Actualités en neurologie vasculaire

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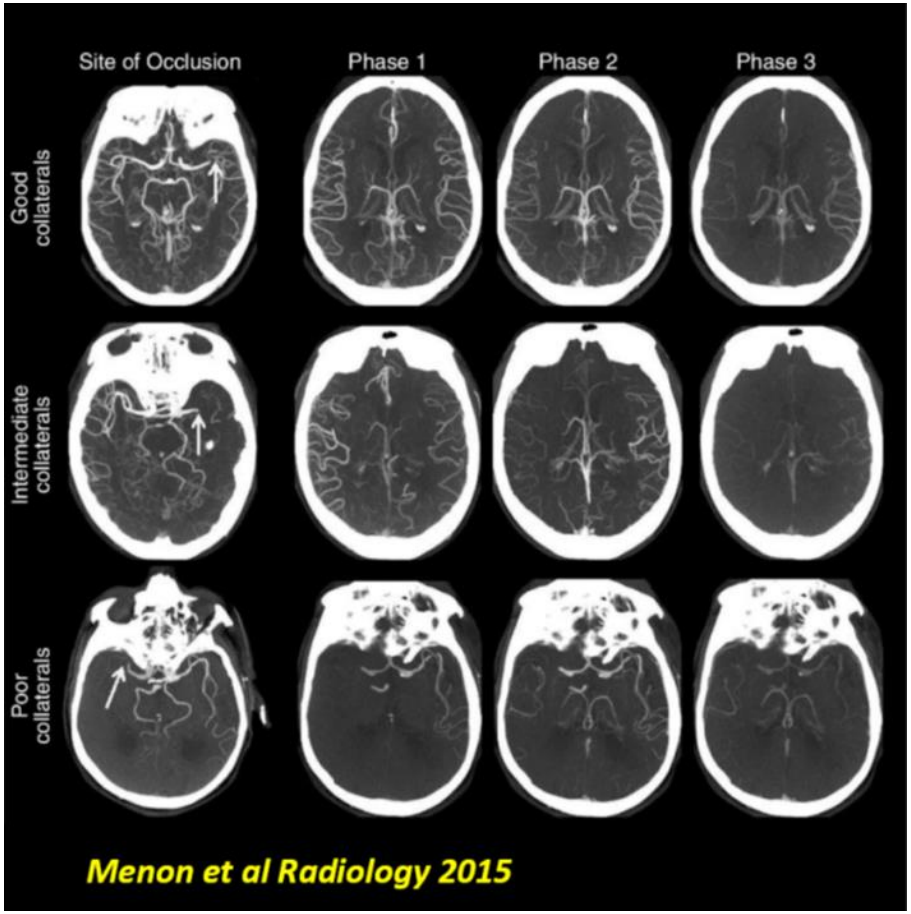
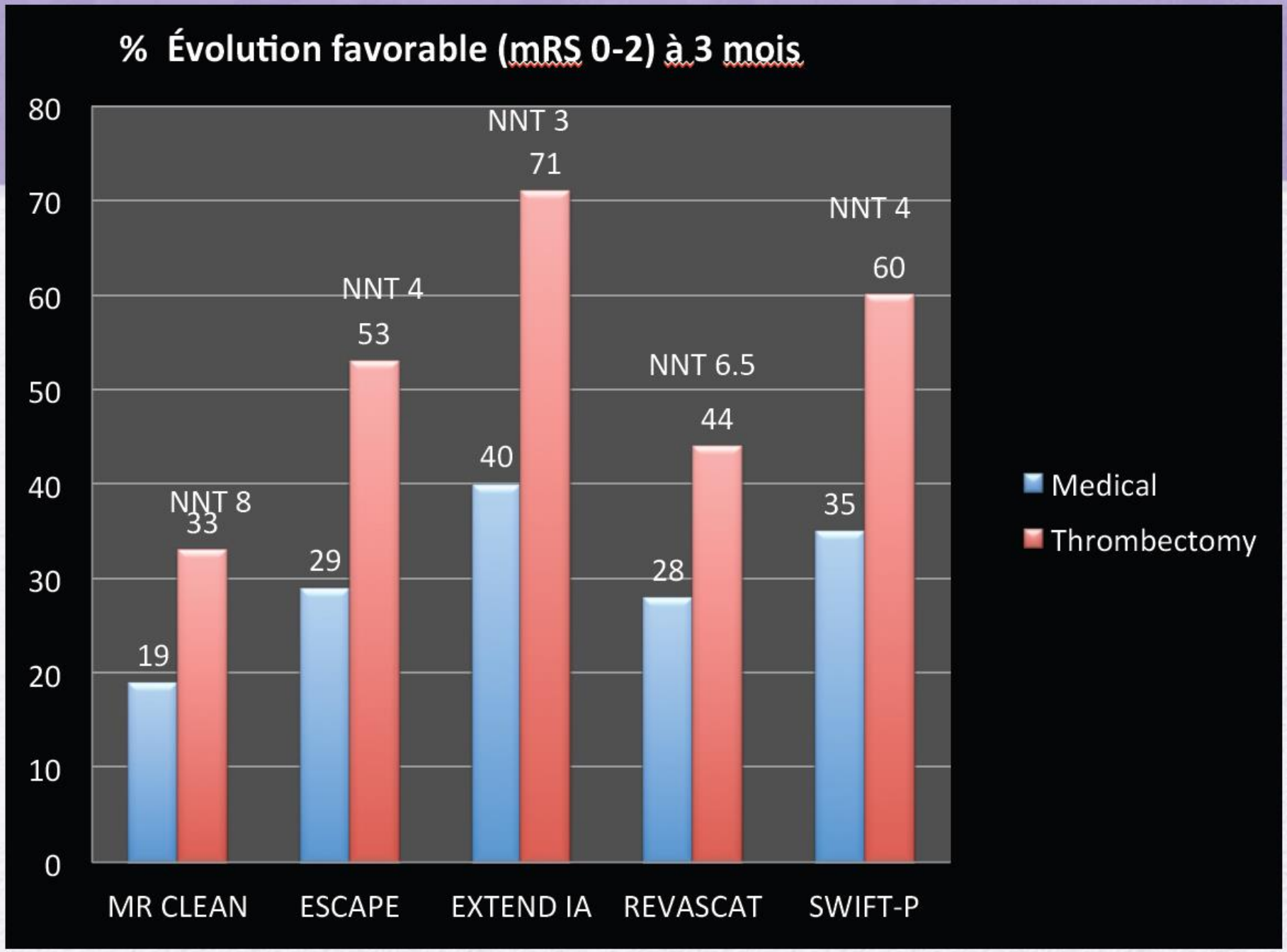
Thrombectomie mécanique

Thrombectomie mécanique: quelle imagerie?
Des critères de sélection variables selon les études

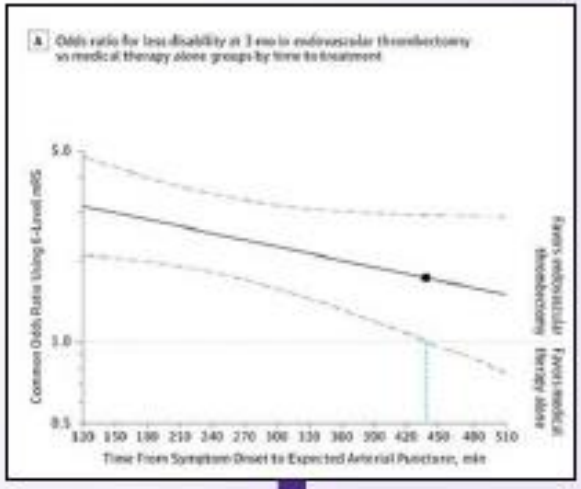
- **MR CLEAN**
  - Pas d'estimation de la « zone pénombrale »
- **EXTEND-IA et SWIFT-PRIME**
  - Estimation de la « zone pénombrale » et du cœur ischémique
- **ESCAPE**
  - ASPECTS ≥ 6 + circulation collatérale (50% territoire sylvien)
- **REVASCAT**
  - ASPECTS > 6 (TDM), > 5 (IRM)




% Évolution favorable (mRS 0-2) à 3 mois
80
70
60
50
40
30
20
10
0
NNT 8
19
33
NNT 4
29
53
NNT 3
40
71
NNT 6.5
28
44
NNT 4
35
60
MR CLEAN
ESCAPE
EXTEND IA
REVASCAT
SWIFT-P
Medical
Thrombectomy

Study background

- Current evidence suggests that benefit of thrombectomy rapidly decays over time and may no longer exist beyond 7.3 hours from stroke onset (or TLSW)[1]
- Indeed, the current AHA and ESO guidelines define a rigid therapeutic window of 6 hours as level 1a evidence[2,3]
- This treatment paradigm disregards individual variations in compensatory mechanisms for ischemia led by but not restricted to collateral flow.
- Growing evidence supports a physiologic rather than a purely time based approach e.g. patients with significant clinical deficits but still limited infarct size (Clinical-Core Mismatch) may benefit from reperfusion regardless the time from stroke onset to treatment.[4]
- Wake-up strokes, strokes with unclear onset time, and witnessed late presenting strokes (> 6 hours) represent a large proportion of LVOS (~40%) yet no proven treatment options exist for this population.



Outcomes = $\frac{\text{Collaterals}}{\text{Time}}$

DAWN TRIAL

[1] Saver et al, JAMA. 2016 [2] Powers et al, Stroke 2015 [3] Wahlgren Int J Stroke 2016 et al, [4] Jovin et al, Stroke 2011

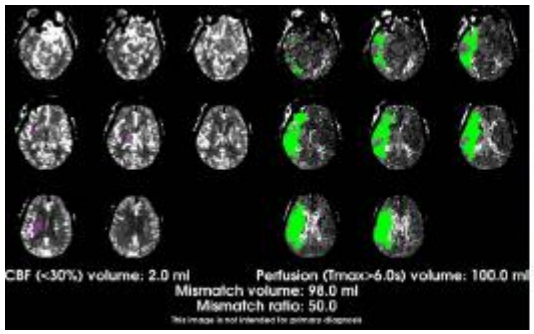
Study Objective

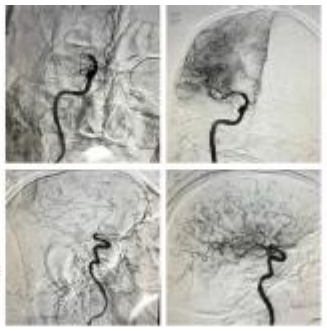
To demonstrate superior functional outcomes at 90 days with Trevo plus medical management compared to medical management alone in appropriately selected patients treated six to 24 hours after last seen well

Study Design

Study design	Global, multi-center, adaptive, population enrichment, prospective, randomized, open, blinded endpoint (PROBE), controlled FDA IDE trial
Patient population	• Acute ischemic stroke (AIS) with large vessel occlusion • Able to be randomized between six to 24 hours after time last known well • Clinical imaging mismatch (CIM) defined by age, core, and NIHSS
Target vessel	Intracranial ICA, M1 segment of the MCA
Randomization	1:1 Trevo + medical management vs. medical management alone
Sites	Up to 50 sites worldwide (30 US and 20 international)
Sample size	500 maximum subjects: 250 in the treatment arm and 250 in the control arm. Minimum sample size is 150 subjects.
Follow-up	24 hours (-6/+24), day 5-7/discharge, day 30 (± 14), and day 90 (± 14)

DAWN
TERUMO

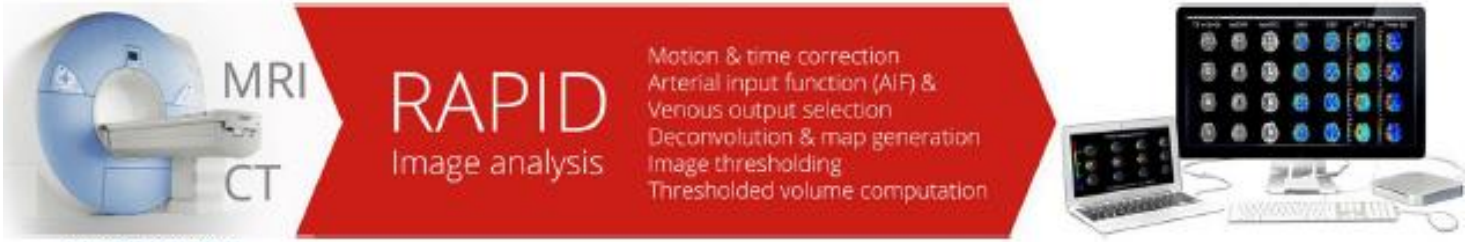


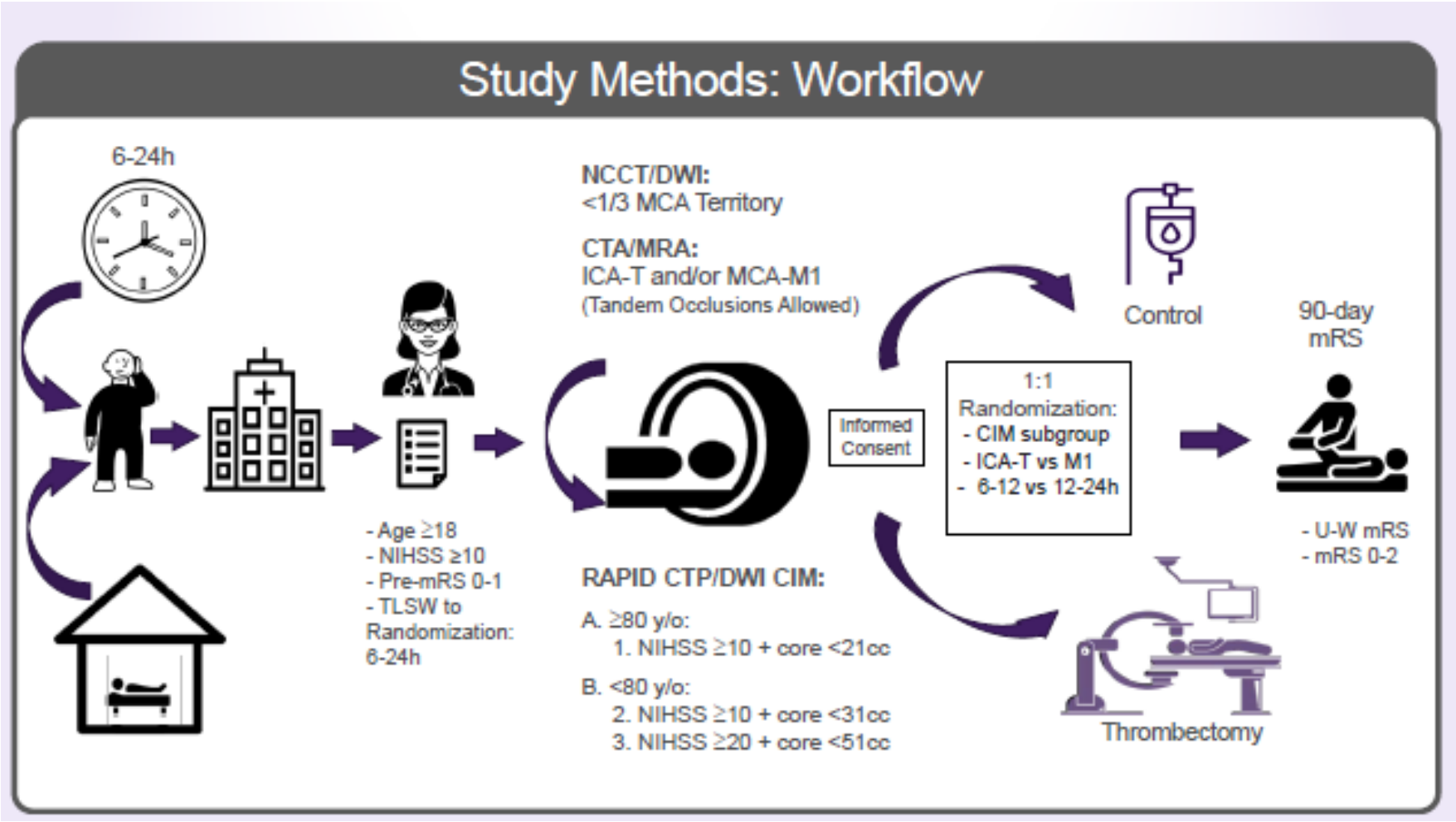


What is RAPID?

stryker Neurovascular

- RAPID is a medical image software package that provides viewing, processing and analysis of brain images.
- RAPID is fast, easy to use and results can be viewed on any computer.
- What is required to run RAPID?
  A computer connected within a hospital network to CT and/or MRI scanners.
- What does RAPID do?
  RAPID computes brain image maps with volumes of interest from diffusion and perfusion MRI scans and CT perfusion scans.



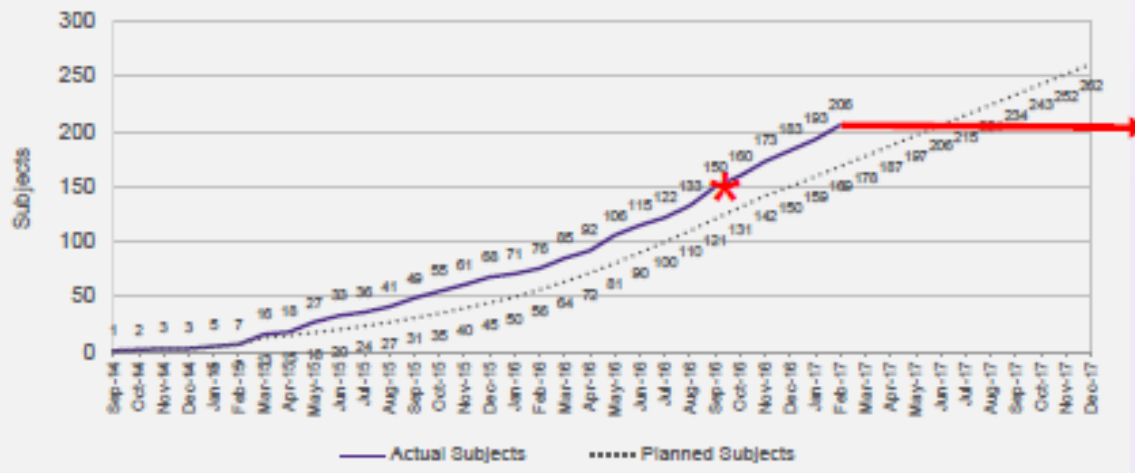


Sélection CTP/DWI de patients avec zone de « tissu à sauver » significative

TRIAL ENROLLMENT RATE AND TERMINATION

Site Status			
Sites Qualified	36	Contracts Executed	31
Sites Initiated	30	Sites Activated to Enroll	30
IRB/EC Approvals	31	Subjects Enrolled	206

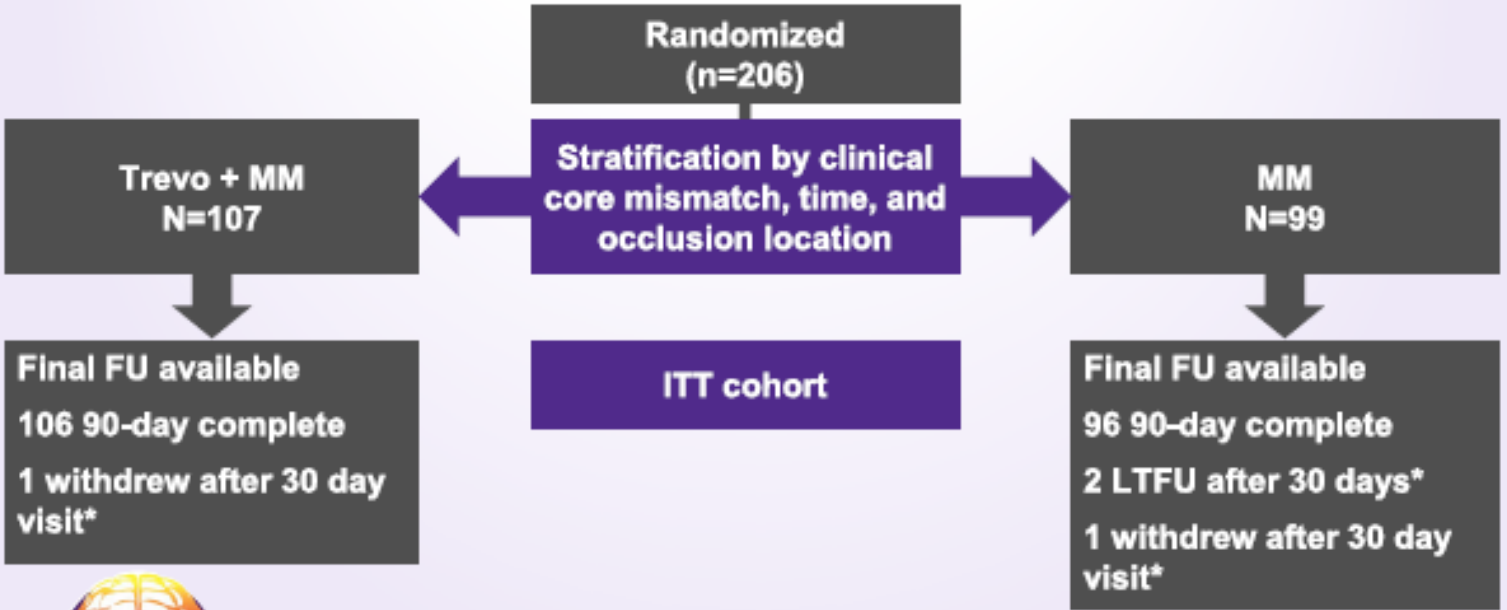
Actual / Projected Enrollment



Enrollment stopped at DSMB recommendation.

*Boundary for first enrichment not crossed.

Randomization and follow-up



DAWN TRIAL

* 30 day mRS carried forward in 4 pts
100% follow-up to 30 days

Demographics

	Treatment arm N=107	Control arm N=99	P-value
Age (years) (median, [IQR])	72.0 [60.0-79.0]	73.0 [61.0-82.0]	0.51
NIHSS, baseline (median, [IQR])	17 [13-21]	17 [14-21]	0.64
Sex, male (%)	39.3%	51.5%	0.09
Race			
White/Caucasian	66.0%	63.6%	0.77
Black or African American	21.7%	15.2%	0.28
Other*	12.3%	21.2%	0.09
IV-tPA administered	4.7%	13.1%	0.05

Patient presentation

	Treatment arm N=107	Control arm N=99	P- value
Time since time last seen well to randomization (hrs)			
Mean ± SD Median (Q1, Q3) Range (min, max)	13.4 ± 4.1 12.2 (10.2, 16.0) (6.1, 23.5)	13.0 ± 4.5 13.2 (9.4, 15.8) (6.4, 23.9)	0.53
Stroke sub-population			
Wake up stroke	64.5%	47.5%	**0.01**
Witnessed stroke	10.3%	14.1%	0.52
Un-witnessed stroke	25.2%	38.4%	0.05

DAWN TRIAL

Baseline imaging characteristics

	Treatment arm N=107	Control arm N=99	P-value
Qualifying infarct volume by site RAPID (median, [IQR])	8.0 [2.0-18.0]	8.8 [3.0-18.1]	0.99
Infarct volume by core lab (median, [IQR])	9.0 [0.0, 19.0]	11.0 [0.0-19.0]	0.78
Patients with baseline MRI (%)*	43.0%	37.8%	0.48
Patients with baseline CT/CTA/CTP(%)*	76.6%	76.5%	1.0

Baseline clot locations – core lab adjudicated

Clot location	Treatment arm N=107	Control arm N=99	P-value
ICA	20.6%	19.2%	0.86
M1	73.8%	74.7%	1.0
M2	2.8%	3.0%	1.0

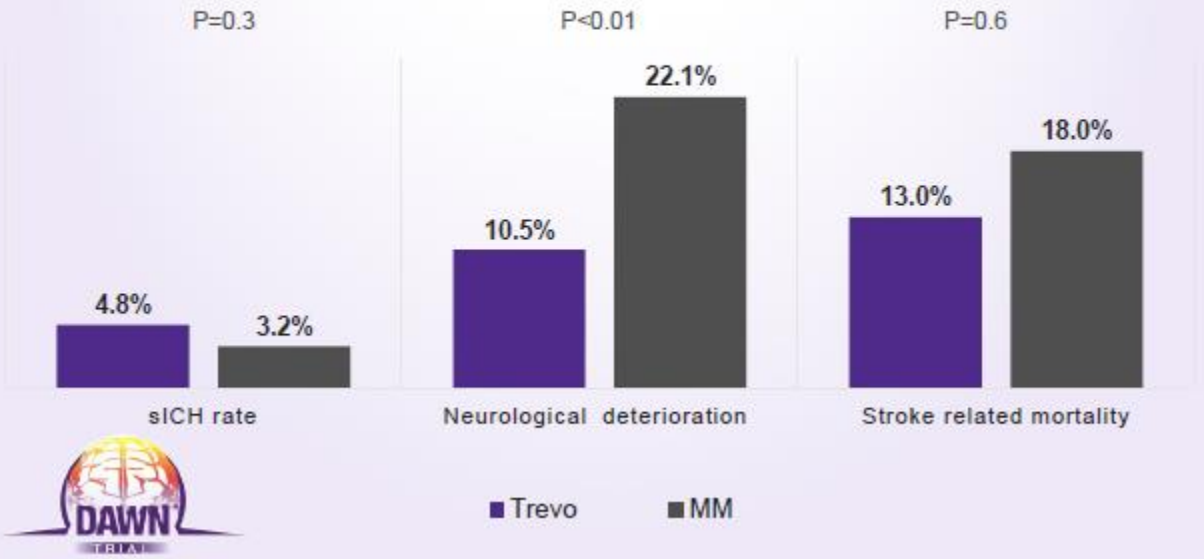
DAWN TRIAL

Procedural characteristics and outcomes

	Treatment arm N=107
Procedure duration (minutes) (median IQR)	56.0 [33.0-90.0]
Total number of Trevo device passes (median IQR)	2.0 [1.0-3.0]

Core lab adjudicated TICIs	Treatment arm N=107
Post procedure mTICI ≥ 2B	84.0%
Post procedure oTICI ≥ 2B*	72.6%
Post procedure TICI 3	10.4%

CEC adjudicated safety outcomes

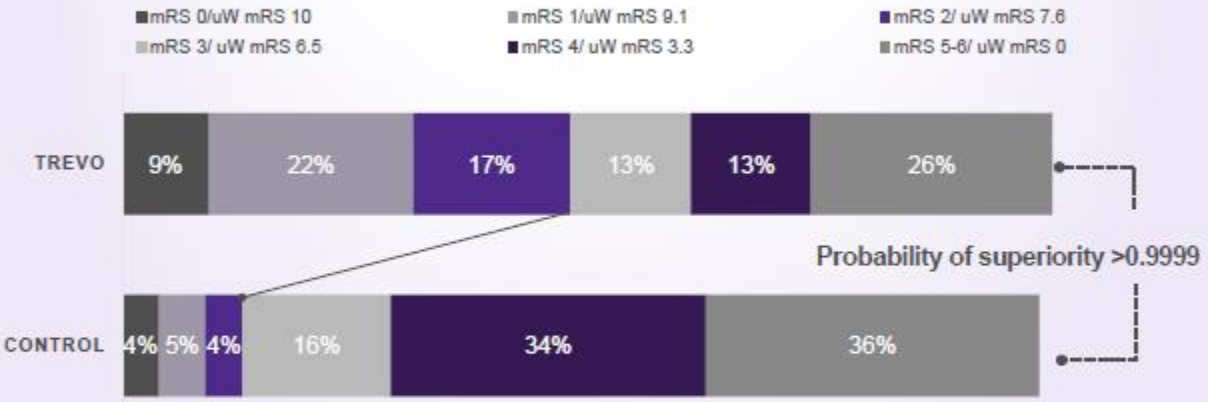


Co-primary endpoints

	Trevo	MM	Treatment benefit (95% CI)	Bayesian probability of superiority
Day 90 weighted mRS	5.5 ± 3.8	3.4 ± 3.1	2.1 (1.20, 3.12)	>0.9999*
Day 90 mRS (0-2)	48.6%	13.1%	35.5% (23.9%, 47.0%)	>0.9999*

NNT for 90-day functional independence = 2.8

Primary outcome

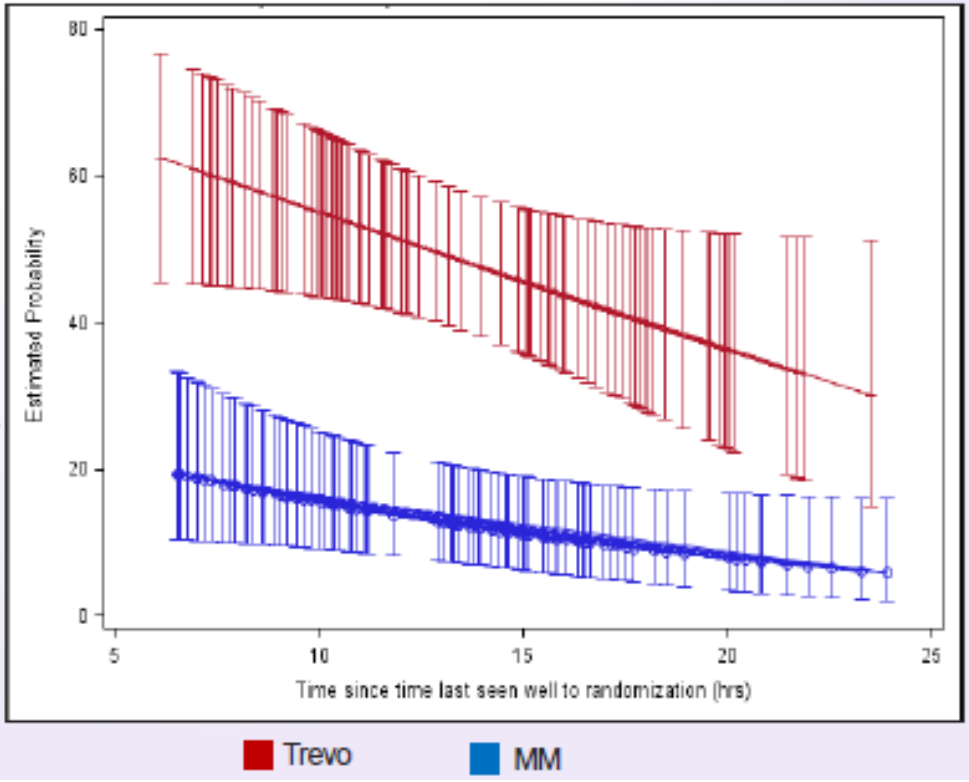


73% relative risk reduction of dependency in ADL's
NNT for any lower disability 2.0

DAWN TRIAL

90 Day mRS 0-2 by TLSW to Randomization

	Trevo	MM	P-value
6-12h	55.1%	20.0%	<0.001
12-24h	43.1%	7.4%	<0.001



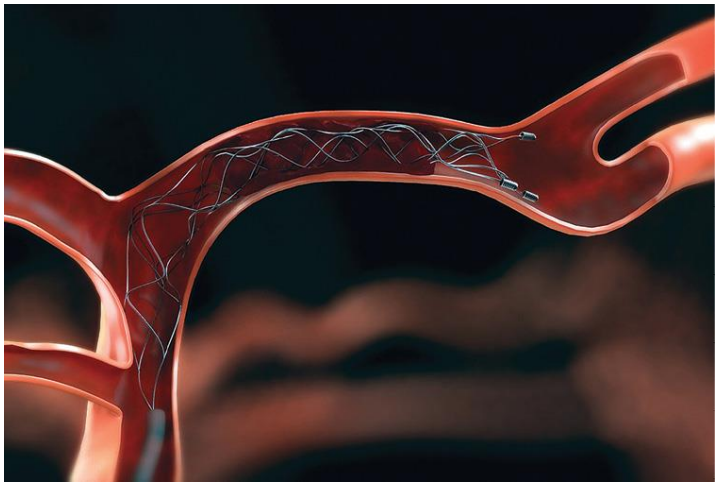
Etude DAWN
Conclusions

- **La thrombectomie mécanique par stent TREVO chez les patients éligibles selon les critères DAWN (fenêtre thérapeutique entre six et 24 heures) augmente très significativement les chances d'indépendance fonctionnelle (m-RS = 0-2) en comparaison au traitement médical (49% versus 13%, NST = 2,8)**

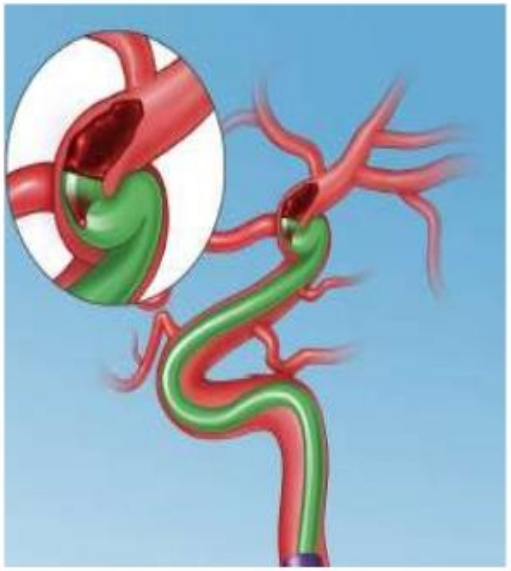
- L'effet du traitement persiste jusqu'à 24 heures mais il est plus important si le patient est traité tôt

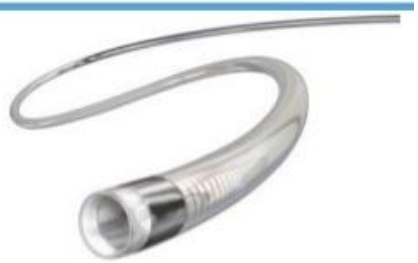
- La sécurité de la thrombectomie mécanique au-delà de six heures apparaît comparable à celle observée avant six heures

Thrombectomie mécanique par stent-retriever versus thrombo-aspiration (ADAPT)



Penumbra Device (ADAPT Technique)





- Direct Aspiration by large catheter at the site of thrombus
- Rapid and Painless Clot Extraction
- Intact Clot Extraction may reduce distal emboli

ASTER Study Design

Design	Prospective, randomized, multicenter, controlled open-label design with blinded outcome evaluation (PROBE)
Population	Patients admitted with suspected ischemic anterior circulation stroke secondary to LVO with onset of symptoms <6 hours
Randomization	➢ Randomized 1:1 to ADAPT or SR ➢ Stratified by center and prior IV thrombolysis.
Rescue	If the assigned treatment technique was not successful after 3 attempts, the procedure was continued with another technique at the operator's discretion.
Sites	8 centers in France
Sample Size	380 patients to detect an absolute difference of 15% in primary outcome ➢ Revascularization rate of 70% in the control (SR) arm ➢ Two-sided test (alpha=5%, power=90%) ➢ Rate of spontaneous recanalization and catheterization failures of 15%

Protocol submitted, IJS

ASTER TRIAL

Lapergue et al., 2017

Etude ASTER

- Age > 18 ans
- Occlusion ACI, ACM M1 ou M2
- Avec ou sans rtPA IV
- Revascularisation dans les six heures
- Evaluation en aveugle

Primary Outcome

Core Lab assessed reperfusion outcomes

Post-Procedure (all treatments)

Frontline Treatment	TICI 2b/3 % Patients
ADAPT	164 (85.4%)
STENT RETRIEVER	157 (83.1%)

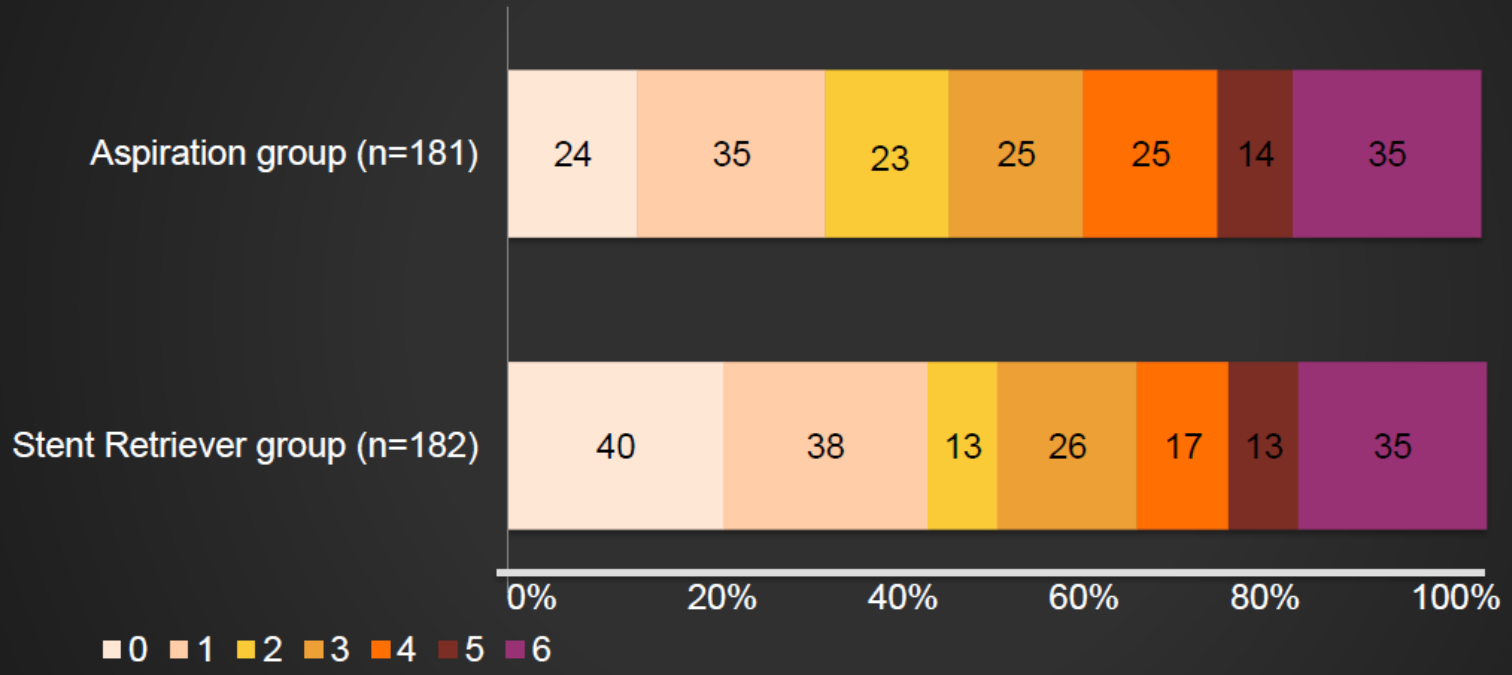
P value = 0.53

ASTER TRIAL

Lapergue et al., 2017

Efficacy endpoints

Distribution of Modified Rankin Scale scores at 3 month



Common odds ratio (OR) for 1 point improvement of 0.76 (95%CI, 0.53 to 1.10)., P=0,15

ASTER TRIAL

Thrombectomie mécanique et anesthésie générale

Thrombectomie mécanique
Pour ou contre l'AG?

- **Pour l'AG**
  - Amélioration de la sécurité de la procédure, pas de mouvements de la tête du patient (risque d'hémorragie intracrânienne), protection des voies aériennes
  - Réduction du délai ponction artérielle - reperfusion angiographique (pas d'agitation)

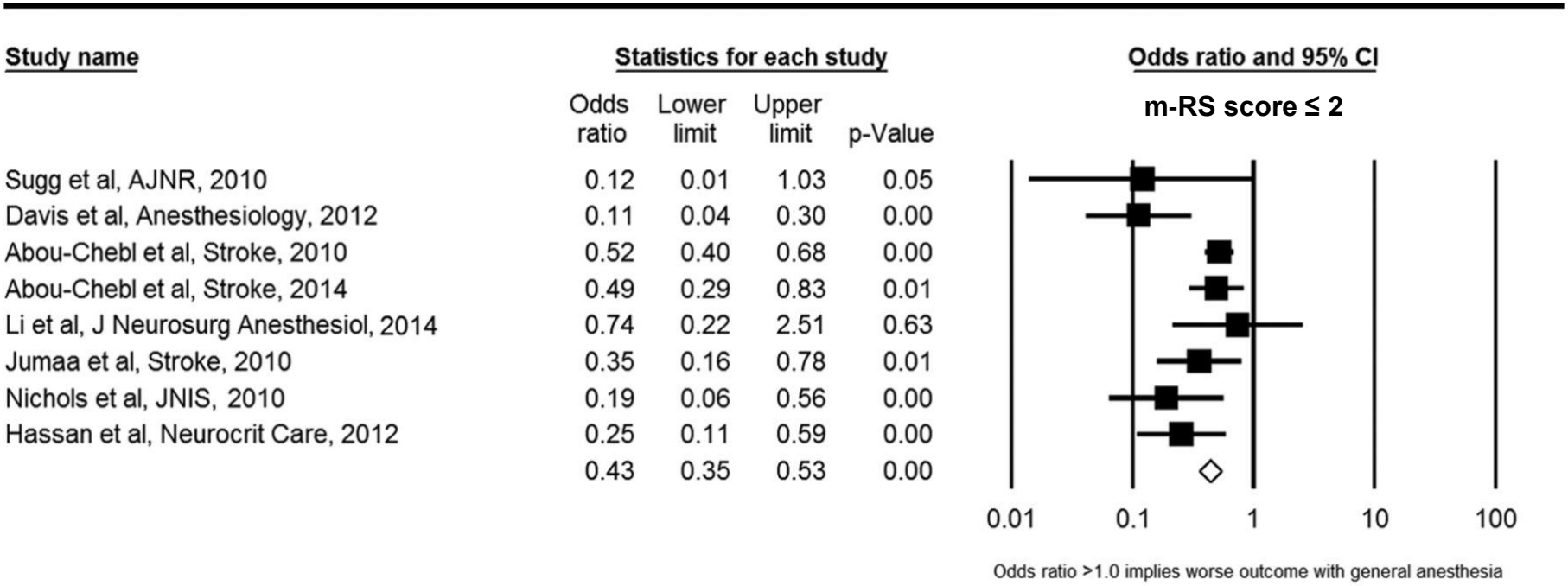
- **Contre l'AG**
  - Retard à la ponction artérielle
  - Perturbations hémodynamiques (hypotension, tachycardie) éventuelles lors de l'induction
  - Effets sur l'autorégulation cérébrale des agents anesthésiques
  - Ne permet pas la surveillance de l'état clinique neurologique

Thrombectomie mécanique et anesthésie générale

- **Peu de données issues d'études prospectives randomisées**
- **Taux d'AG variable selon les études**
  - MR CLEAN et EXTEND-IA : 1/3 des patients
  - REVASCAT et ESCAPE < 10%
- **Rôle crucial de l'anesthésiste**
  - AG systématique dans certains centres
  - L'instabilité de la situation clinique, l'agitation du patient peuvent conduire à transformer une sédation consciente en anesthésie générale
  - La douleur lors de l'extraction du thrombus doit être prise en charge

Conscious Sedation versus General Anesthesia during Endovascular Acute Ischemic Stroke Treatment: A Systematic Review and Meta-Analysis

W. Brinjikji, M.H. Murad, A.A. Rabinstein, H.J. Cloft, G. Lanzino, and D.F. Kallmes



9 études, 1 956 patients

Association AG – mauvaise évolution mais facteurs de confusion (sévérité clinique, site d'occlusion)
► des études randomisées contrôlées sont nécessaires

Brinjikji et al. *AJNR* 2015;36:525-529

JAMA | Original Investigation

Effect of Conscious Sedation vs General Anesthesia on Early Neurological Improvement Among Patients With Ischemic Stroke Undergoing Endovascular Thrombectomy

A Randomized Clinical Trial

SIESTA

Etude randomisée mono-centrique

AG (n = 73) versus sédation consciente (n = 77)

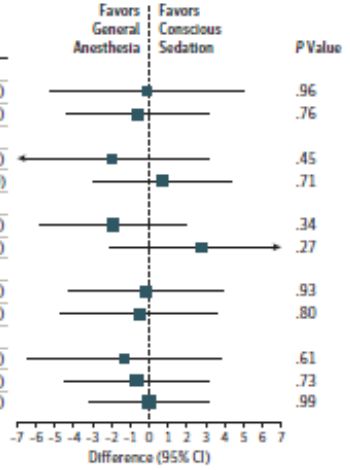
150 patients AIC carotidiens

NIHSS médian = 17

Pas de différence concernant l'amélioration neurologique à 24 heures

Figure 2. Primary Outcome as the Improvement of NIHSS Score in Prespecified Subgroups[a]

Subgroup	No. of Patients by Group: General Anesthesia	No. of Patients by Group: Conscious Sedation	Change in NIHSS Score: General Anesthesia	Change in NIHSS Score: Conscious Sedation	Difference (95% CI)	P Value
NIHSS score[b]						
>17	30	31	-3.4 (-7.5 to 0.8)	-3.5 (-6.9 to -0.2)	-0.14 (-5.29 to 5.01)	.96
≤17	43	46	-3.1 (-6.1 to -0.1)	-3.6 (-6.0 to -1.2)	-0.60 (-4.36 to 3.16)	.76
Age, y						
≤70	29	31	-1.3 (-5.6 to 3.0)	-3.3 (-6.5 to -0.1)	-2.01 (-7.15 to 3.13)	.45
>70	44	46	-4.5 (-7.4 to -1.6)	-3.8 (-6.2 to -1.3)	0.70 (-3.01 to 4.40)	.71
Sex						
Men	48	42	-1.7 (-4.9 to 1.5)	-3.6 (-5.8 to -1.4)	-1.91 (-5.79 to 1.97)	.34
Women	25	35	-6.2 (-9.7 to -2.7)	-3.5 (-7.0 to -0.1)	2.75 (-2.13 to 7.64)	.27
Recombinant tissue-type plasminogen activator						
No	27	27	-3.4 (-6.4 to -0.3)	-3.4 (-6.4 to -0.5)	-0.19 (-4.31 to 3.94)	.93
Yes	46	50	-3.1 (-6.6 to 0.3)	-3.7 (-6.2 to -1.1)	-0.54 (-4.69 to 3.61)	.80
ASPECTS score[c]						
<8	21	32	-1.0 (-6.0 to 3.9)	-2.4 (-5.3 to 0.6)	-1.35 (-6.49 to 3.80)	.61
8-10	52	42	-4.1 (-6.9 to -1.3)	-4.8 (-7.4 to -2.3)	-0.67 (-4.46 to 3.12)	.73
TICI 2b/3[d]	65	62	-4.7 (-7.1 to -2.4)	-4.8 (-6.9 to -2.6)	-0.03 (-3.21 to 3.15)	.99



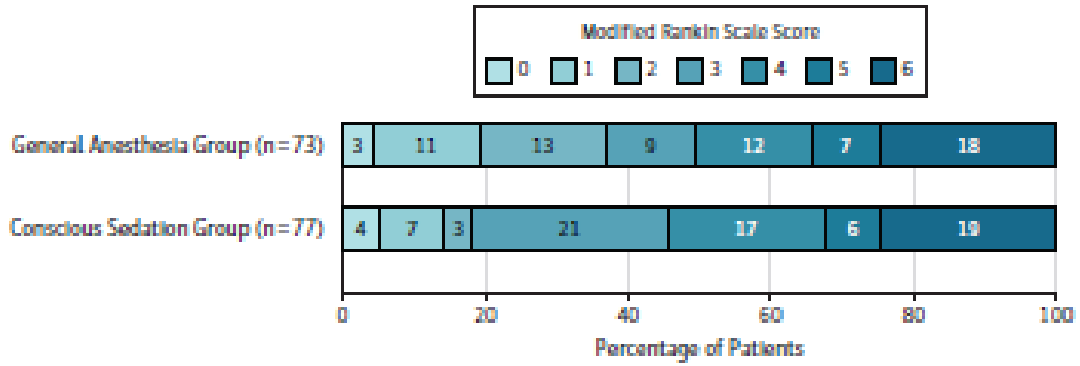
Schönenberger et al. *JAMA.* 2016;316:1986-1996

JAMA | Original Investigation

Effect of Conscious Sedation vs General Anesthesia on Early Neurological Improvement Among Patients With Ischemic Stroke Undergoing Endovascular Thrombectomy

A Randomized Clinical Trial

Figure 3. Functional Outcome at 90-Day Follow-up in the Intent-to-Treat Population



m-RS = 0-2, 37% AG versus 18% SC (P=0,01)

Schönenberger et al. *JAMA.* 2016;316:1986-1996

General Anesthesia Versus Conscious Sedation for Endovascular Treatment of Acute Ischemic Stroke

The AnStroke Trial (Anesthesia During Stroke)

Pia Löwhagen Hendén, MD*; Alexandros Rentzos, MD*; Jan-Erik Karlsson, MD, PhD; Lars Rosengren, MD, PhD; Birgitta Leiram, MD; Henrik Sundeman, MD, PhD; Dennis Dunker, MD; Kunigunde Schnabel, MD†; Gunnar Wikholm, MD, PhD; Mikael Hellström, MD, PhD; Sven-Erik Ricksten, MD, PhD

- **Etude prospective mono-centrique randomisée**
- 90 patients AIC carotidiens randomisés AG versus sédation consciente
- Age médian = 72 ans (65-80)
- Score NIHSS médian = 18 (15-22)

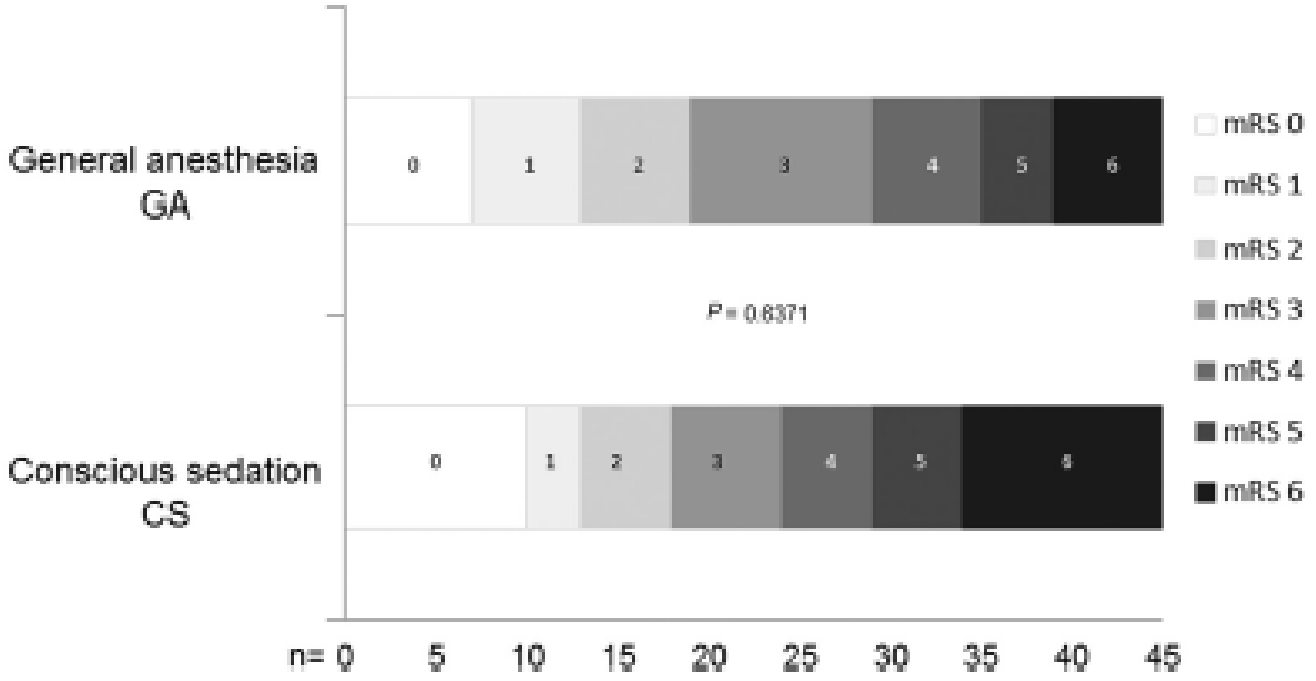
	GA	CS
	n=45	n=45
NIHSS score	20 (15.5–23)	17 (14–20.5)
Intravenous thrombolysis treatment, n (%)	33 (73.3)	36 (80)
Occlusion site, n (%)		
Carotid-T occlusion	15 (33)	9 (20)
Distal ICA	0 (0)	1 (2.2)
First segment of MCA (M1)	26 (58)	26 (58)
First segment of MCA (M1)+distal branches (A2, A3, M2, and M3)	4 (9)	1 (2)
Second segment of MCA (M2)	0 (0)	8 (18)
Left hemisphere, n (%)	26 (58)	17 (38)
ASPECTS score, 1–10	10 (8–10)	10 (9–10)
Collateral circulation, 1–5	2 (1–4)	1 (1–3)

ASPECTS indicates Alberta Stroke Program Early CT score; CS, conscious sedation; GA, general anesthesia; ICA, internal carotid artery; MCA, middle cerebral artery; and NIHSS; National Institutes of Health Stroke Scale.

Hendén et al. *Stroke*. 2017;48:1601-1607

General Anesthesia Versus Conscious Sedation for Endovascular Treatment of Acute Ischemic Stroke

The AnStroke Trial (Anesthesia During Stroke)



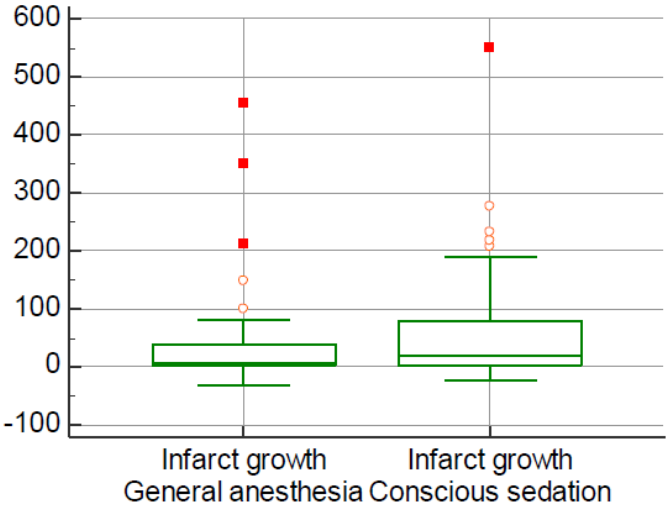
m-RS = 0-2 : 40% groupe sédation consciente versus 42% groupe AG

Hendén et al. *Stroke*. 2017;48:1601-1607

Etude GOLIATH

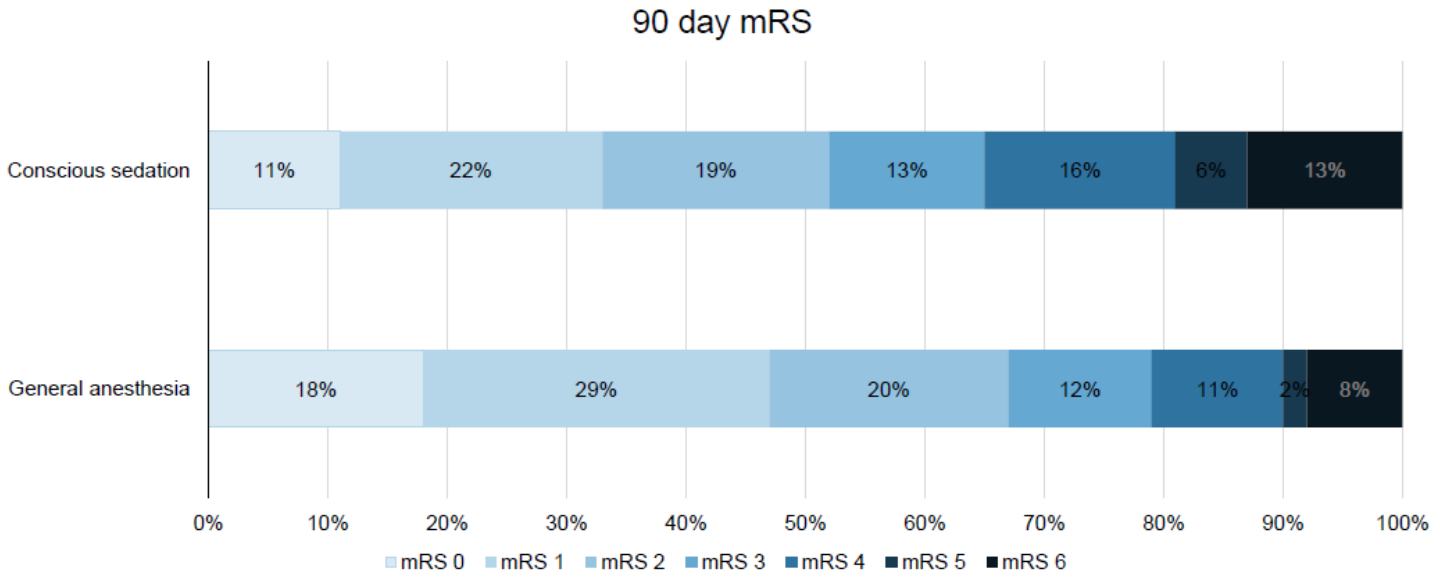
Results, primary outcome

	General anesthesia, n=65	Conscious sedation, n=63	p-value
Median acute infarct (ml)	10.5 (2.4-23.6)	13.3 (5.2-31.1)	0.26
Median final infarct (ml)	22.3 (8.1-64.5)	38.0 (16.7-128.0)	0.04
Median infarct growth (ml)	8.2 (2.2-38.6)	19.4 (2.4-79.0)	0.10



Etude GOLIATH

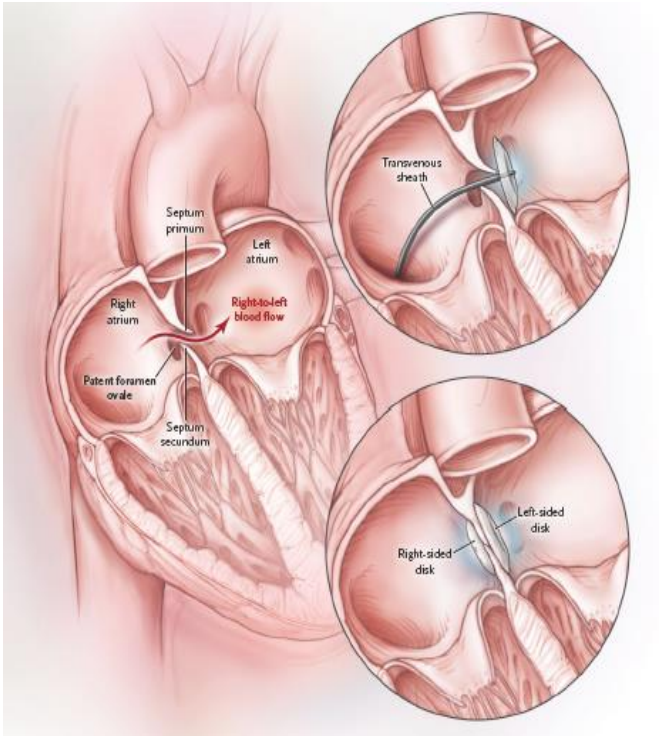
Results, secondary outcome



OR of lower mRS for patients treated with GA = 1.91 (95% 1.03-3.56)

Danish Stroke Centre

Foramen ovale perméable et AVC cryptogéniques



25% des AVC sont de nature cryptogénique

Un FOP est mis en évidence chez 40 à 50% des patients ayant présenté un AVC cryptogénique

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Patent Foramen Ovale Closure or Antiplatelet Therapy for Cryptogenic Stroke

Lars Søndergaard, M.D., Scott E. Kasner, M.D., John F. Rhodes, M.D., Grethe Andersen, M.D., D.M.Sc., Helle K. Iversen, M.D., D.M.Sc., Jens E. Nielsen-Kudsk, M.D., D.M.Sc., Magnus Settergren, M.D., Ph.D., Christina Sjöstrand, M.D., Ph.D., Risto O. Roine, M.D., David Hildick-Smith, M.D., J. David Spence, M.D., and Lars Thomassen, M.D., for the Gore REDUCE Clinical Study Investigators*

N Engl J Med 2017;377:1033-42.
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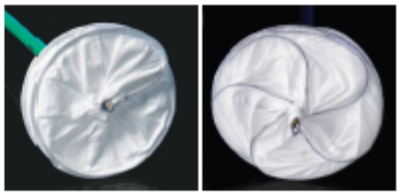
Etude REDUCE



GORE® HELEX® (left) and GORE® CARDIOFORM (right) Septal Occluders

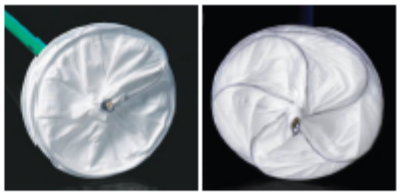
- **Objectif**
  - Etablir la supériorité de la fermeture du FOP en association au traitement antiagrégant plaquettaire sur le traitement antiagrégant plaquettaire seul dans la réduction du risque de récidive clinique d'AVC ischémique ou de nouvel infarctus cérébral

- **Etude randomisée, contrôlée, ouverte**

- **664 patients AVC ou AIT cryptogéniques (18 à 60 ans) randomisés selon un ratio 2/1**
  - 80% de shunt modéré à important
  - Fermeture par prothèse GORE® HELEX ou GORE® CARDIOFORM
  - Traitement médical : traitement antiagrégant plaquettaire seul

- **63 centres dans sept pays**
  - USA, Canada, Royaume-Uni, Danemark, Finlande, Norvège, Suède

Etude REDUCE

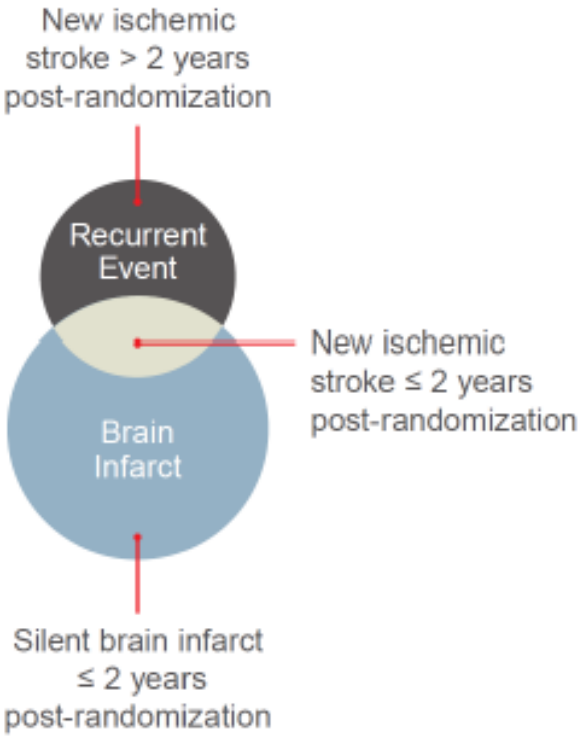


GORE® HELEX® (left) and GORE® CARDIOFORM (right) Septal Occluders

- **Traitement médical**
  - **Différentes options de traitement antiagrégant plaquettaire**
    - Aspirine seule (75 à 325 mg par jour)
    - Aspirine (50 à 100 mg par jour) et Dipyridamole (225 à 400 mg par jour)
    - Clopidogrel (75 mg par jour)
    - Autres associations ou utilisation d'anticoagulants interdites
  - Chez tous les patients pendant toute la durée de l'étude
  - Chaque centre devait traiter l'ensemble des patients avec la même option de traitement antiagrégant plaquettaire
- **Suivi**
  - **Suivi jusqu'à cinq ans**
  - Examen neurologique à 1, 6, 12, 18, 24, 36, 48, et 60 mois
  - Echographie cardiaque avec épreuve de contraste dans le groupe fermeture à 1, 12, et 24 mois
  - IRM encéphalique à l'inclusion et à 24 mois

Etude REDUCE
Critères d'évaluation principaux

- Absence de récidive clinique d'AVC ischémique
- Survenue d'un nouvel infarctus cérébral (y compris infarctus silencieux*) dans les 24 mois



* Nouvelle lésion IRM en hypersignal T2, diamètre ≥3 mm; adjudication centralisée

Etude REDUCE
Résultats

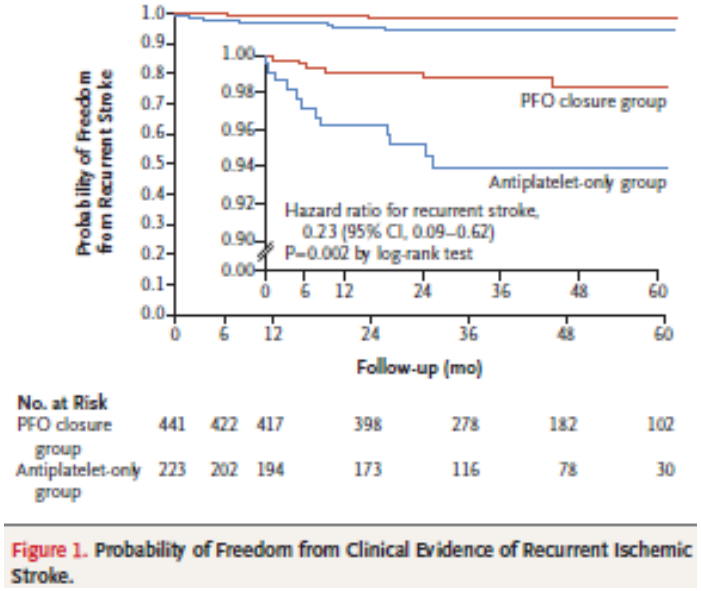


Figure 1. Probability of Freedom from Clinical Evidence of Recurrent Ischemic Stroke.

- **Fermeture effective dans 94,5% des cas**

- **Critère primaire**
  - **Réduction de 77% (p=0,001) du risque de récidive d'AVC ischémique dans le groupe fermeture**
  - Suivi moyen de 3,4 ans
  - **NST = 28 pour prévenir un AVC dans les deux ans**

- **Critère nouvel infarctus cérébral (incluant infarctus silencieux)**
  - Réduction de 49% (p=0,024) du risque de nouvel infarctus cérébral dans le groupe fermeture
  - 5,7% versus 11,3%

- Evénements indésirables graves: pas de différence significative entre les deux groupes (faibles taux d'hémorragie, de TVP et d'EP)

Etude REDUCE
Résultats

- Evénements indésirables graves
  - Liés à la prothèse : 1,4%
  - Liés à la procédure : 2,5%

- **Augmentation significative du risque de fibrillation atriale dans le groupe fermeture (6,6% versus 0,4%)**

- Dans la majorité des cas, la fibrillation atriale survenait en période péri-procédurale (80% dans les 30 jours suivant la fermeture) et était de résolution rapide (70% dans les deux jours)

REDUCE
CLINICAL STUDY

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 14, 2017 VOL. 377 NO. 11

Patent Foramen Ovale Closure or Anticoagulation vs. Antiplatelets after Stroke

J.-L. Mas, G. Derumeaux, B. Guillon, E. Massardier, H. Hosseini, L. Mechtouff, C. Arquizan, Y. Béjot, F. Vuillier, O. Detante, C. Guidoux, S. Canaple, C. Vaduva, N. Dequatre-Ponchelle, I. Sibon, P. Garnier, A. Ferrier, S. Timsit, E. Robinet-Borgomano, D. Sablot, J.-C. Lacour, M. Zuber, P. Favrole, J.-F. Pinel, M. Apoil, P. Reiner, C. Lefebvre, P. Guérin, C. Piot, R. Rossi, J.-L. Dubois-Randé, J.-C. Eicher, N. Meneveau, J.-R. Lusson, B. Bertrand, J.-M. Schleich, F. Godart, J.-B. Thambo, L. Leborgne, P. Michel, L. Pierard, G. Turc, M. Barthelet, A. Charles-Nelson, C. Weimar, T. Moulin, J.-M. Juliard, and G. Chatellier, for the CLOSE Investigators*

CLOSE
Methods

Objective

To assess whether (1) PFO closure with device plus (chronic) antiplatelet therapy on one hand, and (2) oral anticoagulants on the other hand, are superior to antiplatelet therapy, to prevent stroke recurrence in patients 16 to 60 years old with cryptogenic stroke and PFO with atrial septal aneurysm or PFO with large shunt.

Trial design

- Academic-driven, multicenter (32 sites in France and 2 sites in Germany), randomized, open-label, three-arm superiority trial with blinded adjudication of outcome events.
- Funded by the French Ministry of Health.
- 900 patients: 80% power to detect a 50% reduction in the rate of the primary outcome (3.5%/yr in the reference arm) in at least one experimental arm, 5-year study, α=5%.
- 663 patients included from Dec. 2008 to Dec. 2014. Follow-up until Dec. 2016. Mean follow-up 5.3 years (3544 patient-years).

CLOSE
Methods

Key inclusion criteria

- Recent (<= 6 months) ischemic stroke, confirmed by neuroimaging, mRS <= 3
- Strictly defined causes of stroke other than PFO ruled out by appropriate investigations
- PFO with ASA > 10 mm (TTE), PFO with large shunt > 30 microbubbles (TTE,TEE) confirmed by echo core lab before randomization

Key exclusion criteria

- Contraindication to oral anticoagulants and PFO closure
- Contraindication to antiplatelet therapy
- Increased bleeding risk
- Expected poor compliance or inability to attend follow-up visits
- Anatomical to device placement

Outcomes

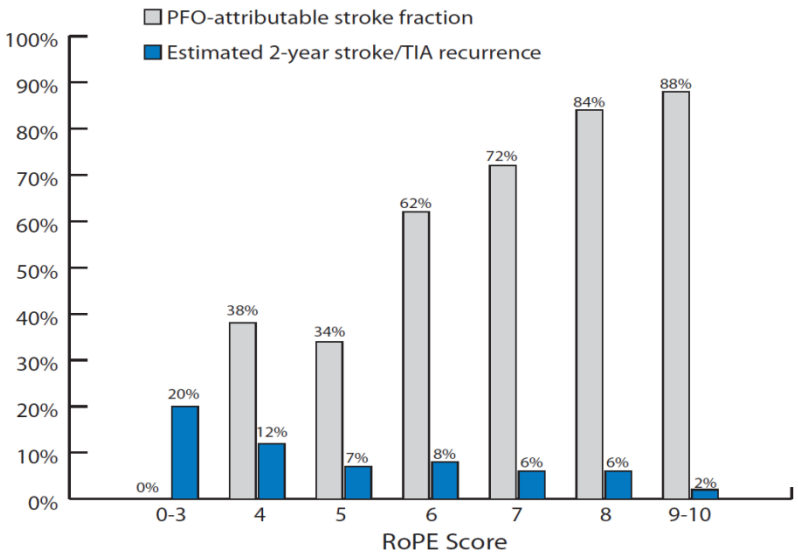
- **Primary** : fatal or nonfatal stroke
- **Secondary** : composite of ischemic stroke, TIA, or systemic embolism, all-cause mortality, vascular death, success of device implantation and success of PFO closure
- **Safety** : major procedural complications and major hemorrhagic complications

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Randomization Groups 1 and 2	
	PFO Closure Group (N=238)	Antiplatelet-Only Group (N=235)
Age — yr	42.9±10.1	43.8±10.5
Male sex — no. (%)	137 (57.6)	142 (60.4)
Medical history		
Hypertension — no. (%)	27 (11.3)	24 (10.2)
Diabetes mellitus — no. (%)	3 (1.3)	9 (3.8)
Current smoker — no. (%)	68 (28.6)	69 (29.4)
Hypercholesterolemia — no. (%)	30 (12.6)	36 (15.3)
Body mass index ≥30 — no. (%)†	32 (13.4)	27 (11.5)
Oral contraceptive pills — no./total no. (%)	42/101 (41.6)	37/93 (39.8)
Migraine — no. (%)‡	67 (28.2)	78 (33.2)
RoPE score**	7.4±1.3	7.2±1.3
Septal anomaly — no. (%)		
PFO with large shunt without atrial septal aneurysm	157 (66.0)	161 (68.5)
PFO with large shunt and atrial septal aneurysm	59 (24.8)	62 (26.4)
PFO with mild-to-moderate shunt and atrial septal aneurysm	22 (9.2)	12 (5.1)

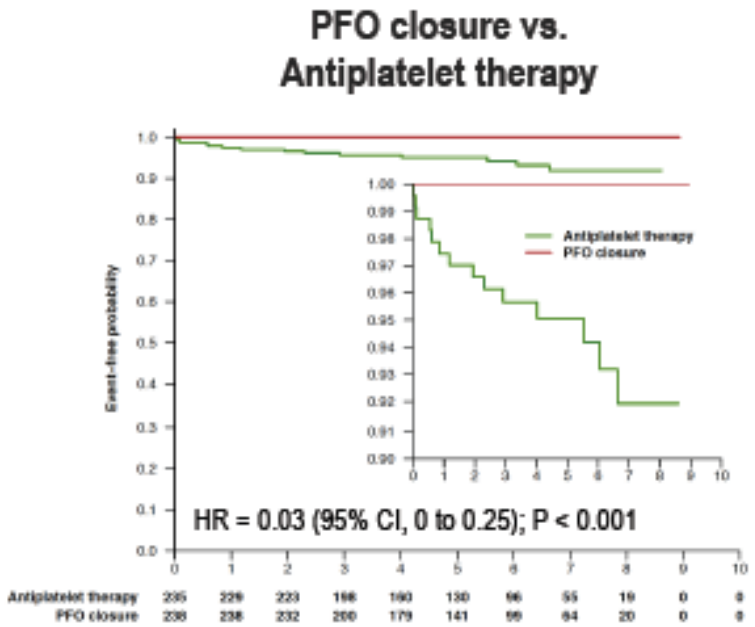
TABLE 1. RoPE SCORE CALCULATOR

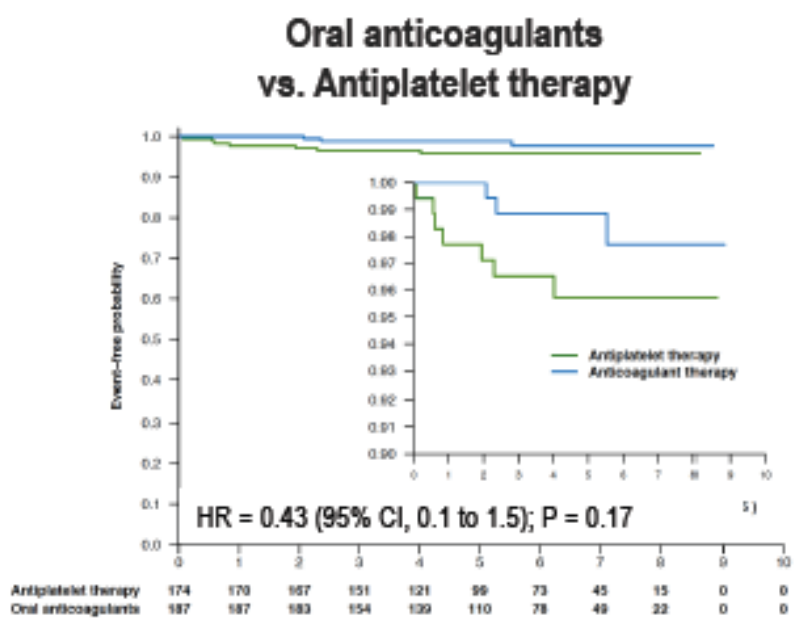
Patient Characteristic	Points
No history of hypertension	+1
No history of diabetes	+1
No history of stroke or TIA	+1
Nonsmoker	+1
Cortical infarct on imaging	+1
Age (y)	
18–29	+5
30–39	+4
40–49	+3
50–59	+2
69–69	+1
≥ 70	+0
Total RoPE score	0–10



Etude CLOSE
Résultats

663 patients AVC cryptogéniques randomisés - Suivi moyen : 5,3 ans
14 AVC dans le groupe AAP (n = 235)





Réduction absolue du risque de récidive d'AVC à 5 ans de 4,9%
NST = 20 pour éviter un AVC dans les 5 ans

Etude CLOSE
Complications

Table 3. Procedural Complications and Serious Adverse Events.*

Complication or Event	Randomization Groups 1 and 2			Randomization Groups 1 and 3		
	PFO Closure Group (N=238)	Antiplatelet-Only Group (N=235)	P Value	Anticoagulant Group (N=187)	Antiplatelet-Only Group (N=174)	P Value
	no. of patients (%)			*no. of patients (%)*		
Major or fatal device-related or procedure-related complication†	14 (5.9)	NA	NA	NA	NA	NA
Major or fatal bleeding complication	2 (0.8)	5 (2.1)	0.28	10 (5.3)	4 (2.3)	0.18
Atrial fibrillation or flutter‡	11 (4.6)§	2 (0.9)	0.02	0	2 (1.1)	0.23
Death	0	0	NA	1 (0.5)¶	0	0.65
At least one serious adverse event	85 (35.7)	78 (33.2)	0.56	62 (33.2)	59 (33.9)	0.88

* Definitions of major or fatal device-related or procedure-related complications, definitions of major or fatal bleeding complications, and a full list of serious adverse events are provided in the Supplementary Appendix.
† Major or fatal device-related or procedure-related complications in the PFO closure group are listed for those that occurred within 30 days after the procedure and included atrial fibrillation (9 patients), atrial flutter (1 patient), supraventricular tachycardia (2 patients), air embolism (1 patient), and hyperthermia resulting in prolongation of hospitalization (1 patient).
‡ Atrial fibrillation or flutter was classified as cases that required treatment for more than 1 month.
§ In 10 patients, atrial fibrillation or flutter occurred within 30 days after the procedure.
¶ The one death was due to pancreatic cancer.

Pas de récidive de FA dans le groupe fermeture (suivi médian 4,4 ans)
11 patients AC/FA, 10 sous anticoagulants, arrêt des anticoagulants chez 7 patients/10

Etude CLOSE
Conclusions

- La fermeture du FOP associée au traitement antiagrégant plaquettaire réduit le risque de récidive d'AVC chez les patients de 16 à 60 ans ayant présenté un AVC cryptogénique et porteurs d'un FOP associé à un ASIA ou d'un FOP à large shunt, en comparaison au traitement antiagrégant plaquettaire seul

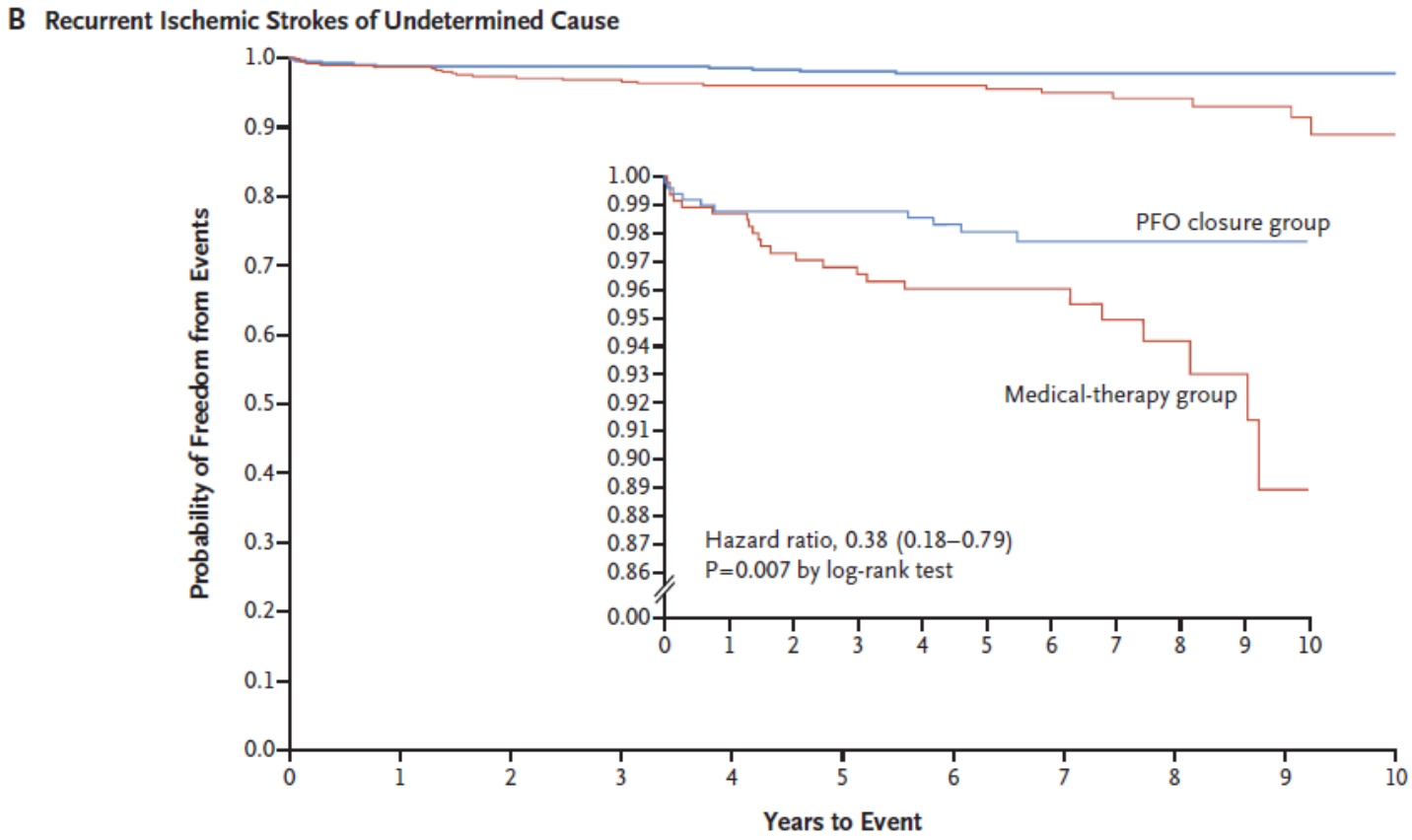
- NST = 20 pour éviter un AVC dans les 5 ans

- La fermeture du FOP est associée à une augmentation du risque de survenue d'une fibrillation atriale (le plus souvent dans le mois suivant la procédure)

Long-Term Outcomes of Patent Foramen Ovale Closure or Medical Therapy after Stroke

N Engl J Med 2017;377:1022-32.

Jeffrey L. Saver, M.D., John D. Carroll, M.D., David E. Thaler, M.D., Ph.D., Richard W. Smalling, M.D., Ph.D., Lee A. MacDonald, M.D., David S. Marks, M.D., and David L. Tirschwell, M.D., for the RESPECT Investigators*



980 patients AIC cryptogénique, âge moyen = 45,9 ans, suivi médian = 5,9 ans

Long-Term Outcomes of Patent Foramen Ovale Closure or Medical Therapy after Stroke

Jeffrey L. Saver, M.D., John D. Carroll, M.D., David E. Thaler, M.D., Ph.D., Richard W. Smalling, M.D., Ph.D., Lee A. MacDonald, M.D., David S. Marks, M.D., and David L. Tirschwell, M.D., for the RESPECT Investigators*

Table 2. Long-Term Efficacy End Points.*

End Point	PFO Closure Group (N=499)		Medical-Therapy Group (N=481)		Hazard Ratio (95% CI)	P Value
	Patients with Event	Event Rate per 100 Patient-Yr	Patients with Event	Event Rate per 100 Patient-Yr		
	no. (%)		*no. (%)*			
Recurrent ischemic stroke	18 (3.6)	0.58	28 (5.8)	1.07	0.55 (0.31–0.999)	0.046
Recurrent ischemic stroke of undetermined cause as adjudicated with the use of ASCOD	10 (2.0)	0.32	23 (4.8)	0.86	0.38 (0.18–0.79)	0.007
Recurrent cryptogenic ischemic stroke as adjudicated with the use of TOAST	1 (0.2)	0.03	11 (2.3)	0.41	0.08 (0.01–0.58)	0.01
Transient ischemic attack	17 (3.4)	0.54	23 (4.8)	0.86	0.64 (0.34–1.20)	0.16

NST pour prévenir un AVC dans les 5 ans = 42

N Engl J Med 2017;377:1022-32.

Tipping Point for Patent Foramen Ovale Closure

Allan H. Ropper, M.D.

Table 1. Six Trials of Patent Foramen Ovale Closure for Stroke with Results Published in the *Journal*.*

Trial Name (Year of Publication)	No. of Patients	Mean or Median No. of Years of Follow-up	Comparator	Primary Outcome	Hazard Ratio†	P Value†
Trials with negative findings						
CLOSURE I (2012)[2]	909	2	Antiplatelet therapy, warfarin, or both	Composite of stroke or transient ischemic attack at 2 years, death from any cause during the first 30 days, or death from neurologic causes between 31 days and 2 years after randomization	0.78	0.37
PC (2013)[3]	909	4.1 (PFO closure group), 4.0 (medical-therapy group)	Antiplatelet therapy or anticoagulation‡	Composite of death, stroke, transient ischemic attack, or peripheral embolism	0.63	0.34
RESPECT (2013)[4]	980	2.1	Antiplatelet therapy or warfarin	Composite of recurrent nonfatal ischemic stroke, fatal ischemic stroke, or early death after randomization	0.49	0.08
Trials with positive findings						
Gore REDUCE (2017)[5]	664	3.2	Antiplatelet therapy	Ischemic stroke and new brain infarction on imaging	0.23	0.002
CLOSE (2017)[6]	663	5.3	Antiplatelet therapy or anticoagulation‡	Stroke	0.03	<0.001
RESPECT extended follow-up (2017)[7]	980	5.9	Antiplatelet therapy or warfarin	Composite of recurrent nonfatal ischemic stroke, fatal ischemic stroke, or early death after randomization	0.55	0.046