

SESSION « Le duo Rythmologue & Neurologue : Optimisation du diagnostic des AVC cryptogéniques »

Embolic Stroke of Undetermined Source : Définition et comment aller plus loin

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Avec le soutien institutionnel des laboratoires

Medtronic



Embolic Stroke of Undetermined Source : Définition et comment aller plus loin

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Quelle définition?

Indéterminé

Classification TOAST

Large-artery atherosclerosis (embolus/thrombosis)*
Cardioembolism (high-risk/medium-risk)*
Small-vessel occlusion (lacune)*
Stroke of other determined etiology*

Stroke of undetermined etiology

- Two or more causes identified
- Negative evaluation
- Incomplete evaluation

***Définition d'une évaluation
incomplète ?***

Cryptogénique

Diagnostic criteria

*Cryptogenic ischaemic stroke**

- No arterial stenosis (>50%) or occlusion coupled with non-lacunar infarct on imaging
- No clinical lacunar syndrome if imaging shows no infarct or small (<1.5 cm) subcortical infarct
- No major-risk or medium-risk cardioembolic sources

ESUS

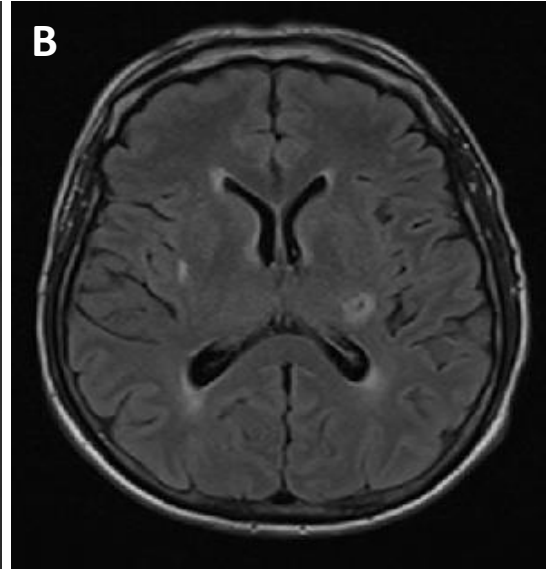
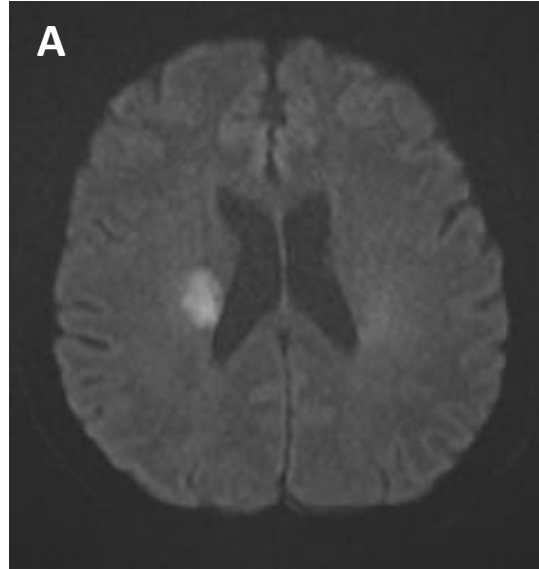
***Panel 2: Criteria for diagnosis of embolic stroke of
undetermined source****

- Stroke detected by CT or MRI that is not lacunar†

Quelle définition?

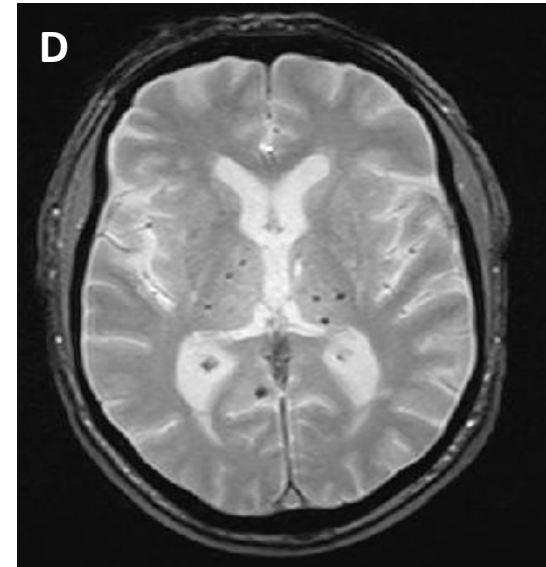
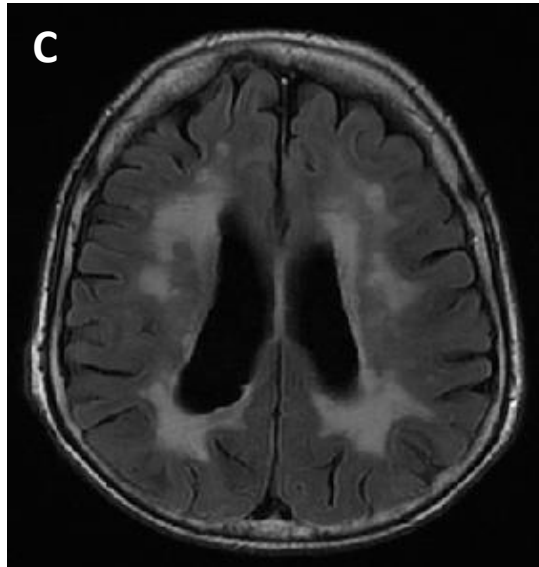
Infarctus par microangiopathie

Infarctus
< 20 mm



Lacunes

Leuco-
encéphalopathie



Micro-
hémorragies

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ESUS

Panel 2: Criteria for diagnosis of embolic stroke of undetermined source*

- Stroke detected by CT or MRI that is not lacunar†
- Absence of extracranial or intracranial atherosclerosis causing ≥50% luminal stenosis in arteries supplying the area of ischaemia
- No major-risk cardioembolic source of embolism‡

Quelle définition?

ESUS

High-risk sources

Mechanical prosthetic valve
Mitral stenosis with atrial fibrillation
Atrial fibrillation (other than lone atrial fibrillation)
Left atrial/atrial appendage thrombus
Sick sinus syndrome
Recent myocardial infarction (<4 weeks)
Left ventricular thrombus
Dilated cardiomyopathy
Akinetic left ventricular segment
Atrial myxoma
Infective endocarditis

Medium-risk sources

Mitral valve prolapse
Mitral annulus calcification
Mitral stenosis without atrial fibrillation
Left atrial turbulence (smoke)
Atrial septal aneurysm
Patent foramen ovale
Atrial flutter
Lone atrial fibrillation
Bioprosthetic cardiac valve
Nonbacterial thrombotic endocarditis
Congestive heart failure
Hypokinetic left ventricular segment
Myocardial infarction (>4 weeks, <6 months)

Minor-risk potential cardioembolic sources*

Mitral valve

- Myxomatous valvulopathy with prolapse
- Mitral annular calcification

Aortic valve

- Aortic valve stenosis
- Calcific aortic valve

Non-atrial fibrillation atrial dysrhythmias and stasis

- Atrial asystole and sick-sinus syndrome
- Atrial high-rate episodes
- Atrial appendage stasis with reduced flow velocities or spontaneous echodensities

Atrial structural abnormalities

- Atrial septal aneurysm
- Chiari network

Left ventricle

- Moderate systolic or diastolic dysfunction (global or regional)
- Ventricular non-compaction
- Endomyocardial fibrosis

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ESUS

Panel 2: Criteria for diagnosis of embolic stroke of undetermined source*

- Stroke detected by CT or MRI that is not lacunar†
- Absence of extracranial or intracranial atherosclerosis causing $\geq 50\%$ luminal stenosis in arteries supplying the area of ischaemia
- No major-risk cardioembolic source of embolism‡
- No other specific cause of stroke identified (eg, arteritis, dissection, migraine/vasospasm, drug misuse)

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Définition d'une évaluation incomplète ?

Cryptogénique

Diagnostic criteria

Une définition...des bilans...

Scanner + ETT + ECG + EDTSA + NFS....

VS

IRM + ETT/ETO + ECGLD + Angioscanner TSA + Bio

ESUS

Panel 2: Criteria for diagnosis of embolic stroke of undetermined source*

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Bilan des études

AOD NON supérieurs à l'Aspirine

TABLE 1 Annualized Rates and HRs of the Main Outcomes in the NAVIGATE ESUS and RE-SPECT ESUS Trials

	NAVIGATE ESUS			RE-SPECT ESUS		
	Rivaroxaban (n = 3,609)	Aspirin (n = 3,604)	HR (95% CI)	Dabigatran (n = 2,695)	Aspirin (n = 2,695)	HR (95% CI)
	Annualized Rate % (Events)	Annualized Rate % (Events)		Annualized Rate % (Events)	Annualized Rate % (Events)	
Any stroke	5.1 (171)	4.7 (158)	1.08 (0.87-1.34)	4.1 (177)	4.8 (207)	0.85 (0.69-1.03)
Ischemic stroke	4.7 (158)	4.7 (156)	1.01 (0.81-1.26)	4.0 (172)	4.7 (203)	0.84 (0.60-1.03)
Major bleeding	1.8 (62)	0.7 (23)	2.72 (1.68-3.39)	1.7 (77)	1.4 (64)	1.19 (0.85-1.66)
Intracranial hemorrhage	0.6 (20)	0.1 (5)	4.02 (1.51-10.70)	0.7 (32)	0.7 (32)	0.98 (0.60-1.60)

ESUS ≠ FA

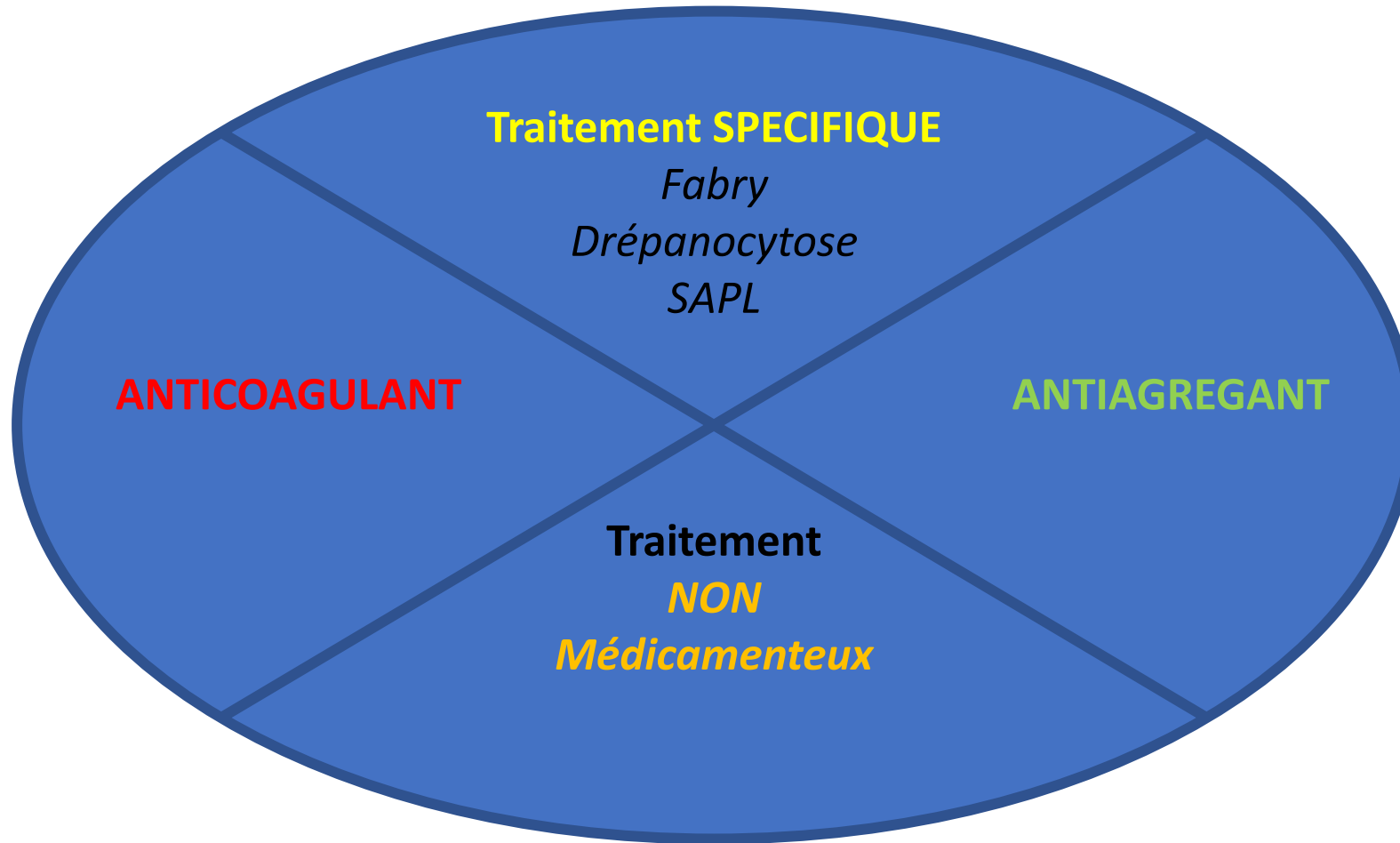
65/75 % de patients SANS FA

Patient subgroup	N	AF DETECTION RATE AFTER 3 YRS OF ICM
RESPECT ESUS ELIGIBLE	118	34%
NAVIGATE-ESUS ELIGIBLE	91	36%
NON-ESUS CS	100	24%

Classification of recurrent ischemic stroke	Classifiable recurrent ischemic stroke, No. (%) (n = 270) ^a
ESUS	156 (58)
Non-ESUS	
Atherosclerosis	26 (10)
Cardioembolism	37 (14)
Lacunar	35 (13)
Other specific causes	16 (6)
Insufficient diagnostic evaluation	NA

ESUS: Une entité Hétérogène...

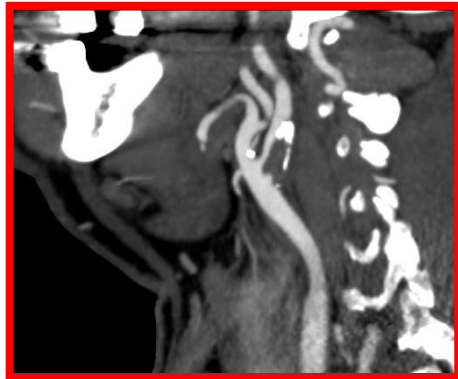
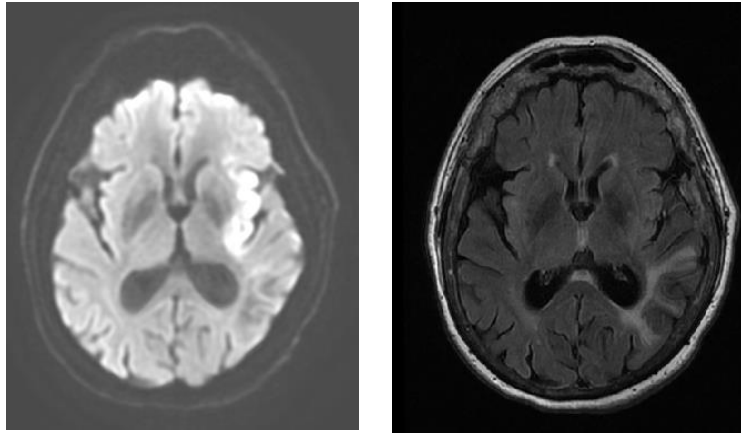
Des thérapies à cibler



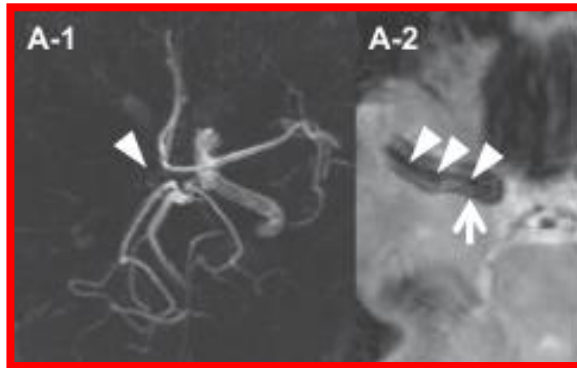
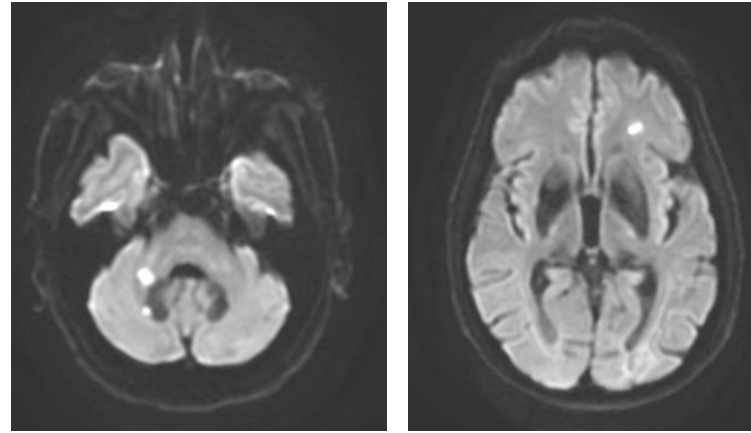
Optimiser le bilan étiologique !

Imagerie et Histologie

Macroangiopathie



Cardio-embolique



Etat procoagulant

Thrombus Histology Suggests Cardioembolic Cause in Cryptogenic Stroke

Boeckh-Behrens et al ; Stroke 2016

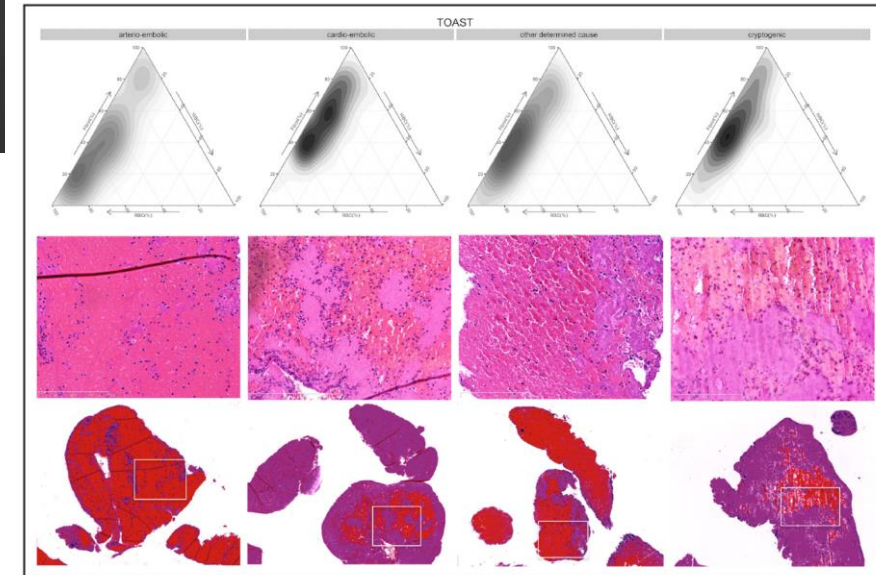
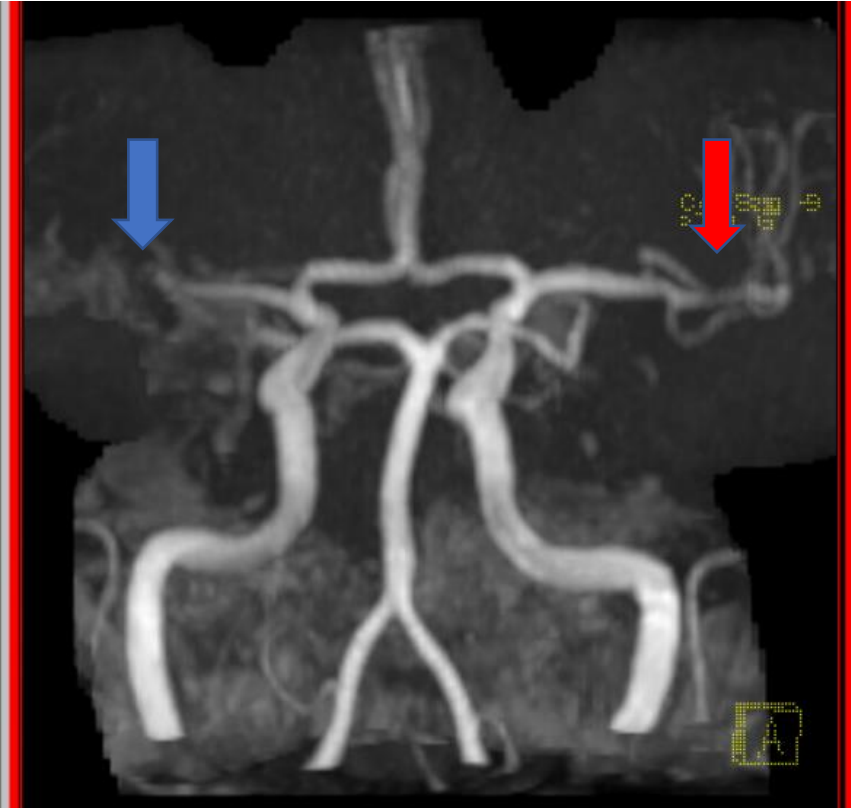
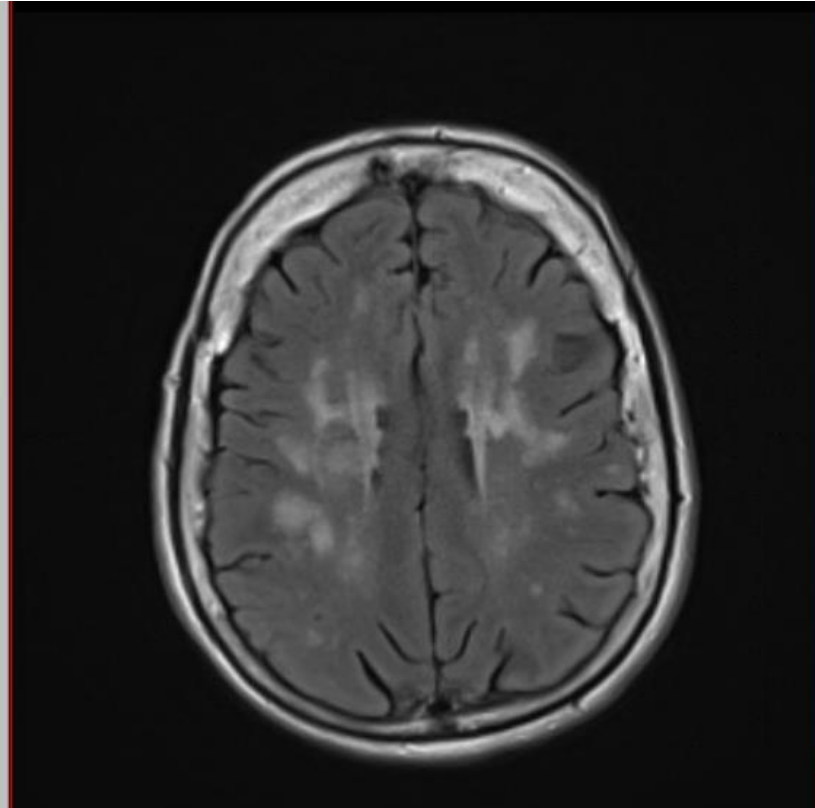
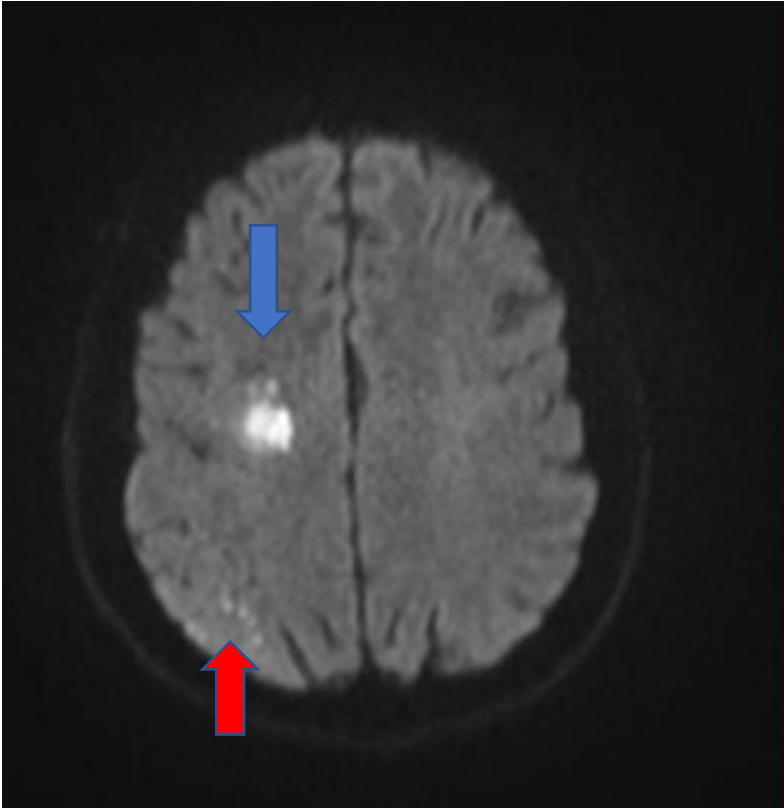


Figure 1. Top. The triangle graphs show similar distributions of the 3 main thrombus components—red blood cells (RBCs), fibrin/platelet, and white blood cells (WBCs)—in Trial of Org 10172 in Acute Stroke Treatment (TOAST) groups 1 and 4 and in TOAST groups 2 and 5, respectively. Dark areas represent higher concentrations of the respective component. **Middle and bottom.** The lower row shows 1 thrombus example of each of the respective TOAST groups (magnification, $\times 50$; the components are segmented for better visualization of thrombus organization). Red color represents RBCs; purple regions represent fibrin; and blue dots represent WBCs. **Middle.** The boxes outlined in the lower row are shown in original hematoxylin and eosin staining at $\times 200$ magnification.

Avez-vous utilisé le bon panel d'investigation ?

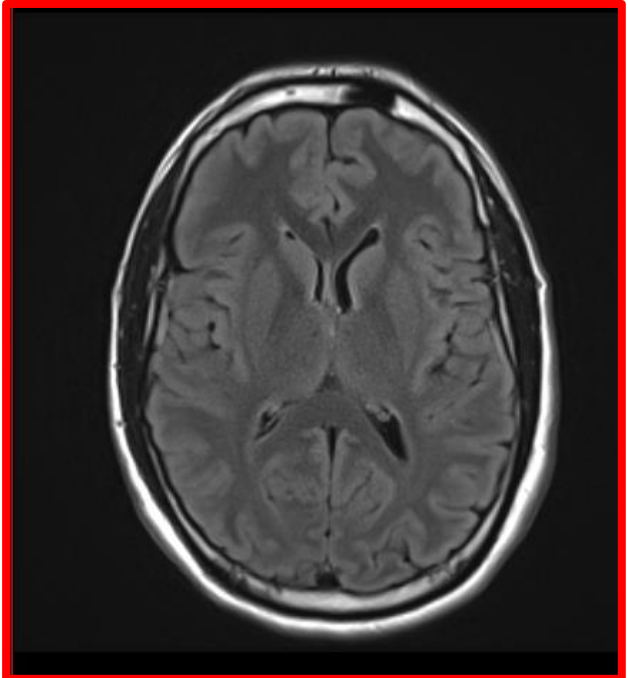
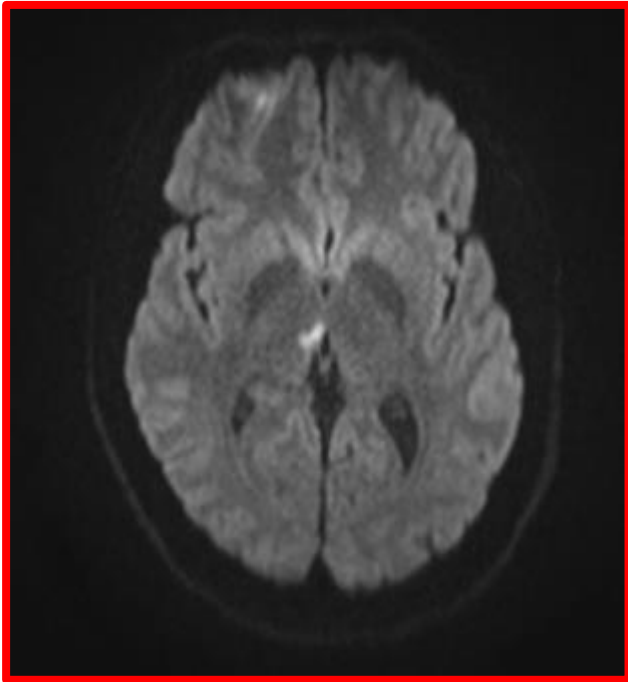
IRM en 1ere intention !!!

US n'excluent pas les sténoses intracrâniennes distales

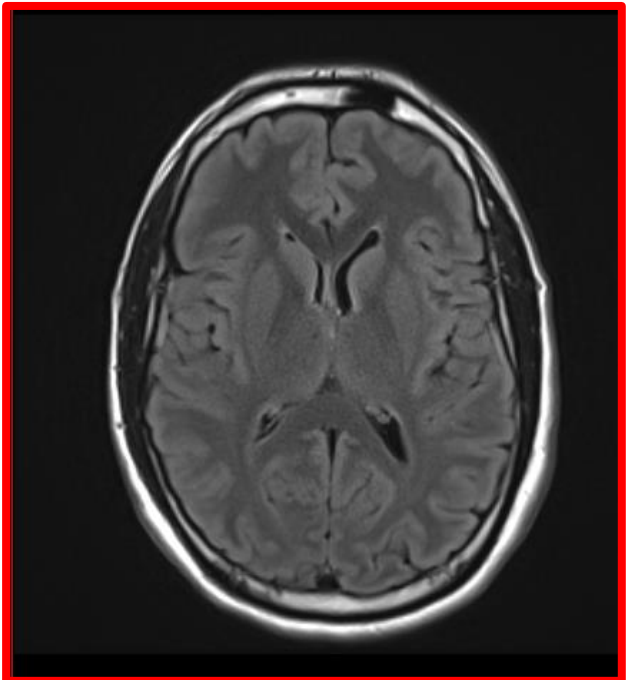
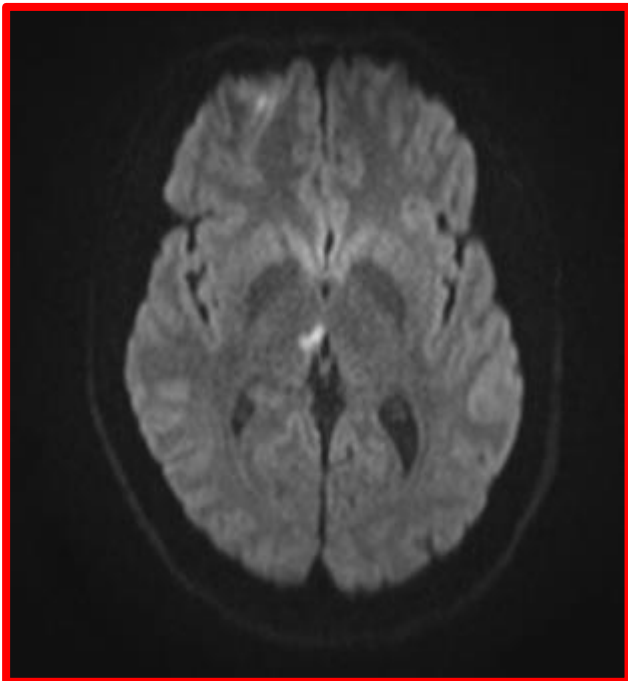


78 ans
Paralysie faciale gauche
ATCDS: Hypertension, Diabète

Exploration optimale des vaisseaux?

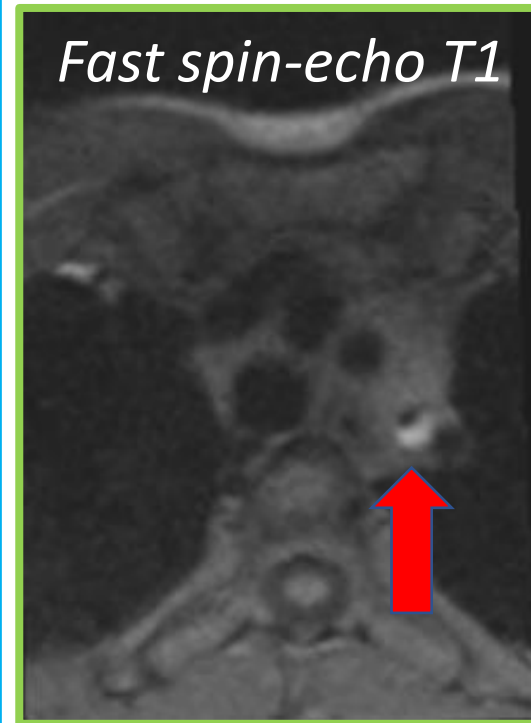


33 ans
Douleurs cervicales depuis 1 sem
Diplopie transitoire
Absence de facteurs de risque vasculaire

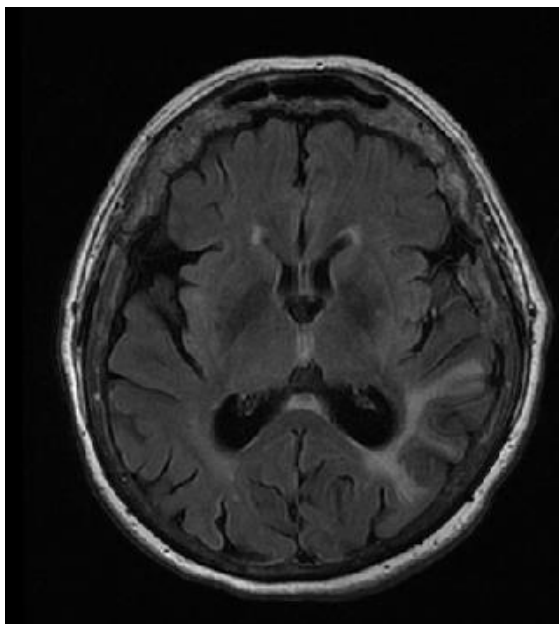
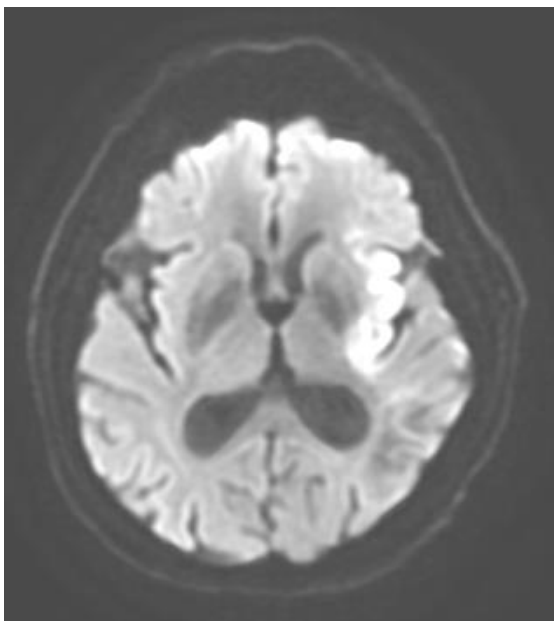


***Exploration
optimale des
vaisseaux?***

Fast spin-echo T1

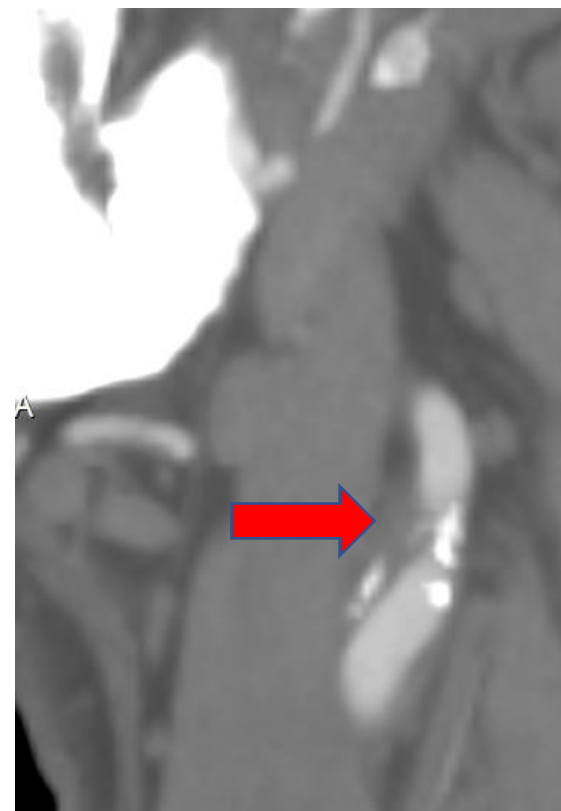
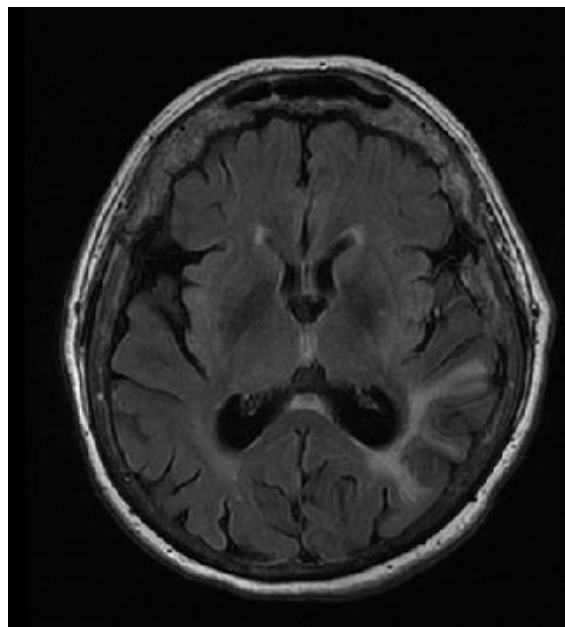
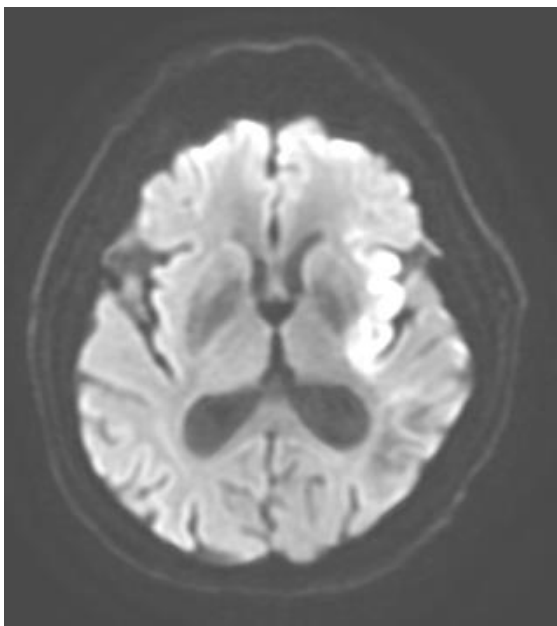


***Utilisation optimale
des séquences ?***



***L'imagerie utilisée
est elle fiable ?***

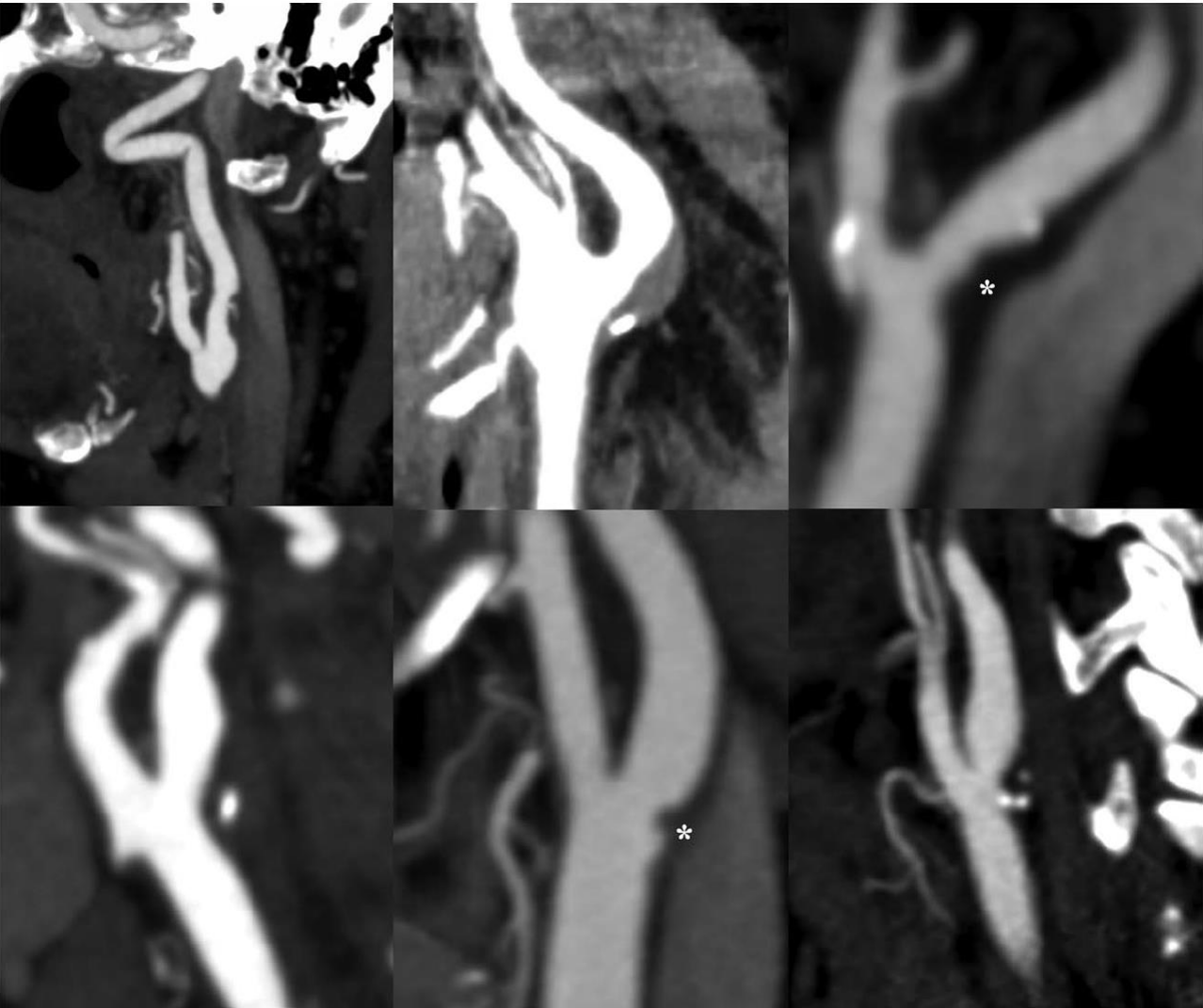
63 ans
Déficit moteur droit
Antécédents:
Coronaropathie
Dyslipidémie
Tabagisme actif
Hypertension
Diabète



Prevalence of Ipsilateral Nonstenotic Carotid Plaques on Computed Tomography Angiography in Embolic Stroke of Undetermined Source

Ospel et al ; Stroke 2020

20 à 30 %



Non-ESUS (n=616 carotid arteries)		
Ipsilateral stroke	Yes	No
Nonstenotic carotid plaque (Yes), n (%)	47 (15.3)	45 (14.6)
Nonstenotic carotid plaque (No), n (%)	261 (84.7)	263 (85.4)
Total, n (%)	308 (100)	308 (100)
ESUS (n=276 carotid arteries)		
Ipsilateral stroke	Yes	No
Nonstenotic carotid plaque (Yes), n (%)	40 (29.2)	26 (18.7)
Nonstenotic carotid plaque (No), n (%)	97 (70.8)	113 (81.3)
Total, n (%)	137* (100)	139* (100)

P=0.821 and 0.041 for the non-ESUS and ESUS population, respectively. ESUS indicates embolic stroke of undetermined source.

Identifier les plaques à haut risque embolique

Large but Nonstenotic Carotid Artery Plaque in Patients
With a History of Embolic Stroke of Undetermined Source

Komatsu et al ; Stroke 2018

Epaisseur de plaque $\geq 1,5$ mm

Morphologie de plaque
Hypoéchogène; Hétérogène
Ulcération; Mobile

Embolic Stroke of Undetermined Source and Carotid Intraplaque
Hemorrhage on MRI

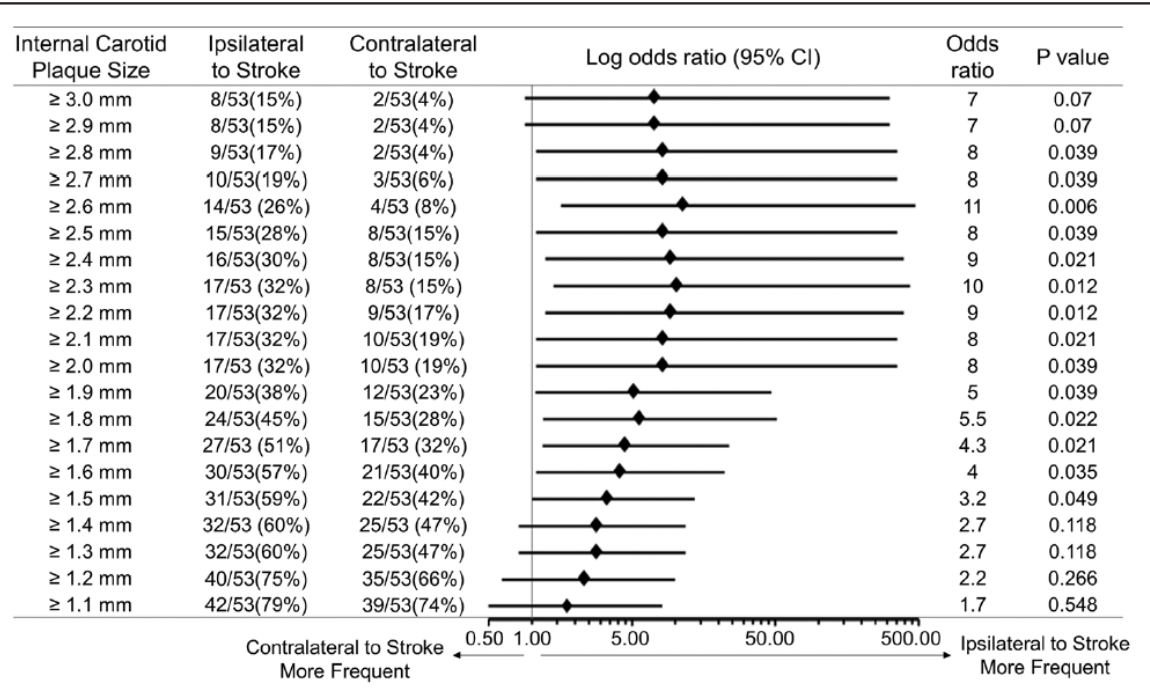
Mark et al., Clin Neuroradiol 2020

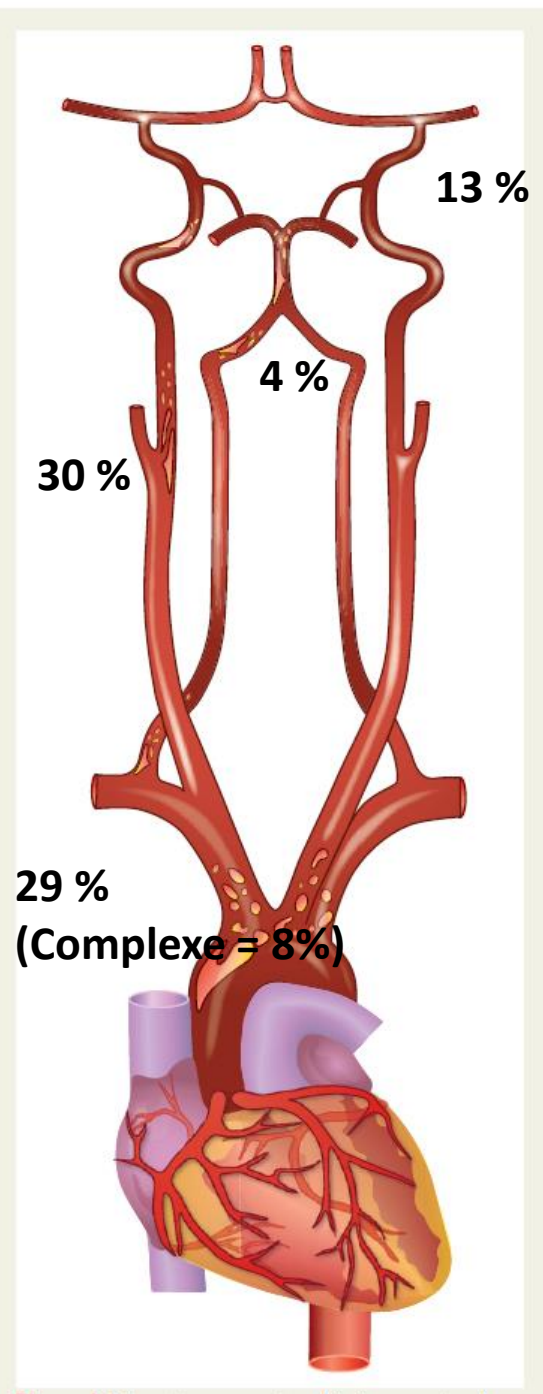
Prévalence IPH ipsilatérale = 25,6 %

Comparaison ipsi vs controlatérale

OR = 6,29

Sténose < 50 % IPH+ = 9% évènement annuels
Sténose < 50 % IPH- = 0,7% évènement annuels
Schindler et al., JACC 2020





Supracardiac atherosclerosis in embolic stroke of undetermined source: the underestimated source

Ntaios et al ; Eur Heart J 2020

Ultrasound

Widely available, accurate and reproducible for plaque measurement. Less useful for the assessment of intraplaque haemorrhage, lipid-rich necrotic core or fibrous cap. The presence of calcification may cause acoustic shadowing

MRA

Reliable for the assessment of ulceration (preferably with contrast enhancement)

MRI

The optimal imaging method to assess intraplaque haemorrhage, lipid-rich necrotic core and fibrous cap (especially on contrast-enhanced T1). It has good reproducibility and wide validation.

CTA

The optimal imaging method for the assessment of ulceration (preferably with contrast enhancement)

CT

The optimal imaging method to assess calcification. It is not reliable for the assessment of intraplaque haemorrhage, lipid-rich necrotic core or fibrous cap.

¹⁸F-FDG PET/CT

The optimal imaging method to assess plaque inflammation. The radiation dose and its limited availability are the main disadvantages.

Angio-IRM

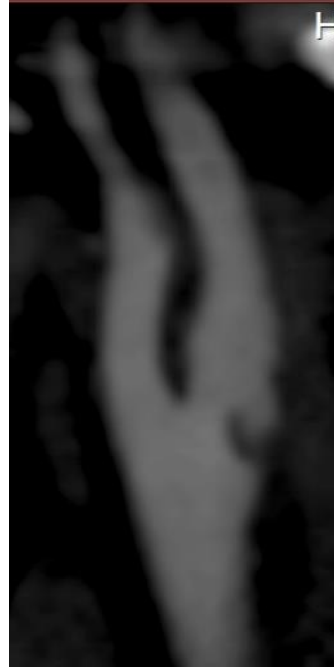
Angio-TDM

EDTSA

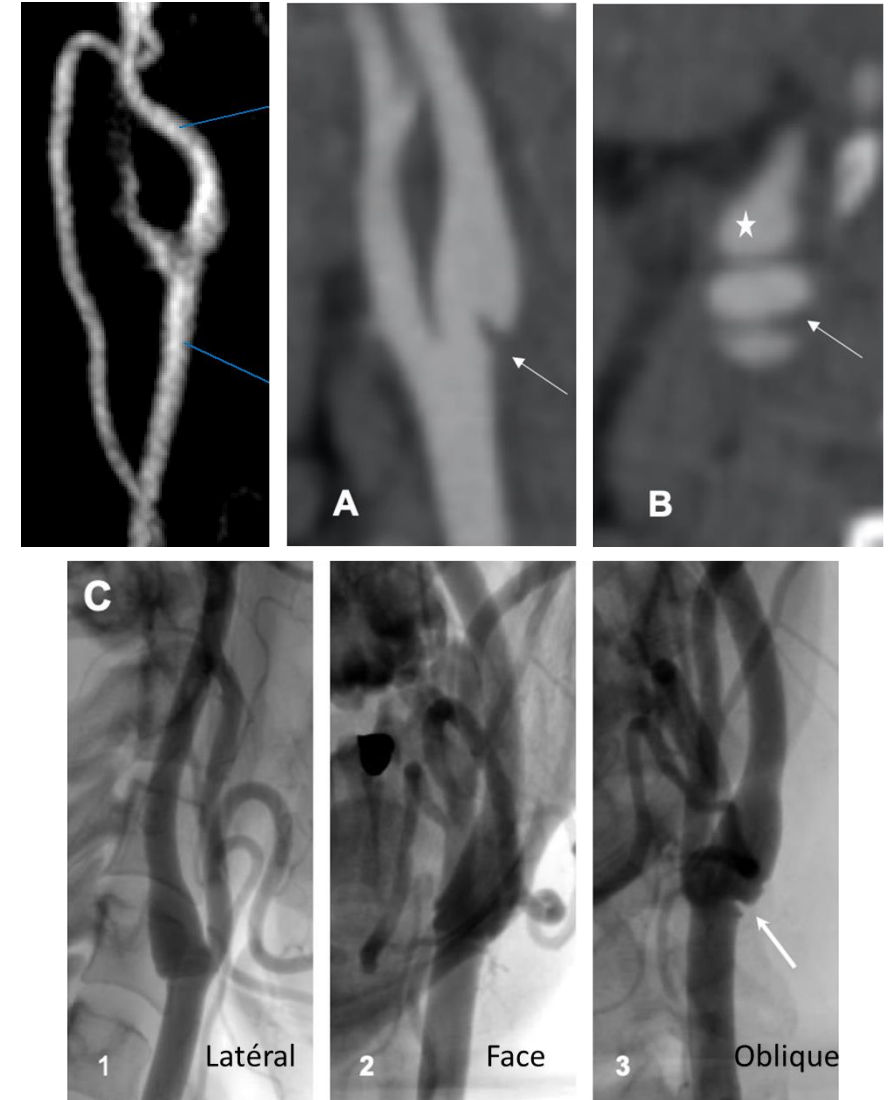
IRM de plaque
TEP-18FDG

Web Carotidien

- ✓ Forme monofocale de dysplasie intimale entraînant une sténose non circonférentielle
- ✓ Localisée à l'origine de la bifurcation carotidienne en miroir par rapport au départ de la carotide externe
- ✓ Bilatéral dans un peu plus d'1 cas sur 4
- ✓ Age moyen du 1^{er} AIC: 46 ans, prédominance féminine 66%
- ✓ Prédisposition génétique (Afro-Caribéen et Afro-Américain) 58% des cas rapportés
- ✓ Présence population générale (peu de données) 2.3%, mais 7% en Martinique



Difficultés diagnostiques



Carotid artery webs in embolic stroke of undetermined source with large intracranial vessel occlusion

Labeyrie et al ; Int J Stroke 2020

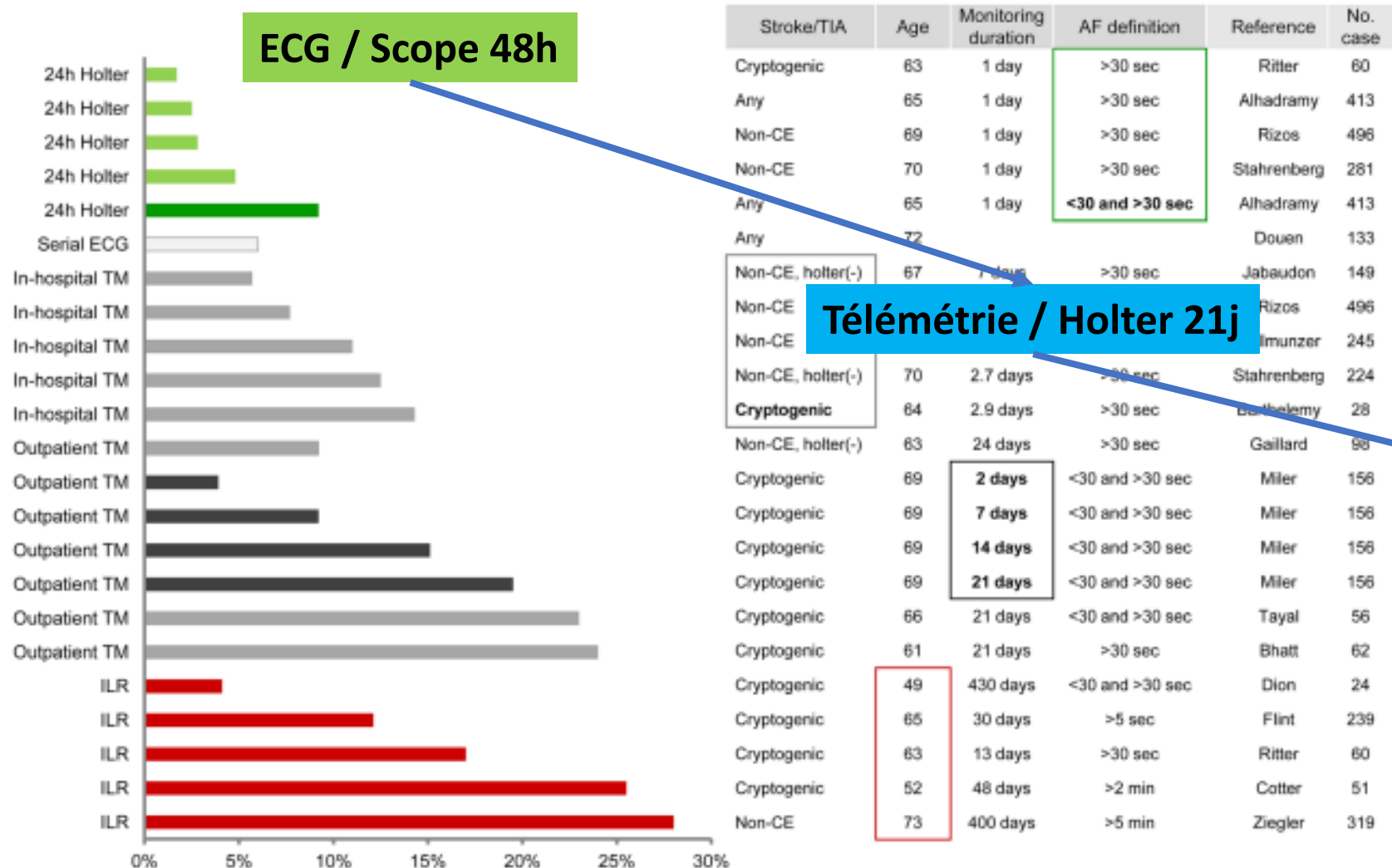
	Total N = 466	Non-ESUS N = 410	ESUS N = 56	P value
Age, years	67 (54–78)	69 (56–79)	54 (43–67)	<0.001
Female, n (%)	228 (49%)	198 (48%)	30 (54%)	0.48
Tobacco, n (%)	130 (28%)	115 (28%)	15 (27%)	1
High blood pressure, n (%)	256 (55%)	242 (59%)	14 (25%)	<0.001
Dyslipidemia, n (%)	177 (38%)	164 (40%)	13 (23%)	0.018
Diabetes, n (%)	93 (20%)	87 (21%)	6 (11%)	0.07
Ipsilateral WEB, n (%)	9 (1.9%)	3 (0.7%)	6 (10.7%)	<0.001
Contralateral WEB, n (%) ^a	7 (2.0%)	6 (1.9%)	1 (2.4%)	0.6
Ipsilateral other abnormality, n (%) ^b	109 (23%)	103 (25%)	6 (11%)	0.017

Récidives sous antithrombotiques => Stenting ?

Traquer la FA avec les moyens adaptés...

Evaluation of Cryptogenic Stroke With Advanced Diagnostic Techniques

Oh Young Bang, MD, PhD; Bruce Ovbiagele, MD; Jong S. Kim, MD, PhD



Détection de FA en fonction de la durée d'enregistrement:
≤ 72 heures : 5.1%
≥ 7 jours: 15%
≥ 3 mois: 29.15%

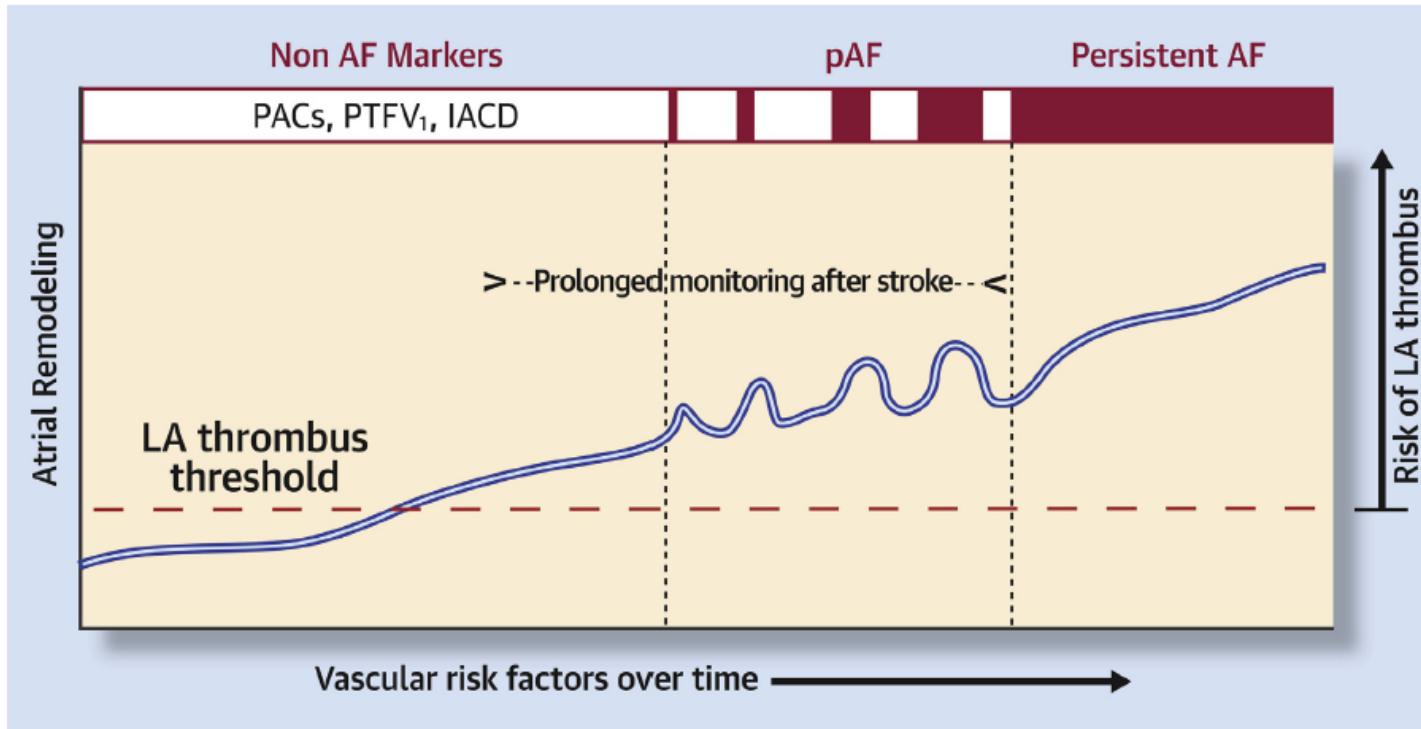
Holter Implantable (Link)

Implantable cardiac monitors to detect atrial fibrillation after cryptogenic stroke

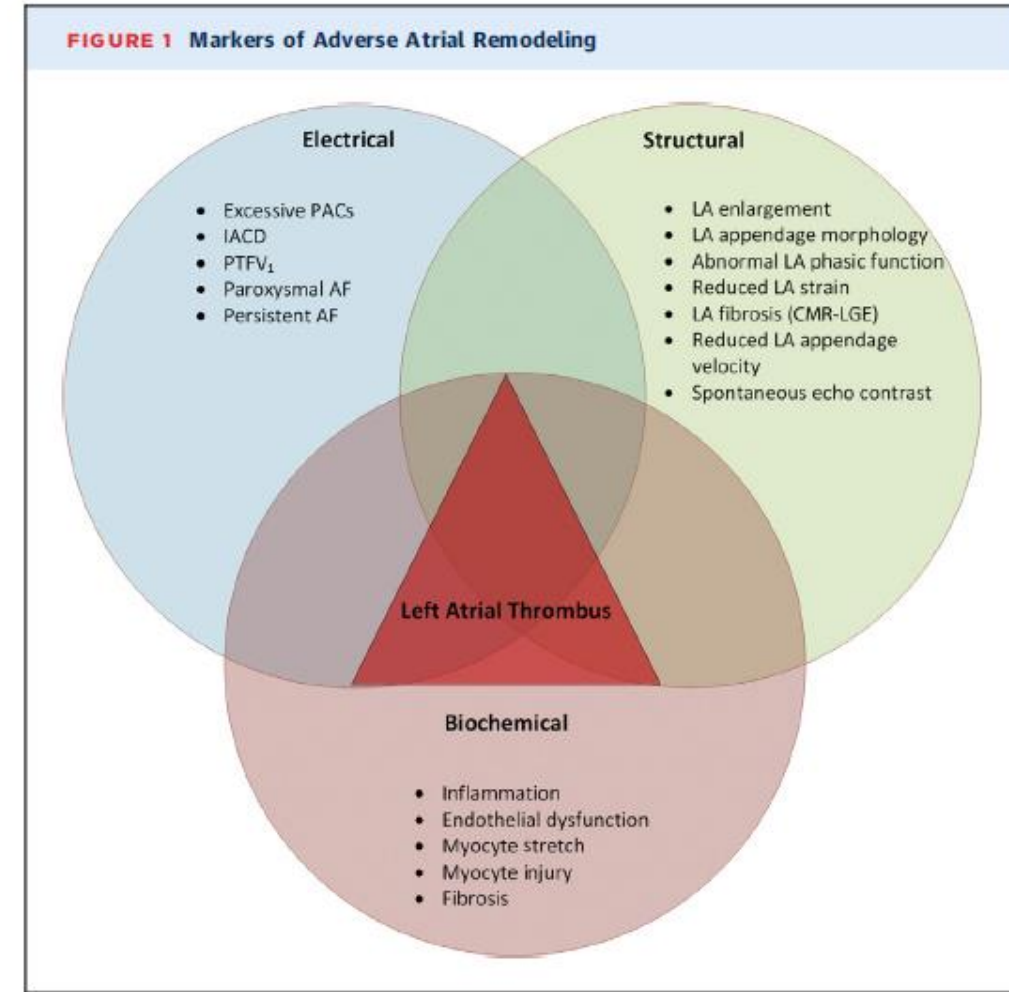
The Atrium and Embolic Stroke

Myopathy Not Atrial Fibrillation as the Requisite Determinant?

Sajeev et al ; JACC 2020



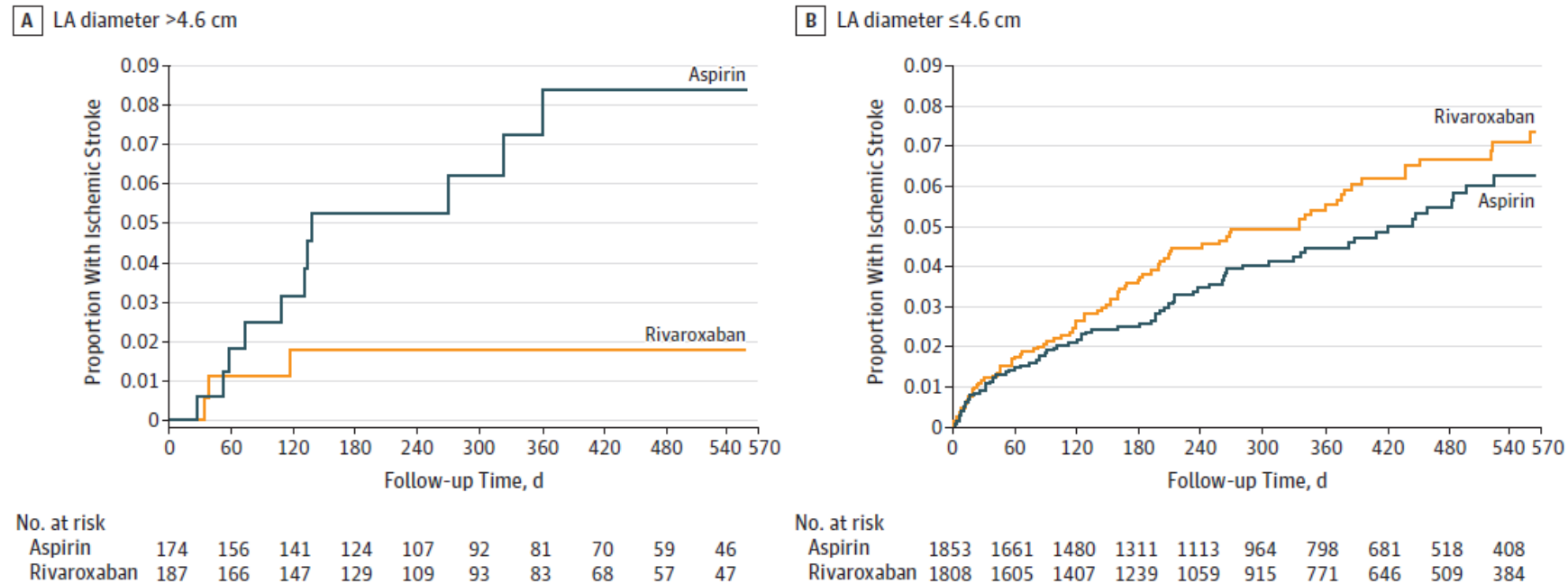
Sajeev, J.K. et al. J Am Coll Cardiol EP. 2020;6(3):251-61.



Recurrent Stroke With Rivaroxaban Compared With Aspirin According to Predictors of Atrial Fibrillation Secondary Analysis of the NAVIGATE ESUS Randomized Clinical Trial

Healey et al ; JAMA Neurol 2019

Figure 2. Kaplan-Meier Curves for Time to First Ischemic Stroke



Patients with left ventricular diameter more than 4.6 cm (A) and 4.6 cm or less (B).

Non significatifs:

HAVOC, Age, Atrial Premature Beats, Critères combinés atriopathie

De l'Auricule au Ventricule ?

Association Between Left Ventricular Ejection Fraction, Wall Motion Abnormality, and Embolic Stroke of Undetermined Source

Ramasamy et al ; J Am Heart Asso 2019

	Odds Ratio	95% CI	P Value
Primary analysis*			
LVEF and ESUS	1.0 [†]	1.0 to 1.1	0.6
LV wall motion abnormality and ESUS	0.9	0.5 to 1.6	0.7
Secondary analysis[‡]			
LVEF and ESUS	1.2 [†]	1.0 to 1.5	0.04
LV wall motion abnormality and ESUS	1.6	0.4 to 6.5	0.5

Left Heart Factors in Embolic Stroke of Undetermined Source in a Multiethnic Asian and North African Cohort

Kamran et al., J Am Heart Assoc 2020

ESUS in Comparison With Cardioembolic Stroke 656 vs 532		
Variable	aOR (95% CI)	P Value
Age	0.98 (0.97–0.99)	0.001
Hypertension	0.81 (0.55–1.19)	0.29
Diabetes mellitus	0.59 (0.42–0.81)	0.001
Dyslipidemia	1.30 (0.93–1.81)	0.12
Smoking	0.92 (0.58–1.45)	0.71
CAD	1.001 (0.72–1.39)	0.99
LAVI	0.98 (0.97–0.99)	0.004
LVDD grade I	1.50 (1.12–2.03)	0.009
LVDD grades II+III	2.90 (1.30–6.32)	0.009
HFrEF	0.70 (0.43–1.17)	0.18
HFmrEF	0.70 (0.39–1.26)	0.24
HFpEF	1.12 (0.47–2.65)	0.81
LVMI	1.006 (1.00–1.01)	0.77
LVWMAs	3.13 (1.95–5.01)	0.001
Global hypokinesia	1.36 (0.73–2.53)	0.34

ESUS in Comparison With Noncardioembolic Stroke 656 vs 1348		
Variable	aOR (95% CI)	P Value
Age	0.988 (0.97–0.99)	0.04
LAVI	1.00 (0.99–1.02)	0.38
EF	1.00 (0.98–1.02)	0.89
LVMI	1.00 (0.99–1.00)	0.19
CHA ₂ DS ₂ VAS _C	1.04 (0.90–1.22)	0.53
Diabetes mellitus	0.83 (0.62–1.12)	0.24
Smoking	0.85 (0.58–1.25)	0.42
Mitral calcification	1.26 (0.90–1.77)	0.18
LVDD grade I DD	0.97 (0.96–0.98)	0.073
LVDD grade II+III DD	2.15 (1.07–4.31)	0.001
LVWMAs	7.14 (4.44–10.87)	0.001
Global hypokinesia	3.72 (1.98–7)	0.001

Quel apport de l'ETO ?

ECHOCARDIOGRAPHY (JM GARDIN AND AH WALLER, SECTION EDITORS)



Role of Echocardiography in Assessment of Cardioembolic Sources: a Strong Diagnostic Resource in Patients with Ischemic Stroke

Table 1 Accuracy of 2D transthoracic and transesophageal echocardiography and 3D echocardiography in various clinical settings

	2D TTE	2D TEE	3D echocardiography
Atrial fibrillation	+	+++	+++
Infective endocarditis	++	+++	++
Cardiac tumors	++	+++	+
LV thrombus	+++	+	+
Prosthetic valve thrombosis	+	+++	+++
Aortic atherosclerosis	+	+++	++
Patent foramen ovale	+	+++	+

+ = denotes low accuracy; ++ = medium accuracy; +++ = high accuracy

LV denotes left ventricular

The value of transesophageal echocardiography for embolic strokes of undetermined source

	No. of patients (% [95% CI]) ^a
TEE findings	
LA enlargement	4 (6.5 [2.1-16.1])
LA thrombus	1 (1.6 [0-9.5])
Vegetations	2 (3.2 [0-11.8])
PFO	17 (27.8 [18.1-40.2])
ASA	8 (13.1 [6.5-24.1])
PFO + ASA	4 (6.5 [2.1-16.1])
Myxoma	0 (0 [0-5.1])
VSD	0 (0 [0-5.1])
Fibroelastoma	1 (1.6 [0-9.5])
Complex aortic arch atheroma	4 (6.5 [2.1-16.1])
Change in management	
Anticoagulation therapy	5 ^b (8.1 [3.2-18.2])
PFO closure procedure	3 ^c (4.9 [1.1-14])
IV antibiotic treatment	2 (3.2 [0-11.8])

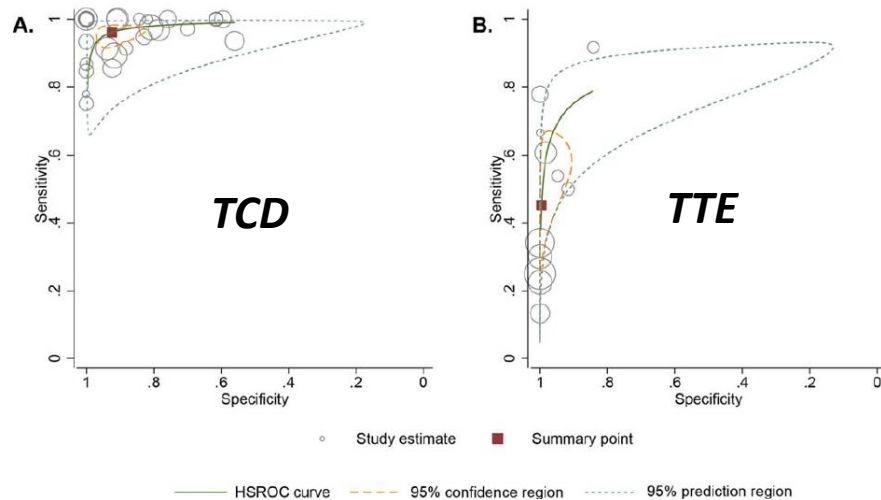
Rare...

Rare...

Anticoagulant
initiation
9 %

Optimiser l'identification du shunt droit-gauche

Transcranial Doppler versus Transthoracic Echocardiography for the Detection of Patent Foramen Ovale in Patients with Cryptogenic Cerebral Ischemia: A Systematic Review and Diagnostic Test Accuracy Meta-analysis



Sensibilité du TCD: 96,1%

Transcranial Doppler to detect right-to-left shunt in cryptogenic acute ischemic stroke

Transcranial Doppler to Detect Right to Left Communication: Evaluation Versus Transesophageal Echocardiography in Real Life

Sensibilité du TCD avec test aux bulles: 100%

European position paper on the management of patients with patent foramen ovale. General approach and left circulation thromboembolism

PFO diagnosis

To achieve the maximal accuracy in PFO diagnosis, the combined use of different techniques is warranted

Strong

A

The technique achieving the highest sensitivity should be used as a first-line investigation in PFO diagnosis

Strong

C

c-TCD has a higher sensitivity than c-TTE as a first-line investigation to detect a R-T-L shunt

Conditional

A

c-TTE has a lower sensitivity for small shunts than other techniques

Conditional

A

c-TOE should be performed by experienced operators in PFO assessment

Strong

C

A strict methodology should be used performing c-TOE

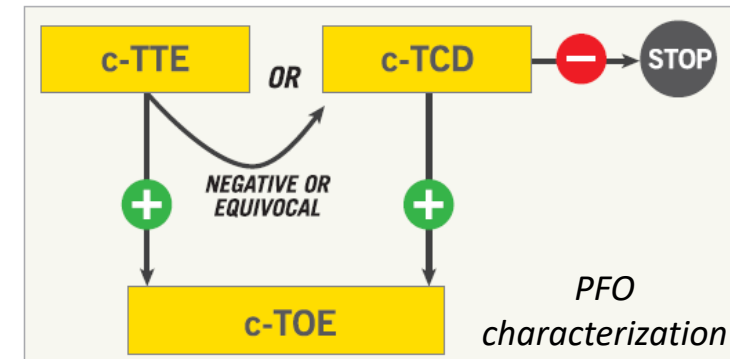
Strong

C

c-TOE should be performed to stratify the risk

Strong

C



FOP/ASIA ≠ ESUS

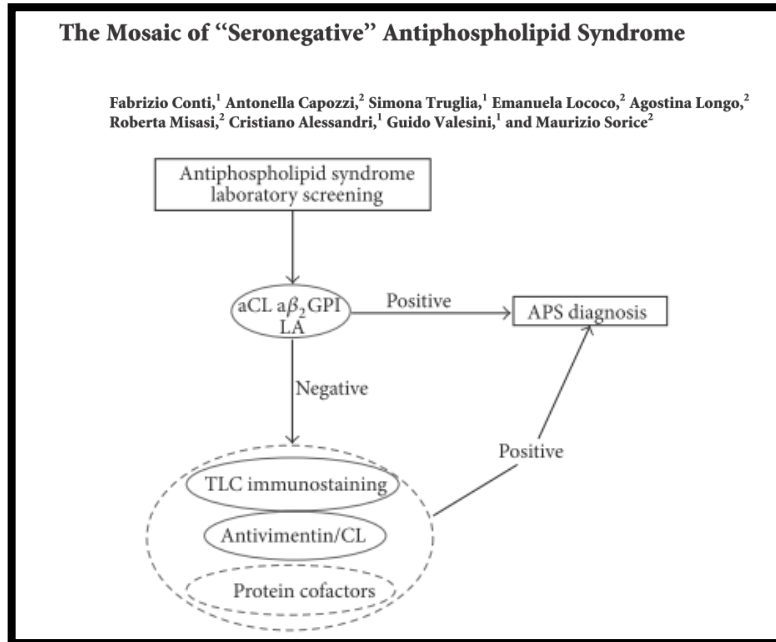
Proposal for Updated Nomenclature and Classification of Potential Causative Mechanism in Patent Foramen Ovale-Associated Stroke

Original approach to PFO		Proposed revised approach to PFO	
TOAST			
Probable	Not assignable based on PFO	Probable	Both (1) cortical/cerebellar infarct or subcortical infarct >1.5 cm in diameter and (2) PFO and straddling thrombus; or all 3 of the following: (1) cortical/cerebellar infarct or subcortical infarct >1.5 cm in diameter, (2) recent preceding or concurrent VTE, and either (3a) a large-shunt PFO present or (3b) a small-shunt PFO plus an atrial septal aneurysm present

ASCOD			
Potentially causal	Either (1a) bihemispheric or supratentorial and infratentorial territorial or cortical infarcts and signs of systemic embolism or (1b) single or no cerebral ischemic lesion and either (2a) a PFO and a thrombus in situ or (2b) a PFO and preceding PE or proximal DVT	Potentially causal	Either (1a) bihemispheric or supratentorial and infratentorial territorial or cortical infarcts and signs of systemic embolism or (1b) a single or no cerebral ischemic lesion, plus any of the following: (2a) a PFO with a thrombus in situ, (2b) a PFO plus an atrial septal aneurysm, (2c) a large-shunt PFO, or (2d) a PFO plus a recently preceding PE or proximal DVT

Etat prothrombotique

Traquer le SAPL



Evoquer les causes rares

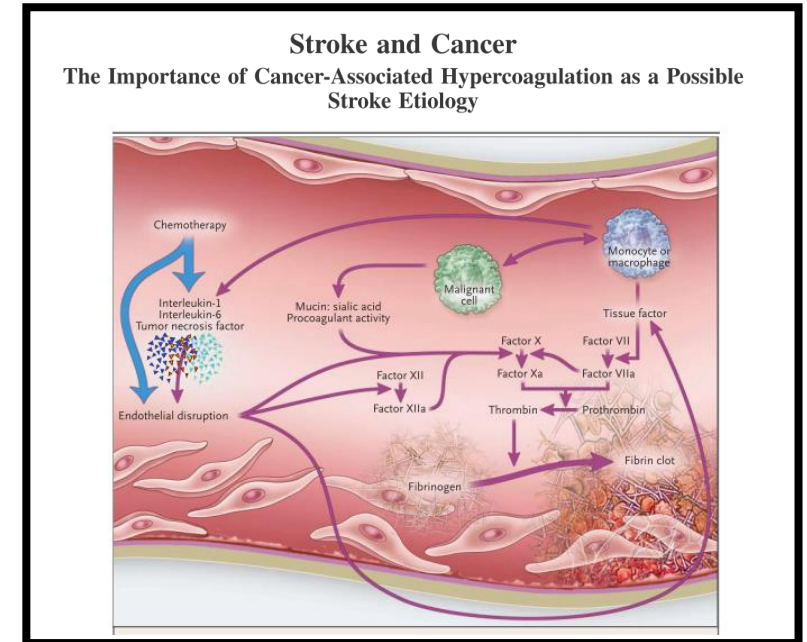
**Syndrome
myéloprolifératifs**

Déficit en ADAMT-13

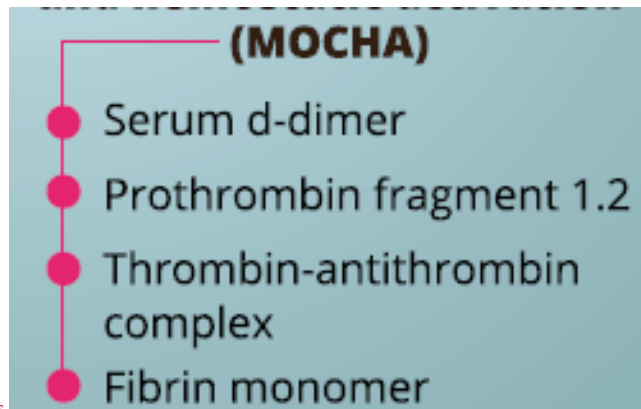
Clone HPN

...

Redouter les Cancers

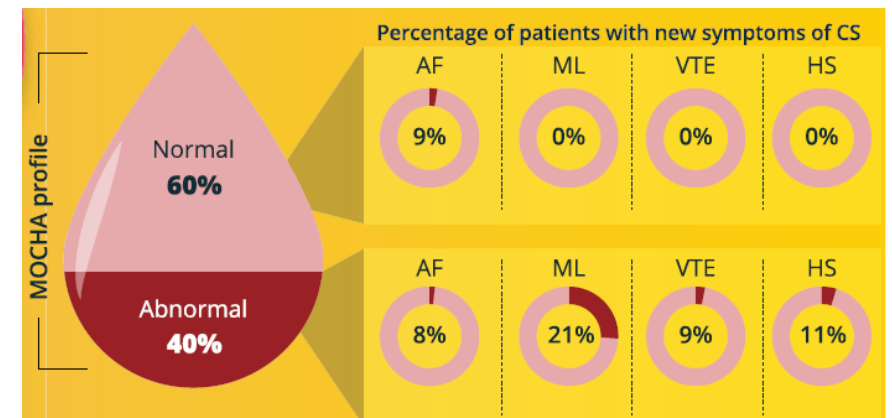


Markers Of Chronic Hemostatic Activation



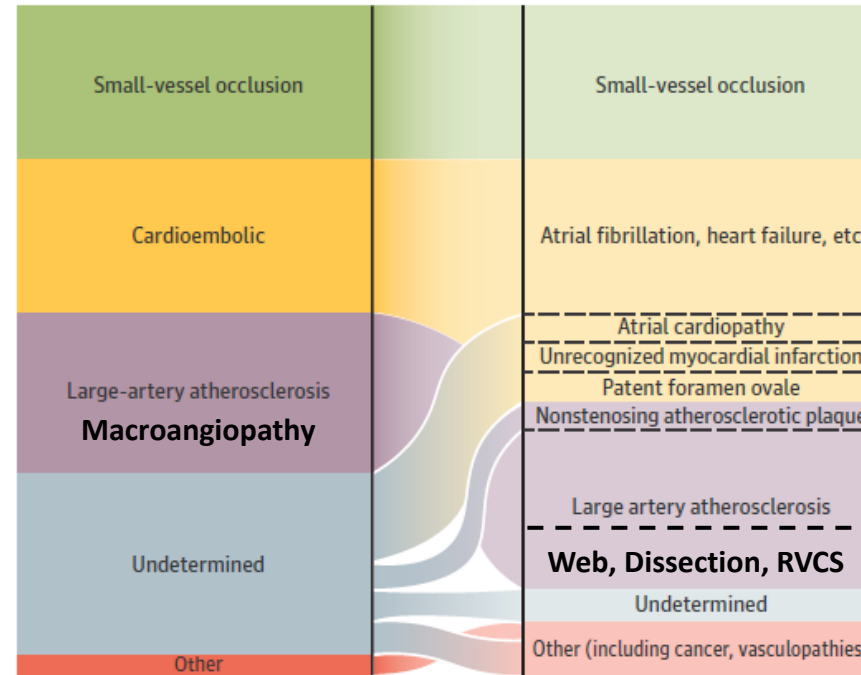
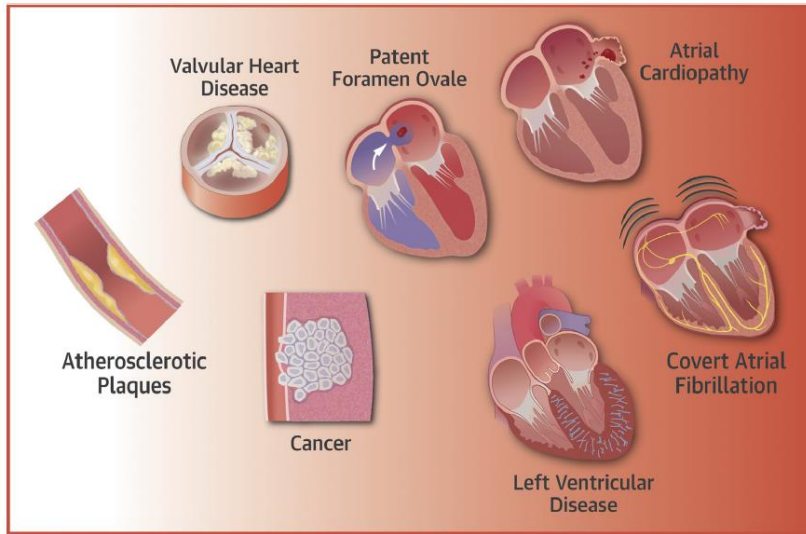
2 semaines
post-AVC

Positif
si 2 marqueurs +

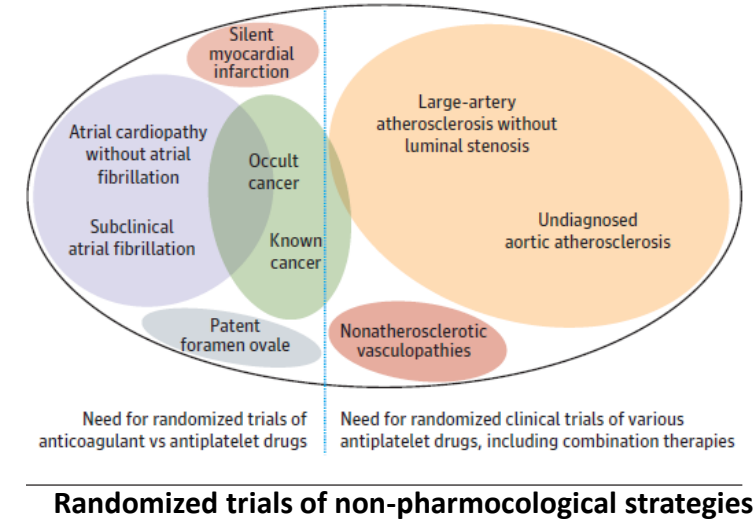


Conclusion

Ntaios et al ; JACC 2020



Kamel et al., JAMA Neurol 2019



IRM // Angio-IRM TSA// ECG-Scope // ETT // NFS-Coag

Angio-TDM TSA - EDTSA // DTC+bulles // Télémétrie – HLD // MOCHA

ETO // Holter implantable // Bio spécifique

IRM plaque // TEP // IRM cardiaque

Bilan à
systématiser

NEGATIF
=
ESUS



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