



GIOVEDÌ 29

# L'emorragia cerebrale nel paziente fibrillante: impieghiamo i NAO senza attendere troppo?

Giuseppe Di Pasquale, *Bologna*



# **L'emorragia cerebrale nel paziente fibrillante: impieghiamo i NAO senza attendere troppo?**

**41° Congresso di Cardiologia *"Conoscere e Curare il Cuore 2024"***

**Firenze, 29 Febbraio 2024**

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**Coordinamento regionale rete cardiologica Emilia Romagna**  
**Editor Giornale Italiano di Cardiologia**

# Emorragia cerebrale, Fibrillazione atriale e DOAC

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## Agenda

- Il rischio di ICH in corso di TAO nella FA
- Il timore di ICH per inizio precoce della TAO dopo stroke ischemico
- La TAO dopo ICH nei pazienti con FA
- Cosa dicono le linee guida
- Take home messages

# Emorragia cerebrale, Fibrillazione atriale e DOAC

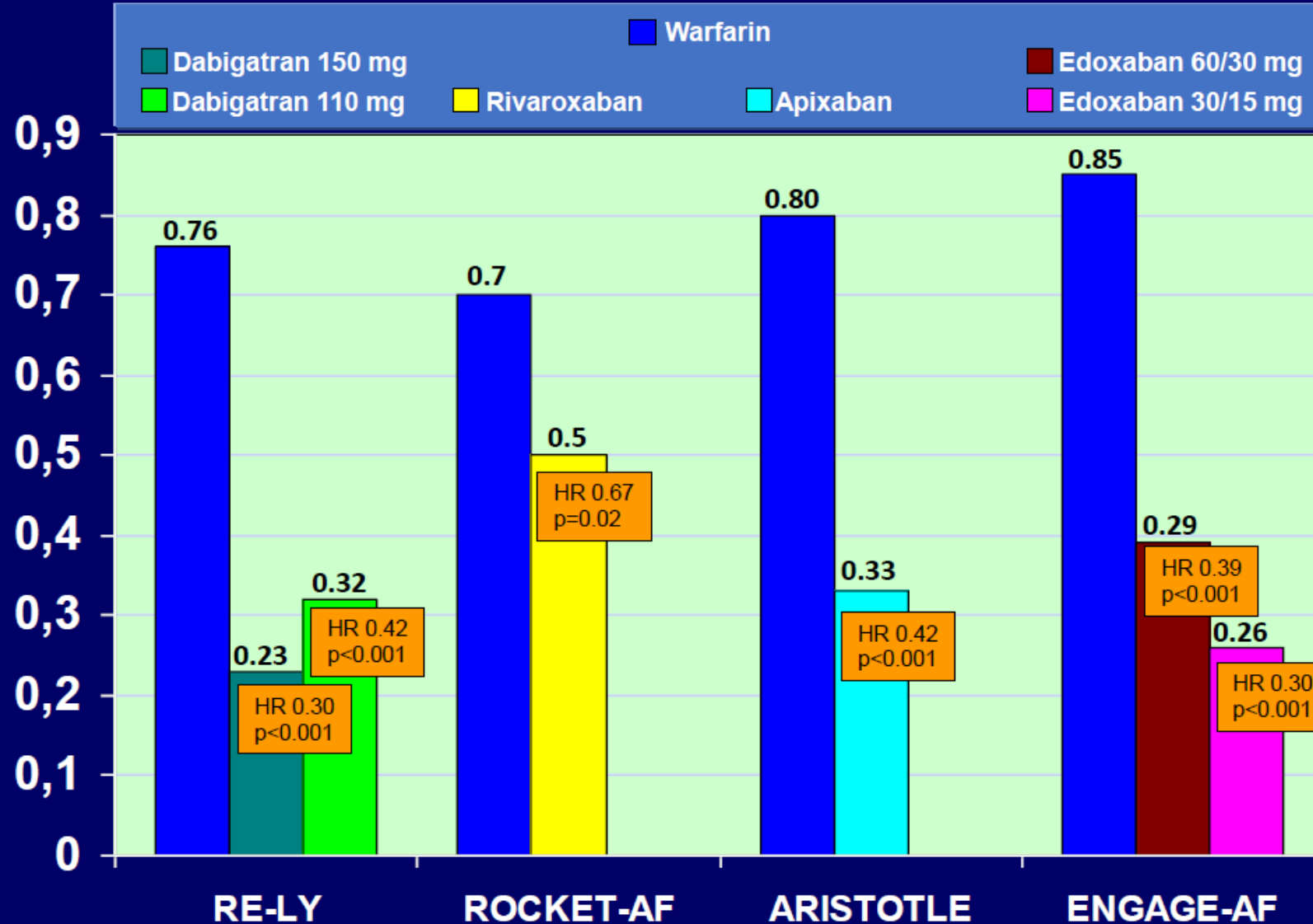
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# Intracranial Bleedings in DOACs Trials

Rate  
(x 100 patients  
per year)



I pazienti con  
pregressa EC  
erano esclusi  
dai trial.

**Le emorragie cerebrali non sono tutte uguali**

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# Cerebral Hemorrhage

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## Major hemorrhage types

- Traumatic vs spontaneous non-traumatic
- Intracerebral (ICH) vs subdural, subarachnoid (eg. ruptured aneurysm)
- Primary ICH vs secondary ICH (AV malformations, cavernous malformations, tumors, infective endocarditis)

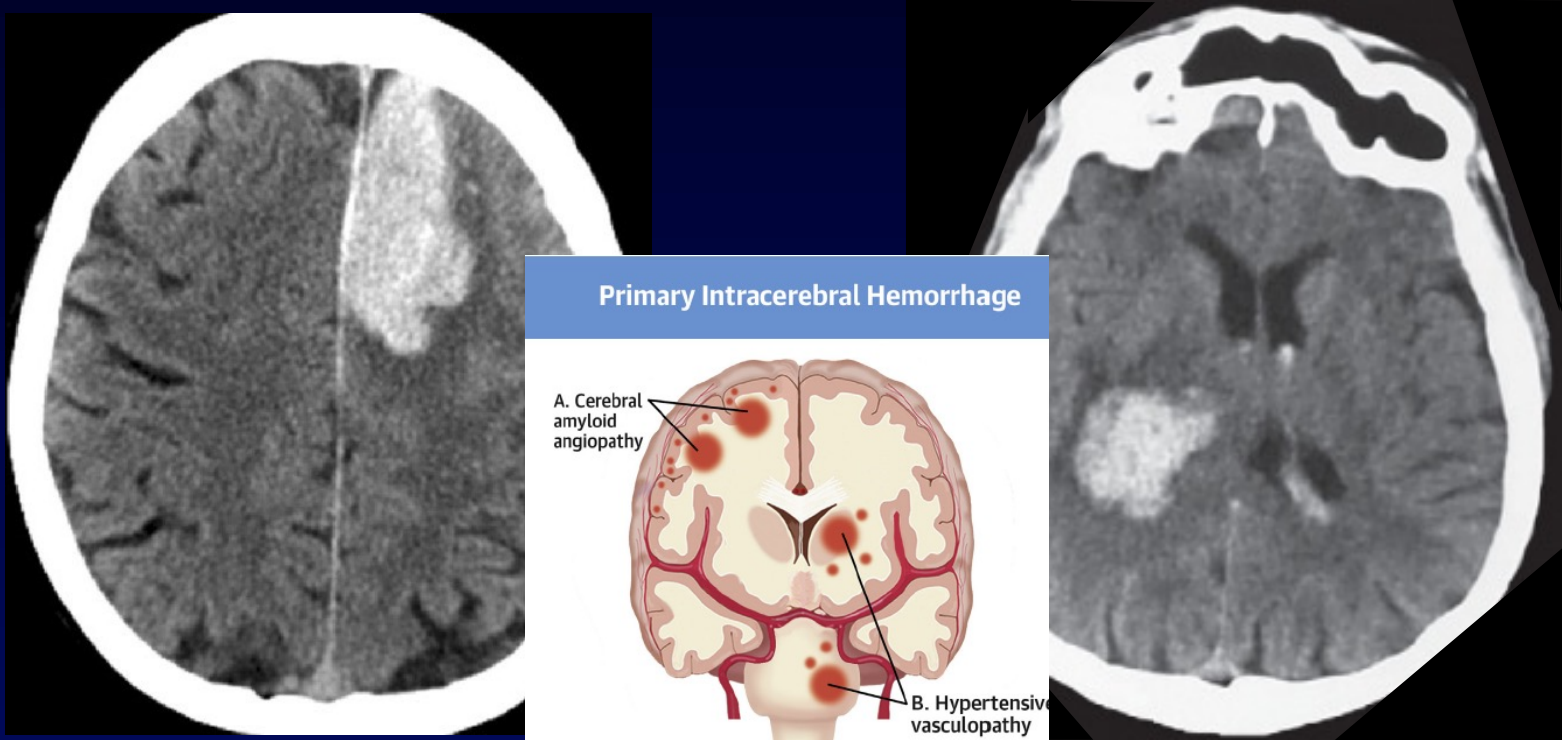
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# Primary ICH



## Lobar ICH

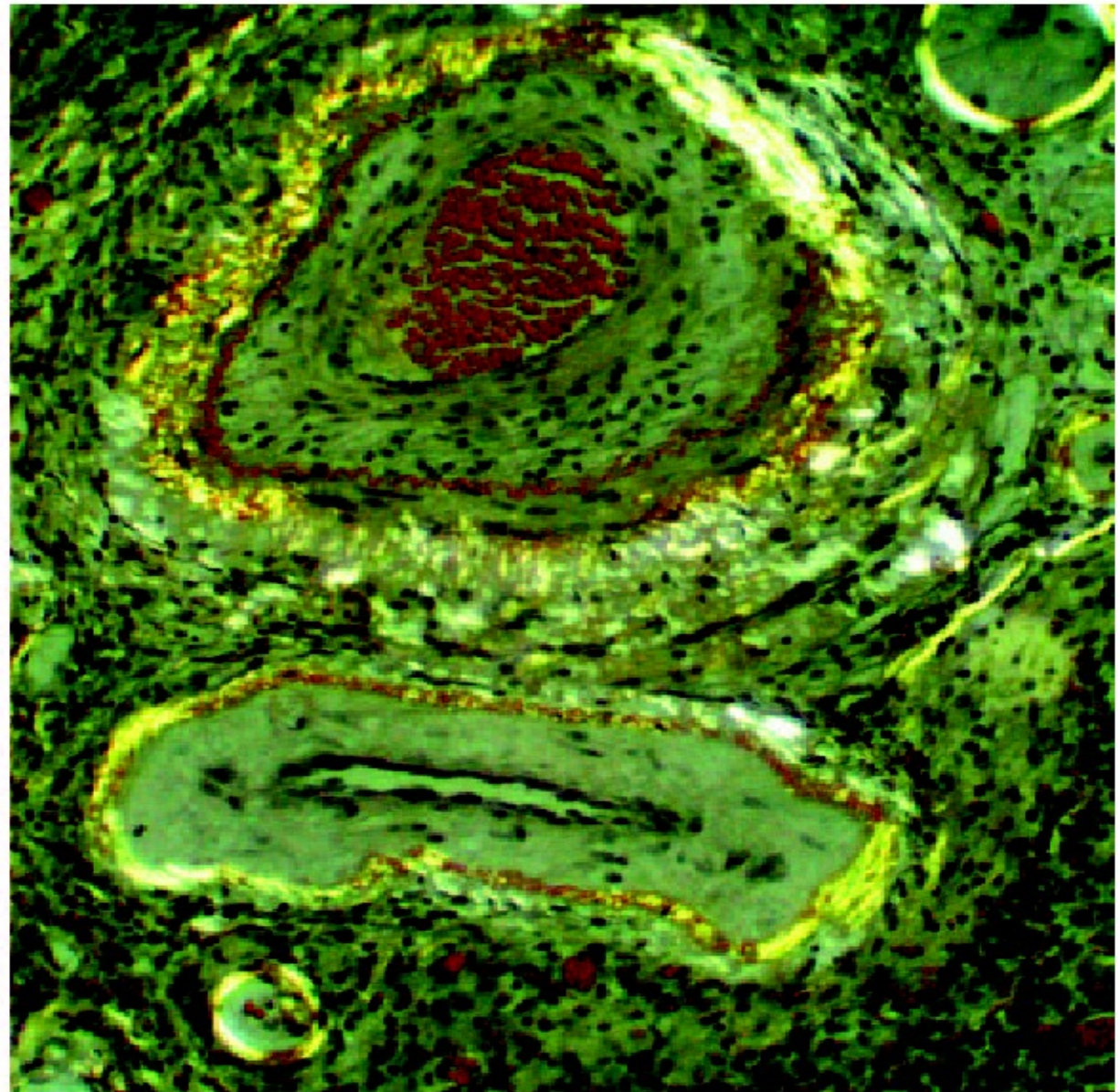
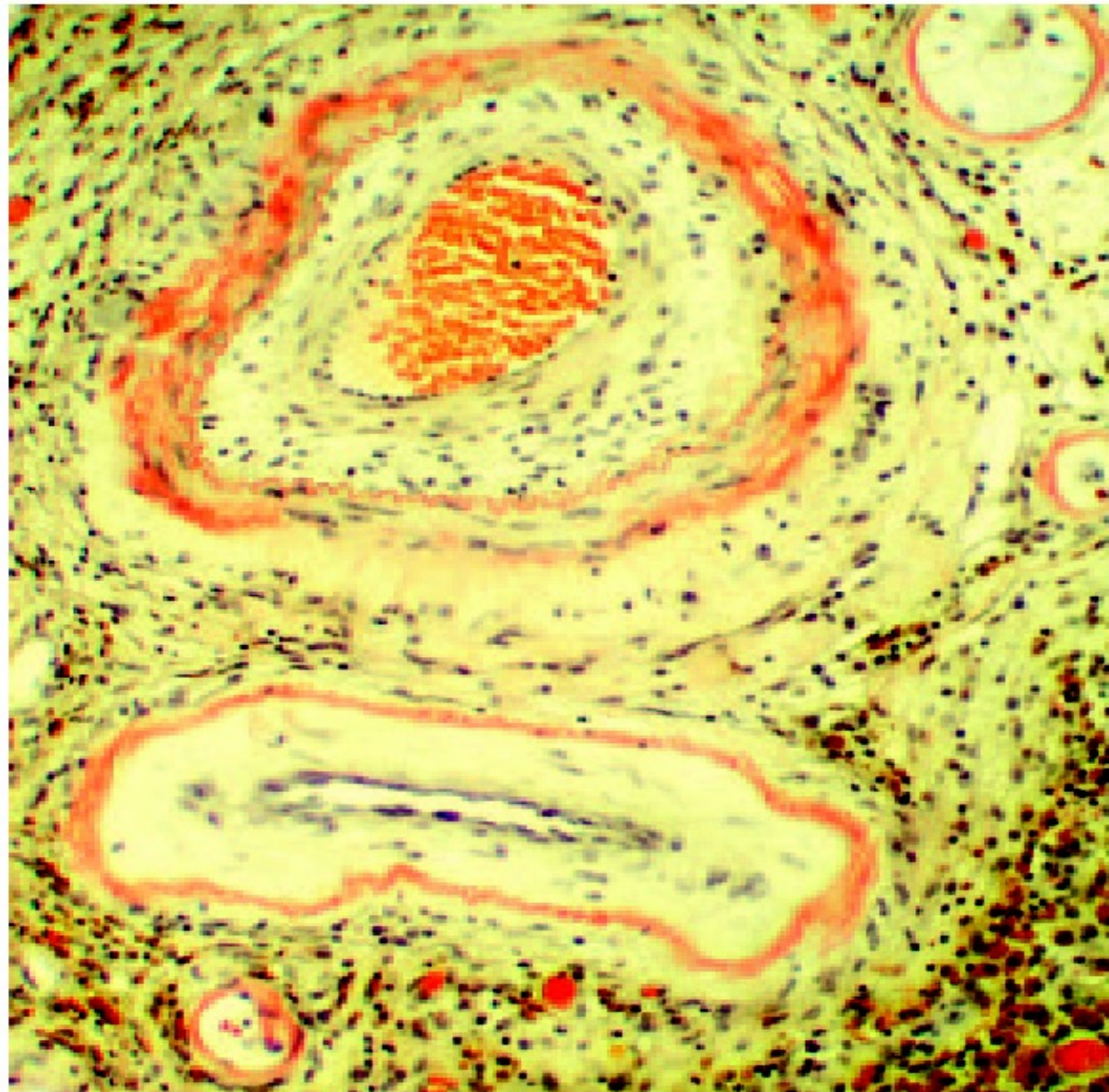
Cerebral Amyloid Angiopathy

## Deep ICH

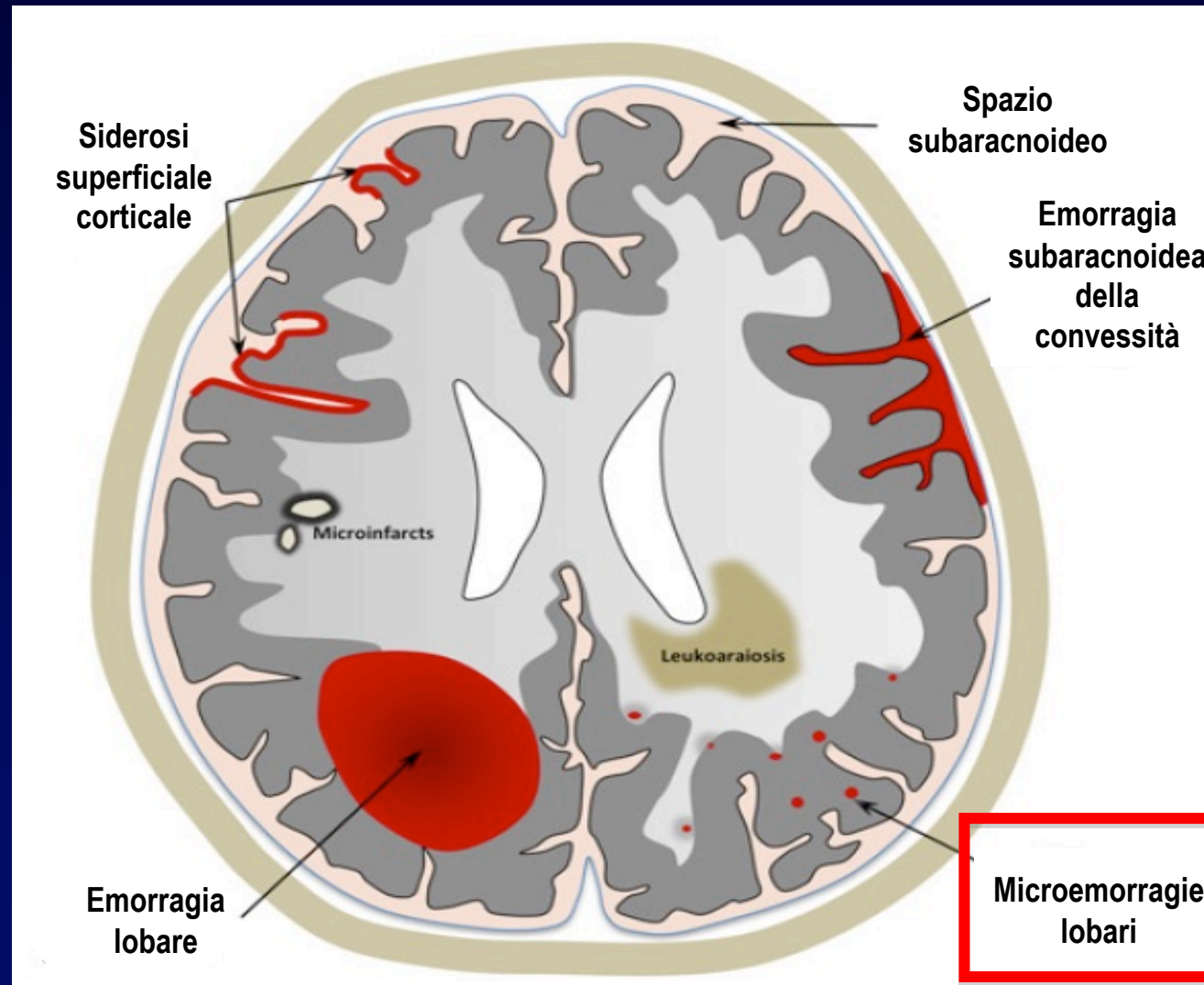
Arteriolosclerosis

|                                           |       |    |      |                                                                                                   |
|-------------------------------------------|-------|----|------|---------------------------------------------------------------------------------------------------|
| 1-year rate                               | ~ 15% | vs | ~ 2% | Eckman MH, et al. <i>Stroke</i> 2003<br>Poon MT, et al. <i>J Neurol Neurosurg Psychiatry</i> 2014 |
| 2-year rate                               | ~ 22% | vs | ~ 4% | Viswanathan A, et al. <i>Neurology</i> 2006                                                       |
| Annual risk recurrence<br>11.8%           |       |    |      |                                                                                                   |
| Samarasekera N, et al. <i>Stroke</i> 2015 |       |    |      |                                                                                                   |

# Lobar ICH: Cerebral Amyloid Angiopathy

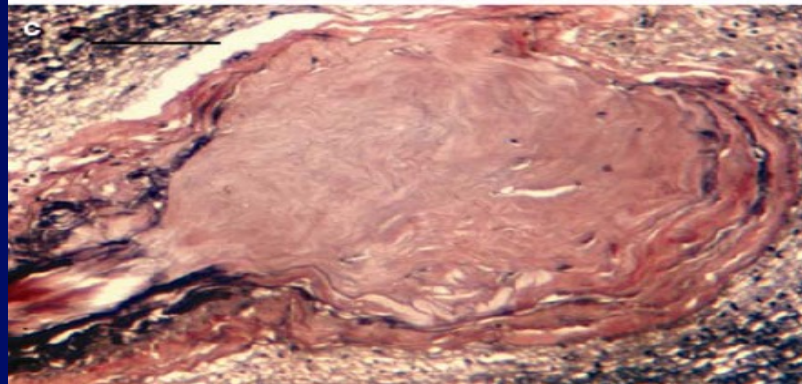
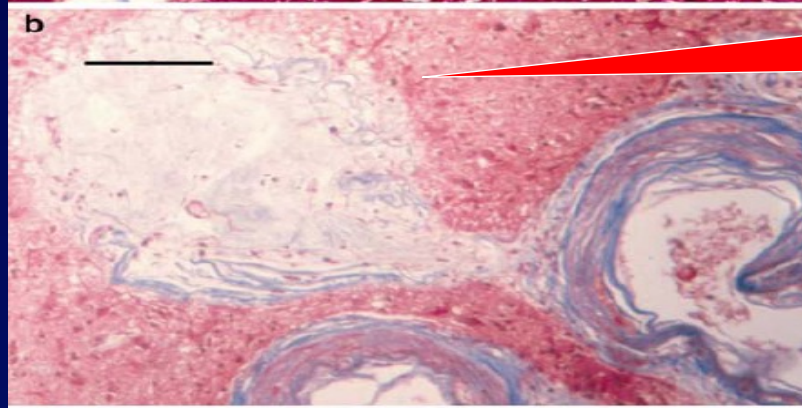
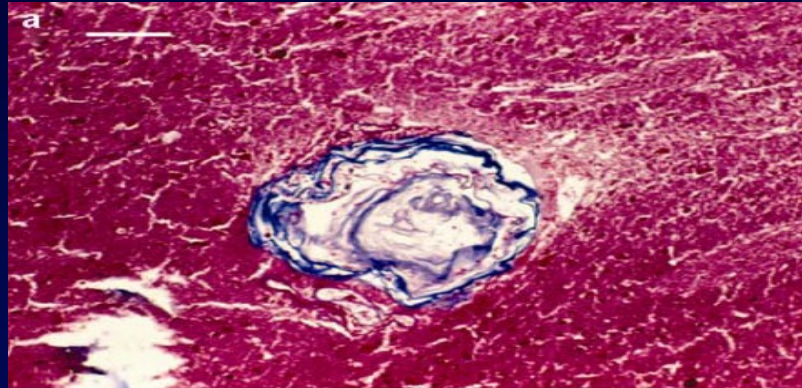
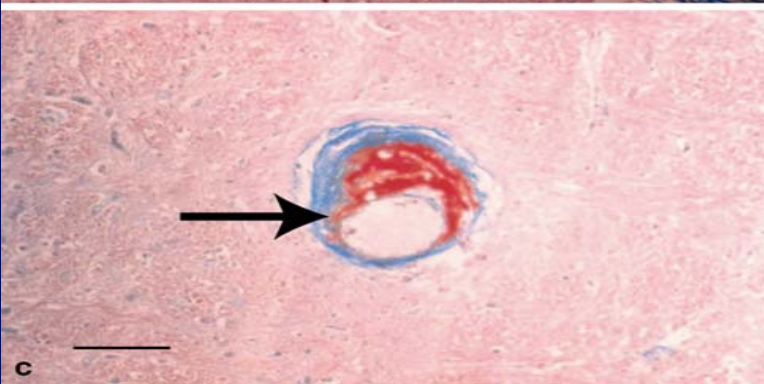
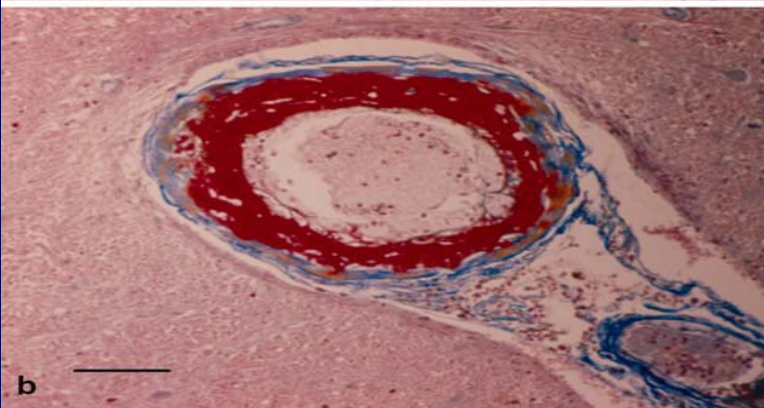


# Neuroimaging Correlates of Cerebral Amyloid Angiopathy



# Deep ICH: Hypertensive Vasculopathy

Necrosi fibrinoide



Aneurismi miliari  
(di Charcot e Bouchard)

“fibrous balls”

Rosenblum WI et al.  
Acta Neuropathol 2008;116:361-369

# Lobar vs Deep Intracerebral Hemorrhage

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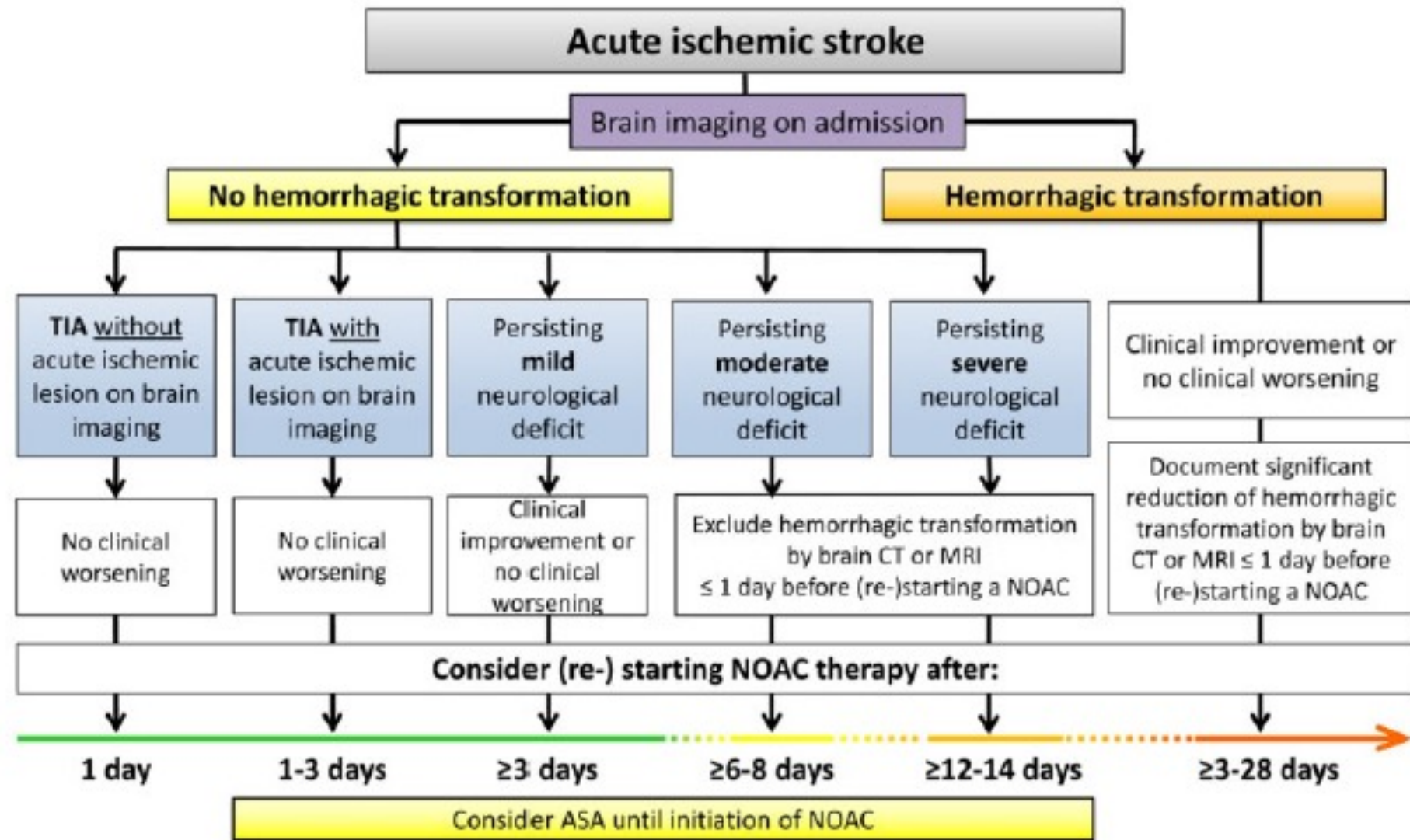
- Hypertensive vasculopathy is the most important mechanism for ICH in the deep hemispheric regions.
  - ➡ *Risk of recurrence can be limited by control of hypertension*
- Cerebral amyloid angiopathy is the most common underlying pathophysiology for lobar ICH.
  - ➡ *Lack of any known treatment for the prevention of recurrence*

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Based on expert opinion! No RCT data available yet

# Early versus Later Anticoagulation for Stroke with Atrial Fibrillation

2013 pts with acute ischemic stroke and AF

Within 48 hours after a minor or moderate stroke or on day 6-7 after a major stroke

Early AC

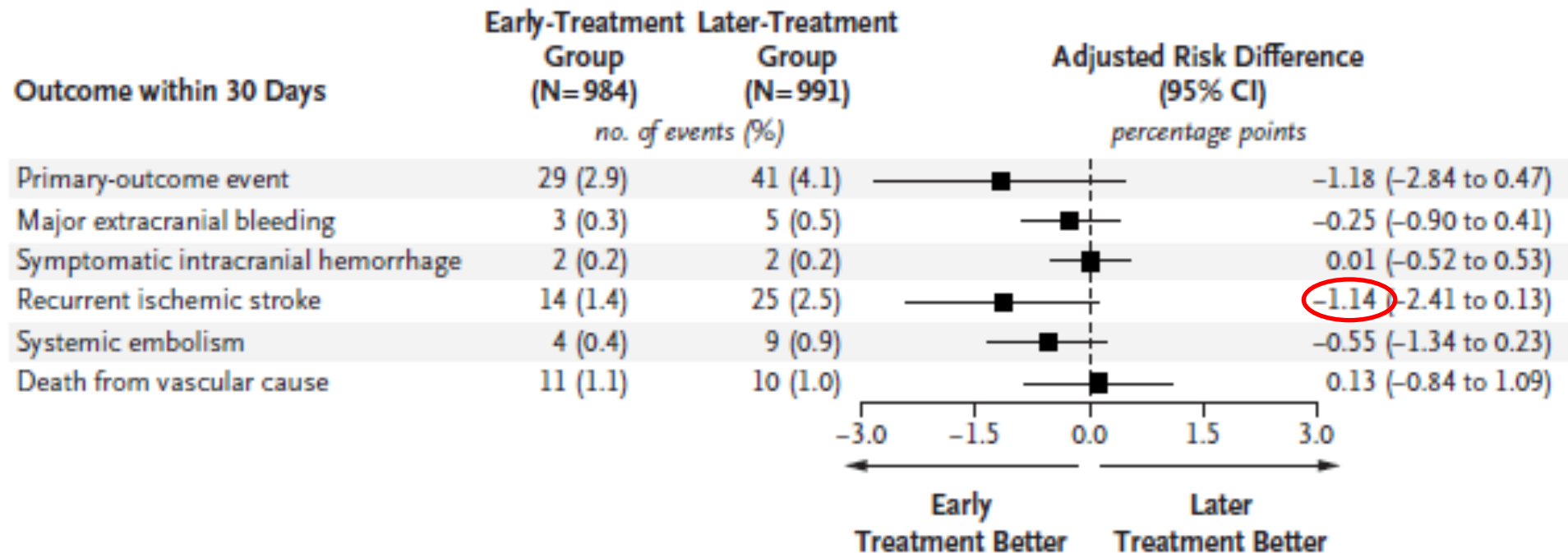
Later AC

Day 3 or 4 after a minor stroke, day 6 or 7 after a moderate stroke, or day 12-14 after a major stroke

Ischemic stroke, SE  
Major extracranial bleeding,  
symptomatic ICH, vascular death within 30 days

# Early versus Later Anticoagulation for Stroke with Atrial Fibrillation

A



# Emorragia cerebrale, Fibrillazione atriale e DOAC

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# 1. Studi di popolazione

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# Risks of recurrent stroke and all serious vascular events after spontaneous intracerebral haemorrhage: pooled analyses of two population-based studies

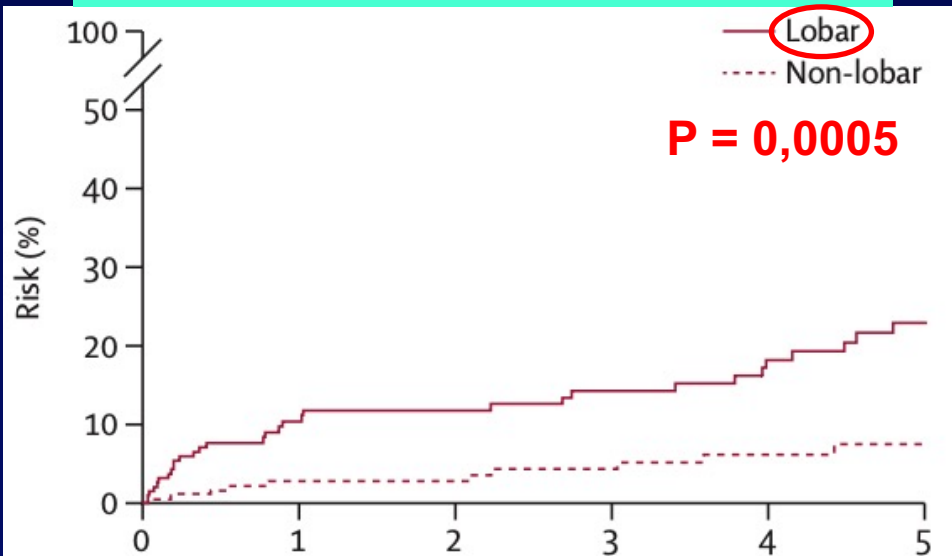


674 pz con ICH di 2 coorti in England e Scotland



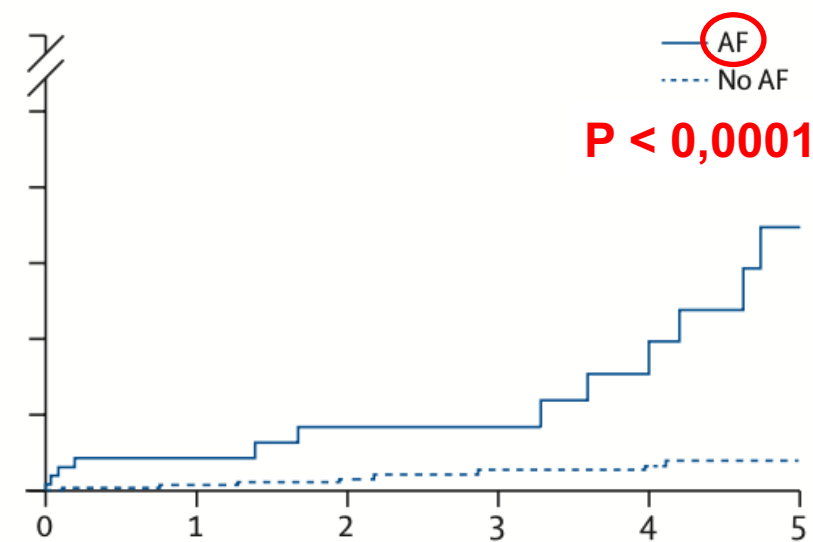
3,2 % /anno recidiva ICH  
1,7 % /anno stroke ischemico

## Sede ICH e incidenza recidiva ICH



Non differente incidenza stroke ischemico

## Presenza FA e incidenza stroke ischemico



Non differente incidenza recidiva ICH

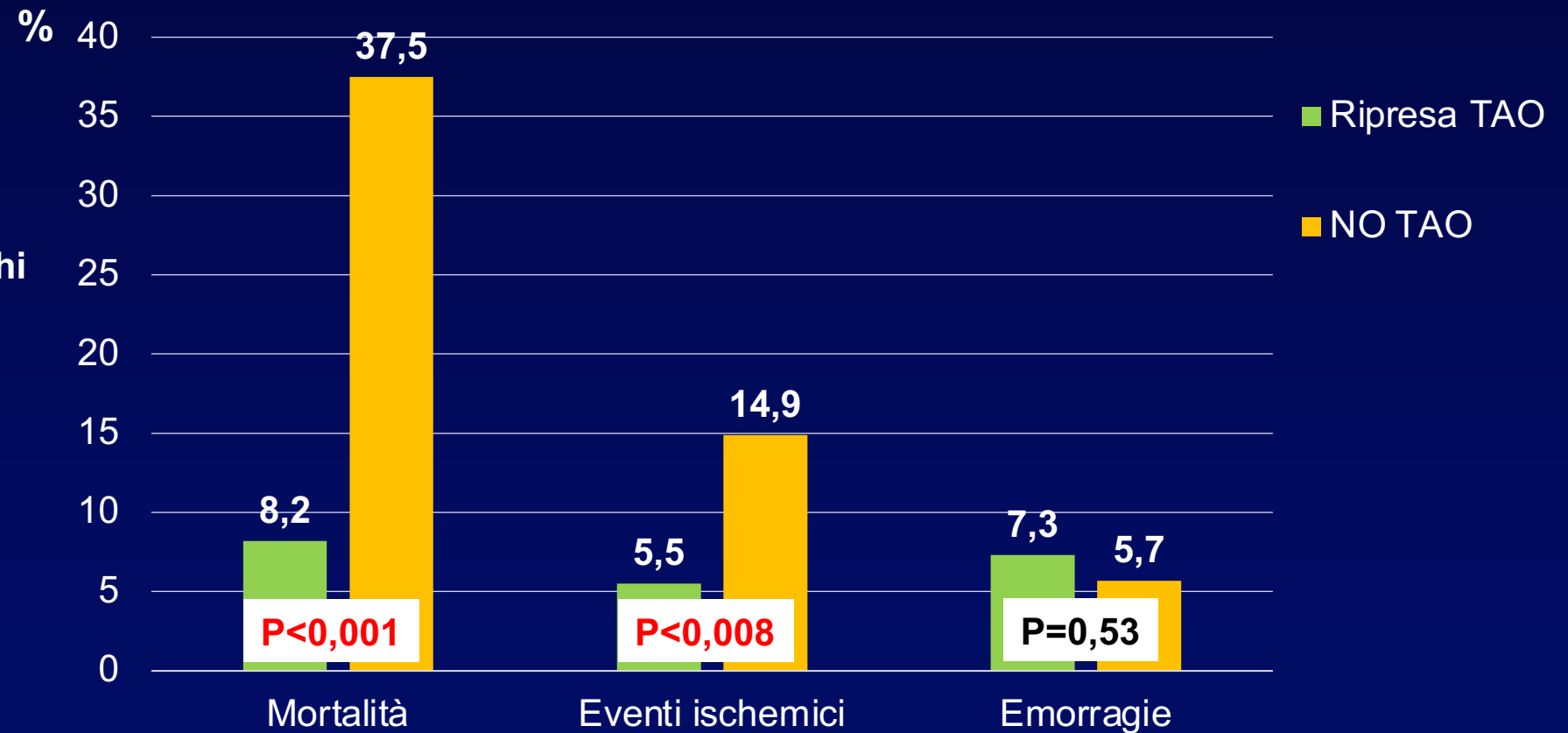
## 2. Studi clinici osservazionali

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Original Investigation

# Anticoagulant Reversal, Blood Pressure Levels, and Anticoagulant Resumption in Patients With Anticoagulation-Related Intracerebral Hemorrhage

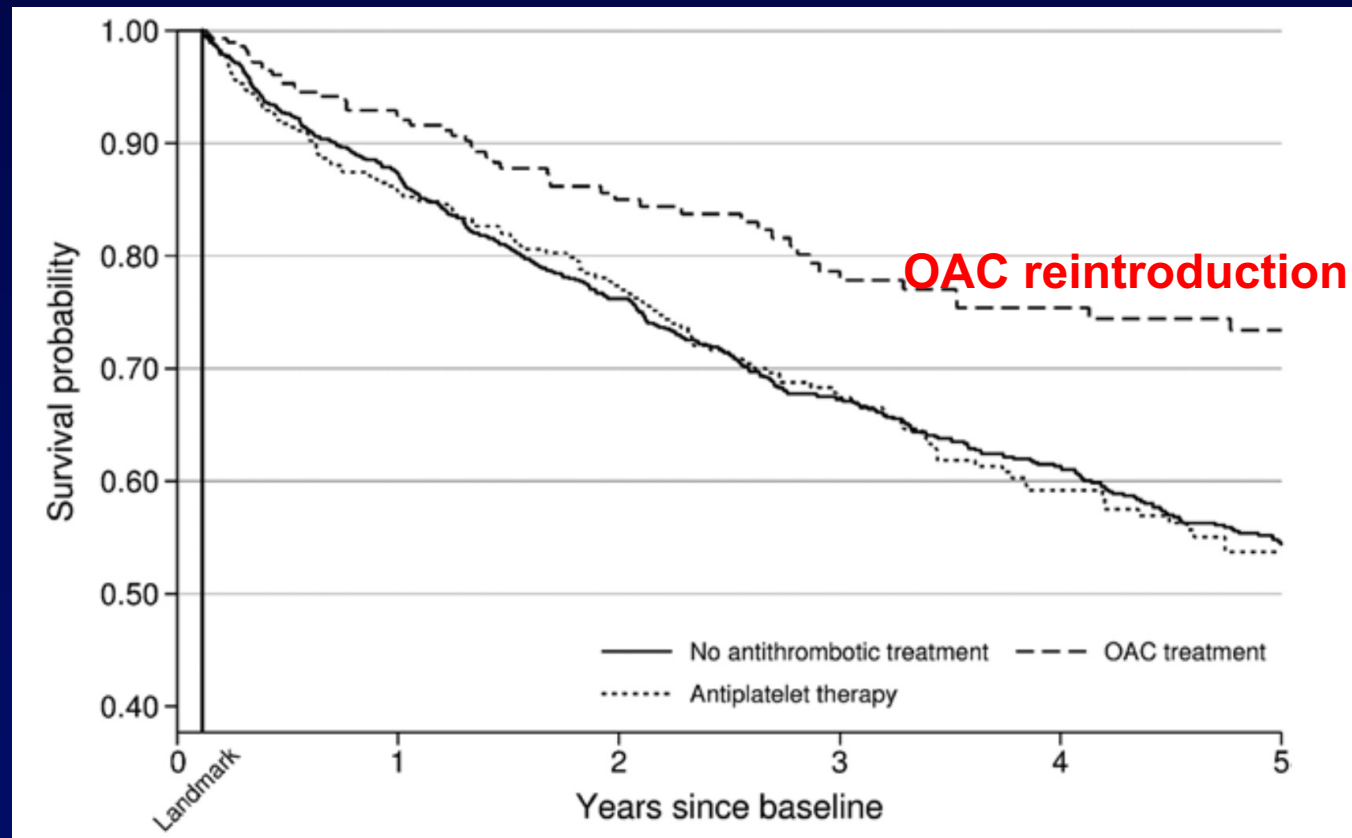
Studio retrospettivo  
566 pz in 19 centri tedeschi  
• FA in AVK  
• ICH spontanea  
Follow-up 1 anno



# Restarting Anticoagulant Treatment After Intracranial Hemorrhage in Patients With Atrial Fibrillation and the Impact on Recurrent Stroke, Mortality, and Bleeding

## A Nationwide Cohort Study

1752 pts with AF in OAC treatment within 6 months before ICH



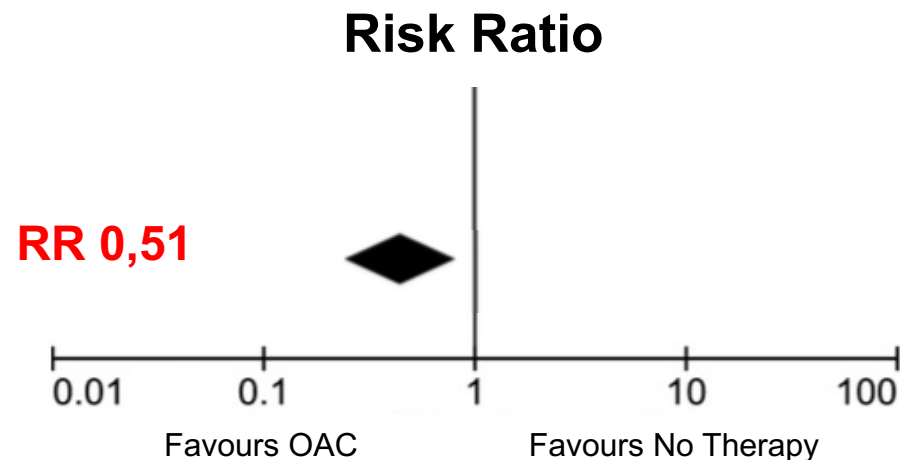
Same risk of recurrent ICH in OAC-treated vs non-OAC treated

# Antithrombotics After ICH in AF

Metanalisi di 20 studi e 50.470 pazienti con FA e ICH spontanea di qualsiasi dimensione e sede:  
TAO dopo ICH vs no TAO dopo ICH

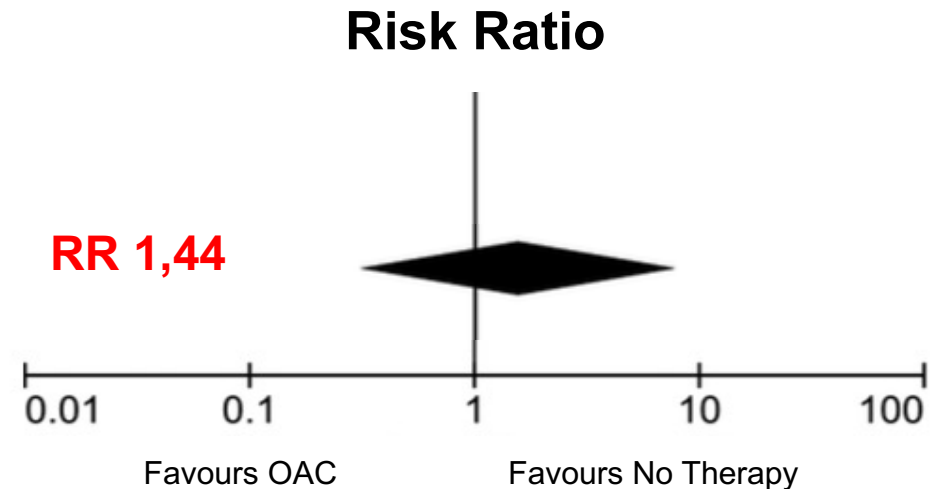
Eventi tromboembolici

TAO vs no terapia



Recidiva ICH

TAO vs no terapia



### 3. Studi clinici randomizzati

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# Effects of oral anticoagulation in people with atrial fibrillation after spontaneous intracranial haemorrhage (COCROACH): prospective, individual participant data meta-analysis of randomised trials



*Rustam Al-Shahi Salman, Jacqueline Stephen, Jayne F Tierney, Steff C Lewis, David E Newby, Adrian R Parry-Jones, Philip M White, Stuart J Connolly, Oscar R Benavente, Dar Dowlathshahi, Charlotte Cordonnier, Catherine M Viscoli, Kevin N Sheth, Hooman Kamel, Roland Veltkamp, Kristin T Larsen, Jeannette Hofmeijer, Henk Kerkhoff, Floris H B M Schreuder, Ashkan Shoamanesh\*, Catharina J M Klijn\*, H Bart van der Worp\*, for the Collaboration of Controlled Randomised Trials of Long-Term Oral Antithrombotic Agents After Spontaneous Intracranial Haemorrhage (COCROACH)†*

- SoSTART (203 participants)
- APACHE-AF (101 participants)
- NASPAF-ICH (30 participants)
- ELDECARE-AF (80 participants)

412 pts; 75% ≥ 75 years  
40% CHA<sub>2</sub>DS<sub>2</sub>-VASc > 4  
DOAC 99%

**Primary Outcome: any stroke or CV death**

# Frequency of the first occurrence of outcome events during FU

|                                                                     | Start oral anticoagulation (n=212) | Avoid oral anticoagulation (n=200) |
|---------------------------------------------------------------------|------------------------------------|------------------------------------|
| <b>Primary outcome</b>                                              | <b>99% DOAC</b>                    | <b>33% antiaggregante</b>          |
| Any stroke or cardiovascular death                                  | 29 (14%)                           | 43 (22%)                           |
| <b>Secondary outcomes</b>                                           |                                    |                                    |
| Ischaemic major adverse cardiovascular events                       | 9 (4%)                             | 38 (19%)                           |
| Ischaemic stroke                                                    | 9 (4%)                             | 31 (16%)                           |
| Systemic arterial embolism                                          | 0                                  | 0                                  |
| Pulmonary embolism                                                  | 0                                  | 4 (2%)                             |
| Myocardial infarction                                               | 0                                  | 4 (2%)                             |
| Haemorrhagic major adverse cardiovascular events                    | 15 (7%)                            | 9 (5%)                             |
| Intracranial haemorrhage                                            | 12 (6%)                            | 5 (3%)                             |
| Major extracranial haemorrhage                                      | 3 (1%)                             | 4 (2%)                             |
| Death from any cause                                                | 38 (18%)                           | 29 (15%)                           |
| Cardiovascular death                                                | 17 (8%)                            | 12 (6%)                            |
| Death from any other cause                                          | 21 (10%)                           | 17 (9%)                            |
| Death or dependence (modified Rankin Scale score 3–6) after 1 year* | 78 (53%)                           | 74 (51%)                           |

# Ongoing RCTs of OAC in AF Patients Following ICH

| Trial; principal investigator                                          | Population                                                          | Intervention                                                                                   | Target sample | Status                                           |
|------------------------------------------------------------------------|---------------------------------------------------------------------|------------------------------------------------------------------------------------------------|---------------|--------------------------------------------------|
| <i>Antithrombotic therapy</i><br>APACHE-AF; Karin Klijn<br>NCT02565693 | Atrial fibrillation and ICH                                         | Apixaban vs. no antithrombotic therapy/antiplatelet monotherapy (open-label)                   | 100           | Recruiting                                       |
| NASPAF-ICH; Ashkan Shoamanesh<br>NCT02998905                           | Atrial fibrillation and ICH                                         | Any DOAC vs. aspirin (open-label)                                                              | 100           | Enrollment completed/ stopped at 30 participants |
| SoSTART; Rustam Al-Shahi Salman<br>NCT03153150                         | Atrial fibrillation and intracranial hemorrhage                     | Any anticoagulant vs. no antithrombotic therapy/antiplatelet monotherapy (open-label)          | 190           | Recruiting                                       |
| STATICH; Eivind Berge<br>NCT03186729                                   | Thrombo-occlusive disease indicating antithrombotic therapy and ICH | Any antithrombotic therapy vs. no antithrombotic therapy/antiplatelet monotherapy (open-label) | 500           | Recruiting                                       |
| PRESTIGE AF; Roland Veltkamp<br>NCT03996772                            | Atrial fibrillation and ICH                                         | Any DOAC vs. no antithrombotic therapy/antiplatelet monotherapy (open-label)                   | 654           | Recruiting                                       |
| ASPIRE; Kevin Sheth<br>NCT03907046                                     | Atrial fibrillation and ICH                                         | Apixaban vs. aspirin (double-blind)                                                            | 700           | Activating                                       |
| ENRICH-AF; Ashkan Shoamanesh<br>NCT03950076                            | Atrial fibrillation and intracranial hemorrhage                     | Edoxaban vs. standard of care (no antithrombotic therapy/antiplatelet monotherapy; open-label) | 1200          | Activating                                       |

# Ongoing RCTs of OAC in AF Patients Following ICH

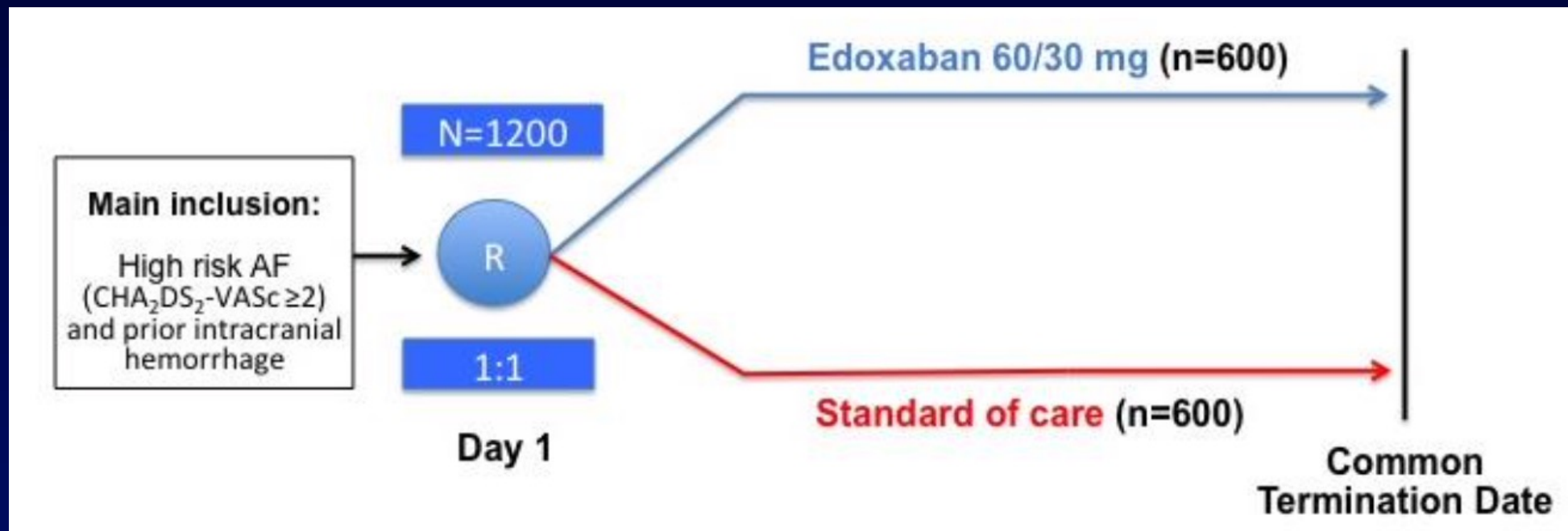
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# ENRICH-AF



EdoxabaN foR IntraCranial Hemorrhage survivors with  
Atrial Fibrillation  
November 14, 2019

# Studio ENRICH-AF



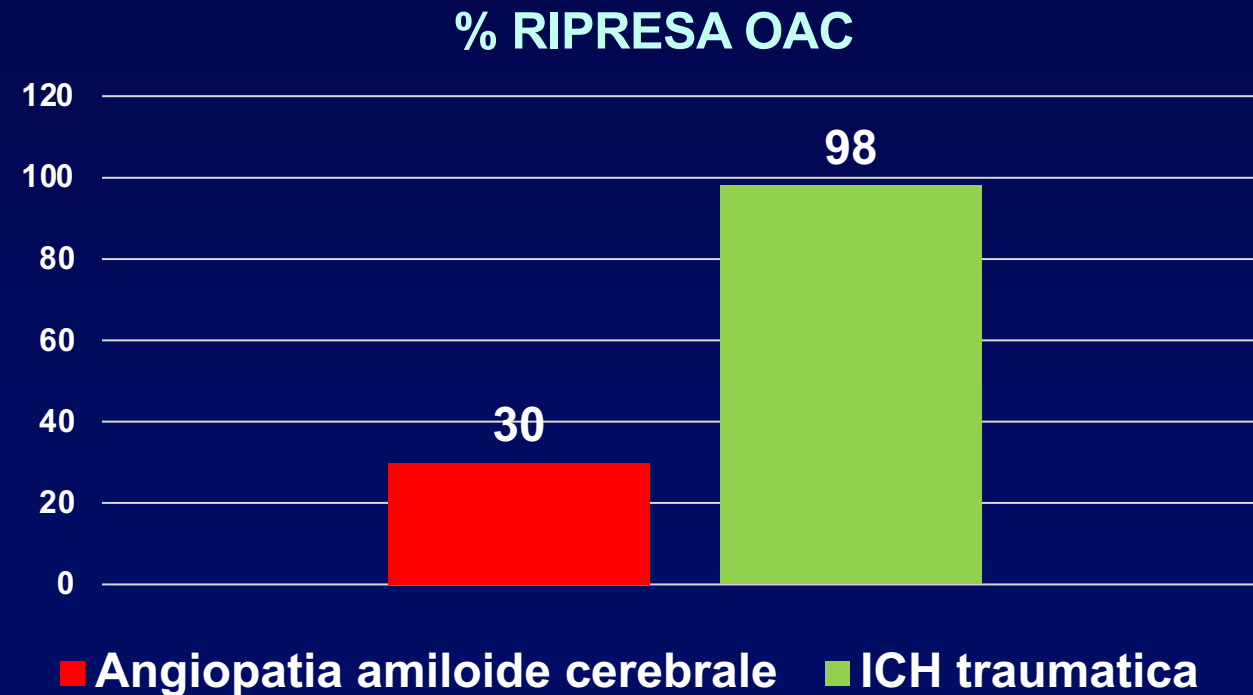
End-point 1° efficacia → ogni stroke (ischemico, emorragico)

End-point 1° sicurezza → ogni emorragia maggiore (criteri ISTH)

**Analisi ad interim DSMB (Giugno 2023):**

interrotto arruolamento sottotipo ICH lobare e subaracnoidea della convessità per elevato rischio di recidiva ICH con DOAC

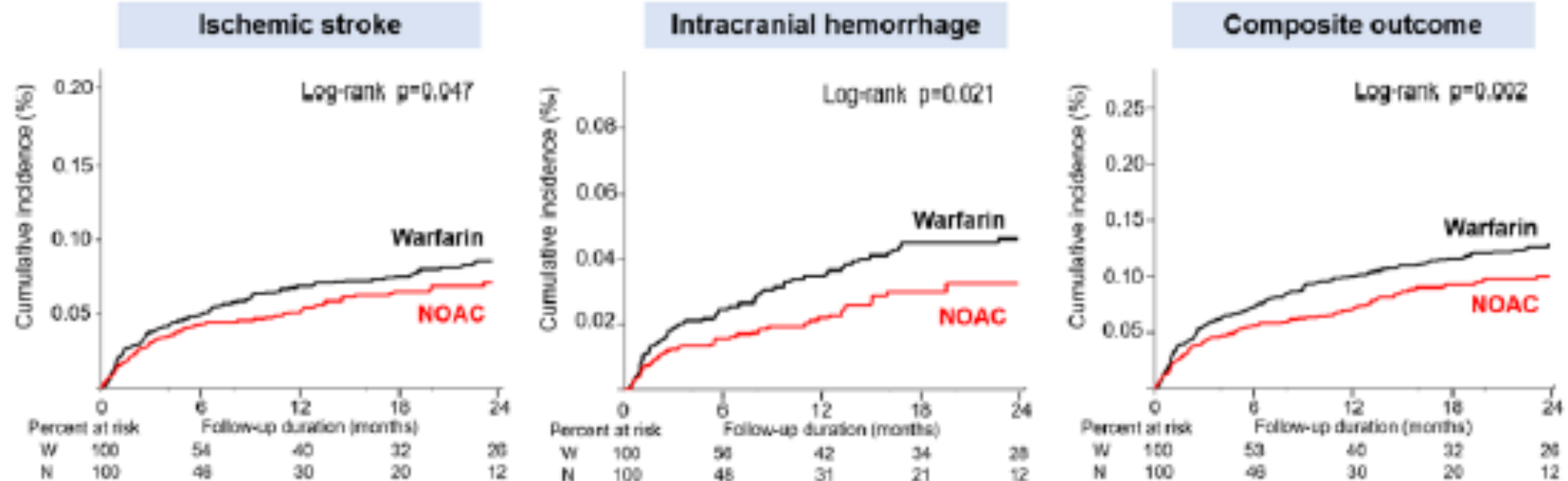
# Oral anticoagulant re-initiation following intracerebral hemorrhage in non-valvular atrial fibrillation: Global survey of the practices of neurologists, neurosurgeons and thrombosis experts



Survey che ha incluso  
228 clinici esperti di  
38 Paesi

# Oral Anticoagulation in Asian Patients With Atrial Fibrillation and a History of Intracranial Hemorrhage

Among 5712 pts with AF with prior ICH, 2434 were treated with warfarin and 3278 with NOAC



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## Recommendations for stroke prevention in AF patients after intracranial haemorrhage

In AF patients at high risk of ischaemic stroke, (re-)initiation of OAC, with preference for NOACs over VKAs in NOAC-eligible patients, should be considered in consultation with a neurologist/stroke specialist after:

- A trauma-related ICH
- Acute spontaneous ICH (which includes subdural, subarachnoid, or intracerebral haemorrhage), after careful consideration of risks and benefits.<sup>c</sup>

**IIa**

**C**

## 2020 ESC Guidelines Atrial Fibrillation

### Recommendations for Management of Patients With AF and ICH

Referenced studies that support the recommendations are summarized in the [Online Data Supplement](#).

| COR | LOE  | RECOMMENDATIONS                                                                                                                                                                                                                                                                                           |
|-----|------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 2a  | C-LD | 1. In patients with AF and conditions associated with very high risk of thromboembolic events (>5%/year), such as rheumatic heart disease or a mechanical heart valve, early (1-2 weeks) resumption of anti-coagulation after ICH is reasonable to reduce the risk of thromboembolic events. <sup>1</sup> |
| 2b  | C-LD | 2. In patients with AF and ICH, delayed (4-8 weeks) resumption of anticoagulation may be considered to balance the risks of thromboembolic and hemorrhagic complications after careful risk benefit assessment. <sup>2-5</sup>                                                                            |
| 2b  | B-NR | 3. In patients with AF and conditions associated with high risk of recurrent ICH (eg, cerebral amyloid angiopathy) anticoagulation-sparing strategies (eg, LAAO) may be considered to reduce the risk of recurrent hemorrhage. <sup>6,7</sup>                                                             |

## 2023 ACC/AHA/ACCP/HRS Guideline Atrial Fibrillation

# 2022 Guideline for the Management of Patients With Spontaneous Intracerebral Hemorrhage: A Guideline From the American Heart Association/American Stroke Association

|    |      |                                                                                                                                                                                                                                                           |
|----|------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 2b | B-NR | 3. In patients with nonvalvular atrial fibrillation (AF) and spontaneous ICH, the resumption of anti-coagulation to prevent thromboembolic events and reduce all-cause mortality may be considered based on weighing benefit and risk. <sup>590-595</sup> |
|----|------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

| Recommendations for BP Management<br>Referenced studies that support recommendations are summarized in Data Supplements 75 and 76. |      |                                                                                                                                                                                                         |
|------------------------------------------------------------------------------------------------------------------------------------|------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| COR                                                                                                                                | LOE  | Recommendations                                                                                                                                                                                         |
| 1                                                                                                                                  | B-R  | 1. In patients with spontaneous ICH, BP control is recommended to prevent hemorrhage recurrence. <sup>563,581</sup>                                                                                     |
| 2a                                                                                                                                 | B-NR | 2. In patients with spontaneous ICH, it is reasonable to lower BP to an SBP of 130 mmHg and diastolic BP (DBP) of 80 mmHg for long-term management to prevent hemorrhage recurrence. <sup>581,582</sup> |

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# Take Home Messages

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- Nei pazienti con FA e pregressa ICH non è necessariamente preclusa la ripresa o l'inizio della TAO, con preferenza per i DOAC.
- La controindicazione assoluta per la TAO riguarda soltanto i pazienti con ICH lobare associate ad angiopatia amiloide cerebrale.
- Negli altri casi è opportuna una valutazione multidisciplinare cardiologica, neurologica e neuroradiologica per valutare nel singolo paziente il rapporto rischio/beneficio della TAO.
- E' inoltre importante correggere i fattori di rischio emorragico eventualmente associati (ipertensione, uso concomitante di aspirina e FANS etc).