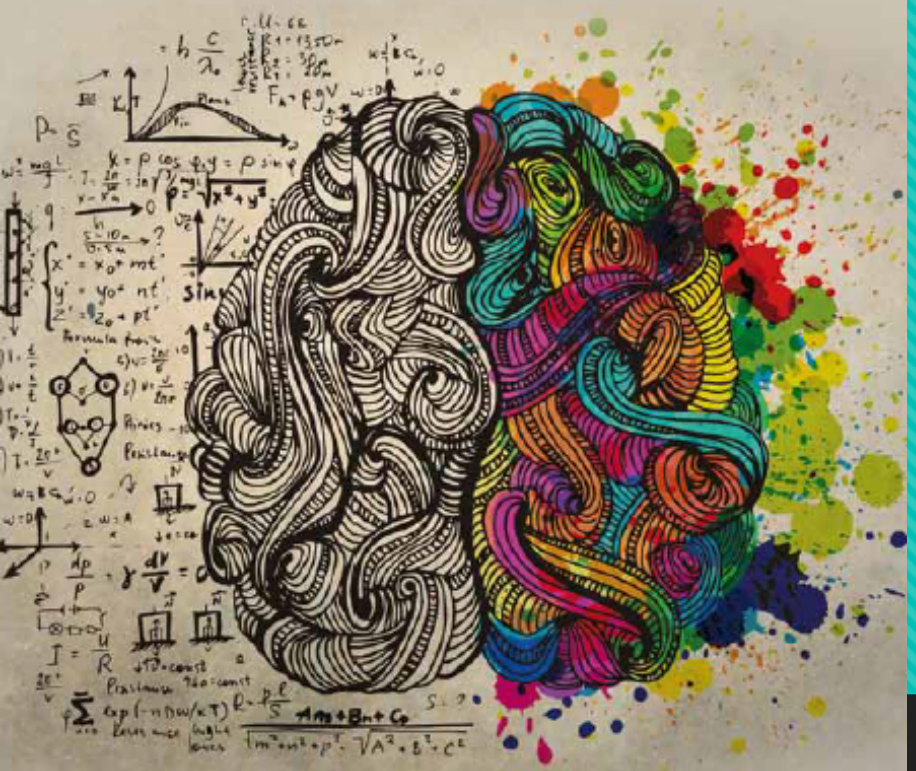
XXVI CONGRESSO NAZIONALE

Società Italiana Interdisciplinare NeuroVascolare



SINERGIE INTERDISCIPLINARI NEL PAZIENTE NEUROLOGICO CRITICO

Lecce, 1-2 dicembre 2017

L'emorragia cerebrale in soggetti in trattamento anticoagulante

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U.O.S.C. Neurologia e Stroke Unit

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L’ Emorragia Cerebrale

- L’incidenza dell’emorragia cerebrale non traumatica (ICH) è di 25 casi/100.000 abitanti/anno, rappresenta circa il 20% di tutti gli ictus

Van Asch CJ et al. Lancet Neurol .2010

- Il tasso di mortalità a 30 giorni è di circa il 50%

Flaherty ML et.al. Semin Neurol .2010

- Nella metà dei casi fatali la morte sopraggiunge nelle prime 48 ore

Nilsson OG et al. J. Neurosurg . 2002

- Dopo 6 mesi solo il 20 % dei pazienti risulta completamente indipendente

Broderick JP et al. Stroke 1999

- Il 20 % dei pz che manifestano una ICH assume terapia anticoagulante

Flaherty ML et.al. Semin Neurol .2010

L’emorragia cerebrale in anticoagulante

- Nei pazienti che assumono anticoagulante orale:

il rischio annuale di emorragia maggiore è del 2-3% (fatale dal 9 al 13%) ,

il rischio di ICH è tra lo 0.3 e lo 0.5 % *Schulman S, et al. Chest .2008*

- In assenza di anticoagulante orale Il rischio annuale di tromboembolismo è :

del 12-22% nei portatori di valvola meccanica - fatale nel 12% -

del 6-18% nei pz con FA e $CHAD_2DS_2$-VASc $\geq$ 3 - stroke embolico fatale nel 27% -

Salem DN et al. Chest 2008, Gage BF JAMA 2001

L’emorragia cerebrale in anticoagulante

- Il volume dell’ematoma e la sua espansione sono fattori prognostici determinanti nella ICH

  Davis Sm et al, Neurology 2006

- Nei pazienti che assumono anticoagulante l’ espansione dell’ematoma avviene nel 30-50 % dei casi

  Aguilar MI et al Mayo Clin Proc 2007

- L’alto rischio di espansione e il tempo prolungato di crescita dell’ematoma (nei pz che assumono anticoagulanti) si associano ad una più alta mortalità rispetto ai pz che non ne assumono

  Fibotte JJ et al. Neurology 2004

- La mortalità raggiunge il 67% nelle ICH in TAO

  Marietta M, et al. Intern Emerg Med 2007

Emorragia cerebrale in AVK – Fattori di Rischio

Table 2 Risk factors for developing intracerebral haemorrhage during oral anticoagulant therapy

- Age (especially over 75 years)
- Hypertension (especially systolic blood pressure >160 mmHg)
- Previous stroke
- INR levels
- Concomitant use of antiplatelet drug
- Cerebral amyloid angiopathy

Marietta M, et al. Intern Emerg Med 2007

Emorragia cerebrale in AVK – Fattori prognostici negativi

- Basso punteggio alla Glasgow Coma Scale all'esordio
- Volume iniziale dell'ematoma
  - Non vi sono differenze significative tra pz non in TAO e in TAO con INR <3.0;
  - L'ematoma è più grande con INR > 3.0;
  - Non vi è relazione lineare tra volume dell'ematoma e INR suggerendo un effetto soglia
- Espansione dell'ematoma (nella maggior parte dei casi entro 24 h)
- Sanguinamento intraventricolare
- Edema

Zubkov AY et al Arch Neurol 2008; Flaherty ML et al. Neurology 2008.

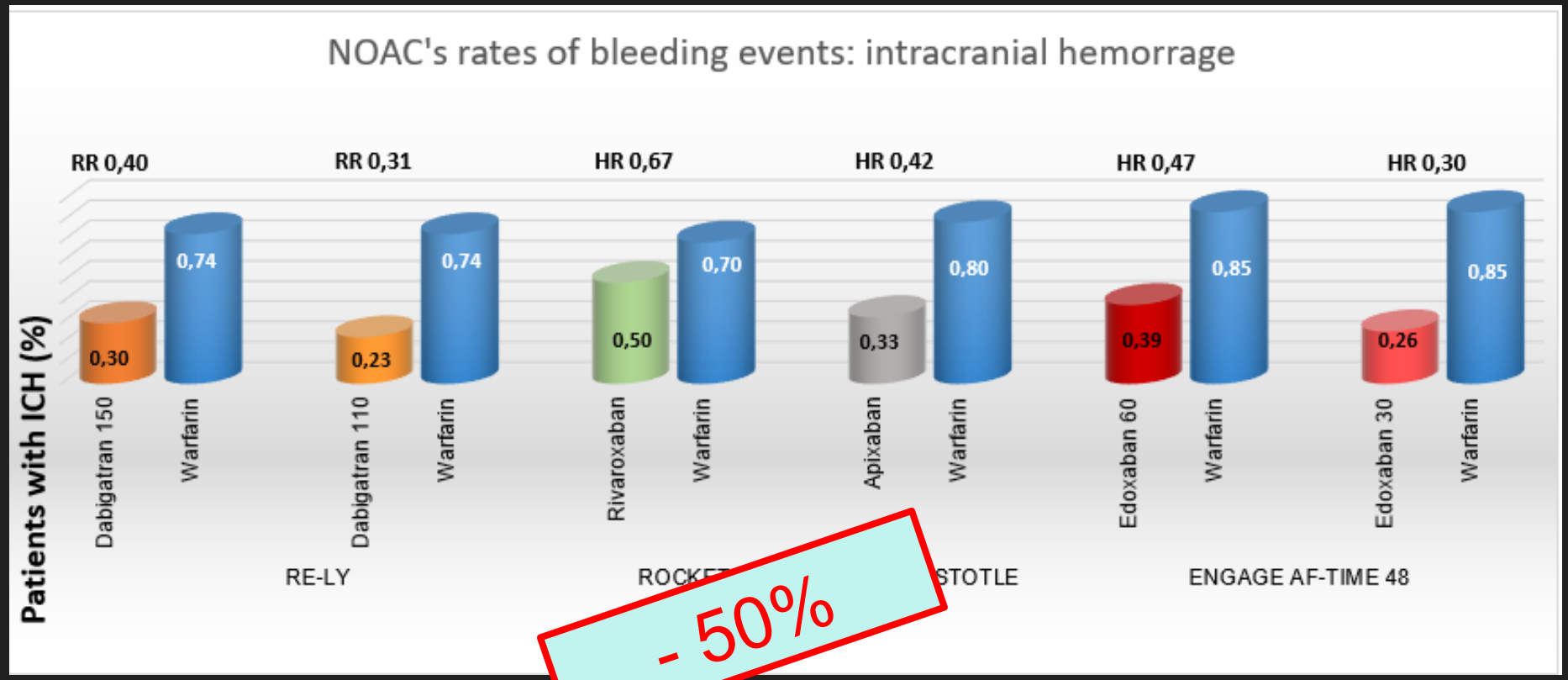
Anticoagulanti Diretti (NAO)

- Sono non inferiori in termini di efficacia agli AVK

- E' dimostrato il maggiore profilo di sicurezza in termini di sanguinamento (eccetto che per i sanguinamenti gastrointestinali)

Ruff CT et al, Lancet 2014

ICH in anticoagulante
TAO vs NAO



1. Connolly et al. N Engl J Med 2009;361:1139–1151; 2. Patel et al. N Engl J Med 2011;365:883–891
3. Granger et al. N Engl J Med 2011;365:981–992; 4. Giugliano et al. N Engl J Med 2013;369(22):2093-104

ICH in anticoagulante TAO vs NAO

CHIRURGIA ORTOPEDICA DVT

F. A.

Conclusions

In patients requiring anticoagulation treatment, the risk of ICH is about half with the NOACs in comparison to standard antithrombotic treatment.

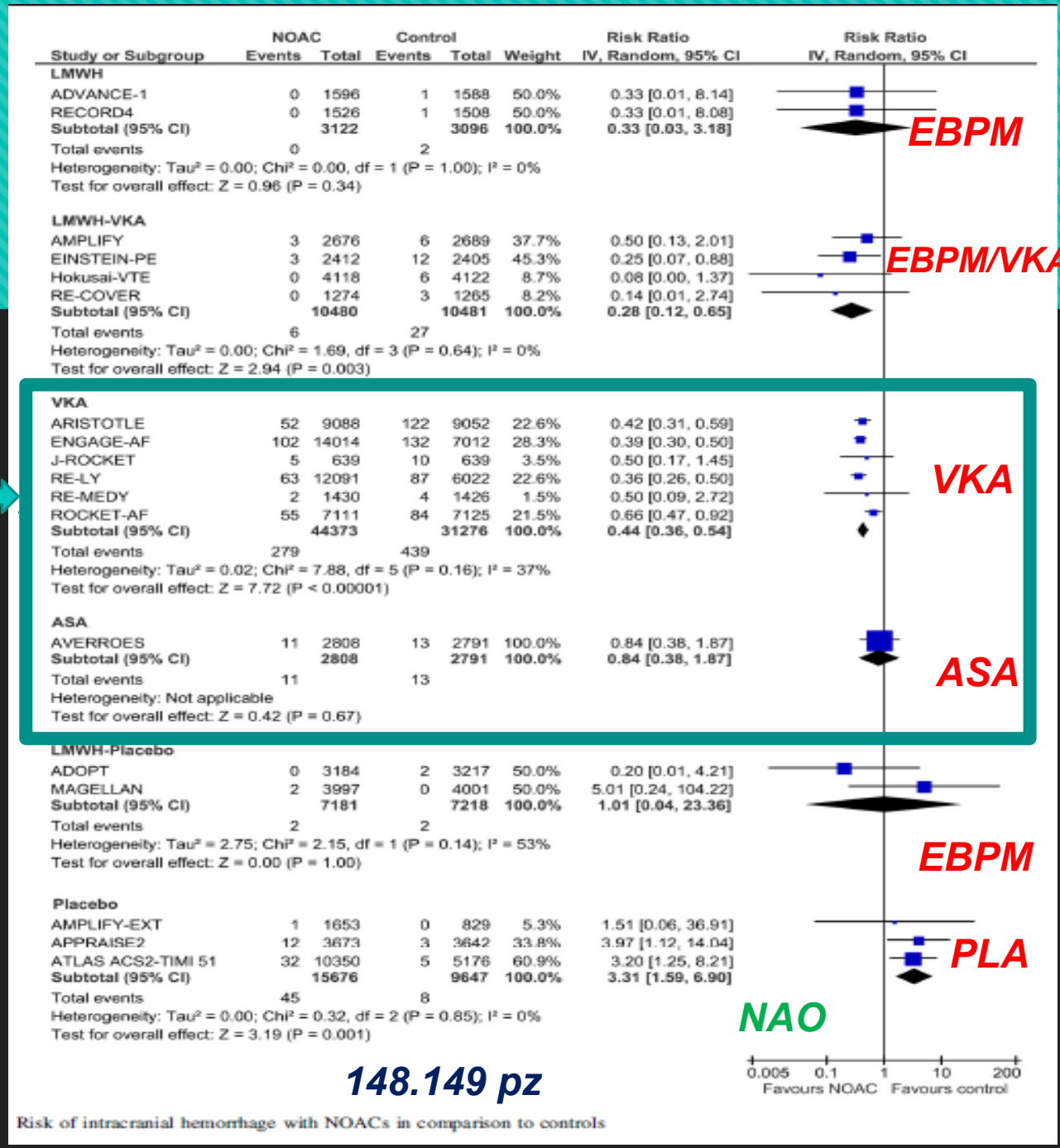
J Neurol (2015) 262:516–522
DOI 10.1007/s00415-014-7462-0

REVIEW

Intracranial hemorrhage risk with the new oral anticoagulants: a systematic review and meta-analysis

Daniel Caldeira · Márcio Barra · Fausto J. Pinto · Joaquim J. Ferreira · João Costa

PROFILASSI POST DTV POST SCA



148.149 pz

Risk of intracranial hemorrhage with NOACs in comparison to controls

Outcome ICH in ACO

Published Ahead of Print on August 16, 2017 as 10.1212/WNL.0000000000004362

Direct oral anticoagulant– vs vitamin K antagonist–related nontraumatic intracerebral hemorrhage

Georgios Tsivgoulis, MD
Vasileios-Arsenios Lioutas, MD
Panayiotis Varelas, MD
Aristeidis H. Katsanos, MD
Nitin Goyal, MD
Robert Mikulik, MD

ABSTRACT

Objective: To compare the neuroimaging profile and clinical outcomes among patients with intracerebral hemorrhage (ICH) related to use of vitamin K antagonists (VKAs) or direct oral anticoagulants (DOACs) for nonvalvular atrial fibrillation (NVAF).

Methods: We evaluated consecutive patients with NVAF with nontraumatic, anticoagulant-related ICH admitted at 13 tertiary stroke care centers over a 12-month period. We also performed a systematic review and meta-analysis of eligible observational studies reporting baseline characteristics and outcomes among patients with VKA- or DOAC-related ICH

Table 1 Baseline characteristics of patients pretreated with DOACs and VKAs

Variable	DOACs (n = 47)	VKAs (n = 114)	*p* Value
Baseline clinical characteristics			
Age, mean ± SD, y	76.6 ± 9.5	75.2 ± 9.9	0.417
Male, %	57.4	57.9	0.958
BMI, mean ± SD, kg/m²	27.0 ± 5.5	28.4 ± 6.6	0.248
NIHSS score at admission, median (IQR)	8 (3-14)	15 (7-25)	0.003
GCS score at admission, median (IQR)	14 (12-15)	13 (7-15)	0.008
Baseline CT findings			
Lobar hemorrhage, %	44.7	58.8	0.102
Intraventricular hemorrhage, %	36.2	43.0	0.424
Baseline ICH volume, median (IQR), cm³	12.8 (4-40)	24.3 (11-58.8)	0.007
Baseline ICH volume >30 cm³, %	25.5	45.6	0.018

Neurology 2017; 89:1-10

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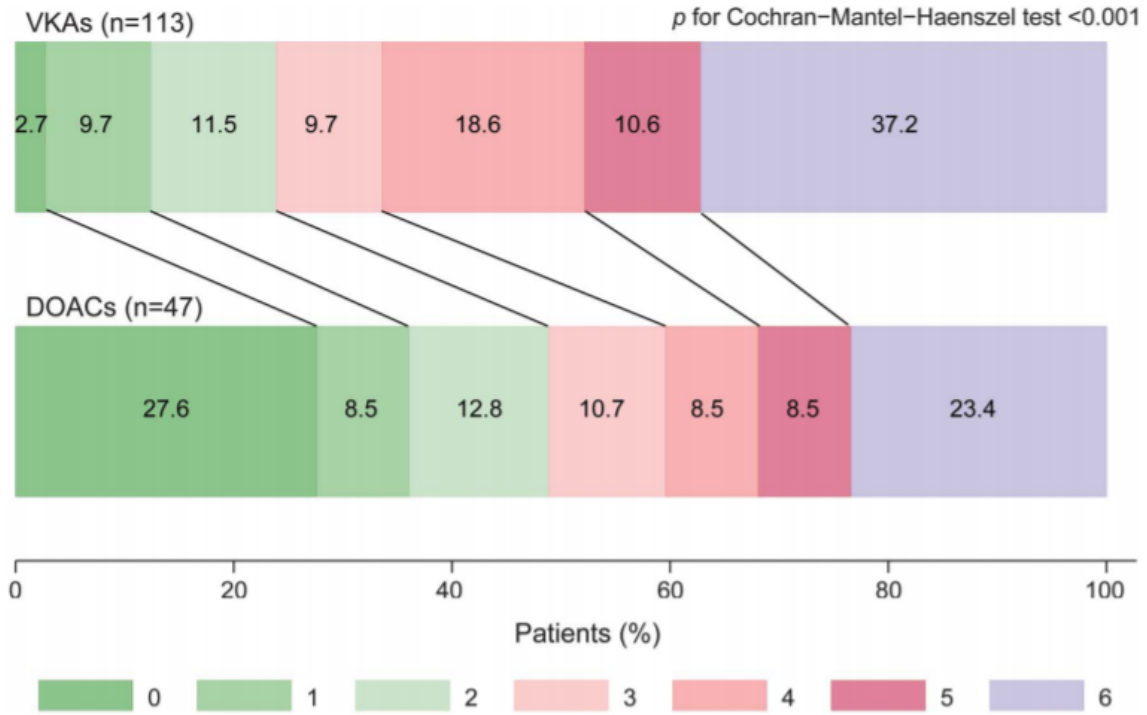
Figure 1 Horizontal "Grotta" bars



Distribution of modified Rankin Scale scores at 3 months in patients with intracerebral hemorrhage pretreated oral anticoagulants (DOACs) or vitamin K antagonists (VKAs)

Conclusions: DOAC-related ICH is associated with smaller baseline hematoma volume and lesser neurologic deficit at hospital admission compared to VKA-related ICH.

Neurology 2017; 89:1-10

Outcome ICH in ACO

ARTICLES

Outcome of intracerebral hemorrhage associated with different oral anticoagulants

OPEN

Duncan Wilson, MD
David J. Seiffge, MD
Christopher Traenka, MD
Ghazala Basir, MBBS, FCPS
Jan C. Purrucker, MD
Timolaos Rizos, MD
Oluwaseun A. Sobowale, MD
Hanne Sallinen, MD
Shin-Joe Yeh, MD
Teddy Y. Wu, MD

ABSTRACT

Objective: In an international collaborative multicenter pooled analysis, we compared mortality, functional outcome, intracerebral hemorrhage (ICH) volume, and hematoma expansion (HE) between non-vitamin K antagonist oral anticoagulation–related ICH (NOAC-ICH) and vitamin K antagonist–associated ICH (VKA-ICH).

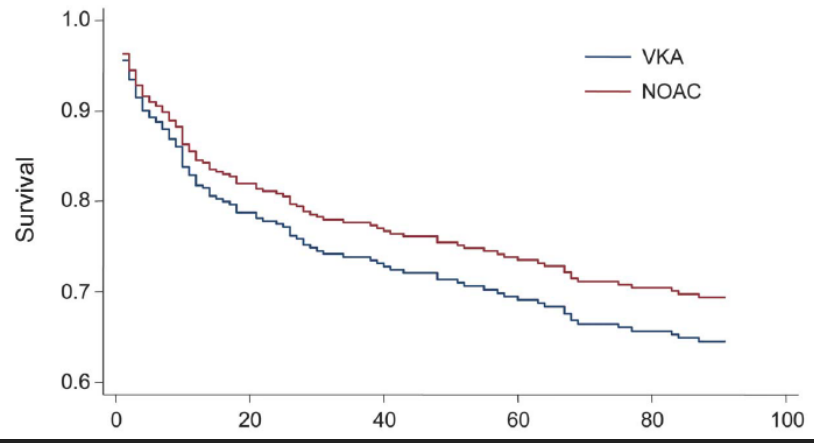
Methods: We compared all-cause mortality within 90 days for NOAC-ICH and VKA-ICH using a Cox proportional hazards model adjusted for age; sex; baseline Glasgow Coma Scale score, ICH location, and log volume; intraventricular hemorrhage volume; and intracranial surgery. We addressed heterogeneity using a shared frailty term. Good functional outcome was defined as discharge modified Rankin Scale score ≤2 and investigated in multivariable logistic regression. ICH volume was measured by ABC/2 or a semiautomated planimetric method. HE was defined as an ICH volume increase >33% or >6 mL from baseline within 72 hours.

Table 2 Characteristics of participants with non-vitamin K antagonist oral anticoagulant (NOAC)-associated intracerebral hemorrhage (ICH) and vitamin K antagonist (VKA)-associated ICH

Variable	NOAC-ICH (n = 97)	VKA-ICH (n = 403)
Age, y, median (IQR)	80 (74-85)	80 (72-85)
Male sex, n (%)	53 (55)	196 (49)
ICH location		
Lobar area	38 (39)	158 (39)
Supratentorial deep areas	40 (41)	198 (49)
Cerebellum	13 (13)	26 (6)
Brainstem	6 (6)	21 (5)
Glasgow Coma Scale, median (IQR)	14 (12-15)	15 (13-15)
Acute neurosurgery, n (%)	7 (7)	24 (6)
IVH extension, n (%)	42 (43)	146 (36)
Premorbid mRS, median (IQR)[a]	1 (0-3)	0 (0-2)
Early palliation, n (%)	11 (13)	28 (7)
Anticoagulation for atrial fibrillation, n (%)	85/86 (99)	267/332 (80)

Abbreviations: IQR = interquartile range; IVH = intraventricular hemorrhage; mRS = modified Rankin Scale.
Values are n (%) or median (IQR).
[a] Available in 431 patients.

Figure 2 Survival curve comparing non-vitamin K oral antagonist anticoagulant (NOAC)-associated intracerebral hemorrhage (ICH) and vitamin K antagonist anticoagulant (VKA)-associated ICH 90-day mortality



Conclusions: In our international collaborative multicenter pooled analysis, baseline ICH volume, hematoma expansion, 90-day mortality, and functional outcome were similar following NOAC-ICH and VKA-ICH.

Neurology 2017; 88 1693-1700

Trattamento ICH in TAO/NAO

ORIGINAL ARTICLE

Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients

S. SCHULMAN* and C. KEARON† ON BEHALF OF THE SUBCOMMITTEE ON CONTROL OF ANTICOAGULATION OF THE SCIENTIFIC AND STANDARDIZATION COMMITTEE OF THE INTERNATIONAL SOCIETY ON THROMBOSIS AND HAEMOSTASIS

Coagulation Unit, Karolinska University Hospital, Stockholm, Sweden and Department of Medicine, HHS-General Hospital, Hamilton, ON, Canada; and †Henderson General Hospital, Hamilton, ON, Canada

Schulman S et al Journal of Thrombosis and Haemostasis, 2005, 3: 692–694

Definition of major bleeding

As general principles, a definition of major bleeding needs to be based on objective criteria, and major bleeds are those that result in death, are life-threatening, cause chronic sequelae or consume major health-care resources. With this in mind, the Control of Anticoagulation Subcommittee recommends the following criteria for major bleeding in non-surgical patients:

1. Fatal bleeding, and/or
2. Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or
3. Bleeding causing a fall in hemoglobin level of 20 g L^{-1} (1.24 mmol L^{-1}) or more, or leading to transfusion of two or more units of whole blood or red cells.

EMORRAGIA in AVK

- COMPLESSO PROTROMBINICO CONCENTRATO *

- 3 FATTORI : II - IX – X

- 4 FATTORI : II - IX - X - VII

- Se non disponibile FFP 10-40 mL /kg

- VITAMINA K 10 mg ev in 30 minuti

- Controllo INR al termine infusione Se INR ≥ 1.5 ripetere infusione di CPC come a lato

VALORE INR	CPC
INR < 2,0	20 UI/ Kg
INR = 2.0-3.0	30 UI/ Kg
INR = 3.0-4.0	40 UI/ Kg
INR > 4.0	50 UI/ Kg

Masotti L et al. reviews in health care, 2011

* Superiore al plasma fresco congelato nella normalizzazione dell'INR *Steiner T et al, Lancet Neurol 2016*

EMORRAGIA in NAO - inib diretti trombina

- SPECIFICO REVERSAL è ATTUALMENTE disponibile solo per DABIGATRAN : IDARUCIZUMAB

  5 g ev (flaconi da 2,5 g) (ultima dose assunta entro 3-5 emivite)

- se non disponibile CPC 3- 4 fattori 50 UI / Kg (ultima dose assunta entro 3-5 emivite)

  o anche FEIBA o di fattore VII

- se recente ingestione (entro 2 ore) 50 g di Carbone attivo

EMORRAGIA in NAO - inib fatt X

- CPC 3- 4 fattori 50 UI / Kg (ultima dose assunta entro 3-5 emivite)
  o anche FEIBA o di fattore VII

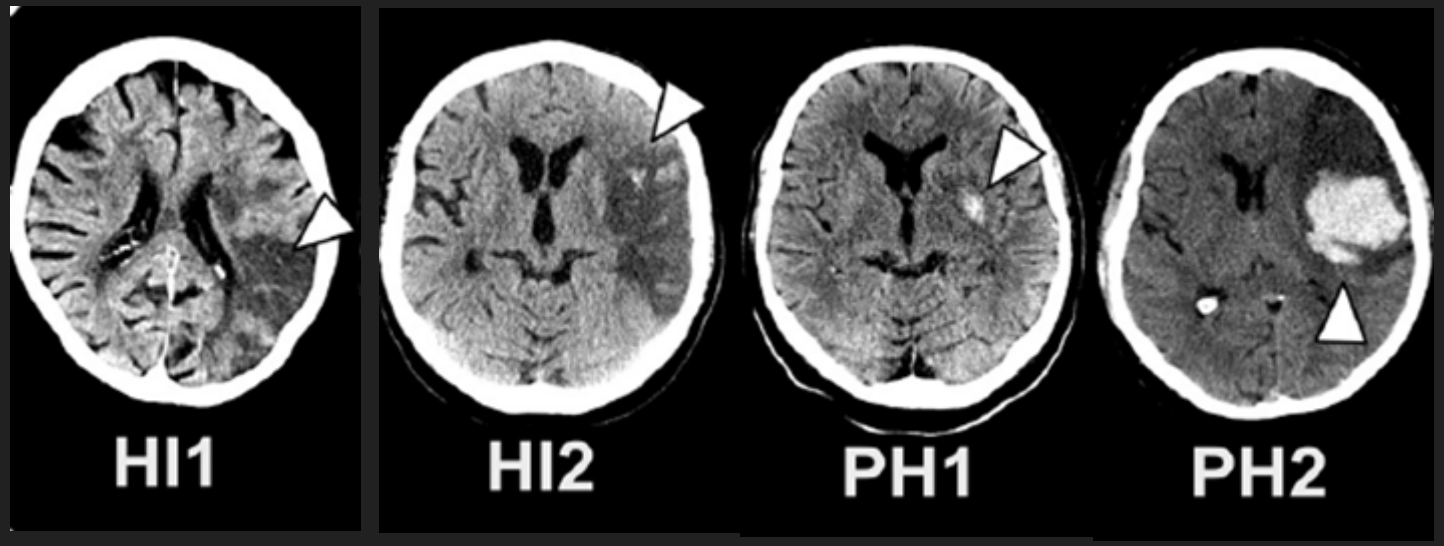
- se recente ingestione (entro 2 ore) 50 g di Carbone attivo

- Non ancora disponibile ANDEXANET specifico antidoto

Trasformazione emorragica

La trasformazione emorragica di un ictus ischemico avviene in circa il 9% di tutti gli stroke

Paciaroni et al. Stroke 2008



Purrucker JC, JOS 2017

HI 1 : piccole petecchie lungo il margine dell'infarto

HI 2 : petecchie confluenti nel corpo dell'infarto senza effetto massa

PH 1 : ematoma parenchimale che non occupa più del 30% dell'area dell'infarto

PH 2 : ematoma che occupa più del 30% con effetto massa

ECASS, JAMA 1995

Trasformazione emorragica

- L'ematoma parenchimale (outcome più sfavorevole) si ritrova nel 3% dei casi ed è associato più frequentemente a ictus di natura cardioembolica e a lesioni ischemiche grandi

Paciaroni et al. Stroke 2008, Stroke 2015

- La terapia anticoagulante con AVK (precedente all'evento) non influisce sulla possibilità di trasformazione emorragica

Paciaroni et al. Stroke 2008, O' Donnel M Lancet Neurol 2006

JoS
JOURNAL OF STROKE

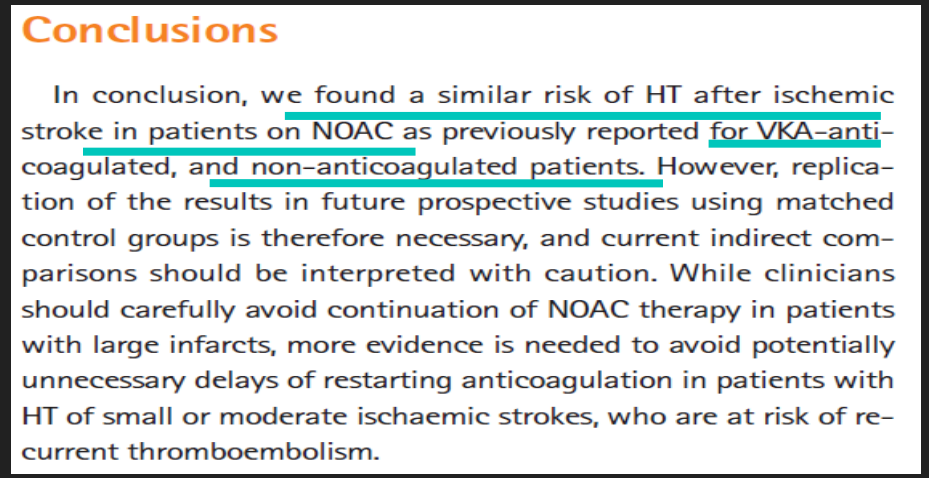
CrossMark

Journal of Stroke 2017;19(1):67-76
https://doi.org/10.5853/jos.2016.00542

Original Article

Haemorrhagic Transformation after Ischaemic Stroke in Patients Taking Non-vitamin K Antagonist Oral Anticoagulants

Jan C. Purrucker,[a] Kirsten Haas,[b] Marcel Wolf,[c] Timolaos Rizos,[a] Shujah Khan,[a] Peter Kraft,[d] Sven Poli,[e]



Conclusions

In conclusion, we found a similar risk of HT after ischemic stroke in patients on NOAC as previously reported for VKA-anticoagulated, and non-anticoagulated patients. However, replication of the results in future prospective studies using matched control groups is therefore necessary, and current indirect comparisons should be interpreted with caution. While clinicians should carefully avoid continuation of NOAC therapy in patients with large infarcts, more evidence is needed to avoid potentially unnecessary delays of restarting anticoagulation in patients with HT of small or moderate ischaemic strokes, who are at risk of recurrent thromboembolism.

Ripresa anticoagulante dopo ICH

Original Contribution

Restarting Anticoagulant Therapy After Intracranial Hemorrhage

A Systematic Review and Meta-Analysis

Santosh B. Murthy, MD, MPH; Ajay Gupta, MD; Alexander E. Merkler, MD; Babak B. Navi, MD, MS; Pitchaiah Mandava, MD, PhD, MSEE; Costantino Iadecola, MD; Kevin N. Sheth, MD; Daniel F. Hanley, MD; Wendy C. Ziai, MD, MPH; Hooman Kamel, MD

Background and Purpose—The safety and efficacy of restarting anticoagulation therapy after intracranial hemorrhage (ICH) remain unclear. We performed a systematic review and meta-analysis to summarize the associations of anticoagulation resumption with the subsequent risk of ICH recurrence and thromboembolism.

Table 2. Overview of AC Indications and Characteristics

Study	Indications for AC (%)*						Received AC	AC Type	Time to Restarting AC, d
	NVAF	Prosthetic Heart Valve	VTE	Previous Stroke	Recent MI	Other			
De Vleeschouwer et al[17]	56 (51.9)	30 (27.8)	11 (10.2)	4 (3.7)	2 (1.9)	5 (4.6)	25 (23.1)	VKA	11
Claassen et al[18]	23 (47.9)	12 (25.0)	10 (20.8)	N/A	N/A	3 (6.3)	23 (47.9)	VKA (warfarin)	10
Majeed et al[20]	135 (58.0)	35 (15.0)	37 (16.0)	N/A	N/A	27 (11.0)	45 (34.1)†	VKA (warfarin)	39.2
Yung et al[19]	191 (67.3)	37 (13.0)	31 (10.9)	N/A	N/A	N/A	91 (32.0)	VKA (warfarin)	N/A
Gathier et al[12]	10 (40.0)	2 (8.0)	6 (24.0)	8 (32.0)	2 (8.0)	4 (16.0)	12 (48.0)	VKA	Within 2 mo
Nielsen et al[16]	1752 (100.0)	0	0	0	0	0	509 (29.1)	VKA/NOAC	N/A
Kuramatsu et al[11]	664 (77.8)	67 (7.9)	71 (8.3)	N/A	N/A	51 (6.0)	172 (23.9)	VKA	31
Ottosen et al[15]	1032 (34.7)	78 (2.6)	236 (7.9)	2139 (71.8)	264 (8.9)	30 (1.0)	160 (6.3)‡	VKA/NOAC	Within first 6 mo

Conclusions—In observational studies, reinstitution of anticoagulation after ICH was associated with a lower risk of thromboembolic complications and a similar risk of ICH recurrence

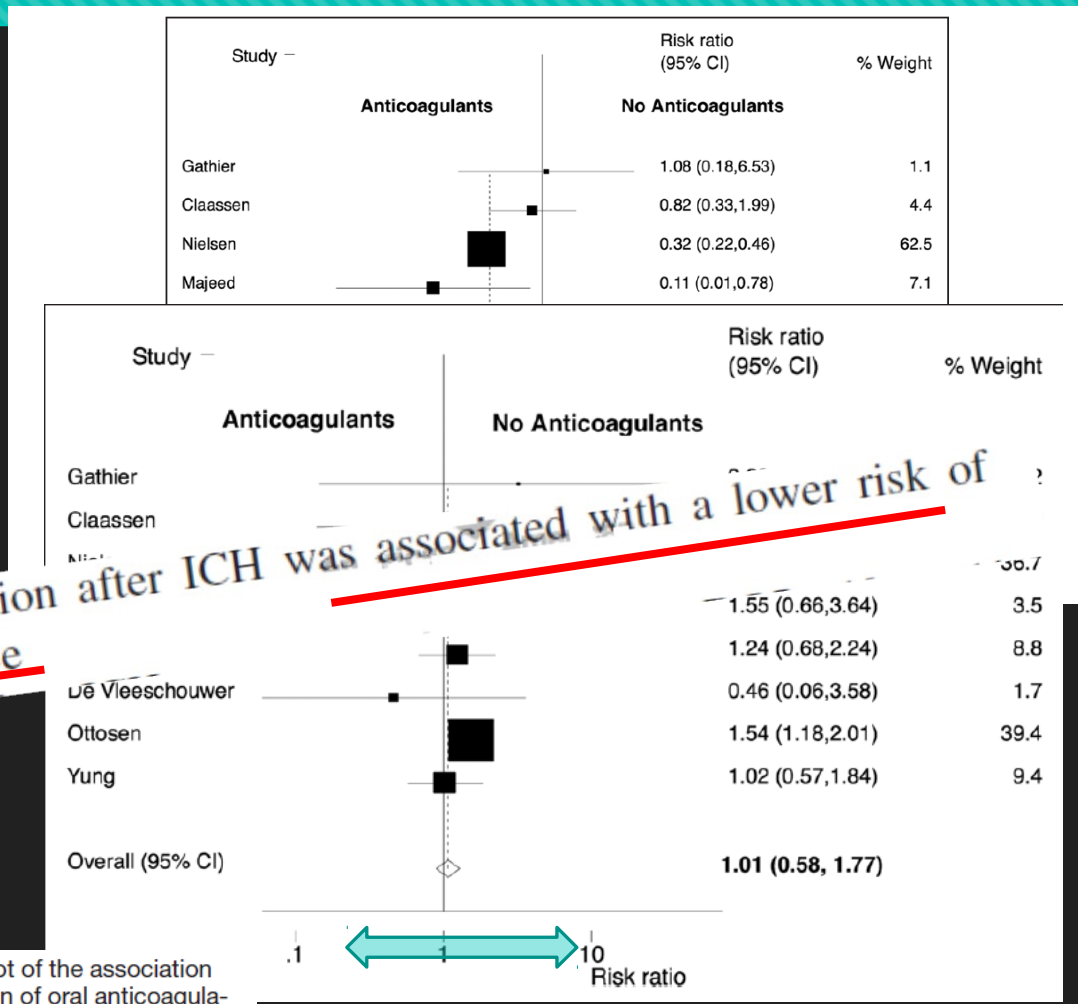


Figure 2. Forest plot of the association between resumption of oral anticoagulation therapy and recurrence of intracranial hemorrhage.

Santosh et al. Stroke2017; 48: 00-00

Ripresa anticoagulante dopo ICH

Raccomandazione 11.5.l **Forte a favore** **Grado A**

In caso di ictus emorragico in pazienti trattati con AVK o antiaggreganti per FANV, dopo aver valutato con attenzione la necessità della ripresa del trattamento anticoagulante mediante CHA_2DS_2-VASc, è raccomandato scegliere un NAO per il netto guadagno, in complicanze emorragiche intracraniche, rispetto alla terapia con AVK*.

***GPP**

Nei casi con rischio tromboembolico ed emorragico elevati, il gruppo ISO-SPREAD ritiene opportuno considerare la chiusura percutanea dell'auricola sinistra.

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%.

Ripresa anticoagulante dopo ICH

- 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.

DOPO 3 SETTIMANE	RISCHIO TROMBOEMBOLICO ELEVATO
TRA 2 mesi e mezzo E 7 mesi	Casi intermedi
DOPO 7 MESI	RISCHIO EMORRAGICO ELEVATO

Ripresa anticoagulante dopo ICH

AHA/ASA Guideline

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

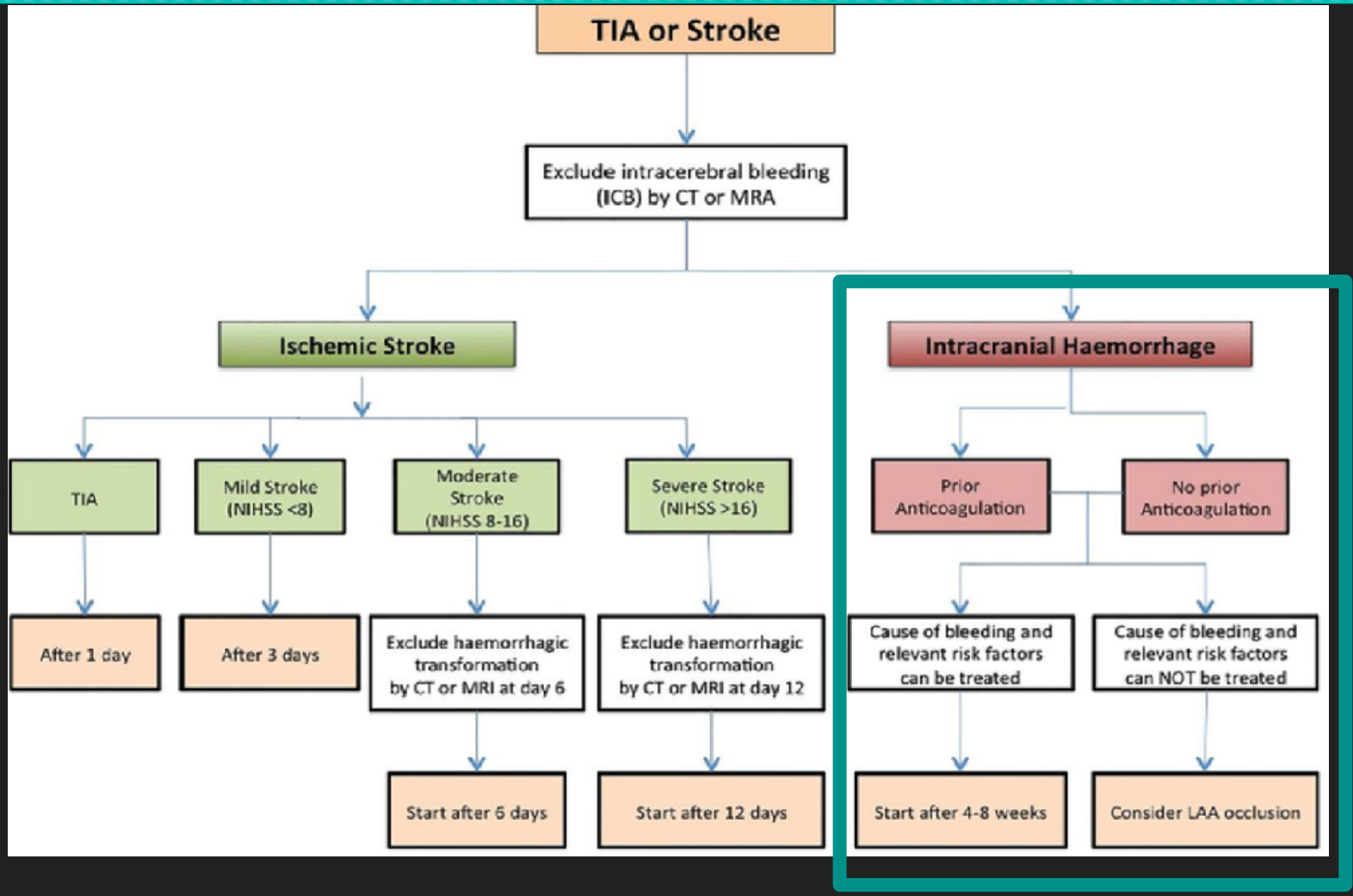
The American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists.

Endorsed by the American Association of Neurological Surgeons and Congress of Neurological Surgeons

Anticoagulation After Intracranial Hemorrhage

1. The decision to restart antithrombotic therapy after intracranial hemorrhage (ICH) related to antithrombotic therapy depends on the risk of subsequent arterial or venous thromboembolism, the risk of recurrent ICH, and the overall status of the patient and must therefore be individualized to each patient. For patients with a comparatively lower risk of cerebral infarction (eg, AF without prior ischemic stroke) and a higher risk of recurrent ICH (eg, elderly patients with lobar ICH or presumed amyloid angiopathy) or with very poor overall neurological function, an antiplatelet agent may be considered for prevention of ischemic stroke *(Class IIb; Level of Evidence B)*.
2. For patients who require resumption or initiation of anticoagulation after an acute ICH, subarachnoid hemorrhage, or subdural hematoma, the optimal timing is uncertain. For most patients, however, it might be reasonable to wait ≥1 week *(Class IIb; Level of Evidence B)*.
3. For patients with hemorrhagic cerebral infarction, continuation of anticoagulation may be considered, depending on the specific clinical scenario and underlying indication for anticoagulant therapy *(Class IIb; Level of Evidence C)*.

Ripresa anticoagulante dopo ICH



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]

TAKE HOME MESSAGE

- I nuovi anticoagulanti orali hanno un profilo di sicurezza maggiore: riducono il rischio di ICH del 50%, sono associati a ematomi di volume più piccolo e evoluzione più favorevole.
- Esiste un reversal per Dabigatran e terapia d'urgenza efficace per gli altri NAO e AVK
- L' assunzione dei NAO prima di un ictus ischemico non espone a maggior probabilità di trasformazione emorragica
- Dopo ICH la ripresa dei NAO è generalmente indicata dopo tempi variabili