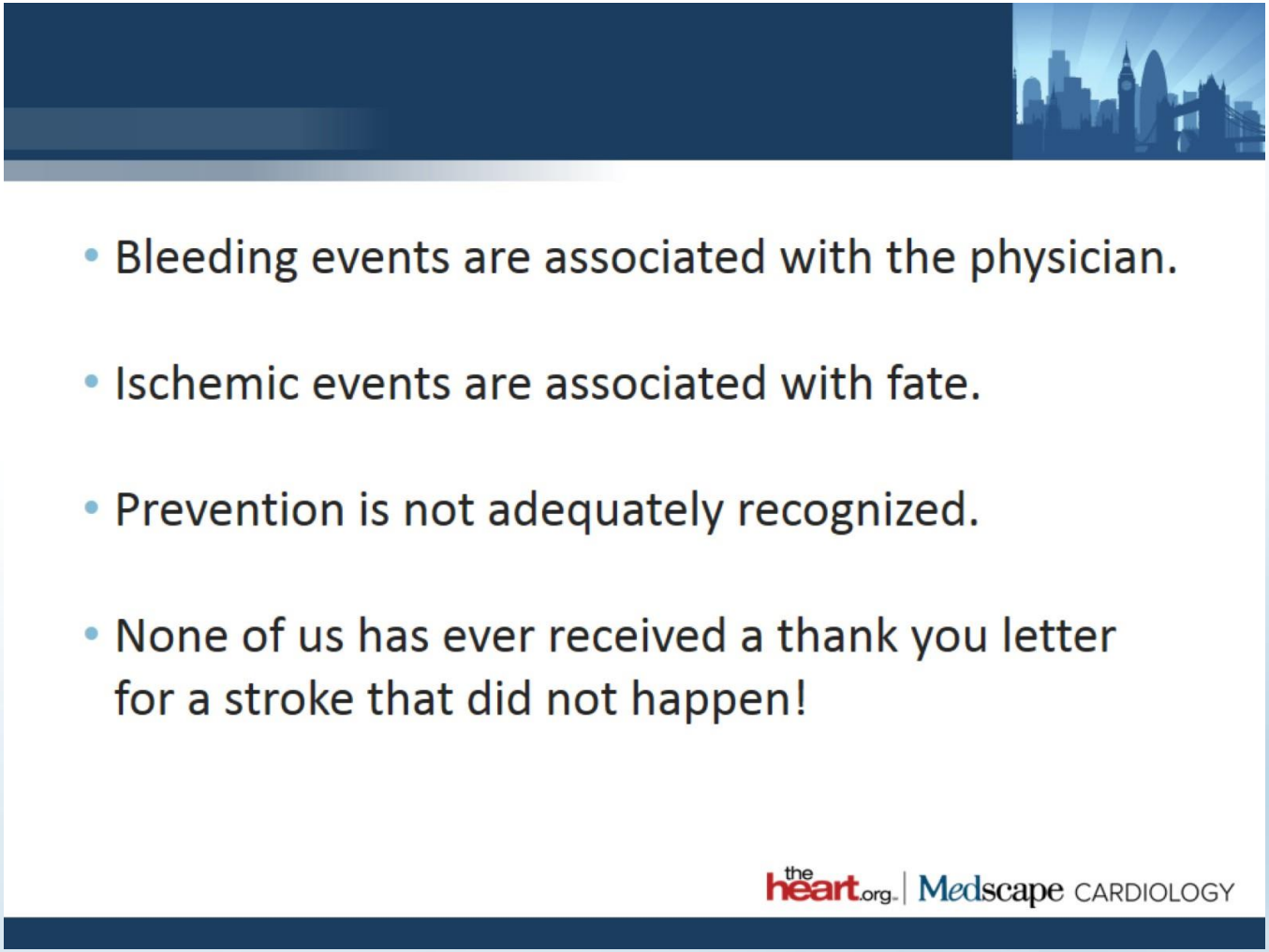
Un trattamento valido deve combinare efficacia, tollerabilità, aderenza e praticità

Registro DRESDEN: alta aderenza alla terapia nella real-life

- 1.665 pazienti registrati
- 967 pazienti hanno assunto **rivaroxaban** per NVAF
  - 51,6% uomini;
  - età media 74,4 anni;
  - *score* CHADS medio 2,4;
  - 62,3% *naïve* agli anticoaugulanti.

- **L'aderenza al trattamento è risultata elevata con il 90,7% dei pazienti che assumevano ancora rivaroxaban dopo 9 mesi**

Come combattere la paura delle emorragie



Il modo migliore è conoscere bene la gestione della TAO e monitorare il paziente

Rischio Emorragie in Real Life (USA)

Rivaroxaban 40mila pazienti

ESC, London sept 2015

3x442)
e corner
ne move

r Bleeding in a Post-Marketing Assessment of 39,052 Nonvalvular Atrial Fibrillation Patients on Rivaroxaban

W. F. Peacock[1], M. Patel[2], CAPT S. Tamayo[3], N. Sicignano[4], K. Hopf [4], Z. Yuan[5]

[1] Baylor College of Medicine, Houston, TX; [2] Duke University Health System and Duke Clinical Research Institute, Durham, NC; [3] Naval Medical Center, Portsmouth, VA; [4] Health ResearchTx, Trevose, PA; [5]Janssen Research and Development, LLC, Titusville, NJ

PURPOSE

To evaluate the incidence of major bleeding (MB) among nonvalvular AF patients on rivaroxaban, in a post-market, real-world clinical setting.

METHODS

U.S. Department of Defense electronic medical records for nearly 10 million patients were queried from January 1, 2013 to December 31, 2014 to identify rivaroxaban users with nonvalvular AF. Major bleeding was identified using a validated algorithm (Cunningham 2011), using inpatient records. Patient demographics, clinical characteristics, bleeding sites, and fatal outcomes were evaluated. Incidence rates were calculated and reported per 100 person-years.

RESULTS

Of 39,052 rivaroxaban users, 970 experienced at least one MB, overall incidence rate of 2.89 per 100 person-years (95% CI 2.71-3.08). The bleeders had higher prevalence of comorbidities than non-bleeders. 51.5% of those who bled received a blood transfusion, and 42.3% were transferred to ICU. For bleeding site, 87.2% were gastrointestinal and 8.1% were intracranial. Within the MB group, 3.6% (35/970) experienced a fatal outcome during hospitalization, fatal outcome rate of 0.10 per 100 person-years (95% CI 0.07-0.15). Of those who died, 26 (74.3%) experienced intracranial hemorrhage, and 9 (25.7%) had gastrointestinal bleeding.

CONCLUSION

In this real-world clinical setting, the rates and pattern of major bleeding among rivaroxaban users with nonvalvular atrial fibrillation were generally consistent with the results reported in the registration trial.

Characteristic	Major Bleed (N=970)	No Major Bleed (N=38,082)
Age, mean (SD), years	78.7 (7.9)	76.0 (9.9)
Male, n (%)	494 (50.9)	21,250 (55.8)
Comorbidities, n (%)		
Hypertension	836 (86.2)	25,667 (67.4)
CHD	514 (53.0)	11,958 (31.4)
Heart Failure	363 (37.4)	7,502 (19.7)
Renal Disease	226 (23.3)	5,827 (15.3)
Diabetes Mellitus	334 (34.4)	10,244 (26.9)
Dementia	85 (8.8)	2,285 (6.0)
Prior Ischemic Stroke	77 (7.9)	1,485 (3.9)
VTE	79 (8.1)	1,904 (5.0)
Mean (SD) CHA_2DS_2-VASc	4.5 (1.5)	3.5 (1.6)
Rivaroxaban Dose, n (%)		
10 mg	36 (3.7)	2,056 (5.4)
15 mg	313 (32.3)	9,330 (24.5)
20 mg	621 (64.0)	26,696 (70.1)

 Declaration of Interest: This study is funded by Janssen Scientific Affairs, LLC, and Bayer Healthcare. Dr. Yuan is a salaried employee at Janssen Research & Development, LLC, who owns stocks/options of Johnson & Johnson. Mr. Sicignano and Ms. Hopf are with Health Research Tx, which has a business relationship with Janssen. Dr. Peacock has research grants from Abbott, Alere, Banyan, Cardiorentis, Portola, Roche, and The Medicines Company; served as a consultant for Alere, BG Medicine, Beckman, Boehringer-Ingelheim, Cardiorentis, Instrument Labs, Janssen, Prevencio, The Medicines Company, and ZS Pharma; and has ownership interests in Comprehensive Research Associates, LLC, and Emergencies in Medicine, LLC. Dr. Patel has research grants from Johnson & Johnson, AstraZeneca, National Heart Lung and Blood Institute, the Agency for Healthcare Research and Quality, and Maquet; consulting interests with Janssen, Bayer, Genzyme, and Merck.

Real Life (Resto del Mondo)
Studio XANTUS

- **Why is "Real World" Evidence Needed Given the Positive Outcomes of Phase III trials?**

- **Phase III studies**
  - **Gold standard for evaluating efficacy and safety against the current standard of care**
  - **Support marketing approval by regulatory authorities**
- **However…**
  - **Strict protocols and inclusion/exclusion criteria may exclude some patients**
    - **Limit translation of results from phase III studies to real world populations**
    - **Event rates, patient characteristics (i.e. co-morbidities), and adherence/persistence may not fully reflect real world settings**
- **Real world studies**
  - **Unselected patient populations typical of those seen in routine clinical practice**
  - **Observational design with little interference in patient management**

Patients were enrolled from June 2012 to December 2013 from 311 centres in Europe and Canada:

Belgium, Canada, Czech Republic, Denmark, France, Germany, Hungary, Ireland, Israel, Moldova, The Netherlands, Norway, Poland, Portugal, Russia, Slovakia, Slovenia, Sweden, Ukraine, UK

XANTUS: Rationale

- **Rivaroxaban approved for the reduction of stroke/SE in patients with NVAF and ≥1 additional stroke risk factor(s)[1]**
  - **ROCKET AF: rivaroxaban was non-inferior to warfarin for the reduction of stroke/SE and provided safety benefits in terms of a significantly reduced risk of ICH and fatal bleeding but an increase in GI bleeds[2]**
- **Safety and effectiveness data for unselected NVAF patients from everyday practice is needed**
- **XANTUS included a diverse range of patients representative of those seen in routine clinical practice[3]**

1. Rivaroxaban SmPC; 2. Patel MR *et al*, *N Engl J Med* 2011;365:883–891;
3. Camm AJ *et al*, *Eur Heart J* 2015; doi: 10.1093/eurheartj/ehv466

XANTUS: Primary and Secondary Outcomes

- **Primary outcomes**
  - **Major bleeding**
  - **All-cause mortality**
  - **Any other AEs**
  - **Any other serious AEs**
- **Secondary outcomes**
  - **Symptomatic thromboembolic events**
  - **Non-major bleeding events**
    - **Any bleeding event that does not meet the criteria for a major haemorrhage**
  - **AEs and serious AEs across risk scores**
  - **AEs and serious AEs in important subgroups**
  - **Other outcomes collected included:**
    - **Patient treatment satisfaction using standardized questionnaires**
    - **Persistence with therapy**
    - **Healthcare resource use**
    - **Details of interventions and how they were managed**
    - **Concomitant medication use**
    - **Reasons for switching/interrupting rivaroxaban therapy**

1. Camm AJ *et al*, *Vasc Health Risk Manag* 2014;10:425–434

XANTUS: Patient Flow

Major events, specifically major bleeding, stroke, SE, TIA and MI, adjudicated centrally by an independent CAC blinded to individual patient data

Screened (N=10,934)

4149 patients excluded*
- Patient decision (n=1222)
- Administrative reason (n=456)
- Availability of drug (n=18)
- Medical guidelines (n=399)
- Price of drug (n=473)
- Medical reasons (n=442)
- Internal hospital guidelines (n=30)
- Type of health insurance (n=183)
- Other (n=1454)

Enrolled (N=6785)

1 patient
- Did not take any rivaroxaban (n=1)

Primary analysis population: defined as all patients who had taken at least one dose of rivaroxaban

Safety population (N=6784)

Rivaroxaban 20 mg od (n=5336)

Rivaroxaban 15 mg od (n=1410)

Another dose (n=35)#

*Reasons for not continuing in the study included, but were not limited to, patient decision, administrative or medical reasons. Some patients could have more than one reason for exclusion; #other dose includes any initial daily rivaroxaban dose besides 15/20 mg od (excluding missing information, n=3)

1. Camm AJ *et al*, *Eur Heart J* 2015; doi: 10.1093/eurheartj/ehv466

XANTUS:

Baseline Demographics – Clinical Characteristics (6.784 pts)

	Rivaroxaban (N=6784)
Age (years)	
Mean ± SD	71.5±10.0
Age <65, n (%)	1478 (21.8)
Age ≥65–≤75, n (%)	2782 (41.0)
Age >75, n (%)	2524 (37.2)
Gender (male): n (%)	4016 (59.2)
Weight (kg): mean ± SD	83.0±17.3
BMI (kg/m^2): mean ± SD	28.3±5.0
BMI >30 kg/m^2, n (%)	1701 (25.1)
AF, n (%)	
First diagnosed	1253 (18.5)
Paroxysmal	2757 (40.6)
Persistent	923 (13.6)
Permanent	1835 (27.0)
Missing	16 (0.2)

	Rivaroxaban (N=6784)
Creatinine clearance, n (%)	
<15 ml/min	20 (0.3)
≥15–<30 ml/min	75 (1.1)
≥30–<50 ml/min	545 (8.0)
≥50–≤80 ml/min	2354 (34.7)
>80 ml/min	1458 (21.5)
Missing	2332 (34.4)
Existing co-morbidities, n (%)	
Hypertension	5065 (74.7)
Diabetes mellitus	1333 (19.6)
Prior stroke/non-CNS SE/TIA	1291 (19.0)
Congestive HF	1265 (18.6)
Prior MI	688 (10.1)
Baseline hospitalization, n (%)	1226 (18.1)

. Camm AJ *et al*, *Eur Heart J* 2015; doi: 10.1093/eurheartj/ehv466

XANTUS:

Baseline Demographics – Prior Antithrombotic Use

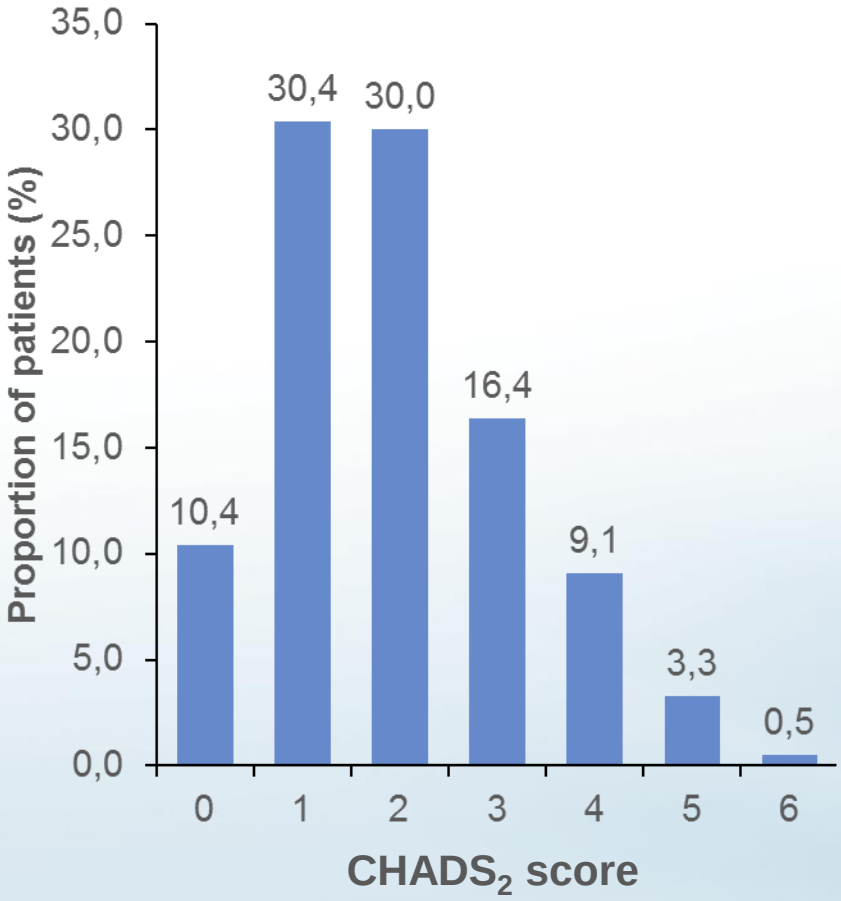
	Rivaroxaban (N=6784)
VKA	
Experienced	3089 (45.5)
Naïve	3695 (54.5)
Prior use of antithrombotics, n (%)	
VKA alone	2767 (40.8)
Direct thrombin inhibitor	208 (3.1)
Acetylsalicylic acid (excluding dual antiplatelet therapy)	1224 (18.0)
Dual antiplatelet therapy	68 (1.0)
Factor Xa inhibitor (excluding rivaroxaban)	10 (0.1)
Heparin group	217 (3.2)
Other	55 (0.8)
Multiple	410 (6.0)

1. Camm AJ *et al*, *Eur Heart J* 2015; doi: 10.1093/eurheartj/ehv466

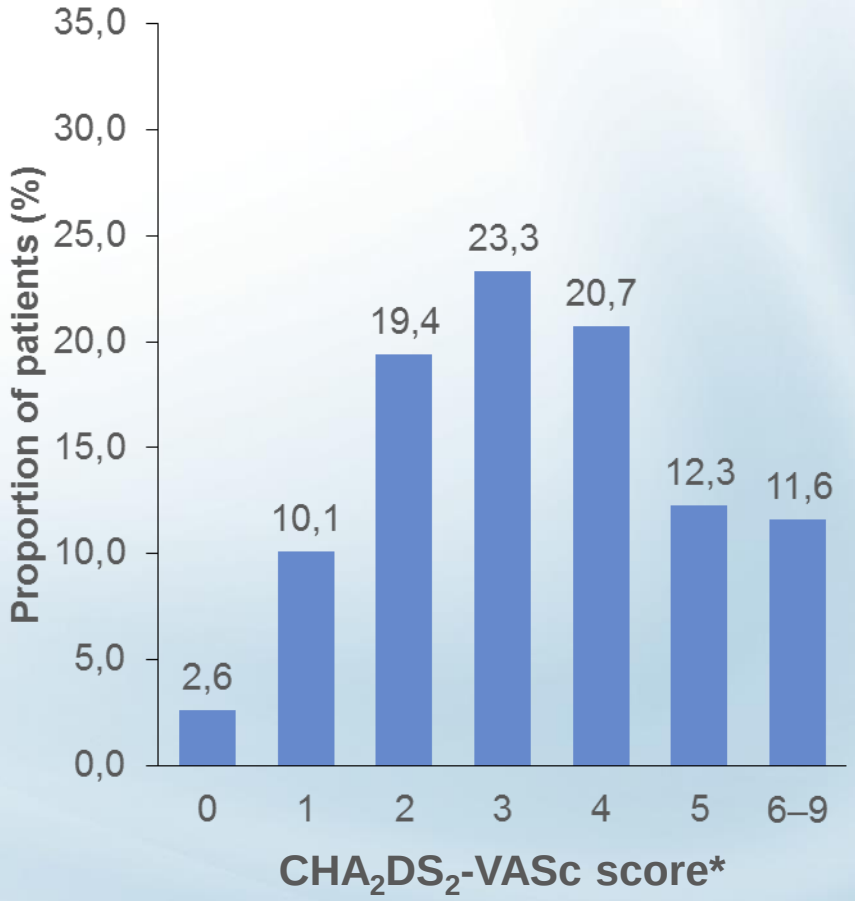
XANTUS:

Baseline Demographics – Distribution of Stroke Risk Factors

Mean score±SD = 2.0±1.3



Mean score±SD = 3.4±1.7

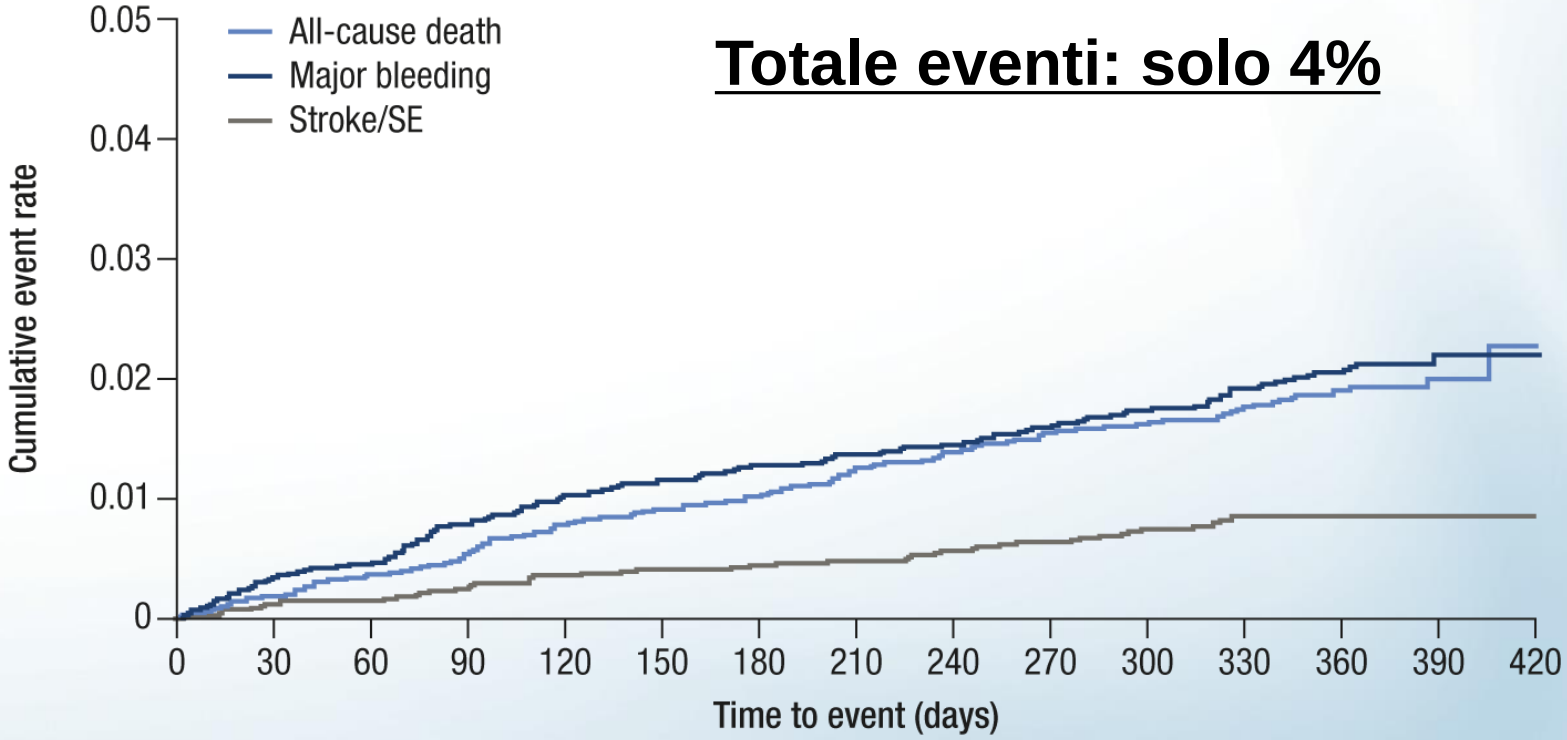


*3 patients had missing CHA_2DS_2-VASc scores

1. Camm AJ *et al*, *Eur Heart J* 2015; doi: 10.1093/eurheartj/ehv466

XANTUS:

Cumulative Rates (Kaplan–Meier) for Treatment-Emergent Primary Outcomes



Totale eventi: solo 4%

Patients at risk:

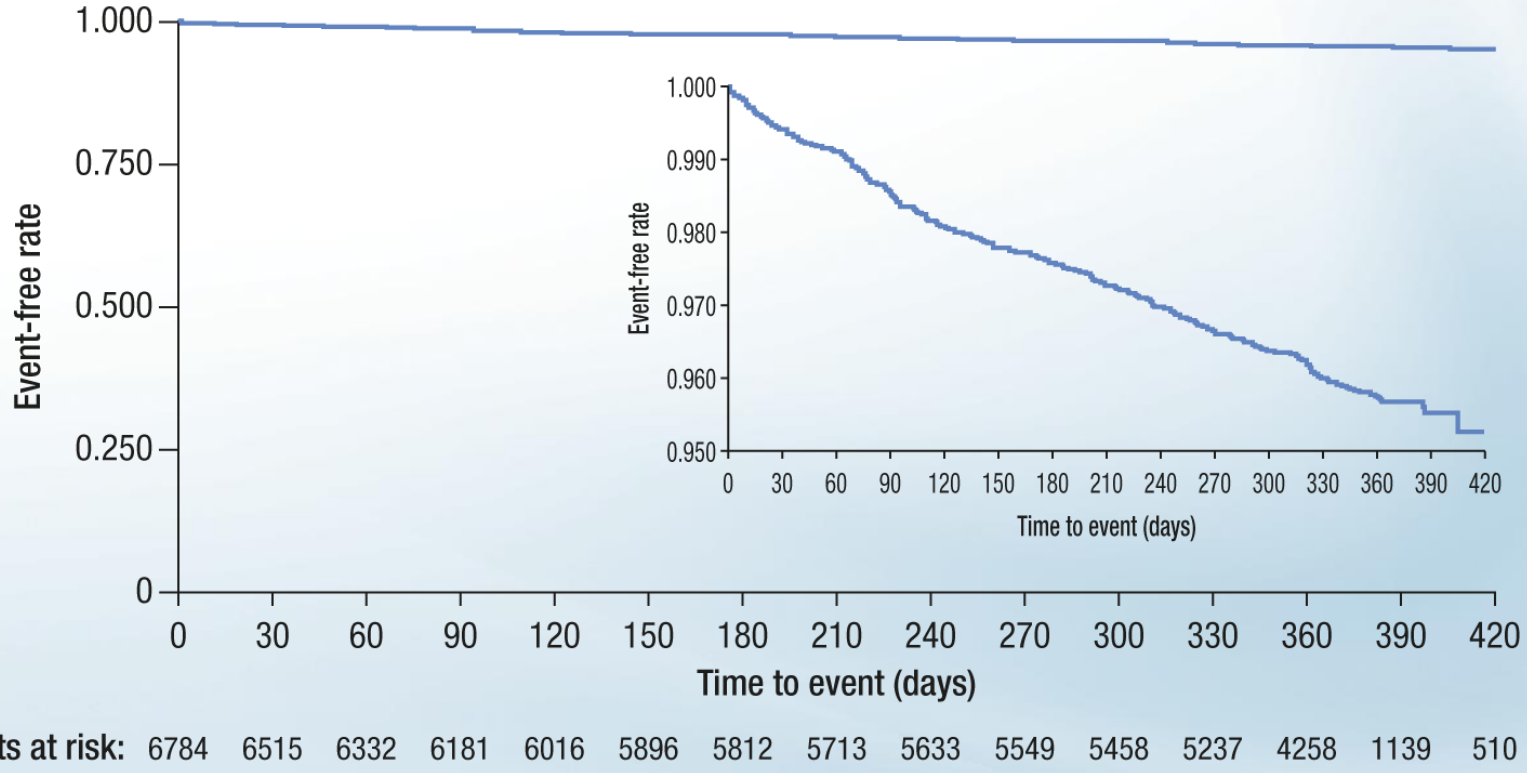
All-cause death	6784	6530	6349	6211	6054	5938	5853	5754	5679	5597	5512	5295	4307	1153	514
Major bleeding	6784	6522	6340	6197	6033	5909	5824	5726	5649	5559	5471	5256	4273	1144	513
Stroke/SE	6784	6532	6353	6216	6053	5933	5848	5752	5674	5587	5499	5282	4296	1149	513

1. Camm AJ *et al*, *Eur Heart J* 2015; doi: 10.1093/eurheartj/ehv466

XANTUS:

Event-Free Rate (Kaplan–Meier) for Treatment-Emergent Primary Outcomes

- In total, 6522 (96.1%) patients did not experience any of the outcomes of treatment-emergent all-cause death, major bleeding or stroke/SE



1. Camm AJ *et al*, *Eur Heart J* 2015; doi: 10.1093/eurheartj/ehv466

XANTUS:

Treatment-Emergent Bleeding Events

	Rivaroxaban (N=6784)	
	Incidence proportion, n (%)	Incidence rate, %/year (95% CI)*
Major bleeding	**128 (1.9)**	**2.1 (1.8–2.5)**
Fatal	12 (0.2)	0.2 (0.1–0.3)
Critical organ bleeding	43 (0.6)	0.7 (0.5–0.9)
Intracranial haemorrhage	26 (0.4)	0.4 (0.3–0.6)
Mucosal bleeding[#]	60 (0.9)	1.0 (0.7–1.3)
Gastrointestinal	52 (0.8)	0.9 (0.6–1.1)
Haemoglobin decrease ≥2 g/dl[‡]	52 (0.8)	0.9 (0.6–1.1)
Transfusion of ≥2 units of packed RBCs or whole blood[‡]	53 (0.8)	0.9 (0.6–1.1)
Non-major bleeding events	**878 (12.9)**	**15.4 (14.4–16.5)**

Patients could experience multiple bleeding events in different categories. *Events per 100 patient-years; [#]numbers are for major mucosal and gastrointestinal bleeding events; [‡]representing major bleeding

1. Camm AJ *et al*, *Eur Heart J* 2015; doi: 10.1093/eurheartj/ehv466

XANTUS:

Treatment-Emergent Thromboembolic Events and All-Cause Death

	Rivaroxaban (N=6784)	
	Incidence proportion, n (%)	Incidence rate, %/year (95% CI)*
All-cause death	118 (1.7)	1.9 (1.6–2.3)
Thromboembolic events (stroke, SE, TIA, and MI)	108 (1.6)	1.8 (1.5–2.1)
Stroke/SE	51 (0.8)	0.8 (0.6–1.1)
Stroke	43 (0.6)	0.7 (0.5–0.9)
Primary haemorrhagic	11 (0.2)	
Primary ischaemic	32 (0.5)	
SE	8 (0.1)	0.1 (0.1–0.3)
TIA	32 (0.5)	0.5 (0.4–0.7)
MI	27 (0.4)	0.4 (0.3–0.6)

*Events per 100 patient-years

1. Camm AJ *et al*, *Eur Heart J* 2015; doi: 10.1093/eurheartj/ehv466

XANTUS:
Adjudicated Causes of Death

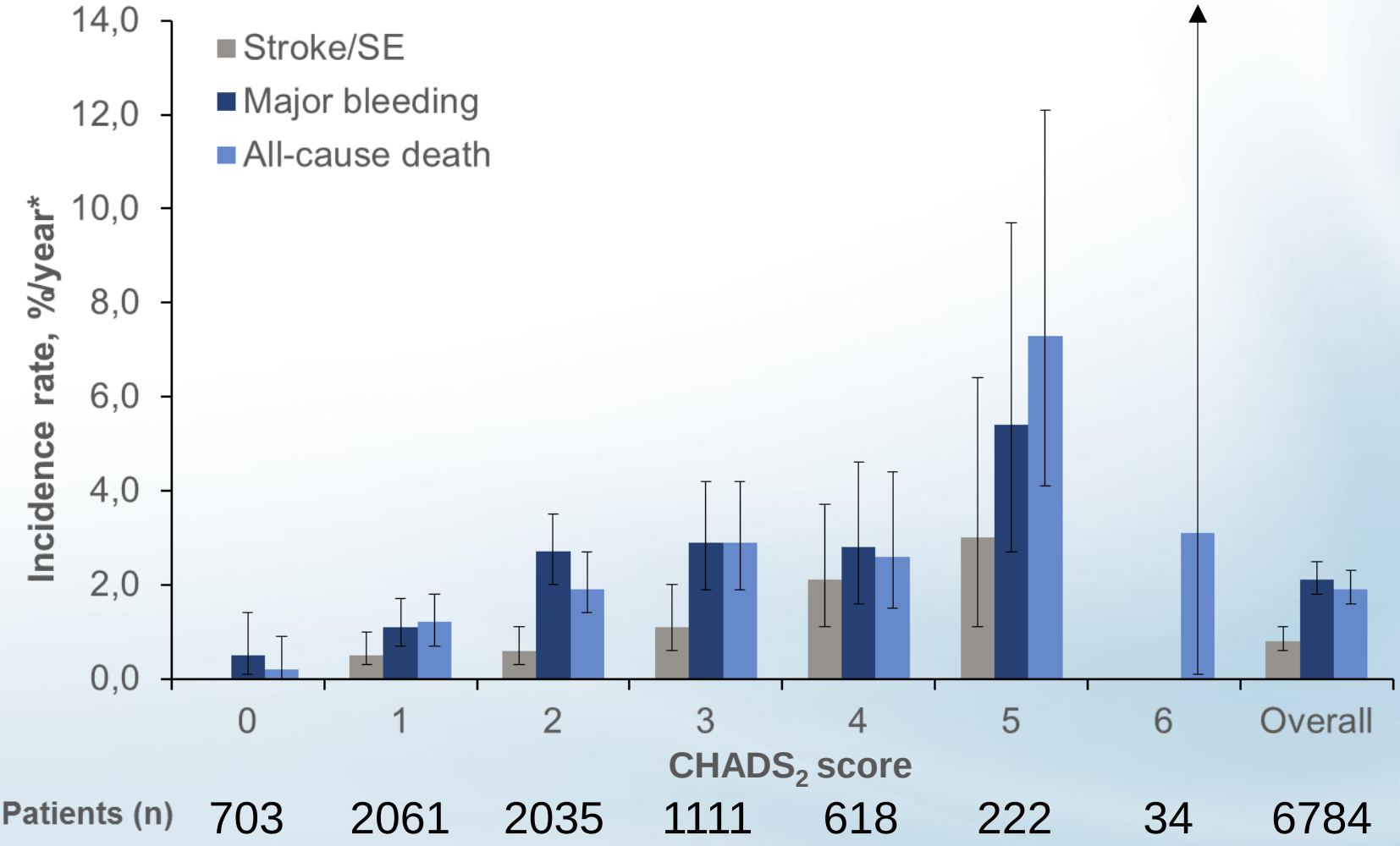
	Number of patients (N=118*), n (%)
Cardiovascular	**49 (41.5)**
Cardiac decompensation, heart failure	24 (20.3)
Sudden or unwitnessed death	14 (11.9)
MI	6 (5.1)
Non-haemorrhagic stroke	4 (3.4)
Dysrhythmia	1 (0.8)
Cancer	**23 (19.5)**
Other	**16 (13.6)**
Bleeding	**12 (10.2)**
Extracranial haemorrhage	5 (4.2)
Intracranial bleeding	7 (5.9)
Infectious disease	**10 (8.5)**
Unexplained	**9 (7.6)**

*Multiple reasons were recorded for the cause of treatment-emergent adjudicated death of some patients

Camm AJ *et al*, *Eur Heart J* 2015; doi: 10.1093/eurheartj/ehv466

XANTUS:

Incident Rate for Treatment-Emergent Stroke/SE, Major Bleeding and All-Cause Death by $CHADS_2$ Score

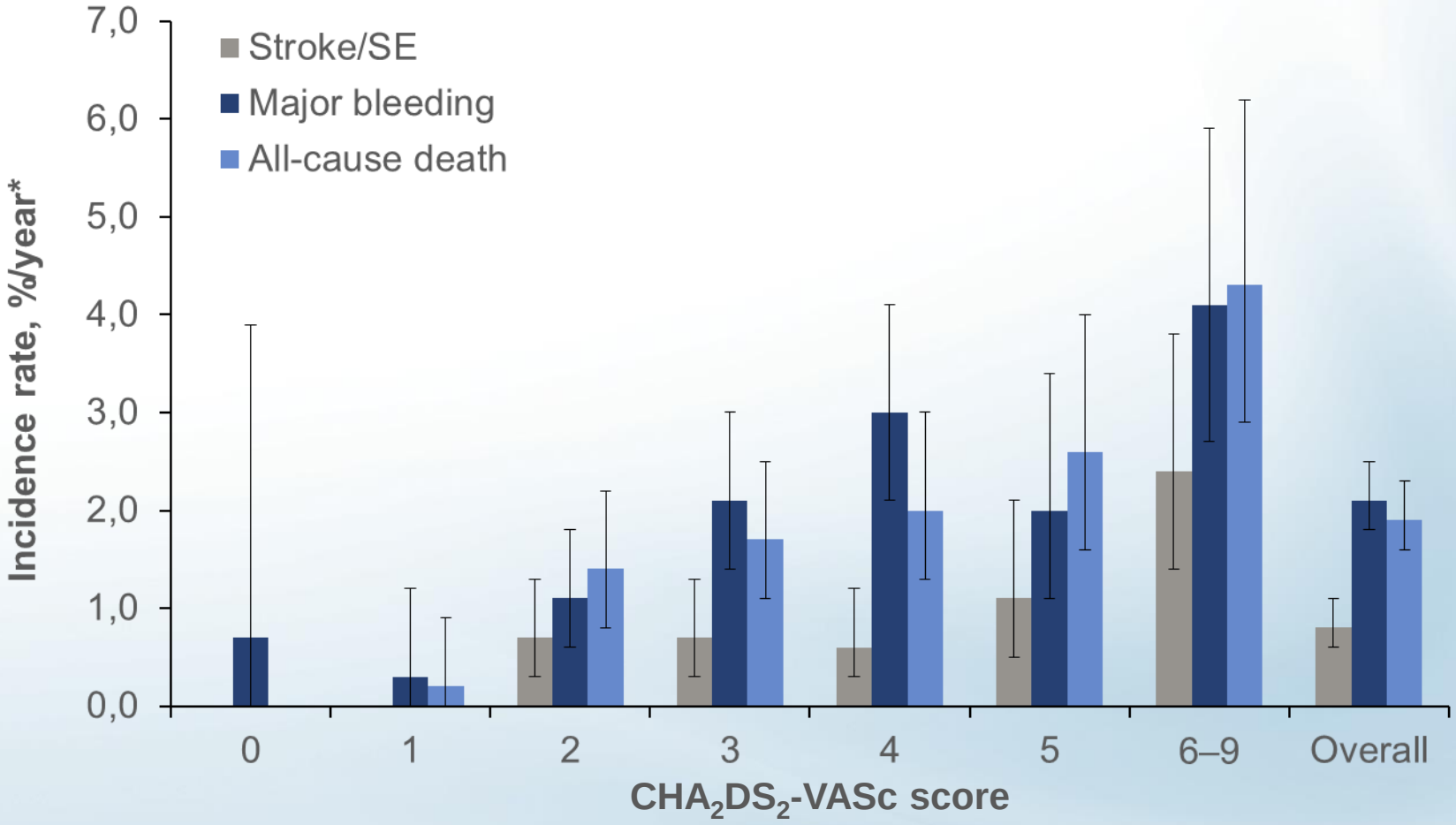


Events were centrically adjudicated *Events per 100 patient-years

1. Camm AJ *et al*, *Eur Heart J* 2015; doi: 10.1093/eurheartj/ehv466;

XANTUS:

Incident Rate for Treatment-Emergent Stroke/SE, Major Bleeding and All-Cause Death by CHA_2DS_2-VASc Score



Events were centrically adjudicated *Events per 100 patient-years

1. Camm AJ *et al*, *Eur Heart J* 2015; doi: 10.1093/eurheartj/ehv466;

XANTUS:
Treatment Persistence and Patient Satisfaction

- Persistence with rivaroxaban in XANTUS was 80% at 1 year
- Over 75% of patients were ‘very satisfied/satisfied’ with their treatment

1. Camm AJ *et al*, *Eur Heart J* 2015; doi: 10.1093/eurheartj/ehv466

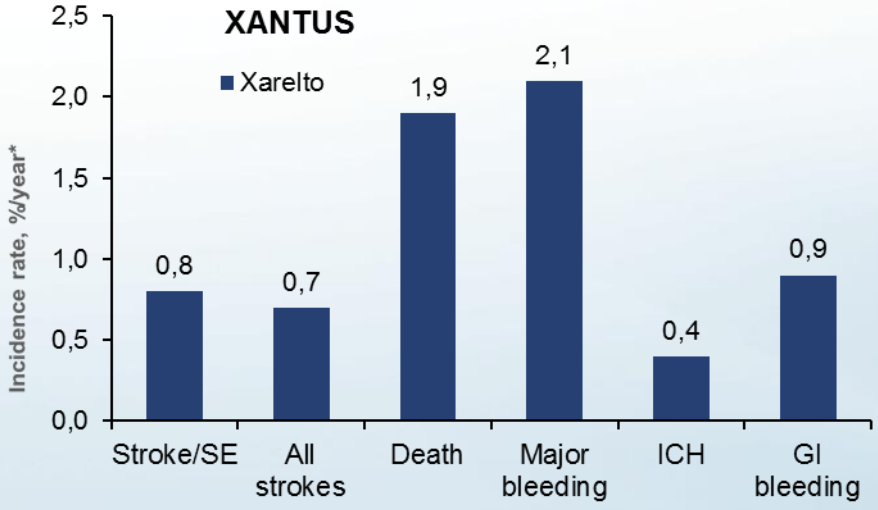
XANTUS: Management of Major Bleeding

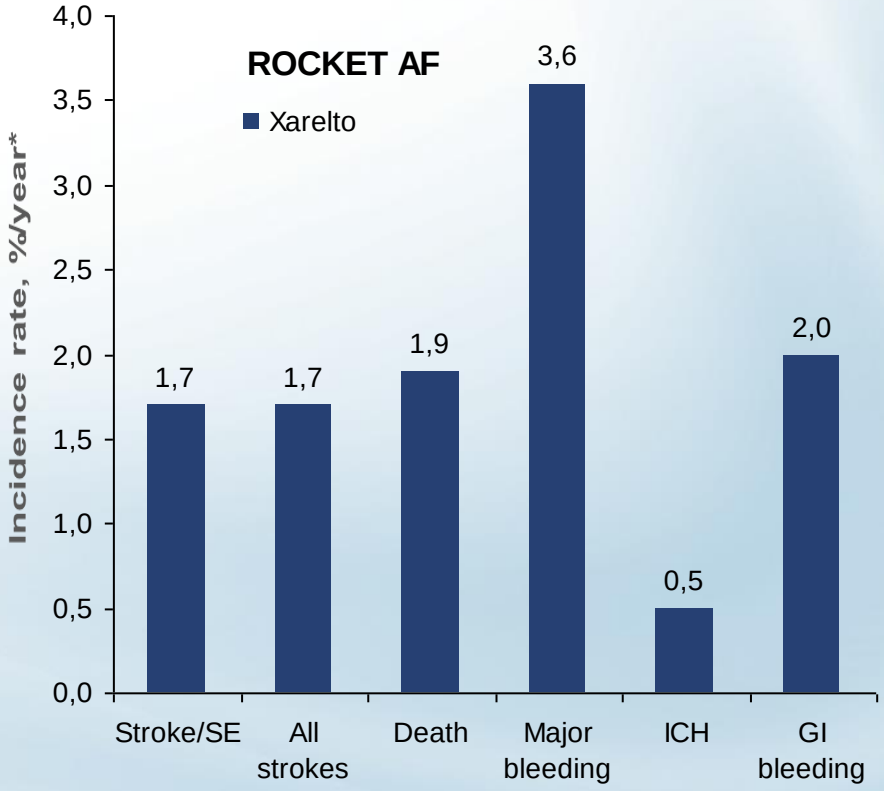
- Major bleeding occurred in 1.9% of patients (n=128) [1]
- Major bleeding was mostly treated using conservative methods[1]
  - 0.8% of patients (n=53) received transfusions of ≥2 units of packed RBCs or whole blood
- Throughout the study use of non-specific reversal agents – such as prothrombin complex concentrate (PCC) - was low[1]
  - Use of PCC documented in two patients
  - Use of tranexamic acid documented in three patients
  - Use of etamsylate documented in one patient
- These findings are in line with outcomes from ROCKET AF [2] and the Dresden NOAC Registry[3]

1. Camm AJ *et al*, *Eur Heart J* 2015; doi: 10.1093/eurheartj/ehv466; 2. Piccini JP *et al, Eur Heart J* 2014; 35(28):1873-80;
3. Beyer-Westendorf J *et al, Blood* 2014; 124(6):955-62

Confronto RCT Study-Real World study

	$CHADS_2$	Prior stroke#
ROCKET AF[1]	3.5	55%
XANTUS[2]	2.0	19%





#Includes prior stroke, SE or TIA; *Events per 100 patient-years

1. Patel MR *et al, N Engl J Med* 2011;365:883–891; 2. Camm AJ *et al*, *Eur Heart J* 2015; doi: 10.1093/eurheartj/ehv466

XANTUS:
Module Summary

- XANTUS is the first large, international prospective study to describe rivaroxaban use in a broad patient population with NVAF
  - Patients were at lower overall risk than in the phase III ROCKET AF trial
- Over 96% patients receiving rivaroxaban did not experience any of the outcomes of stroke/SE, treatment-emergent major bleeding or all-cause death
- In XANTUS, rivaroxaban demonstrated low rates of stroke/SE and major bleeding, including intracranial and GI bleeding
  - Incidences of these outcomes generally increased with higher stroke risk scores
  - Major bleeding was mostly treated conservatively; reversal agents were rarely used
- Treatment persistence and patient satisfaction were high
  - 80% of patients remained on rivaroxaban
  - 75% reported they were satisfied with their treatment at 1 year

1. Camm AJ *et al*, *Eur Heart J* 2015; doi: 10.1093/eurheartj/ehv466

Rischio emorragico negli studi dei NAO

non crediamo all'enfasi del marketing aziendale!

Take-home Message

- **Il rischio emorragico dipende più dal fenotipo del paziente (rischio HAS-BLED, es, anziani fragili, peso inf a 60Kg, insuff epatica, ecc) che dal tipo di NAO (apixaban rivaroxaban o dabigatran).**
- **Il confronto andrebbe fatto "head by head" tra i NAO e non in studi diversi con pazienti diversi e diversi CHADS-HASBLED.**
- **Finora non ci sono studi in tal senso!!!**
- **Il rischio si riduce significativamente se si valuta e monitora il paziente attentamente correggendo ove possibili i suoi fattori di rischio correlati**
- **Monitorare la funzione renale durante le terapie dei NAO: specie se si parte da e-GFR < 60 (indipendentemente se siamo con pazienti in apixaban edoxaban o dabigatran e a qualsiasi dosaggio anche basso)**
- **Considerazioni di buon senso da cardiologo esperto, ancora non esiste letteratura scientifica a riguardo data la tempistica breve dell'esperienza clinica nel mondo 1-2 anni e nessun studio RCT ad hoc….**

Attenzioni particolari

- **Motivare il paziente e familiari** ***all'assunzione continua*** **per evitare l'ictus**
  terapia"nuova": sì senza monitoraggio! ma non è come l'antipertensivo o la statina!
  - materiale illustrativo, tesserino personale
  - blister marcati con calendario, controllo assunzioni

- **Alleanza terapeutica medico-paziente**
  - sono pazienti delicati, con controlli periodici, oggi a cura prevalentemente dello specialista prescrittore poi del MMG, anche prescrittore:
  ogni 6 o 3 mesi con creatinina clearance (dosi!!) emocromo transaminasi

  – **Problema dell'ADERENZA TERAPEUTICA**
  La OD aumenta l'aderenza del 25% rispetto alla BID.

  – **I sanguinamenti minori:**
  non ridurre o sospendere la dose privando il paziente dell'importante effetto tromboprofilattico del farmaco ma valutare attentamente il caso
  (non sono predittivi di sanguinamenti maggiori per-sé)

Assorbimento e metabolismo dei NAO

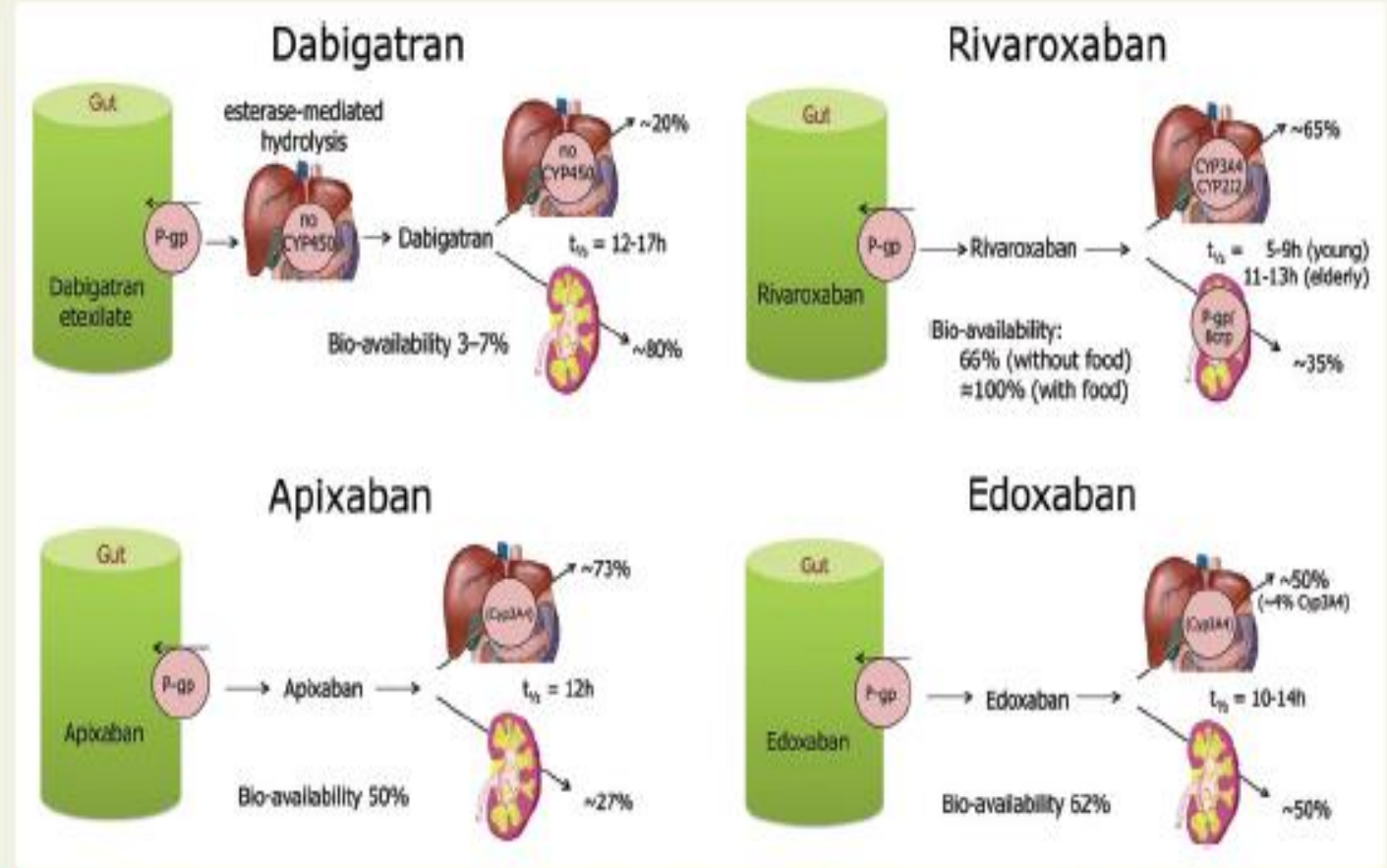


Figure 3 Absorption and metabolism of the different new anticoagulant drugs. There are interaction possibilities at the level of absorption or first transformation, and at the level of metabilization and excretion. See also *Table 5* for the size of the interactions based on these schemes.

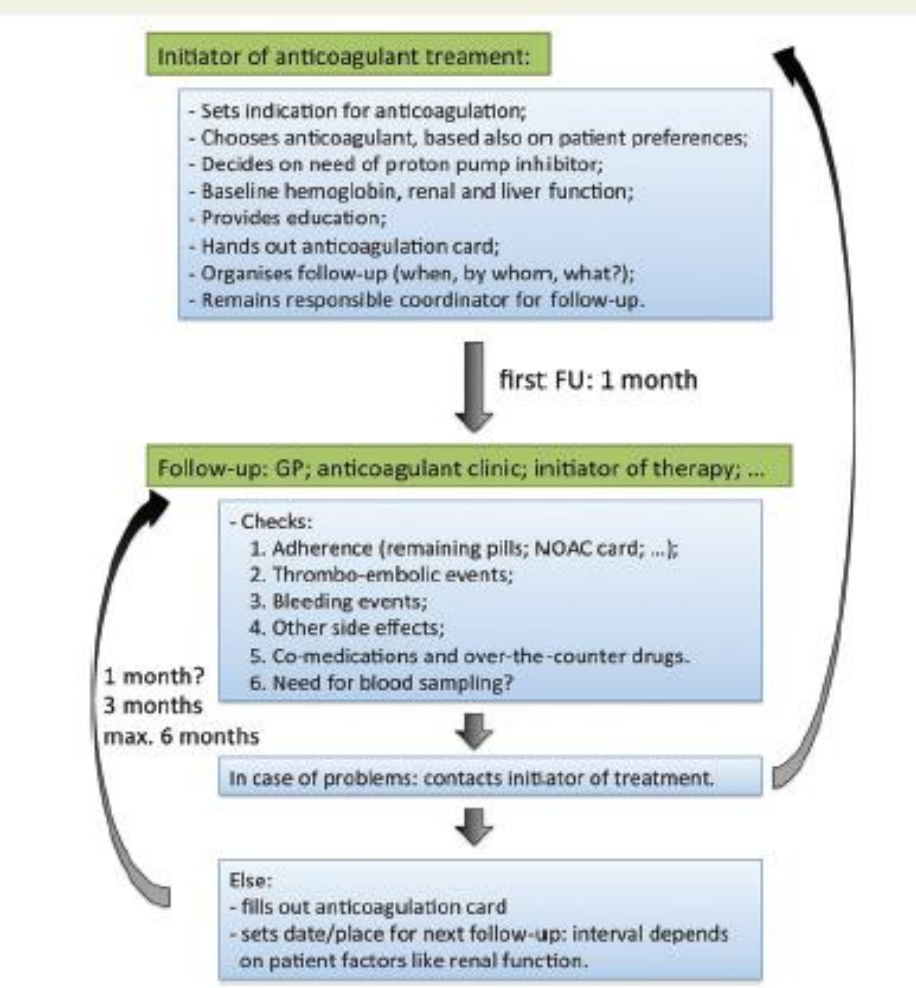
Valvulopatie e NAO

Table 1 Valvular indications and contraindications for NOAC therapy in AF 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)	
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.[8]

FU in terapia con NAO



Update Out Now!

Europace
doi:10.1093/europace/euv309

EHRA PRACTICAL GUIDE

Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation

Hein Heidbuchel[1]*, Peter Verhamme[2], Marco Alings[3], Matthias Antz[4], Hans-Christoph Diener[5], Werner Hacke[6], Jonas Oldgren[7], Peter Sinnaeve[2], A. John Camm[8], and Paulus Kirchhof[9,10]

EUROPEAN Heart Rhythm ASSOCIATION
A Registered Branch of the ESC

	via	Dabigatran	Apixaban	Edoxaban*	Rivaroxaban
Antiarrhythmic drugs					
Amiodarone	Moderate P-gp competition	+12-60%	no PK data	+40%	minor effect (caution if CrCl 15-50 ml/min)
Digoxin	P-gp competition	no effect	no data yet	no effect	no effect
Diltiazem	P-gp competition and weak CYP3A4 inhibition	no effect	+40%	no data yet	minor effect (caution if CrCl 15-50 ml/min)
Dronedarone	P-gp and CYP3A4 inhibitor	+70-100% (US: 2 x 75 mg if CrCl 30-50 ml/min)	no PKor PD data: caution	+85% (Reduce NOAC dose by 50%)	Moderate effect but no PK or PD data: caution and try to avoid
Quinidine	P-gp competition	+53%	no data yet	+77% (No dose reduction required by label)	Extent of increase unknown
Verapamil	P-gp competition (and weak CYP3A4 inhibition)	+12-180% (reduce NOAC dose and take simultaneously)	no PK data	+53% (SR) (No dose reduction required by label)	minor effect (use with caution if CrCl 15-50 ml/min)
Other cardiovascular drugs					
Atorvastatin	P-gp competition and CYP3A4 inhibition	+18%	no data yet	no effect	no effect

Heidbuchel H, et al. *Europace*. 2015 Aug 31. [Epub ahead of print], by permission of Oxford University Press.

Esami di controllo in corso di NAO

Table 4 Interpretation of coagulation assays in patients treated with different NOACs and range of values at trough (P5–P95) in patients with normal function and the standard dose, as measured in clinical trials

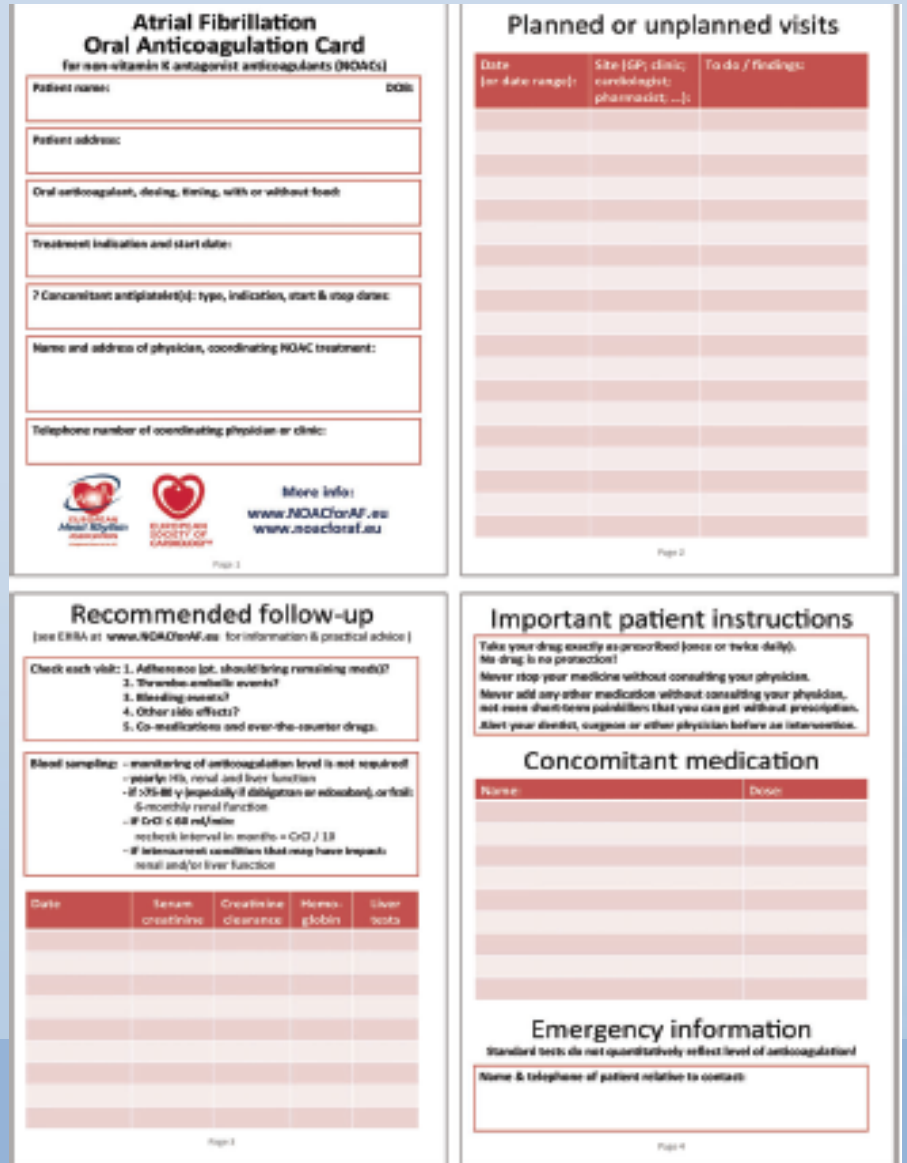
	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Plasma peak level	2 h after ingestion	1–4 h after ingestion	1–2 h after ingestion	2–4 h after ingestion
Plasma trough level	12 h after ingestion	12 h after ingestion	24 h after ingestion[36]	24 h after ingestion
PT	Cannot be used	Can be prolonged but no known relation with bleeding risk[37]	Prolonged but variable and no known relation with bleeding risk[36,38] Range at trough: NA	Prolonged but no known relation with bleeding risk Range at trough: 12–26 s with Neoplastin Plus as reagent; local calibration required
INR	Cannot be used	Cannot be used	Cannot be used	Cannot be used
aPTT	Range (P10–P90) at trough D150: 40.3–76.4 s Range (P10–P90) at trough D110: 37.5–60.9 s At trough: >2× ULN may be associated with excess bleeding risk[39]	Cannot be used	Prolonged but no known relation with bleeding risk[36]	Cannot be used
dTT	No data from RE-LY trial on range of values At trough: >200 ng/mL ≥65 ≤ may be associated with excess bleeding risk[39,40]	Cannot be used	Cannot be used[41]	Cannot be used
Anti-FXa chromogenic assays	Not applicable	Quantitative; no data on threshold values for bleeding or thrombosis Range at trough: 1.4–4.8 IU/mL	Quantitative[41]; no data on threshold values for bleeding or thrombosis Range at trough: 0.05–3.57 IU/mL[a]	Quantitative; no data on threshold values for bleeding or thrombosis Range at trough: 6–239 μg/L
ECT	Range (P10–P90) at trough D150: 44.3–103 Range (P10–P90) at trough D110: 40.4–84.6 At trough: ≥3× ULN: excess bleeding risk[39]	Not affected[37]	Not affected	Not affected
ACT	Rather flat dose response. No investigation on its use. Limited utility	No data. Cannot be used	No data. Cannot be used	Minor effect. Cannot be used

Routine monitoring is not required. Assays need cautious interpretation for clinical use in special circumstances, as discussed in the text.

PT, prothrombin time; aPTT, activated partial thromboplastin time; dTT, diluted thrombin time; ECT, ecarin clotting time; INR, international normalized ratio; ACT: activated clotting time; ULN, upper limit of normal.

[a](P2.5–P97.5) for edoxaban.

Carta al Paziente in cura con NAO



Atrial Fibrillation Oral Anticoagulation Card

For non-vitamin K antagonist anticoagulants (NOACs)

Patient name: DOB:

Patient address:

Oral anticoagulant, dosing, timing, with or without food:

Treatment indication and start date:

? Concomitant antiplatelet(s): type, indication, start & stop dates:

Name and address of physician, coordinating NOAC treatment:

Telephone number of coordinating physician or clinic:

More info:
www.NOACforAF.eu
www.noacforaf.eu

Planned or unplanned visits

Date (or date range):	Site (GP; clinic; cardiologist; pharmacist; ...):	To do / findings:

Recommended follow-up

(see ESRA at www.NOACforAF.eu for information & practical advice)

Check each visit: 1. Adherence (pt. should bring remaining meds)?
2. Thrombo-embolic events?
3. Bleeding events?
4. Other side effects?
5. Co-medications and over-the-counter drugs.

Blood sampling: – monitoring of anticoagulation level is not required!
– yearly: Hb, renal and liver function
– if >75-80 y (especially if dabigatran or edoxaban), or frail: 6-monthly renal function
– if CrCl < 60 ml/min: recheck interval in months = CrCl / 10
– if intercurrent condition that may have impact: renal and/or liver function

Date	Serum creatinine	Creatinine clearance	Haemo-globin	Liver tests

Important patient instructions

Take your drug exactly as prescribed (once or twice daily).
No drug is no protection!

Never stop your medicine without consulting your physician.

Never add any other medication without consulting your physician, not even short-term painkillers that you can get without prescription.

Alert your dentist, surgeon or other physician before an intervention.

Concomitant medication

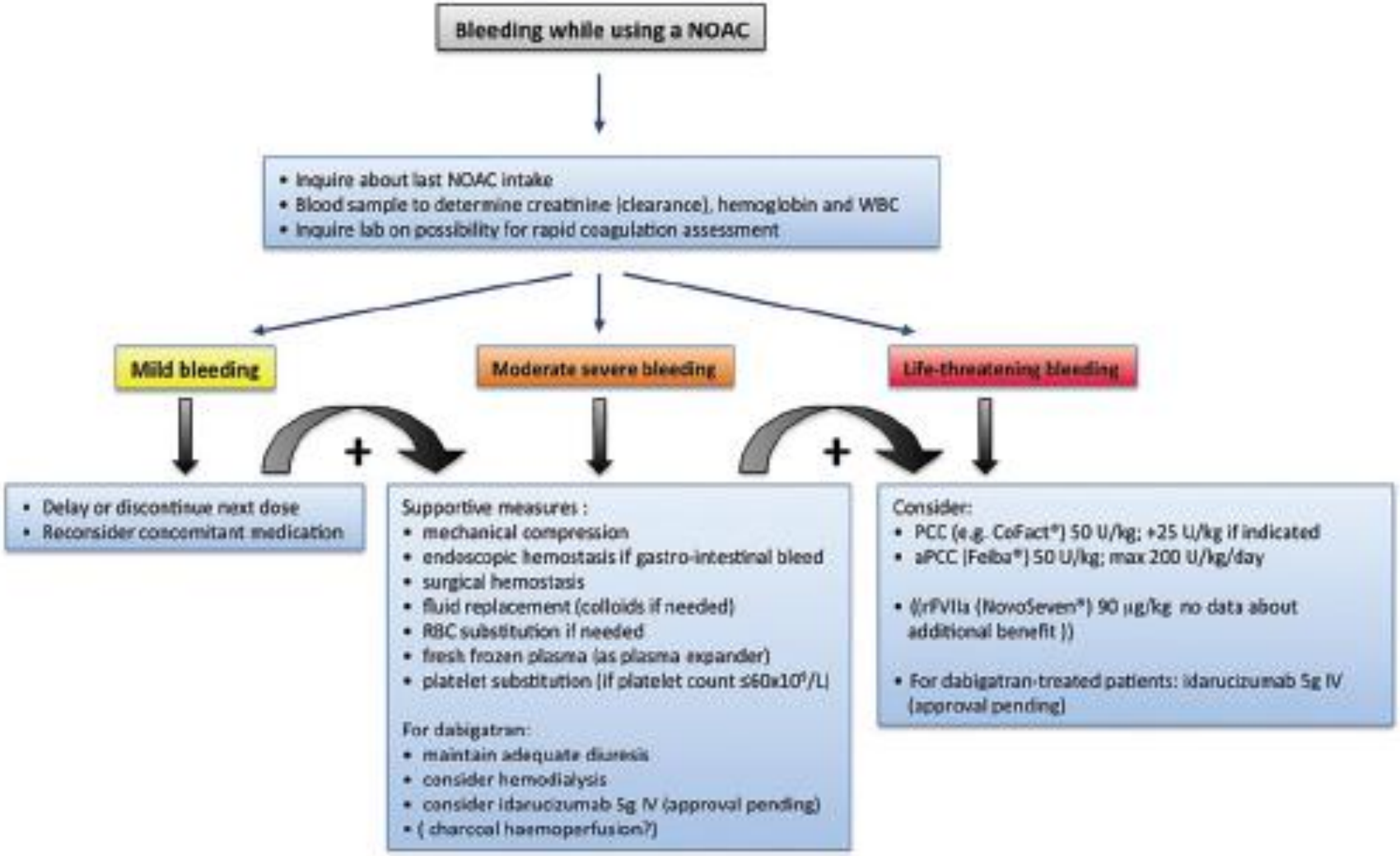
Name:	Dose:

Emergency information

Standard tests do not quantitatively reflect level of anticoagulation!

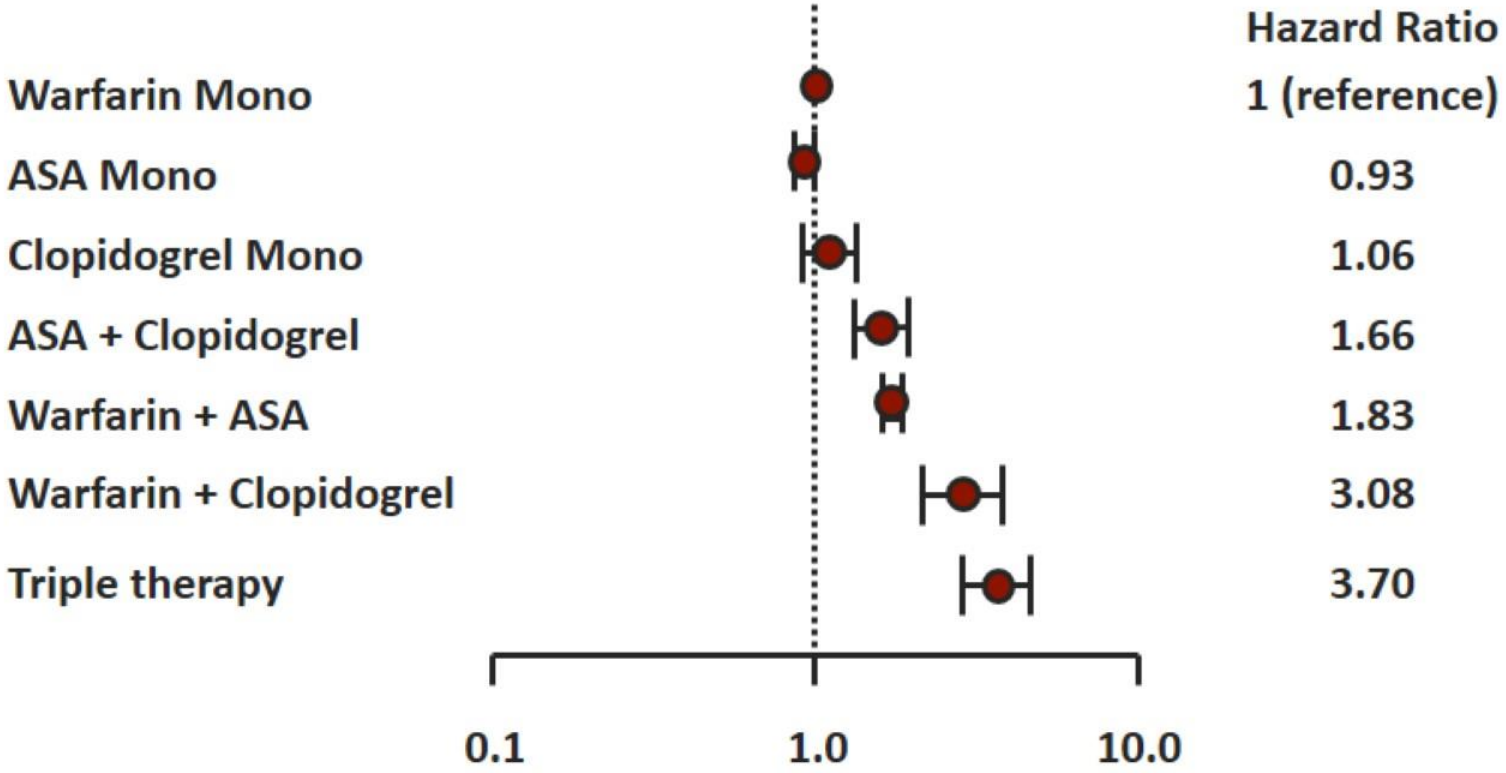
Name & telephone of patient relative to contact:

Gestione emorragie



Denmark Triple – Bleeding

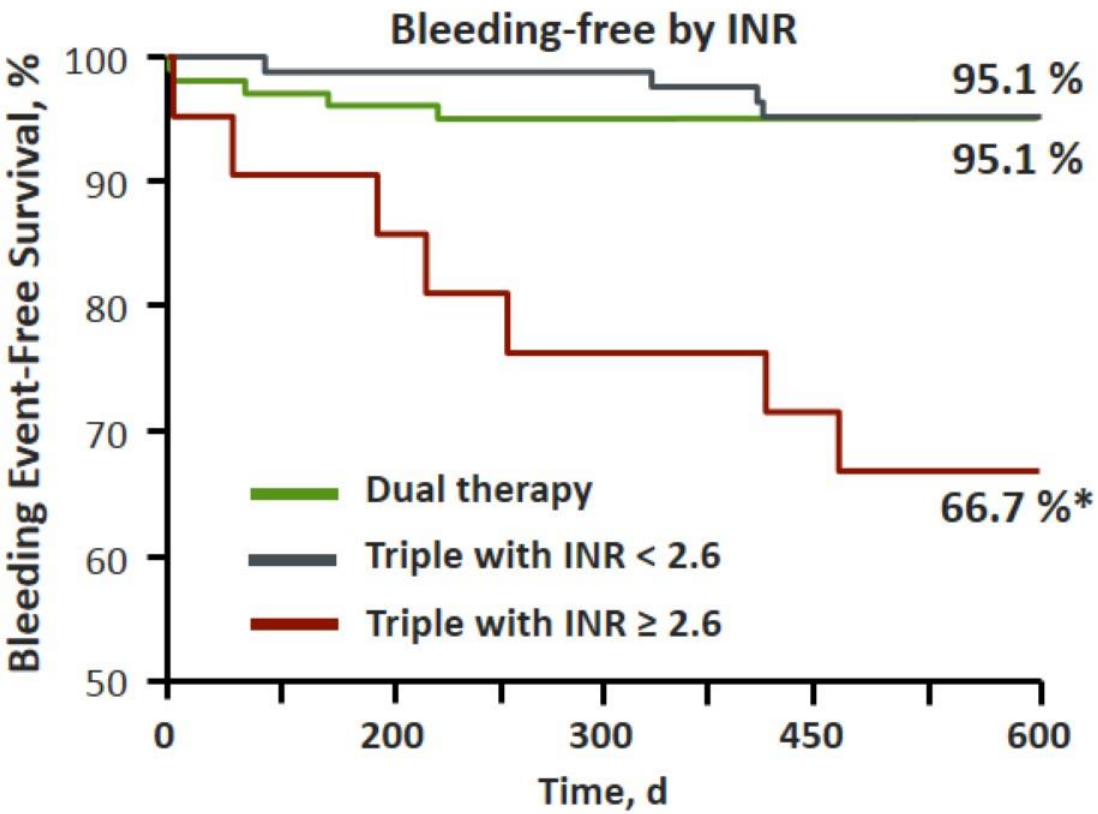
Danish cohort study: all patients with AF discharged from hospital 1997-2006 with ≥ 1 prescription of warfarin, aspirin, clopidogrel, or a combination, n = 82,854, mean follow-up 3.3 years. Bleeding risk according to antithrombotic therapy.

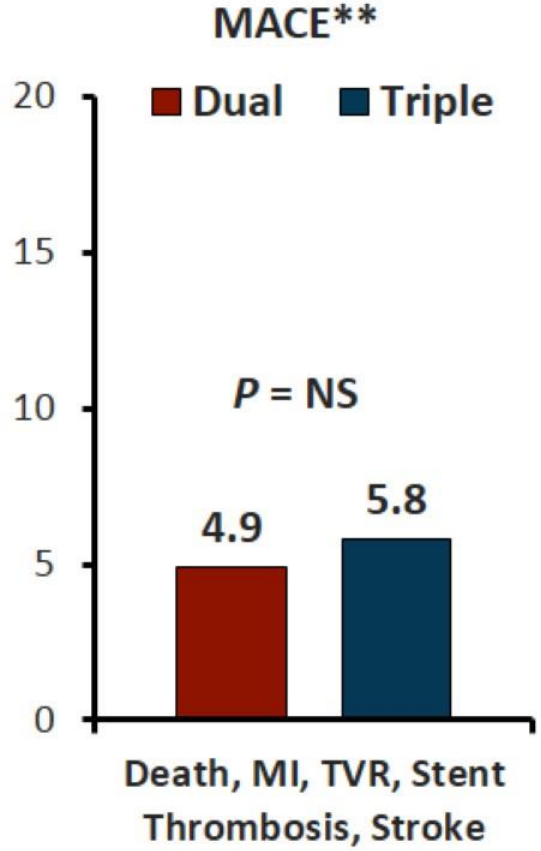


Hansen ML, et al. *Arch Int Med.* 2010;170:1433-1441.

Italy/Florida Triple

4 centers: 102 pts with consecutive stent with ASA + clopidogrel + warfarin (66.6% AF, 17.6% LV thrombus, mean 158 d of triple therapy), 102 matched controls with ASA + clopidogrel





*$P < .001$ vs dual therapy / $P < .001$ vs triple with INR < 2.6.

Reprinted from Rossini R, et al. *Am J Cardiol.* 2008;102:1618-1623.

FA + SCA e/o PCI: **la "triplice"DAPT(A+C)+NAO tenere INR <2,5**

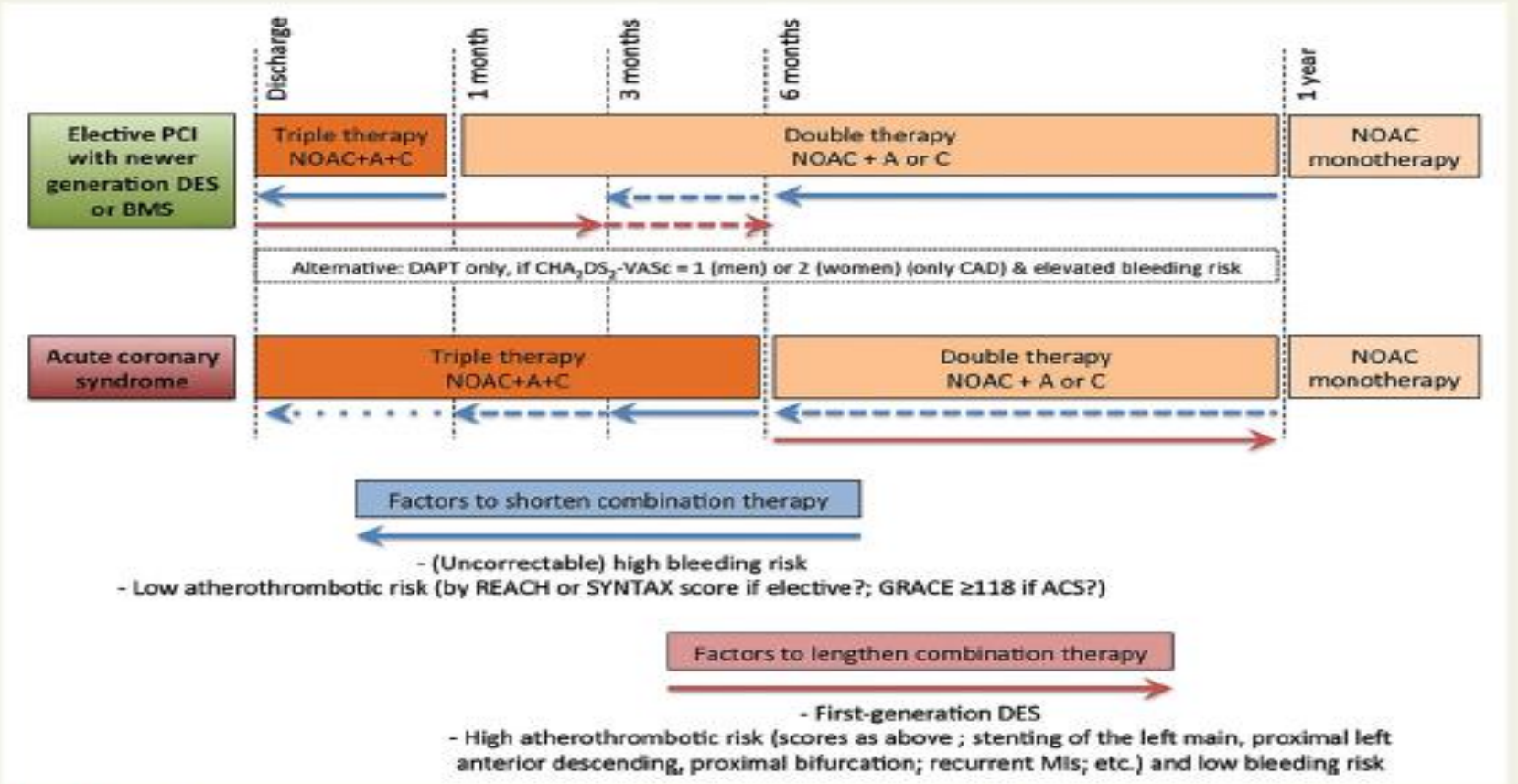


Figure 7 Default scenarios and criteria for adaptation for long-term treatment of patients on NOAC therapy after revascularization or ACS. There are innumerable possible variations on this global theme, as discussed in the text. Patient characteristics and institutional practices should be taken into account to individualize the approach. This figure wants to create a 'backbone' as guidance for such tailored approaches. A: aspirin 75–100 mg OD; C: clopidogrel 75 mg OD.

In studio nuovo schema rivaroxaban 2,5mgX2 + TICAGRELOR

NAO e CV E-F

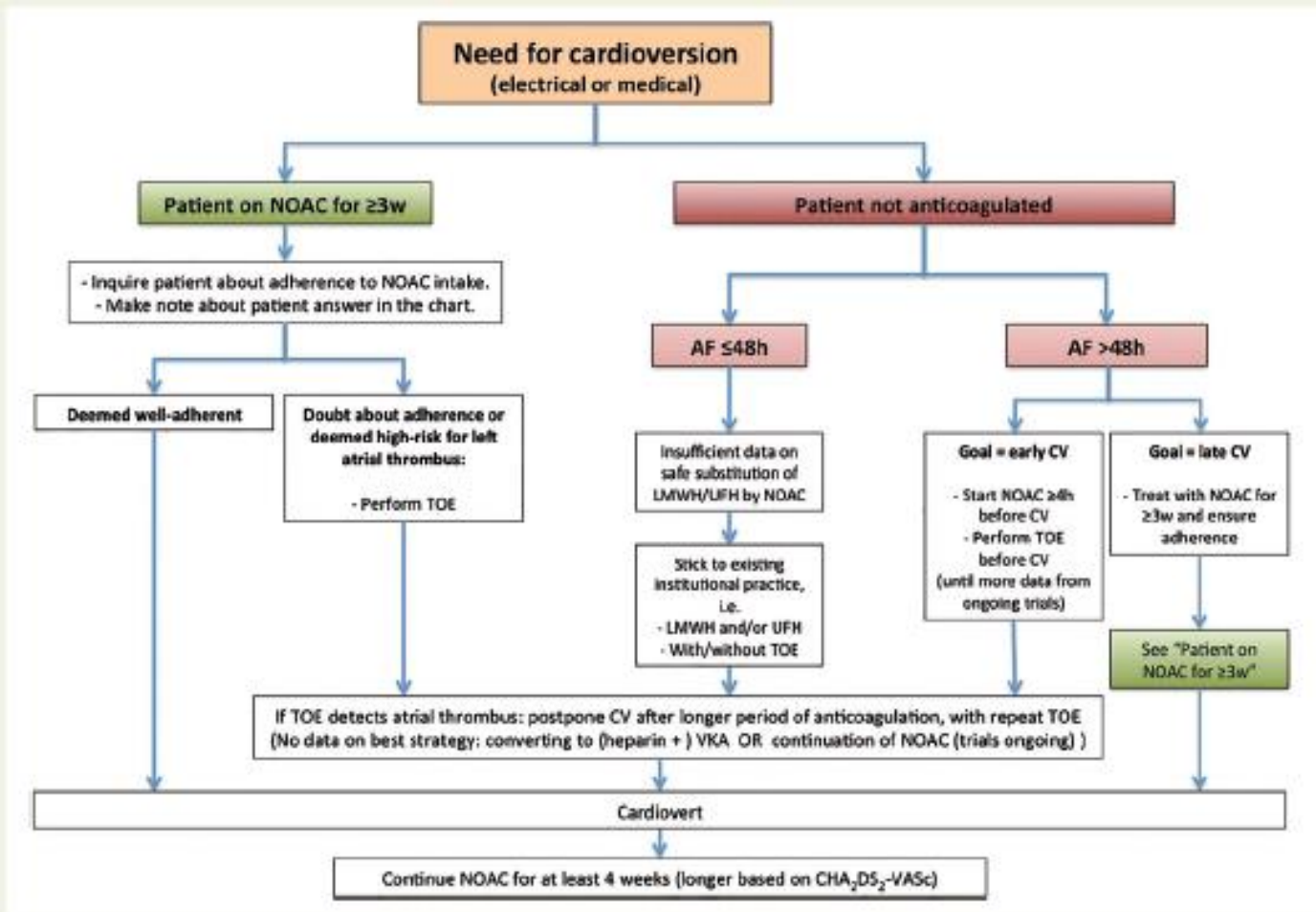


Figure 8 Cardioversion work-flow in AF patients treated with NOAC, depending on the duration of the arrhythmia and prior anticoagulation.

Chirurgie e NAO

Table 11 Classification of elective surgical interventions according to bleeding risk

Interventions not necessarily requiring discontinuation of anticoagulation
Dental interventions
Extraction of one to three teeth
Paradontal surgery
Incision of abscess
Implant positioning
Ophthalmology
Cataract or glaucoma intervention
Endoscopy without surgery
Superficial surgery (e.g. abscess incision, small dermatologic excisions, etc.)
Interventions with minor bleeding risk (i.e. infrequent or with low clinical impact)
Endoscopy with biopsy
Prostate or bladder biopsy
Electrophysiological study or catheter ablation for right-sided supraventricular tachycardia
Non-coronary angiography (for coronary angiography and ACS: see 'Patient with atrial fibrillation and coronary artery disease' section)
Pacemaker or ICD implantation (unless complex anatomical setting, e.g. congenital heart disease)
Interventions with major bleeding risk (i.e. frequent and/or with high impact)
Catheter ablation of simple left-sided supraventricular tachycardia (e.g. WPW)
Spinal or epidural anaesthesia; lumbar diagnostic puncture
Thoracic surgery
Abdominal surgery
Major orthopaedic surgery
Liver biopsy
Transurethral prostate resection
Kidney biopsy
Extracorporeal shockwave lithotripsy (ESWL)
Interventions with major bleeding risk AND increased thrombo-embolic risk[a]
Complex left-sided ablation (PVI; some VT ablations)

For each patient, individual factors relating to bleeding and thrombo-embolic risk need to be taken into account, and be discussed with the intervening physician.
[a]Last intake can vary from ≥ 24 to 1 h before intervention: see text.

Sospensione NAO per Chirurgie

Table 10 Last intake of drug before elective surgical intervention

	Dabigatran		Apixaban–edoxaban–rivaroxaban	
	No important bleeding risk and/or adequate local haemostasis possible: perform at trough level (i.e. ≥12 or 24 h after last intake)			
	Low risk	High risk	Low risk	High risk
CrCl ≥ 80 mL/min	≥24 h	≥48 h	≥24 h	≥48 h
CrCl 50–80 mL/min	**≥36 h**	**≥72 h**	≥24 h	≥48 h
CrCl 30–50 mL/min[a]	**≥48 h**	**≥96 h**	≥24 h	≥48 h
CrCl 15–30 mL/min[a]	Not indicated	Not indicated	**≥36 h**	**≥48 h**
CrCl < 15 mL/min	No official indication for use			
There is no need for bridging with LMWH/UFH				

Bold values deviate from the common stopping rule of ≥24 h low risk, ≥48 h high risk.

Low risk: with a low frequency of bleeding and/or minor impact of a bleeding; high risk with a high frequency of bleeding and/or important clinical impact. See also *Table 11*.

CrCl, creatinine clearance.

[a]Many of these patients may be on the lower dose of dabigatran (i.e. 110 mg BID) or apixaban (i.e. 2.5 mg BID), or have to be on the lower dose of rivaroxaban (i.e. 15 mg OD) or edoxaban (i.e. 30 mg OD).

Switch di TAO a NAO e viceversa

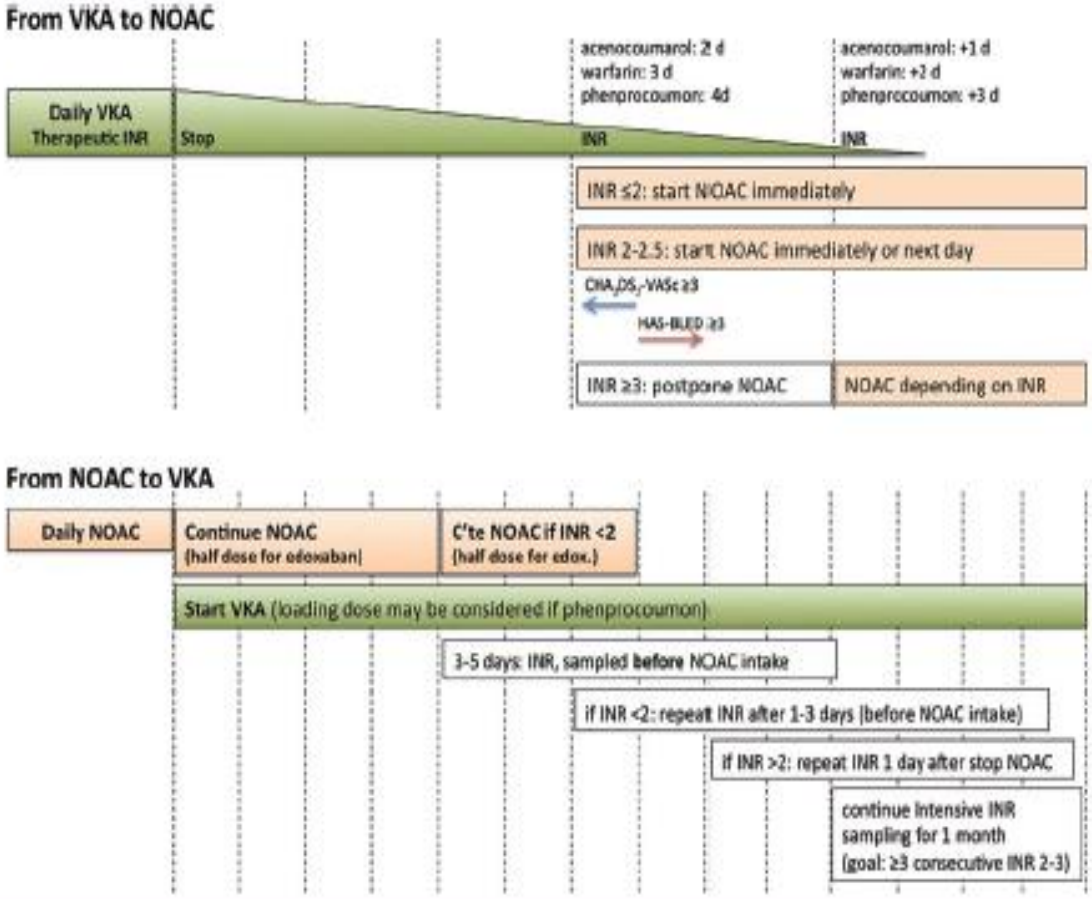


Figure 4 Switching between VKAs and non-VKA oral anticoagulants and vice versa.

NAO e Chirurgia Urgente

11. Patients requiring an urgent surgical intervention

If an emergency intervention is required, the NOAC should be discontinued. Surgery or intervention should be deferred, if possible, until at least 12 h and ideally 24 h after the last dose. Data from RE-LY have shown that the bleeding rate in dabigatran patients requiring urgent surgery was not higher (and even tended to be lower) than in VKA-treated patients (although it is not known in how many patients actions had been undertaken to optimize coagulation).[163] Evaluation of common coagulation tests (aPTT for DTIs; sensitive PT for Factor Xa inhibitors) or of specific coagulation tests (dTT for DTI; chromogenic assays for FXa inhitibors) can be considered if there is concern about the PK waning of the anticoagulant effect (e.g. renal insufficiency and/or concomitant conditions as in *Table 6*; see also 'Drug–drug interactions and pharmacokinetics of non-vitamin K antagonist anticoagulants' section). There are anecdotal reports of emergency surgery in dabigatran-treated patients after a normal aPTT was confirmed.[45] Such a strategy, however, has never been tested systematically. Moreover, some have reported normal aPTT values despite prolonged TTs.[188]

If surgery cannot be delayed, reversal of the anticoagulant may be considered. As mentioned in 'Management of bleeding complications' section, data in healthy volunteers have shown that PCC or aPCC dose-dependently reverse the anticoagulant effects of NOACs in healthy volunteers.[154,155] Despite isolated experience of their use in emergency surgery settings,[136] this has never been evaluated prospectively.

First results with idarucizumab, a specific antibody fragment, showed that in 39 patients under dabigatran therapy requiring urgent surgery, there was a rapid and near maximal reversal of the anticoagulant effects by idarucizumab, with normal intraoperative haemostasis in all except for two and one patients with mildly to moderately abnormal hemostasis as judged by the operator.[138] The agent is under consideration for expedited approval by EMA and FDA. A prospective open-label Phase III trial with andexanet alfa, a recombinant FXa inhibitor antidote, is enrolling patients experiencing an acute major bleed under therapy but not patients requiring urgent surgical interventions (Clinicaltrials.gov NCT02329327).

GRAZIE dell'attenzione

Ordine provinciale dei Medici Chirurghi
e Odontoiatri di Vicenza

Linee Guida ESC, ANMCO, AIAC
L'ingresso dei NAO

Linee guida ESC 2012

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

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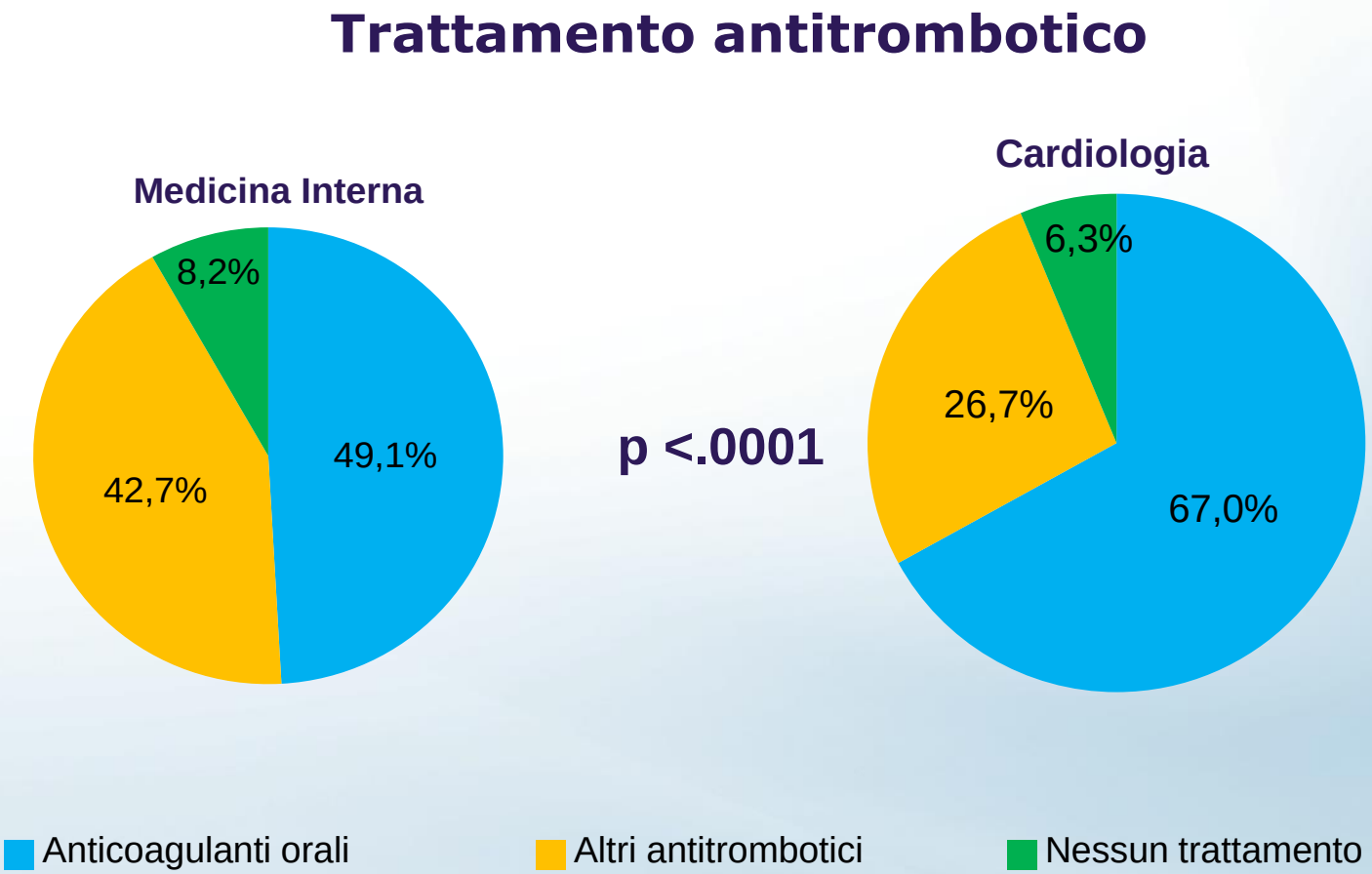
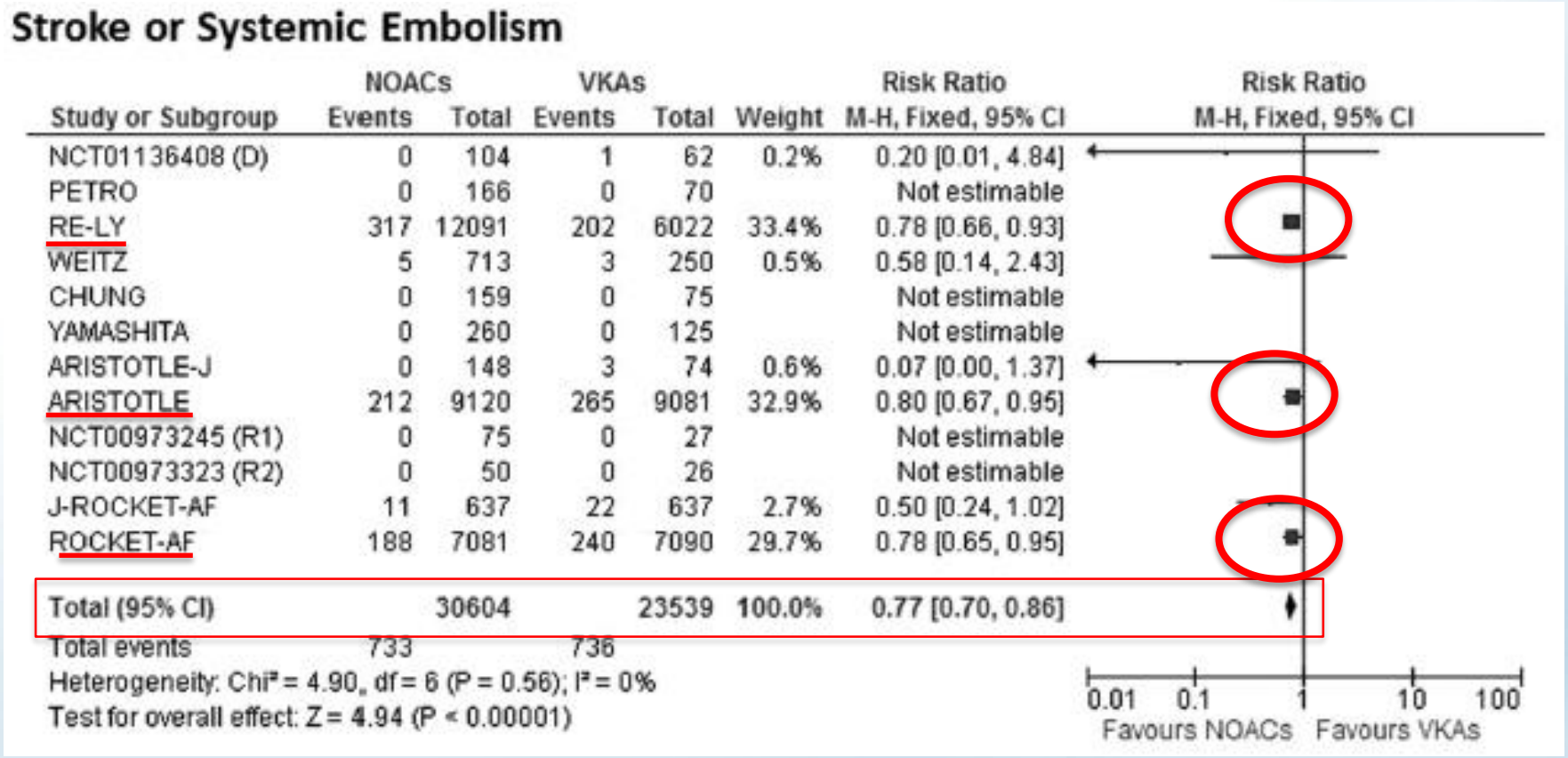
Camm A.J. *et al.*; Eur Heart Jour 2012; doi:10.1093/eurheartj/ehs253

Trattamenti antitrombotici nella FA non valvolare (4.845 pazienti)



NAO vs. AVK (1/2)

Outcome primario di efficacia



Stroke or Systemic Embolism

Study or Subgroup	NOACs Events	NOACs Total	VKAs Events	VKAs Total	Weight	Risk Ratio M-H, Fixed, 95% CI
NCT01136408 (D)	0	104	1	62	0.2%	0.20 [0.01, 4.84]
PETRO	0	166	0	70		Not estimable
RE-LY	317	12091	202	6022	33.4%	0.78 [0.66, 0.93]
WEITZ	5	713	3	250	0.5%	0.58 [0.14, 2.43]
CHUNG	0	159	0	75		Not estimable
YAMASHITA	0	260	0	125		Not estimable
ARISTOTLE-J	0	148	3	74	0.6%	0.07 [0.00, 1.37]
ARISTOTLE	212	9120	265	9081	32.9%	0.80 [0.67, 0.95]
NCT00973245 (R1)	0	75	0	27		Not estimable
NCT00973323 (R2)	0	50	0	26		Not estimable
J-ROCKET-AF	11	637	22	637	2.7%	0.50 [0.24, 1.02]
ROCKET-AF	188	7081	240	7090	29.7%	0.78 [0.65, 0.95]
Total (95% CI)		30604		23539	100.0%	0.77 [0.70, 0.86]
Total events	733		736			

Heterogeneity: Chi² = 4.90, df = 6 (P = 0.56); I² = 0%

Test for overall effect: Z = 4.94 (P < 0.00001)

Risk Ratio M-H, Fixed, 95% CI

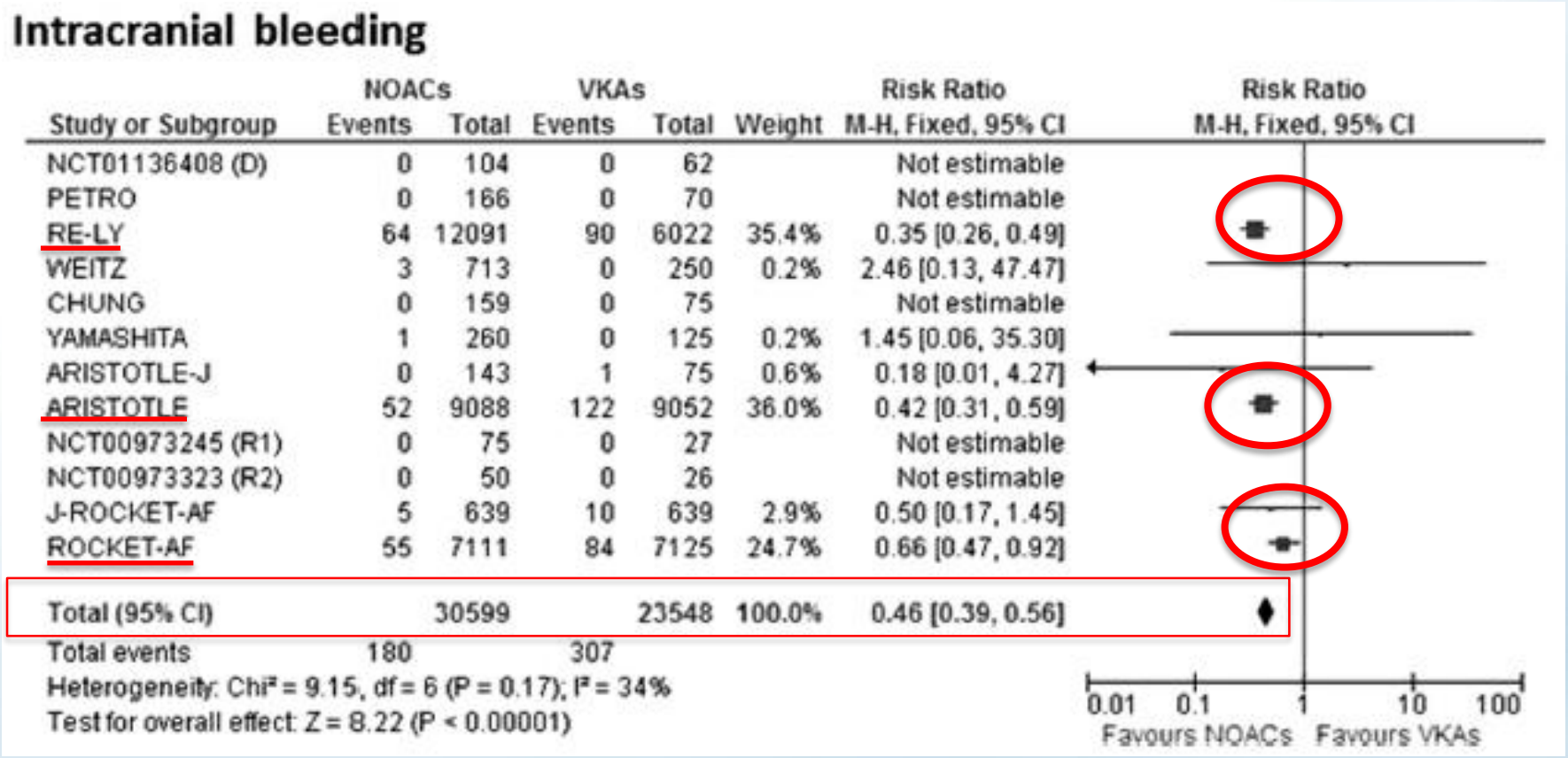
0.01 0.1 1 10 100

Favours NOACs Favours VKAs

Dentali F. *et al.;* Circulation 2012; 126: 2381-91

NAO vs. AVK (2/2)

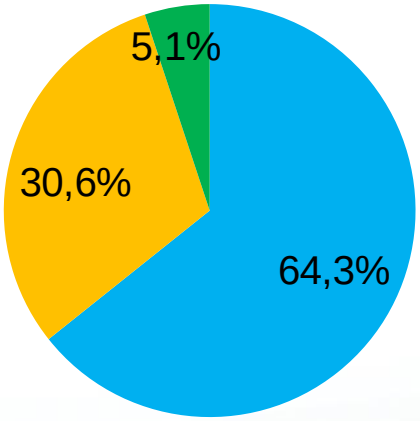
Sanguinamenti intracranici



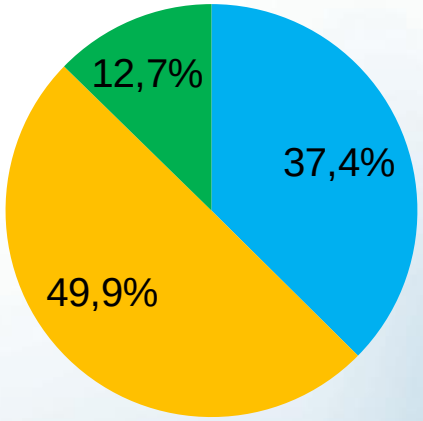
Dentali F. *et al.;* Circulation 2012; 126: 2381-91

ATT in base al tipo di FA

Permanente (3510 pazienti)

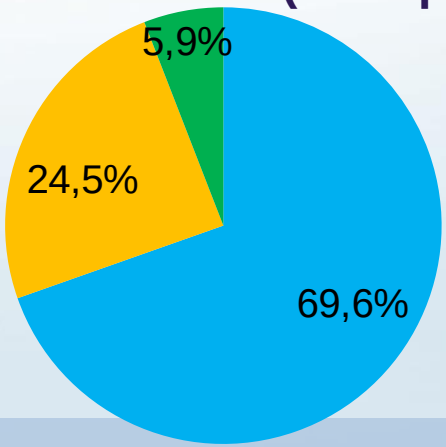


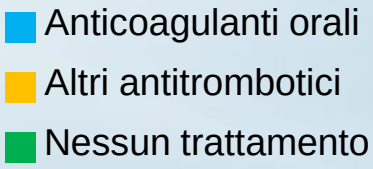
Parossistica (1712 pazienti)



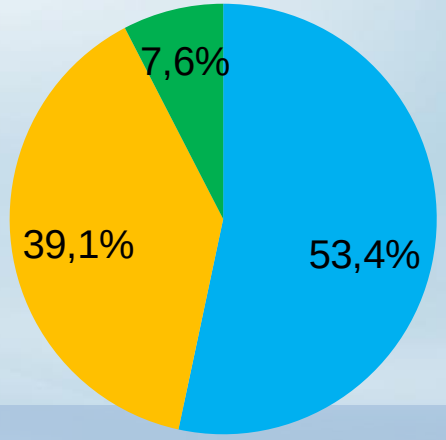
p < 0,0001

Persistente (1688 pazienti)

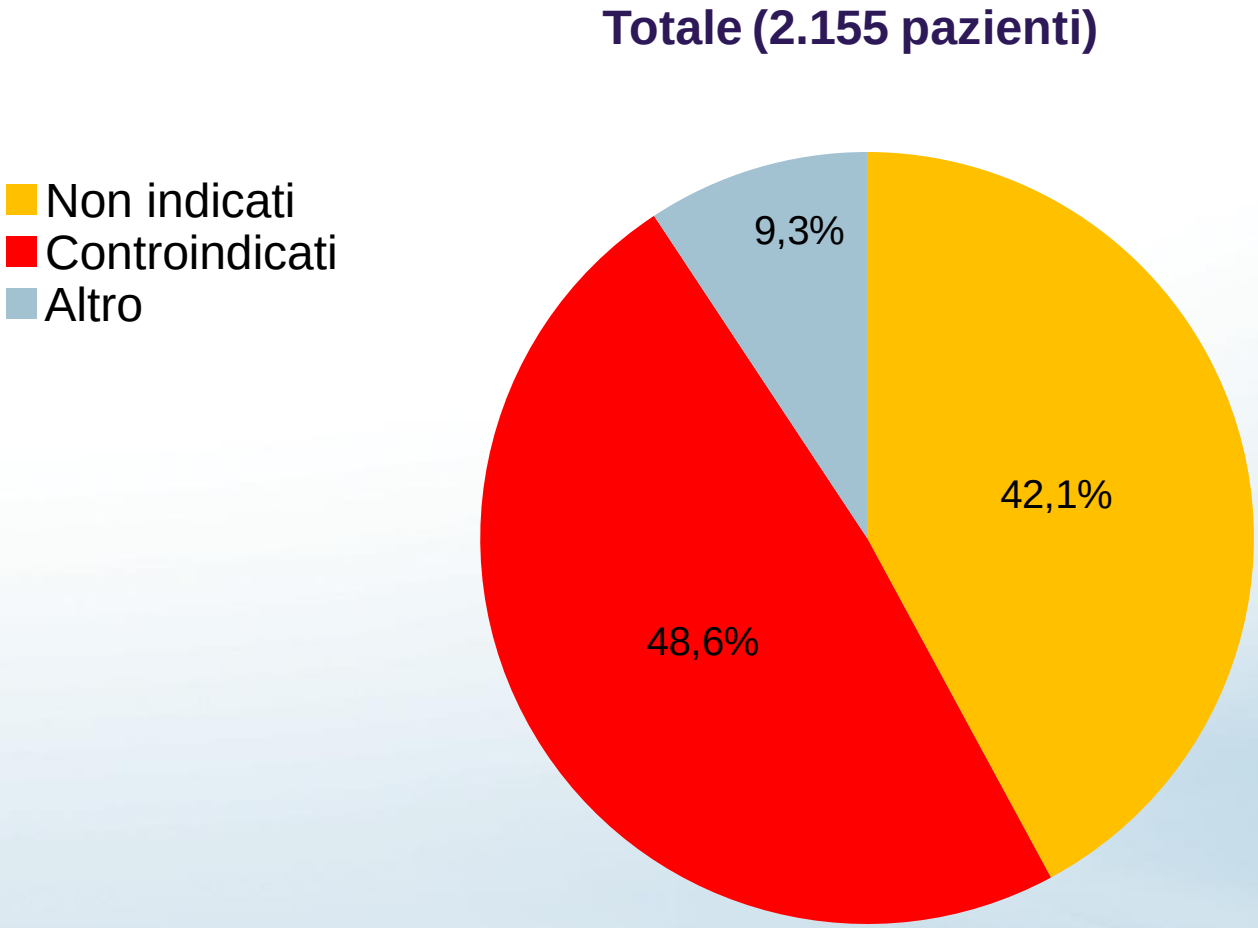




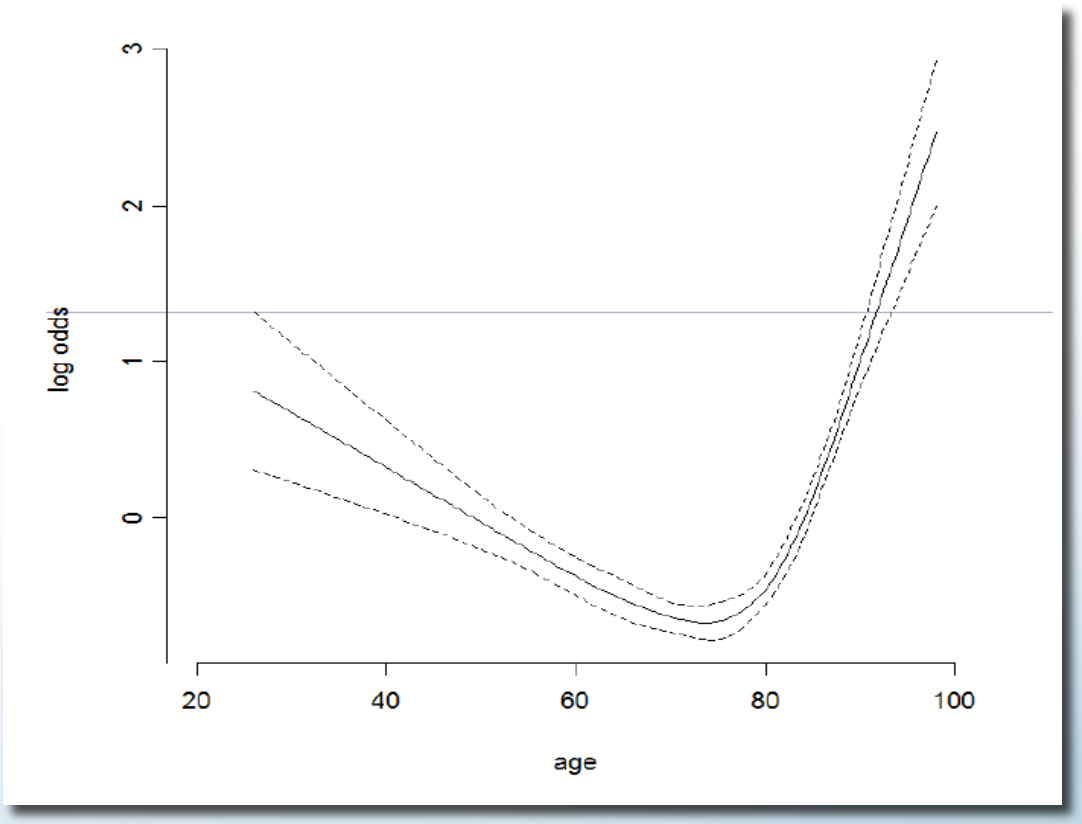
Non noto (238 pazienti)



Ragioni della non prescrizione degli OAC nei pazienti con FA non valvolare

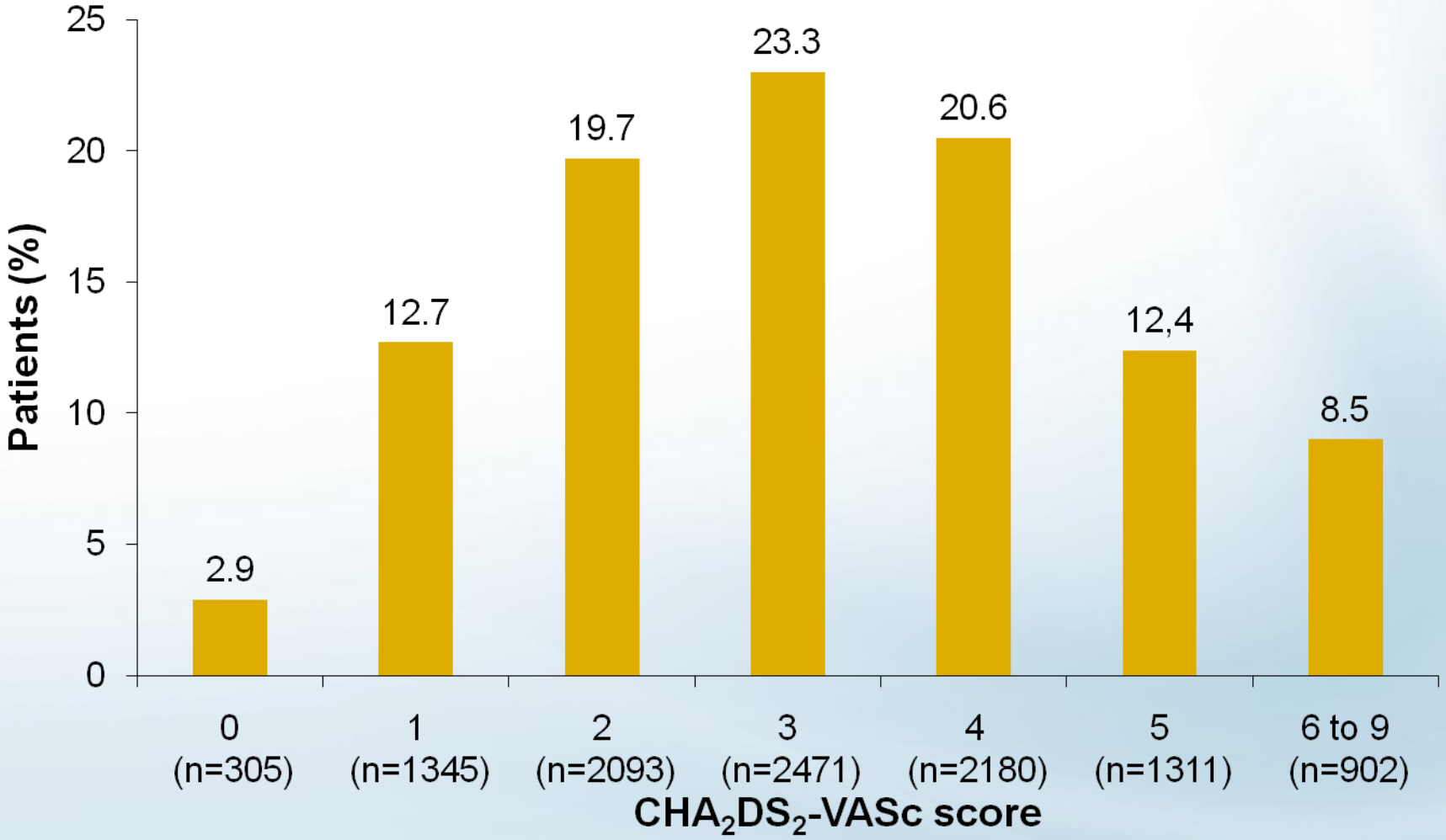


La prescrizione della terapia AO è inversamente correlata all'aumento dell'età dei pazienti*



* Attuale presentazione e gestione di 7.148 pazienti con fibrillazione atriale in cura presso centri ospedalieri di cardiologia e medicina interna: studio ATA AF

Coorte 1: distribuzione del rischio CHA_2DS_2-VASc



Kakkar *et al*.; PLoS One 2013; 8: e63479

Caratteristiche dei pazienti con FA: dati provenienti dallo studio ATA-AF (1/2)

		Clinical Setting		
	Total (n. 7148)	Cardiology (n. 3862)	Internal Medicine (n. 3286)	p
Females, %	47.0	43.4	51.3	<.0001
Age >75 years, %	56.8	44.6	71.3	<.0001
Age (years), median [IQR]	77 [70-83]	74 [66-80]	80 [74-86]	<.0001
BMI >25, %	61.9	67.1	55.9	<.0001
SBP (mmHg), mean±SD	130±18	130±17	130±19	0.16

Qualità sub-ottimale della TAO con VKA

FA e ictus cardioembolico

il problema visto nella stroke unit

1.549 pazienti con ictus ischemico

Età (anni)	75,8 ±12,8
FA non nota (%)	15,8
Nuova diagnosi di FA (%)	4,9

52,1% nessun trattamento
34.9% farmaci antipiastrinici
13% anticoagulanti

Solo il 10,1% è stato trattato in modo adeguato

Paciaroni & Agnelli; JTH 2005

Limiti della reale pratica clinica: il sottotrattamento nel mondo (1/2)

Incidenza di ictus:

In Italia si verificano circa 200.000 episodi di ictus ogni anno e 660 casi al giorno. (1)

La maggior parte dei pazienti con FA e rischio intermedio/alto di ictus non è trattata in modo appropriato

→ SOTTOTRATTAMENTO documentato

1. Il sole 24 ore Sanità – I quaderni di medicina – Sett 2011.

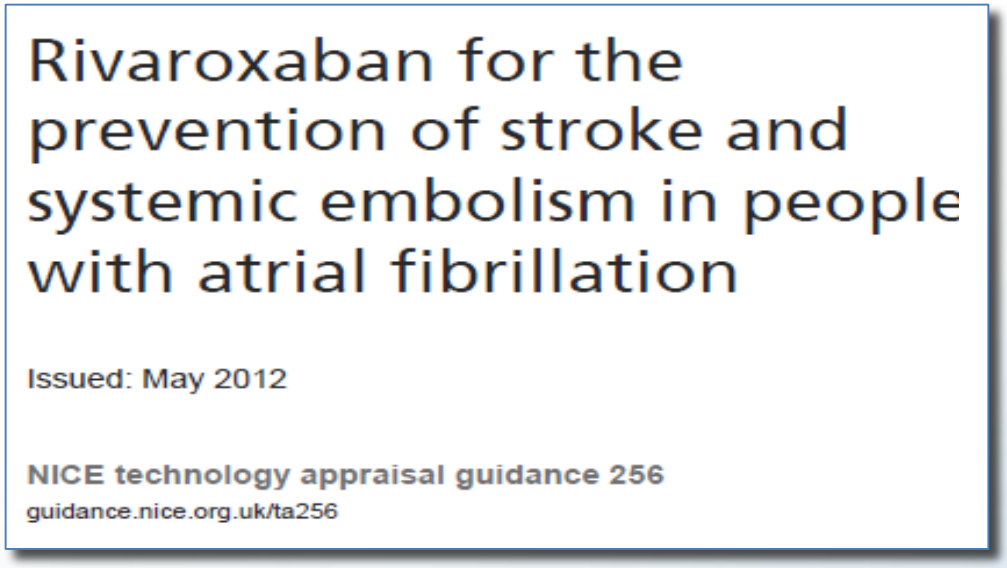
Limiti della reale pratica clinica: il sottotrattamento nel mondo (2/2)

- Da una recente revisione della letteratura risulta che: (1)
  - <u>non riceve alcuna terapia:</u>
    - fino al **47%** dei pazienti a rischio moderato di ictus;
    - fino al **27%** dei pazienti a rischio elevato di ictus;
  - <u>è trattato con antiaggreganti piastrinici:</u>
    - fino al **49%** dei pazienti a rischio moderato di ictus;
    - fino al **64%** dei pazienti a rischio elevato di ictus.

1. Ogilvie I.M. *et al*.; Am J Cardiol 2011; 108: 151-161.

Linee guida NICE 2012

NHS
National Institute for
Health and Clinical Excellence



Fra le indicazioni approvate**, rivaroxaban è raccomandato** come opzione terapeutica nella prevenzione dell'ictus e dell'embolismo sistemico in pazienti adulti con fibrillazione atriale non valvolare.

Il Comitato ha riconosciuto dei potenziali benefici delle terapie alternative, come rivaroxaban, in pazienti con fibrillazione atriale, inclusi gli **effetti positivi sulla qualità di vita che hanno risolto i problemi e le difficoltà associate all'assunzione di warfarin.**

Table 3. AF Definitions: A Simplified Scheme

Term	Definition
Paroxysmal AF	• AF that terminates spontaneously or with intervention within 7 d of onset. • Episodes may recur with variable frequency.
Persistent AF	• Continuous AF that is sustained >7 d.
Longstanding persistent AF	• Continuous AF of >12 mo duration.
Permanent AF	• Permanent AF is used when there has been a joint decision by the patient and clinician to cease further attempts to restore and/or maintain sinus rhythm. • Acceptance of AF represents a therapeutic attitude on the part of the patient and clinician rather than an inherent pathophysiological attribute of the AF. • Acceptance of AF may change as symptoms, the efficacy of therapeutic interventions, and patient and clinician preferences evolve.

January, CT et al.
2014 AHA/ACC/HRS Atrial Fibrillation Guideline

Nonvalvular AF	• AF in the absence of rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve, or mitral valve repair.

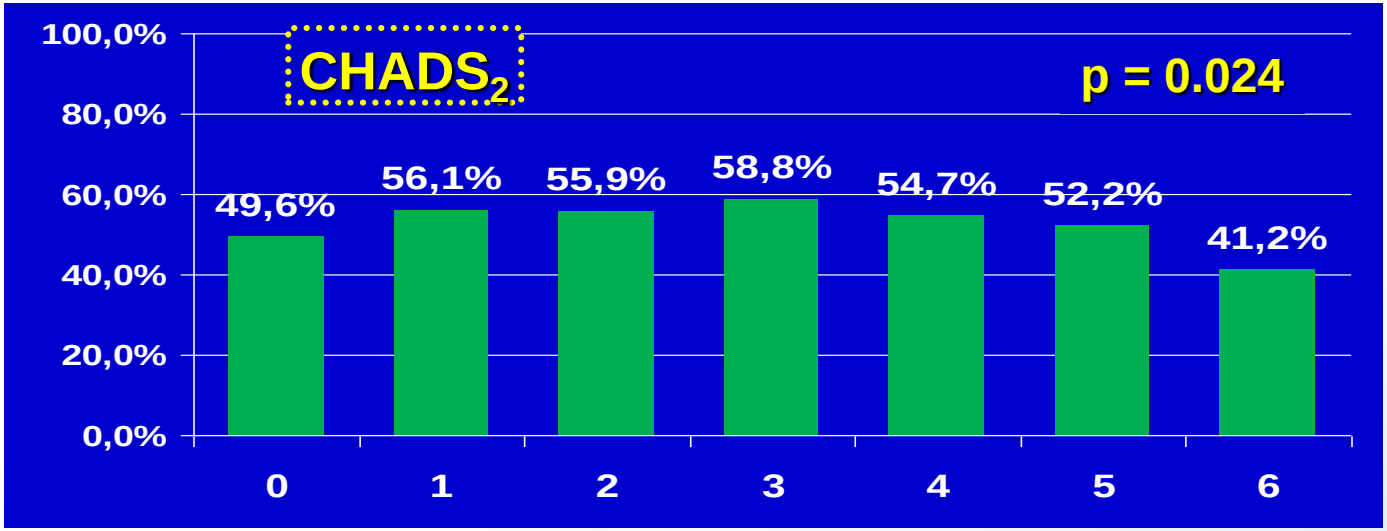
AF indicates atrial fibrillation.

Le società scientifiche italiane: ANMCO e AIAC 2013

Documento ANMCO su prevenzione del tromboembolismo nella fibrillazione atriale e ruolo dei nuovi anticoagulanti orali

Linee guida AIAC per la gestione e il trattamento della fibrillazione atriale. Aggiornamento 2013

Caratteristiche dei pazienti con FA: dati provenienti dallo studio ATA-AF



FA non valvolare
4.845 pazienti