Hémorragies cérébrales associées aux anticoagulants: *traitement aigu et reprise de l'anticoagulation*

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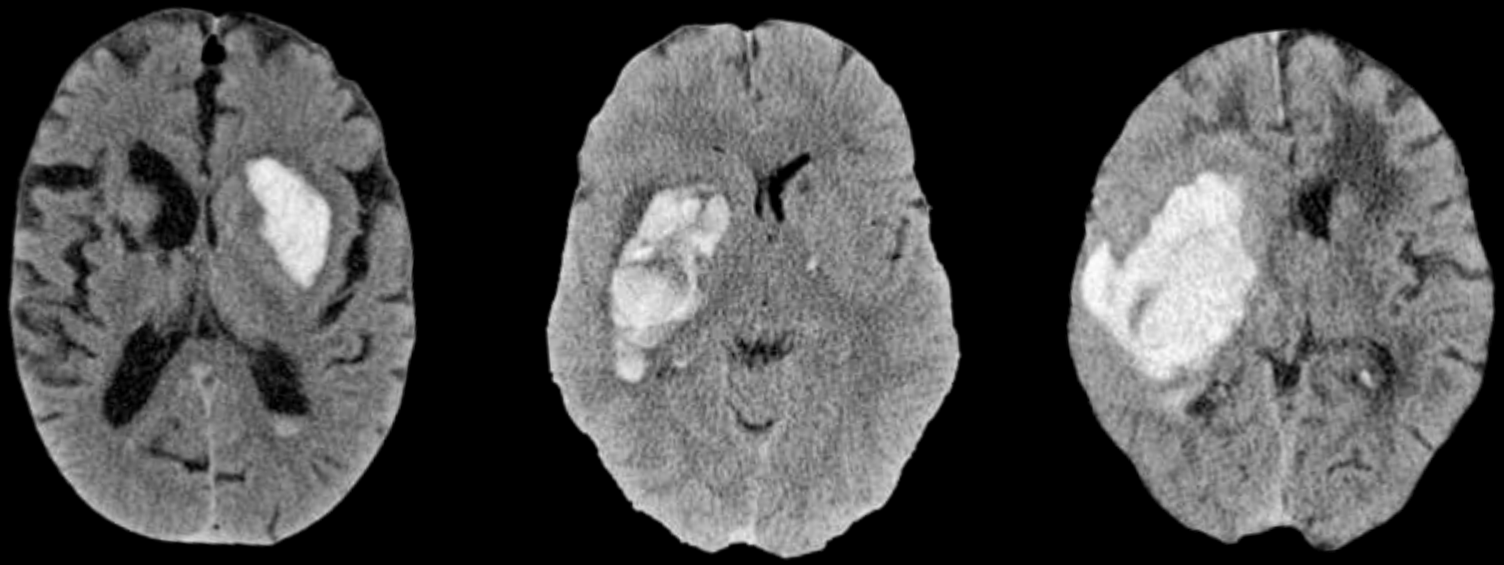
16 novembre 2018

(Remerciements à Dr A. Shoamanesh (PHRI))

Divulgations de conflits d’intérêt

- Honoraires reçues:
  - Bayer Inc
  - BMS Pfizer
  - Servier

Le volume de l'hématome prédit la mortalité à 30 jours

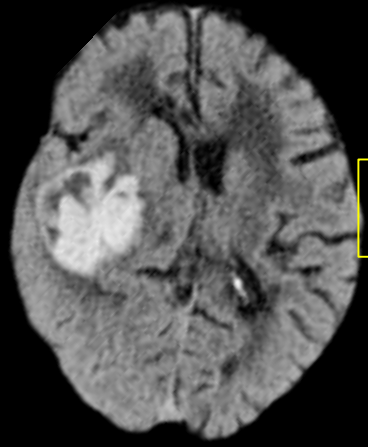


Volume	<30 cc	30-60 cc	>60 cc
% Mortalité			
-Lobaire	7%	60%	70%
-Profond	23%	64%	93%

Broderick J et al. Stroke 1993

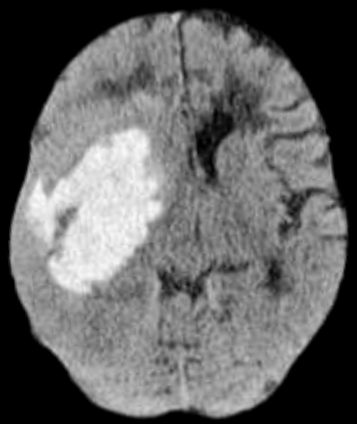
Cible: L'expansion de la taille de l'hématome

NCCT

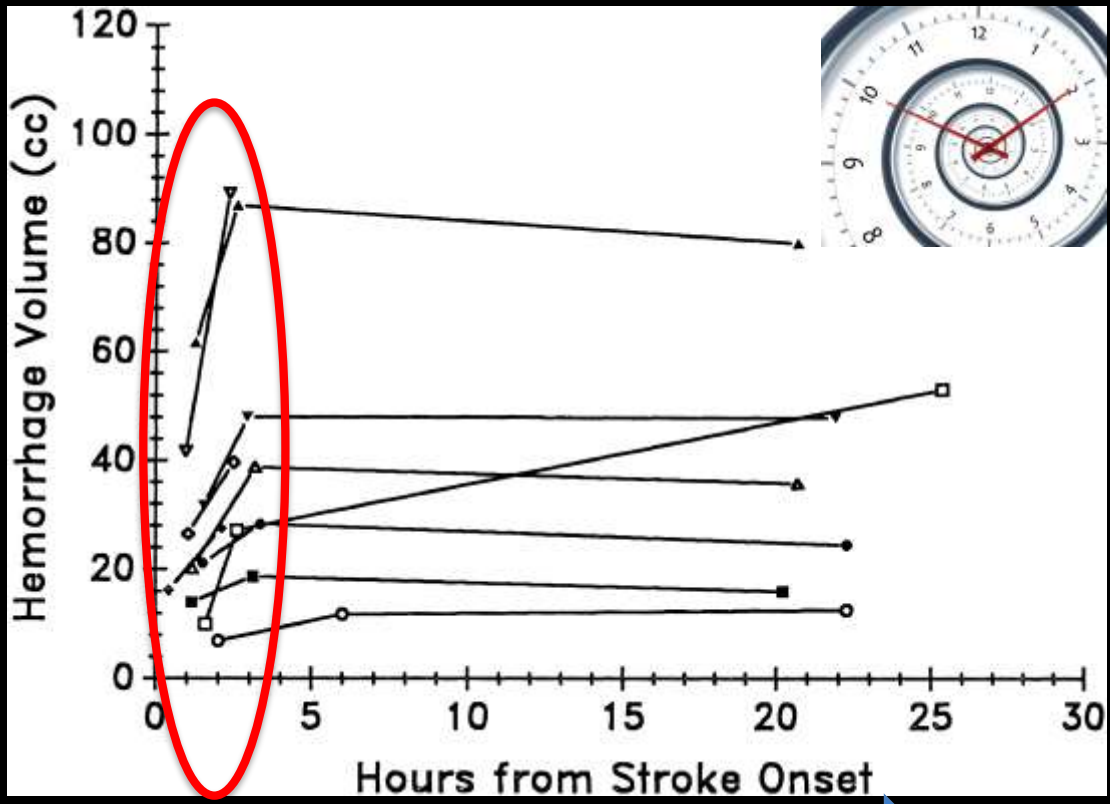


33.9 cc

Ct contrôle



90.8 cc

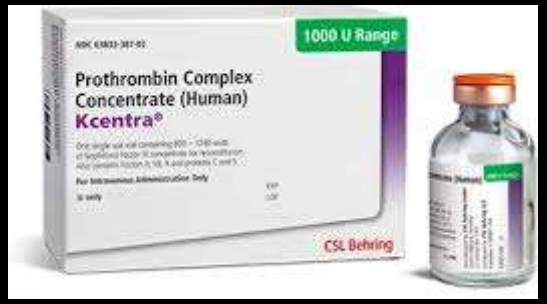


- *33% HIC => expansion +*
- *54% HIC associées à l'anticoagulation*

Interventions Potentielles

1. Réduction de la TA

1. Traitement hémostatique (selon l'anticoagulant)
    1. Warfarin
    2. Héparine et HBPM
    3. NACO
        - Anti-thrombine
        - Anti-Xa



1) HIC avec warfarine (et INR élevé)

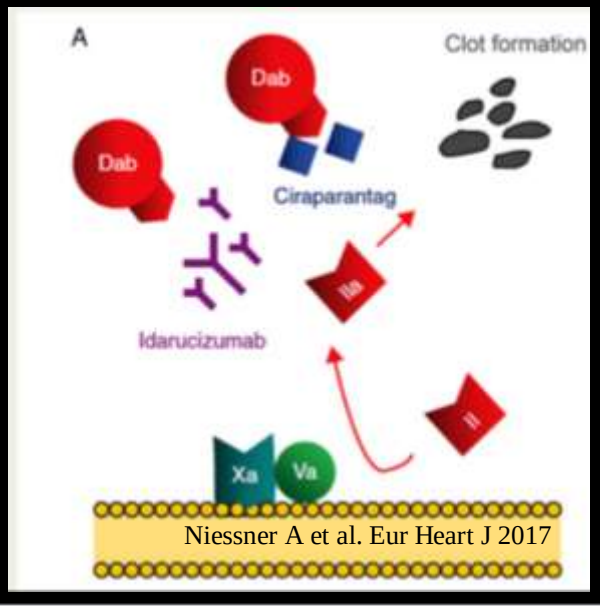
1. Vitamine K 10 mg IV
2. Réplacement des facteurs de coagulation dépendants à la vitamine K (II, VII, IX, X)

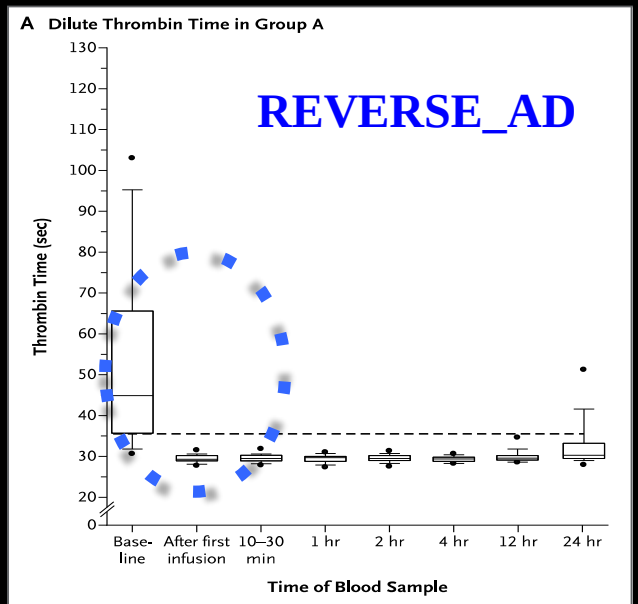
Etude INCH	Fresh frozen plasma (n=23)	Prothrombin complex concentrate (n=27)	Treatment effect (95% CI)	p value
Primary outcome				
INR ≤1·2 within 3 h	2 (9%)	18 (67%)	OR 30·6 (4·7 to 197·9)*	0·0003
Secondary imaging outcomes				
Time until INR ≤1·2 normalisation of INR (min)	1482 (1335–1610)	40 (30–1610)	No proportional hazard assumed	0·050†
Imaging data at 3 h¶				
Haematoma expansion (mL)	23·7 (28·4)	9·7 (20·9)	16·9 (2·5 to 31·3)‡	0·023
≥15% growth‖	16/22 (73%)**	15/26 (58%)**	OR 2·0 (0·6 to 7·3)*	0·29
≥33% growth‖	13/22 (59%)**	12 (44%)**	OR 3·8 (1·1 to 16·0)*	0·048
Imaging data at 24 h				
Haematoma expansion (mL)	22·1 (27·1)	8·3 (18·3)	16·4 (2·9 to 29·9)‡	0·018
≥15% growth or death‖	14/20 (70%)††	12/27 (44%)	OR 3·9 (1·0 to 17·6)*	0·044
≥33% growth or death‖	12/20 (60%) ††	8/27 (30%)	OR 4·8 (1·3 to 20·4)*	0·024

Steiner T et al. Lancet Neurol 2016;15:56-73

2) HIC associées au dabigatran

- Fragment d'Ac monoclonal
- Antidote *SPÉCIFIQUE* au dabigatran
- Haute affinité (350x) pour dabigatran que pour la thrombine
- Efficacité presque immédiate (<5-10 min) et soutenue
- Pas d'effet sur plaquettes, coagulation
  - 5 événements prothrombotiques (associés au risque de base?)
- Bolus 2.5 mg IV x 2
- Durée (12) 24h
- Disponible au Québec

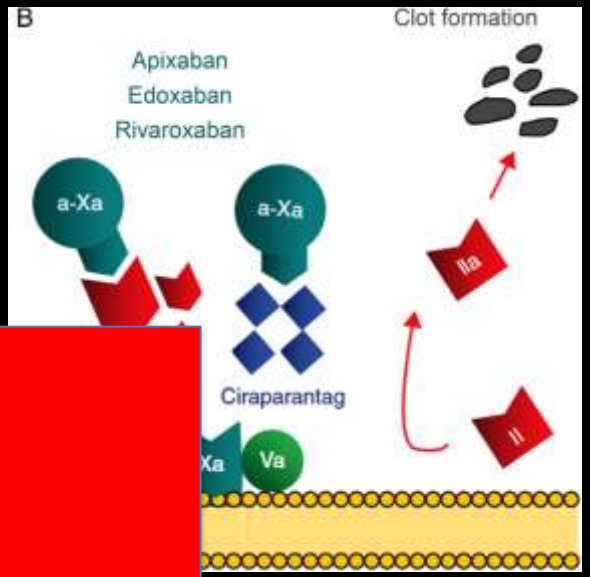


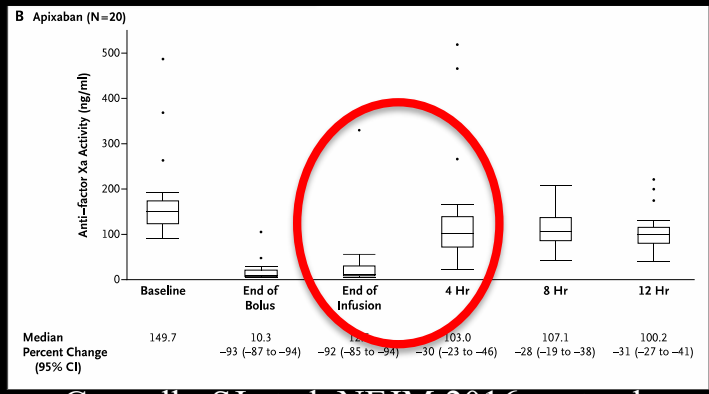


3) HIC associées aux anti-Xa

- Andaxanet-alfa
  - Antidote contre apixaban, edoxaban, enoxaparin, rivaroxaban
  - Analogue recombiné de facteur Xa
  - Bolus sur 15-
    heures (dep s
    dose)
- ANNEXA-4
  - Effet transitoire (durée <4h) avec rebond vers niveaux placebo par la suite
  - 10% évenements prothrombotiques
    - 1 IM, 5 AVC, 7 TPP, 1 EP
    - <30 jours post-andaxanet

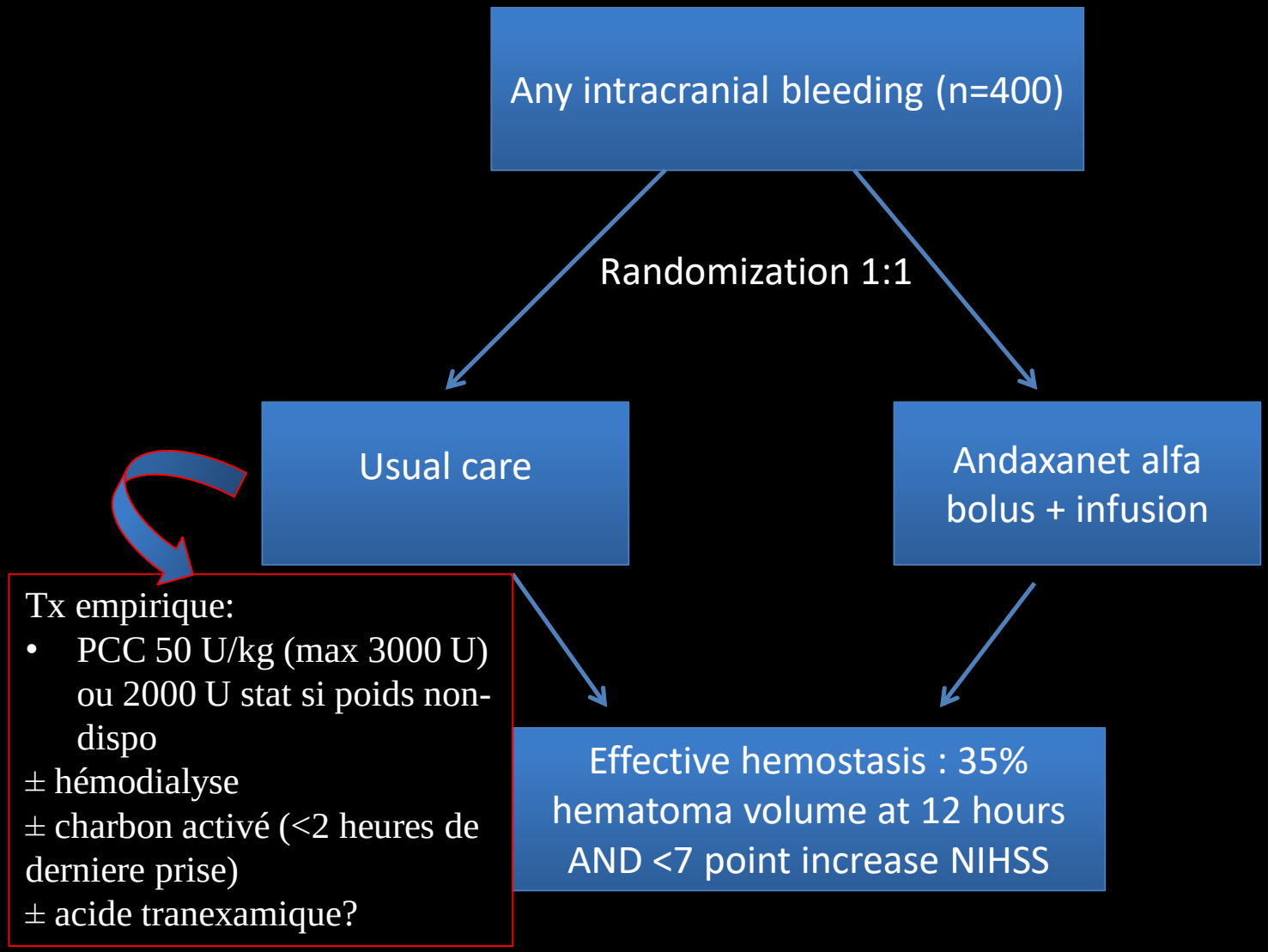
Approuvé aux EU (fast track)
Pas en approuvé au Canada





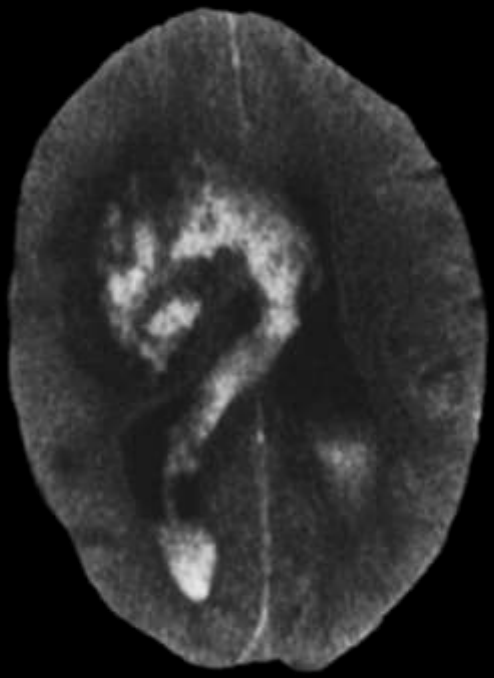
Connolly SJ et al. NEJM 2016 septembre

ANNEXA-4 phase 4

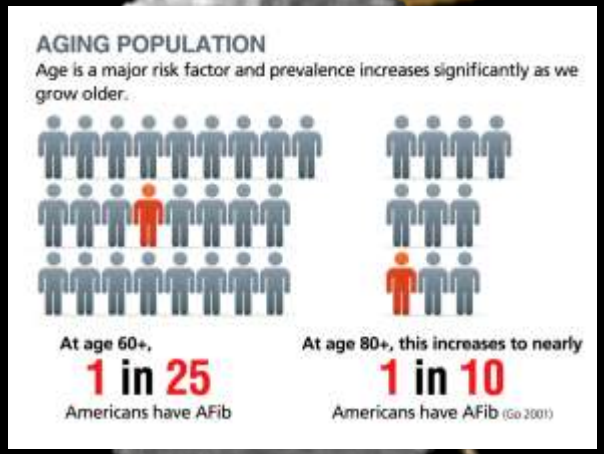


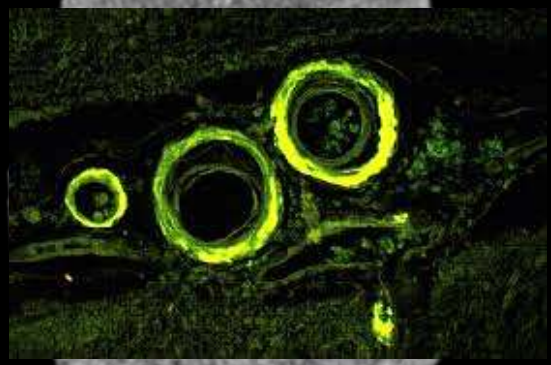
Ciraparantag: antidote universelle?

- Antidote pour:
  - Anti-Xa oraux
  - Anti-thrombine (IIa),
  - HBPM,
  - Héparine IV,
  - Fondaparinux
  - (pas warfarine)
- Molecule synthétique
- Renversement immédiat (<20 min)
- Pas effet pro-coagulant
- Durée 24h
- Etudes en cours (ok phase I)



II. Reprise de l’anticoagulation post-HIC?





Risque AVC ischémique:

- Indication l'anticoagulation:
  - FA (CHADS, CHADS-VASC)
  - Valve métallique
  - TPP/EP

Risque HIC récidivant:

- Cause
  - Reversible ou pas
    - cure anévrysme, hsd trauamtique, contusion
    - Microangiopathie (HTA, CAA)
- Localisation
  -lobaire (7-10%) > profond (2-3%)
- Reprise d'ACO
- Contrôle HTA

Lignes directrices (?)

13b. There is insufficient evidence from RCTs to make strong recommendations about how, when, and for whom anticoagulation should be given to prevent DVT or improve outcome.

2014

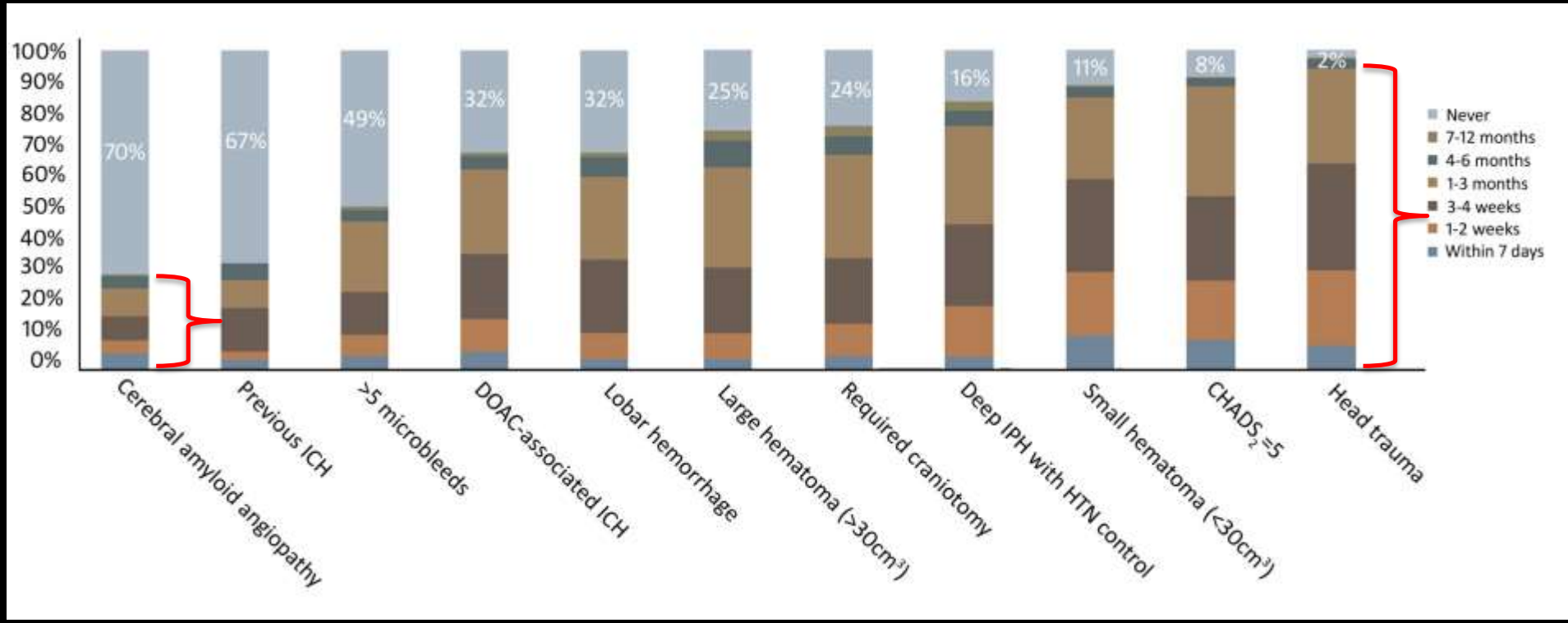
5. Anticoagulation after nonlobar ICH and antiplatelet monotherapy after any ICH might be considered, particularly when there are strong indications for these agents *(Class IIb; Level of Evidence B)*. (Revised from the previous guideline)

2015

7. The usefulness of dabigatran, rivaroxaban, or apixaban in patients with atrial fibrillation and past ICH to decrease the risk of recurrence is uncertain *(Class IIb; Level of Evidence C)*. (New recommendation)

- Pas de recommendation spécifique *2015*
- *(Écriture des lignes directrices sur HIC sous peu)*

Sondage d'experts mondial (n=228)



Taux de réintialisation variable (30-98%) selon le scénario clinique

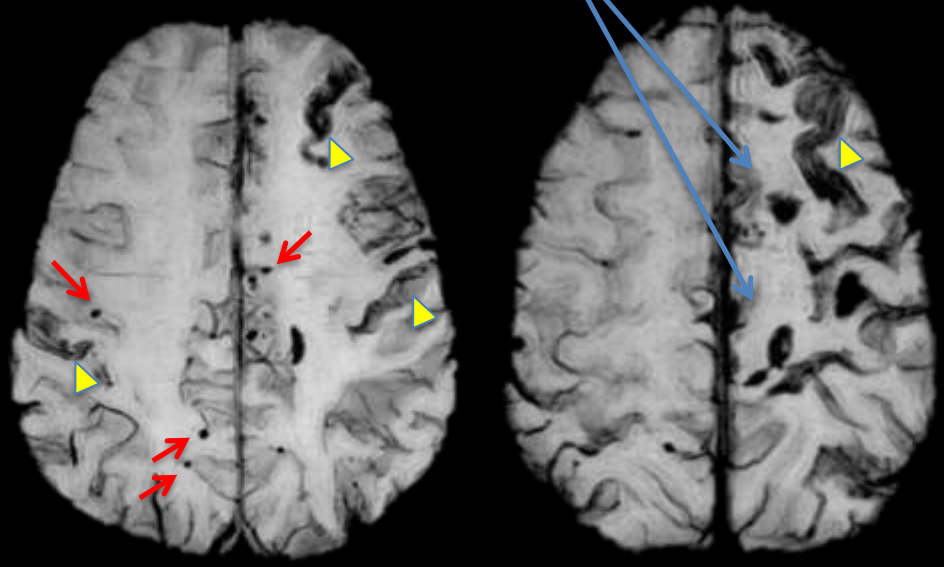
Xu Y et el. PLOS One 2018

CAA: Critères modifiées de Boston

Table 1. Modified Boston Criteria for CAA

Definite CAA
Full postmortem examination demonstrating:
Lobar, cortical, or cortical–subcortical hemorrhage
Severe CAA with vasculopathy
Absence of other diagnostic lesion
Probable CAA with supporting pathology
Clinical data and pathological tissue (evacuated hematoma or cortical biopsy) demonstrating:
Lobar, cortical, or cortical–subcortical hemorrhage (including ICH, CMB, or cSS)
Some degree of CAA in specimen
Absence of other diagnostic lesion
Probable CAA
Clinical data and MRI or CT demonstrating:
Multiple hemorrhages (ICH, CMB) restricted to lobar, cortical, or cortical–subcortical regions (cerebellar hemorrhage allowed), or single lobar, cortical, or cortical–subcortical hemorrhage and cSS (focal or disseminated)
Age ≥55 y
Absence of other cause of hemorrhage*
Possible CAA
Clinical data and MRI or CT demonstrating:
Single lobar, cortical, or cortical–subcortical ICH, CMB, or cSS (focal or disseminated)
Age ≥55 y
Absence of other cause of hemorrhage*

D 57 ans,
HIC symptomatique



Sensitivity 95% (95% CI 76-99%)
Specificity 81% (95% CI: 62-93%)
Linn J et al. Neurology 2010.

Edinburgh CT/APOE criteria for CAA-ICH

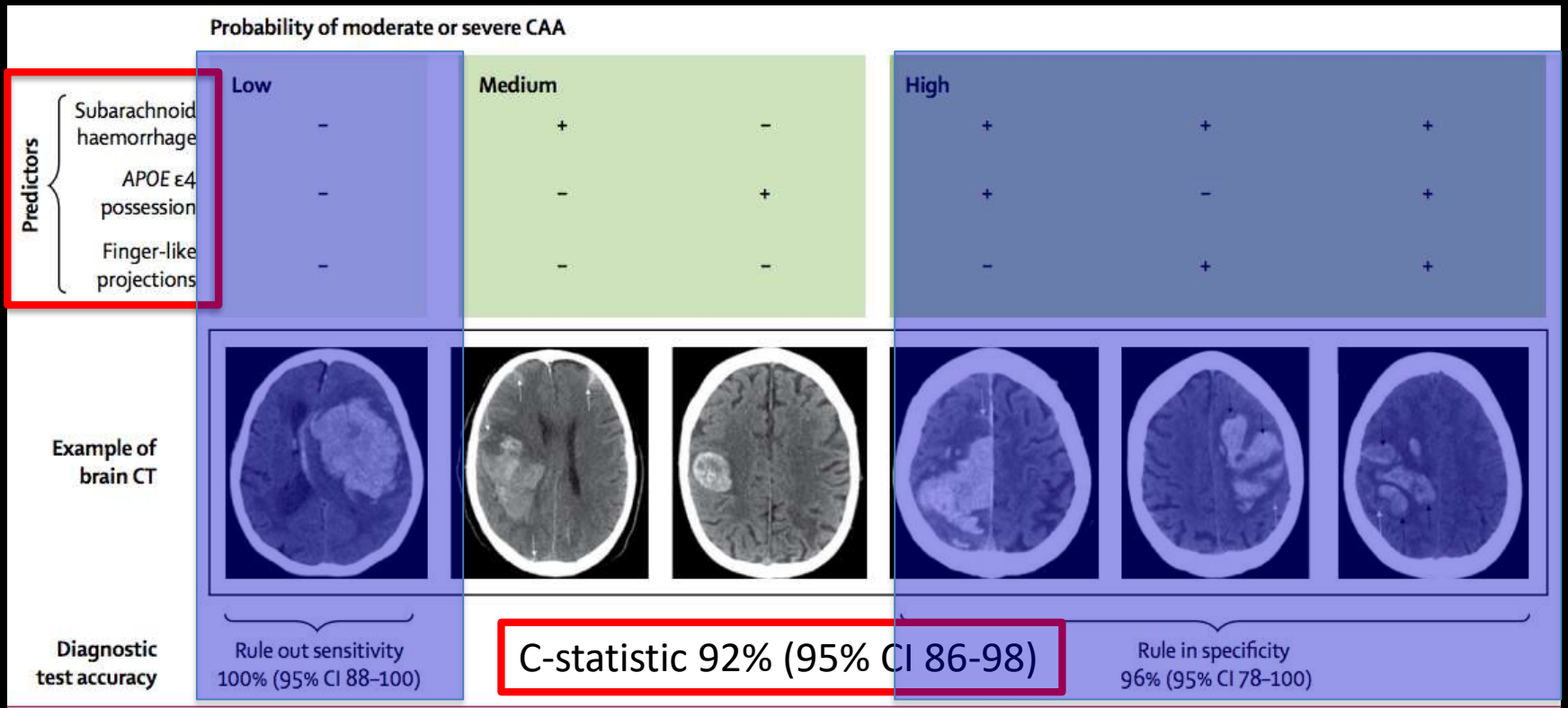
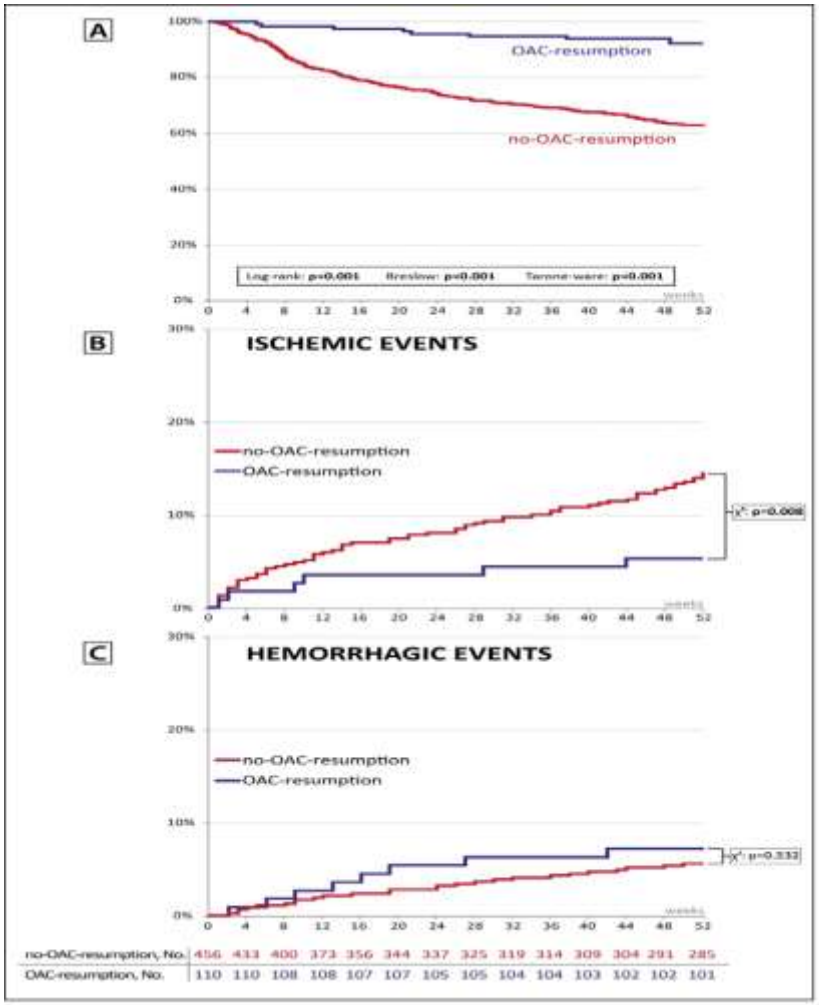


Figure 3: **Categorisation of probability of lobar intracerebral haemorrhage associated with moderate or severe cerebral amyloid angiopathy according to the three predictor variables, with example CT images**

CAA=cerebral amyloid angiopathy. Adapted from Salman and Rodrigues (Creative Commons 4.0).[23]

Rodrigues MA et al. Lancet Neurology 2018;17:232-40

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



19 German centers, 2006-2010

- 110 of 556 OAC-related ICH survivors with atrial fibrillation (19.4%) restarted on OAC

Median time to OAC resumption: 31 days

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

eTable 9. Propensity-matched Cox regression analyses of long-term mortality in A-fib patients.

Patients with atrial fibrillation (n=261)	No. of patients	No. of events (%)	Hazard ratio (95%CI)	*P* Value	Adjusted Hazard ratio 95%CI)	*P* Value
Overall	261	56 (21.5%)				
OAC resumption	108	9 (8.3%)	0.233 (0.114-0.476)	**<0.001**	0.258 (0.125-0.534)	**<0.001**
No OAC resumption	153	47 (30.7%)	1 (reference)		1 (reference)	

Cox regression analysis included all OAC-ICH patients with A-fib after propensity matching. Hazard ratio model was adjusted for events (new ischemic, recurrent hemorrhagic) during 1 year of follow-up and by propensity score (age, ICH volume, IVH, hematoma growth, NIHSS, $CHADS_2$ score as well as pre- and discharge-mRS). Assumption of proportionality was tested by locally weighted scatterplot smoothing of partial Schoenfeld residuals and PH testing. All covariates met the assumption. Significant parameters are expressed in bold.

74% RR in long-term mortality

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

eTable 8. Propensity-matched analysis of event and incidence rates in A-fib patients – new ischemic stroke *versus* recurrent ICH.

Patients with atrial fibrillation	No. of Patients	No. of events (%)	*P* Value	Incidence rate per 100 patient years (95%CI)	*P* Value
New cerebral Infarction	261	20 (7.7%)		8.7 (3.8-12.6)	
According to treatment					
OAC resumption	108	4 (3.7%)	**0.04**	3.9 (1.9-5.8)	**0.02**
No OAC resumption	153	16 (10.5%)		12.7 (6.5-19.1)	
Recurrent ICH	261	9 (3.4%)		3.9 (1.4-6.5)	
According to treatment					
OAC resumption	108	4 (3.7%)	0.55	3.9 (1.9-5.8)	0.92
No OAC resumption	153	5 (3.3%)		3.9 (2.2-5.7)	

Analysis included all OAC-ICH patients with A-fib after propensity matching. Given are: total number of patients for analysis, raw number of events and incidence rates (per 100 patient-years) calculated for time on each specific treatment (OAC *versus* no-OAC as defined) during 1 year of follow-up. Significant parameters are expressed in bold.

65% RR new cerebral infarcts

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

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No difference in recurrent ICH rate

warfarin

Deep ICH 47.5%
Lobar ICH 37.9%
Infratentorial 14.4%

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

A Nationwide Cohort Study

Peter Brønnum Nielsen, MSc, PhD; Torben Bjerregaard Larsen, MD, PhD; Flemming Skjøth, MSc, PhD; Anders Gorst-Rasmussen, MSc, PhD; Lars Hvilsted Rasmussen, MD, PhD; Gregory Y.H. Lip, MD

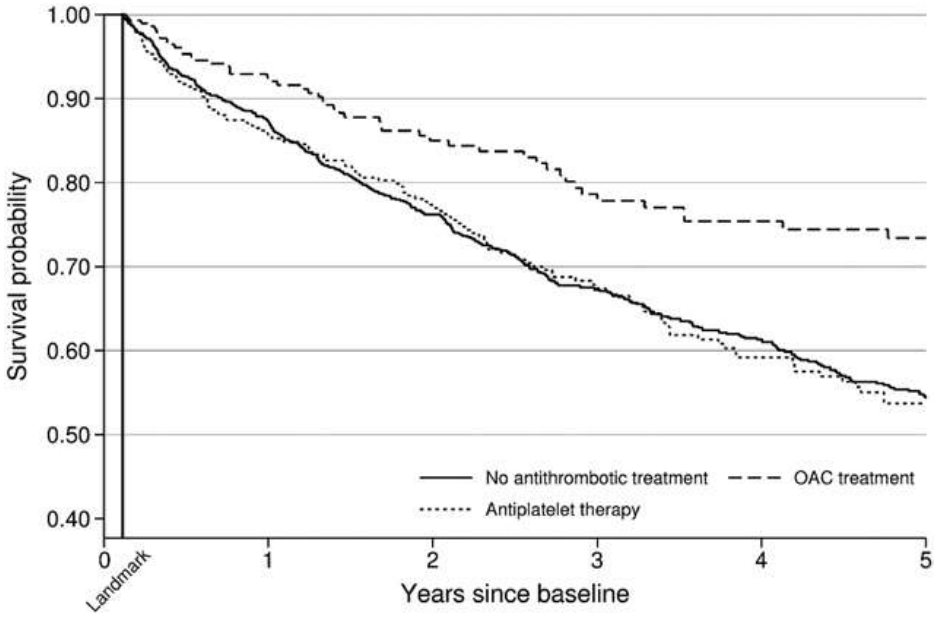
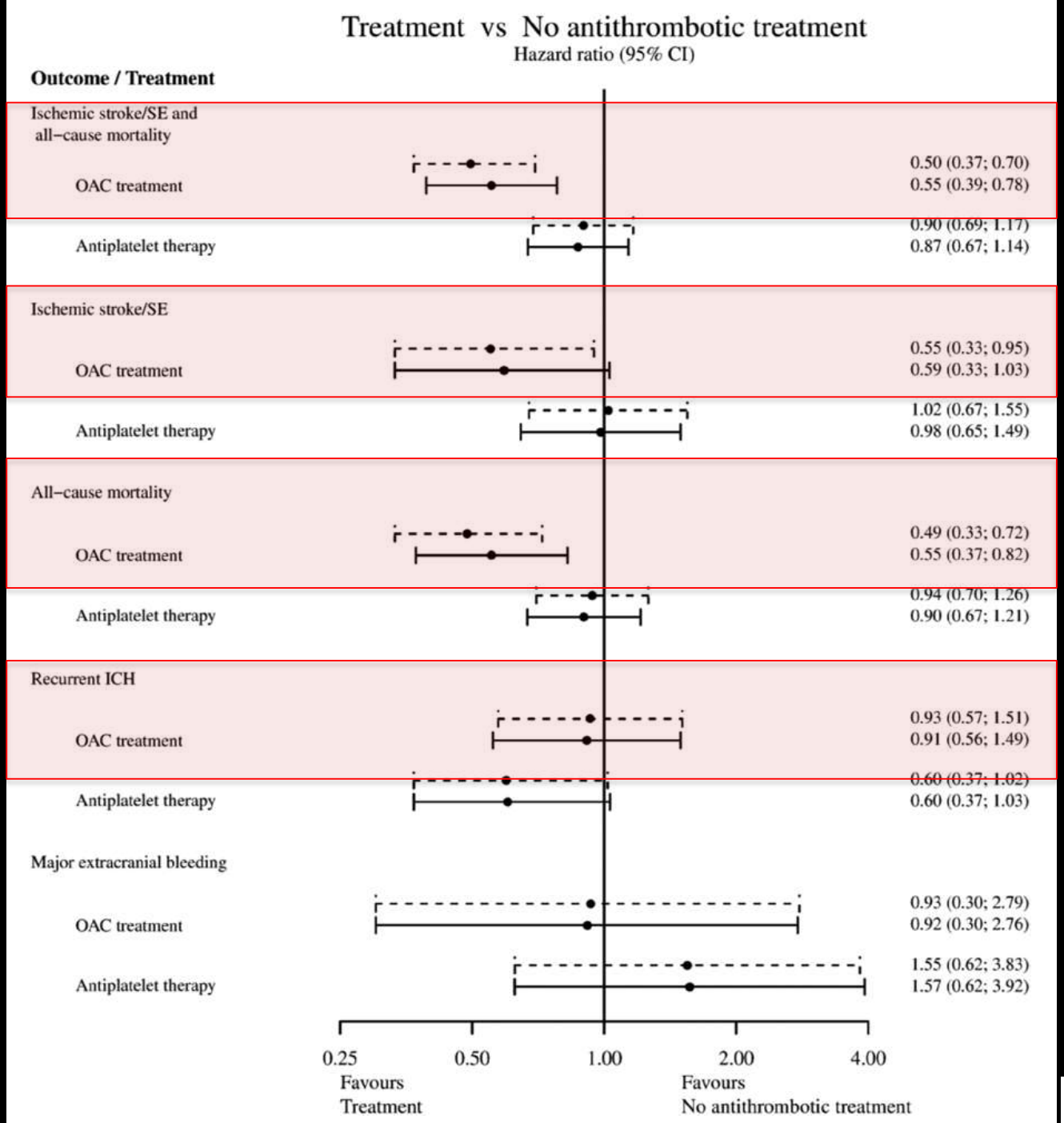


Figure 3. Five-year Kaplan–Meier survival curve for restarting OAC treatment, for receiving antiplatelet therapy, and for not receiving antithrombotic treatment with the use of a landmark at 6 weeks (relative to discharge from hospital) for treatment regimens stratification. OAC indicates oral anticoagulation.

Danish National Prescription Registry 1997-2013

1752 of 6138 (29%) patients with AF and ICH restarted on anticoagulation

(*Circulation*. 2015;132:517-525.



45% RR in IS/SE and all-cause mortality

41% RR in IS/SE

45% RR in all-cause mortality

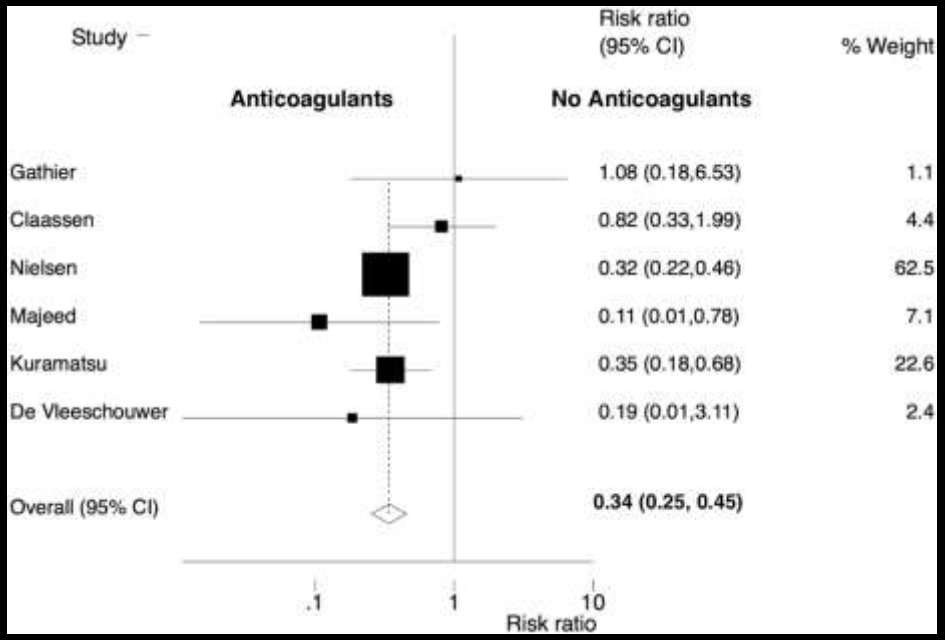
No difference in recurrent ICH rate

(*Circulation*. 2015;132:517-525.

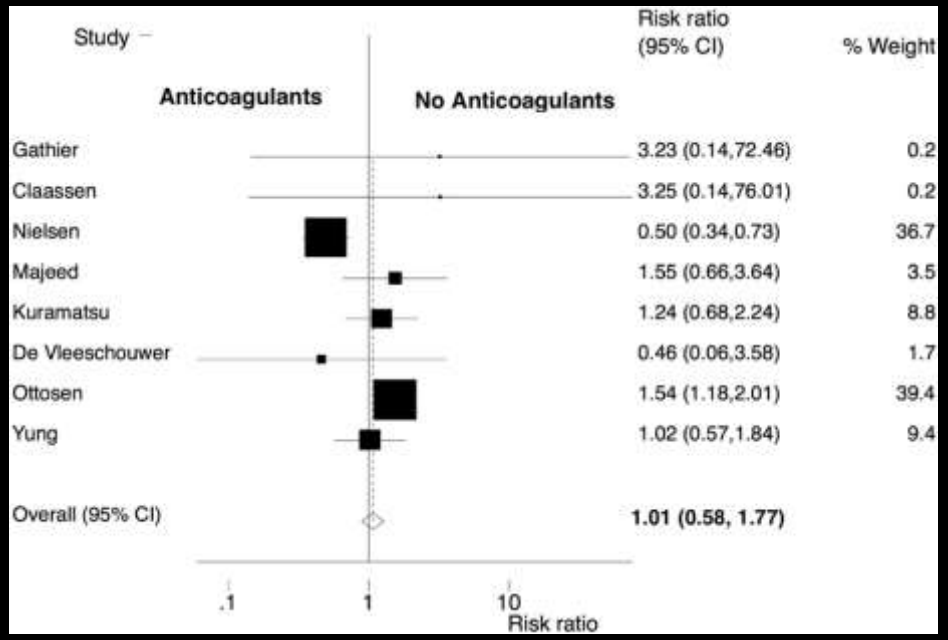
Restarting Anticoagulant Therapy After Intracranial Hemorrhage

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



Thromboembolic events



Recurrent ICH

Stroke. 2017 Jun;48(6):1594-1600.

Oral Anticoagulation and Functional Outcome after Intracerebral Hemorrhage

Alessandro Biffi, MD,[1,2,3]* Joji B. Kuramatsu, MD,[4]* Audrey Leasure, BS,[5] Hooman Kamel, MD,[6] Christina Kourkoulis, BS,[1,2,3] Kristin Schwab, BA,[1,3] Alison M. Ayres, BA,[1,3] Jordan Elm, PhD,[7] M. Edip Gurol, MD, MSc,[1,3] Steven M. Greenberg, MD, PhD,[1,3] Anand Viswanathan, MD, PhD,[1,3] Christopher D. Anderson, MD, MMSc,[1,2,3] Stefan Schwab, MD,[4] Jonathan Rosand, MD, MSc,[1,2,3] Fernando D. Testai, MD, PhD,[8] Daniel Woo, MD, MS,[9] Hagen B. Huttner, MD,[4]* and Kevin N Sheth, MD[5]*

- 1,012 OAC-related ICH survivors with atrial fibrillation
  - 633 nonlobar ICH (28% resumed OAC)
  - 379 lobar ICH (23% resumed OAC)

- Median time resumption 35-44 days

ANN NEUROL 2017;82:755–765

Oral Anticoagulation and Functional Outcome after Intracerebral Hemorrhage

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TABLE 3. Oral Anticoagulation Resumption and Outcomes following Intracerebral Hemorrhage

	All ICH			Nonlobar ICH			Lobar ICH		
Outcome[a]	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*
Mortality	0.27	0.19–0.40	<0.0001[b]	0.25	0.14–0.44	<0.0001[b]	0.29	0.17–0.45	<0.0001[b]
Favorable outcome, mRS = 0–3	4.15	2.92–5.90	<0.0001[b]	4.22	2.57–6.94	<0.0001[b]	4.08	2.48–6.72	<0.0001[b]
All-cause stroke	0.47	0.36–0.64	<0.0001[b]	0.41	0.25–0.67	0.0004[b]	0.51	0.37–0.76	0.0006[b]
Recurrent ICH	1.20	0.95–1.58	0.21	1.17	0.89–1.54	0.27	1.26	0.88–1.71	0.22
Ischemic stroke	0.44	0.29–0.66	<0.0001[b]	0.39	0.21–0.74	0.004[b]	0.48	0.25–0.75	0.003[b]

[a]All analyses were adjusted by means of propensity score matching using the following parameters: Glasgow Coma Scale at presentation, ICH volume, presence of intraventricular hemorrhage, discharge mRS, CHA_2DS_2-VASc score, and HAS-BLED score.

[b]Statistically significant.

CI = confidence interval; HR = hazard ratio; ICH = intracerebral hemorrhage; mRS = modified Rankin Scale.

71% RR in all-cause mortality (lobar ICH) vs. 75% RR (deep ICH)

4-fold increase in favorable outcome

No difference in recurrent ICH rate

52% RR in IS (lobar ICH) vs. 61% RR (deep ICH)

ANN NEUROL 2017;82:755–765

Oral Anticoagulation and Functional Outcome after Intracerebral Hemorrhage

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TABLE 5. Oral Anticoagulation Resumption and Outcomes following Lobar Intracerebral Hemorrhage related to Possible versus Probable CAA

Outcome[a]	Possible CAA			Probable CAA		
	HR	95% CI	*p*	HR	95% CI	*p*
Mortality	0.27	0.08–0.86	0.028[b]	0.30	0.10–0.92	0.037[b]
Favorable outcome, mRS 0–3	3.40	1.22–9.46	0.020[b]	3.11	1.08–8.97	0.038[b]

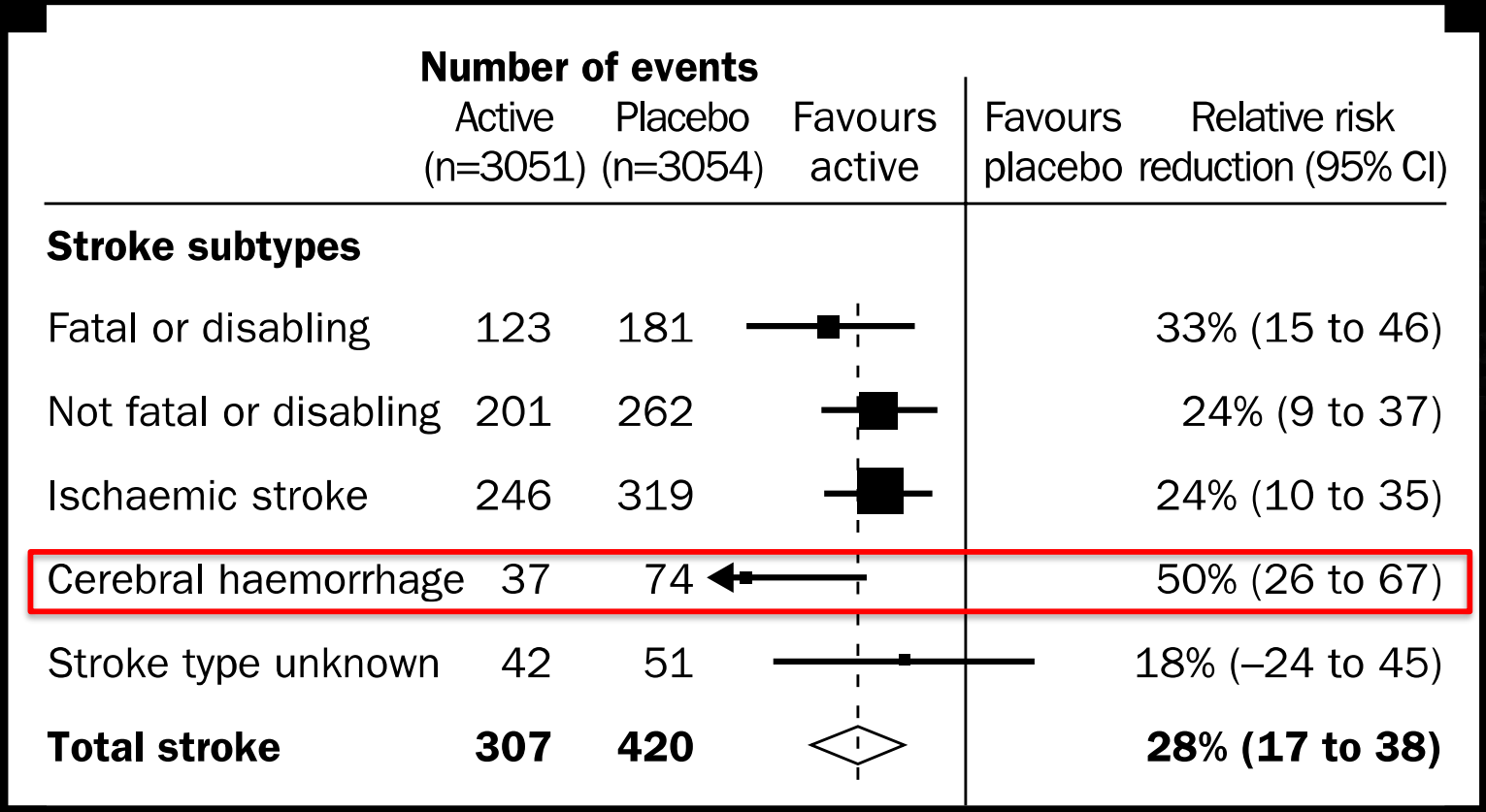
[a]All analyses were adjusted by means of propensity score matching using the following parameters: Glasgow Coma Scale at presentation, intracerebral hemorrhage volume, presence of intraventricular hemorrhage, discharge mRS, CHA_2DS_2-VASc score, and HAS-BLED score.

[b]Statistically significant.

CAA = cerebral amyloid angiopathy; CI = confidence interval; HR = hazard ratio; mRS = modified Rankin Scale.

ANN NEUROL 2017;82:755–765

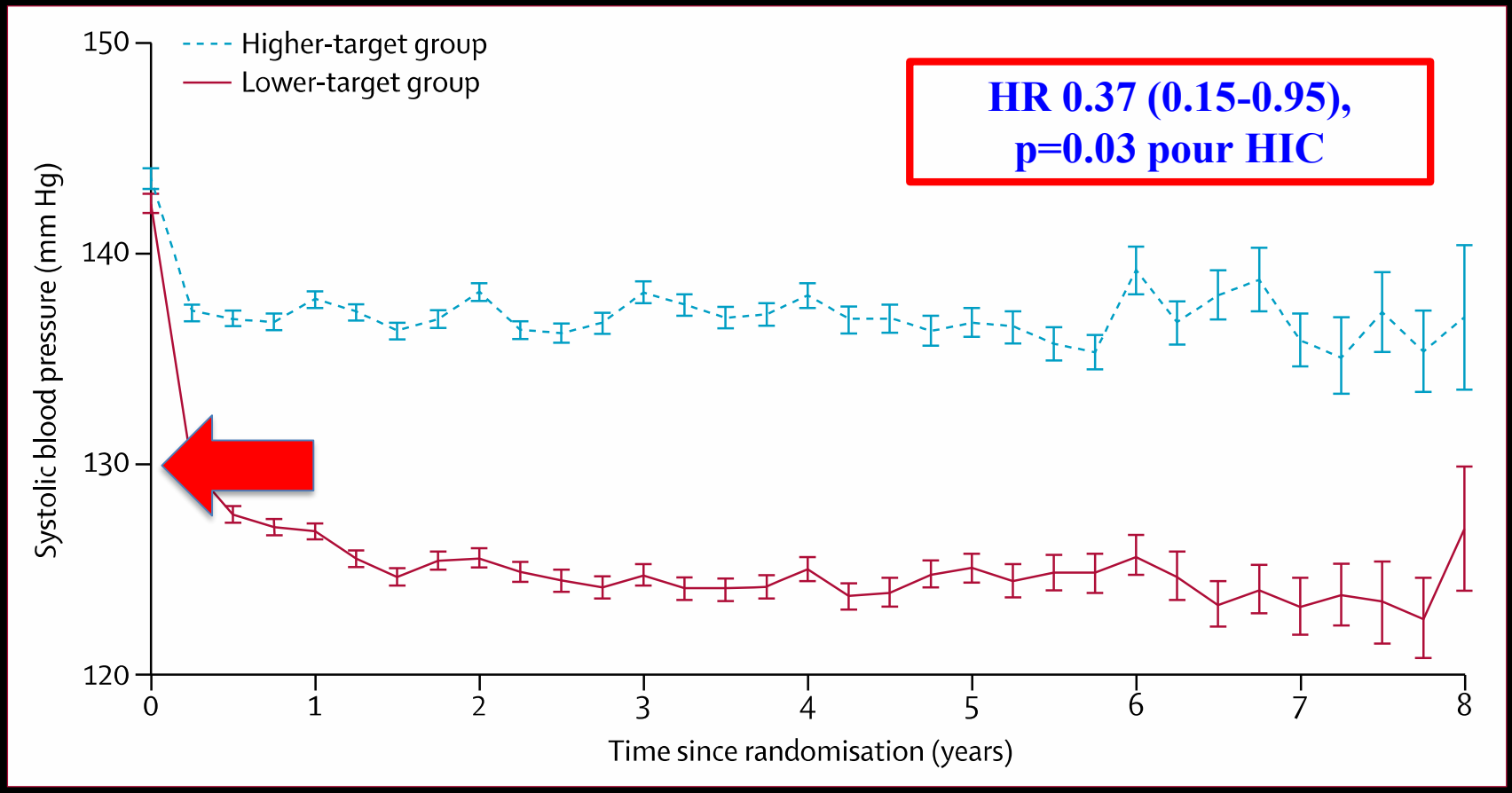
PROGRESS: Réduction de la TA diminue le risque d'HIC



Réduction TA moyenne: 12 mmHg/5 mmHg

Progress investigators. Lancet 2001;358:9297:1033-41

SPS3: Réduction TA intesive (<130 mmHg) bénéfique pour la prévention d'HIC

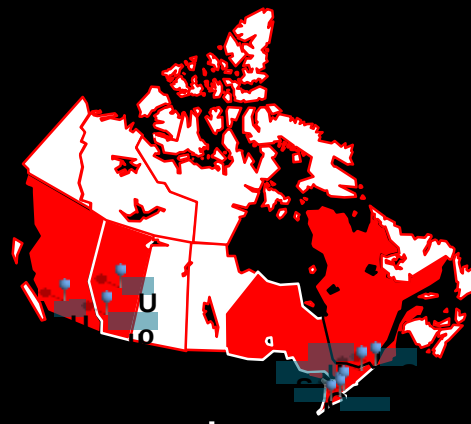



• Études observationelles
• Échantillons de petite taille
• Possible bias de selection

Ongoing recruitment in OAC after ICH RCTs

Acronym	Sites	Patients	Target sample
APACHE-AF 	16	54	100
NASPAF-ICH 	10	16	100
SoSTART 	26	41	190
STATICH 	3	2	500
A_3ICH 	-	-	300
PRESTIGE AF 	-	-	~650
ASPIRE 	-	-	~650

NASPAF-ICH



NOAC (n=67)

N=100

Main in

High risk A
≥2) and

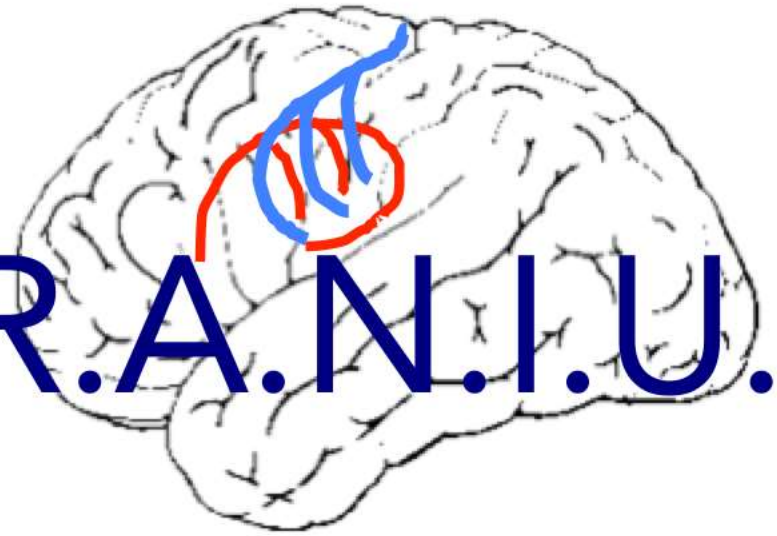
laura.gioia@umontreal.ca
Clinique neurovasculaire CHUM
Fax: 514-412-7711

ate

Last participant followed: 6 months

Total study duration: ~ 3 years
Mean follow-up per participant: 12 months (range 6 - 30 months)

Special procedure: MRI at study entry for post-hoc risk stratification according to burden of CSVD and end study for accrual of CMBs and covert infarcts



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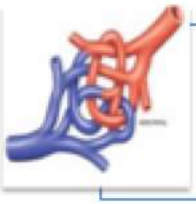
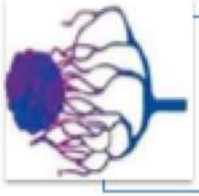
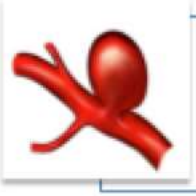


Malformation artérioveineuses
Fistules durales



Cavernomes



Anévrismes familiaux

Moyamoya

SYMPTOMATOLOGIE

- AVC hémorragique
- Épilepsie
- Déficit neurologique
- AVC ischémique
- Céphalée chronique
- Asymtomatique

PRISE EN CHARGE

- Multidisciplinaire
- Suivi spécialisé
- Interventionnel
- Non-interventionnel

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Centre de **R**éférence des **A**nomalies **N**eurovasculaIres rares du Centre Hospitalier de l'**U**niversité de **M**ontréal

Réunion Multidisciplinaire

Neurovasculaire
- Dr Grégory JACQUIN
- Dr Christian STAPF

Neuroradiologie:
- Dr Jean RAYMOND
- Dr Daniel ROY
- Dr Alain WEILL

Neurochirurgie
- Dr Michel BOJANOWSKI
- Dr Chiraz CHAALALA
- Dr Mouiahed LABIDI

Radiothérapie
- Dr Jean-Paul BAHARY
- Dr Cynthia MÉNARD
- Dr David ROBERGE

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MERCI
QUESTIONS?