

# **ESUS**

**(Embolic Stroke of Undetermined Significance)**

—  
**Un concept utile ?**

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## Liens d'intérêt

Code de santé publique. Article L 4113-13

### Stocks

None

### Studies (Drug trials / Registers) (< 5 years)

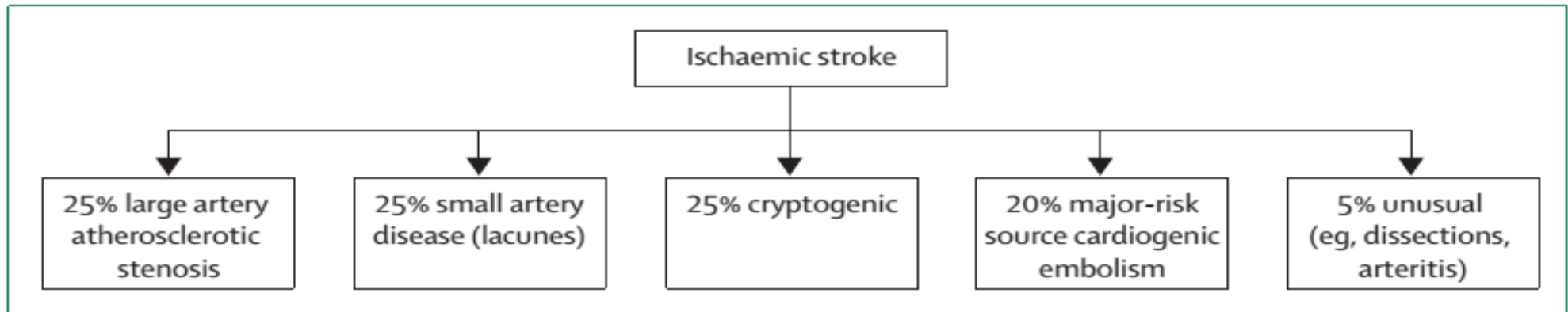
Sanofi	TAFI	(Investigator)
Servier	PERFORM	(Investigator)
Johnson & Johnson	GARFIELD	(Investigator)
Biogen	CHOLINE	(Investigator)
Pierre Fabre	LIFE	(Investigator)
Boehringer Ingelheim	RESPECT-ESUS	(Investigator)

### Advisory boards & speaker fees (< 3 years)

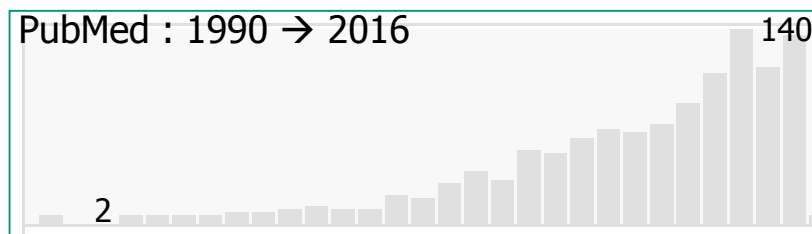
Bayer	Pfizer
Sanofi	Esai
BMS	Teva
Boehringer-Ingelheim	
Euthérapie	

# D'« Infarctus cérébral de cause indéterminée » à « Infarctus cryptogénique » ...

- Terme « cryptogénique » → cause occulte mais bien présente (épilepsie)
- Entre 20 et 40% de l'ensemble des infarctus cérébraux (↑ si âge < 50 ans)

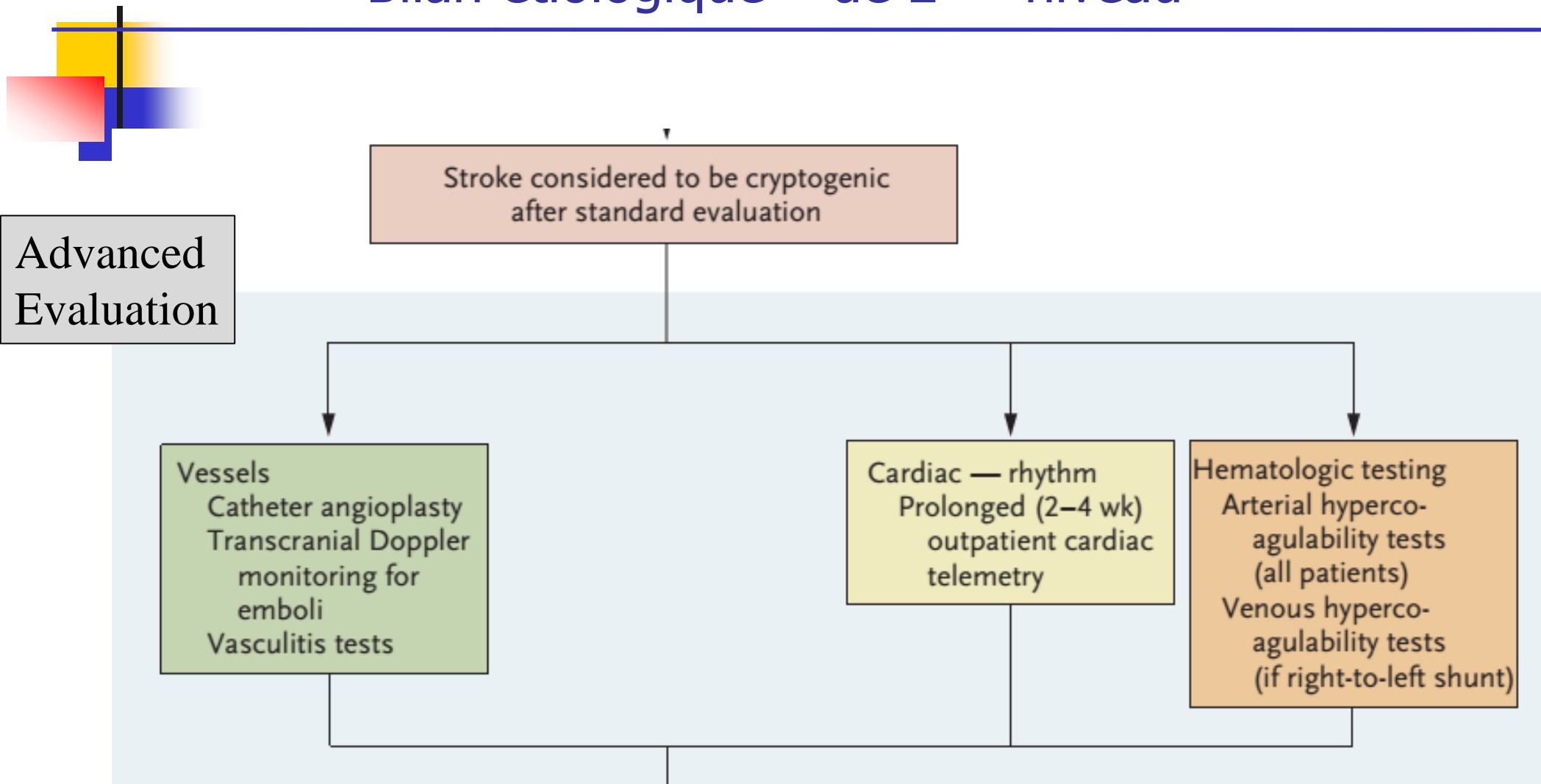


- De plus en plus étudiés :
  - Aspects diagnostiques → limites du bilan étiologique ?



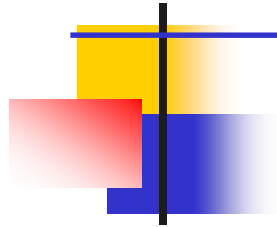
# Infarctus cérébraux cryptogéniques

Bilan étiologique « de 2<sup>ème</sup> niveau »



# Infarctus cérébraux cryptogéniques

Bilan étiologique « de 3<sup>ème</sup> niveau »



## Specialized Evaluation

Stroke considered to be cryptogenic after advanced evaluation

Genetic testing  
Mitochondrial disease  
CADASIL, Fabry's disease, other genetic causes

Vessels  
Detailed autoimmune evaluation  
CSF examination  
Brain biopsy

Cardiac — structure  
Cardiac CT  
Cardiac MRI

Cardiac — rhythm  
Prolonged (1–3 yr) outpatient loop recording

Hematologic testing  
Workup for occult cancer

# Infarctus cryptogéniques : quelle prévention secondaire ?

- Pas d'étude spécifique
- Par extension, application des traitements antithrombotiques proposés en cas d'infarctus cérébral non cardioembolique :  
→ antiplaquettaires
- **Analyse post-hoc de l'étude WARSS** (Warfarine-Aspirin Recurrent Stroke Study)  
N=2206 dont 576 (26%) avec infarctus cryptogéniques

Subgroup	Cryptogenics		hazard ratio (95% CI) <sup>1</sup>	p value <sup>2</sup>
	proportion with event, % (n)			
	warfarin	aspirin		
Age, years				
<60	9.8 (123)	7.1 (129)	1.41 (0.59–3.34)	0.44
≥60	19.0 (158)	23.7 (166)	0.80 (0.50–1.29)	0.35
	Interaction (treatment/age 60)			0.26
Gender				
Males	16.2 (167)	15.6 (174)	1.07 (0.63–1.82)	0.82
Females	13.2 (114)	17.7 (121)	0.73 (0.38–1.42)	0.36
	Interaction (treatment/gender)			0.39
History of hypertension				
Yes	21.1 (152)	16.7 (158)	1.33 (0.79–2.22)	0.29
No	7.9 (127)	16.9 (132)	0.45 (0.22–0.96)	0.04
	Interaction (treatment/history of hypertension)			0.02
History of diabetes				
Yes	26.0 (66)	22.7 (59)	1.26 (0.61–2.59)	0.53
No	11.7 (214)	15.1 (235)	0.77 (0.46–1.28)	0.31
	Interaction (treatment/history of diabetes)			0.28
History of cardiac disease <sup>3</sup>				
Yes	20.8 (48)	25.4 (64)	0.86 (0.39–1.90)	0.71
No	13.8 (233)	14.0 (231)	0.99 (0.61–1.61)	0.96
	Interaction (treatment/cardiac disease)			0.74
Sedentary lifestyle				
Yes	19.4 (109)	22.1 (109)	0.89 (0.49–1.59)	0.68
No	12.5 (169)	13.5 (182)	0.94 (0.52–1.68)	0.83
	Interaction (treatment/ sedentary lifestyle)			0.89
History of TIA, TMB, or stroke				
Yes	22.3 (72)	19.1 (69)	1.24 (0.60–2.58)	0.57
No	12.2 (198)	15.6 (214)	0.77 (0.46–1.31)	0.33
	Interaction (treatment/TIA, TMB, or stroke)			0.30
NIH stroke scale				
>5	25.2 (64)	11.3 (65)	2.57 (1.06–6.25)	0.04
≤5	12.0 (217)	17.9 (230)	0.65 (0.40–1.07)	0.09
	Interaction (treatment/ NIH stroke scale)			0.008
Arterial territory				
Carotid/anterioe <sup>4</sup>	16.7 (193)	12.6 (187)	1.38 (0.81–2.36)	0.24
Vertebral/basilar/posterior (with brainstem lesions)	36.8 (19)	10.7 (28)	3.99 (1.03–15.46)	0.05
Vertebral/basilar/posterior (excluding brainstem lesions)	4.4 (69)	27.5 (80)	0.14 (0.04–0.47)	0.001
	Interaction (treatment/ vertebral-brainstem)			0.14
	Interaction (treatment/ vertebral-no brainstem)			0.0007

# Infarctus embolique de source indéterminée ou ESUS

Personal View

## Embolic strokes of undetermined source: the case for a new clinical construct



Robert G Hart, Hans-Christoph Diener, Shelagh B Coutts, J Donald Easton, Christopher B Granger, Martin J O'Donnell, Ralph L Sacco, Stuart J Connolly, for the Cryptogenic Stroke/ESUS International Working Group

*Lancet Neurol 2014, 13 : 429-38*

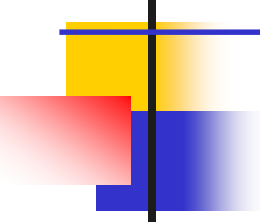
### ESUS : critères diagnostiques

- 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)

### Bilan requis

- Brain CT or MRI
- 12-lead ECG
- Precordial echocardiography
- Cardiac monitoring for  $\geq 24$  h with automated rhythm detection†
- Imaging of both the extracranial and intracranial arteries supplying the area of brain ischaemia (catheter, MR, or CT angiography, or cervical duplex plus transcranial doppler ultrasonography)

\*Imaging of the proximal aortic arch is not needed; special blood tests for prothrombotic states only if the patient has a personal or family history of unusual thrombosis or associated systematic signs or disorder. †Cardiac telemetry is not sufficient.



# Infarctus cryptogéniques – ESUS : quelles différences ?

## 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

### *Embolic stroke of undetermined source (ESUS)*

- Non-lacunar brain infarct on imaging
- Open arteries (<50% stenosis) proximal to the infarct
- No major-risk cardioembolic source

## Necessary diagnostic assessment

### *Cryptogenic ischaemic stroke\**

Not specified†

### *Embolic stroke of undetermined source (ESUS)*

- Brain CT or MRI showing non-lacunar infarct
- Precordial echocardiography
- ECG and cardiac monitoring for  $\geq 24$  h
- Imaging of the extracranial and intracranial arteries supplying the area of the brain infarct

## Limitations

### *Cryptogenic ischaemic stroke\**

- Inclusion of variable fraction of lacunar infarcts and intracranial arterial stenosis dependent on extent of diagnostic assessment (varies from study to study, and usually not described in detail)

### *Embolic stroke of undetermined source (ESUS)*

- Transoesophageal echocardiography not recommended, and hence aortic arch atherosclerosis not characterised

ECG=electrocardiogram. \*Criteria for cryptogenic stroke are not standardised; TOAST criteria for stroke of undetermined cause are considered here, excluding those with two or more potential causes.<sup>115</sup> †Some patients will have no likely cause established despite an extensive assessment. In others, no cause is found but the assessment was cursory.<sup>115</sup> In most studies of cryptogenic stroke, the extent of diagnostic imaging is not reported.



## Registre AVC d'Athènes :

- N = 2731
- 1992 - 2011
- AIT/récidives exclus
- suivi moyen =  $30,5 \pm 24$  mois

*Ntaios et al, Stroke 2015, 46 : 176-81*

*Ntaios et al, Stroke 2015, 46 : 2087-93*

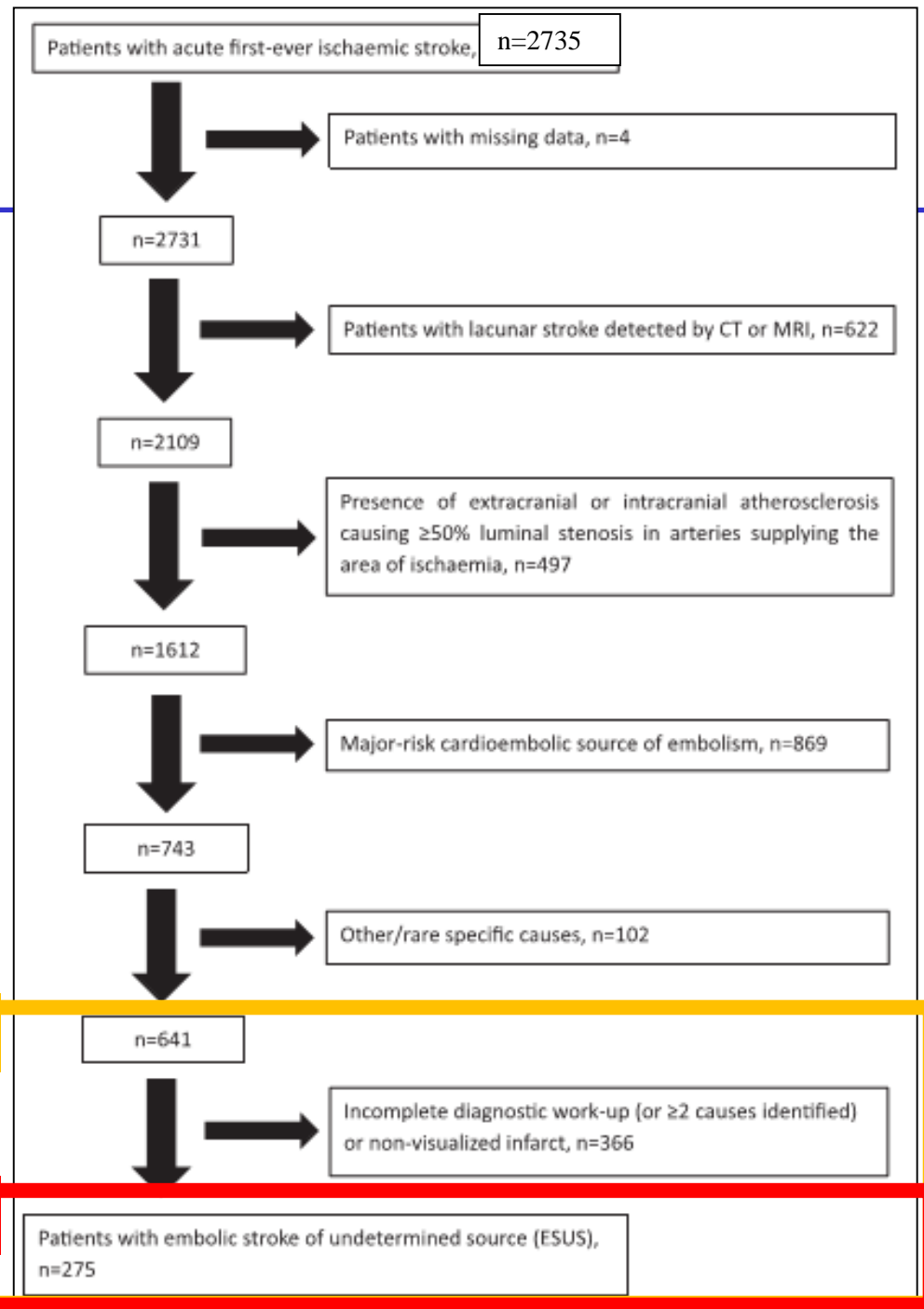
*Ntaios et al, J Stroke Cerebrovasc Dis 2016, 25 : 2975-80*

*Ntaios et al, Stroke 2016, 47 : 2278-85*

*Ntaios et al, Neurology 2017, Aug 8*

Infarctus cryptogéniques :  $641/2731 = 24,5\%$

ESUS :  $275/2731 = 10 \%$



# ESUS : Pronostic

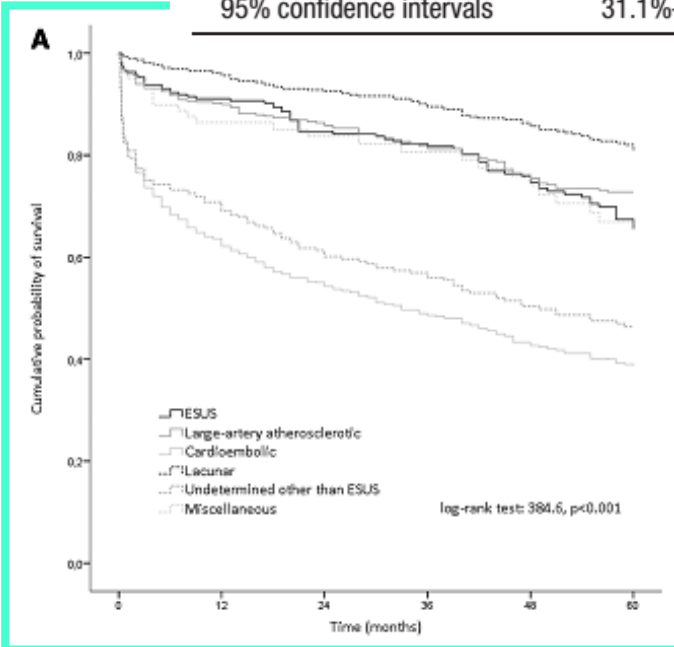
**Table 4. Prognosis of ESUS Patients\***

Study	n/Mean Follow-Up (y)	Mean Age, y	Antithrombotic Therapy	AF During Follow-Up†	Stroke (Est Annualized Rate)†	Stroke, MI, Vascular Death (Est Annualized Rate)	Total Mortality (Est Annualized Rate)
Ntaios et al <sup>13,26‡</sup>	275 (3.2)	68	74% APT only, 22% OAC	80 (29%)	6.8%/y	9.0%/y§	8.2%/y
Li et al <sup>15</sup>	189 (1)	65	NR	NR	≈5%/y	NR	NR
Putala et al <sup>16‡</sup>	46 (1.8)	62	85% APT, 11% OAC	NR	5.1%/y	NR	1.3%/y
Ntaios et al <sup>24‡</sup>	1095 (3.0)	68	87% APT only, 12% OAC	NR	4.8%/y	NR	4.5%/y
Masina et al <sup>12¶</sup>	84 (2.1)	73	99% APT	NR	2.3%/y	NR	NR
Ueno et al <sup>22#</sup>	177 (3.5)	64	72% APT, 29% OAC	NR	3.9%/y	5.0%/y**	1.3%/y
Arauz et al <sup>23††</sup>	149 (2.3)	44	91% APT, 5% OAC	NR	2.3%/y	NR	0%/y
Pooled – unweighted average‡,††	1545 (2.4)	68	87% APT, 12% OAC	...	4.0%/y	...	2.9%/y
Pooled – weighted average‡,††	1605 (2.7)	65	86% APT, 13% OAC	...	4.5%/y	...	3.9%/y

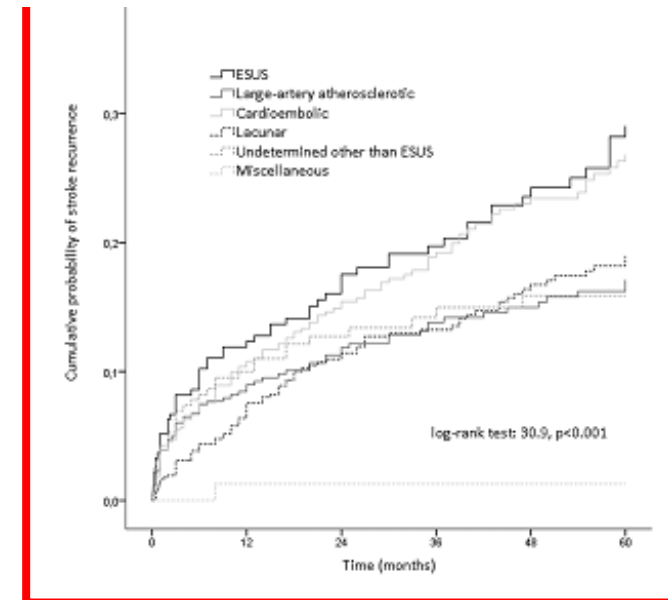
# ESUS : Pronostic comparatif

**Table. Cumulative 5-Year Probabilities of Survival, Stroke Recurrence, and Composite Cardiovascular Event**

	ESUS (n=275)	Cardioembolic (n=869)	Large-Artery Atherosclerotic (n=497)	Lacunar (n=622)	Undetermined Other Than ESUS (n=366)	Miscellaneous (n=102)
<b>Survival</b>						
Cumulative probability	65.6%	38.8%	72.8%	81.0%	46.4%	66.9%
95% confidence intervals	58.9%–72.2%	34.9%–42.7%	68.3%–77.3%	77.1%–84.9%	40.1%–52.7%	55.7%–78.1%
<b>Stroke recurrence</b>						
Cumulative probability	29.0%	26.8%	17.1%	18.9%	15.9%	1.3%
95% confidence intervals	22.3%–35.7%	22.1%–31.5%	13.2%–21.0%	14.2%–23.6%	10.8%–21.0%	0%–3.9%
<b>Composite cardiovascular event</b>						
Cumulative probability	38.1%	38.2%	29.8%	28.2%	29.0%	24.3%
95% confidence intervals	31.1%–45.2%	33.3%–43.1%	24.9%–34.7%	23.7%–32.7%	22.7%–35.3%	13.5%–35.1%



*Ntaios et al, Stroke 2015, 46 : 2087-93*  
*Arauz et al, Plos One 2016, Nov 10*  
*Ntaios et al, Neurology 2017, Sept 22*



# CRYSTAL AF study

Recherche d'une FA occulte après un AVC

## Objectif

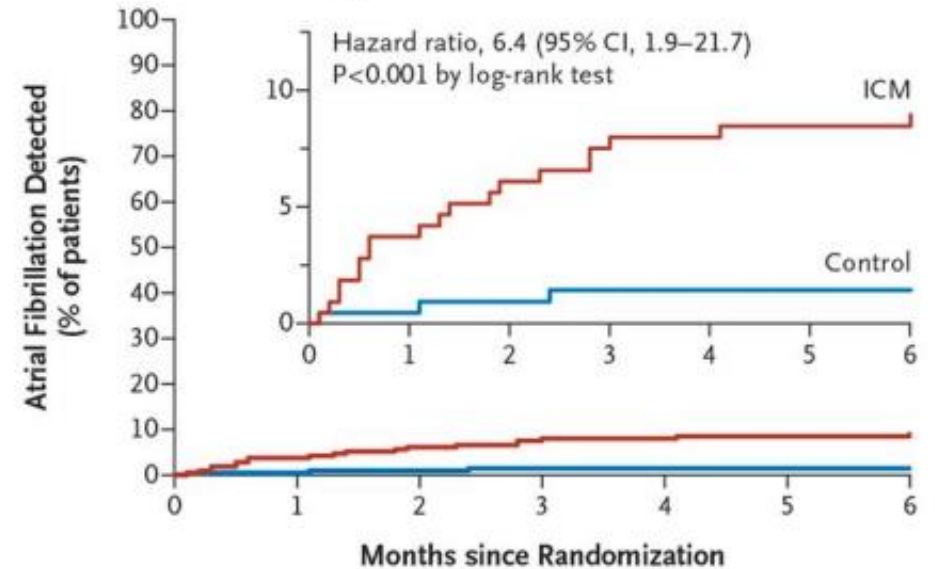
Comparer la détection de la FA à l'aide d'un dispositif implantable (REVEAL, Medtronic) versus la détection habituelle

Définition d'une FA: Durée > 30 secondes

## Critères d'inclusion

- Episode récent de moins de 60 jours d'un AIT ou un AIC cryptogénique
- Examens indispensables pour établir le caractère cryptogénique
  - IRM ou scanner
  - ECG
  - Monitoring des 24 heures
  - Echographie transoesophagienne
  - Angioscanner ou angio IRM des vaisseaux du cou

## A Detection of Atrial Fibrillation by 6 Months

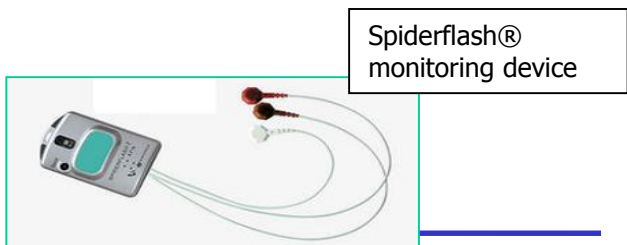


## No. at Risk

	0	1	2	3	4	5	6
Control	220	214	200	198	197	197	194
ICM	221	205	198	195	194	193	191

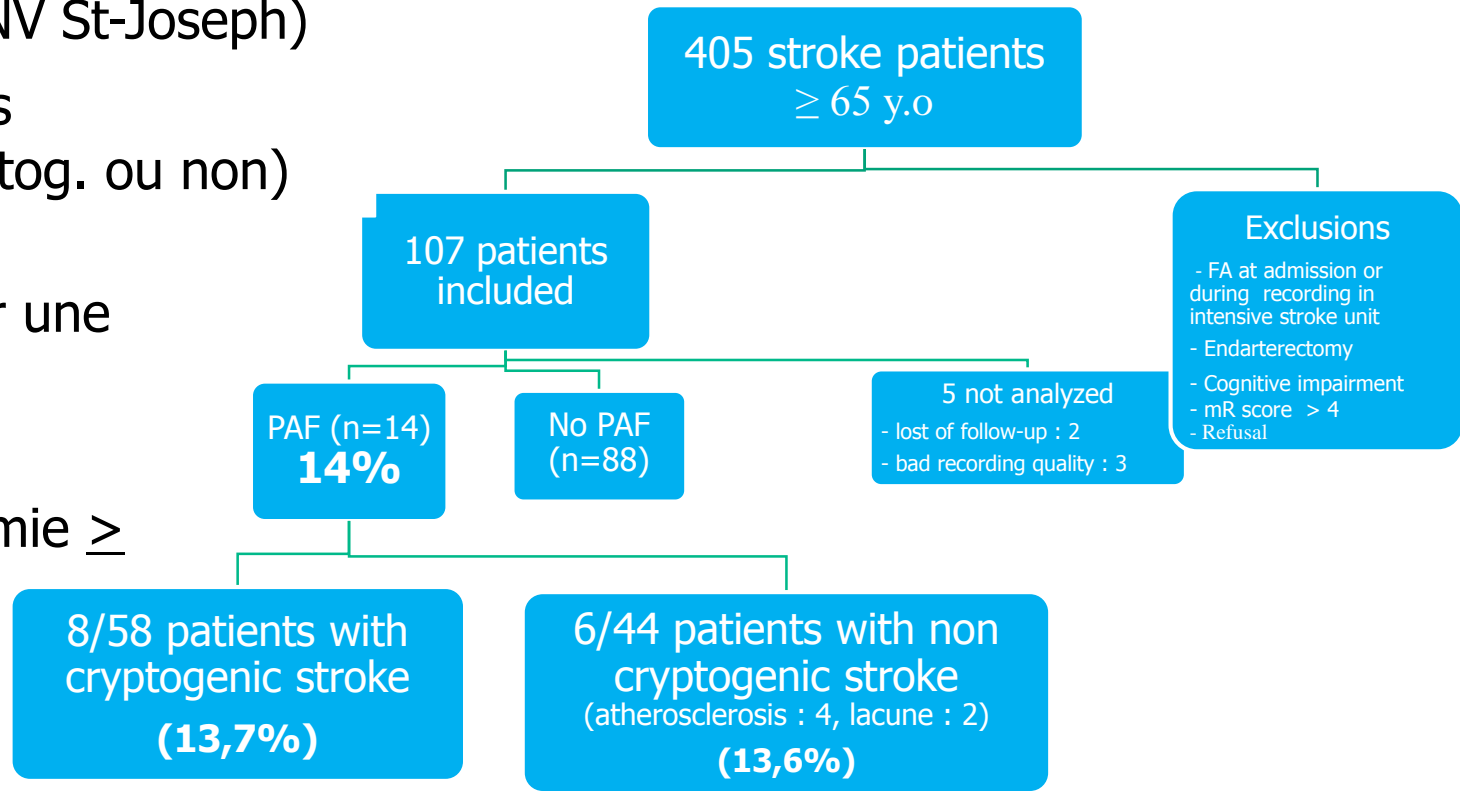
	ICM	Control	p
6 Mois	8.9%	1.4%	< 0.001
12 Mois	12.4%	2.0 %	< 0.001
36 Mois	30%	3.0%	< 0.001

ICM: Insertable Cardiac Monitor



# Découverte d'une FA occulte : signification clinique ?

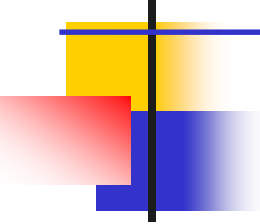
- Etude monocentrique (UNV St-Joseph)
- 107 pts > 65 ans recrutés prospectivement (IC cryptog. ou non)
- Enregistrement débuté précocement ( $J5 \pm 1$ ) pour une moyenne de  $19 \text{ jours} \pm 2$  d'enregistrement.
- Diagnostic de FA si arythmie  $\geq 30$  sec



- **Résultats :**
  - **14% de FA occulte**
  - **Taux identique en cas d'IC cryptogénique ou non**
  - Episode de FA enregistré en moyenne à  $J9 \pm 6$  du début de l'enregistrement

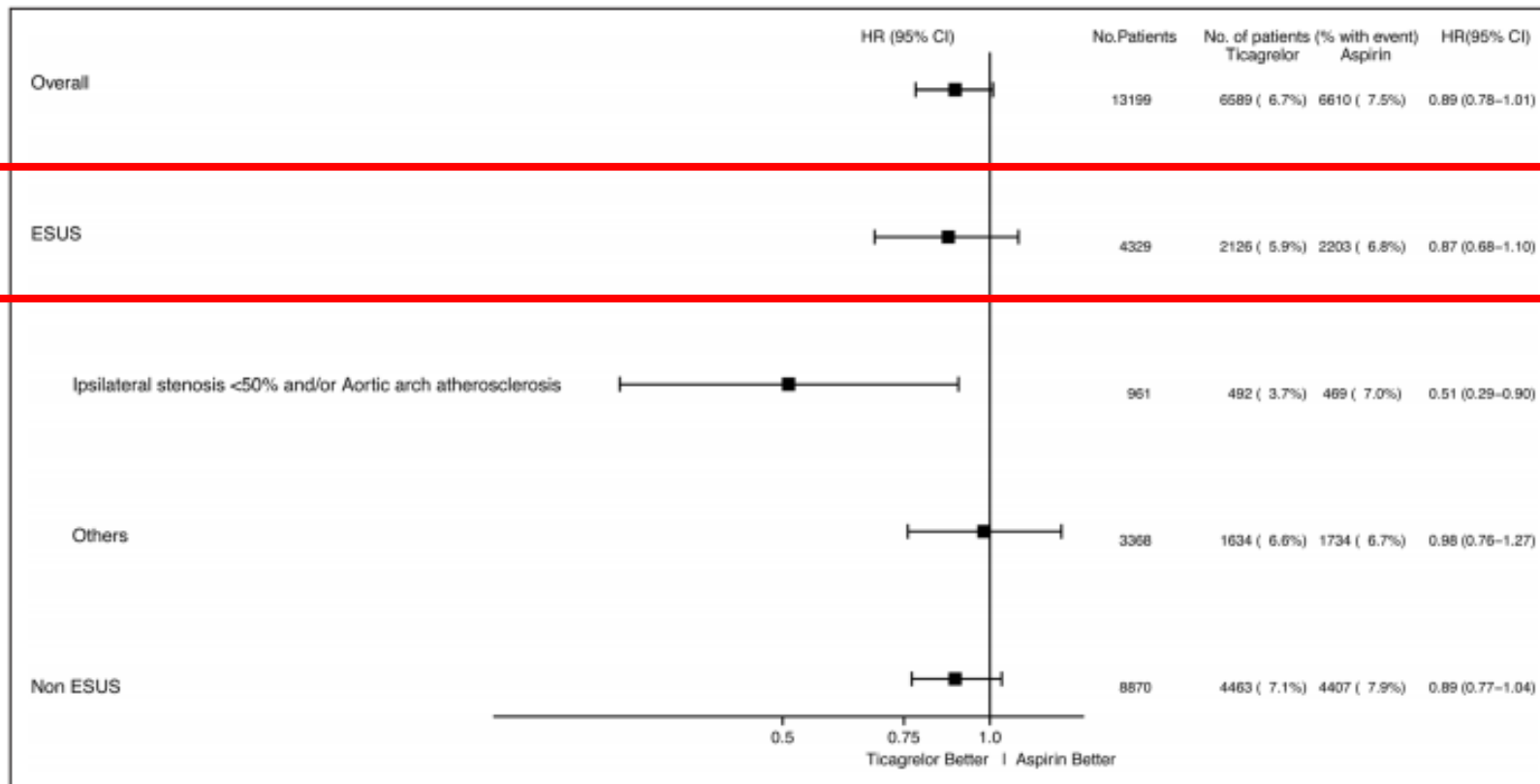
# ESUS : des explorations au traitement...

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- Antiagrégant ?
  - Anticoagulant ?
    - Possible réduction du risque de récurrence sous anticoagulant, dans certains sous-groupes de patients avec infarctus cryptogénique (étude WARSS)
    - Disponibilité de nouveaux anticoagulants (AOD)
      - Efficacité  $\geq$  AVK pour réduire le risque de récurrence d'AVC
      - Sécurité  $>$  AVK pour le risque hémorragique (cérébral)
- AOD = candidats à un rapport bénéfice/risque meilleur que les antiplaquettaires en cas d'ESUS ?

# ESUS et antiplaquettaires

- Analyse post-hoc sur étude SOCRATES
- N= 13 199 patients dont 4 329 (32,8%) avec ESUS
- Ticagrelor 180mg/j vs Aspirine 300 puis 100mg/j → M3



**Figure 3.** Effect of ticagrelor and aspirin in embolic stroke of unknown source (ESUS) and non-ESUS groups and in ESUS subcategories. CI indicates confidence interval; and HR, hazard ratio.

# Essai phase III (1) : NAVIGATE ESUS study

<https://clinicaltrials.gov/ct2/show/NCT02313909>

**Primary efficacy outcome : Composite Isch./Hemorr. Stroke + Systemic embolism**  
**Primary safety outcome : Major hemorrhage**

Patients with recent ischemic stroke and

1. • N = 7213

2. • Analyse intermédiaire prédéterminée à M11

3. • Efficacy : Groupe R 5,1% vs Groupe A 4,7% (HR 1,07 95%CI [0,87-1,33])

4. • Safety : Groupe R 1,8% vs Groupe A 0,7% (HR 2,72 95%CI [1,68-4,39])

→ Arrêt de l'étude

Age ≥ 18 years (max 10% patients <60 years)

Target RRR 30%; superiority w/ 90% power  $\alpha=0.05$

Enrollment ~24 months; minimum treatment ~12 months; study duration ~36 months

Estimated mean treatment duration 18 - 24 months;

... 15 mg od

n ~ 3,500

1 month  
post study  
drug

EOS

Hart et al, *N Engl J Med* 2018 Jun 7, 378 (23) : 2191-2201

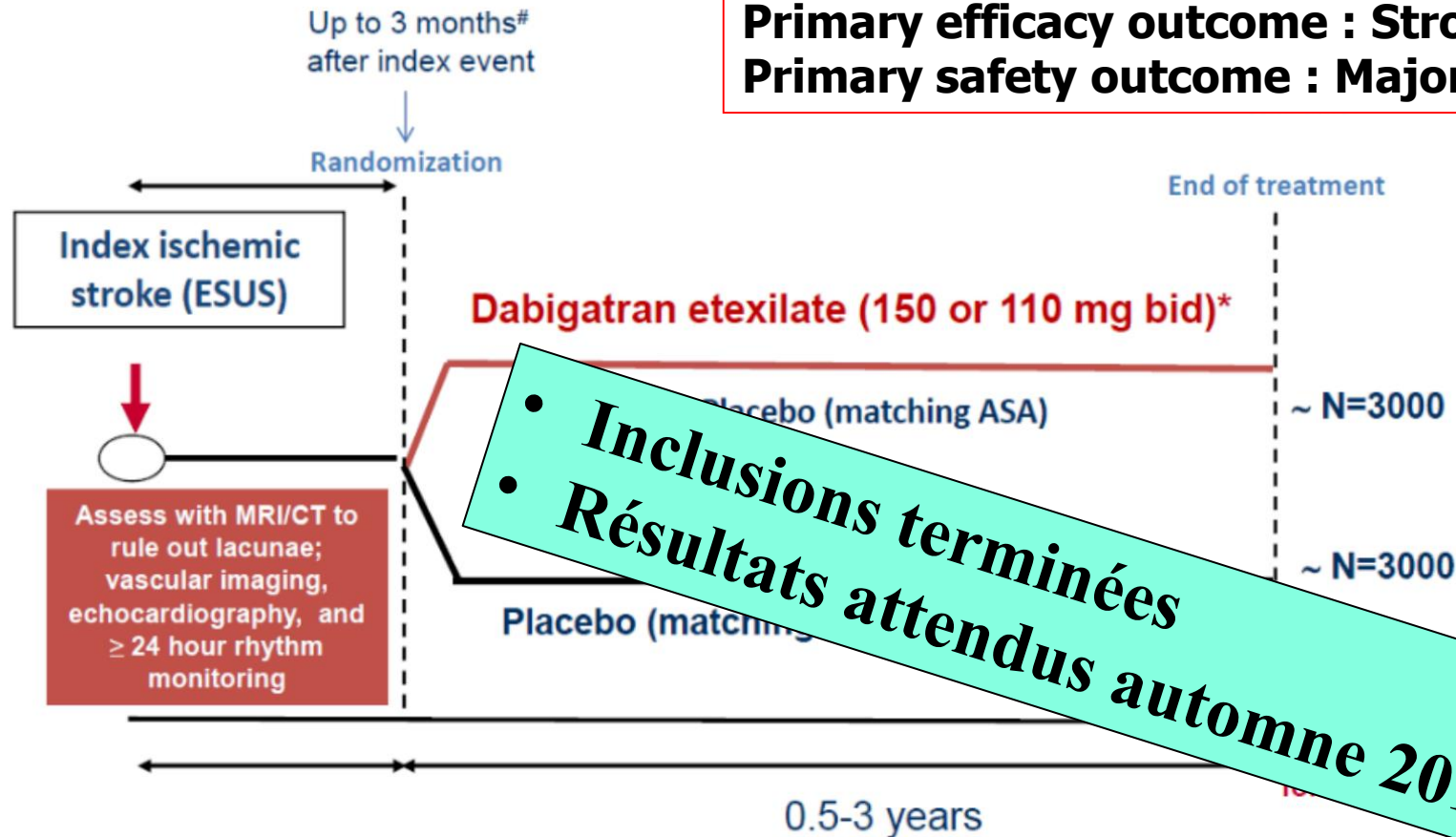
Randomization 7 days to 6 months



# Essai phase III (2) : RES-PECT ESUS study

Diener et al, *Int J Stroke* 2016, 10 : 1309-12

**Primary efficacy outcome : Stroke**  
**Primary safety outcome : Major hemorrhage**



\*All patients will receive dabigatran etexilate 150 mg bid, unless they are  $\geq 75$  years of age or have a CrCL of  $\geq 30$  to  $< 50$  ml/min, who will receive 110 mg bid

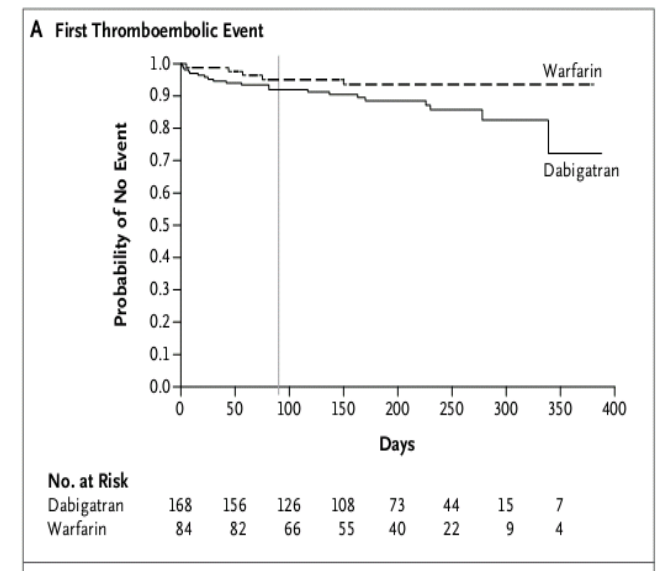
# The time window for inclusion is 6 months in patients aged  $\geq 60$  years + risk factors

# ESUS : un concept utile ?

- Concept apparu en contexte particulier du développement des AOD...
- Risque de simplification du bilan étiologique :
  - ETO absente de la définition ESUS
    - Anormale 50% ESUS – décisive pour le traitement chez 1 pt sur 7 *Katsanos et al, Neurology 2016, 87 : 988-95*
- Risque de glissement des concepts :
  - ESUS ≠ « CESUS » → autres causes de E possibles que CE
- Risque thérapeutique potentiel :
  - ESUS ≠ Cause cardio-embolique pouvant bénéficier d'un AOD
  - Un AOD reste un anticoagulant, avec son risque hémorragique (cf NAVIGATE ESUS study)

Epaisseur plaque	Ipsilat. à AVC	Controlat. à AVC	<i>p</i>
≥ 5 mm	11%	1%	0,008
≥ 4 mm	19%	5%	0,002
≥ 3 mm	35%	15%	0,001

**Epaisseur de plaque carotidienne en cas d'ESUS**  
*Coutinho et al, Neurology 2016, 87 : 665-72*



## Dabigatran et Valves mécaniques

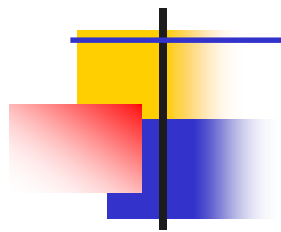
*Eikelboom et al, N Eng J Med 2013, 369 : 1206-14*

# ESUS

## « Take home messages »

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- Le concept d'ESUS permet d'insister sur l'importance d'un bilan étiologique protocolisé en présence d'un infarctus cérébral dont la cause n'apparaît pas d'emblée évidente
  - Mais importance d'une réflexion individualisée...
- Importance, vu les implications thérapeutiques potentielles, de traquer FA occulte face à tout infarctus cérébral d'origine indéterminée/cryptogénique
- ESUS = groupe hétérogène. Pas de conséquence thérapeutique
  - A ce jour : infarctus cérébral cryptogénique → antiplaquettaire



# ESUS : Stratification du risque de récurrence selon les scores CHADS<sub>2</sub> et CHA<sub>2</sub>DS<sub>2</sub>-VASc

## 11 registres AVC Europe/USA :

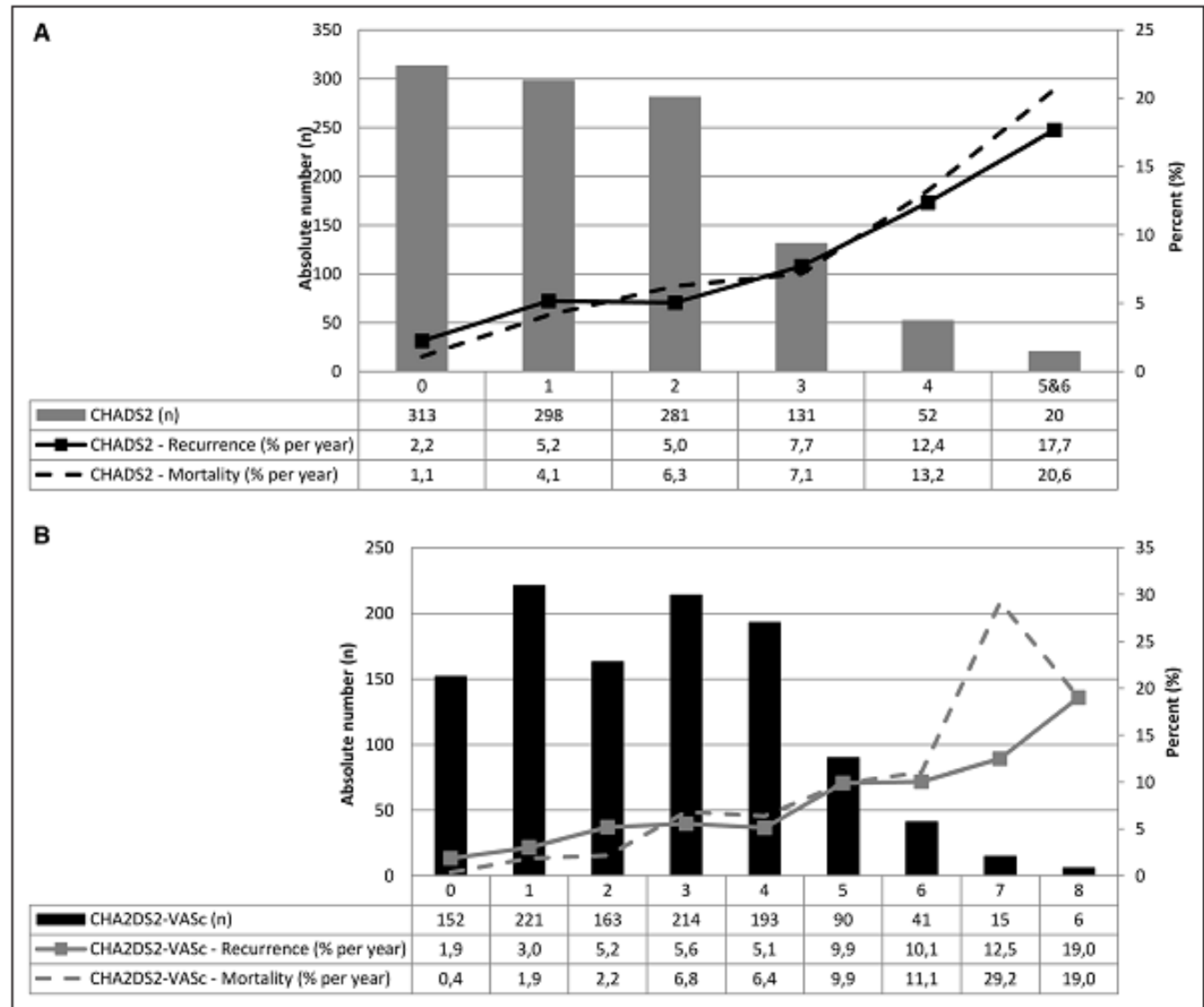
- n = 1095 ESUS
- suivi moyen = 31 mois

### Evènements :

- 155 infarctus/AIT
- 148 décès

### Stratification

- CHADS<sub>2</sub>
  - CHA<sub>2</sub>DS<sub>2</sub>-VASc
- calculés rétrospectivement en « pré-AVC »



**Figure 1.** Frequency distribution and annualized event rates for ischemic stroke/transient ischemic attack (TIA) recurrence and mortality for congestive heart failure, hypertension, age  $\geq 75$  years, diabetes mellitus, and stroke or TIA (CHADS<sub>2</sub>; top) and congestive heart failure, hypertension, age  $\geq 75$  years, diabetes mellitus, stroke or TIA, vascular disease, age 65–74 years, sex category (CHA<sub>2</sub>DS<sub>2</sub>-VASc; bottom) scores' strata.

# Essai phase III (3) : ATTICUS study

*Geisler et al, Int J Stroke 2017, 12 : 985-90*

## Abstract

**RATIONALE:** Optimal secondary prevention of embolic stroke of undetermined source is not established. The current standard in these patients is acetylsalicylic acid, despite high prevalence of yet undetected paroxysmal atrial fibrillation.

**AIM:** The ATTICUS randomized trial is designed to determine whether the factor Xa inhibitor apixaban administered within 7 days after embolic stroke of undetermined source, is superior to acetylsalicylic acid for prevention of new ischemic lesions documented by brain magnetic resonance imaging within 12 months after index stroke.

**DESIGN:** Prospective, randomized, blinded, parallel-group, open-label, German multicenter phase III trial in approximately 500 patients with embolic stroke of undetermined source. A key inclusion criterion is the presence or the planned implantation of an insertable cardiac monitor. Patients are 1:1 randomized to apixaban or acetylsalicylic acid and treated for a 12-month period. It is an event-driven trial aiming for core-lab adjudicated primary outcome events.

**STUDY OUTCOMES:** The primary outcome is the occurrence of at least one new ischemic lesion identified by axial T2-weighted FLAIR magnetic resonance imaging and/or axial DWI magnetic resonance imaging at 12 months when compared with the baseline magnetic resonance imaging. Key secondary outcomes are the combination of recurrent ischemic strokes, hemorrhagic strokes, systemic embolism; combination of MACE including recurrent stroke, myocardial infarction, and cardiovascular death and combination of major and clinically relevant non-major bleeding defined according to ISTH, and change of cognitive function and quality of life (EQ-5D, Stroke Impact Scale).

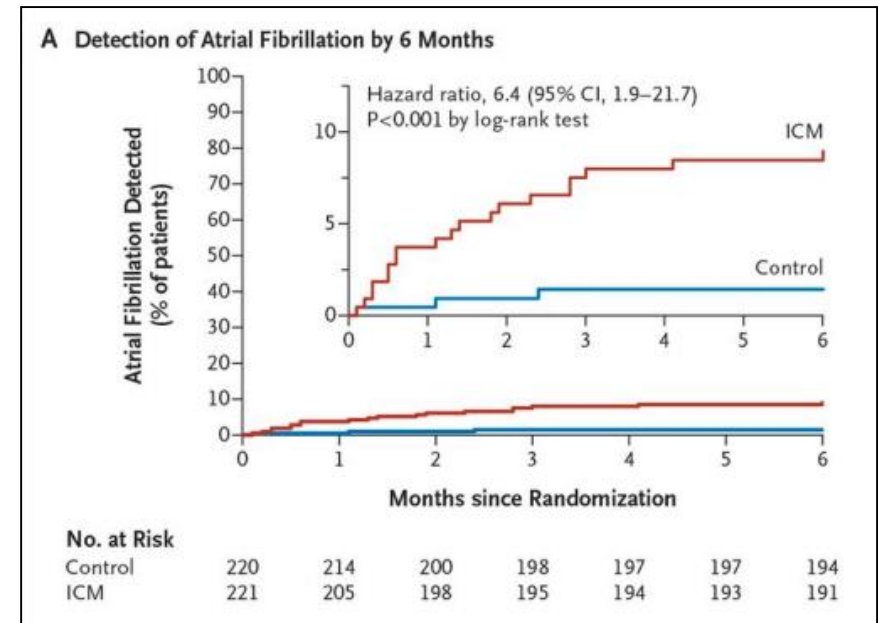
**DISCUSSION:** Embolic stroke of undetermined source is caused by embolic disease and associated with a high risk of recurrent ischemic strokes and clinically silent cerebral ischemic lesions. ATTICUS will investigate the impact of atrial fibrillation detected by insertable cardiac monitor and the effects of early anticoagulation with apixaban compared with antiplatelet therapy with acetylsalicylic acid on the incidence of new ischemic lesion after embolic stroke of undetermined source.

# Relations ESUS $\leftrightarrow$ Infarctus Cardio-Emboliques

- Taux de récurrences
- Données bio/histologiques
  - Troponine + élevée *Merkler et al, Jam Heart Assoc 2017, Sept 22*
  - Thrombus riches en érythrocytes ou mixtes (vs riches en plaquettes)

*Gratz et al, Lancet Neurol 2014, 13 : 967 ; Boekhs-Behrens et al, Stroke 2016, 47 : 1864-71*

- Fréquence de découverte de FA occulte
  - Etude Crystal – AF
- Biomarqueurs de dysfonction atriale
  - Diamètre de l'OG, Modifications de l'onde P, intervalle P-R,...



*Sanna et al, NEJM 2014, 370 : 2478-86*