



Anticoagulazione in Neurologia: algoritmi decisionali nel post-ictus

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Conflitti di interesse

- Grant per organizzazione congressi: Bayer, Pfizer, Lundbeck, Genzyme, UCB, PIAM, Epitech, Ecupharma, Merck Serono, Novartis, Roche, Sanofi, Teva, Biogen, Istituto Lusofarmaco, Daiichi-Sankyo
- Grant per ricerca: Regione Lombardia, Pfizer
- Fees per consulenze: Pfizer-BMS, Bayer

AF decision support tool



RESULTS

Back Stroke & Bleeding Risks QALY Scale AHA/ACC/HRS Guidelines What are QALYs CHA₂DS₂-VASc HAS-BLED Anticoagulant Medication Details

Risk Factors

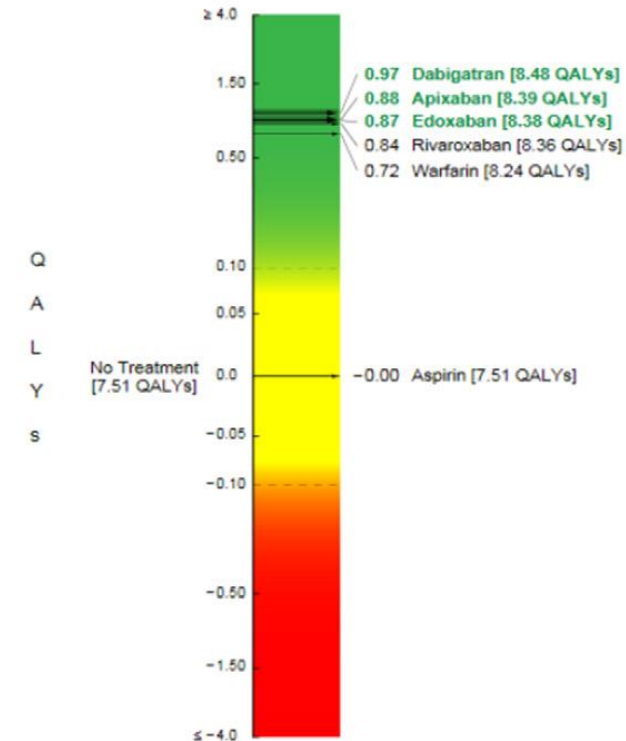
01234567
Boaty McBoatface
Age: 80
eGFR: 70 ml/min/1.73m²

Current Treatment:
No Treatment

Age 65-74	Age ≥ 75	HAS-BLED = 1
Female Gender	CHF	CHA ₂ DS ₂ -VASc = 5
HTN	Poorly Controlled HTN	Annual rate of ischemic stroke without treatment 6.7% / year
DM	Hx of Stroke	
Bleeding Hx	Hx ICH	Annual rate of major non-CNS bleed with warfarin 0.7% / year
Labile INR	Non-aspirin NSAIDs	
CAD	Hx MI	Annual rate of ICH with warfarin 0.29% / year
ETOH	Vascular Disease	
Abnl Liver	Abnl Renal	

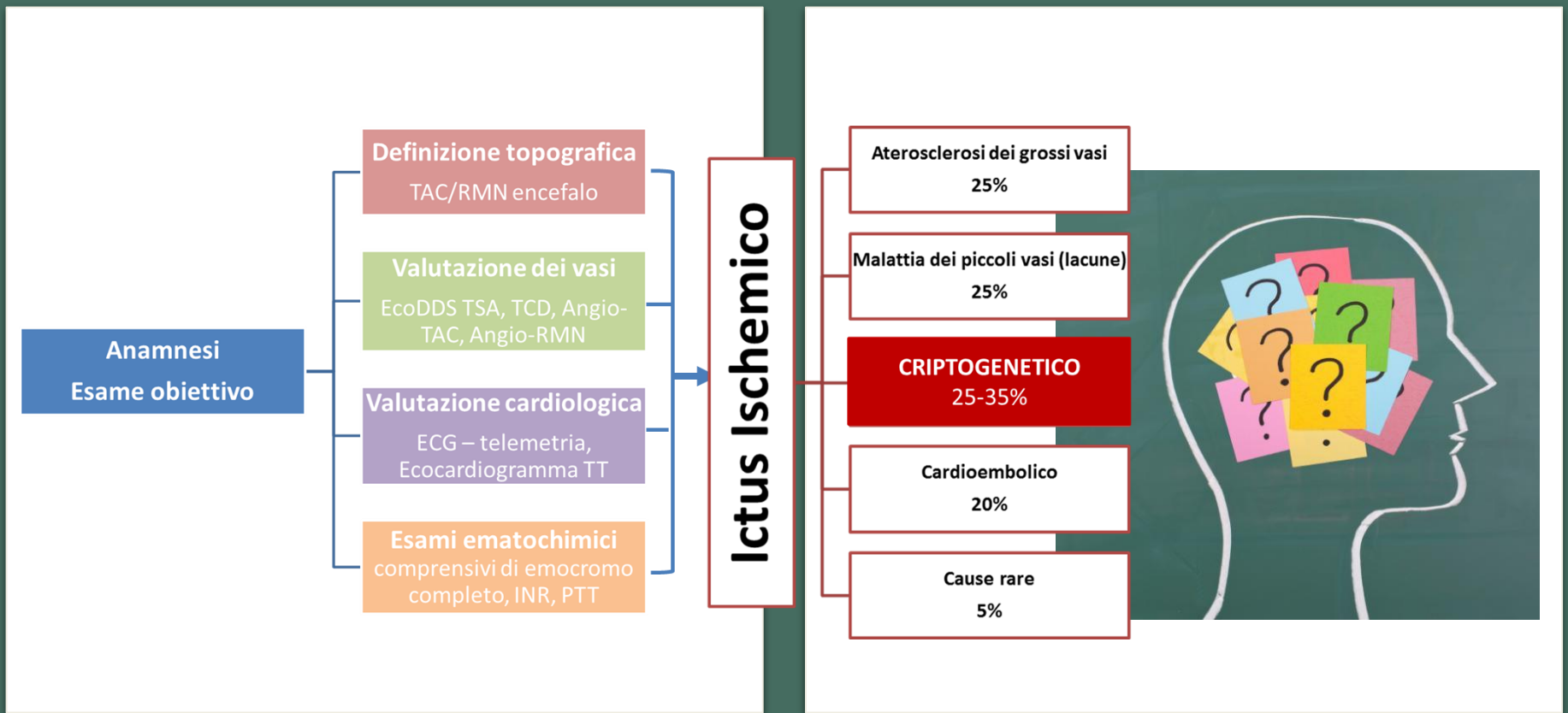
Red bolded terms indicate clinical risk factors from the EMR used to predict this patient's risk of stroke and major bleeding.

Gain/Loss in Quality Adjusted Life Years (QALYs) Compared to No Treatment



PRINT





Sottotipi di ictus secondo la classificazione TOAST (1985)

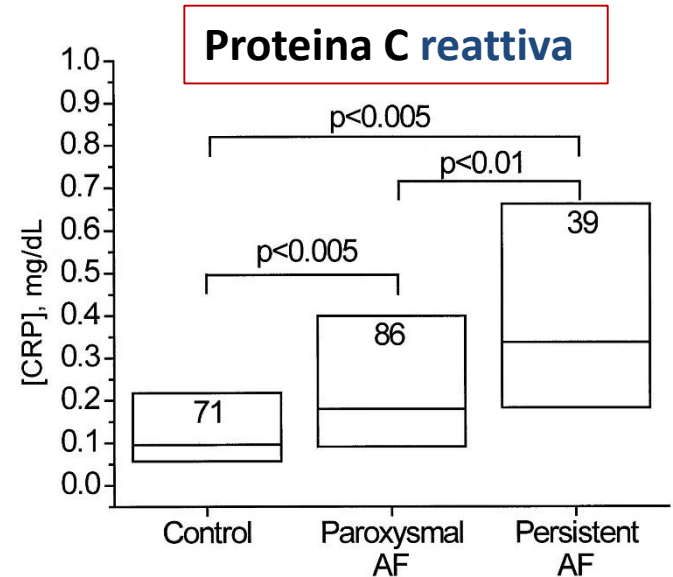
Diagnosi di FA dopo un evento ischemico cerebrale

Al Pronto Soccorso	
ECG 12 derivazioni	7,7% (5,0-10,8)
Durante il ricovero	
ECG seriati	5,6% (3,6-7,9)
Monitoraggio ECG continuo	7,0% (3,9-10,8)
Telemetria cardiaca	4,1% (0,9-9,2)
ECG secondo Holter	4,5% (2,7-6,7)
Totale	5,1% (3,8-6,5)
Ambulatoriale entro 1-7 giorni	
Holter ECG	10,7% (5,6-17,2)
Ambulatoriale dopo 7 giorni	
Telemetria cardiaca mobile ambulatoriale	15,3% (5,3-29,3)
Loop recording esterno	16,2% (9,3-24,6)
Loop recording impiantabile	16,9% (10,3-24,9)
Totale	16,9% (13,0-21,2)

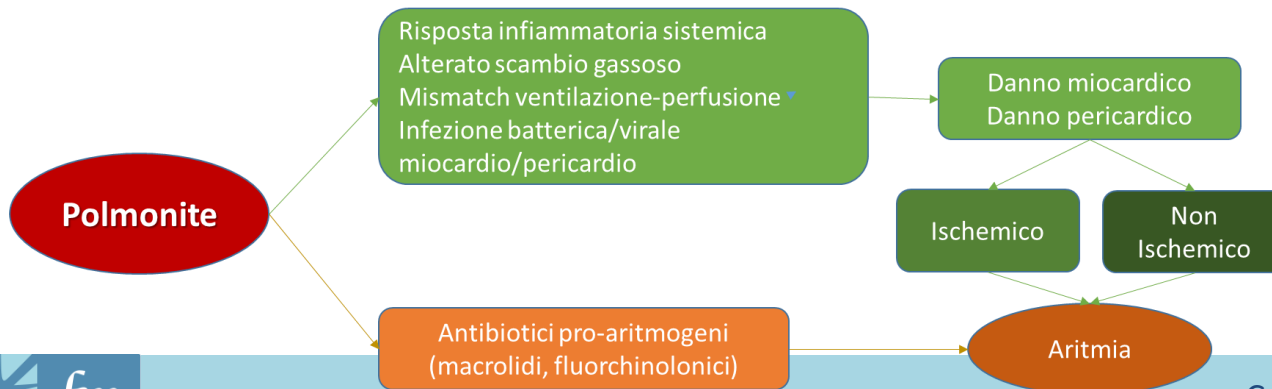
FA atriale cardiogena o neurogena?

	New-onset AF (n=23)	Known AF (n=64)	p	Sinus Rhythm (n=188)	p
Età, anni	72	79		69	0,032
Sesso M (%)	78,3	53,1	0,035	66	
Dilatazione atrio sn (%)	60,9	91,2	0,001	49,3	
Dimensioni atrio sn, mm	22,0	26,0	0,021	20	
CHADS2	2,0	2,6	0,030	2	
CHA2DS2-VASc	3,5	4,4	0,014	3,4	
Lesione ischemica ≥ 15 mm	60,9	46,9		37,2	0,029
Infarto insulare	30,4	9,5	0,17	7,3	<0,001

Gonzalez Toledo ME et al, J Stroke and Cerebrovasc Dis 2013

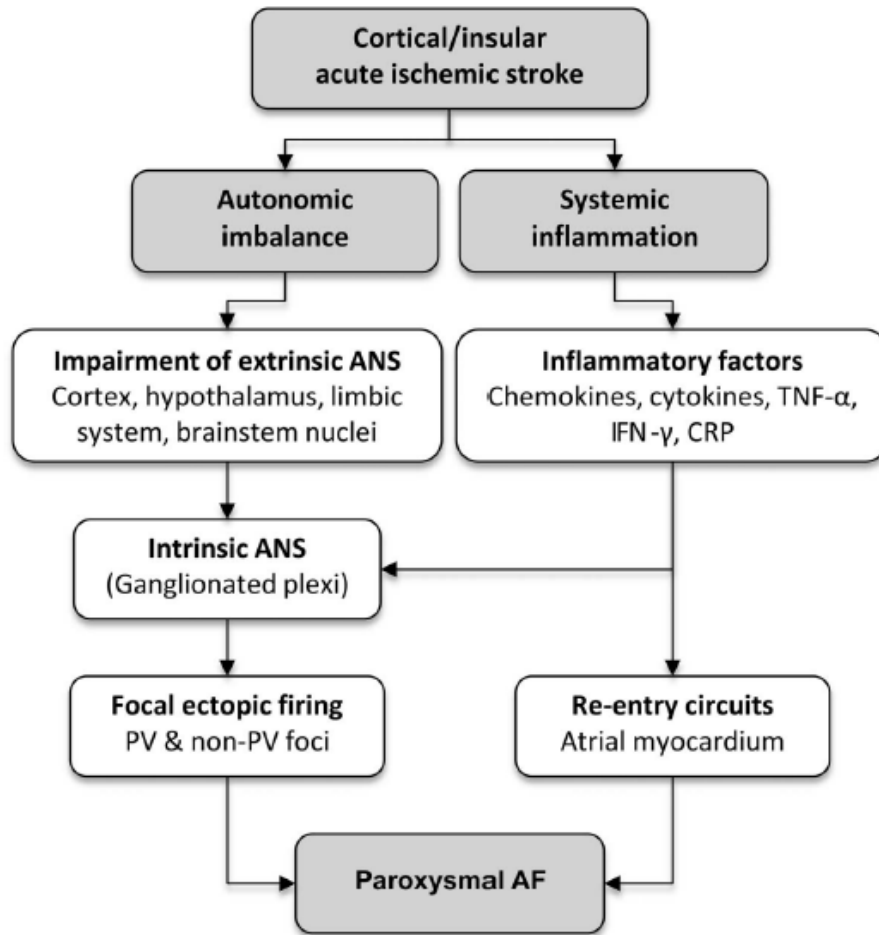


Chung MK et al, Circulation 2001

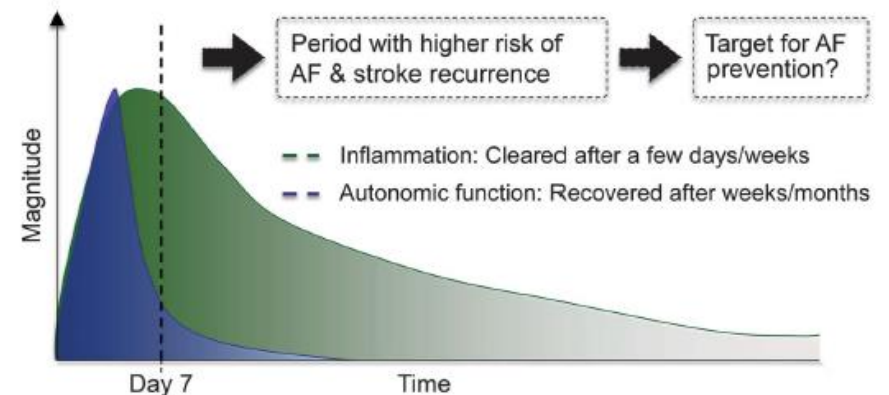


Corrales-Medina VF et al, Lancet 2013

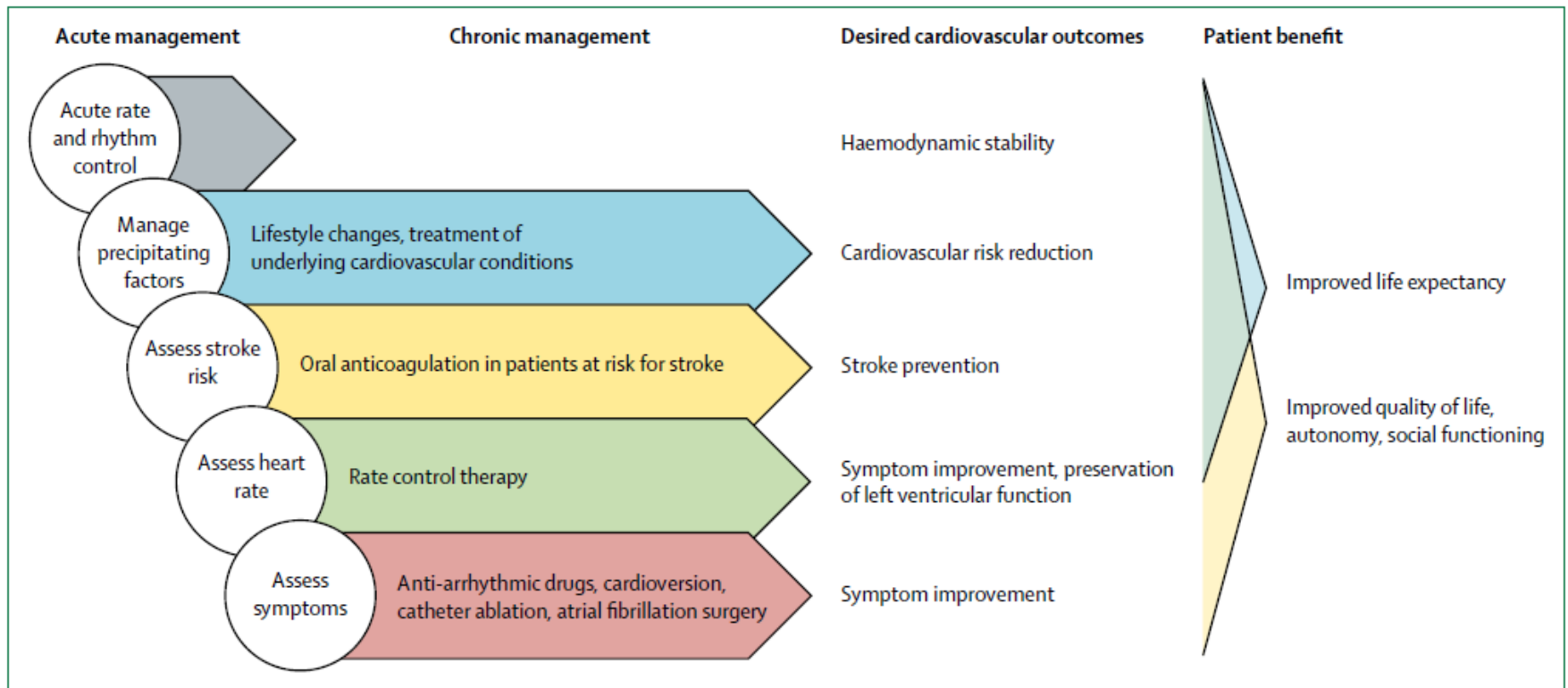
Proposed neurogenic mechanisms causing poststroke atrial fibrillation



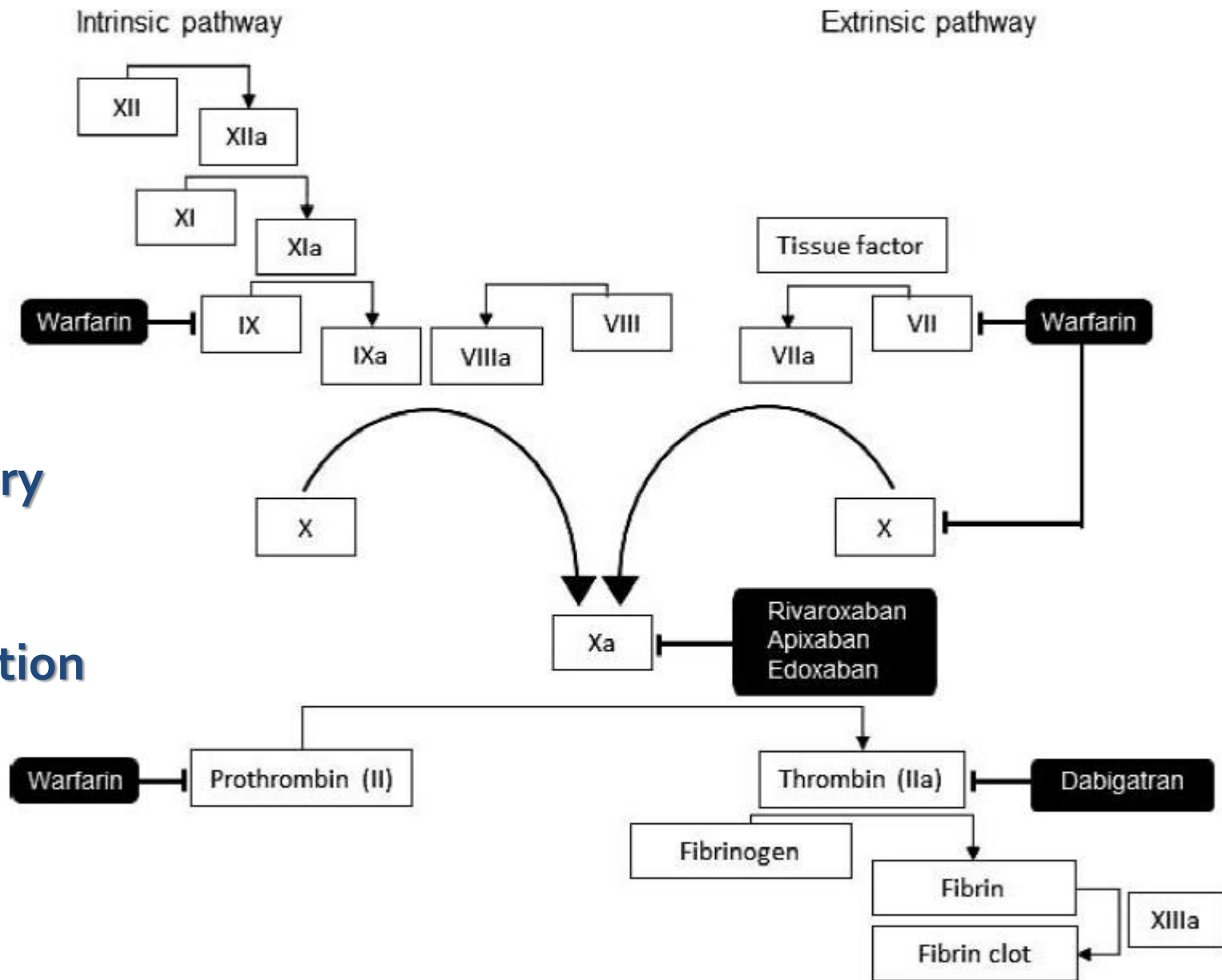
Time course of autonomic and inflammatory responses after acute ischemic stroke



The five domains of atrial fibrillation management

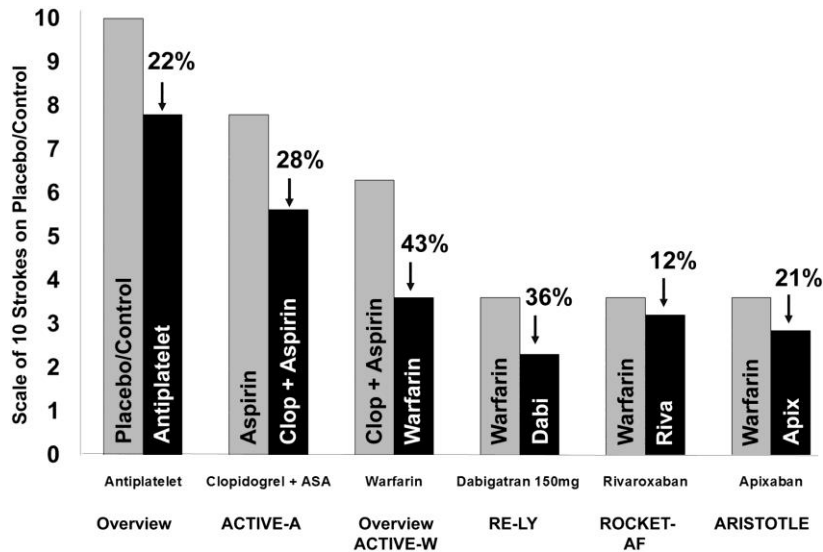


DOACs: an innovatory approach to anticoagulation



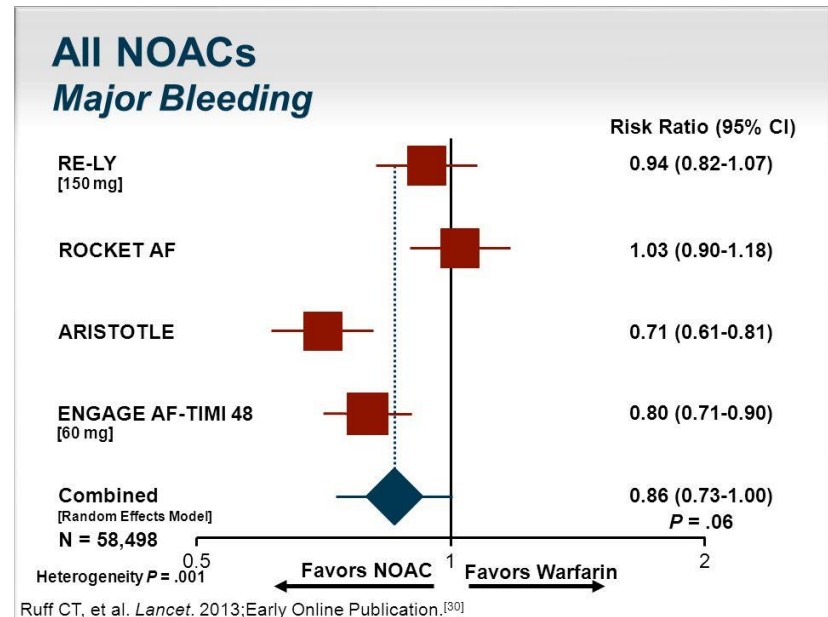
Anticoagulanti orali diretti

Efficacia



Granger C B , Armaganijan L V *Circulation* 2012

Sicurezza

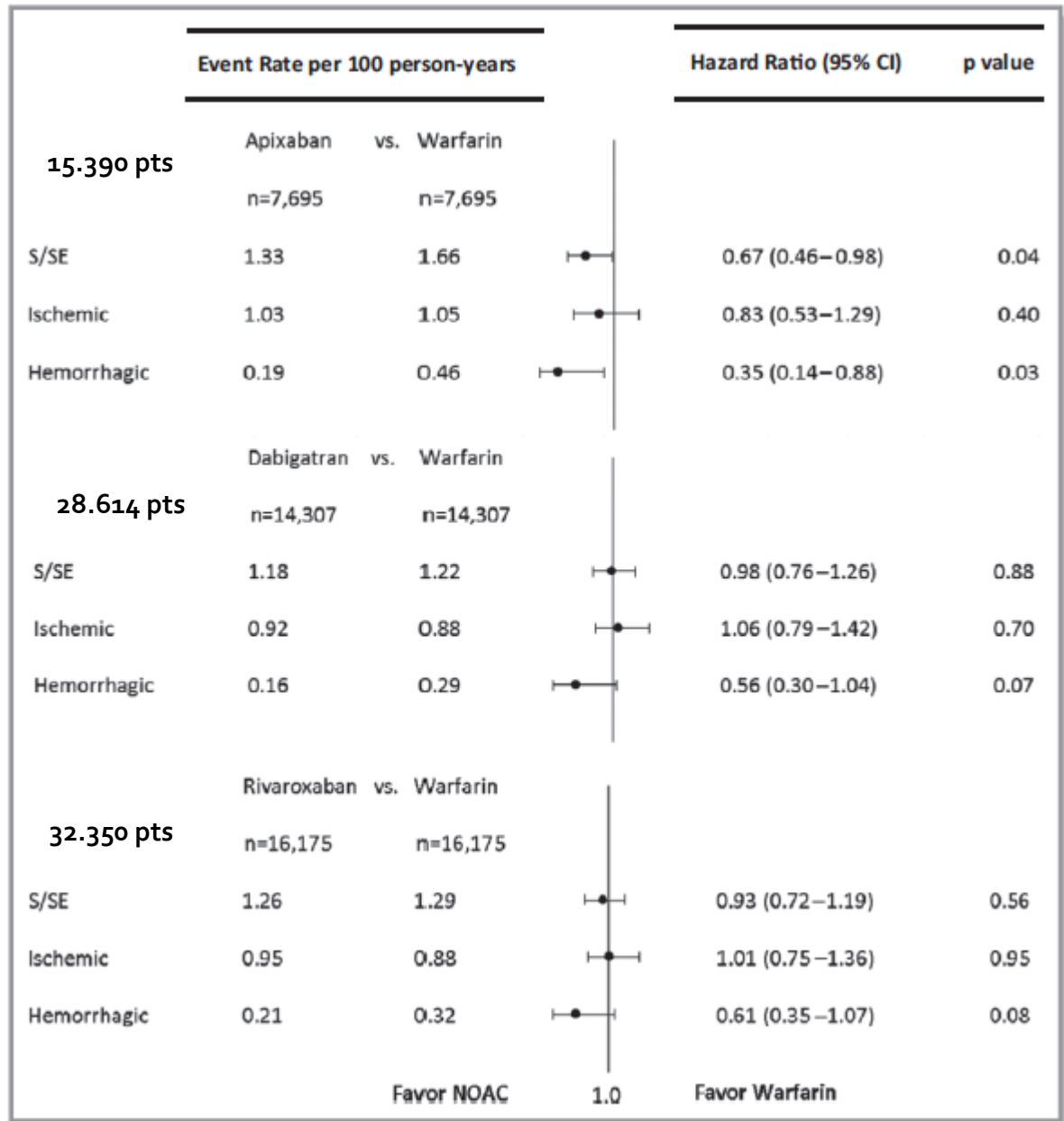


Raccomandazione 11.5.f

Forte a favore

Grado A

In caso di ictus ischemico o TIA attribuibile a FANV è raccomandato l'utilizzo dei NAO per la loro almeno uguale efficacia e per la loro maggiore sicurezza in confronto alla terapia con anticoagulanti AVK*.



HR for each pairwise propensity-matched DOAC medication comparison (a)

Medicare Advantage
October 1 – June 30, 2015



	Event Rate per 100 person-years			Hazard Ratio (95% CI)	p value
15.390 pts	Apixaban vs. Warfarin				
	n=7,695	n=7,695			
	Major Bleeding	2.33	4.46	0.45 (0.34 – 0.59)	<0.001
	Intracranial	0.29	1.06	0.24 (0.12 – 0.50)	<0.001
Gastrointestinal	1.78	3.04	0.51 (0.37 – 0.70)	<0.001	
28.614 pts	Dabigatran vs. Warfarin				
	n=14,307	n=14,307			
	Major Bleeding	2.37	3.03	0.79 (0.67 – 0.94)	<0.01
	Intracranial	0.28	0.79	0.36 (0.23 – 0.56)	<0.001
Gastrointestinal	1.97	1.95	1.03 (0.84 – 1.26)	0.78	
32.350 pts	Rivaroxaban vs. Warfarin				
	n=16,175	n=16,175			
	Major Bleeding	4.04	3.64	1.04 (0.90 – 1.20)	0.60
	Intracranial	0.44	0.79	0.51 (0.35 – 0.75)	<0.001
Gastrointestinal	3.26	2.53	1.21 (1.02 – 1.43)	0.03	

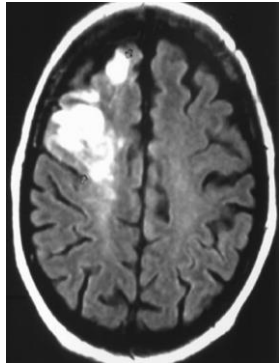
Favor NOAC 1.0 Favor Warfarin

HR for each pairwise propensity-matched DOAC medication comparison (a)

Medicare Advantage
October 1 – June 30, 2015



Practical guidance to the use of DOACs in NVAF patients



Ongoing therapy with DOACs

no → Starting DOACs

→ yes Continuing DOACs

After stroke

- Adequate timing of initiation on lesion size
- Assess bleeding and thromboembolic risk
- Check for possible drug interactions

In elderly patients

- Assess bleeding risk
- Check for thrombocytopenia (avoid if platelet count < 50000)
- Monitor renal function
- Evaluate risk of fall

Recurrent stroke while on anticoagulants

- Carefully examine feasibility of urgent recanalization interventions

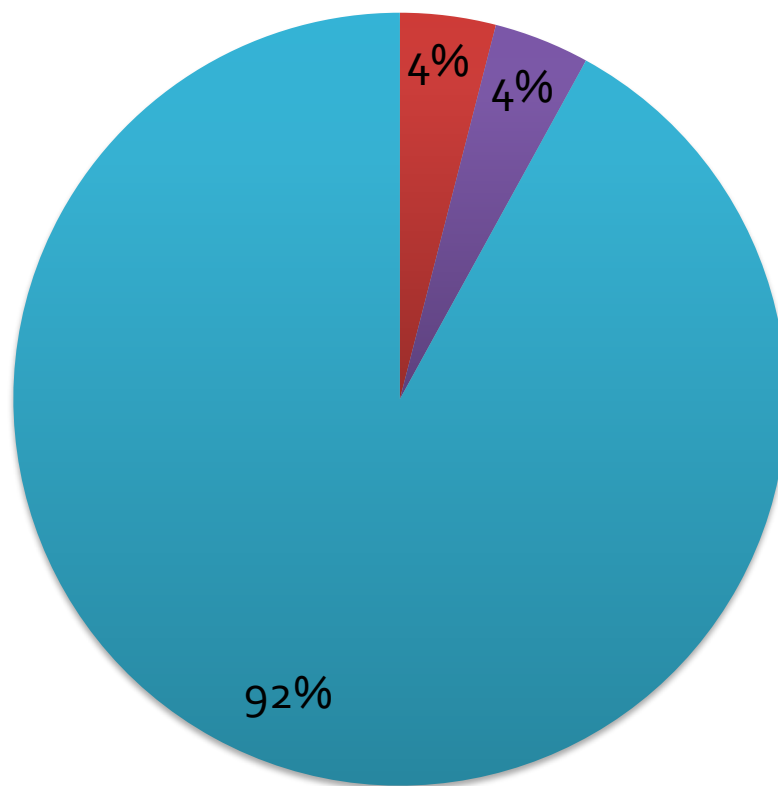
ACS and PCI

- Continue current anticoagulant
- Combine with antiplatelet

ICH

- Use specific or non-specific strategies to reverse anticoagulation
- Examine brain parenchyma in depth with MRI
- Early restart anticoagulation

Quali sono gli elementi che condizionano i tempi di somministrazione dell'anticoagulante orale dopo uno stroke acuto cardioembolico?



- Entità del rischio tromboembolico
- Presenza di infarcimento emorragico
- Dimensioni e sede della lesione
- Non risponde
- Tutte le precedenti

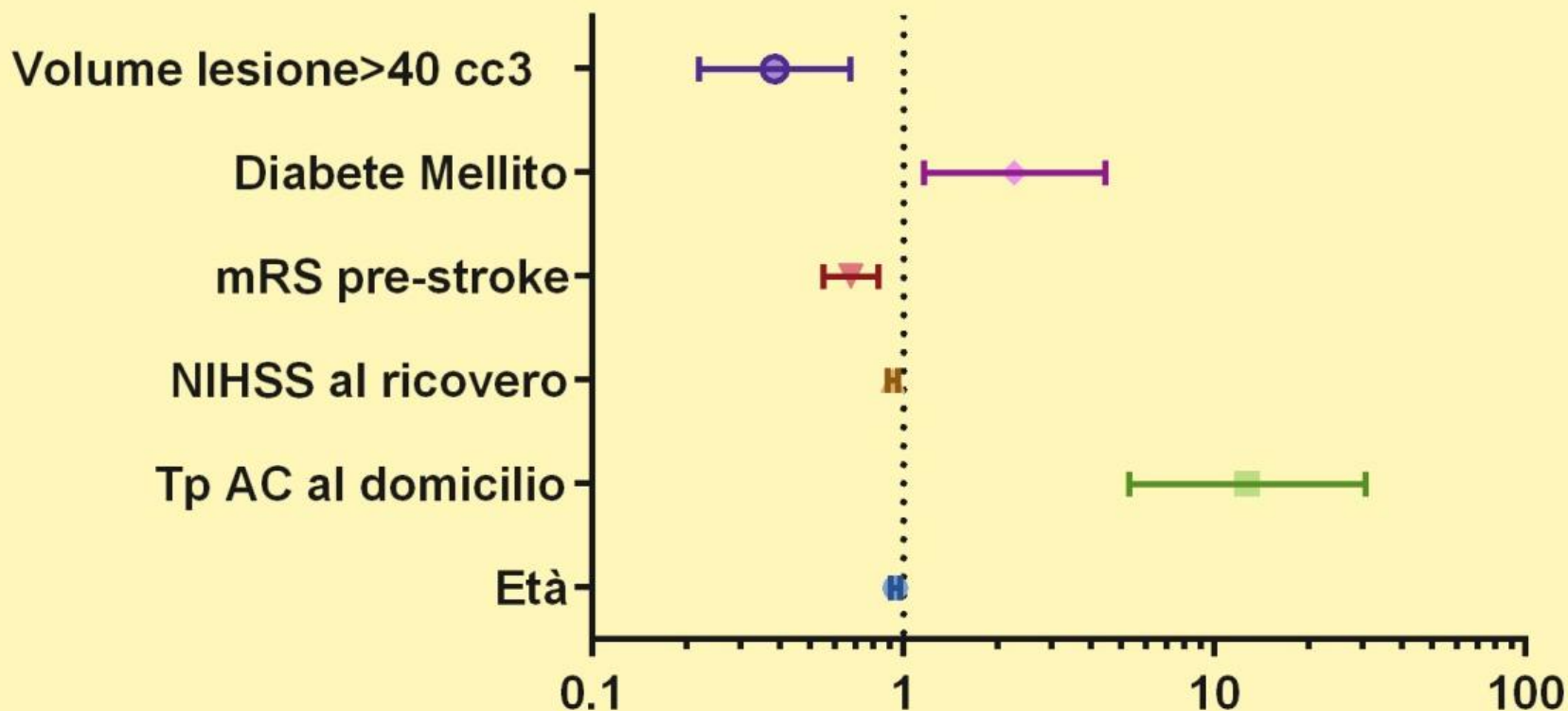
Rischio recidiva precoce

- IST rischio di recidiva ischemica entro 48 h: 4,8%
- Trial norvegese rischio recidiva ischemica entro 7 g: 8%
Yasaka, 1993 9,2%
- HAEST rischio di recidiva ischemica entro 14 g: 7,5%
CETF 12%
Yasaka, 1993 13,7%

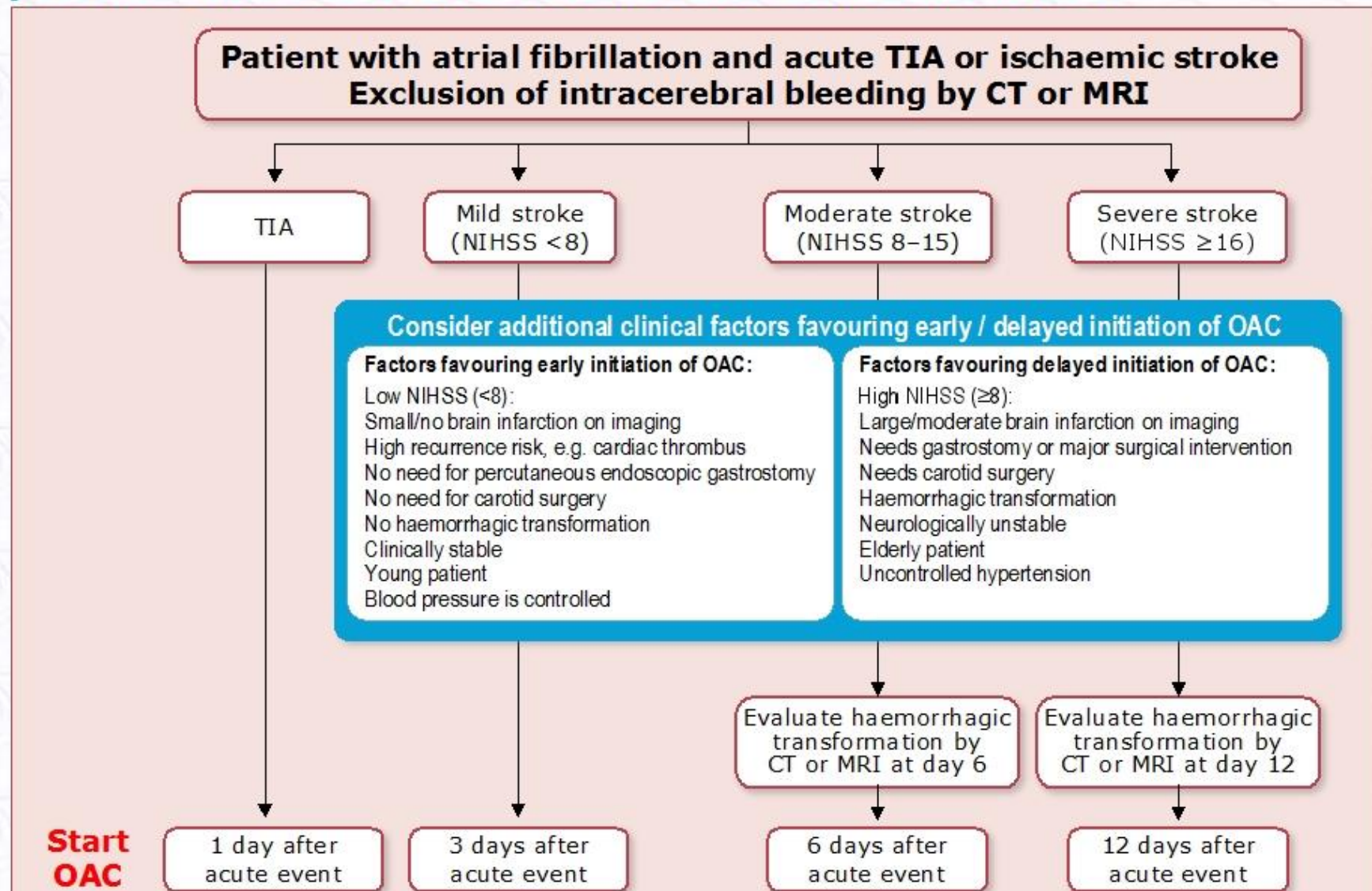
Quando iniziare la terapia con DOAC dopo stroke ischemico in AF?

- **ARISTOTLE:** Patients with a previous intracranial haemorrhage (ICH) or any stroke within 7 days before random assignment were excluded.
- **RE-LY:** excluded patients with a stroke within 14 days or severe stroke within 6 months before screening
- **ROCKET AF:** excluded patients with a severe, disabling stroke within 3 months or any stroke within 14 days before randomization
- **ENGAGE AF-TIMI 48:** excluded patients with stroke within the previous 30 days

Fattori favorenti la prescrizione della terapia anticoagulante durante il ricovero



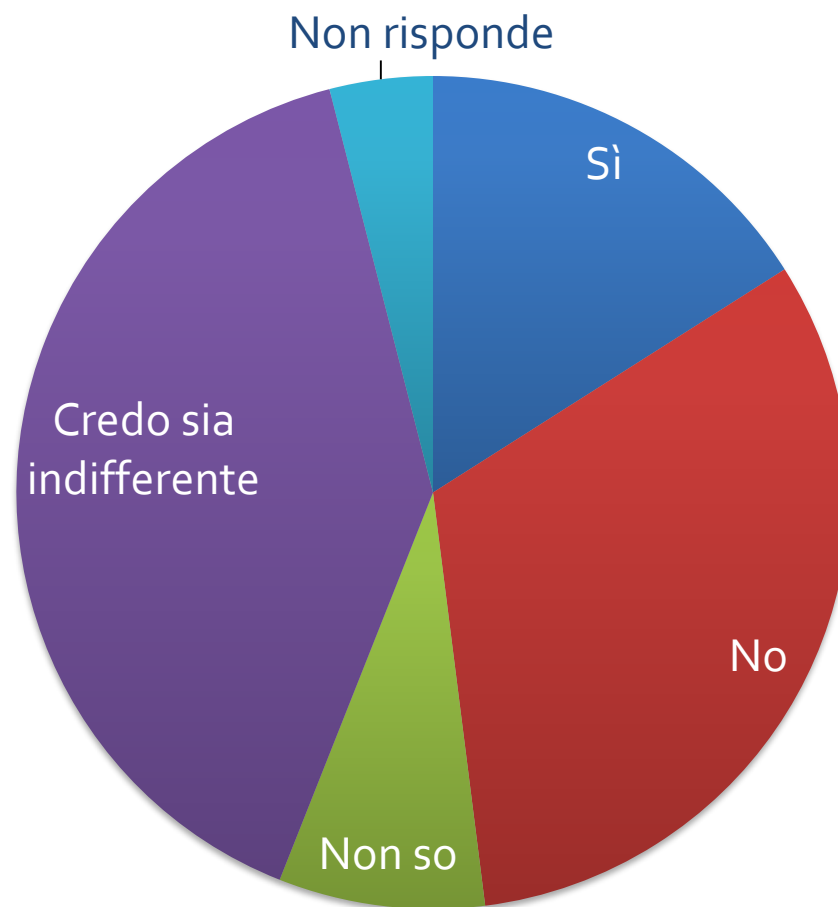
Initiation or continuation of anticoagulation in atrial fibrillation patients after a stroke or transient ischaemic attack



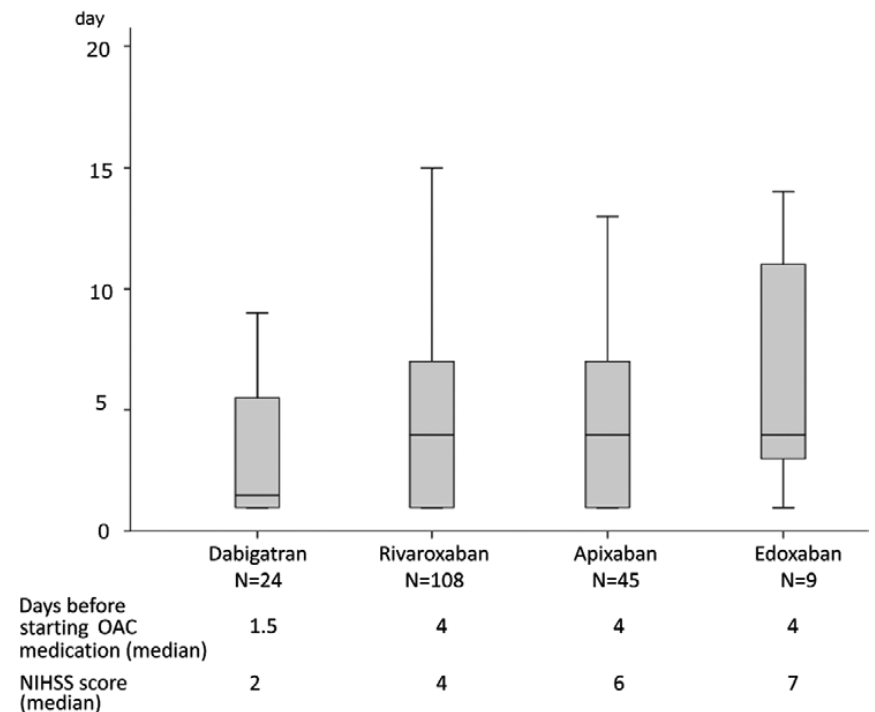
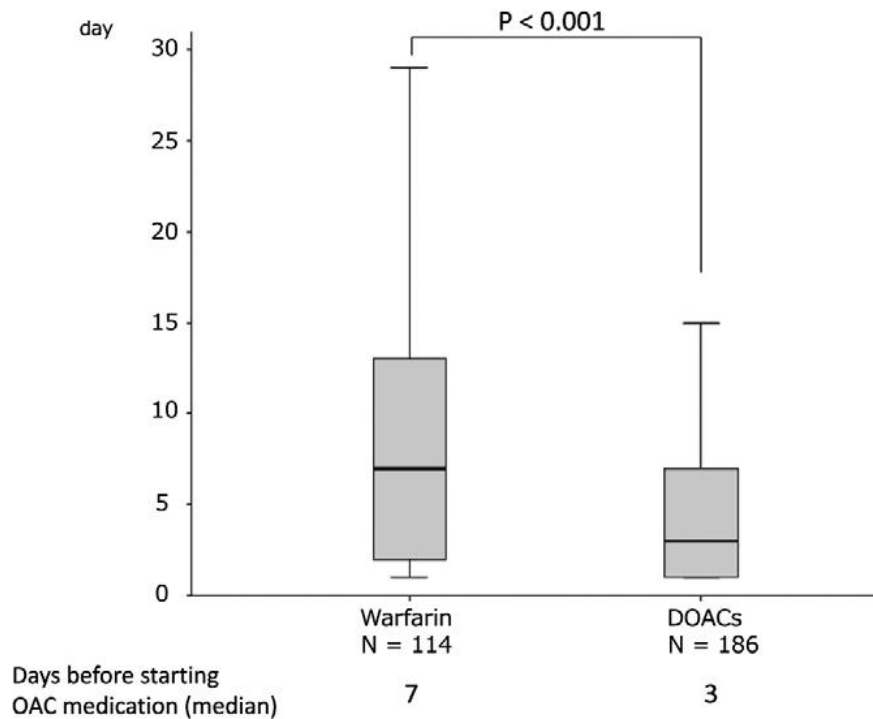
This approach is based on consensus within the Task Force, not on evidence.

NIHSS = National Institutes of Health Stroke Scale

Ritieni che gli anticoagulanti diretti possano essere somministrati più precocemente degli anticoagulanti vitamina K-dipendenti dopo uno stroke cardioembolico?

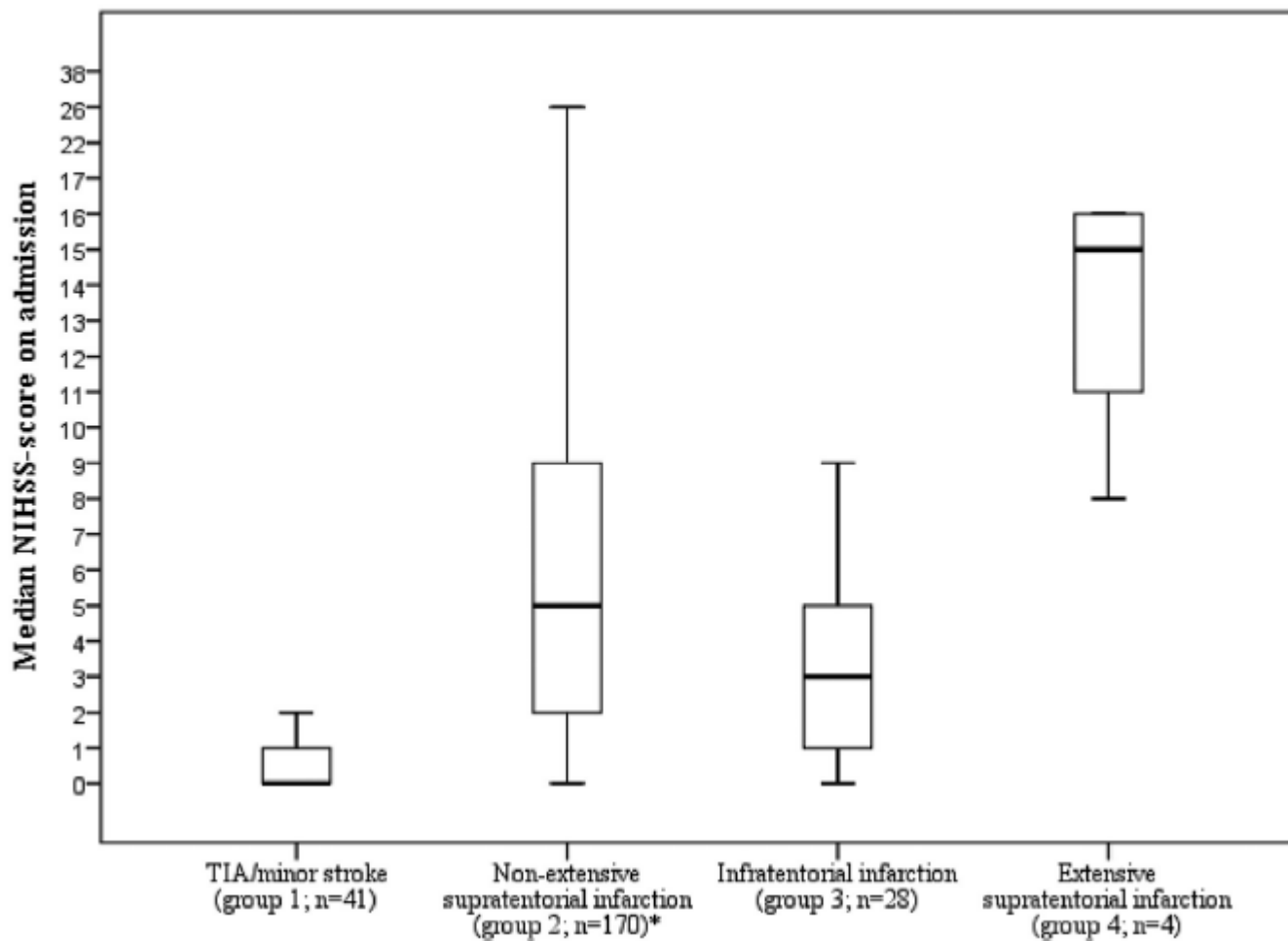


Number of days before starting treatment in W or DOAC groups and by type of DOAC

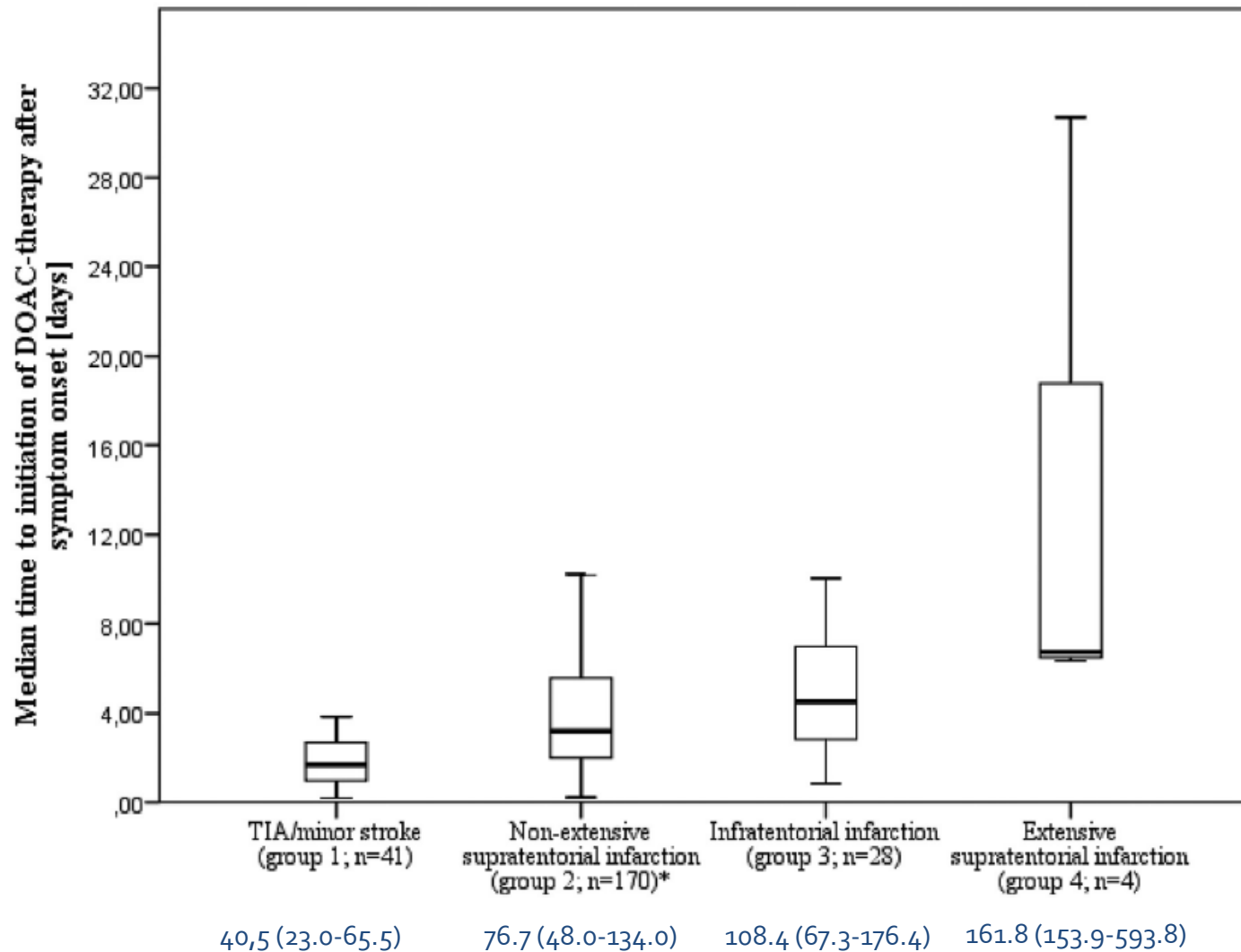


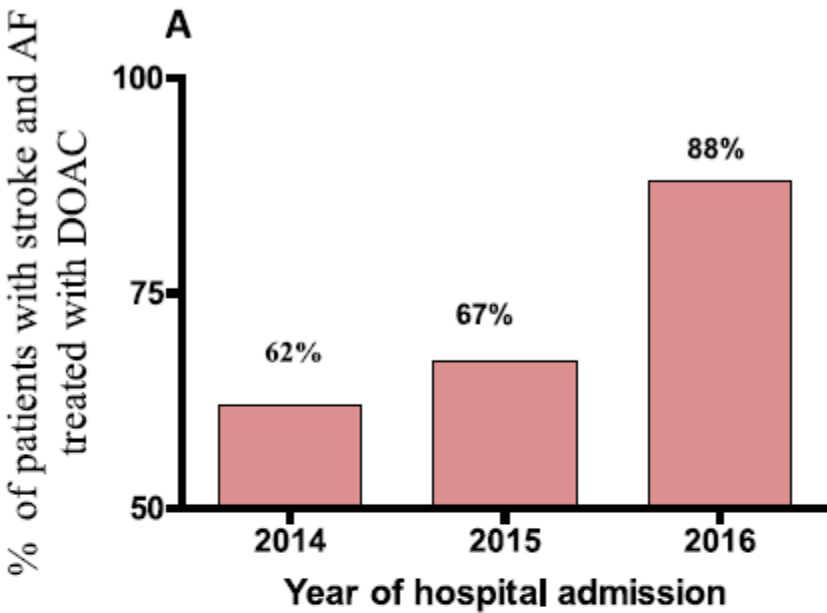
300 stroke patients with NVAF
April 2012- March 2016

NIHSS score distribution (243 consecutive cases)

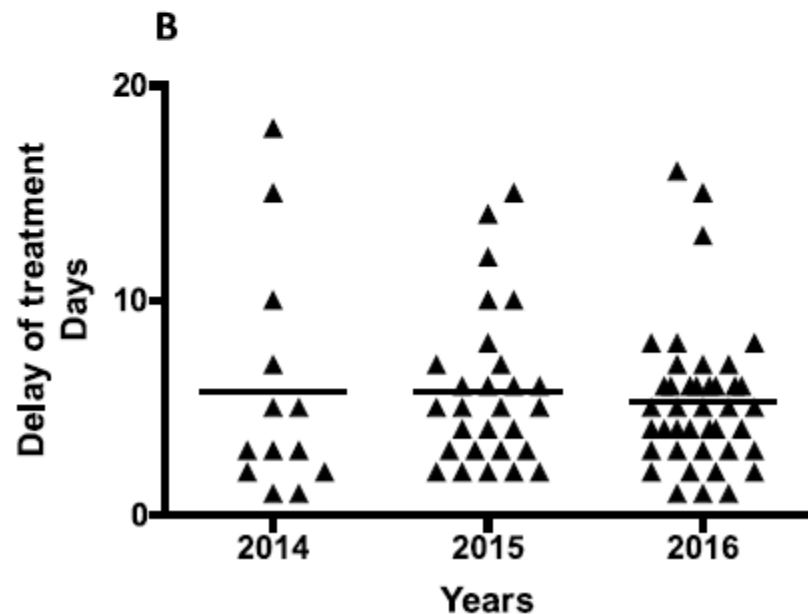


Time of DOAC initiation (243 consecutive cases)

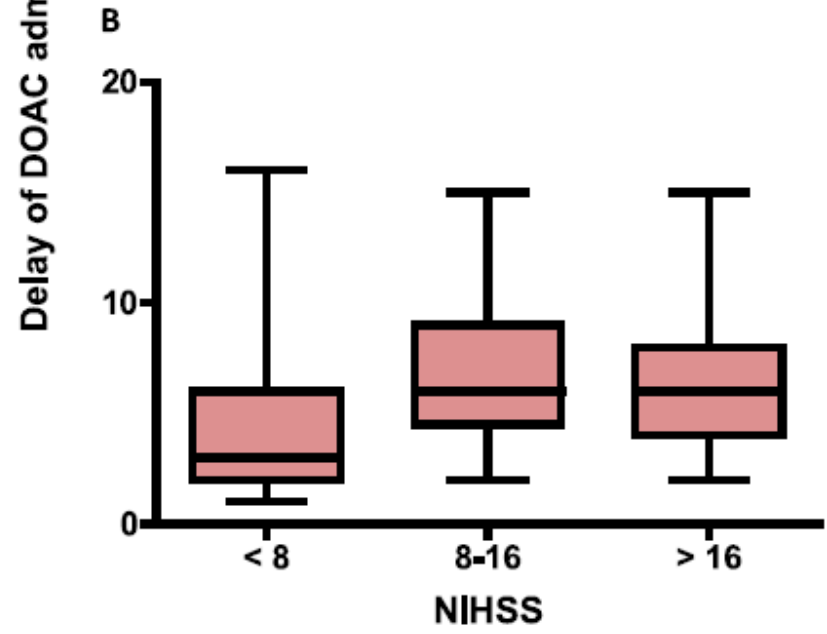
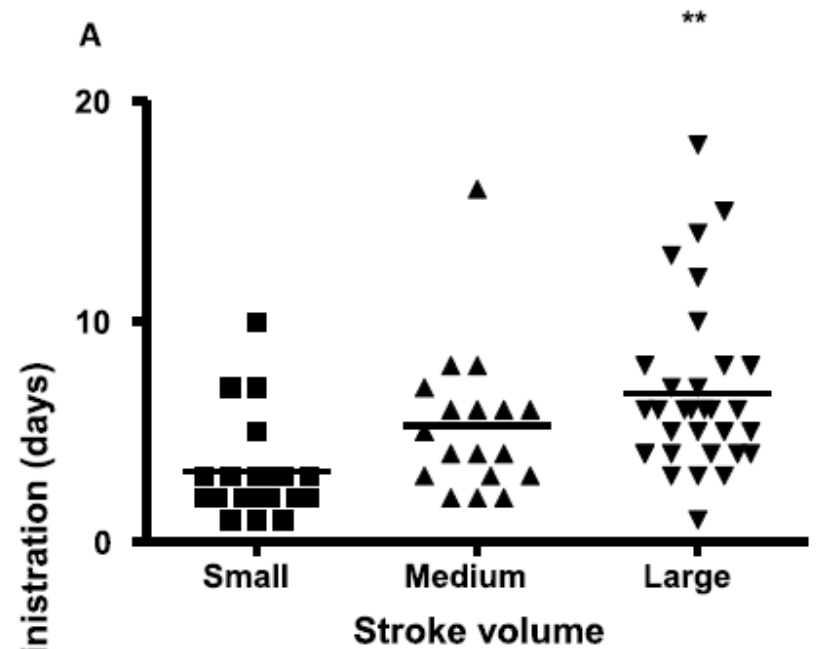




Use of DOACs in the acute phase of NVAF-related ischemic stroke



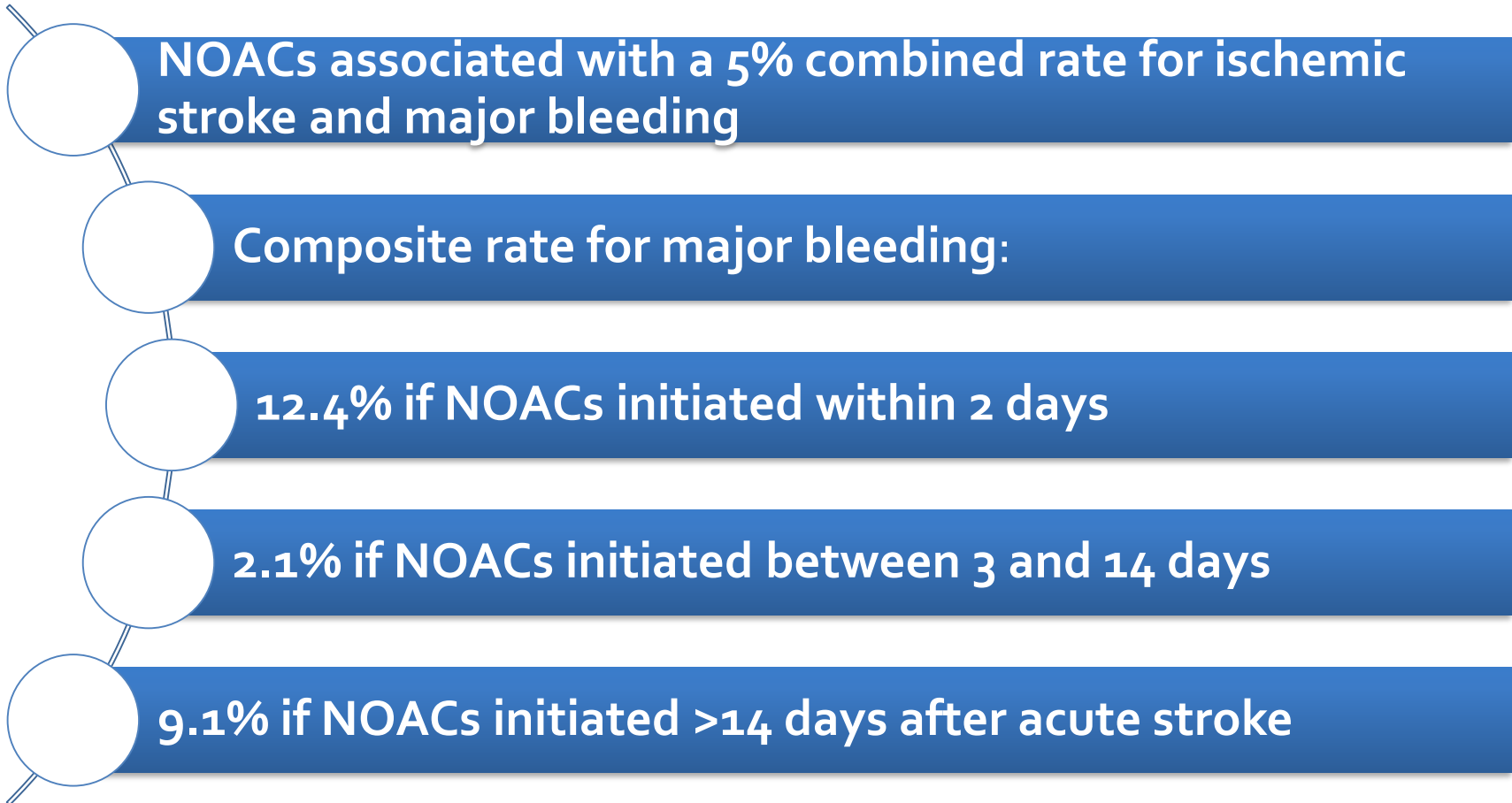
Single Centre: Florence SM Nuova
 Consecutive cases 2014-2016
 147 pazienti



Delay of DOACs administration after an acute ischemic stroke in patients with AF

Single Centre: Florence SM Nuova
 Consecutive cases 2014-2016
 147 pazienti

RAF-NOACs Study: ischemic stroke recurrence and major bleeding within 90 days

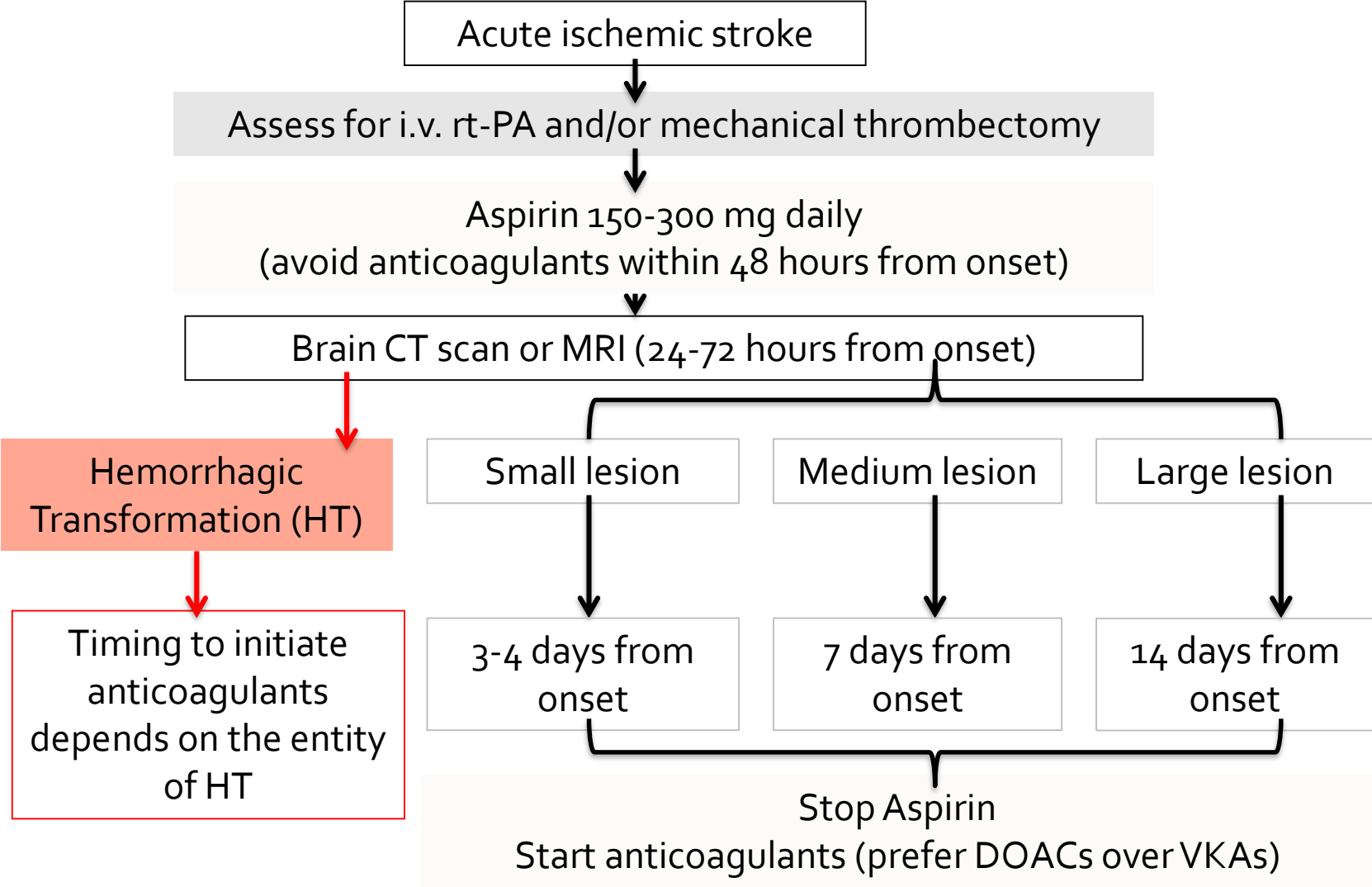


1127 acute ischemic stroke patients: 90 days follow-up

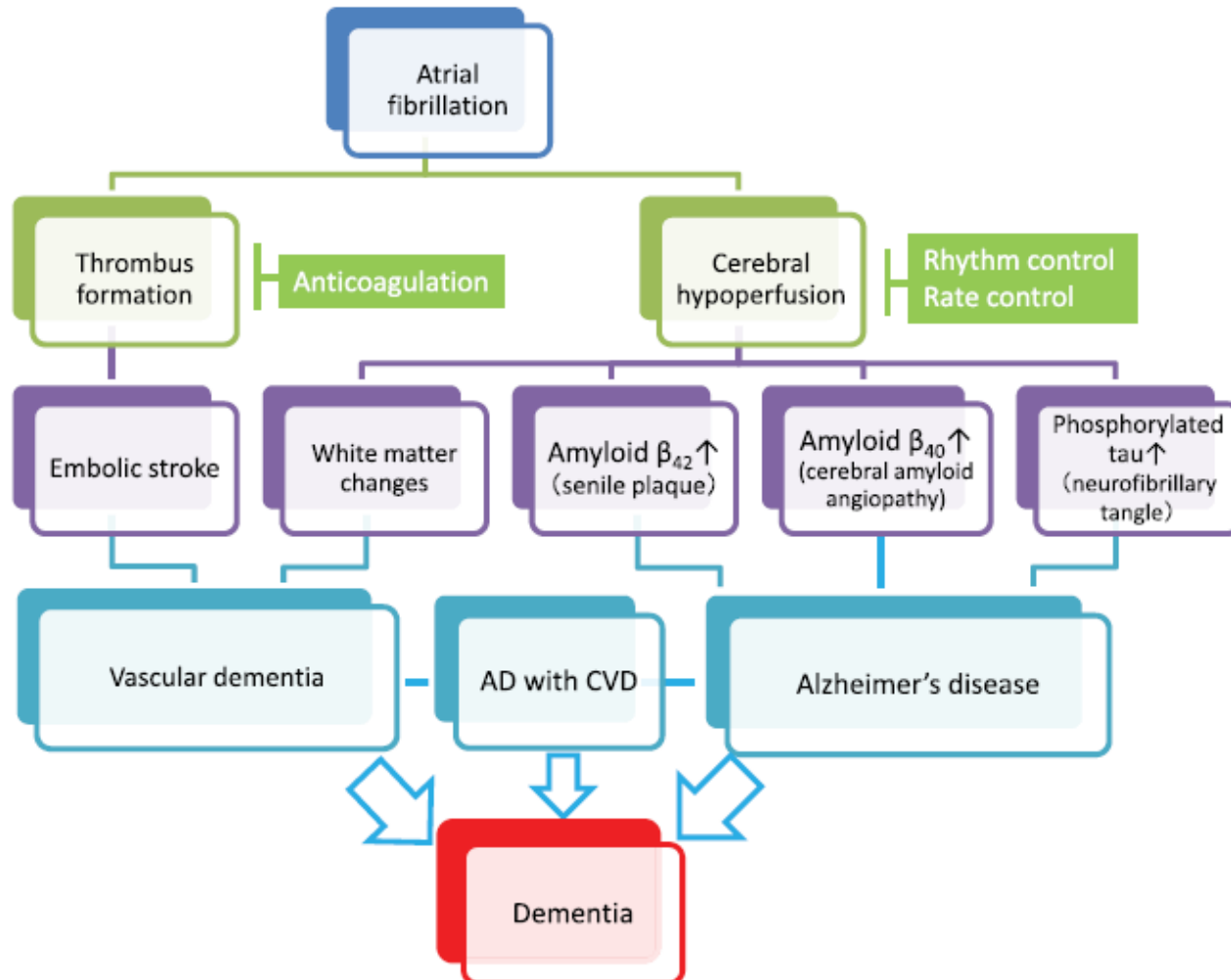
Ischemic recurrences : 2.8%

Hemorrhagic complications: 2.4

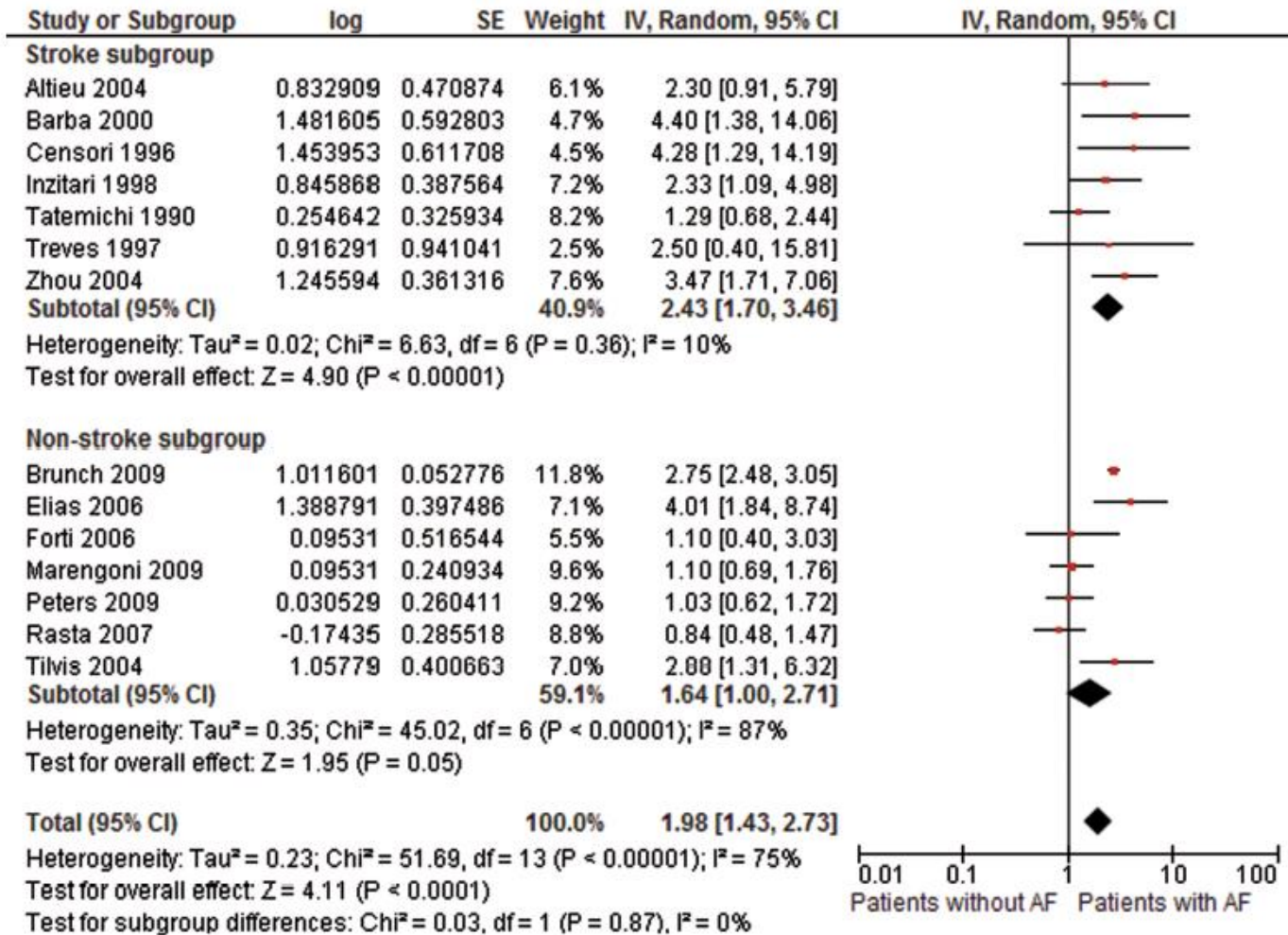
Timing of anticoagulation therapy flow chart in patients with acute ischemic stroke and AF



Plausible mechanisms by which AF induces vascular dementia and Alzheimer's disease



Meta-analysis of risk of dementia in patients with or without AF

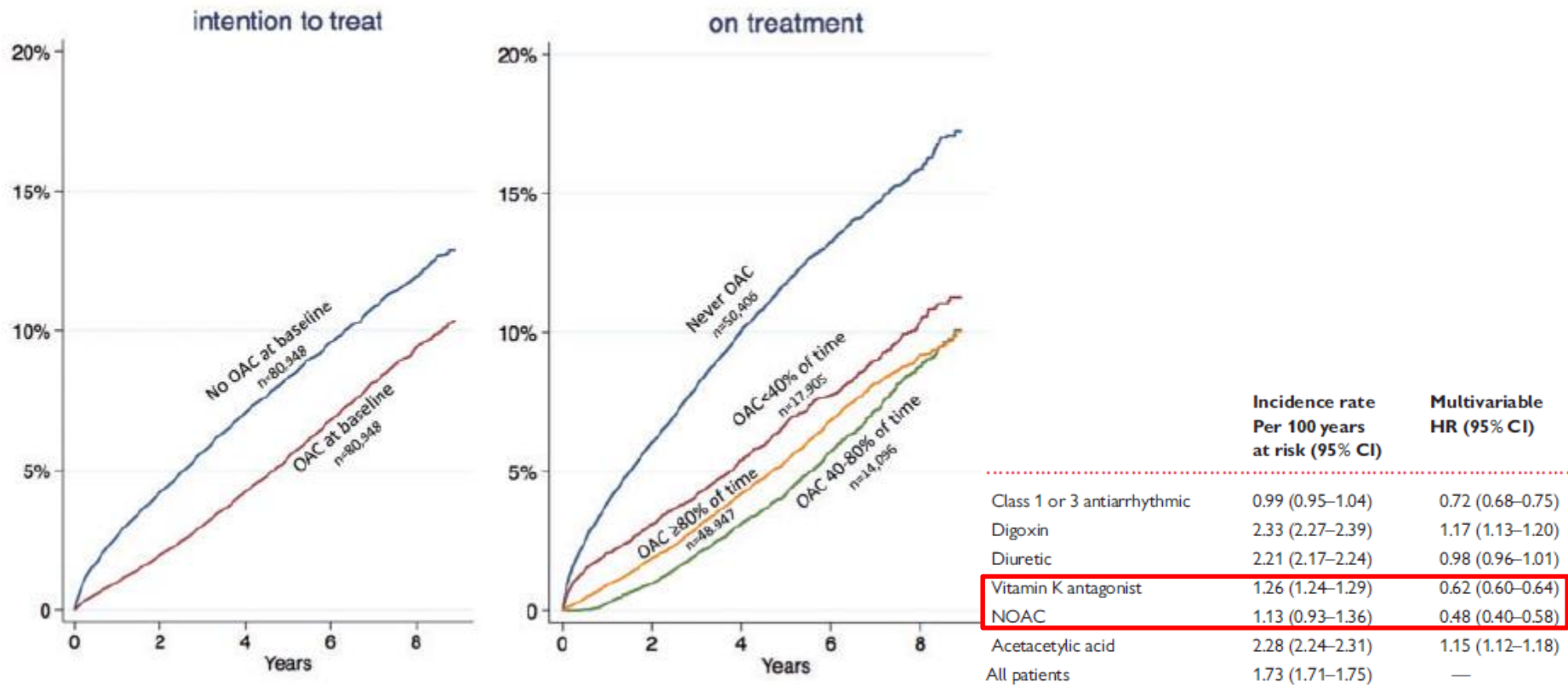


Stroke subgroup
OR 2.4, 95%CI 1.7-3.5,
p<0.001

Non-stroke subgroup
OR 1.6, 95%CI 1.0-2.7,
P<0.05

Conversion of MCI to dementia
(1 study): Significant association with AF
(OR 4.6;95%CI 1.7-12.5
P<0.002)

Incidence of dementia in relation to OAC treatment

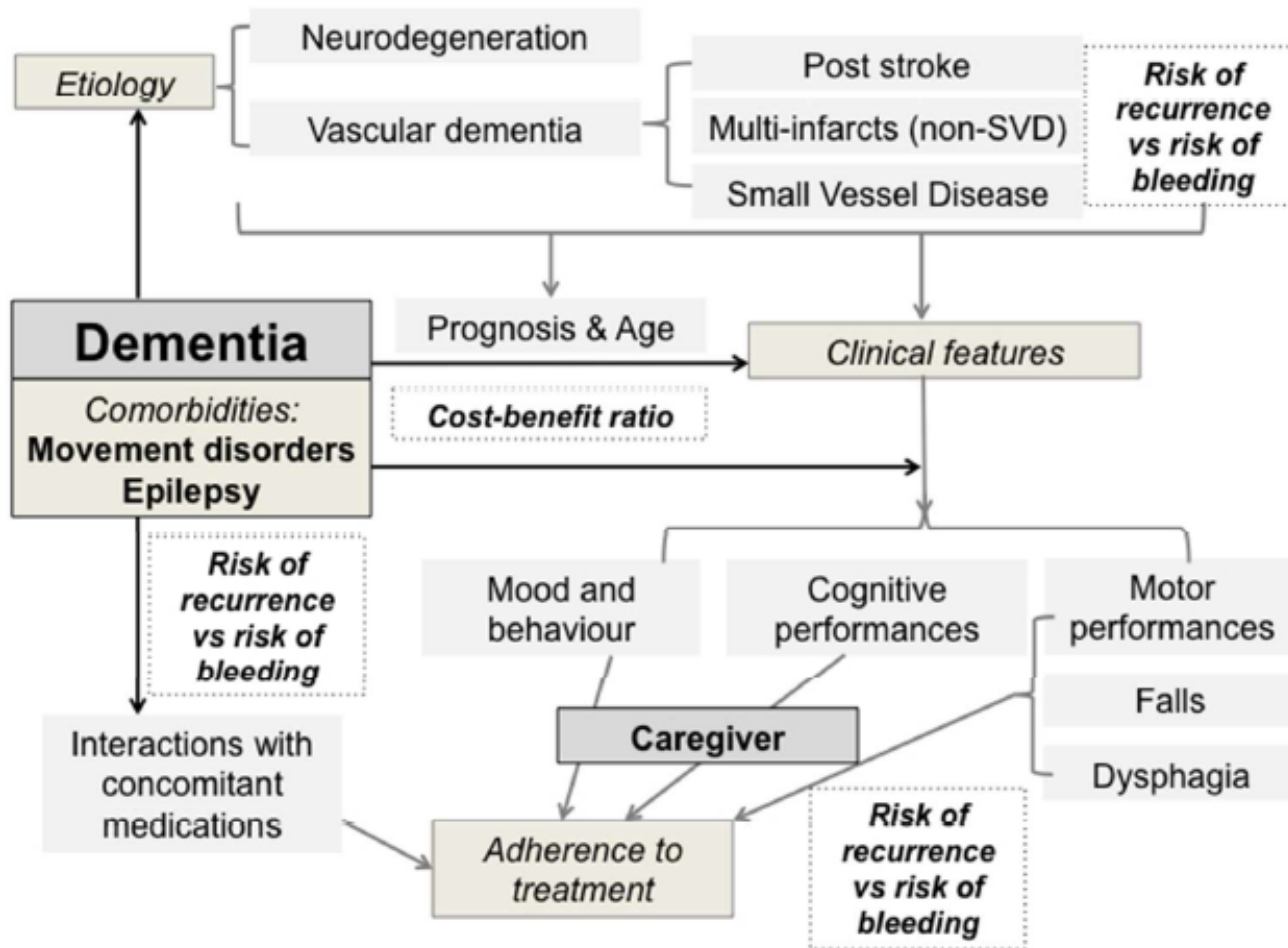


Retrospective swedish study (2006-2014)
444,106 patients with AF hospital diagnosis

29% lower risk of dementia in OAC treated patients



Factors to be considered in DOACs prescription in patients with dementia



Safety of Intravenous Thrombolysis among Stroke Patients Taking New Oral Anticoagulants—Case Series and Systematic Review of Reported Cases

Shima Shahjouei, MD, MPH,* Georgios Tsivgoulis, MD,†‡§
Reza Bavarsad Shahripour, MD,|| G. Morgan Jones, PharmD, BCPS,¶
Andrei V. Alexandrov, MD,† and Ramin Zand, MD, MPH†

Journal of Stroke and Cerebrovascular Diseases, Vol. 24, No. 12 (December), 2015: pp 2685–2693

Leading Opinion

Thrombolysis and thrombectomy in patients treated with dabigatran with acute ischemic stroke: Expert opinion

HC Diener¹, R Bernstein^{2,3}, K Butcher⁴, B Campbell⁵, G Cloud⁶,
A Davalos⁷, S Davis⁸, JM Ferro⁹, M Grond¹⁰, D Krieger^{11,12},
G Ntaios¹³, A Slowik¹⁴ and E Touzé¹⁵

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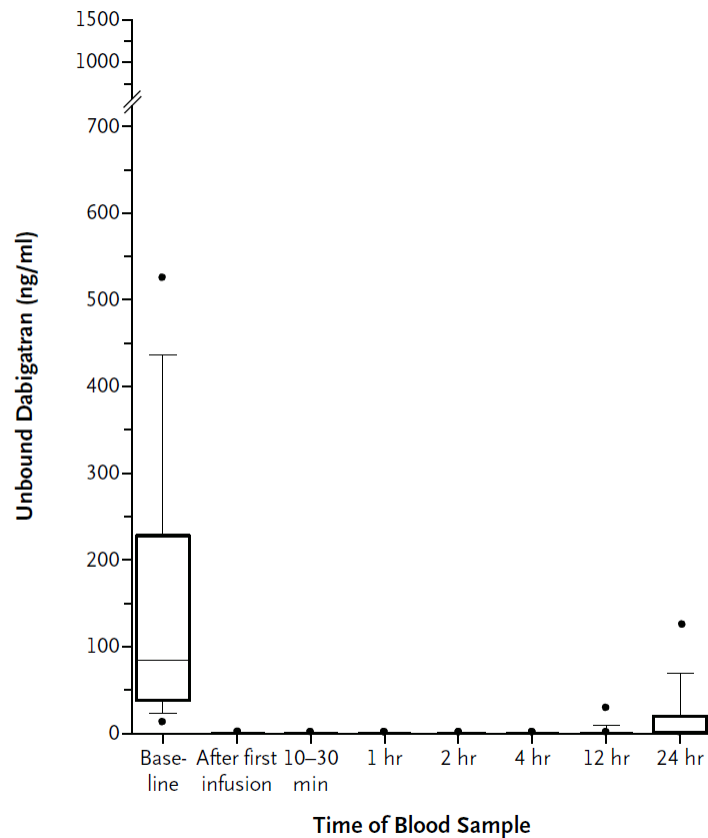
International
Journal of Stroke 

DOACs reversal agents: main properties

	Idarucizumab	AndeXanet	Ciraparantag
Target	Dabigatran	Factors Xa inhibitors	Dabigatran, Argatroban, LMWH, UFH, oral and parental factor Xa inhibitors
Structure	Humanized Fab fragment	Recombinant protein derived from human factor Xa	Synthetic, water-soluble, small molecule
Binding	Non competitive inhibitor	Competitive binding	Non covalent hydrogen binding (DOACs); charge-charge interactions (heparin)
Administration	Intravenous (bolus or rapid infusion)	Intravenous (bolus followed by infusion)	Intravenous (bolus)
Dosing	Fixed dose, 5 g, administered as two 2.5-g vials no more than 15 min apart	400–800 mg IV bolus followed by infusion of 4–8 mg/min	100–300 mg IV bolus
Onset of action	<5 min	2 min	5–10 min
Half-life	Initial: 47 min Terminal: 10.3 h	1 h	Approximately 1.5 h
Storage	Refrigerated	Refrigerated	Room temperature
Clinical status	Approved by FDA and EMA	Submitted to FDA	Studies in healthy volunteers

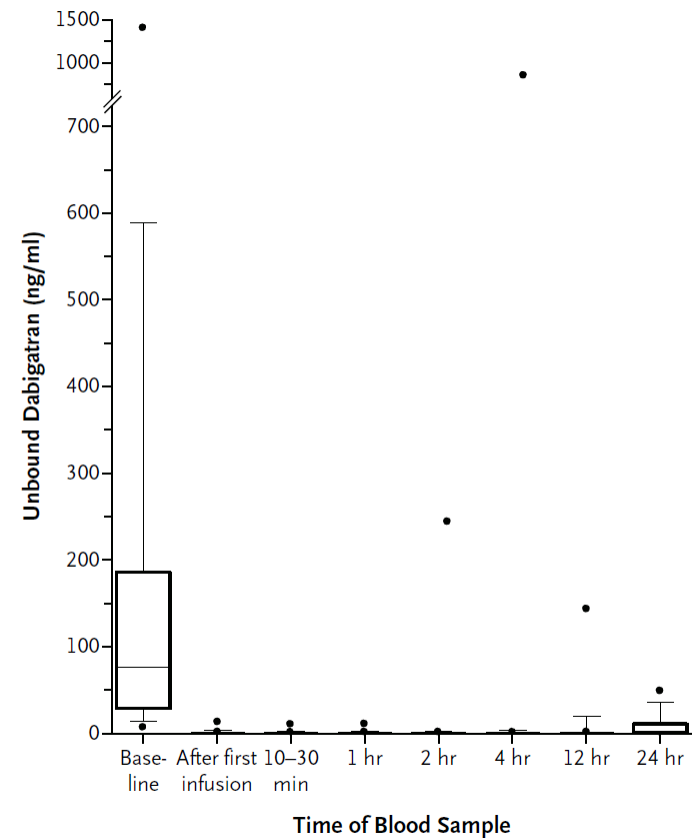
Time courses of plasma concentration of unbound Dabigatran before and after the administration of Idarucizumab

A Concentration of Unbound Dabigatran in Group A



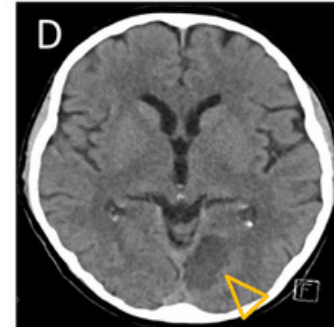
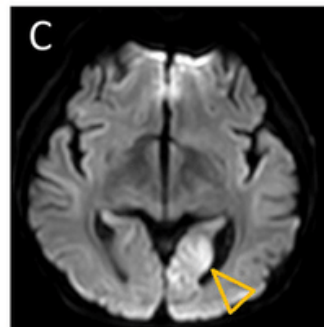
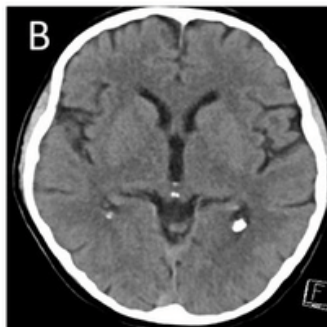
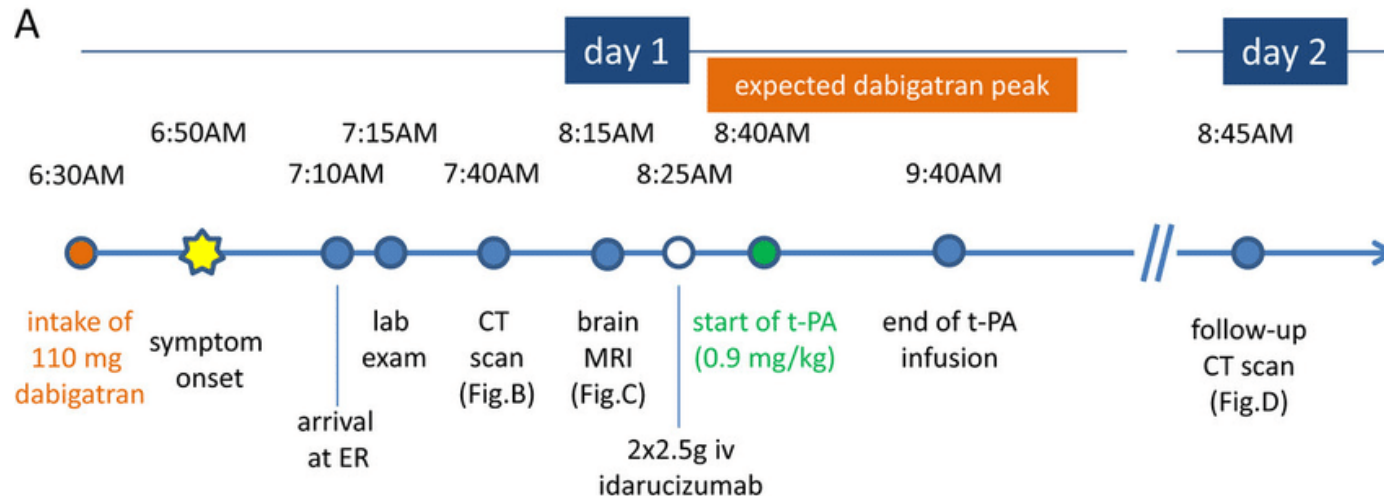
patients who had serious bleeding

B Concentration of Unbound Dabigatran in Group B

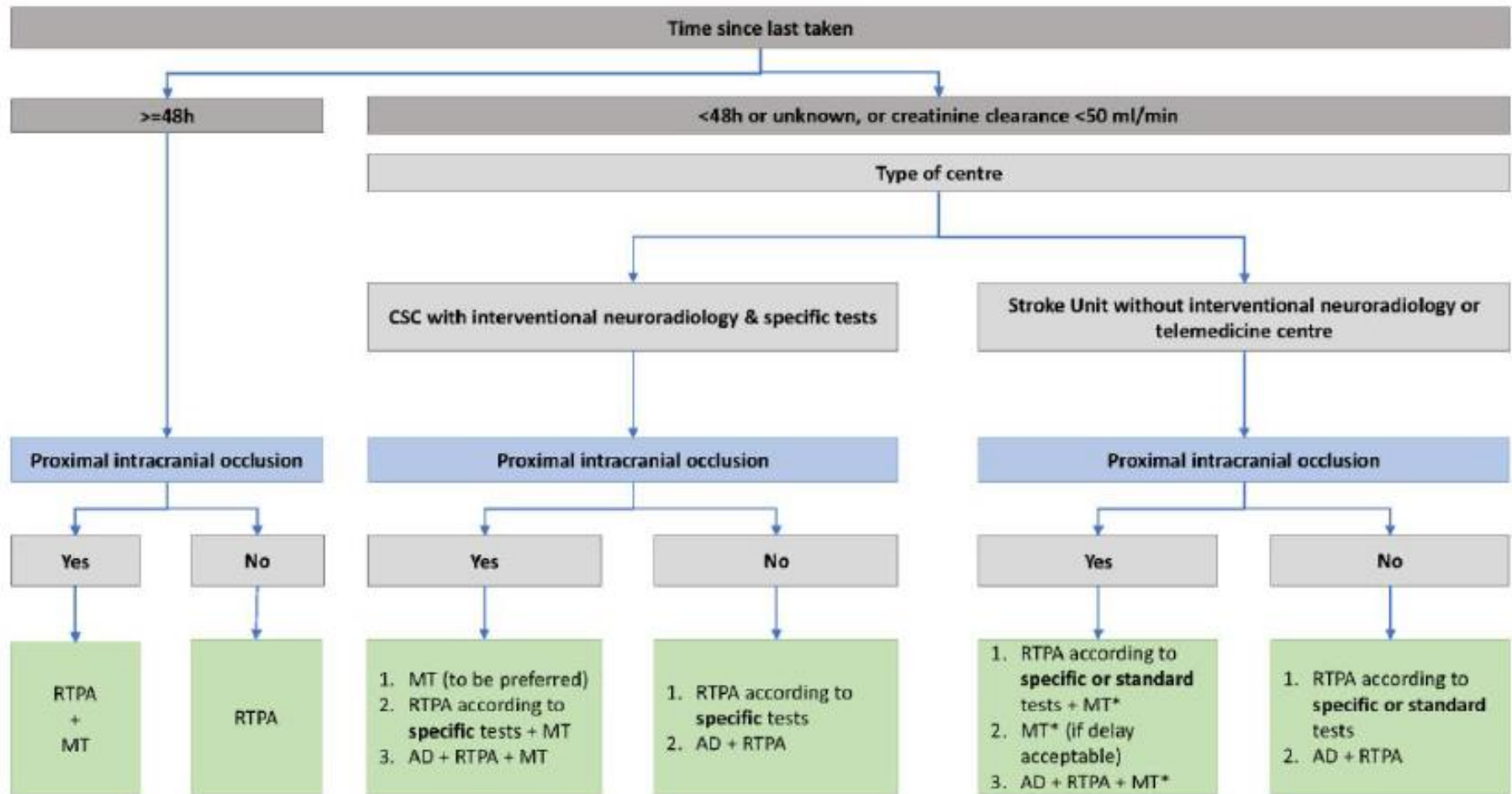


patients who required urgent surgery

Idarucizumab e trombolisi sistemica



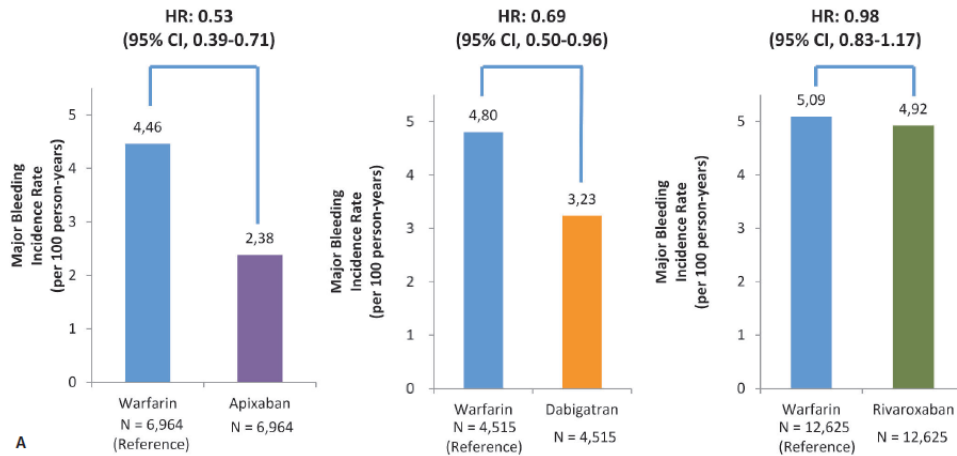
Decision algorithm for recanalization in a cerebral infarction patients on DOAC



AD=idarucizumab (only for patients on dabigatran)

*MT, only feasible after transfer to CSC

Major bleeding incidence rates and HR Propensity Score matched cohorts

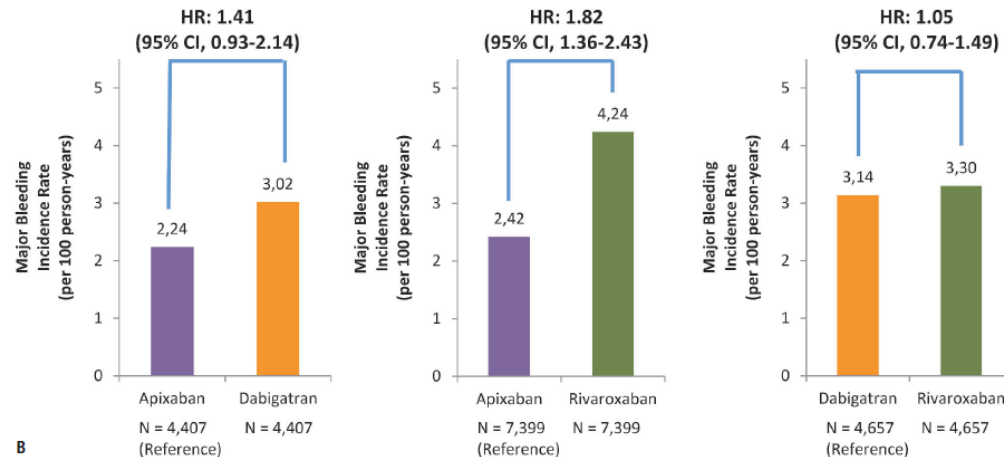


Truven MarketScan Commercial & Medicare supplemental US claim database

45,361 newly AC NVAF pts

Warfarin-DOAC cohort

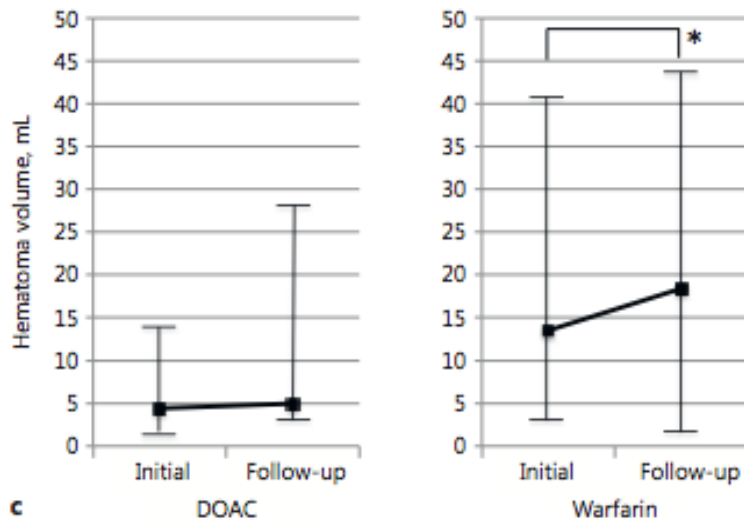
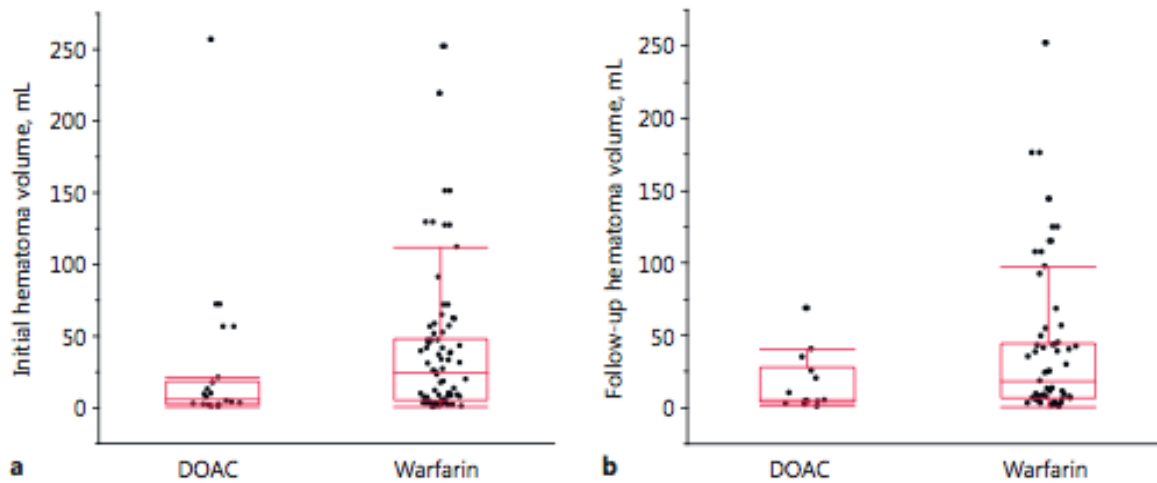
DOAC-DOAC cohort



Incidence of serious hemorrhagic complications associated with DOAC use

	Intracranial hemorrhage		Serious gastrointestinal hemorrhage	
	Incidence per year (%)	Estimated number per year	Incidence per year (%)	Estimated number per year
Dabigatran	0.3	900	0.4	1200
Rivaroxaban	0.5	4000	0.8	6400
Apixaban	0.4	2000	0.2	1000

Hematoma volume of ICHs associated with DOACs and warfarin

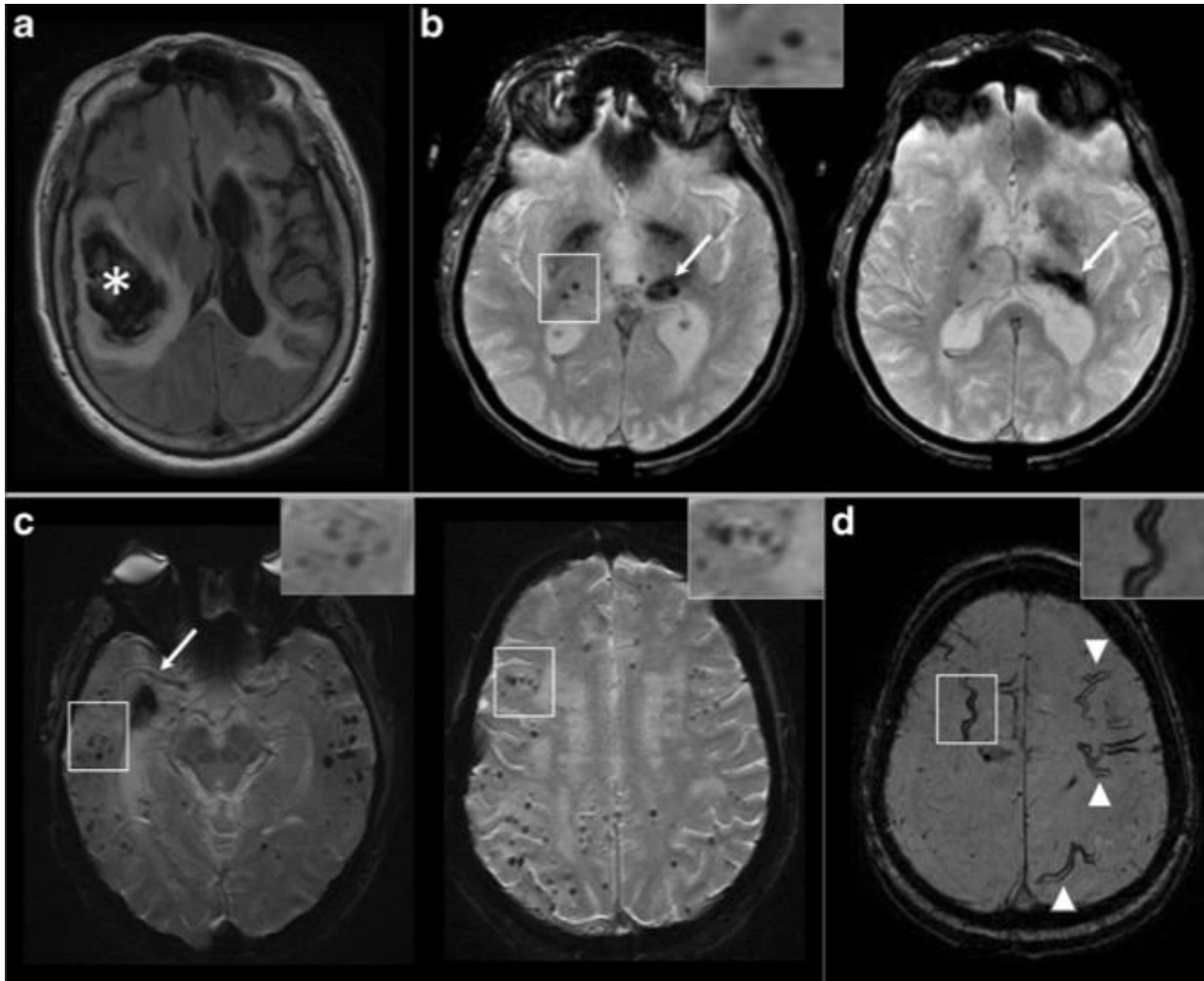


Prospective
Multicentre
Cross-sectional study

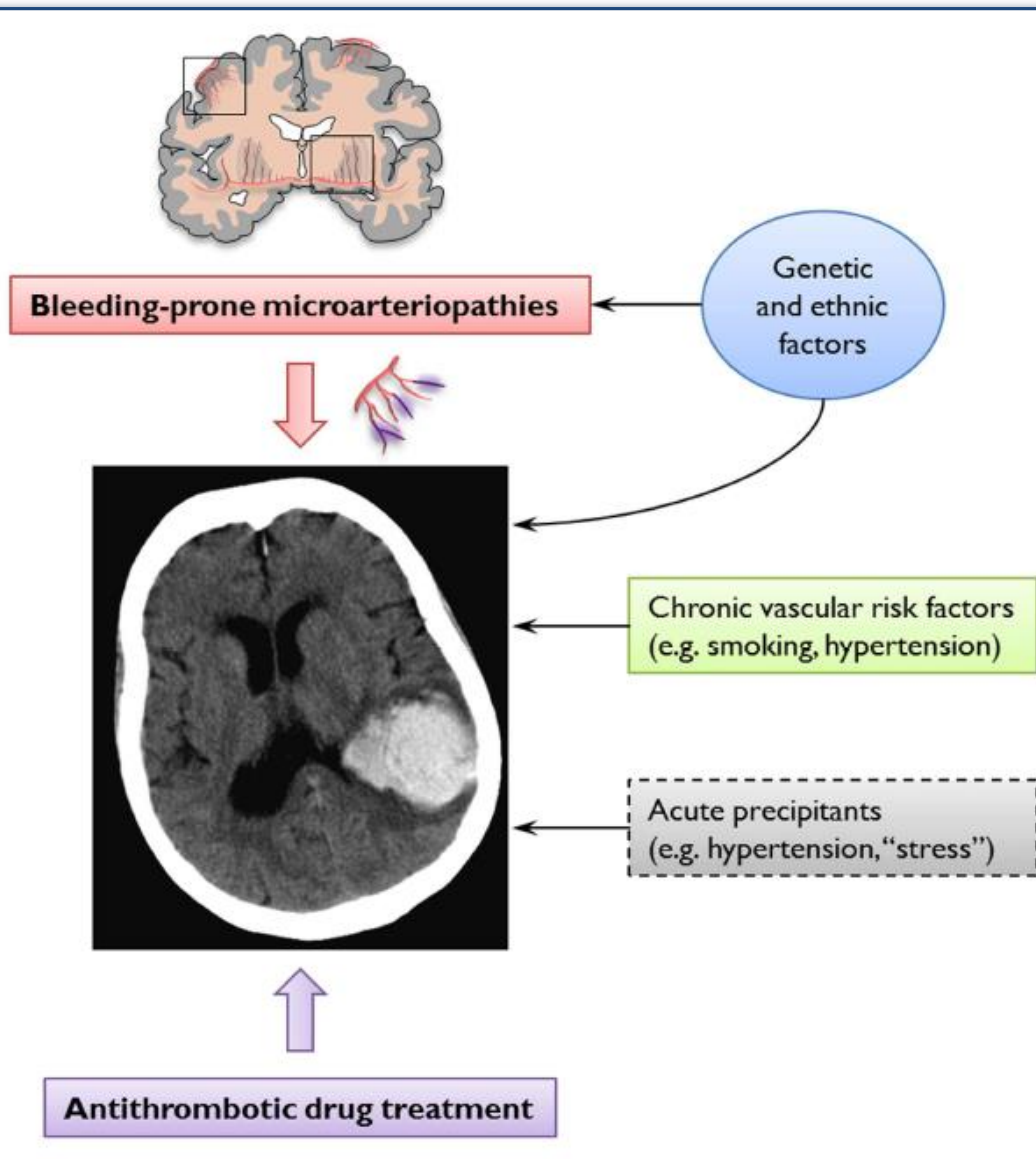
DOAC group: 18 pts
Warfarin group: 71 pts

	DOAC (n = 18)	Warfarin (n = 71)	p value
Initial hematoma volume, mL	6.2 (2.3–18.4)	24.2 (5.1–48.2)	0.04
Prevalence of surgery	2 (11)	3 (4)	
Mortality	2 (11)	17 (24)	0.34

Hemorrhage-prone small vessel disease markers



Pathogenesis of spontaneous and anticoagulation-associated ICH



Risk of recurrence in general intracerebral hemorrhage

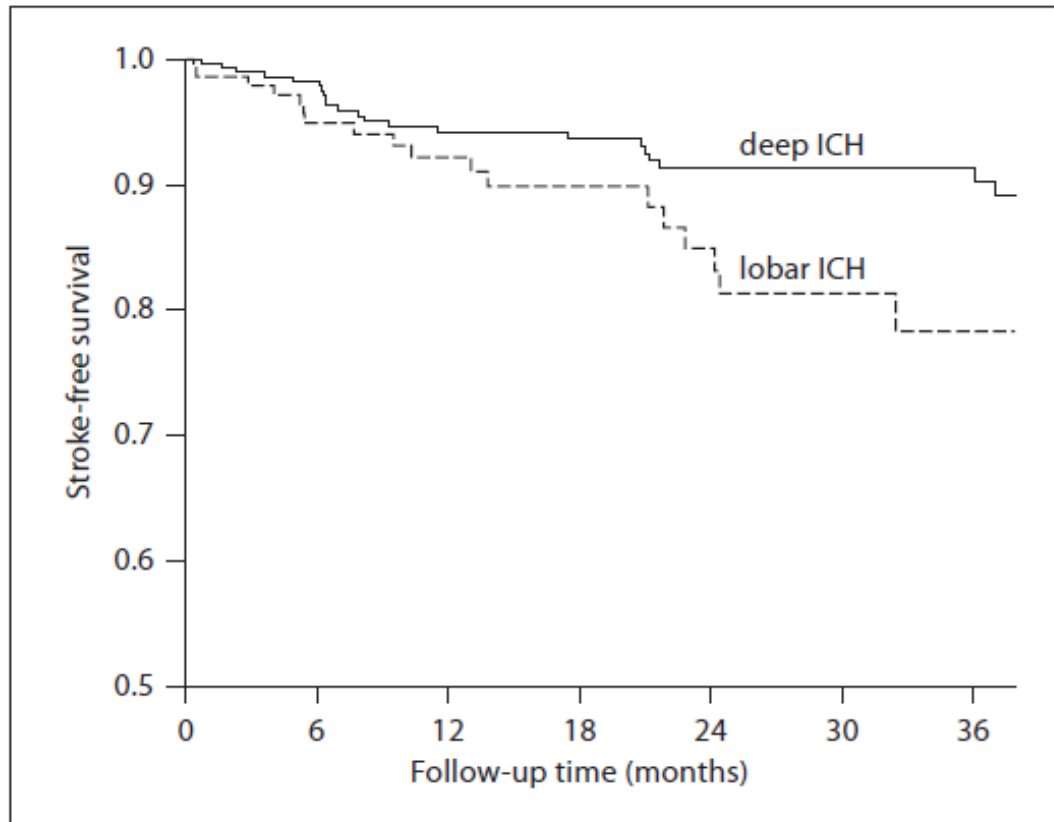
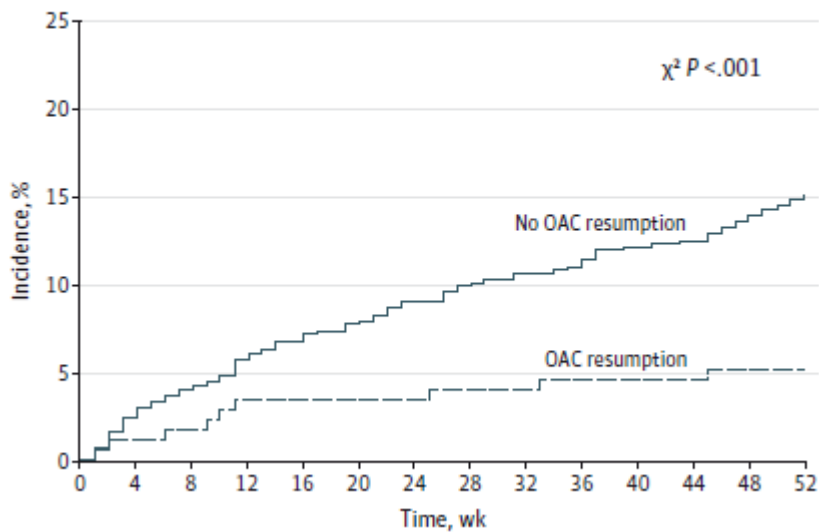


Fig. 1. Kaplan-Meier curves for stroke-free survival after deep (n = 308) and lobar (n = 157) ICH.

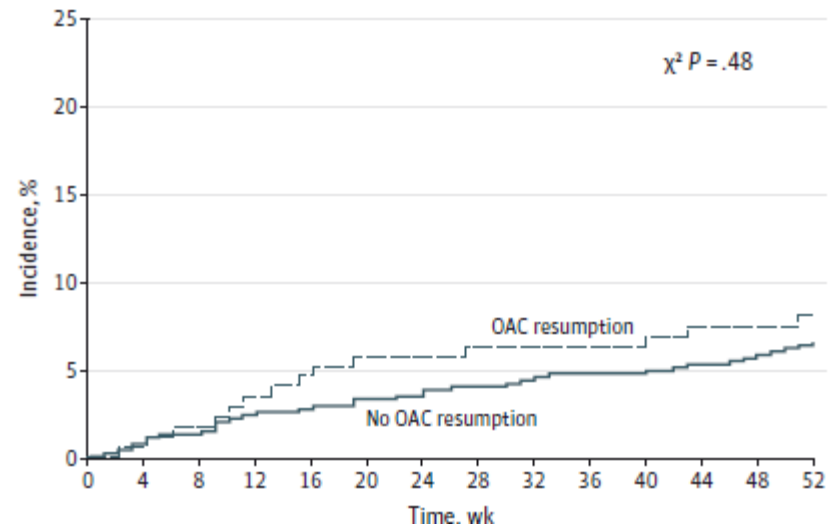
Incidence rate of ischemic and hemorrhagic complications during 1-year follow-up in patients with and without OAC resumption

A Ischemic events



19 Germany tertiary care centers
1176 individuals
853 for analysis of hematoma enlargement
719 for analysis of OAC resumption

B Hemorrhagic events

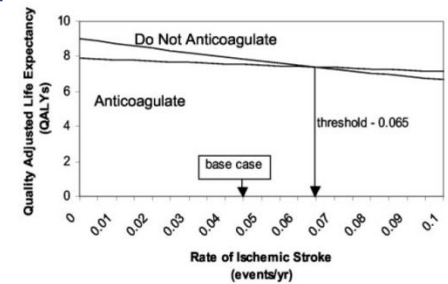


The risk of recurrent intracranial bleeding

- **Deep hemorrhage**

for 1000 anticoagulated patients for 1 year:

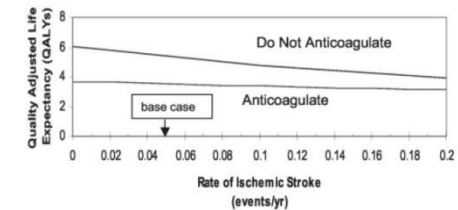
- 31 fewer thromboembolic strokes
- 19 additional ICHs



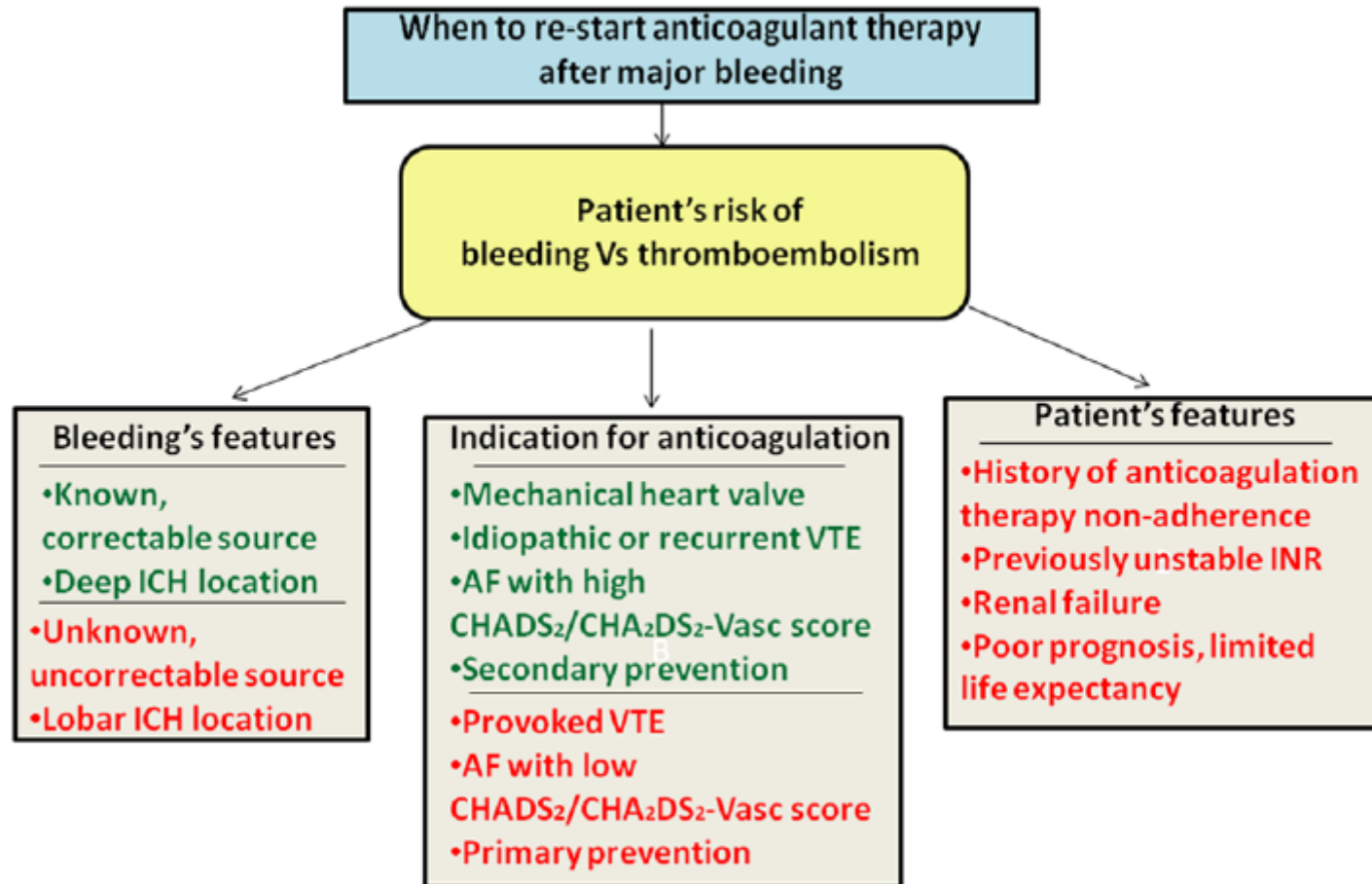
- **Lobar hemorrhage**

for 1000 anticoagulated patients for 1 year:

- 31 fewer thromboembolic strokes
- 150 additional ICHs



Indication to re-start anticoagulation after major bleeding



Decision-making process in OAC resumption after OAC-related intracranial bleeding

