STRUMENTI DI SOSTENIBILITA':
L'ESEMPIO DEL DISEASE MANAGEMENT OPTIMIZATION NELLA FIBRILLAZIONE ATRIALE

NAPOLI, 2.10.2015

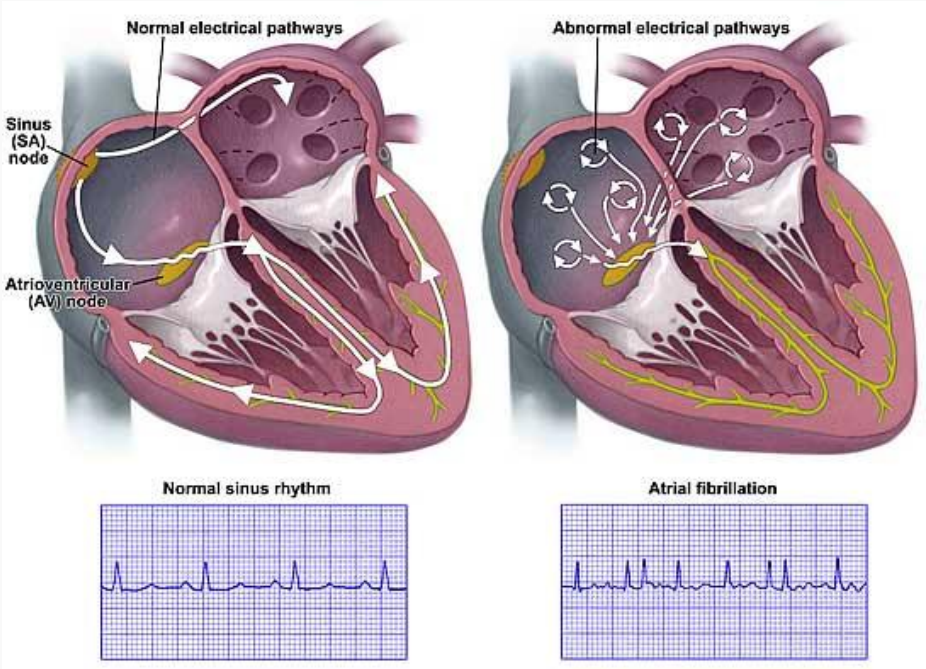
Clinica e Terapia del Paziente con Fibrillazione Atriale

Salvatore D'Isa

- **Nessun conflitto di interesse da dichiarare**

FIBRILLAZIONE ATRIALE

Aritmia caratterizzata da una rapida e disordinata attivazione elettrica degli atri (400-600 b/m) con perdita della contrazione atriale.



La trasmissione degli impulsi atriali ai ventricoli è parziale, per cui il battito cardiaco risulta irregolare e spesso (ma non obbligatoriamente) rapido.

FIBRILLAZIONE ATRIALE
cause

- **Cardiache**:
  - organiche (post-infarto, ipertensione, Ipertrofia Ventricolare Sinistra, scompenso cardiaco, valvulopatia, cardiopatia congenita)
  - della conduzione elettrica (malattia del nodo del seno)

- **Non cardiache**:
  - infezioni (polmonite), squilibri elettrolitici, carcinoma polmonare, EP, ipertiroidismo, obesità, apnea notturna, diabete

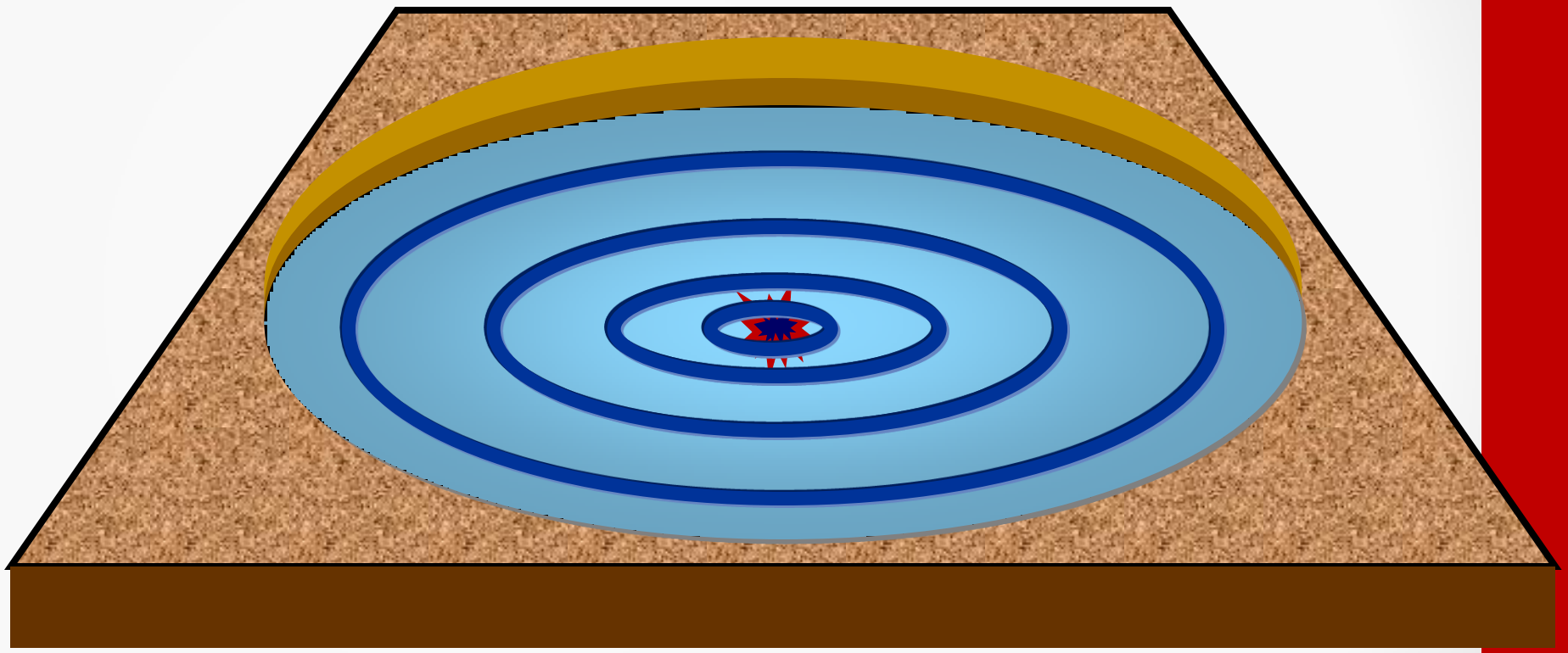
- **Chirurgiche**: toracotomia, bypass aorto-coronarico
- **Alimentazione/stile di vita**: alcool, caffeina, stress
- **Idiopatiche**

FIBRILLAZIONE ATRIALE
cause

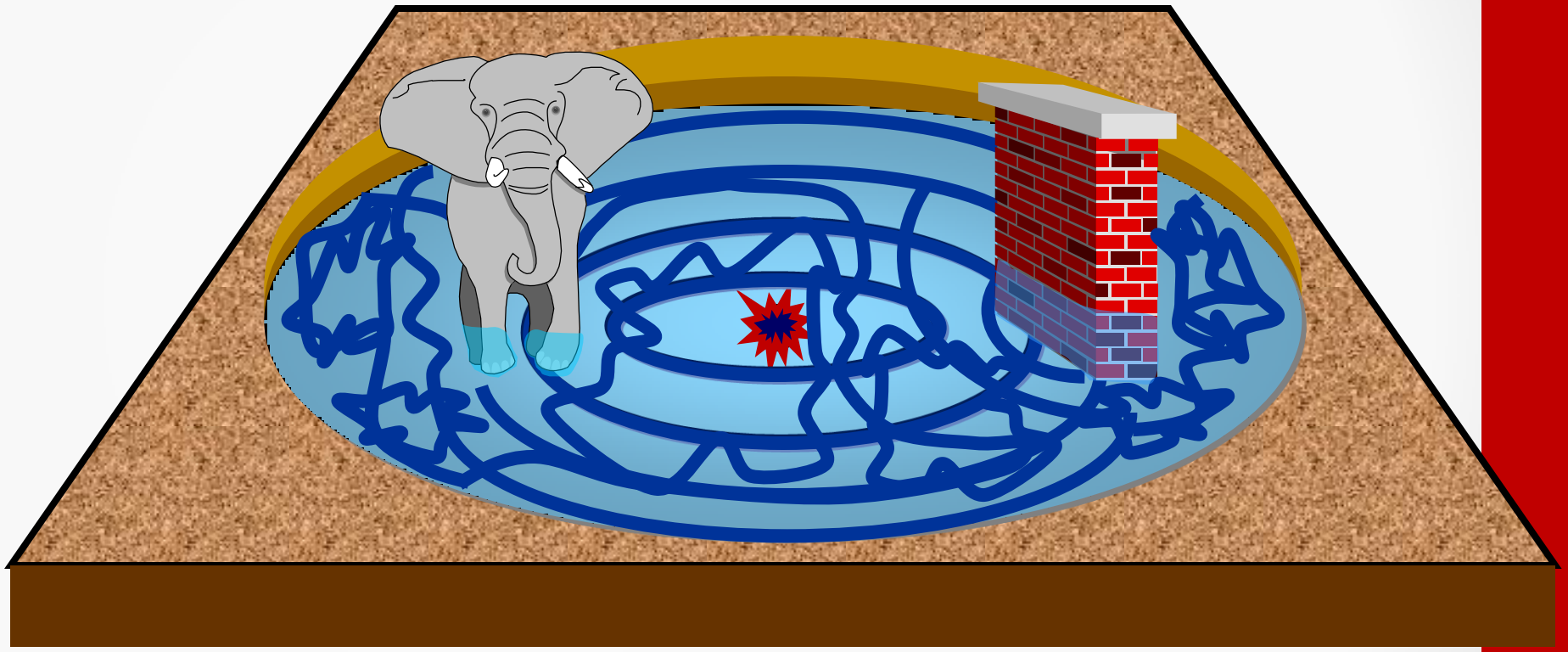
- **FA VALVOLARE:**
  - Il disturbo del ritmo cardiaco è associato a problemi alle valvole cardiache che possono richiedere una sostituzione con valvole meccaniche o biologiche
  - stenosi mitralica reumatica
  - rigurgito moderato/severo da prolasso mitralico.

    La valvulopatia reumatica, in declino nei paesi occidentali, potrebbe subire una impennata in seguito ai nuovi flussi migratori.

- **FA NON VALVOLARE:**
  - Il disturbo del ritmo cardiaco NON è associato a problemi della valvola mitrale del cuore.



Prof. Maria Grazia Bongiorni
Direttore U.O. Malattie Cardiovascolari 2
Azienda Ospedaliero-Universitaria Pisana



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Azienda Ospedaliero-Universitaria Pisana

FIBRILLAZIONE ATRIALE definizioni

- **Di nuova diagnosi:**

Documentate per la prima volta, indipendentemente dalla presenza di sintomi, dall'eventuale riconversione spontanea a ritmo sinusale, dalla durata dell'episodio o da eventuali precedenti episodi non documentati

- **Ricorrente:**

Due o più episodi accertati di FA

- **Isolata (o primitiva o idiopatica)**

Comprende le forme di FA che colpiscono principalmente individui di giovane età o, comunque, di età <60 anni che non presentano segni clinici o ecocardiografici di concomitante patologia cardiopolmonare, né ipertensione arteriosa né qualsiasi altro fattore noto e chiaro come le diverse forme di FA non siano mutuamente esclusive nello stesso paziente e come nel tempo ogni identificabile di FA.

- **Secondaria**

Comprende le forme di FA in cui è possibile individuare la causa dell'aritmia

- **Fibrillazione Atriale SILENTE o ASINTOMATICA**

Comprende le forme di FA che non si associano a sintomi.

Antonio Raviele et al; G Ital Cardiol 2013;14(3); Linee guida AIAC

FIBRILLAZIONE ATRIALE
definizioni

- **Parossistica**

Comprende le forme di FA che terminano spontaneamente entro 48h o che sono interrotte con cardioversione (farmacologica o elettrica) entro questo periodo;

- **Persistente**

Comprende le forme di FA che persistono oltre 48h (fino a 1 anno) e/o che sono interrotte con cardioversione (elettrica o farmacologica) dopo questo periodo.

- **Di lunga Durata**

Comprende le forme di FA che durano ininterrottamente da più di 1 anno.

- **Permanente (o cronica)**

Comprende le forme di FA nelle quali non sono stati effettuati tentativi di cardioversione o, se effettuati, non hanno avuto successo

Antonio Raviele et al; G Ital Cardiol 2013;14(3); Linee guida AIAC

Progressione della FA

- La FA è una malattia progressiva:

  * nel 14-24% la FA parossistica evolve in FA persistente

    Schoonderwoerd BA et al Prog Cardiovasc Dis 2005

  * nel 30% la FA “lone” evolve in FA permanente

    Jahangir A et al Circulation 2007

- Se non viene gestita adeguatamente la FA puo’ determinare conseguenze temibili: danno emodinamico, ictus, scompenso cardiaco, morte

  Fuster V et al Eur Heart J 2006

Cornerstones of AF Management

Rate Control	Rhythm Control	Anticoagulation
Control of symptoms	Control of symptoms	Prevention of thromboembolism
Treatment or prevention of Tachycardia Induced Cardiomyopathy (CMP)	Reduction in Hospitalizations	Minimization of bleeding risk
Reduction in Hospitalizations		

Rate versus Rhythm Control for AF

- The AFFIRM, RACE and AF-CHF trials have shown no mortality benefit from a rhythm control strategy compared to a rate control strategy.
- Therefore, a rate control strategy, without attempts at restoration or maintenance of sinus rhythm (SR), is reasonable in some patients with AF, especially those who are elderly and asymptomatic.
- If rate control offers inadequate symptomatic relief, restoration of SR may become a long-term goal.
- Restoration and maintenance of SR continues to be a reasonable treatment approach in many patients with AF.

Knight, et al, *Practical Rate and Rhythm Management of Atrial Fibrillation,* January 2010 ed.

Rate Control for AF

Principles of a Rate Control Strategy:

- Adequate control of the ventricular response during AF can significantly improve symptoms and is critical to avoid tachycardia-mediated cardiomyopathy.
- Most patients managed using a rhythm control strategy also require medications for rate control.
- Rate control during atrial flutter tends to be more difficult than during AF.

What is Adequate Rate Control?

- Control of the ventricular rate during AF is important both at rest and with exertion.
- No standard method for assessment of heart rate control has been established.
- Criteria for rate control vary with patient age but usually involve achieving ventricular rates between 60 and 80 bpm at rest and between 90 and 115 bpm during moderate exercise.
- For the AFFIRM trial, adequate control was defined as an average HR up to 80 bpm at rest and either an average rate up to 100 bpm during Holter monitoring with no rate above 100% of the maximum age-adjusted predicted exercise HR, or a maximum HR of 110 bpm during a 6-min walk test.
- In the RACE trial, rate control was defined as less than 100 bpm at rest.
- Only about 5%of patients from these trials required AV ablation to achieve HR control.

Knight, et al, *Practical Rate and Rhythm Management of Atrial Fibrillation,* January 2010 ed.

Ventricular Rate Control: Drugs to Control the Ventricular Response

- Beta blockers are the most effective drug class for rate control.
- Calcium channel antagonists (nondihydropyridine) are good choices for patients with asthma or COPD requiring beta agonist inhaler therapy.
- Digoxin provides relatively poor rate control during exertion and should be reserved for patients with systolic HF.
- Digoxin does not convert AF to SR and may perpetuate AF.
- Digoxin is marginally effective as a sole agent, but may prove useful in combination with beta blocker or calcium channel antagonists, particularly in hypotensive patients.

Knight, et al, *Practical Rate and Rhythm Management of Atrial Fibrillation,* January 2010 ed. with modifications.

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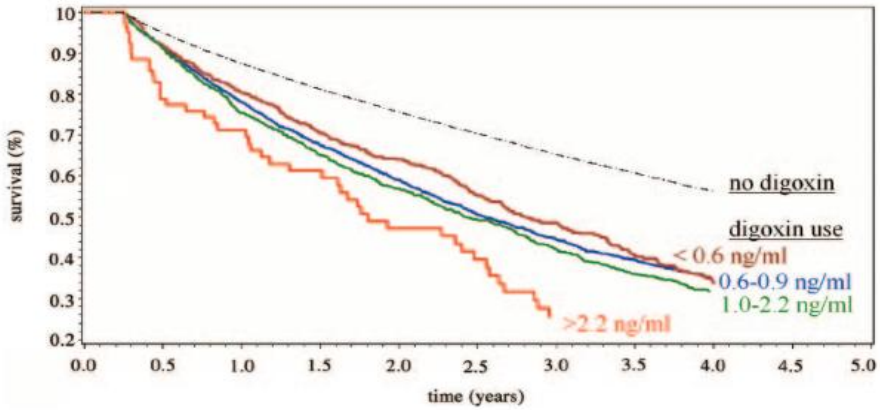
Digoxin Associates with Mortality in ESRD

Kevin E. Chan,*† J. Michael Lazarus,* and Raymond M. Hakim*

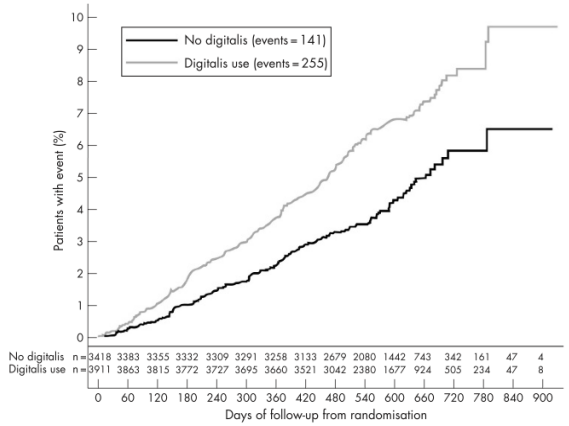
*Fresenius Medical Care NA, Waltham, Massachusetts; and †Nephrology Division, Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts



Digitalis: a dangerous drug in atrial fibrillation? An analysis of the SPORTIF III and V data

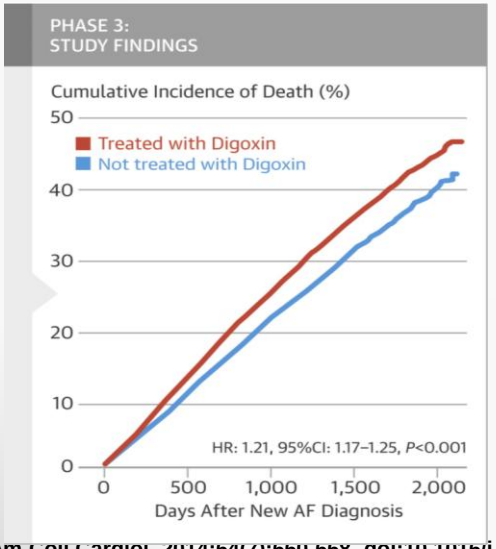
K Gjesdal,[1] J Feyzi,[2] S B Olsson[3]

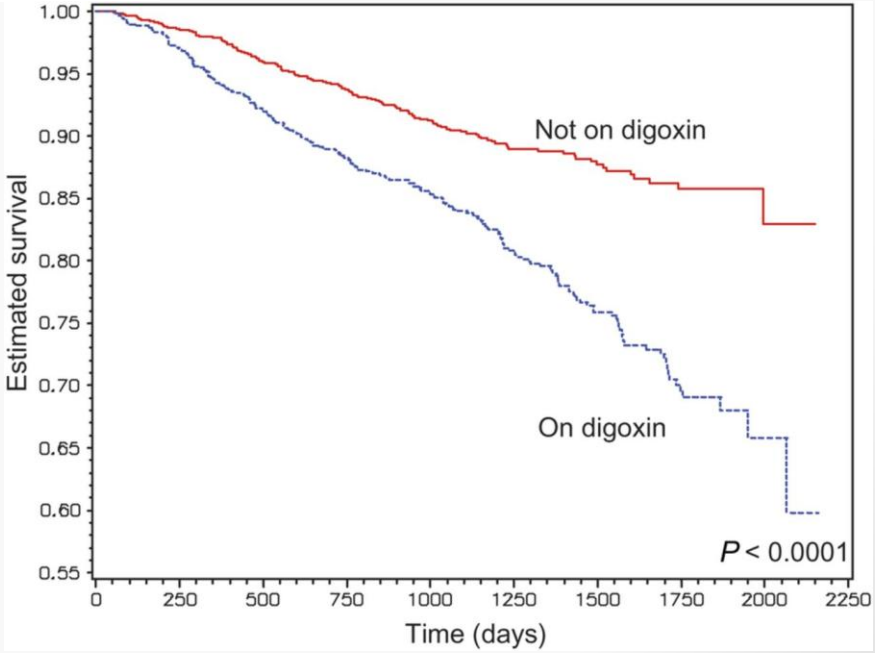
Figure 1 Kaplan–Meier plot of time to event (all-cause mortality) in 7329 patients with moderate-to-high risk atrial fibrillation. Digitalis users had a significantly higher event rate than non-users (p<0.0001; hazard ratio, 1.58 (95% CI 1.29 to 1.94)).



Heart 2008;**94**:191–196. doi:10.1136/hrt.2006.108399 193

Increased Mortality Associated With Digoxin in Contemporary Patients With Atrial Fibrillation: Findings From the TREAT-AF Study





J Am Coll Cardiol. 2014;64(7):660-668. doi:10.1016/j.jacc.2014.03.060

Ventricular Rate Control: Drugs to Control the Ventricular Response

- Some antiarrhythmic drugs that are used to maintain sinus rhythm, such as sotalol, dronedarone, and amiodarone, also provide some control of the ventricular response when patients are in AF.
- Amiodarone should rarely be used for rate control because of its potential for toxicity.
- IV digoxin or nondihydropyridine calcium channel antagonists given to patients with AF and WPW may accelerate the ventricular response and are not recommended.

Ventricular Rate Control: AV Nodal Ablation

- Ablation of the AV conduction system and permanent pacing (the "ablate and pace" strategy) is an option for patients who have rapid ventricular rates despite maximum medical therapy and often yields remarkable symptomatic relief.
- There is growing concern about the negative effects of long-term RV pacing.
- Biventricular pacing, on the other hand, may overcome many of the adverse hemodynamic effects associated with RV pacing and is preferred when systolic dysfunction is present.
- Catheter ablation of the AV node should not be attempted without a prior trial of medication to control the rate.

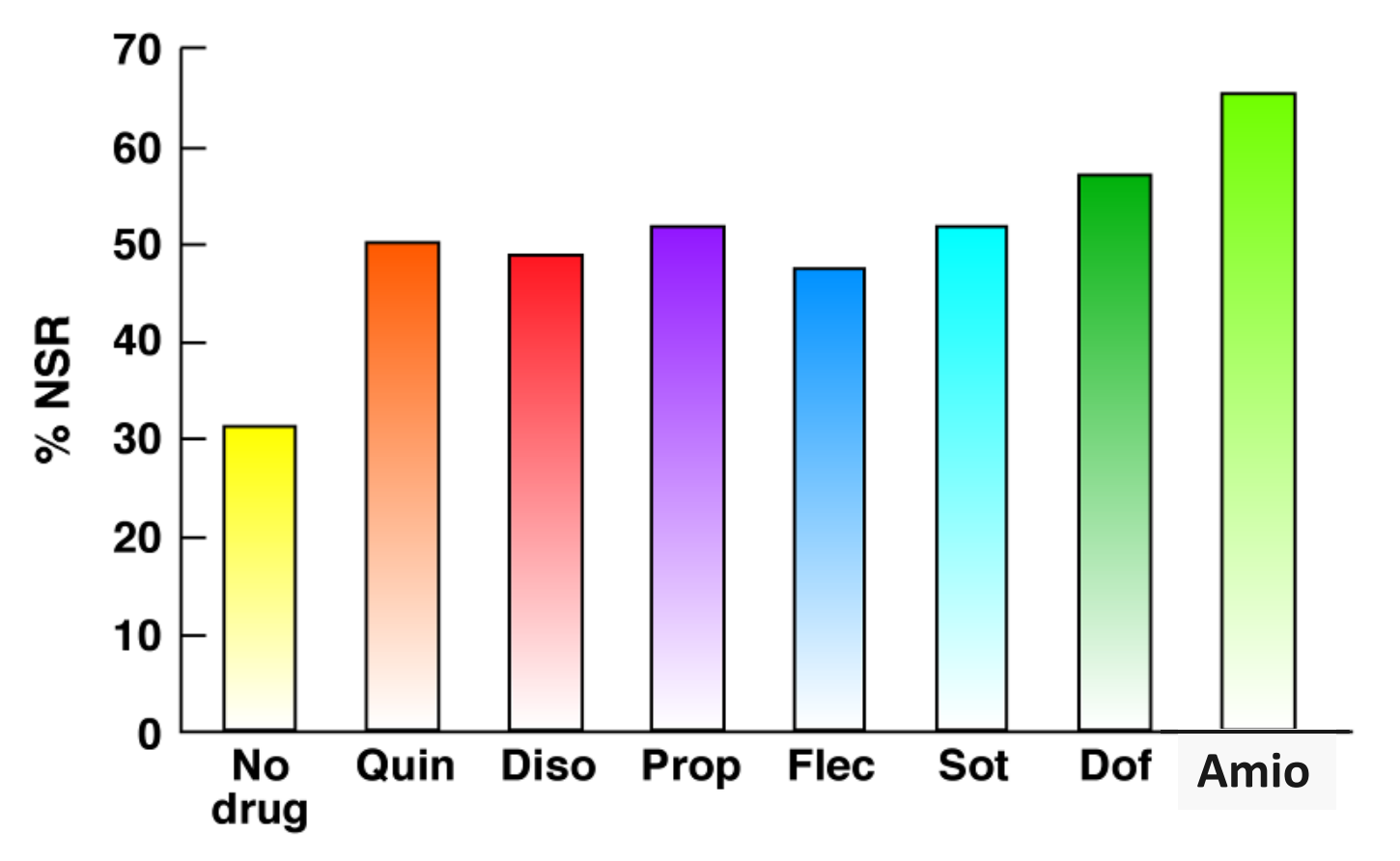
Knight, et al, *Practical Rate and Rhythm Management of Atrial Fibrillation,* January 2010 ed. with modifications.

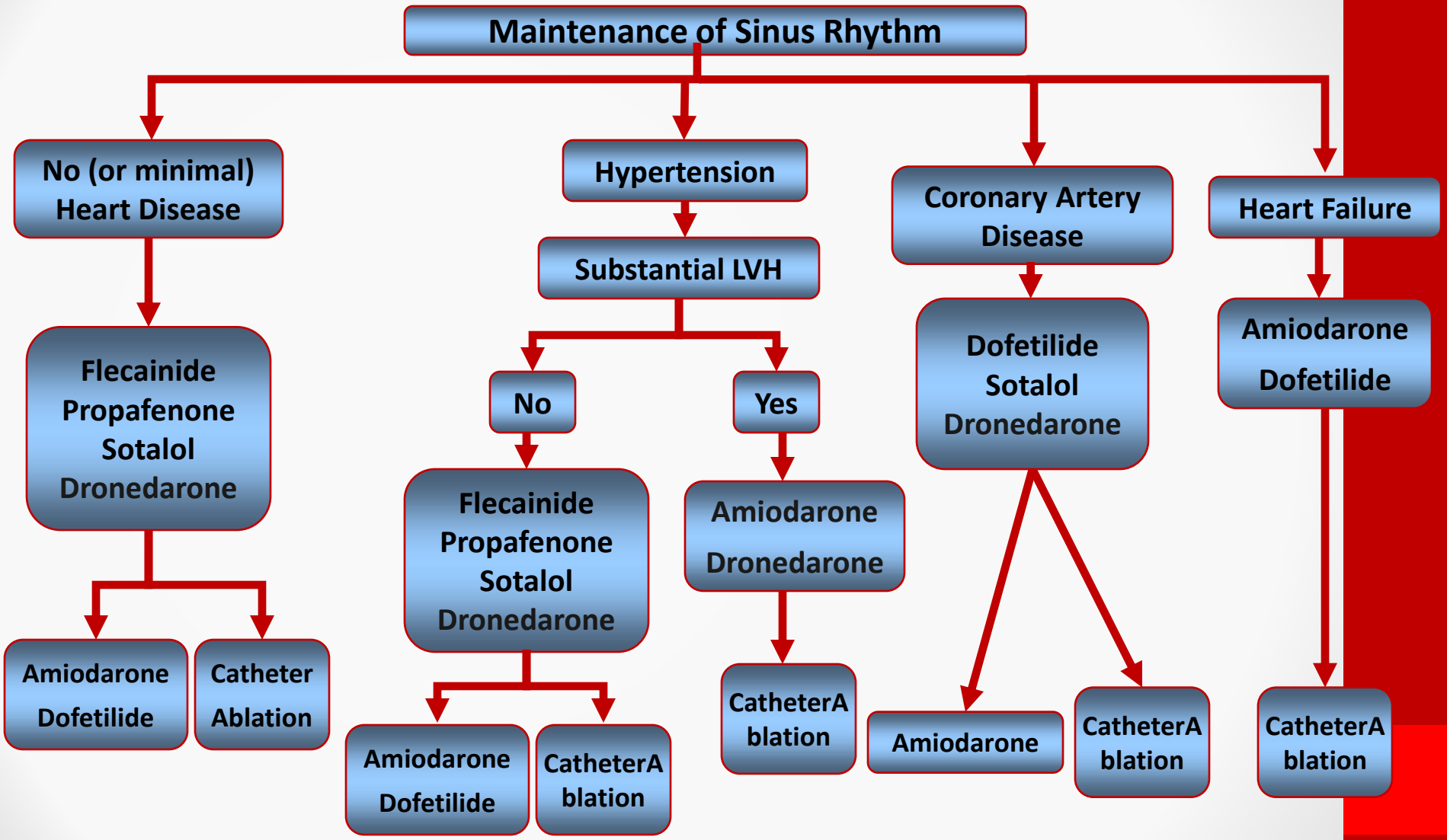
Maintenance of Sinus Rhythm: Principles of Antiarrhythmic Drug Therapy

- Before administering an antiarrhythmic drug, precipitants of AF such as hypertension, valve disease, CHF, hyperthyroidism, and OSA should be identified and corrected.
- Ensure normal electrolyte status and appropriate anticoagulation prior to starting antiarrhythmic drug therapy.
- The risk of stroke may not be reduced by suppression of AF.
- AF is likely to recur in most patients with and without antiarrhythmic drugs (AADs).
- Pharmacological therapy is indicated in patients who can tolerate AADs and who have a reasonable chance to maintain sinus rhythm.
- AADs choice is based on side-effect profiles and presence of structural heart disease, heart failure, or hypertension.
- Drug choice should be individualized and account for underlying renal and hepatic function.

Knight, et al, *Practical Rate and Rhythm Management of Atrial Fibrillation,* January 2010 ed. with modifications.

Antiarrhythmic Drugs: Efficacy Maintaining NSR ≥ 6 Months





Modified from Fuster, V. et al. J. Am. Coll. Cardiol. 48, e149–e246 (2006).

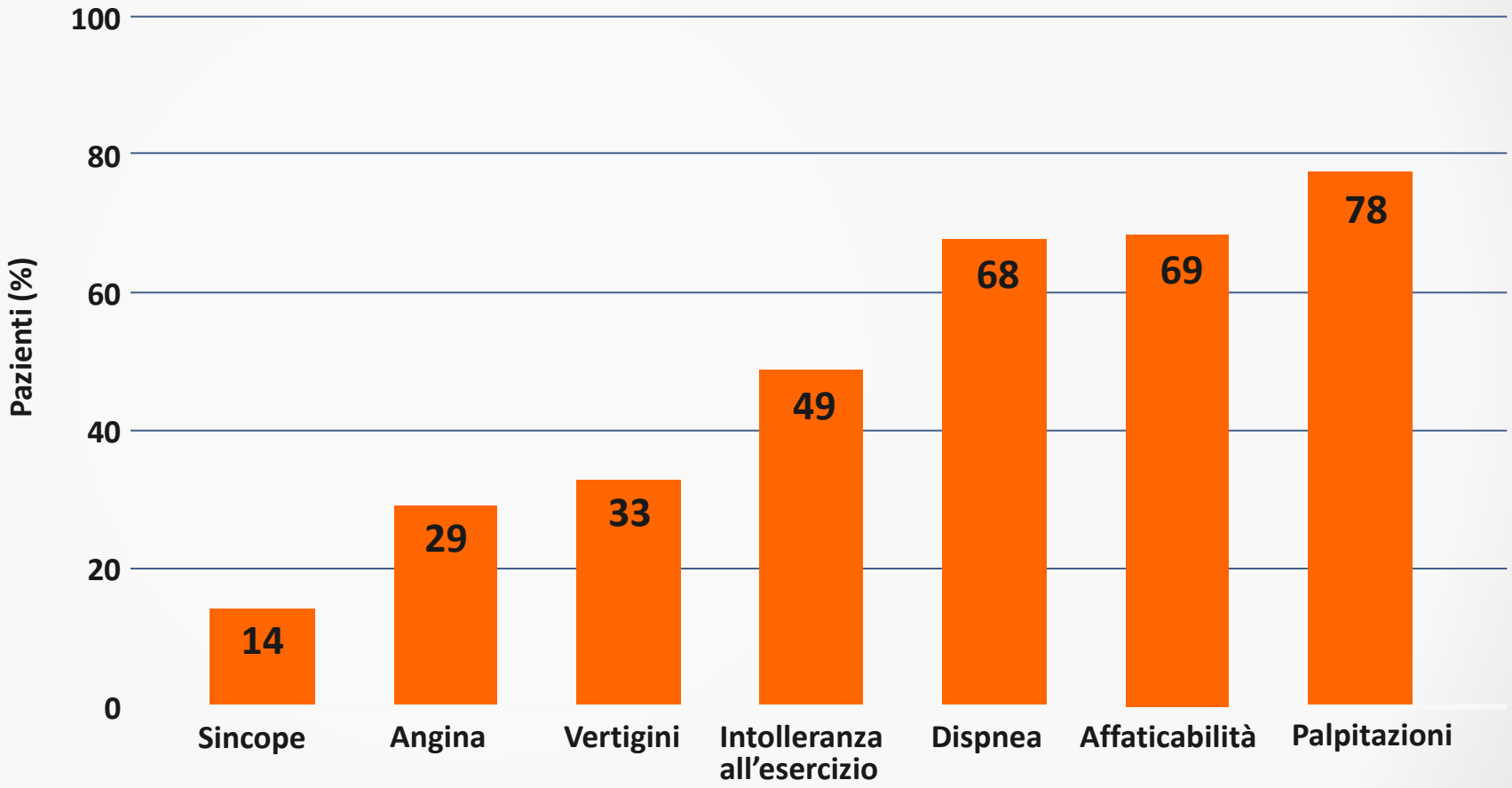
Antiarrhythmic Drug Therapy vs Ablation

- AAD Therapy:
  - Adverse event rate: 30% (common but less severe)
  - Success rate: 52%
- Ablation:
  - Complication rate: 5.9%
  - Single-procedure success rate without AADs: 57%
  - Multiple-procedure success rate without AADs: 71%
  - Multiple-procedure success rate with AADs: 77%
    - Symptomatic Paroxysmal or Persistent Atrial Fibrillation
    - Second-line Therapy
    - Failure of Class IC or Class III agent
    - Intolerance to Medical Therapy, Refusal of Medical Therapy
    - Young patients with paroxysmal atrial fibrillation, in whom decades-long drug therapy is undesirable
    - Congestive Heart Failure due to tachycardia-induced cardiomyopathy, in whom drug choices are limited by the presence of CHF

Calkins et al. *CircEP*. 2009;2:349-361.

Living with atrial fibrillation

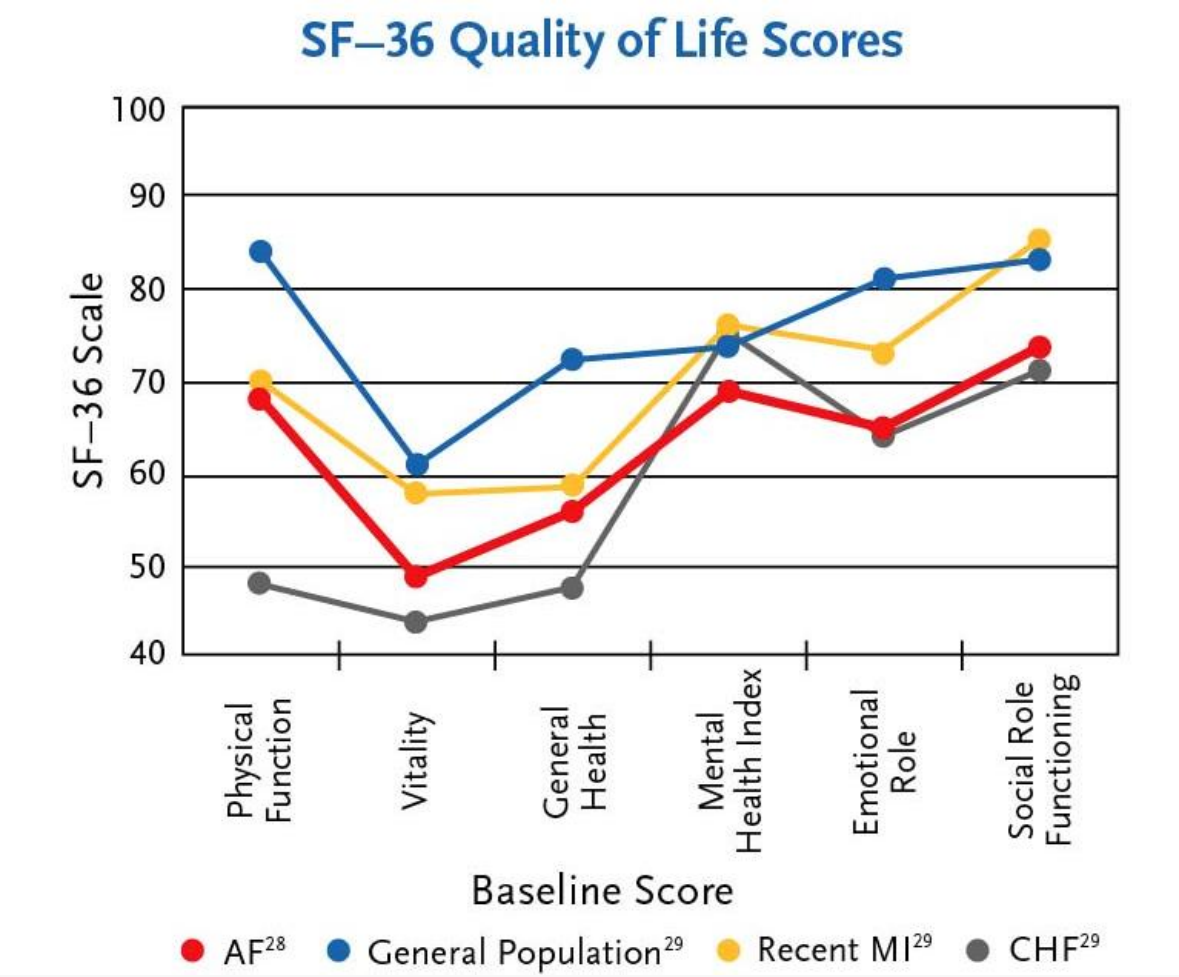
FIBRILLAZIONE ATRIALE
sintomi



Levy S et al Alfa Study 1999

Nieeuwlaat R et al Euro Heart Survey 2005

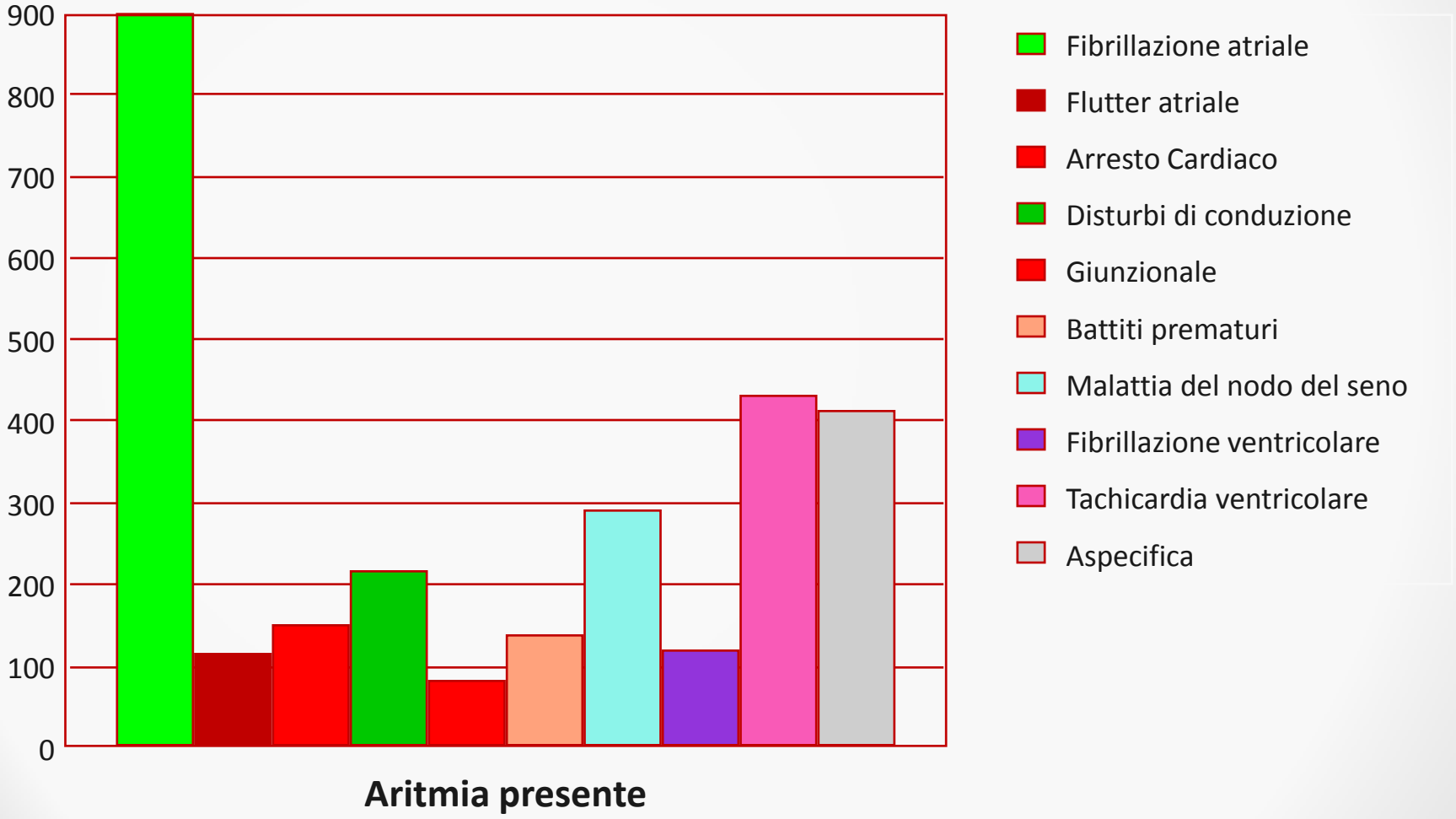
FIBRILLAZIONE ATRIALE
qualità di vita



Jung W et al,JACC 1999; 33(2): 104A

Ware JE et al SF-36 Health Survey: Manual & Interpretation Guide. 1993; 10:14-25

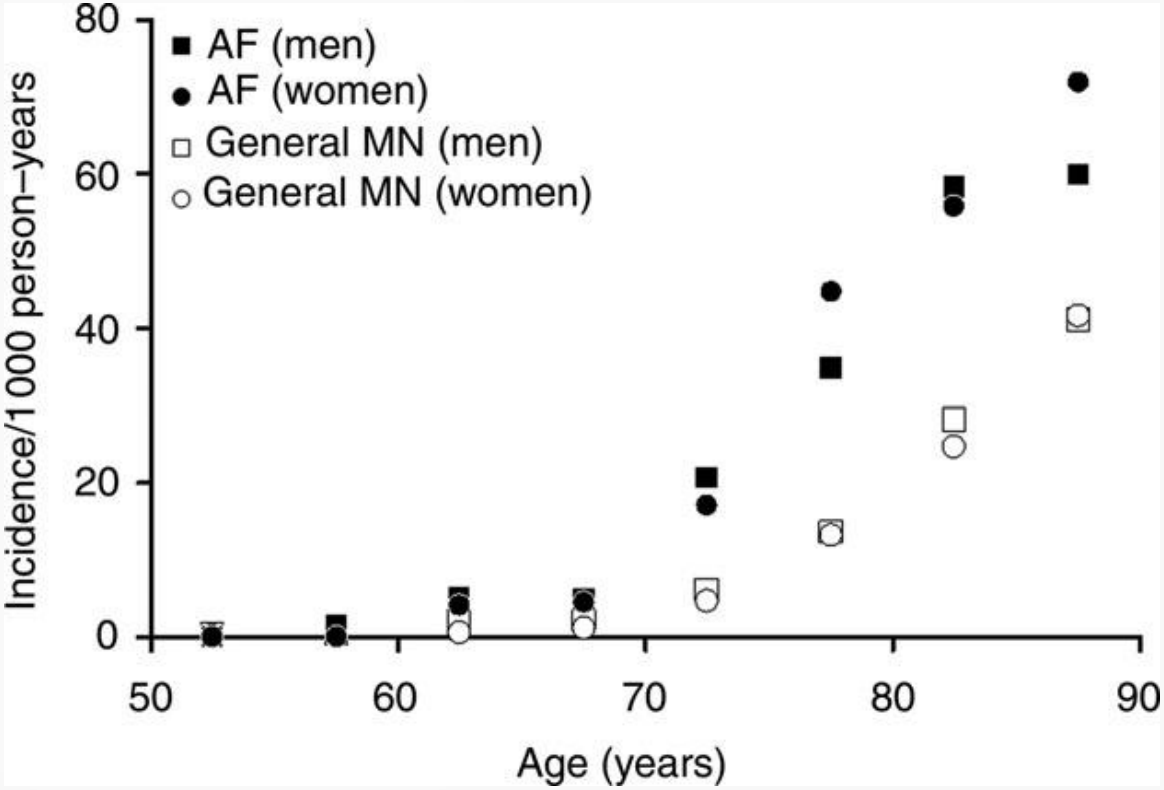
La FA e' l'aritmia che causa le ospedalizzazioni di maggiore durata



Camm AJ. Am J Cardiol. 1996;78(8A):3-11.

Risk of dementia in stroke-free patients diagnosed with atrial fibrillation: data from a community-based cohort

Yoko Miyasaka1,4, Marion E. Barnes1, Ronald C. Petersen2, Stephen S. Cha3, Kent R. Bailey3, Bernard J. Gersh1, Grace Casaclang-Verzosa1, Walter P. Abhayaratna1, James B. Seward1, Toshiji Iwasaka4, and Teresa S.M. Tsang1*



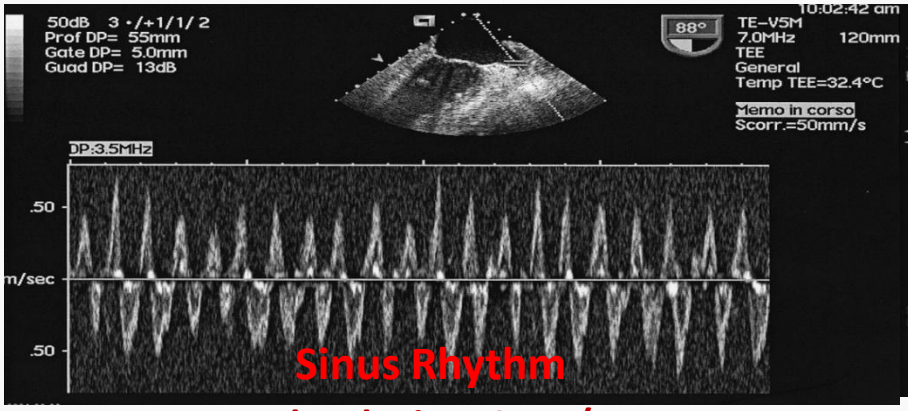
Demenza e deficit cognitivo sono frequenti dopo la diagnosi di FA

European Heart Journal (2007) 28, 1962–1967

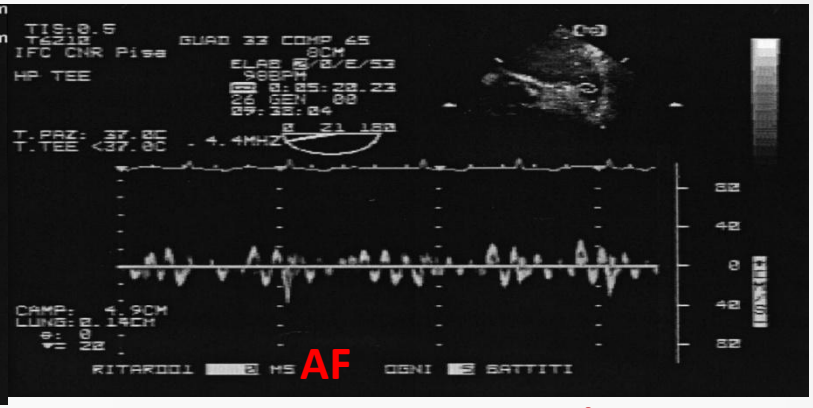
AF and stroke: the link

Left Atrial Appendage blood flow velocity decreases, increasing risk of thrombus formation

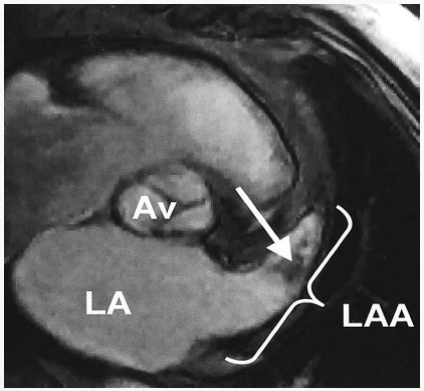
LAA Emptying Flow Velocity Echo Signals



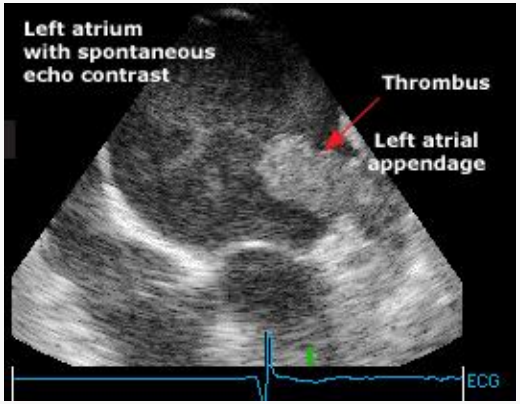
Mean peak velocity 52 cm/s



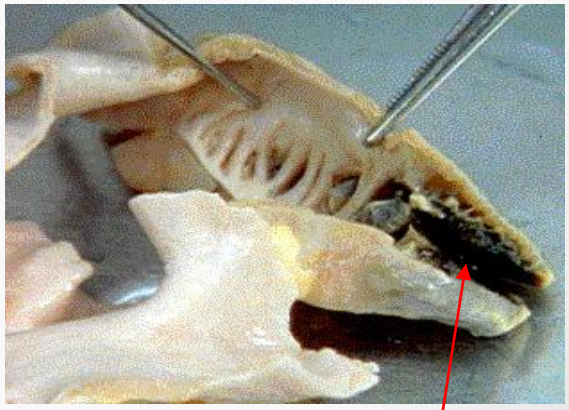
Mean peak velocity 26 cm/s



Clot in the LAA on MRI



Clot in the LAA on Echo



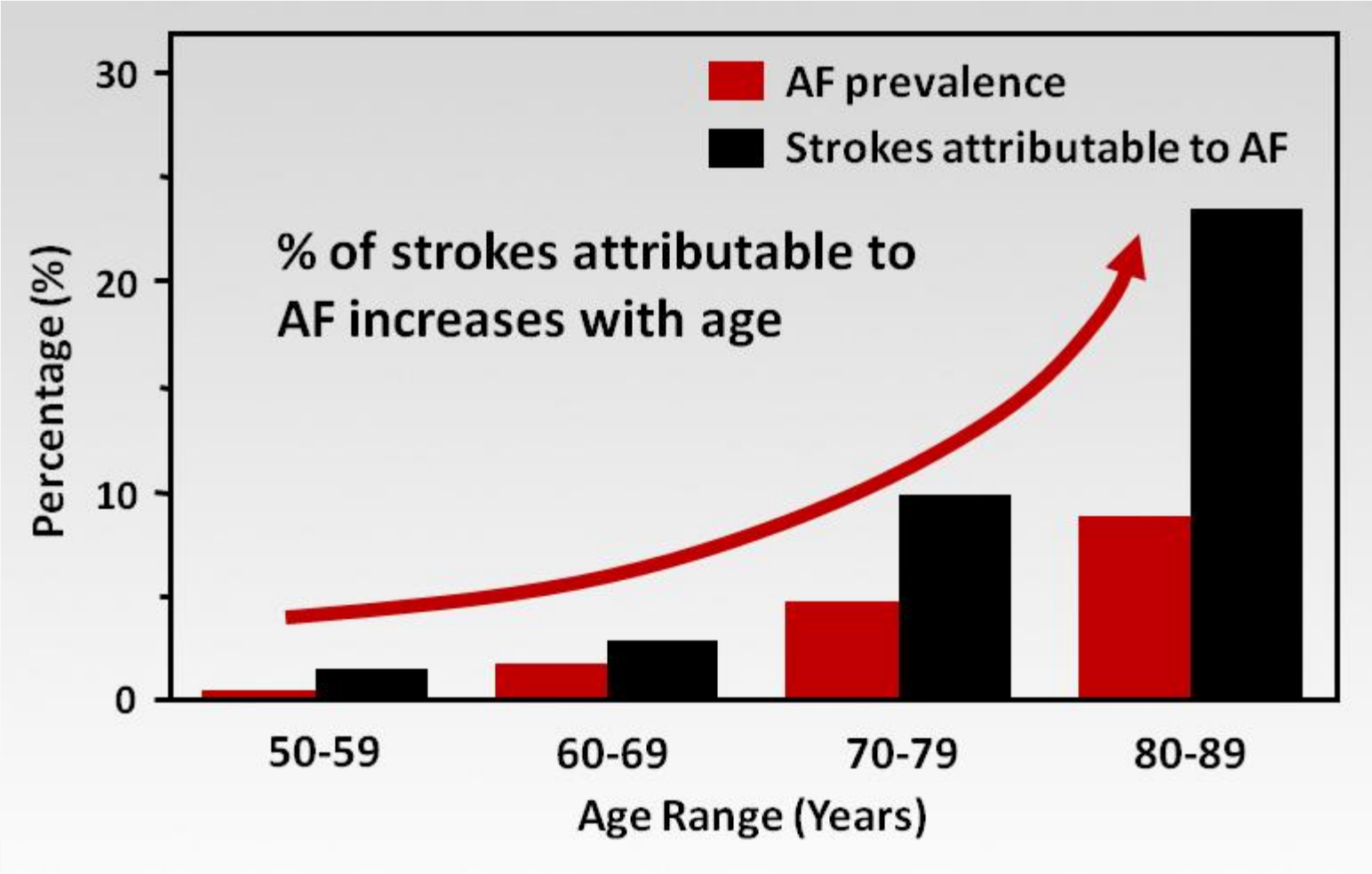
Thrombus

La FA è il più importante fattore di rischio per ictus

Patologia	Rapporto di rischio (vs soggetti senza la malattia)
Fibrillazione atriale	4,8
Insufficienza cardiaca	4,3
Ipertensione	3,4
Malattia coronarica	2,4

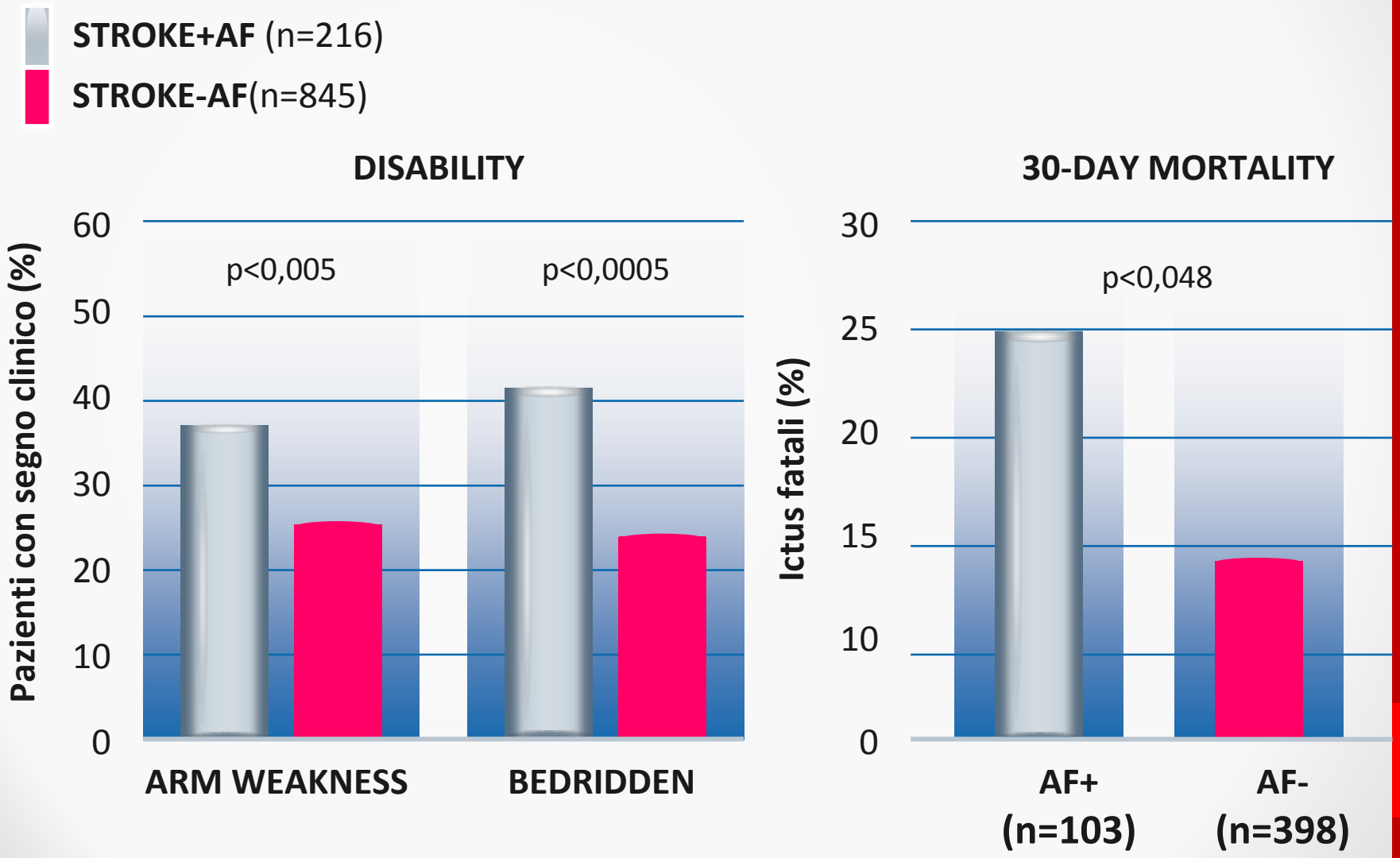
Wolf *et al. Stroke* 1991

La prevalenza della FA aumenta con l'età



Wolf PA, et al. *Stroke.* 1991;22:983-988.

AF-RELATED STROKE IS LINKED TO HIGHER MORTALITY AND MORBILITY RISK



Dulli DA ,et al. *Neuroepidemiology* 2003;22:118-123.
Lin HJ, et al. *Stroke* 1996;27:1760-1764.

Pazienti con FA e rischio di ictus: CHA_2DS_2 – VASc Score

C: Congestive heart failure or left ventricular systolic disfunction **1**

H: Hypertension (ipertensione) 1

A_2: Age (età ≥ 75 anni) **2**

D: Diabetes mellitus (diabete) 1

S_2: Stroke or TIA (precedente ictus o TIA) **2**

V: Vascular disease (malattia vascolare eg IM, placca aortica) 1

A: Age 65-74 (età compresa tra 65 e 74 anni) 1

Sc: Sex category (genere femminile) 1

Massimo punteggio = 9

Score	Rischio
0	Basso
1	Moderato
≥ 2	Alto

Rischio di stroke in base al CHA2DS2-VASc

CHA_2DS_2-VASc Score	Adjusted Stroke Rate (%/year)
0	0%
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	15.2%

Lip GY et al. Stroke 2010,41:2731-38

HAS-BLED score

- Uno HAS-BLED score ≥3 indica un rischio elevato di sanguinamento e richiede cautela e controlli regolari del paziente sia se in terapia con VKA che con ASA

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

Recommendations	Class[a]	Level[b]
Assessment of the risk of bleeding should be considered when prescribing antithrombotic therapy (whether with VKA or aspirin), and the bleeding risk with aspirin should be considered as being similar to VKA, especially in the elderly.	IIa	A
The HAS-BLED score [hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly (>65), drugs/alcohol concomitantly] should be considered as a calculation to assess bleeding risk, whereby a score of ≥3 indicates 'high risk' and some caution and regular review is needed, following the initiation of antithrombotic therapy, whether with OAC or aspirin.	IIa	B

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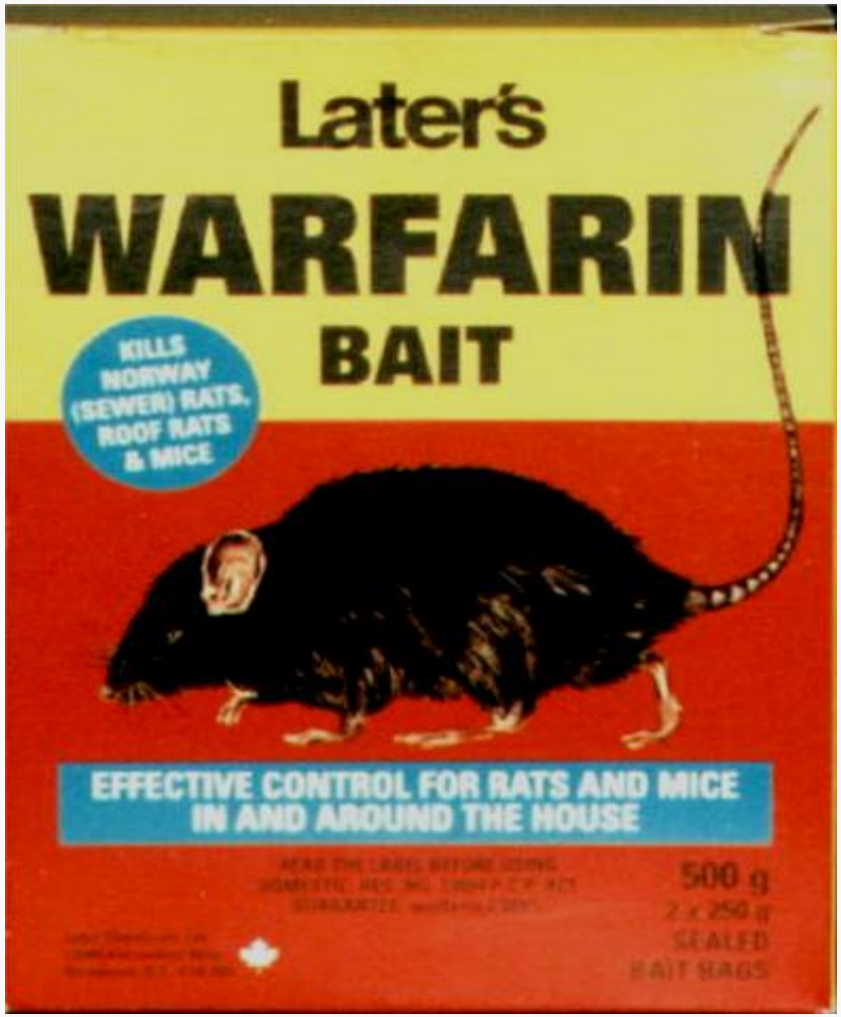
DWIGHT EISENHOWER and NIKITA KHRUSHCHEV SURVIVORS THANKS TO WARFARIN

1939


Later's
WARFARIN
BAIT
KILLS NORWAY (SEWER) RATS, ROOF RATS & MICE
EFFECTIVE CONTROL FOR RATS AND MICE IN AND AROUND THE HOUSE
500 g
2 x 250 g
SEALED
BAIT BAGS

Warfarin therapy has several limitations that make it difficult to use in practice

- Unpredictable response
- Narrow therapeutic window (INR range 2-3)
- Routine coagulation monitoring
- Frequent dose adjustments
- Slow onset/offset of action
- Numerous food-drug interactions
- Numerous drug-drug interactions
- Risk of Bleeding Complications

J Thromb Thrombolysis 2008; 25: 52-60

- AVK inibiscono la formazione del coagulo antagonizzando le funzioni della vitamina K, essenziale per maturare completamente
  - 4 fattori della coagulazione
    - FII (protrombina), FVII, FIX, FX
  - 3 fattori anticoagulanti
    - Proteina S, proteina C, e Z
- Effetto anticoagulante non prevedibile (monitoraggio INR)
- Lento inizio e lento termine dell'attività
- Lunga emivita plasmatica circa 36-42 h
  - durata di azione di 2-5 giorni
  - necessità di un rapido antagonismo in caso di grave emorragia
- Metabolismo epatico - citocromo CYP450
  - Metaboliti inattivi eliminati con urine e feci

Warfarin - molteplici interazioni farmacologiche

acetaminofene
alcol
allopurinolo
amiodarone HCl
argatroban
ASA
atorvastatina
azitromicina
bivalirudin
cefamandolo
cefazolina
cefoperazone
cefoxitina
ceftriaxone
celecoxib
chenodiol
cloramfenicolo
cloralio idrato
colestiramina
cimetidina
ciprofloxacina
claritromicina
clofibrato
danazolo
destrano
destrotiroxina
diclofenac
dicumarolo
diflunisal
doxiciclina
eritromicina
esomeprazolo
ezetimibe
fenofibrato
fenoprofene
fluconazolo
fluoxetina
flutamide
fluvastatina
gefitinib
gemfibrozil
glucagone
eparina
ibuprofene
ifosfamide
vaccino antiinfluenzale
itraconazolo
ketoprofene
lansoprazolo
lepirudina
levamisolo
levotiroxina
liotironina
lovastatina
metimazolo
metildopa
metilfenidato
metronidazolo
acido nalidixico
naproxene
norfloxacina
ofloxacina
olsalazina
oxandrolone
oxaprozina
oxymetolone
pantoprazolo
paroxetina
penicillina G, ev
fenitoina
piperacillina
pravastatina
prednisone
propafenone
propranololo
propiltiouracile
chinidina
rabeprazolo
ranitidina
rofecoxib
simvastatina
stanozololo
streptokinasi
sulfametoxazolo
sulfinpirazone
sulfisoxazolo
tamoxifene
tetraciclina
tiroide
ticlopidina
plasminogeno tissutale
attivatore (t-PA)
tolbutamide
tramadolo
urokinasi
valdecoxib
vitamina E
zafirlukast

*La lista non è completa

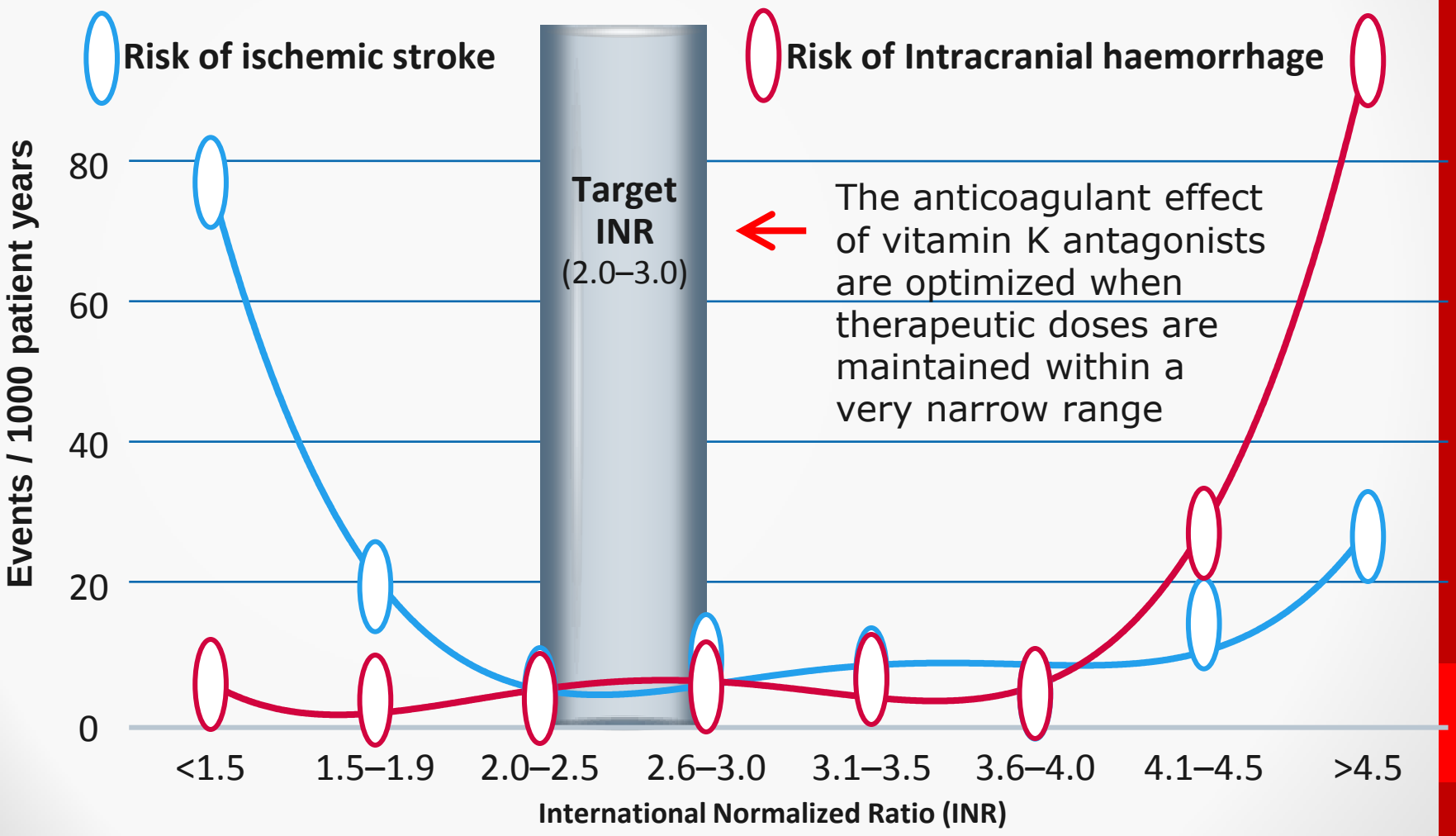
- Da evidenziare:
  - Atorvastatina
  - Esomeprazolo, lansoprazolo
  - Paracetamolo (acetaminofene), ASA, ibuprofene
  - Propranololo, naproxene
  - Cloramfenicolo, claritromicina, tetraciclina, penicillina G, metronidazolo …
  - Alcool

RCP Warfarin

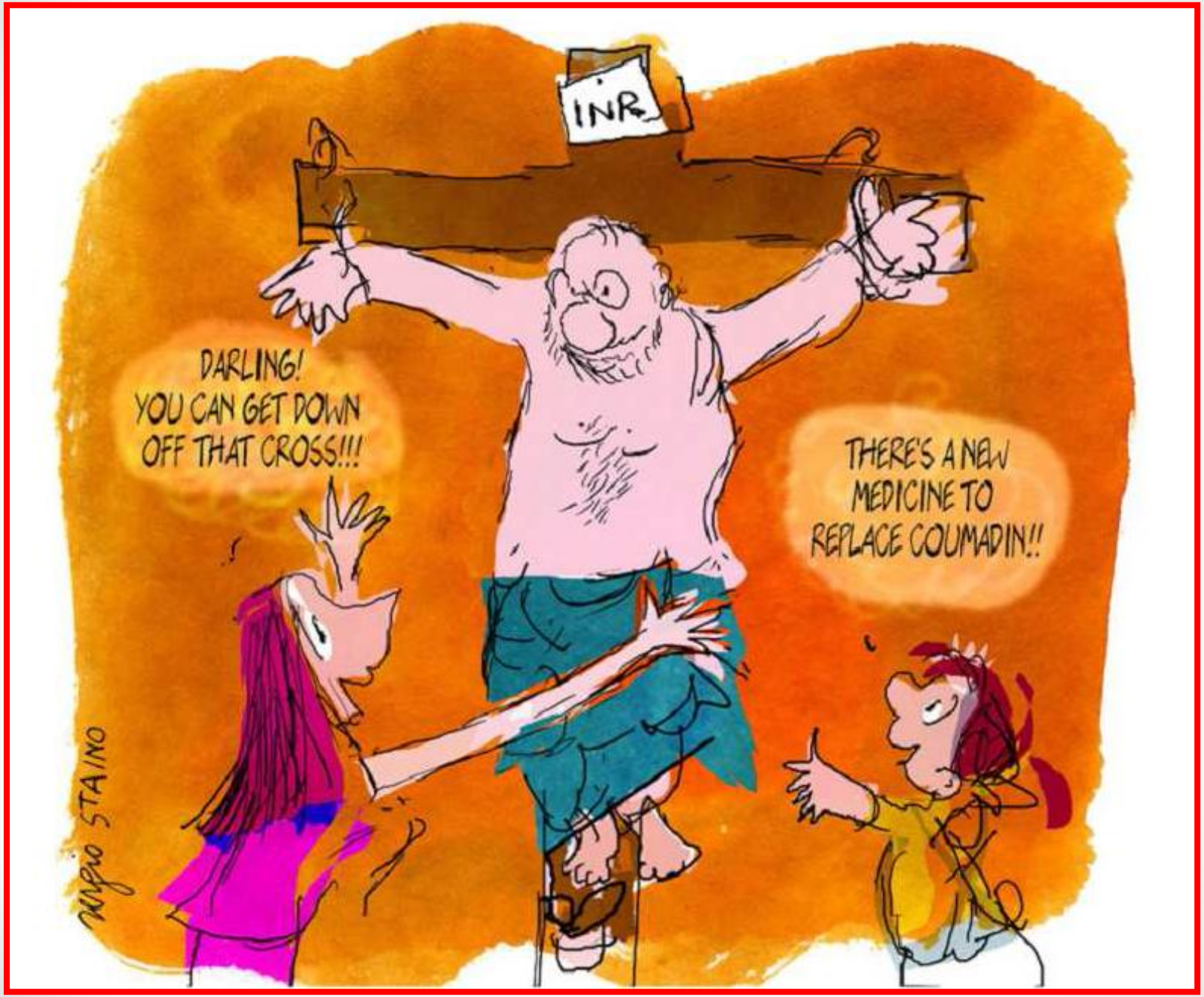
Gli AVK hanno diverse interazioni con il cibo

- Gli alimenti, soprattutto quelli che contengono la vitamina K, possono compromettere l'efficacia della terapia con AVK[1]
- I pazienti devono
  - prestare attenzione al contenuto di vitamina K degli alimenti che vengono consumati e mantenere un apporto stabile di vitamina K[2,3]
  - avere una dieta normale e bilanciata
  - evitare cibi ad elevato contenuto di vitamina K: broccoli, cavolfiori, cavoli, cavolini di Bruxelles e oli vegetali.

LIMITATIONS OF WARFARIN THERAPY IN AF: NARROW THERAPEUTIC WINDOW



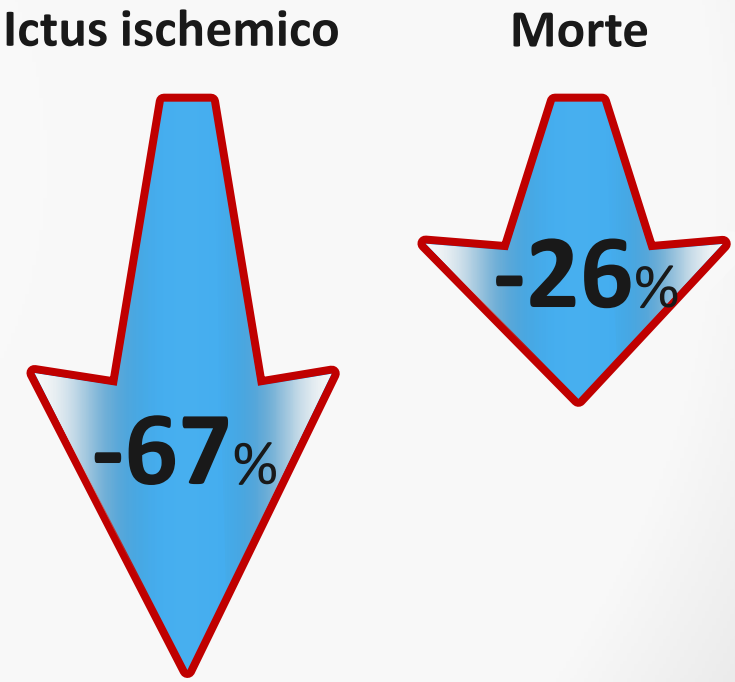
Hylek EM, et al. N Eng J Med 2003;349:1019-1026


INR
DARLING! YOU CAN GET DOWN OFF THAT CROSS!!!
THERE'S A NEW MEDICINE TO REPLACE COUMADIN!!
Angelo STAINO

FIBRILLAZIONE ATRIALE
Prevenzione dell'ictus

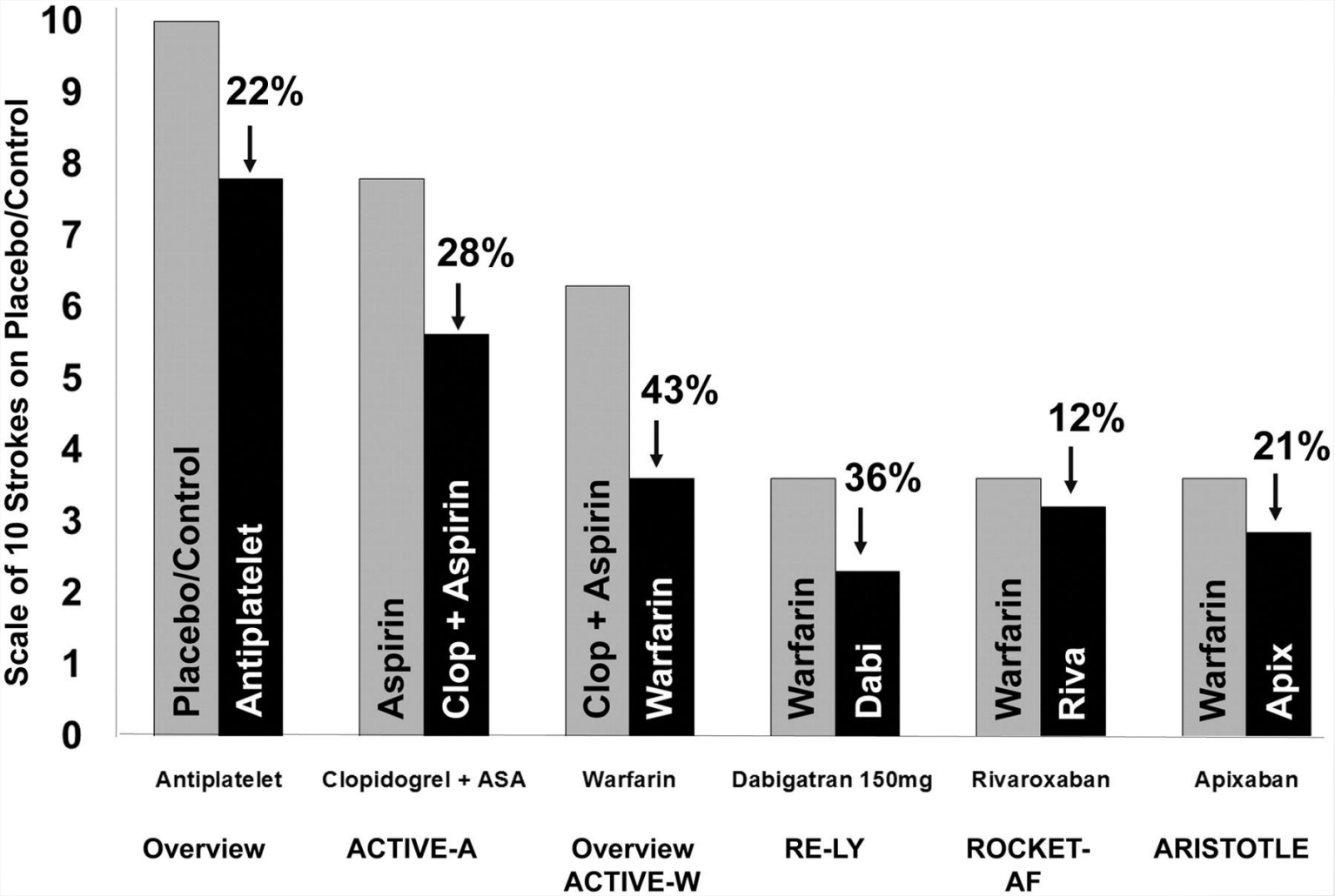
- Due terzi degli ictus dovuti a FA possono essere **prevenuti** mediante un adeguato trattamento anticoagulante con un **antagonista della vitamina K (VKA) con PT-INR= 2,0–3,0**
- Una meta-analisi di 29 trials su 28.044 pazienti ha mostrato che warfarin con dosaggio ben controllato determina **una riduzione del tasso di ictus ischemico e di mortalità per tutte le cause**

Effetto di VKA rispetto al placebo



1. Hart RG, et al. *Ann Intern Med* 2007;146:857-867. 2. Fuster V, et al. *J Am Coll Cardiol* 2006;48:854-906.

Stroke risk reductions from randomized trials of antithrombotic agents in atrial fibrillation



Granger C B , Armaganijan L V Circulation 2012;125:159

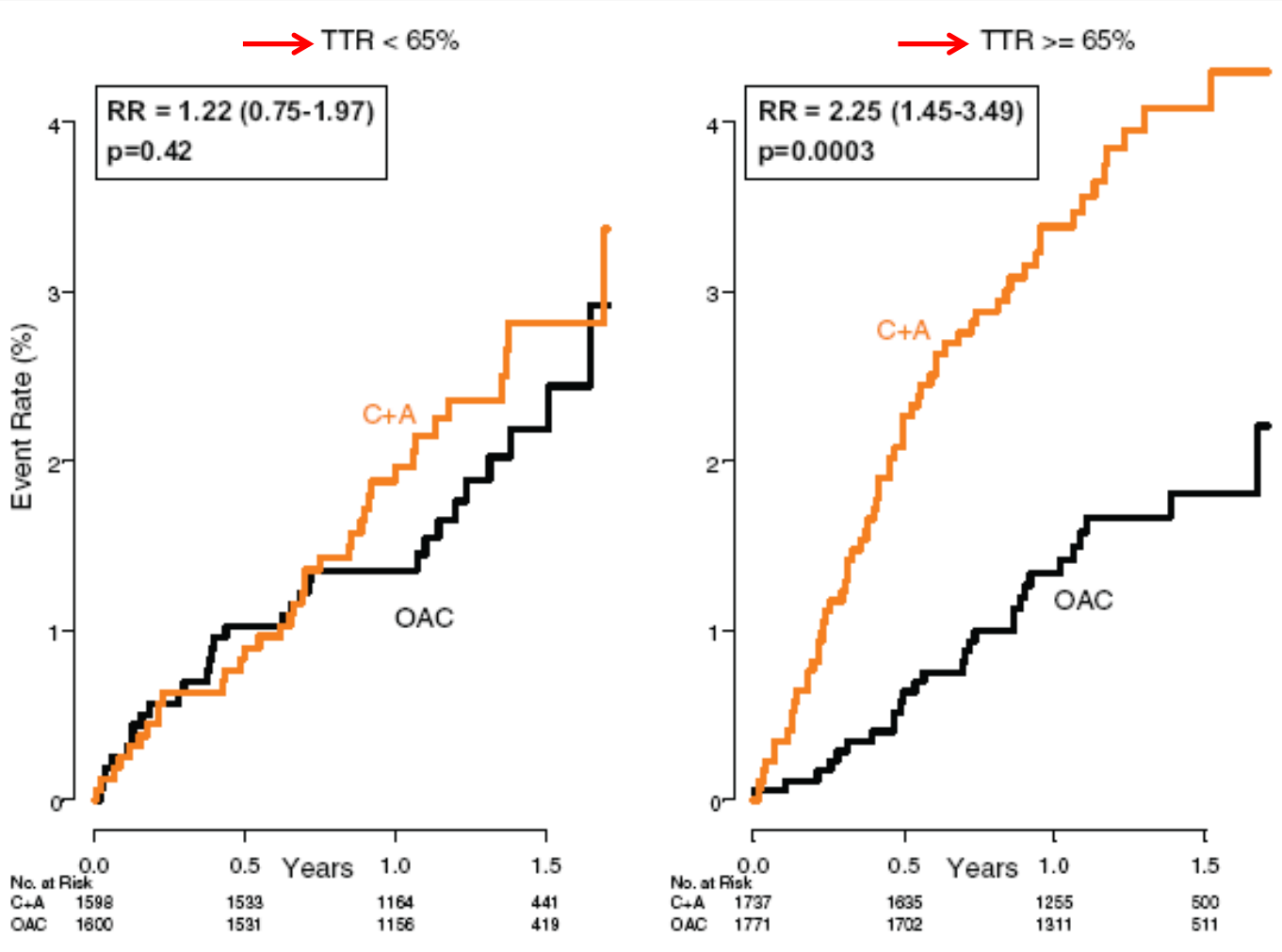
Inappropriatezza a confrontare tra loro i nuovi anticoagulanti

- **Il NICE** ha concluso che, a causa delle differenze nelle caratteristiche basali dei pazienti arruolati nei trials clinici, i risultati dei confronti indiretti e metanalisi tra rivaroxaban, dabigatran e apixaban dovrebbero essere interpretati con estrema cautela in quanto **non sono sufficientemente robusti** per differenziare in modo realistico le molecole tra loro

- L'agenzia canadese - il **CADTH** - dopo un'estesa revisione del profilo di sicurezza, efficacia e costo-efficacia dei nuovi anticoagulanti orali ha concluso che le differenze tra i trial **rendono il confronto tra le molecole difficoltoso e non realistico** sia in termini di efficacia relativa che di costo-efficacia

- Le stesse **Linee guida Europee** non hanno dato nessuna indicazione su quale molecola preferire dato che "*non ci sono evidenze sufficienti per raccomandare un farmaco rispetto all'altro*"

Rischio di ictus in pazienti con fibrillazione atriale, trattati con Clopidogrel + Aspirina (C+A) o anticoagulanti (OAC).



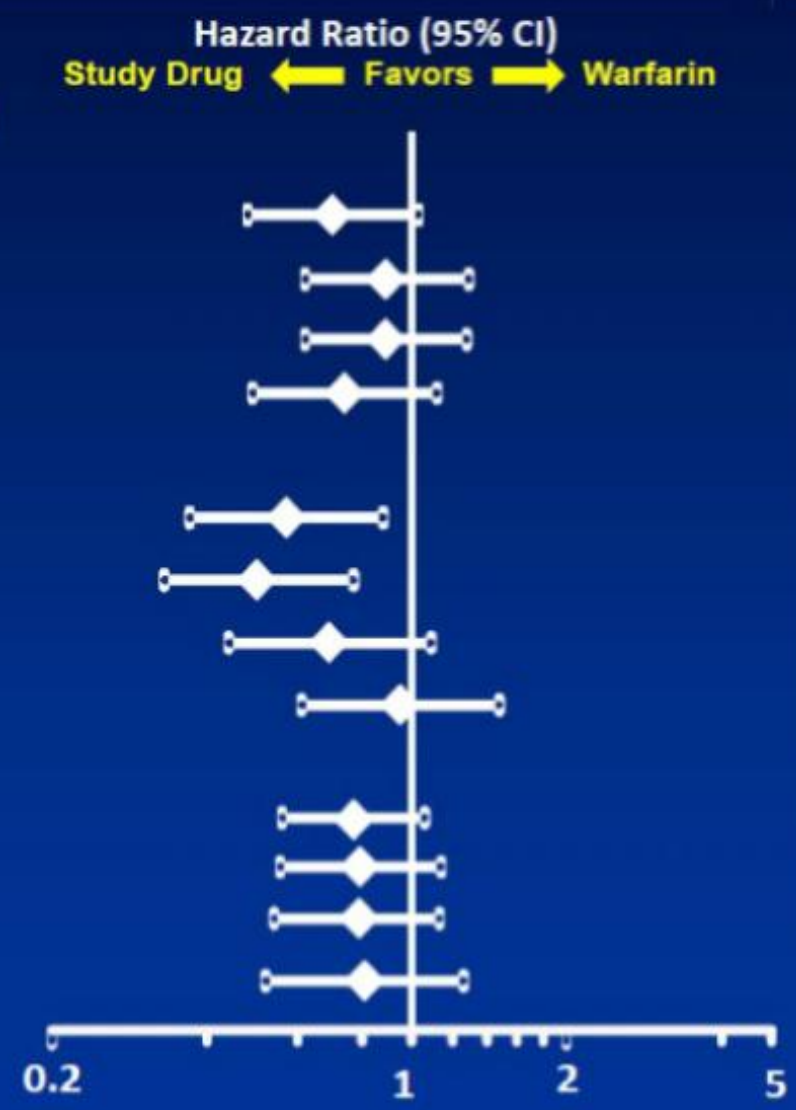
(TTR: tempo trascorso con PT-INR in range terapeutico)

Connolly et al., Circulation 2008, 118: 2029

	Treatment Group n/J (rate)	Warfarin n/J (rate)	p-value (interaction)
ROCKET AF			0.736
0.00-50.62%	45/1735 (1.77)	62/1689 (2.53)	
50.71-58.54%	53/1746 (1.94)	63/1807 (2.18)	
58.63-65.71%	54/1734 (1.90)	62/1758 (2.14)	
65.74-100.0%	37/1676 (1.33)	55/1826 (1.80)	
RE-LY (Dabigatran 150 mg)[†]			0.20
<57.1%	32/1509 (1.1)	54/1504 (1.92)	
57.1–65.5%	32/1526 (1.04)	62/1514 (2.06)	
65.5–72.6%	31/1484 (1.04)	45/1487 (1.51)	
>72.6%	38/1514 (1.27)	40/1509 (1.34)	
ARISTOTLE[‡]			0.29
< 58.0%	70/2266 (1.75)	88/2252 (2.28)	
58.0–65.7%	54/2251 (1.30)	68/2278 (1.61)	
65.7–72.2 %	51/2256 (1.21)	65/2266 (1.55)	
> 72.2 %	36/2266 (0.83)	44/2251 (1.02)	

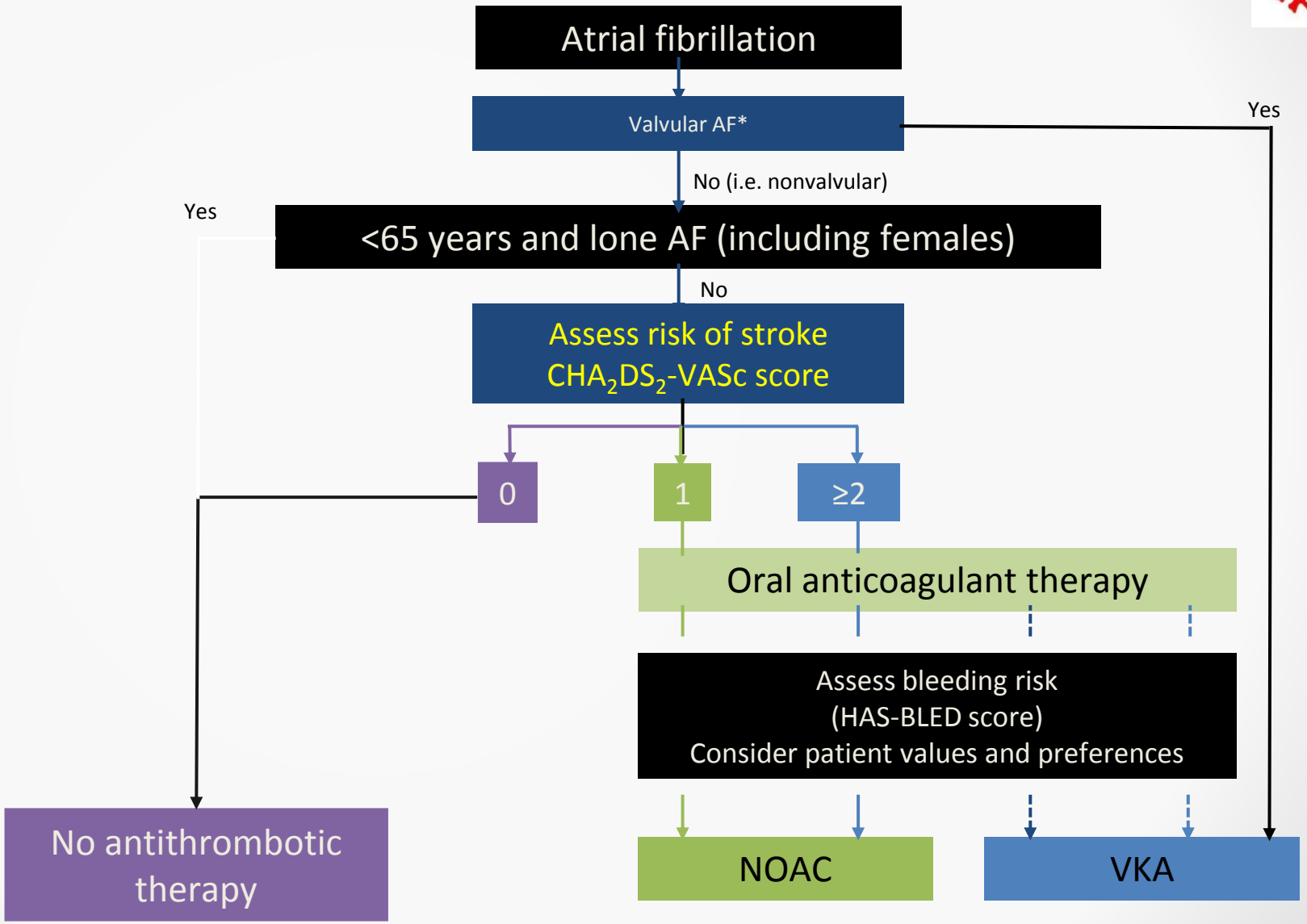
[†]Wallentin L, et al. Lancet 2010;376:975–983.
[‡]Granger, CB. Results of the ARISTOTLE Trial. ESC, France, August, 2011

Rate = number of events per 100 patient-years
n = subjects with events; J = number of subjects in each subgroup



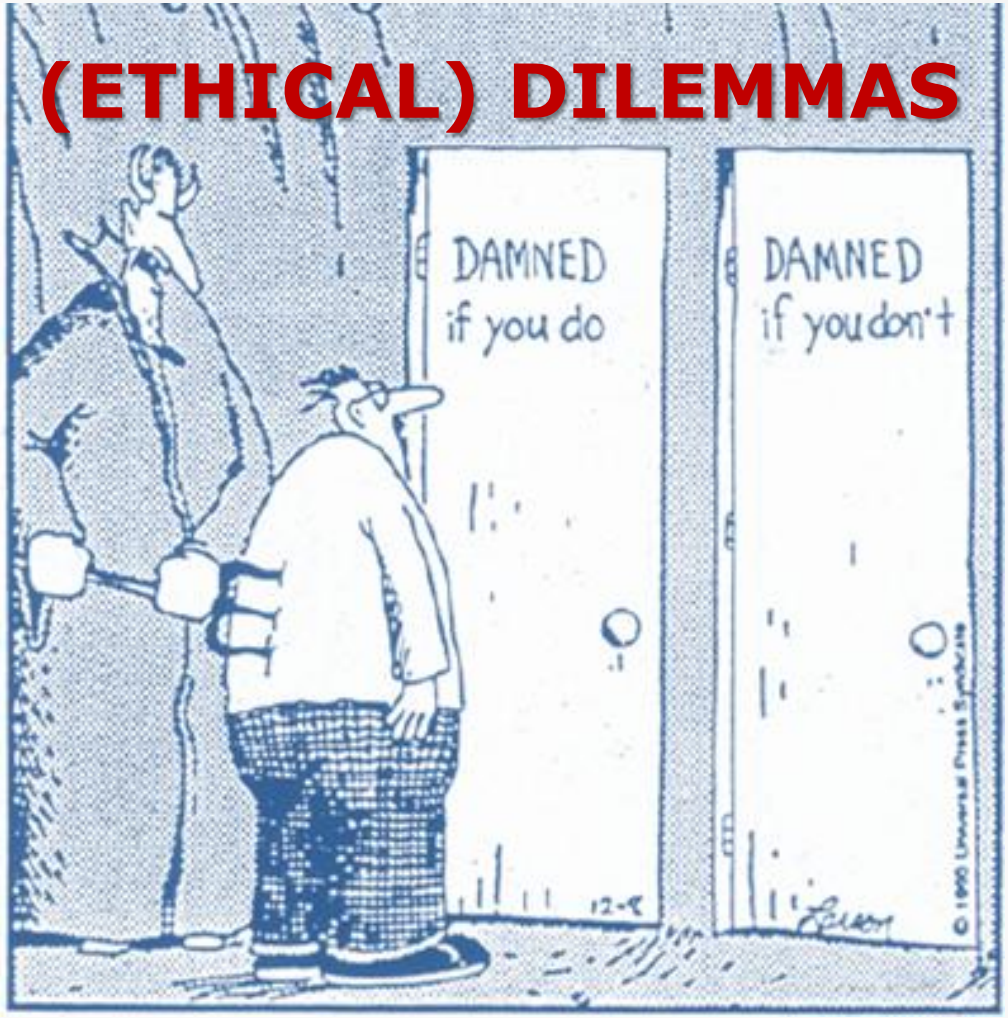
FDA Commettee Meeting, 8 sept 2011

Linee Guida ESC 2012



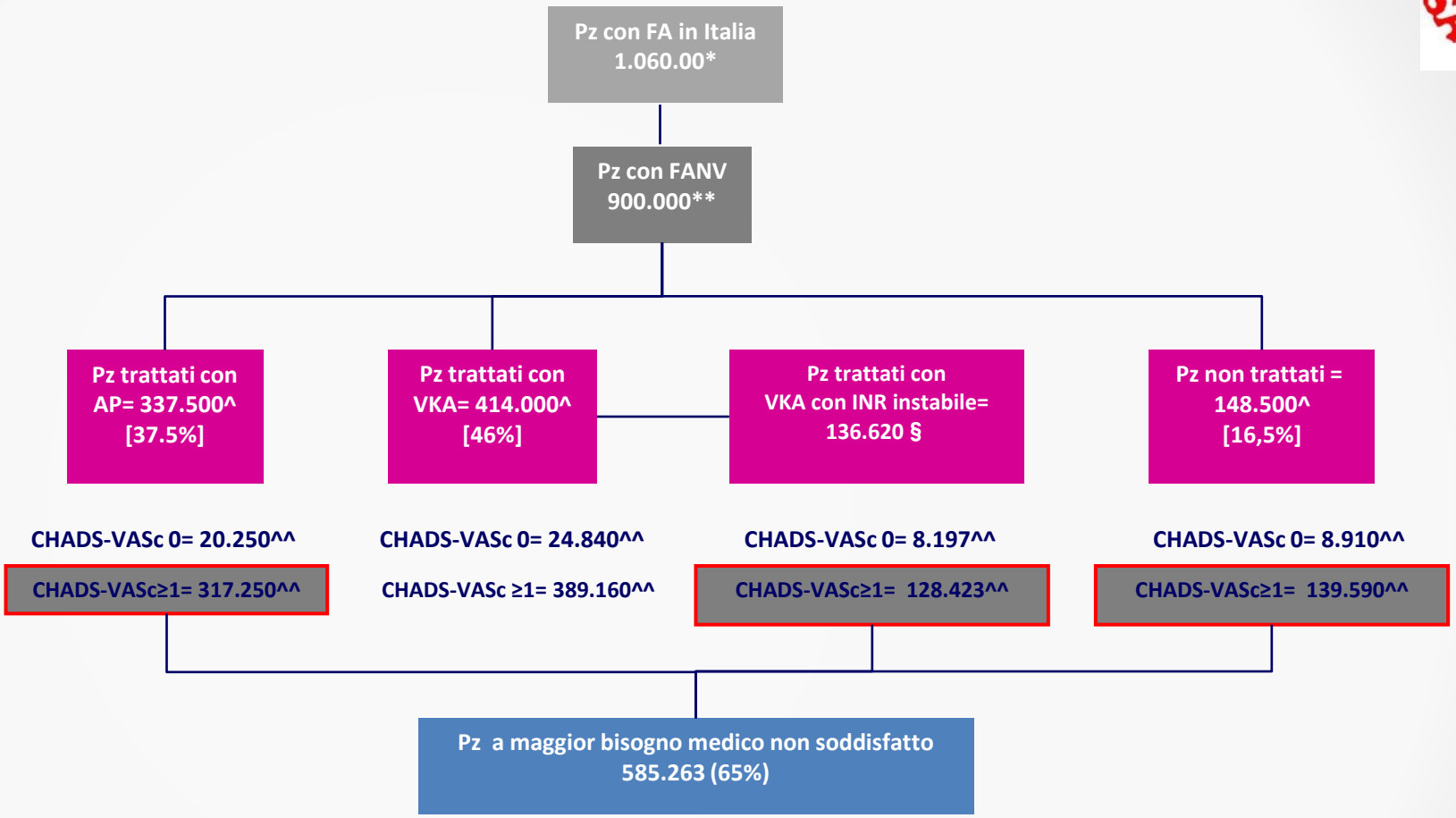
Camm AJ et al. Eur Heart J doi:10.1093/eurheartj/ehs253

(ETHICAL) DILEMMAS



Warfarin was #1 in 2003 and 2004 in the number of mentions of "deaths for drugs causing adverse effects in therapeutic use"

Warfarin caused 6% of the 702,000 ADEs treated in the ED/year; 17% required hospitalization



Epidemiologia della fibrillazione atriale. Bollettino informativo a cura del Sistema Epidemiologico Regionale del Veneto. Informazione Epidemiologia Salute Anno VI - numero 4 - dicembre 2009. Disponibile online al sito: www.ser-veneto.it (Ultimo accesso:21.08.2012). Proiezione sulla popolazione italiana residente – ISTAT 2011

**Lévy S, Maarek M, Coumel P, Guize L, Lekieffre J, Medvedowsky JL, et al. Characterization of different subsets of atrial fibrillation in general practice in France: the ALFA study. The College of French Cardiologists. Circulation 1999;99:3028-35

^Massimo Zoni-Berisso et al. Frequency, patient characteristics, treatments strategies, and resource usage of atrial fibrillation (from the italian Survey of atrial fibrillation management [ISAF] study. Am. J. cardiol 2013; 111: 705-711

§Morelli FB, Mandelli PM, Venturini M, Granati Allori A, Giustini S. La gestione dei pazienti in terapia anticoagulante orale in Medicina Generale e lo score CHADS2: una revisione fra pari. Rivista SIMG n 6, dicembre 2008

^^Leif Friberg Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study, European Heart Journal33, 1500-1510, Gennaio 2012.

Rischio annuale di ictus in pazienti con FANV		
NON trattati	5%[1]	
Trattati con antiaggreganti	3,9%	Gli antiaggreganti riducono il rischio di ictus del 22% rispetto al NON trattamento[2]
Trattati con warfarin	1,8%	Il warfarin riduce il rischio di ictus del 64% rispetto al NON trattamento[2]

Oggi nella reale pratica clinica…		
	N. pazienti	N. ictus
NON trattati	139.590	6.980
Trattati con antiaggreganti	317.250	12.373
Trattati con antagonisti della vitamina K (VKA) MA INR instabile	128.423	2.312

N. TOT ictus 21.664

In una situazione «ideale»…		
	N. pazienti	N. ictus
Pazienti in trattamento con un NOAC di efficacia almeno pari a quella del warfarin	585.263	10.535

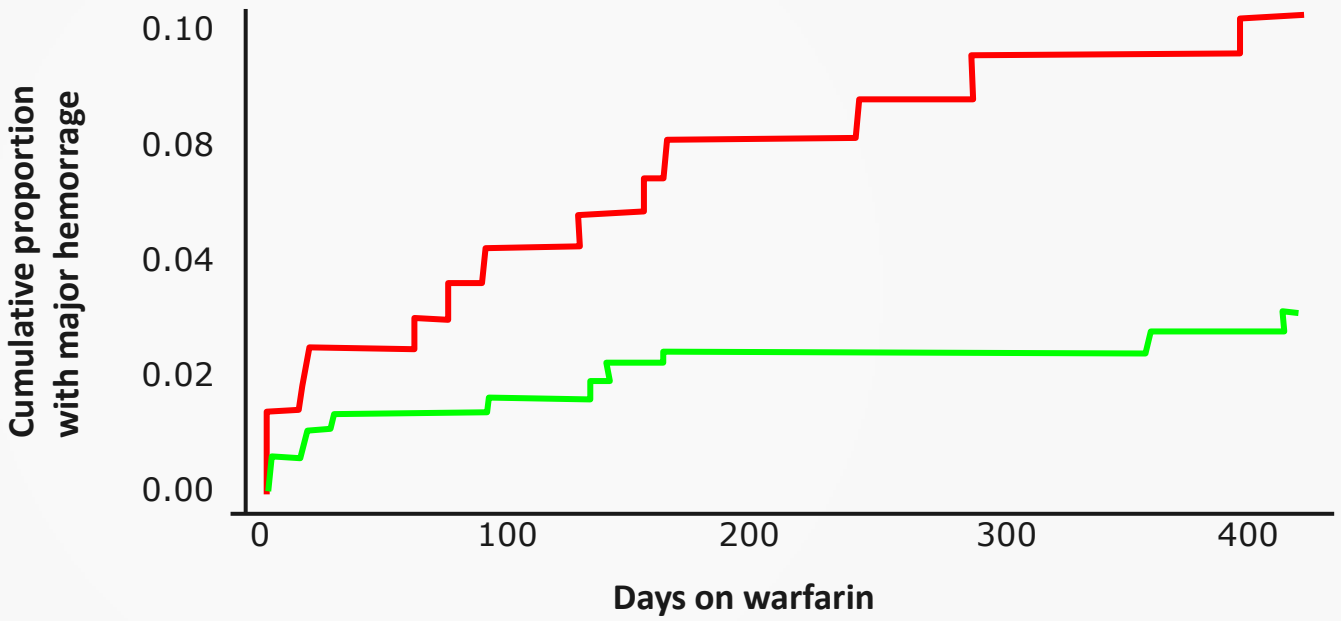
Ictus evitabili 11.129

(1) Fonte dati:rivaroxaban per la prevenzione dell'ictus in pazienti con fibrillazione atriale: risultati di una valutazione HTA. QIJPH- Year 2013, Volume 2, number 7;

(2) Fuster V. *et al*. Eur Heart J. 2006; 27(16): 1979-2030; (3) Hart R. *et al*. Ann Intern Med 2007; 146(12): 857-67

MAJOR HEMORRAGE ON WARFARIN

FIRST YEAR OF THERAPY AMONG ELDERLY PATIENTS WITH AF

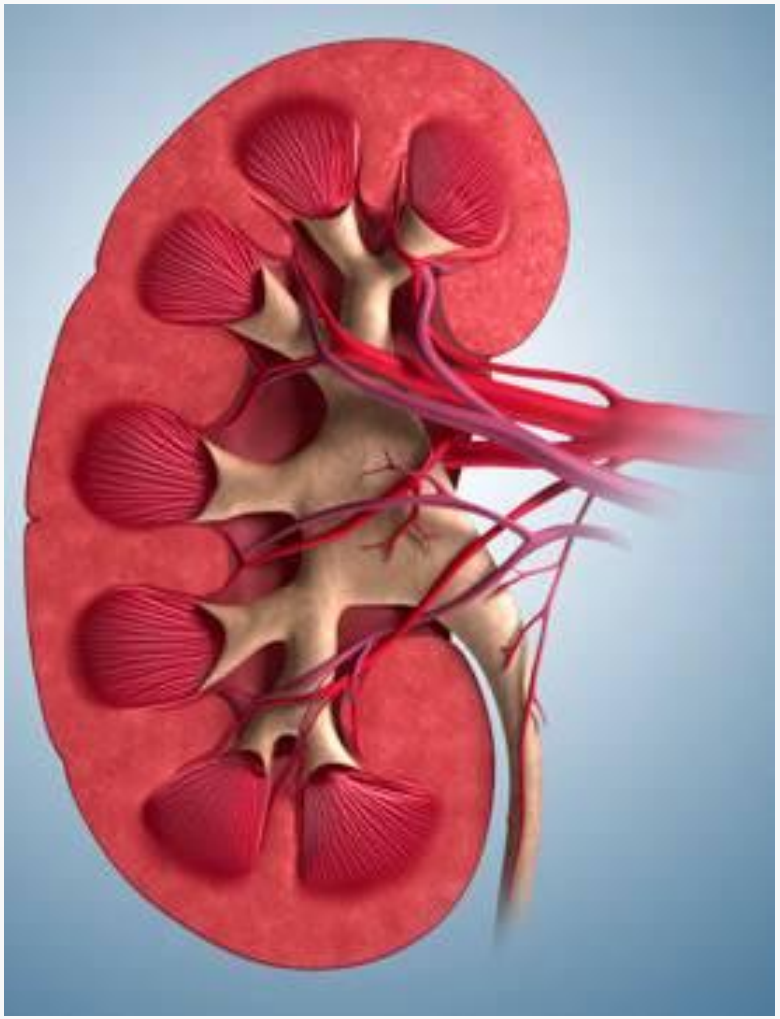


Age <80 yrs

Age ≥80 yrs

Hylek EM et al, Circulation 2007

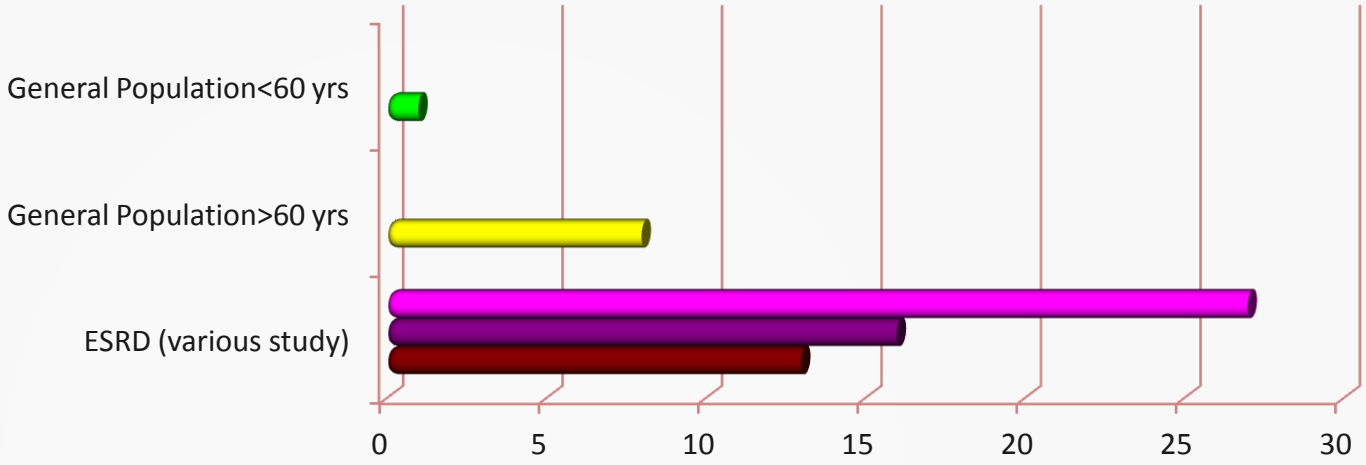
CHRONIC KIDNEY DISEASE



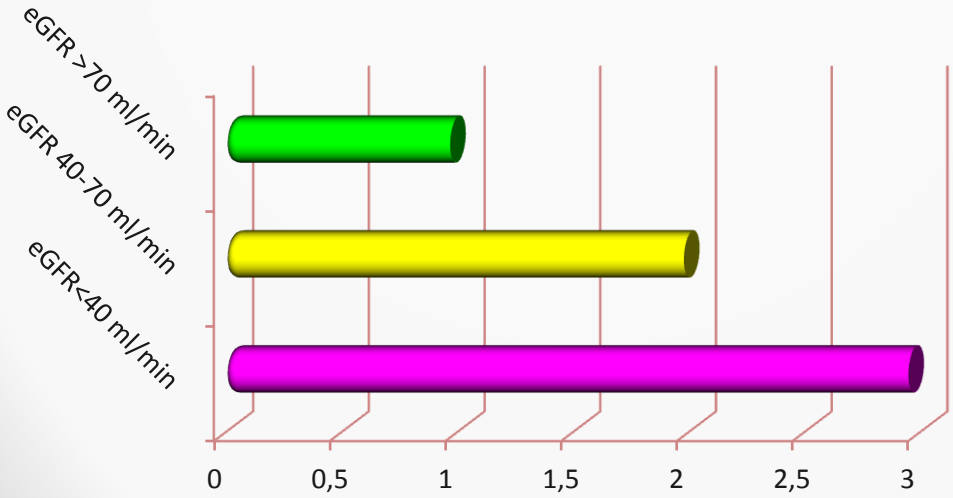
G. Cice

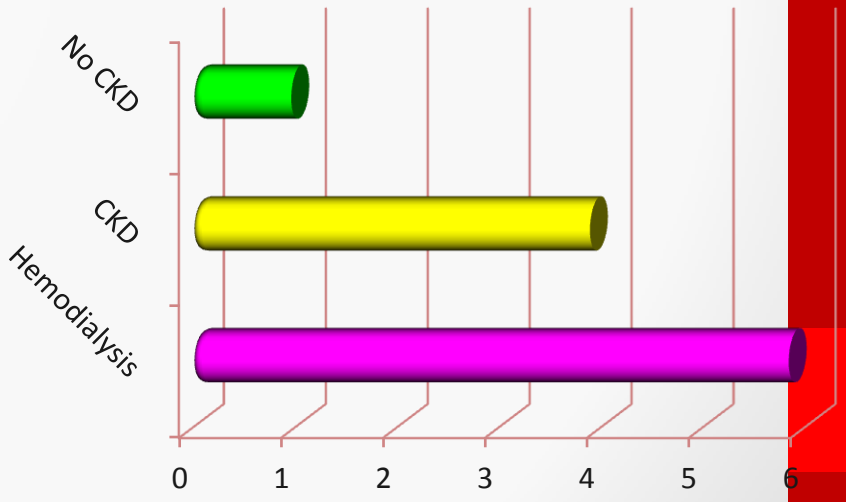
AF AND STROKE IN CHRONIC KIDNEY DISEASE

PREVALENCE OF ATRIAL FIBRILLATION (%)



RISK OF STROKE (HR)



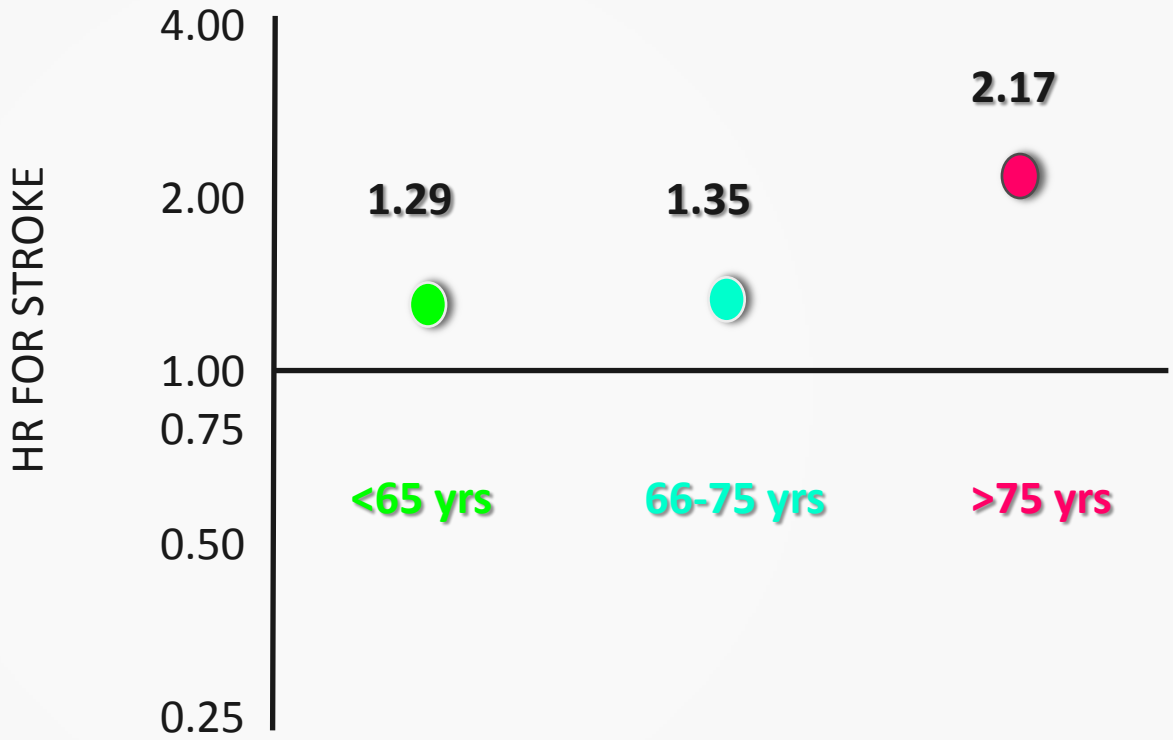


US Renal Data System: USRDS 2005

STUDIES OF WARFARIN IN HD PATIENTS WITH ATRIAL FIBRILLATION

STUDY (year, design)	HD pts WITH AF	MEAN FOLLOW-UP	MAJOR FINDINGS
To *et al.* (2007, retrospective)	40	26 months	No difference in cerebrovascular event AF vs non AF pts (5.0%/year vs. 2.4%/year; NS)
Genovesi et al (2008, prospective)	127	36 months	No difference in stroke incidence AF vs non AF pts (15.4 vs. 12.4%; $P = 0.4$).
DOPPS (2010, retrospective)	3245	Not reported	Warfarin use was associated with **higher stroke risk**; significantly in patients >75 years of age (HR = 2.17; 95% CI 1.04–4.53, P=0.04).
Chan *et al.* (2010, retrospective)	1671	19 months	Warfarin use **increased haemorrhagic stroke** risk (1.2%/year among warfarin users vs. 0.5%/year among non-users) and **ischaemic stroke** risk (5.8%/year among warfarin users vs. 2.3%/year among non-users)

ATRIAL FIBRILLATION, WARFARIN AND STROKE IN HD PATIENTS



Hazard ratio (HR) for stroke according to warfarin use, by age categories among patients with a diagnosis of atrial fibrillation at DOPPS enrollment

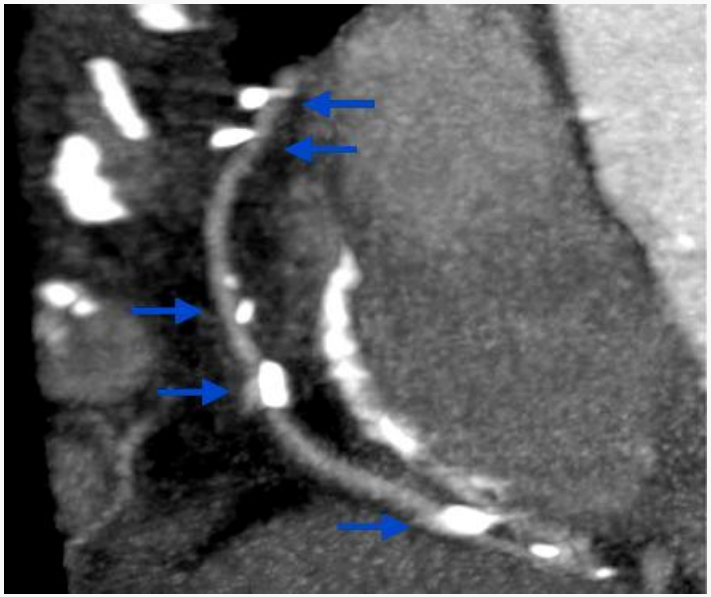
Wizemann V,. Kidney Int. 2010;77(12):1098-106

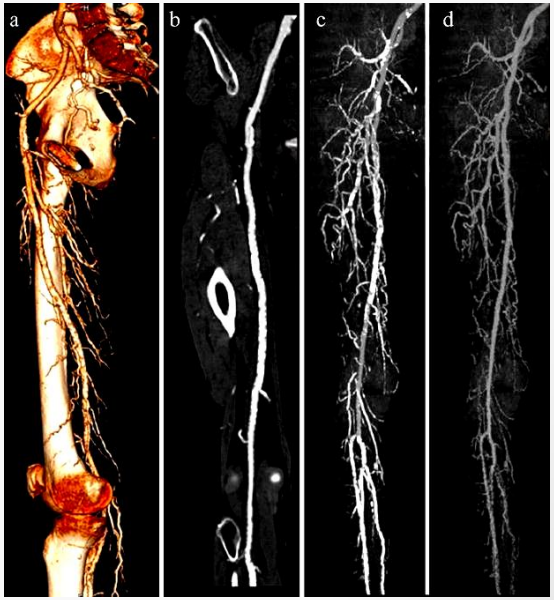
WARFARIN IN CKD PATIENTS

Calcific uraemic arteriopathy occurs in 1–4% of dialysis patients and portends a poor prognosis (45% mortality at 12 months).

Vitamin K antagonists affect the synthesis and function of the matrix Gla protein, which is a potent inhibitor of tissue calcification.

In dialysis patients, warfarin has been linked to calcific uraemic arteriopathy (calciphylaxis) as well as aortic valve calcification.





Koos R, Mahnken AH, Muhlenbruch G, Brandenburg V, Pflueger B, Wildberger JE *et al.*
Relation of oral anticoagulation to cardiac valvular and coronary calcium assessed by multislice spiral computed tomography.
Am J Cardiol 2005;96:747–9.

AGE-RELATED RENAL DECLINE MAY BE ACCELERATED BY ANTICOAGULATION WITH VKAS

Patients with renal impairment have worse clinical outcomes[1]

Renal function declines with age in most individuals, and rate of decline can be affected by various comorbidities[2]

Renal decline can be accelerated by increased calcification of renal arteries associated with VKA treatment[3–5]

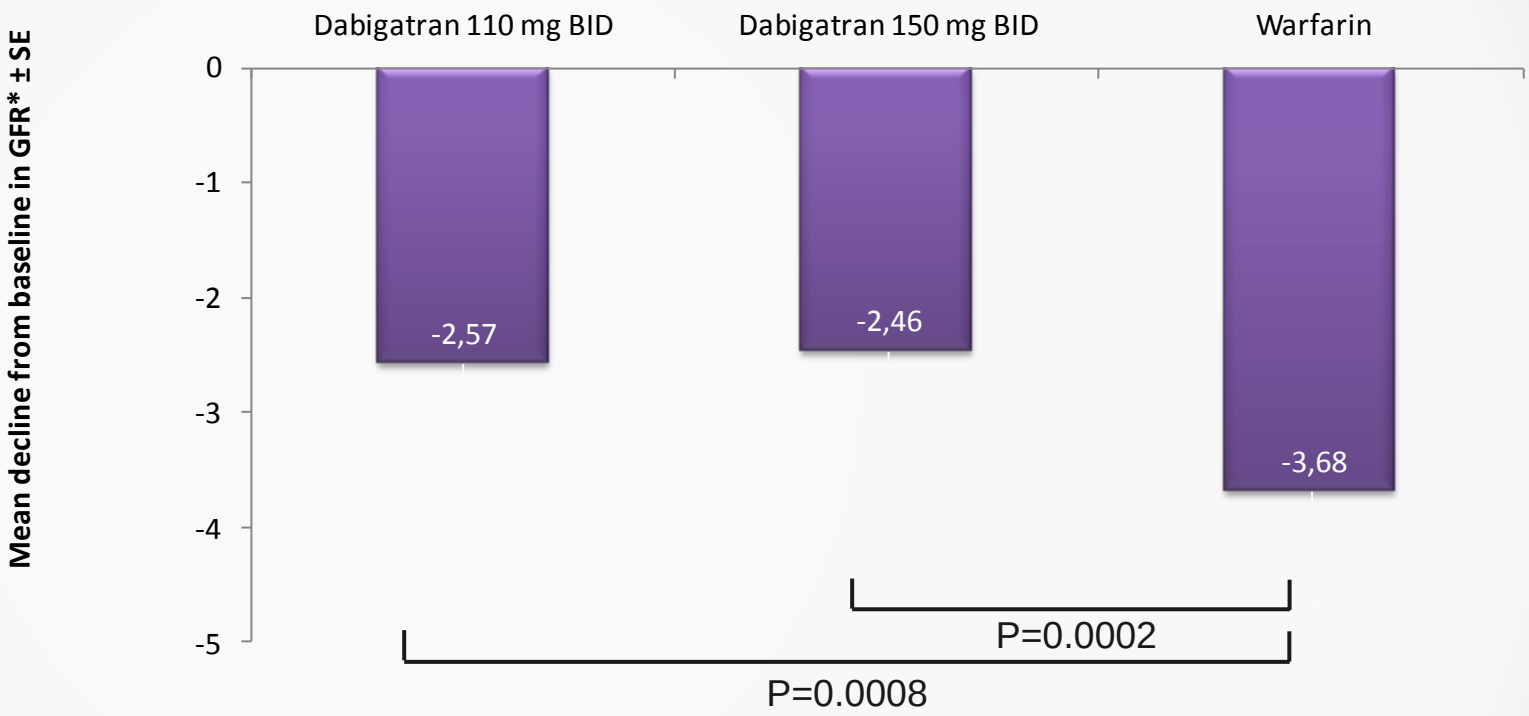
Direct thrombin inhibition may reduce vascular damage in atherosclerosis [6,7]

Hypothesis: Patients receiving NOACs may have preserved renal function compared with patients receiving VKAs

VKA = Vitamin K antagonist

1. Tonelli M et al. Clin Nephrol 2014;81:192–7; **2.** Glassock RJ et al. Kidney Int 2012;82:270–7; **3.** Zhang YT & Tang ZY. J Cardiovasc Pharmacol 2014;63:76–82; **4.** Chatrou MLL et al. Blood Reviews 2012;26:155–66; **5.** Brodsky SV et al. Kidney Int 2011;109:181–9; **6.** Bea et al. Arterioscler Thromb Vasc Biol 2006;26:2787–92; **7.** Lee et al. J Pharmacol Exp Ther 2012;343:253–7

DECLINE IN GFR AT 30 MONTHS WAS SIGNIFICANTLY REDUCED WITH BOTH DOSES OF DABIGATRAN VS VKA



*According to CKD-EPI equation

CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; HR = hazard ratio; SE = standard error

Böhm M et al. Presented at ESC 2014

NOACS IN RENAL DYSFUNCTION

	DABIGATRAN	APIXAN	EDOXABAN	RIVAROXABAN
Fraction renally excreted of absorbed dose	80%	27%	50%	35%
Bio-availability	3-7%	50%	62%	66% 100% W. FOOD
Fraction renally excreted of administered dose	4%	14%	37%	33%

Il carico renale è basso per tutte e tre le molecole (<10mg):
8,4 per dabigatran 150, 7mg per rivaroxaban, 6,2 mg per dabigatran 110mg, poco meno di 1 mg per apixaban.

Heidbuchel H. Europace (2013) 15, 625–651

NOACS IN RENAL DYSFUNCTION

	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
CrCl ≥60 ml/min CKD Stage I and II	~14 h	No data	~8.6 h	~8.5 h
CrCl 30–60 ml/min CKD Stage III	~18 h	No data	~9.4 h	~9 h
CrCl 15–30 ml/min CKD Stage IV	~28 h	No data	~16.9 h	~9.5 h
CrCl ≤15 ml/min CKD Stage V	No data	No data	No data	No data
Approved for CrCl	≥30 ml/min	≥15 ml/min	Not available	≥15 ml/min

Heidbuchel H. Europace (2013) 15, 625–651

European Heart Journal Advance Access published September 1, 2015

European Heart Journal
doi:10.1093/eurheartj/ehv466

FASTTRACK
ESC Clinical Registry

XANTUS: a real-world, prospective, observational study of patients treated with rivaroxaban for stroke prevention in atrial fibrillation

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

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)

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

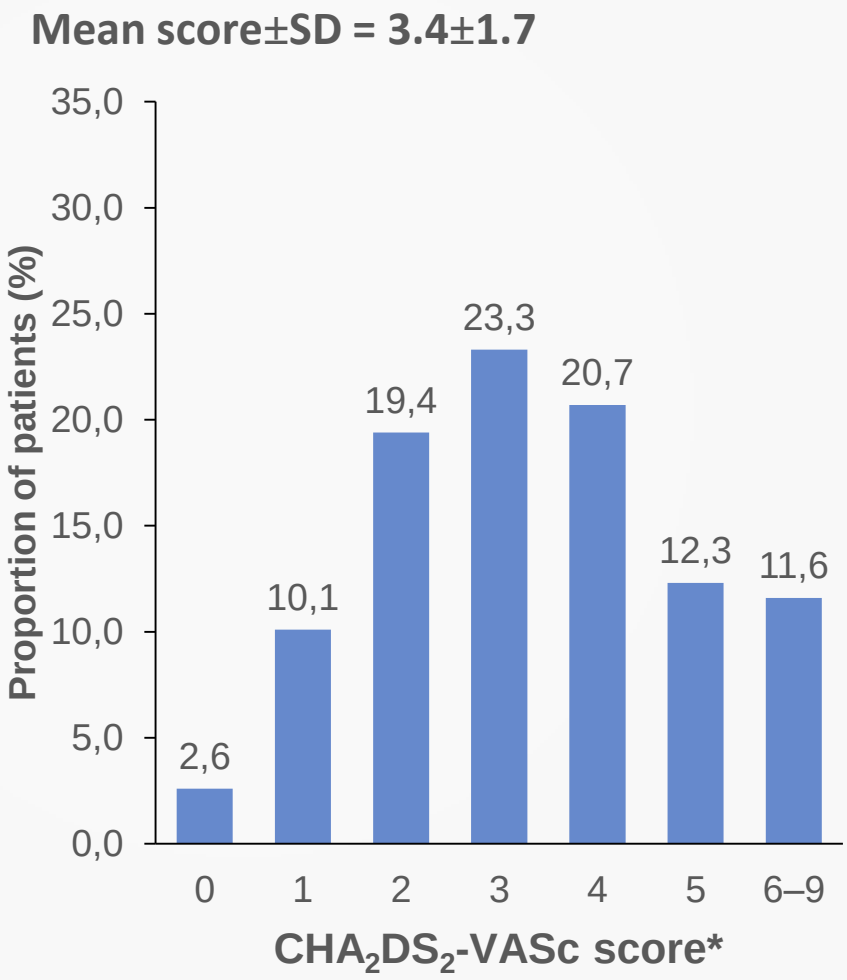
Baseline Demographics

	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

Baseline CHA_2DS_2-VASc score



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

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

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

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

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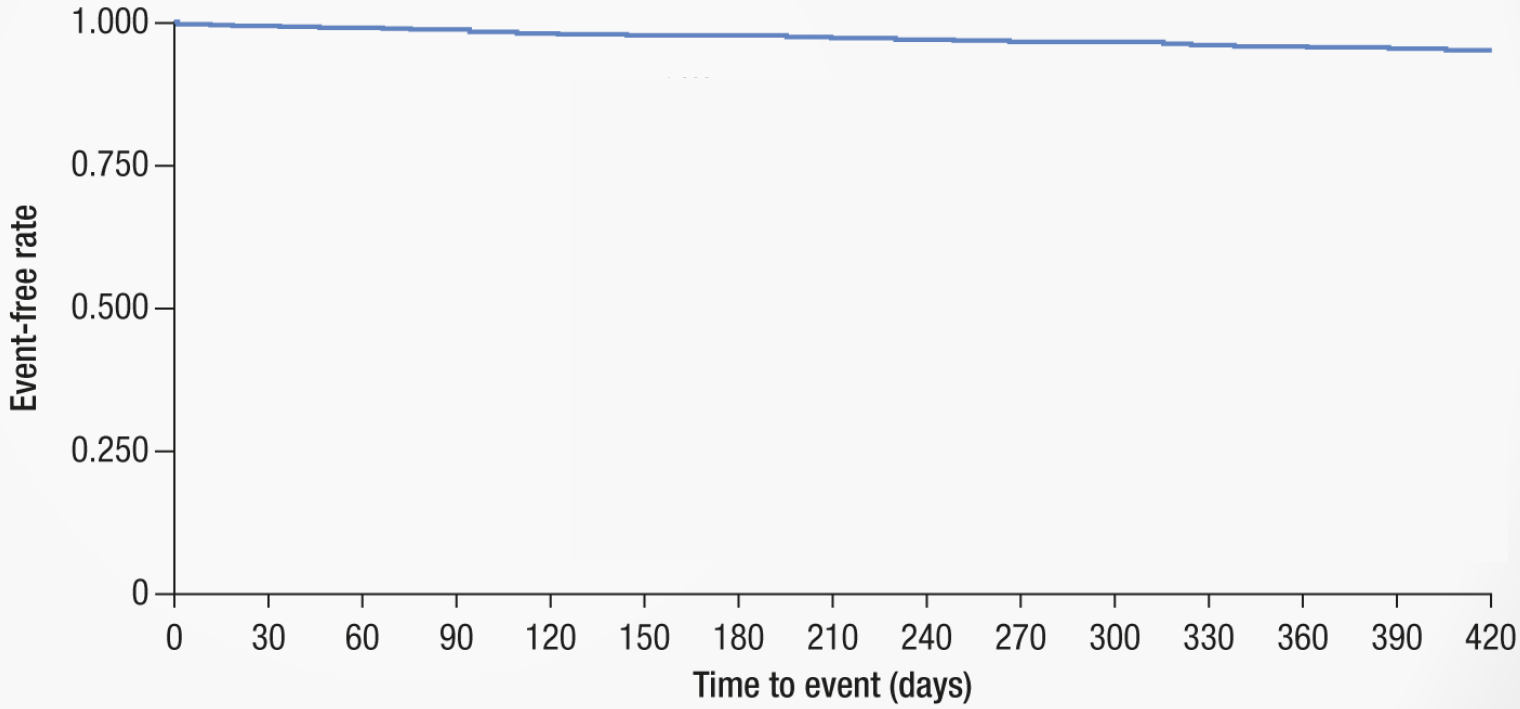
Event-Free Rate (Kaplan–Meier) for Primary Outcomes

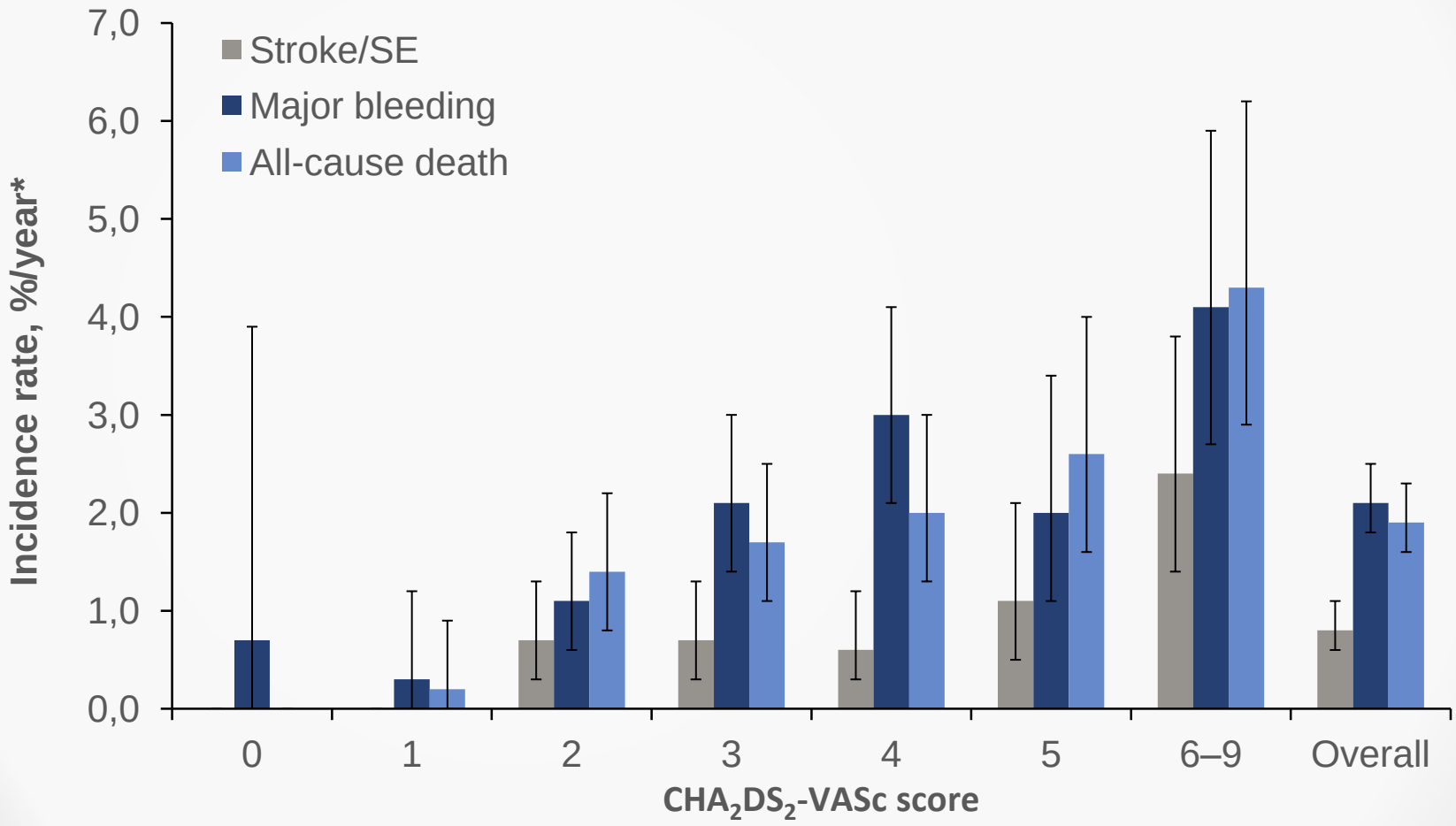
In total, 6522 (96.1%) patients did not experience any of the outcomes of treatment-emergent all-cause death, major bleeding or stroke/SE



Patients at risk: 6784 6515 6332 6181 6016 5896 5812 5713 5633 5549 5458 5237 4258 1139 510

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

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



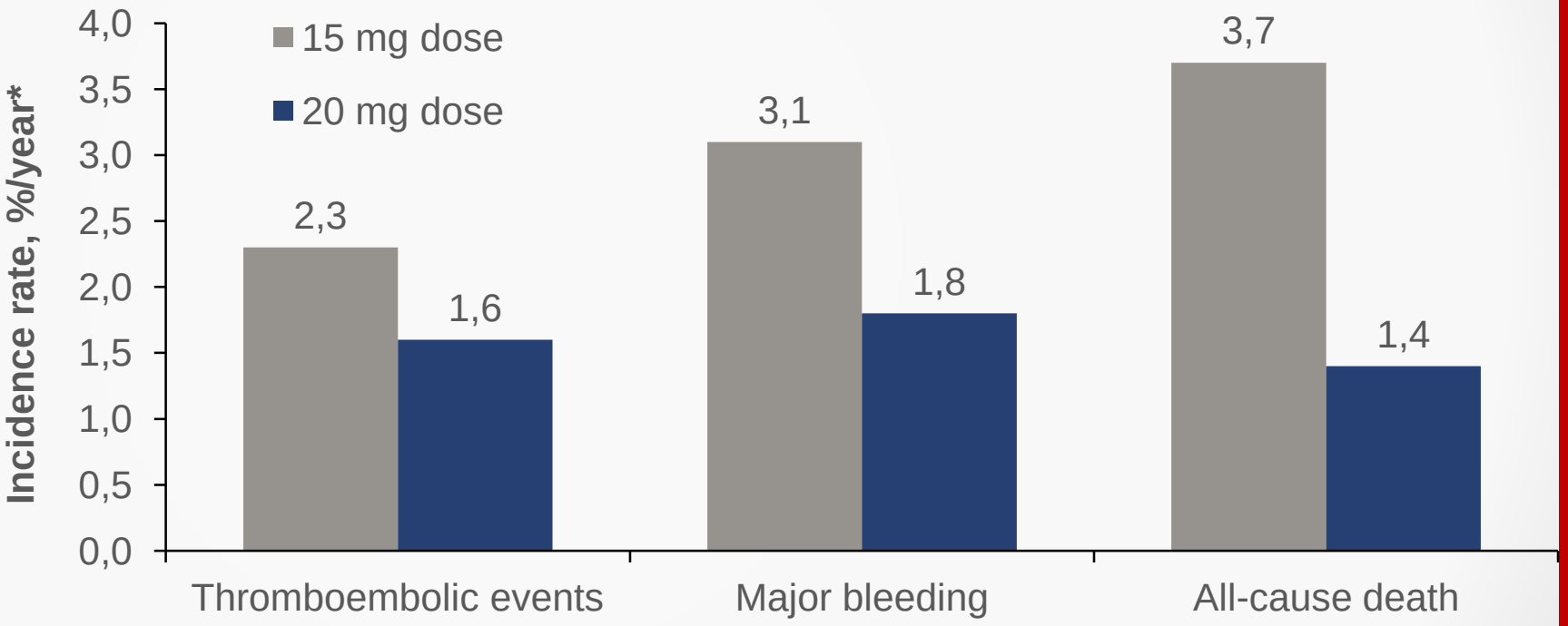
Patients (n)	174	685	1313	1578	1405	837	789	6781

Events were centrically adjudicated *Events per 100 patient-years

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

Outcomes According to Dosing (20/15 mg od)

- Major bleeding, all-cause death and thromboembolic events (stroke/SE/TIA/MI) occurred at higher incidence rates for the 15 mg od versus the 20 mg od dose



- Dosing decisions may have been based on other clinical considerations besides impaired renal function

*Events per 100 patient-years

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