La gestione dell'ictus ischemico o emorragico nel paziente sotto NAO

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Acute stroke treatment decision making

Outline of the presentation

1. Can patients with AIS who are taking DOAC be treated with i.v. thrombolysis and/or endovascular thrombectomy?

2. When to start DOAC in patients with recent AIS?

3. Can patients be given DOAC after ICH?

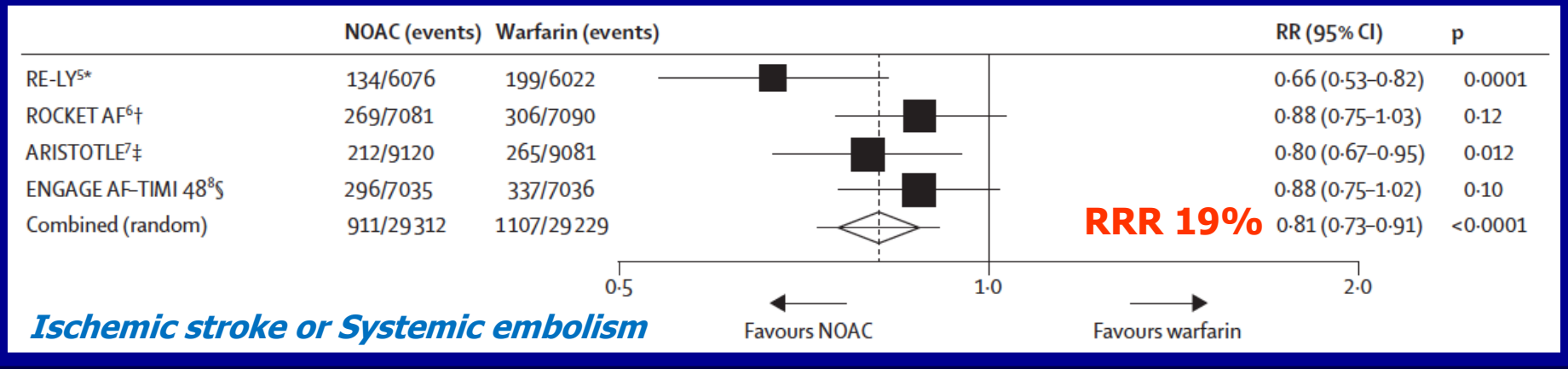
4. How to manage DOAC-related ICH?

Acute ischemic stroke and anticoagulants

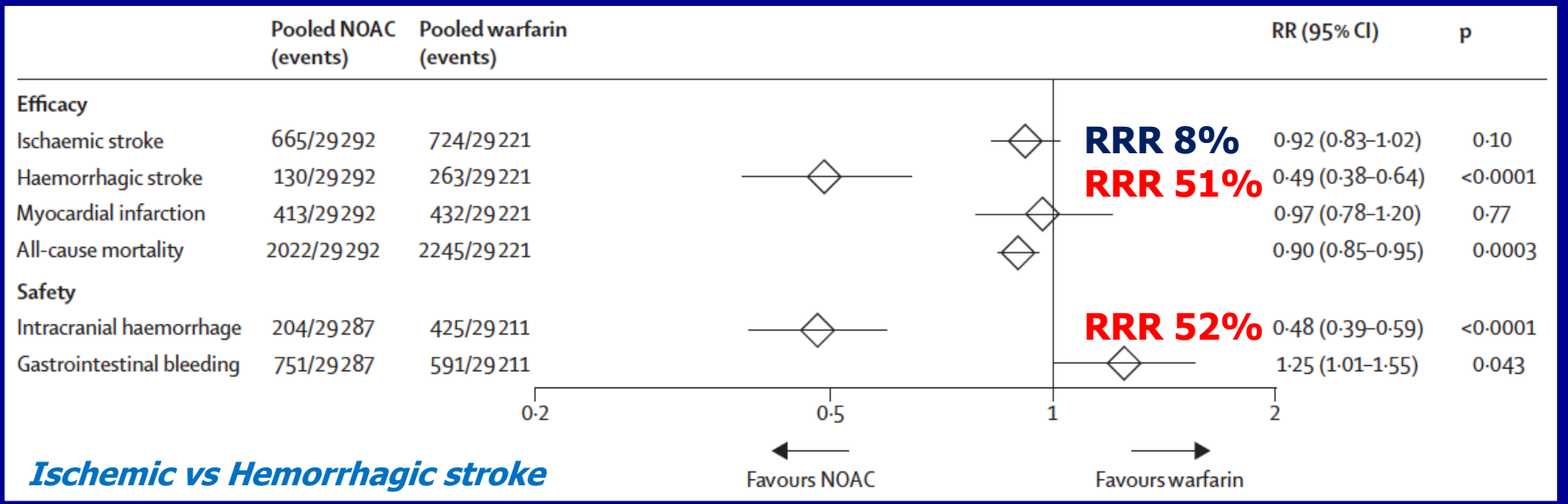
Anticoagulants are effective in *stroke prevention* but despite treatment a number of subjects develop a stroke

Anticoagulation may favour *bleeding* and the *risk*, in patients with AIS, may be further increased by *any revascularization treatment*

Efficacy of DOAC in the SPAF Trials



Ischemic stroke or Systemic embolism



Ischemic vs Hemorrhagic stroke

Lancet 2014;383:955-962

AHA/ASA Guideline

Guidelines for the Early Management of Patients With Acute Ischemic Stroke

A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

The use of *i.v. rtPA* in patients taking direct thrombin inhibitors or direct factor Xa inhibitors *may be harmful* and is not recommended unless *sensitive laboratory tests* (aPTT, INR, platelet count, ECT, TT, or appropriate direct factor Xa activity assay) are *normal*, or *the patient has not received a dose of these agents for >2 days* (assuming *normal renal* metabolizing *function*)

Similar consideration should be given to patients being considered for *intra-arterial rtPA*

(Class III; Level of Evidence C)

Stroke 2013;44:870-947

AHA/ASA Guideline

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Exclusion criteria for thrombolysis

Current use of direct thrombin inhibitors or direct factor Xa inhibitors *with elevated sensitive laboratory tests* (such as aPTT, TT, INR, platelet count, and ECT; or appropriate factor Xa activity assays)

Under some circumstances - considering and weighting risk to benefit - patients may receive iv rtPA despite 1 or more relative contraindications

Consider risk to benefit of iv rtPA administration carefully if any of the relative contraindications are present

Stroke 2013;44:870-947

Coagulation assays for DOACs

	Dabigatran	Rivaroxaban	Apixaban
Peak Concentration (h)	2-3	2-4	1.5-3
Half-life (h)	12-17 (19-28 impaired renal function)	5-9 (11-13 moderate renal imp./age ≥75)	8-15 (17-18 CrCl<50 mL/min)
aPTT	↑↑	↑ to↔	↔ to ↑
PT/INR	↑	↑-↑↑	↑
TT	↑↑↑↑	↔	↑
ECT	↑↑↑↑	↔	↔
Anti-Xa activity	↔ to ↑	↑↑↑↑	↑↑↑↑
Peak value	aPTT	Anti-Xa activity (PT, aPTT)	Anti-Xa activity (PT, aPTT)
Trough value	Thrombin time	Anti-Xa activity	Anti-Xa activity
Specific test system	Hemoclot test	Calibrated anti-Xa activity	Calibrated anti-Xa activity

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Trough value	Thrombin time	Anti-Xa activity	Anti-Xa activity
Specific test system	Hemoclot test	Calibrated anti-Xa activity	Calibrated anti-Xa activity

No data on a cut-off of these specific tests below which thrombolysis is safe

ANTITHROMBOTIC	REVERSAL AGENT
DIRECT THROMBIN INHIBITORS (DTIs) **PO:** – Dabigatran (Pradaxa®) Half-life 12-17 hours in normal renal function **IV:** – Argatroban – Bivalirudin (Angiomax®) Half-life 10-90 minutes The thrombin time (TT) may be used to QUALITATIVELY measure dabigatran. A normal TT rules out clinically relevant dabigatran levels. **Do not use PT/INR**	**IV DTIs**: Short half-life and discontinuation of IV DTIs are primary means of attenuating bleed – support with crystalloid and blood products to facilitate rapid renal clearance of drug. IV DTIs should be discontinued immediately upon bleeding discovery and rarely require other means of reversal. **Idarucizumab (Praxbind®)** – *only used for reversal of dabigatran (Pradaxa®)* Restrictions: patients confirmed to have recent dabigatran use who: – Require anticoagulant reversal for life-threatening hemorrhage OR – Require urgent/emergent invasive procedure within next 8 hours Dose: 5 gram Administration: Infuse *two* 2.5 gram/50 mL vials undiluted over 5-10 minutes each, consecutively – Line should be flushed with NS prior to infusion – Second vial should be infused within 15 minutes of first vial Onset: Immediate **4 Factor PCC (KCentra®)** **May be considered for dabigatran reversal if idarucizumab not available** Dose*: 50 units/kg, round to nearest whole vial **(dose cap at 100 kg to mitigate thrombotic risk)** Administration: Place in empty IV bag and give slow IV push over 10 minutes – Use within 4 hours of reconstitution Onset: <30 minutes Caution: thrombotic risk

Clinical trials on endovascular treatment for AIS

Trial	Publ (year)	Exclusion criteria	
PROACT	1998	INR >1.5	
PROACT-II		INR >1.7 or aPTT >1.5 X normal	
MERCI	2005	INR >1.7 in part I	INR >3.0 in part II,heparin within 48 h, and a PTT 2X normal
IMS	2004	INR >1.5 or normal PTT if heparin	
IMS-II	2007	INR >1.5 or normal PTT if heparin	
MELT	2007	INR >1.7	
TREVO 2	2012	INR >3.0 or aPTT >2 X normal	
IMS-III	2013	INR >1.5	
MR RESCUE	2013	INR >3.0 or PTT >3X normal	
SYNTHESIS	2013	INR >1.5, aPTT >1.5 X normal	

Patients on anticoagulants have been excluded from earlier trials

Clinical trials on endovascular treatment for AIS

Trial	Publ (year)	Exclusion criteria	
STAR	2013	INR >3.0	
MR CLEAN	2015	Exclusion criteria for intrarterial thrombolysis: INR >1.7 or NOACs	Exclusion criteria for mechanical thrombectomy: aPTT>50 s or INR >3
ESCAPE	2015	None	
EXTEND-IA	2015	Standard contraindications to rtPA	
SWIFT PRIME	2015	INR >1.7 or full-dose heparin within the last 24h	
REVASCAT	2015	INR >3.0	
THERAPY	2016	Use of IV heparin in the past 48 hours with PPT >1.5 times the normalized ratio. Known hemorrhagic diathesis, coagulation deficiency, or on anticoagulant therapy with an INR >1.7	
TRACE	2016	Contraindications for intravenous thrombolysis	

If *intravenous thrombolysis* is *contraindicated* (e.g. warfarin-treated patients with therapeutic INR) while *mechanical thrombectomy* is *recommended* as first-line treatment in large vessel occlusions (Grade A, Level 1a, KSU Grade A)

Consensus statement on mechanical thrombectomy in acute ischemic stroke - ESO-Karolinska Stroke Update 2014 in collaboration with ESMINT and ESNR - 20 february, 2015

Current evidence and Clinical practice Recommendations

Patients on DOACs

Avoid i.v. thrombolysis except in highly selected pts (age, time from stroke onset, stroke severity, time from last dose, coagulation status)

Provide mechanical thrombectomy in pts with large vessel occlusion

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Acute IS treatment in pts on NOAC

Sintesi 9.3

La letteratura suggerisce la possibilità di prendere in considerazione la trombolisi e.v. in pazienti trattati con farmaci anticoagulanti orali diretti con verosimile effetto sub-terapeutico, evidenziato dalla storia clinica (dose e intervallo temporale dall'ultima assunzione, funzionalità renale) e da test specifici e standardizzati (Tempo di Trombina, Tempo di Ecarina o Hemoclot per il dabigatran, anti-Xa per il rivaroxaban o l'apixaban).

Sintesi 9.22

L'intervento endoarterioso meccanico può essere preso in considerazione, previa valutazione del rapporto rischi/benefici, in pazienti trattati con anticoagulanti diretti e con alto rischio di emorragia, definito dai test di laboratorio specifici (o dall'impossibilità della loro esecuzione) e dal tempo dell'ultima assunzione, in quanto non sembra associato a un incremento del rischio di complicanze emorragiche.

Acute stroke treatment decision making

Outline of the presentation

1. Can patients with AIS who are taking DOAC be treated with i.v. thrombolysis and/or endovascular thrombectomy?

2. When to start DOAC in patients with recent AIS?

3. Can patients be given DOAC after ICH?

4. How to manage DOAC-related ICH?

Timing for DOAC introduction after stroke

- **Ischemic stroke recurrence**
- **Systemic embolism**
- **Cerebral bleeding**

Guidelines for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack

A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

Secondary stroke prevention

For most patients with a stroke or TIA in the setting of AF, it is reasonable to initiate oral anticoagulation within 14 days after the onset of neurological symptoms (*Class IIa, Level of evidenze B*)

In the presence of high risk for hemorrhagic conversion (ie, large infarct, hemorrhagic transformation on initial imaging, uncontrolled hypertension, or hemorrhage tendency), it is reasonable to delay initiation of oral anticoagulation beyond 14 days (*Class IIa; Level of Evidence B*)

Stroke 2014;45:2160-36

How long should we wait to start oral anticoagulation after cardioembolic stroke?

Expert consensus has suggested starting *warfarin within 2 weeks* after stroke except in those with large infarcts, with the understanding that it will typically take an additional 3 to 5 days after starting therapy to achieve full anticoagulation

As the *DOAC anticoagulation is achieved within hours of the first dose*, *optimal timing* of initiation is even more *uncertain* given lack of data

Neurology 2016;87:1852–53

*Initiation or resumption of anticoagulation depends on severity of stroke**

Time to re-initiation depends on infarct size:
1 – 3 – 6 – 12 day rule (Diener's Law)

TIA	Mild stroke	Moderate stroke	Severe stroke
As soon as imaging has excluded a cerebral haemorrhage	3–5 days after symptom onset	5–7 days after stroke onset	2 weeks after stroke onset
Day 1	3	6	12

Mild = NIHSS score <8; moderate = NIHSS score 8–16; severe = NIHSS score >16
NIHSS, National Institutes of Health Stroke Scale

Thromb Haemost 2012;107:838–47

Early Recurrence and Cerebral Bleeding in Patients With Acute Ischemic Stroke and Atrial Fibrillation

Effect of Anticoagulation and Its Timing: The RAF Study

1029 consecutive patients with AIS and AF without contraindication to anticoagulation

14.7% LMWH alone
37.1% VKA
12.1% DOAC (dabigatran, rivaroxaban, or apixaban)
36.0% LMWH followed by VKA

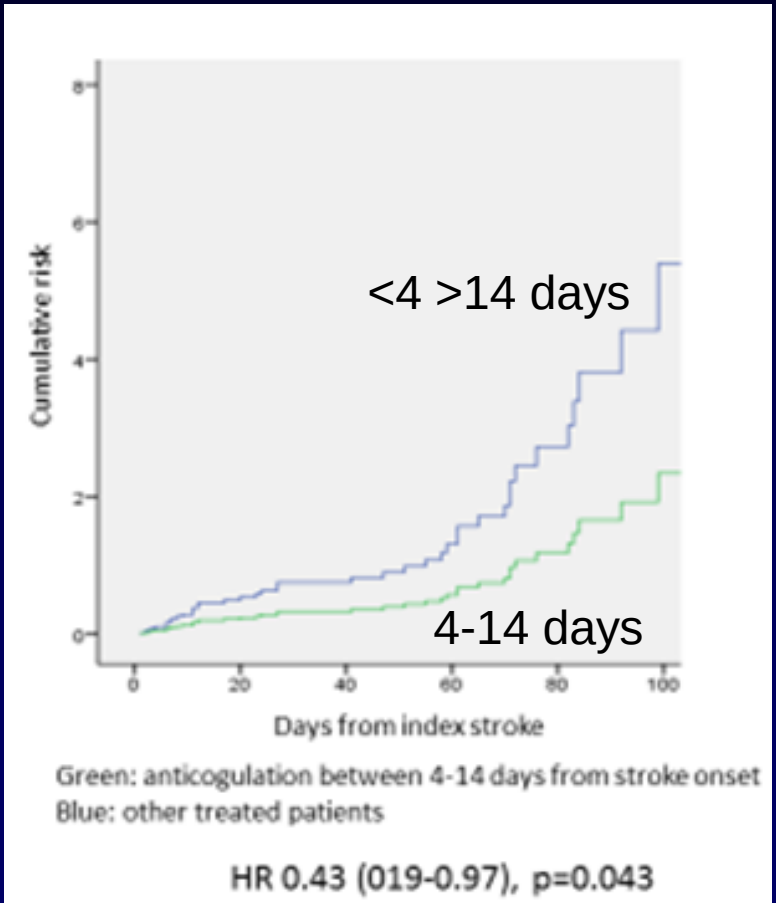
Outcome events (90 days)	N (%)
Symptomatic hemorrhagic transformation	37 (3.6)
Major extracranial bleeding	14 (1.4)
Ischemic stroke/TIA/systemic embolism	77 (7.6)
Total outcome events	128 (12.6)

Stroke 2015;46:2175-82.

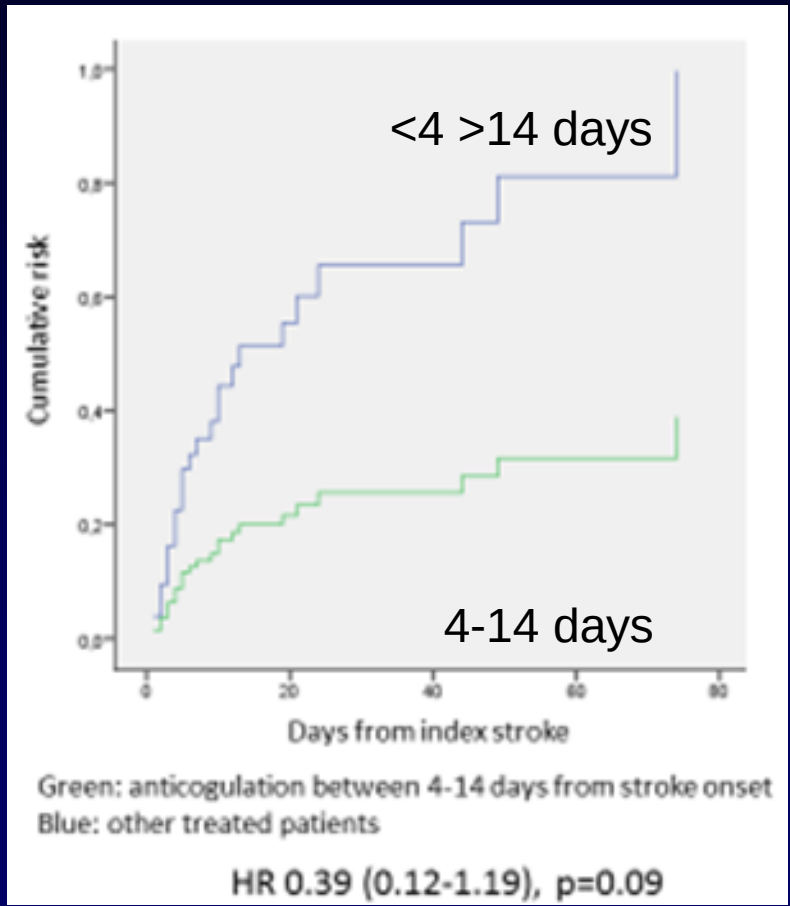
Early Recurrence and Cerebral Bleeding in Patients With Acute Ischemic Stroke and Atrial Fibrillation

Effect of Anticoagulation and Its Timing: The RAF Study

Ischemic outcome events



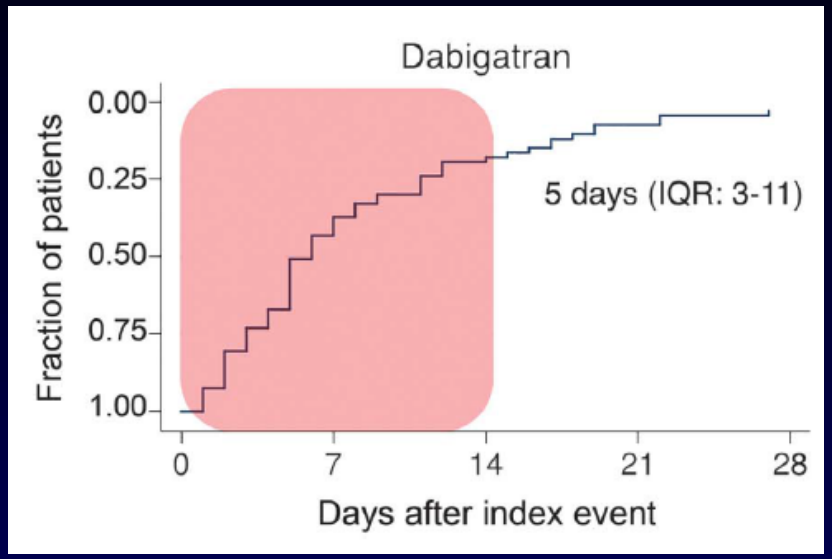
Hemorrhagic outcome events

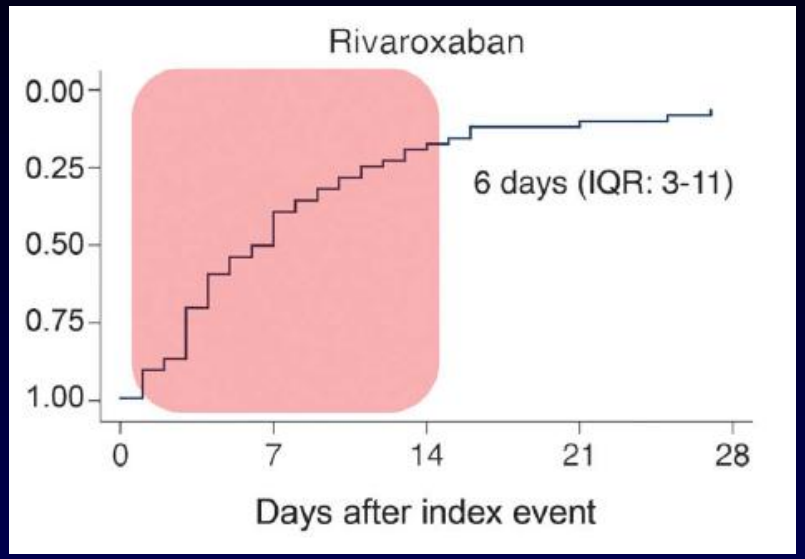


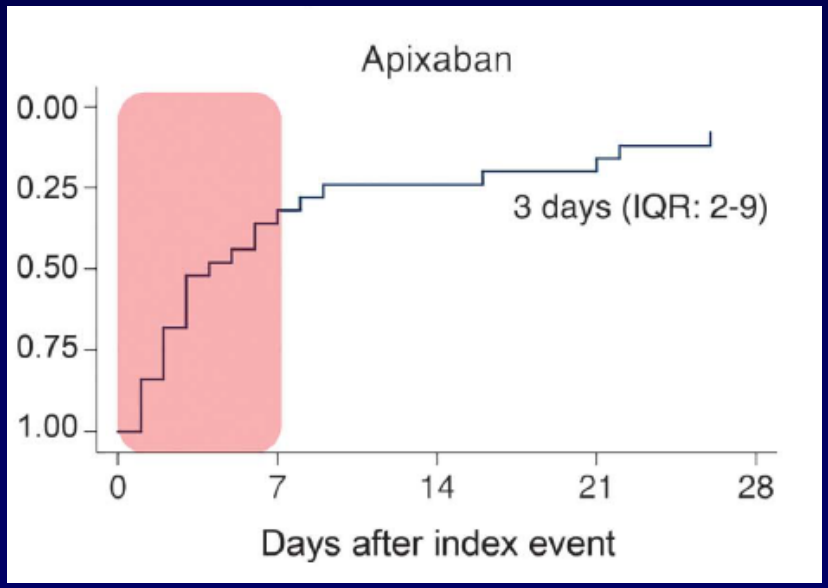
Stroke 2015;46:2175-82.

Early start of DOAC after ischemic stroke

Risk of intracranial hemorrhage and recurrent events







204 patients with AIS or TIA and with NVAF: after the index event a DOAC was started within 7 days in 65% (DOACearly) while in 35% patients, DOAC was started after day 7 (DOAClate)

The study demonstrates that in clinical practice, DOACs are often started earlier among patients with AIS or TIA than in the RCTs

Neurology 2016;87:1856–62

Early start of DOAC after ischemic stroke

Risk of intracranial hemorrhage and recurrent events

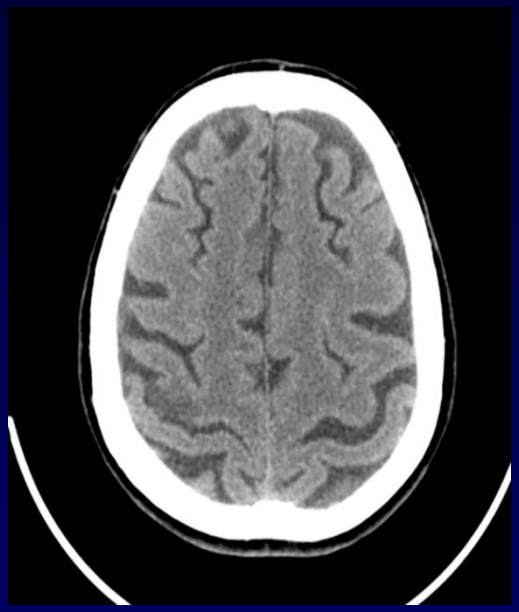
	All patients (n = 204)	$DOAC_{early}$ (n = 100)	$DOAC_{late}$ (n = 55)	p[a]
Age, median (IQR), y	79 (73-84)	79 (72-84)	81 (73-85)	0.33
Women, n (%)	94 (46)	43 (43)	25 (45)	0.87
Index event, n (%)				
Acute ischemic stroke	181 (89)	88 (88)	51 (93)	0.42
TIA	23 (11)	12 (12)	4 (7)	
Clinical data, median (IQR)				
NIHSS at admission, points	4 (2-8)	3 (1-7)	7 (3-14)	<0.001[c]
Endpoints between 3 and 6 mo, n (%)[b]				
Intracranial hemorrhage	1 (0.5)	0 (0)	0 (0)	NA
Recurrent event[c]	6 (3)	2 (2)	2 (4)	0.62

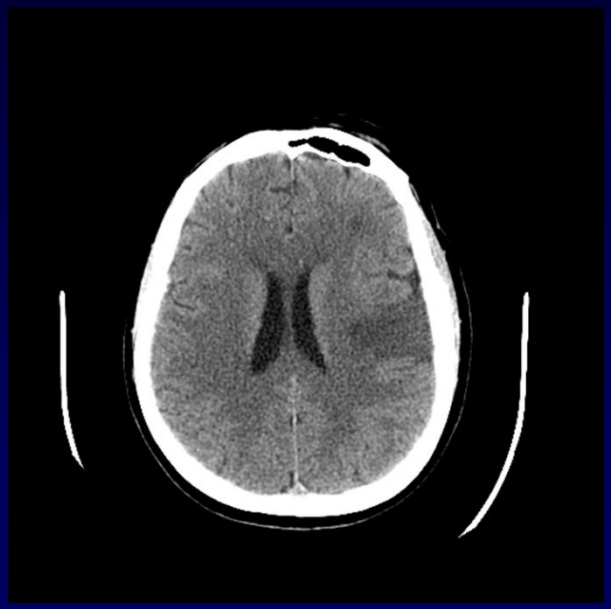
These findings apply mostly to patients with minor stroke

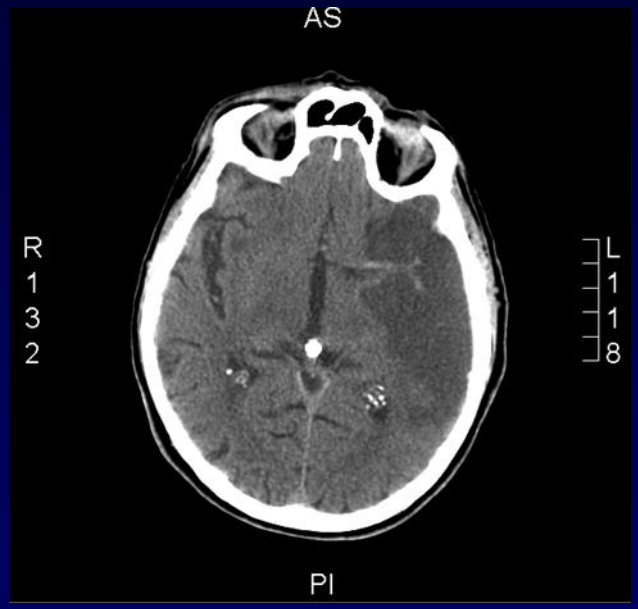
Perhaps other factors, such as size of infarct or presence of hemorrhagic trasformation were also used to select patients for early vs late therapy

Neurology 2016;87:1856–62

Size of the ischemic lesion







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Restart anticoagulant in pts with IS

Sintesi 11.5.f

L'introduzione della terapia anticoagulante orale in caso di ictus ischemico o TIA attribuibile a FA non necessita del bridging con ASA o EBPM se si adoperano i NAO e i dati di letteratura tendono a evitare il bridging, per la mancanza di efficacia e di sicurezza, se si usano gli anticoagulanti AVK.

Sintesi 11.5.e

In caso di ictus ischemico attribuibile a FANV, il trattamento anticoagulante orale con i NAO va iniziato o ripreso prima possibile. La scelta del timing si basa sulla gravità clinica dell'ictus, sulla estensione e sulle caratteristiche della lesione cerebrale all'imaging, sul calcolo individuale del rischio tromboembolico ed emorragico. Nel caso di TIA il trattamento può essere ripreso subito.

Acute stroke treatment decision making

Outline of the presentation

1. Can patients with AIS who are taking NOAC be treated with i.v. thrombolysis and/or endovascular thrombectomy?

2. When to start NOAC in patients with recent AIS?

3. Can patients be given NOAC after ICH?

4. How to manage NOAC-related ICH?

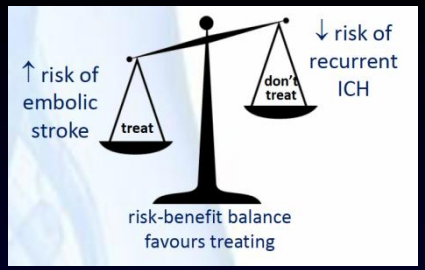
Anticoagulation after ICH

No RCT to establish which may be the best treatment

Lack of adequate data regarding events occurrence after restarting anticoagulants in patients with a previous ICH (probably reflecting the ethical challenge of prescribing patients an apparently contraindicated medication)

Extrapolation of the risk of thromboembolism/ICH *from available RCT* on primary and secondary prevention is *inappropriate*

ICH recurrence vs thromboembolism



CHA_2DS_2-VASc criteria	Score
Congestive heart failure/ left ventricular dysfunction	1
Hypertension	1
Age ≥75 yrs	2
Diabetes mellitus	1
Stroke/transient ischaemic attack/TE	2
Vascular disease (prior myocardial infarction, peripheral artery disease or aortic plaque)	1
Age 65–74 yrs	1
Sex category (i.e. female gender)	1

TE = thromboembolism

HAS-BLED criteria	Score
Hypertension	1
Abnormal liver and renal function (1 point each)	1 or 2
Stroke	1
Bleeding	1
Labile INRs	1
Elderly	1
Drugs or alcohol (1 point each)	1 or 2

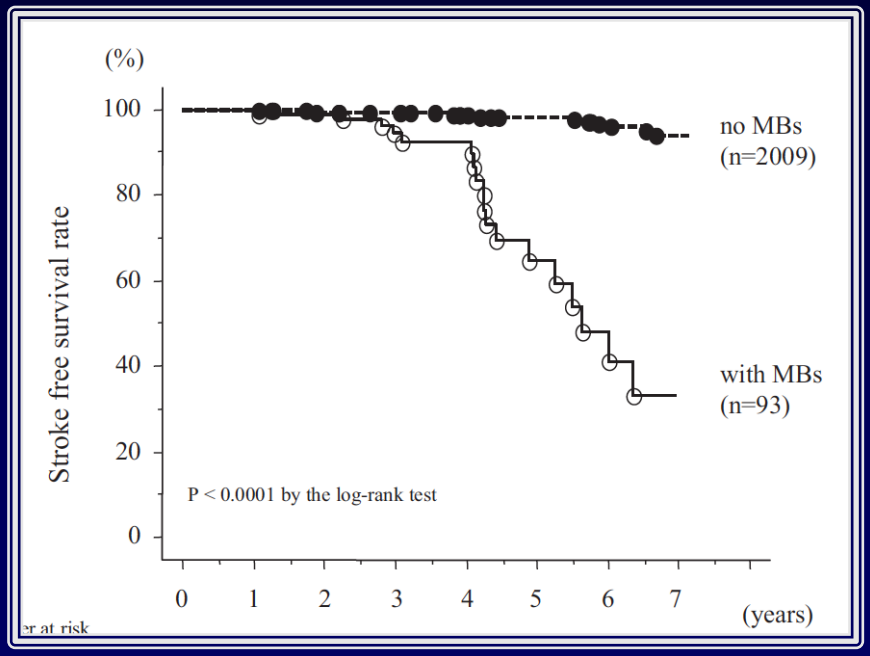
The benefit of warfarin in patients with atrial fibrillation is unequivocal in high risk subgroups without strong contraindications to anticoagulation, that is in patients with prior thromboembolism

Whether to resume anticoagulation after the complete reabsorption of ICH is a difficult dilemma that requires balancing the competing risks of recurrent ICH versus a thromboembolic event

For the anticoagulation therapy to be of benefit, *the decrease in thromboembolic risk should outweigh the risk of a new ICH*

Clinical implications of CMBs

Future stroke risk

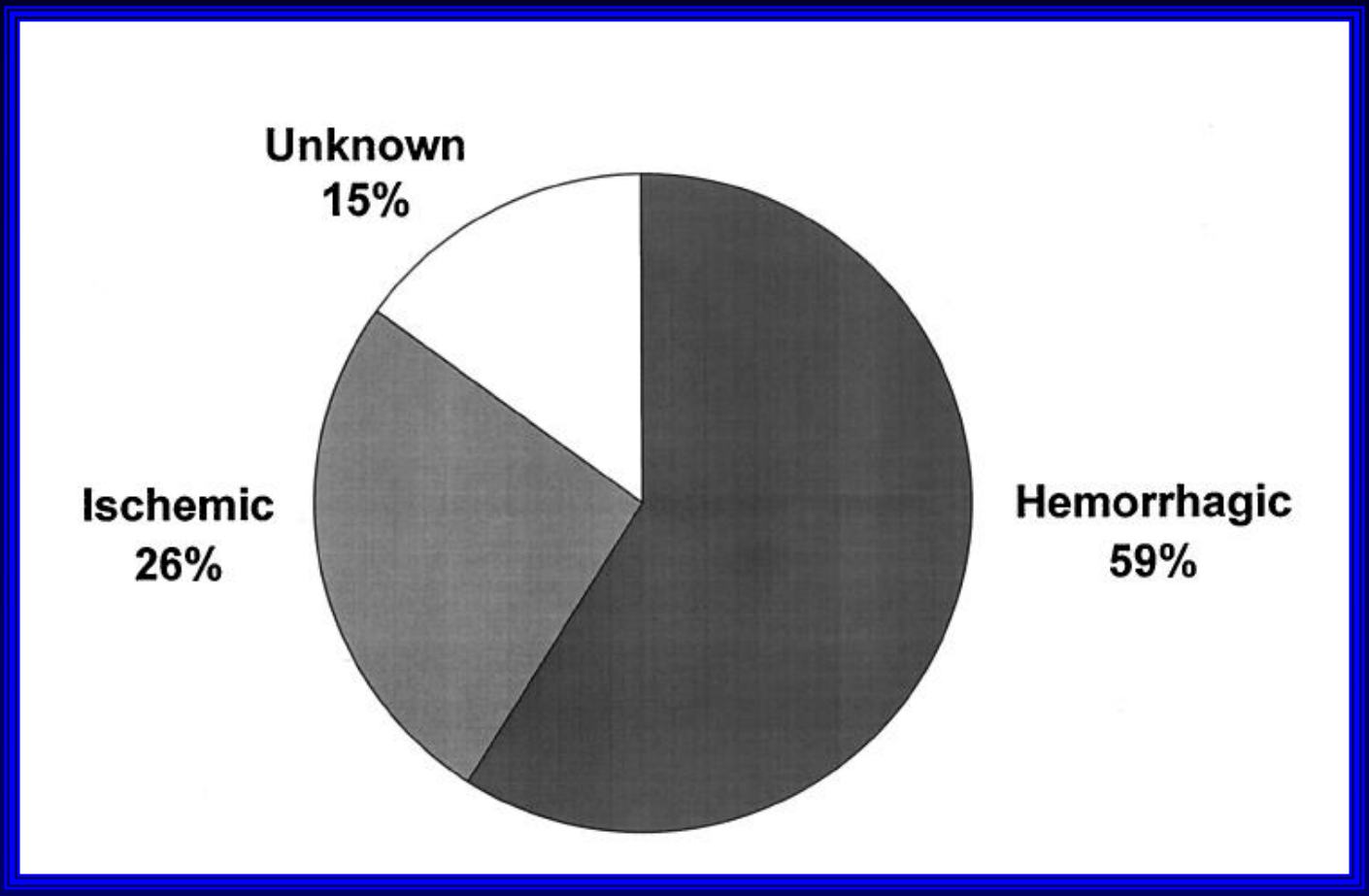


	Ischemic Stroke		ICH	
Variables	HR (95% CI)	*P*	HR (95% CI)	*P*
MBs, yes	4.48 (2.20–12.2)	<0.0001	50.2 (16.7–150.9)	<0.0001
SBI, yes	2.94 (1.26–6.82)	0.012	. . .	. . .

Subjects who had MBs were 5 and 50 times as likely to experience ischemic stroke and ICH, respectively, than those who did not have MBs

Stroke 2011;42:1867-1871

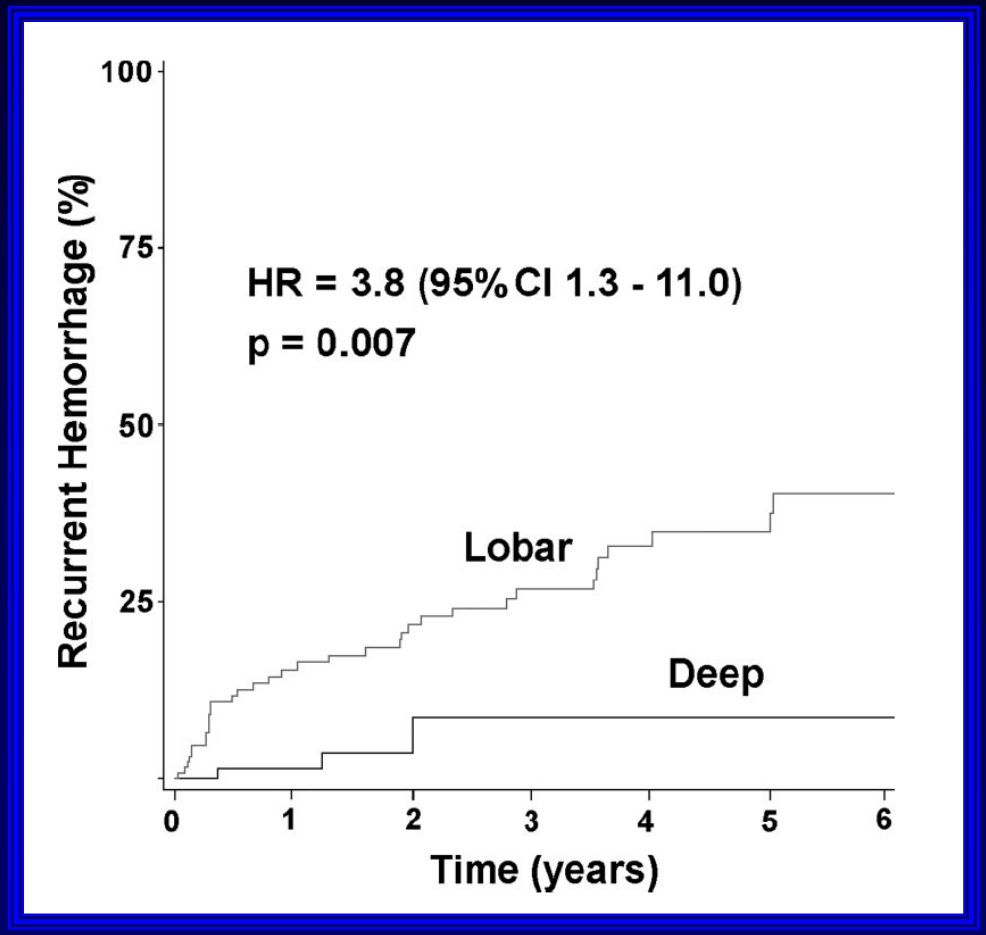
Distribution of stroke recurrences among survivors of primary ICH



Neurology 2001;56:773-777

Lobar ICH location has consistently been associated with an increased risk of ICH recurrence

Kaplan–Meier plot of recurrent intracerebral hemorrhage in survivors of lobar and deep hemorrhage



There is currently no way to modify the risk of ICH associated with *cerebral amyloid angiopathy*

On the other hand, in patients with *hypertensive hemorrhage*, antihypertensive therapy likely reduces the risk of recurrent ICH

Viswanathan et al. Neurology 2006;66:206-209

Suggested risk stratification for recurrent intracranial hemorrhage

High risk	Cerebral amyloid angiopathy or lobar intracranial hemorrhage Microbleeds on magnetic resonance imaging Apolipoprotein E genotype
Moderate risk	Hypertensive vasculopathy or deep intracranial hemorrhage with any of the following: Normal international normalized ratio at the time the hemorrhage is diagnosed Patient not compliant with the dosing and monitoring of vitamin K antagonist therapy Patient not compliant with antihypertensive therapy
Low risk	Hypertensive vasculopathy or deep intracranial hemorrhage in a compliant patient

Clev Clin J Med 2010;77:743-746

Even without anticoagulation, ICH is the deadliest form of stroke

	7-Day			30-Day		
Type	n	Percent	95% CI	n	Percent	95% CI
ICH confirmed by neuroimaging (n=464)	111	23.9	20.0–27.8	192	41.4	36.9–45.9
Lobar (n=205)	55	26.8	20.8–32.9	91	44.4	37.6–51.2
Deep (n=210)	39	18.6	3.3–23.8	75	35.7	29.2–42.2
Posterior fossa (n=44)	15	34.1	20.1–48.1	23	52.3	37.5–67.1
Intraventricular or multiple localized (n=5)	2	40.0	0–82.9	3	60.0	17.1–102.9
Probable ICH without brain neuroimaging (n=85)	79	92.9	87.4–98.4	84	98.8	96.5–101.1
All ICH (n=549)	190	34.6	30.6–38.6	276	50.3	46.1–54.5

Stroke 2009;40:394-399

Alternatives to oral anticoagulation

In patients with atrial fibrillation and an unfavorable risk/benefit profile to restarting anticoagulation, *antiplatelet therapy* is a reasonable alternative

In some, the use of a *left atrial appendage occlusion device* or procedure may be another consideration

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Restart anticoagulant in pts with ICH

Sintesi 11.5.d

In caso di ictus emorragico in pazienti con FANV il trattamento anticoagulante orale, preferibilmente condotto con NAO per il miglior profilo di sicurezza in questa tipologia di pazienti, va iniziato o ripreso non appena possibile.
Per la ripresa del trattamento anticoagulante in pazienti con pregressa emorragia cerebrale va tenuto conto che:
A) il rischio emorragico è del 2,1%- 3,7 % annuo.
B) la ripresa della terapia anticoagulante aumenta il rischio di sanguinamento cerebrale di cinque volte ma riduce il rischio di eventi ischemici del 90%.

- Controindicazioni assolute alla ripresa della TAO: emorragia lobare correlabile ad angiopatia amiloidea

- Ripresa della TAO dopo tre settimane: nel paziente a rischio tromboembolico elevato per: CHA_2DS_2-VASc ≥ 5 o $CHADS_2 \geq 4$, protesi valvolare meccanica mitralica, trombosi delle camere cardiache, tromboembolismo venoso e arterioso < 30 giorni

- Ripresa della TAO dopo la trentesima settimana: pazienti ad alto rischio emorragico per: microbleeds multiple alla RM-gradient ECHO, leucoaraiosi, emorragie lobari non correlabili ad angiopatia amiloidea

- In tutti gli altri casi ripresa della TAO tra la decima e la trentesima settimana.

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3. Can patients recive DOAC after ICH ?

4. How to manage DOAC-related ICH?

Management of DOAC-related ICH

NOAC reversal agents

NOAC	Direct Thrombin Inhibitor	Factor Xa inhibitor		
	Dabigatran (Pradaxa®)	Rivaroxaban (Xarelto®)	Apixaban (Eliquis®)	Edoxaban (Lixiana®)
Dialysis Removable	✓	✗	✗	✗
Specific Antidote	Idarucizumab	Andexanet alpha		
Universal Antidote	Aripazine/Ciraparantag			

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Management of ICH in pts on NOAC

Raccomandazione 9.25 **GPP**

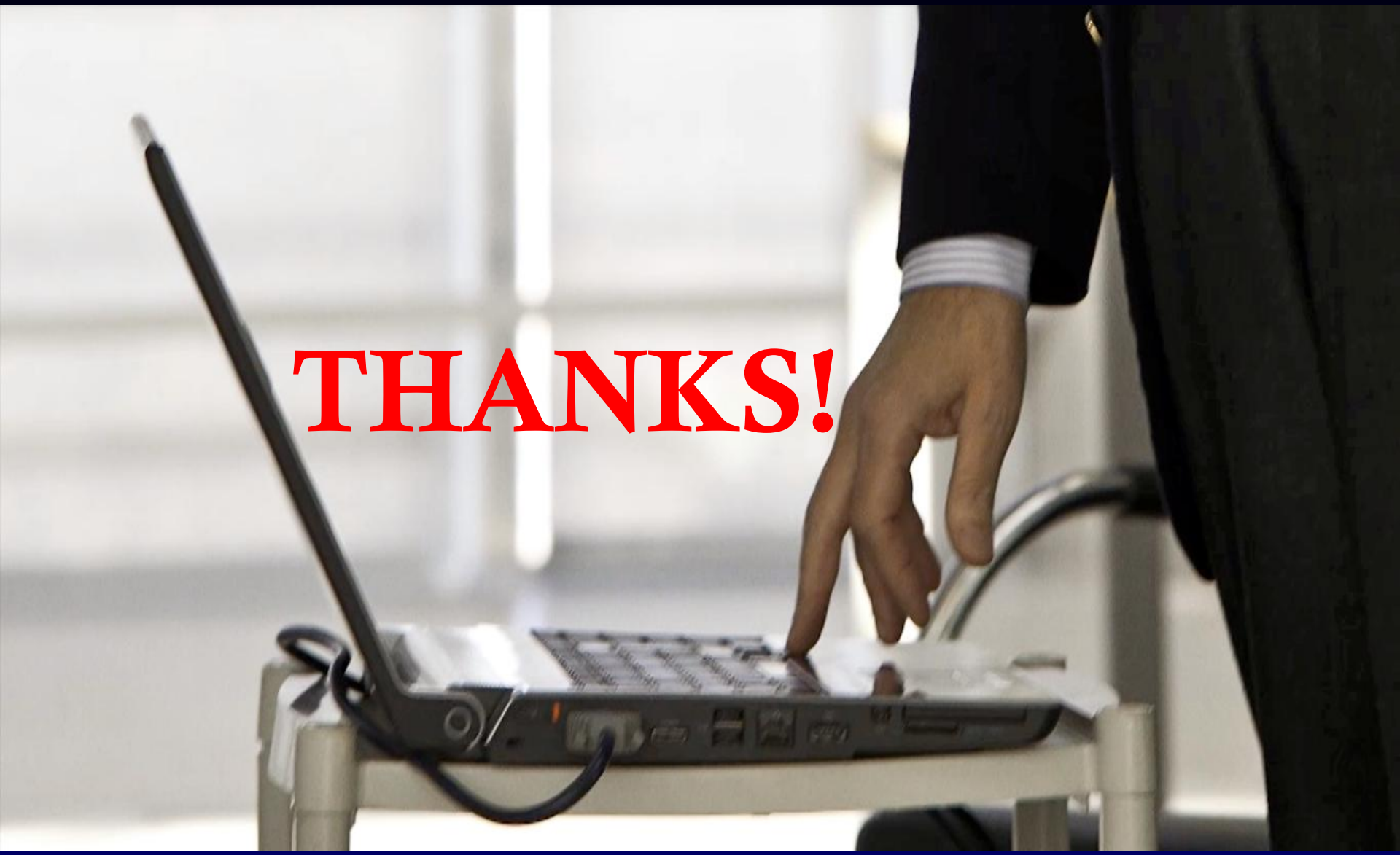
Nei pazienti con emorragia cerebrale il Gruppo ISO-SPREAD suggerisce di iniziare il trattamento dell'ipertensione ed il reversal delle eventuali terapie anticoagulanti sin dall'arrivo in Pronto Soccorso.

Raccomandazione 9.31 **Forte a favore**

Attualmente la somministrazione di idarucizumab è raccomandata per pazienti in trattamento con dabigatran etexilato che debbano sottoporsi a interventi chirurgici di emergenza o in caso di emorragia cerebrale o di sanguinamento incontrollato.

Raccomandazione 9.32 **GPP**

In caso di emorragia cerebrale in pazienti in terapia con anticoagulanti anti-fattore X, il Gruppo ISO-SPREAD suggerisce la somministrazione di PCC a 4 fattori o a 3 fattori, o di FEIBA o di fattore VII.


THANKS!