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STROKEUPDATE

AVC – Actualités thérapeutiques 2022

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Séquelles après AVC : la face cachée

Paralysie et troubles des mouvements
Troubles sensitifs
Douleurs
Trouble du langage
Troubles visuels

Fatigue
Vertiges
Maux de tête (céphalées)
Impulsivité et agressivité
Changement de personnalité
Troubles de la concentration
Problèmes de planification
Troubles émotionnels
Troubles du sommeil
Dépression
Démence
Epilepsie

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Menu

1. **Situation actuelle**
2. **Thrombolyse intraveineuse (TIV)**
   - altéplse, ténectéplase
3. **Traitement endovasculaire (TEV)**
   - TEV directe / bridging ?
   - TEV distale ?
   - Traitement des AVC à large core
4. **Protocole AVC Valais**
   - aujourd'hui et demain
5. **Antithrombotiques : ça se complique …**
   - antiagrégant vs anticoagulant, pour qui et quand ?

https://2021.eso-conference.org/scientific-programme/

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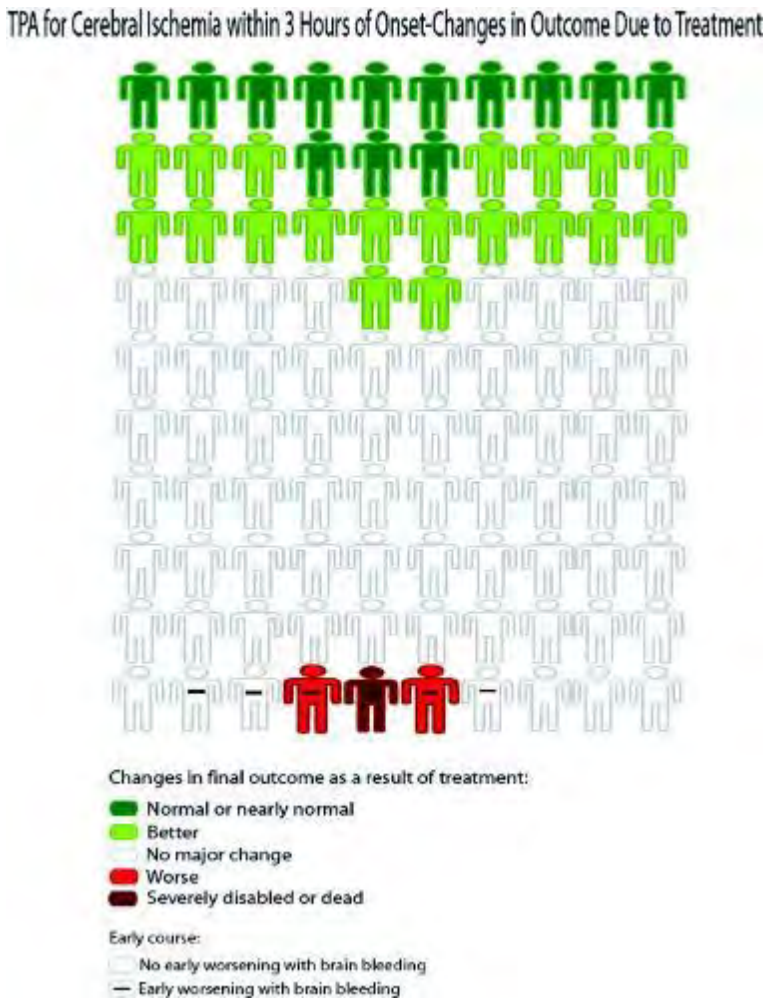
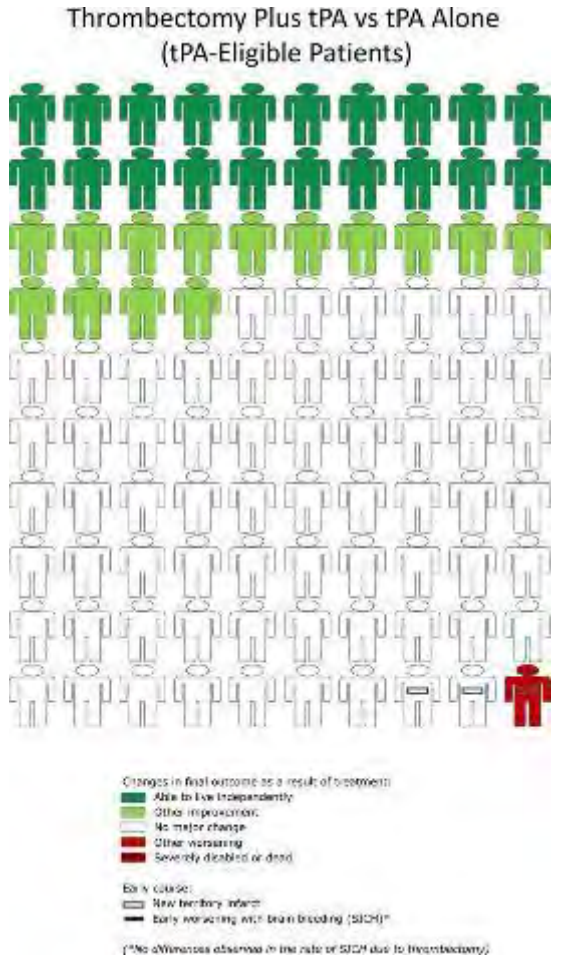
1. Situation actuelle

Bénéfice et risque de la TIV et TEV

Thrombolyse (TIV)



Thrombectomie (TEV)



https://doi.org/10.1161/STROKEAHA.109.566935 - Stroke. 2010;41:300-306
https://doi.org/10.1161/STROKEAHA.117.018715 - Stroke. 2018;49:90-97

L'AVC est une urgence !

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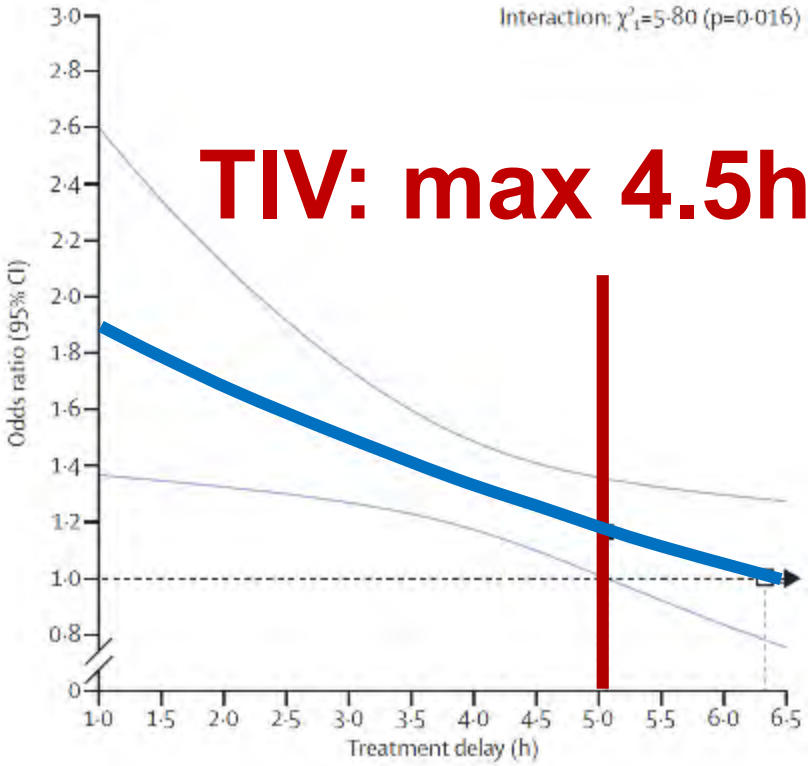
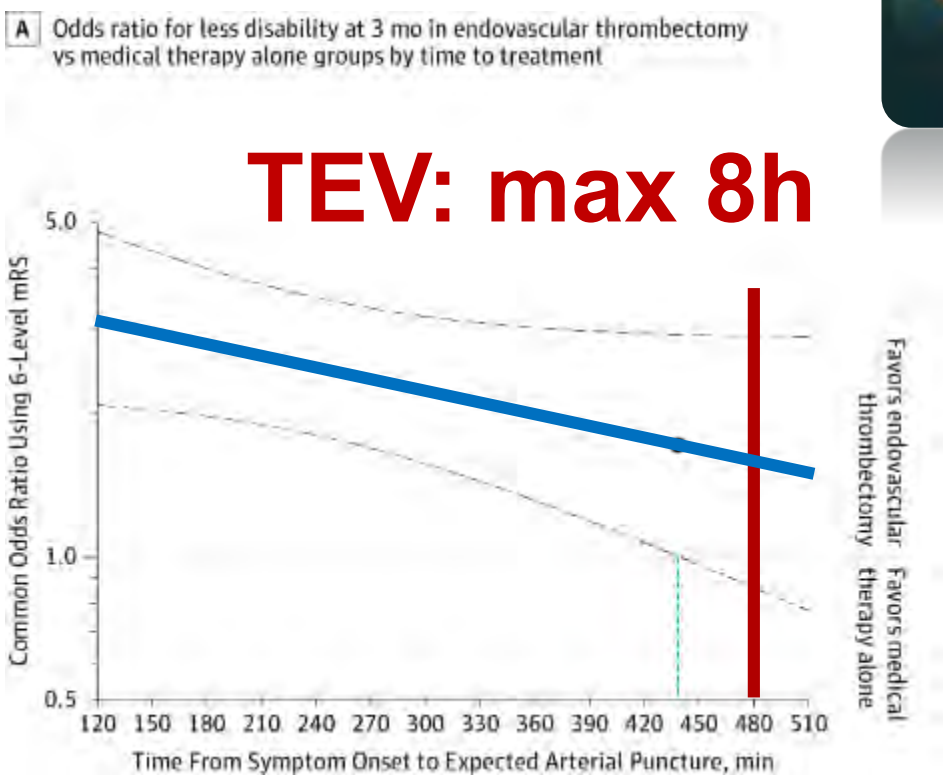
Le pronostic dépend de la rapidité de traitement



TIV: max 4.5h



TEV: max 8h

Emberson, Lees, Lyden et al, The Lancet 2014 – JL Saver, JAMA. 2016;316(12):1279

Thrombolyse intraveineuse (TIV)
Thrombectomie endovasculaire (TEV)

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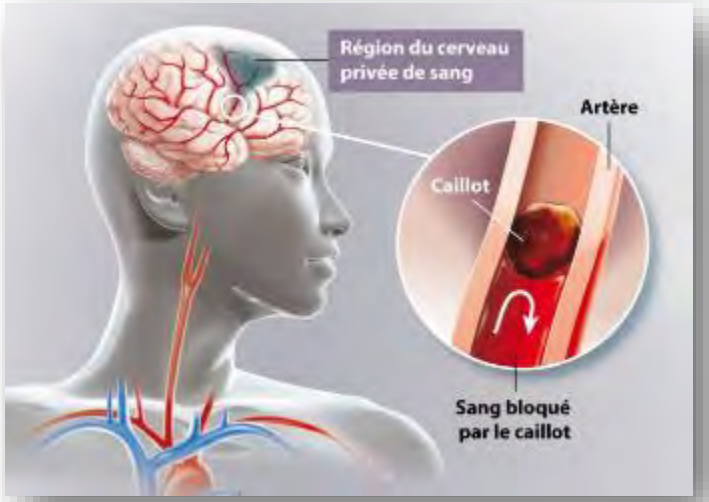
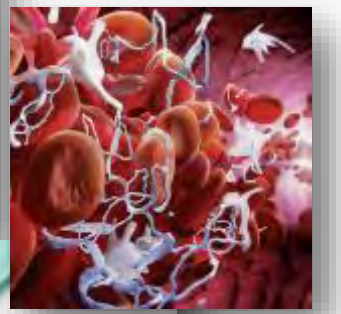
Stroke Unit ou Center

1995 (TIV)



MHS : Stroke Center

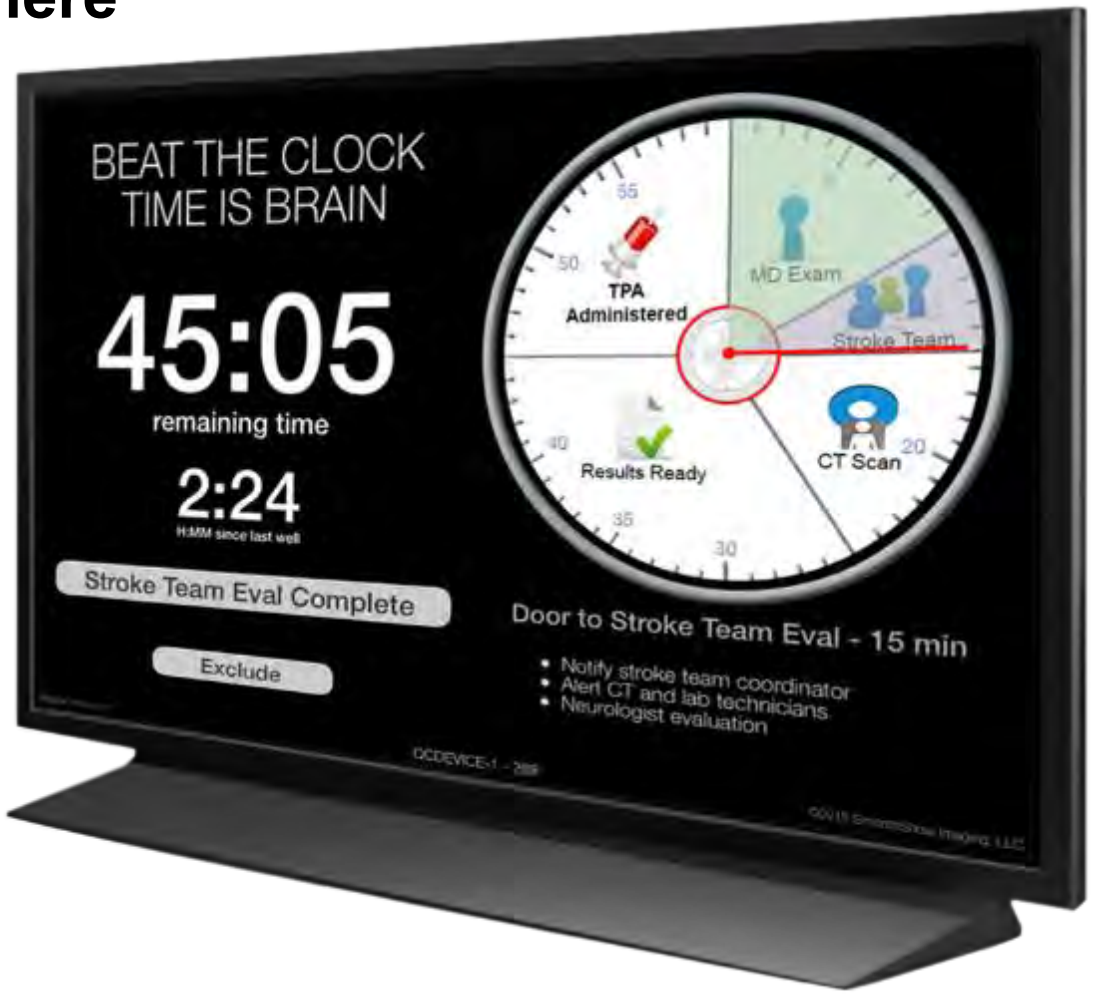
2015 (TEV)



1/3

Gagner du temps à chaque étape !

1. **Améliorer la filière préhospitalière**
2.
   - ➔ Door to CT < 15 min
   - ➔ Door to TIV < 30 min
   - ➔ Door-in-door-out < 60 min
3. **Connaître le protocole**



Recanalisation des AVC : résumé des nouvelles évidences depuis 2019

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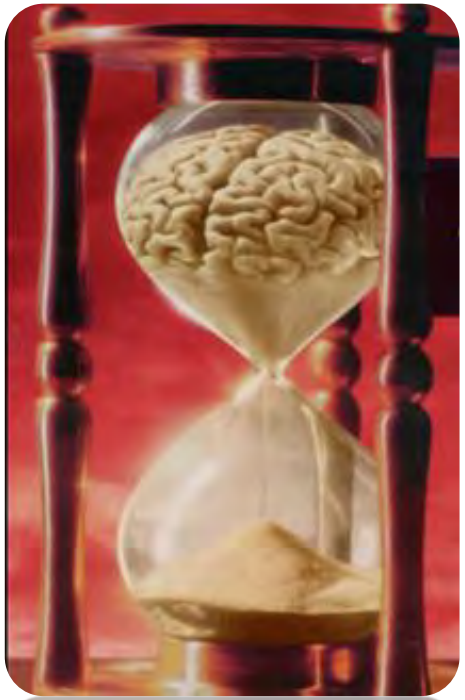
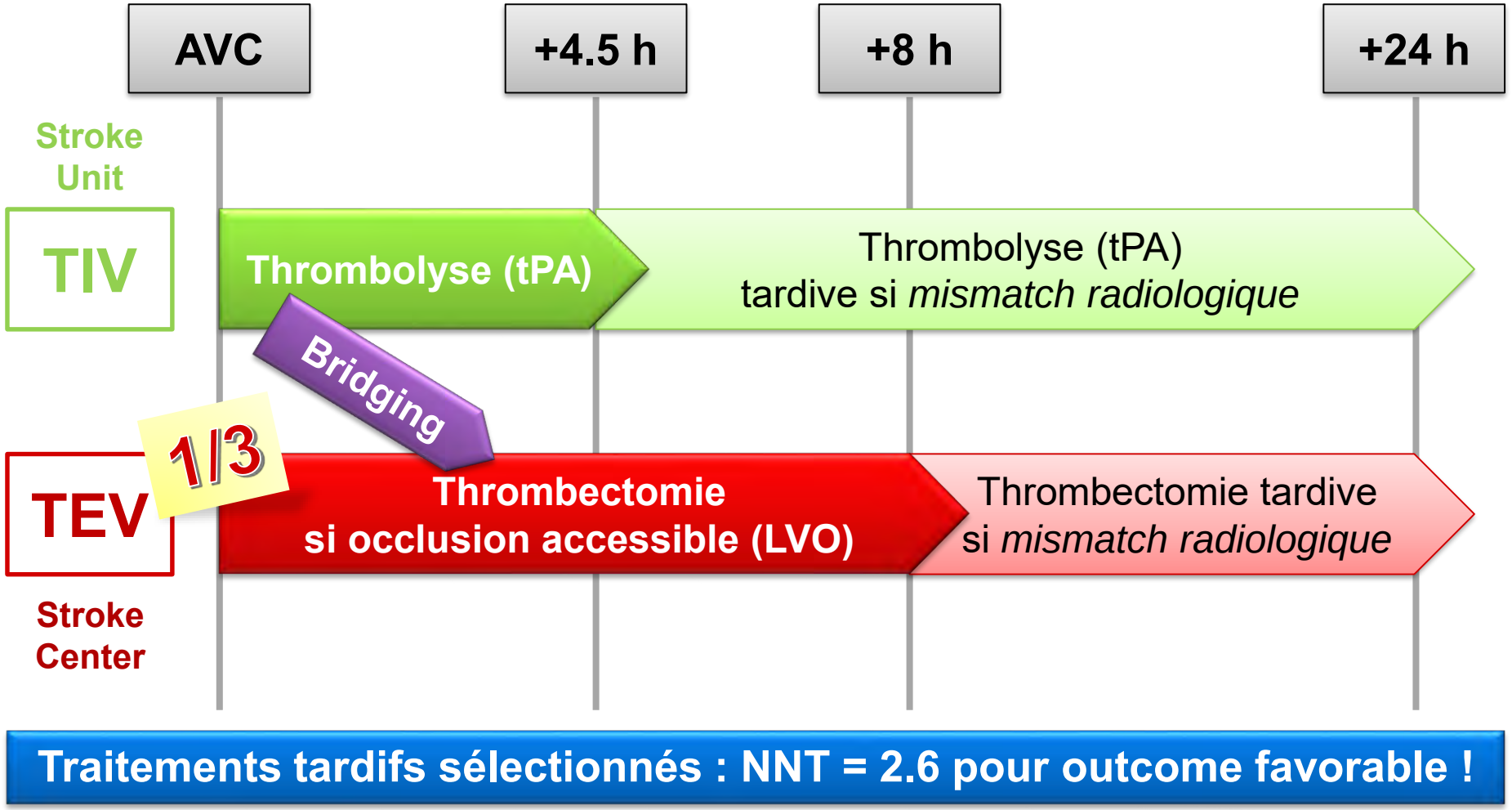
Chaque minute compte !





Traitements tardifs sélectionnés : NNT = 2.6 pour outcome favorable !

TIV = Thrombolyse intraveineuse, TEV = Traitement endovasculaire (Stroke Center), Bridging = TIV puis TEV, LVO = large vessel occlusion
mismatch radiologique = imagerie spécialisée CT/IRM montrant une pénombre > core ischémique (potentiel de réversibilité)

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OCVS organisation cantonale valaisanne des secours
kantonale walliser rettungsorganisation KWRO 144

Filière AVC Valais

«Time is brain!»

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► **SUSPICION D'AVC : déficit neurologique nouveau**

Faiblesse :	visage / bras / jambe
Tr. sensitif :	visage / bras / jambe
Tr. d'élocution :	parler / articuler / comprendre
Tr. visuel :	déviation du regard / vision double hémianopsie / perte de vision
Vertiges :	intenses, persistants, avec tr. équilibre
Céphalées :	violentes, brutales, avec tr. neurologique

144 **AMBULANCE** | **HÉLI**
↳ PAS de médicalisation
sauf critères d'instabilité →

instabilité
- patient non alerte
- instabilité hémodynamique
- dyspnée sévère
- TAS > 220 mmHg

Évaluation du patient

► **Considérer**
1. hypoglycémie
2. crise d'épilepsie
3. infection aiguë

Etat préalable du patient
mRS (score de Rankin)
0-1 pas de handicap / mini-symptômes
2 handicap minime, autonome AVQ
3 dépendant AVQ, marche autonome
4-5 dépendant pour marche / alité

Bonne qualité de vie
(mRS ≤ 3)

à relativiser !

Qualité de vie limitée
(mRS ≥ 4)

ou

Début des symptômes ou Dernière preuve de bonne santé (DPBS)

≤ 24h ou au réveil

24 – 72h

> 72h

Évaluation clinique
Checklist ②

G-FAST ①

G-FAST ①

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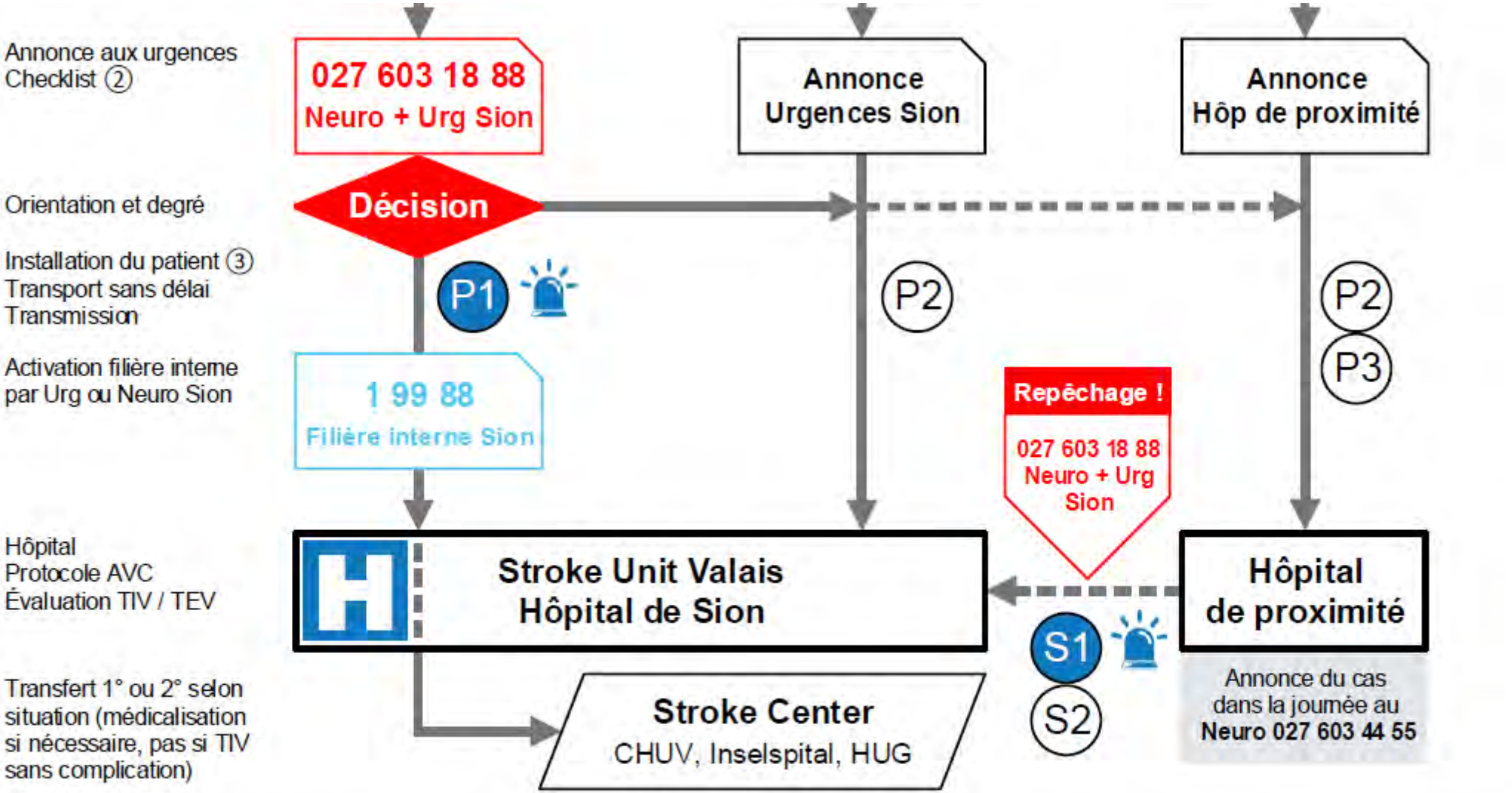

► **CONCEPT GÉNÉRAL : Chaque minute compte !** Perdre le moins de temps possible à chaque étape. Ne pas attendre la confirmation de la décision pour lancer la filière. Evaluer et transporter rapidement le patient vers Stroke Unit. Les étapes d'annonces et de conférence téléphonique ne sont là que pour valider la filière, orienter le patient et gagner du temps aux urgences.

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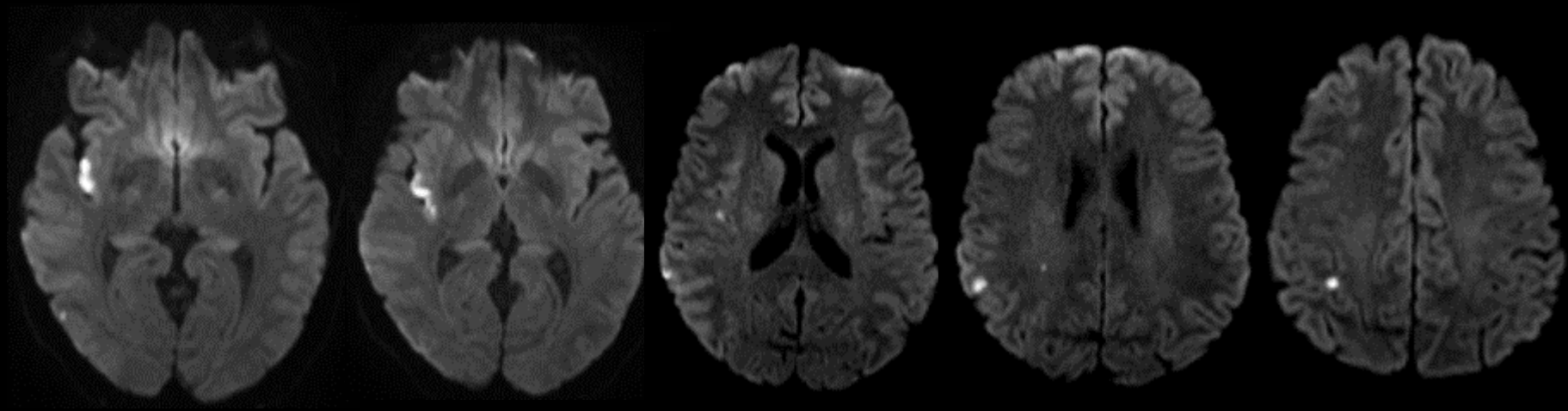
F 36y, BSH, pas de FRCV, pas de médic, pas de CO

- 2 sem grippe, toux, EF, Zithromax, Resyl+
- Malaise en rentrant de marche (bon effort). Idées pas claires. Difficulté d'élocution et tr. compréhension. Paresthésie joue et doigts G. Gauchère
- Mieux couchée. Durée complète 15 min.
- Urg : complètement asymptomatique. ABCD3-I=2



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Sérieux !

Considérez l'AIT comme un AVC qui a eu de la chance…

Le nombre d'AVC augmente
Le nombre de traitements de recanalisation TIV-TEV augmente

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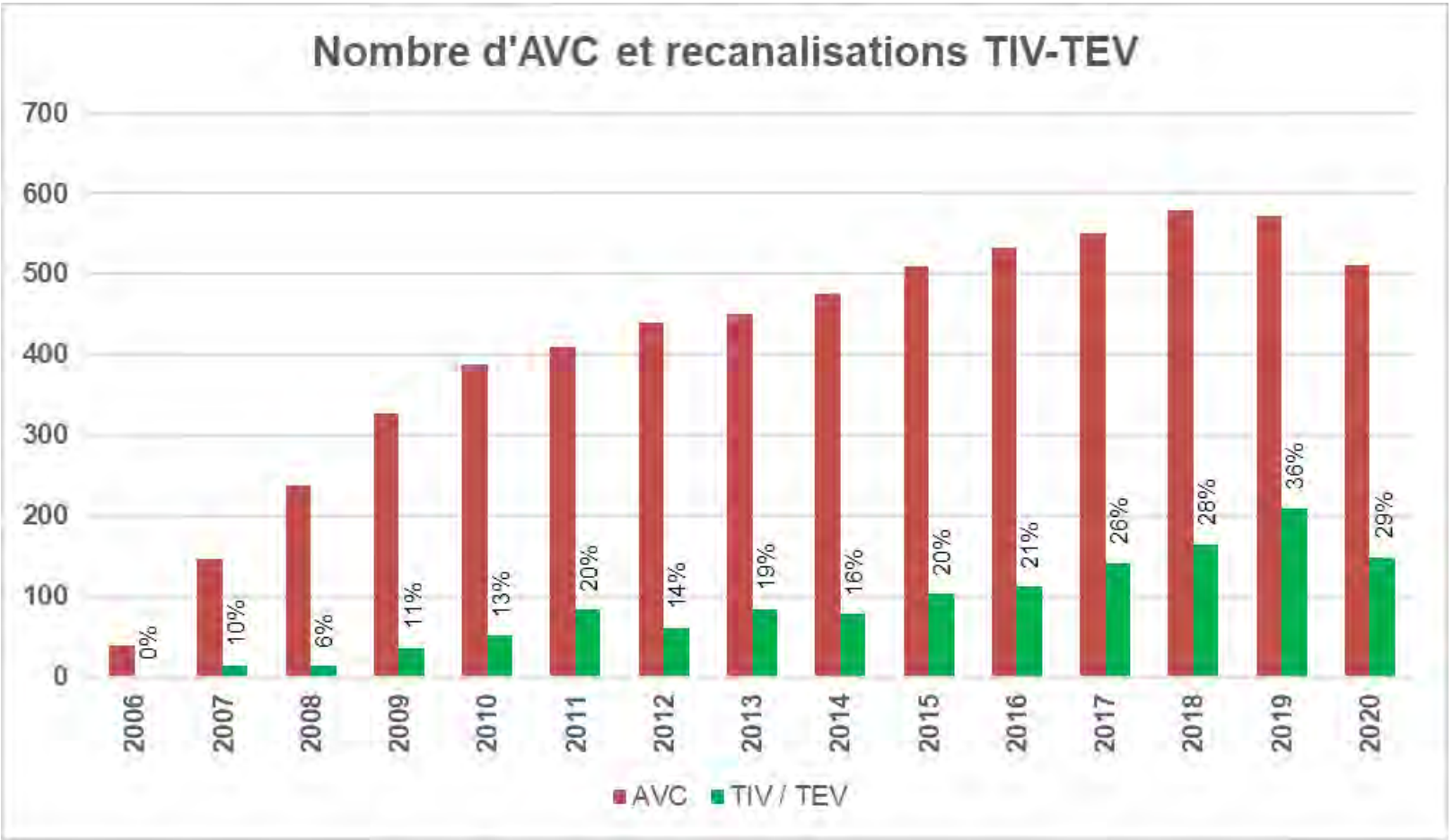
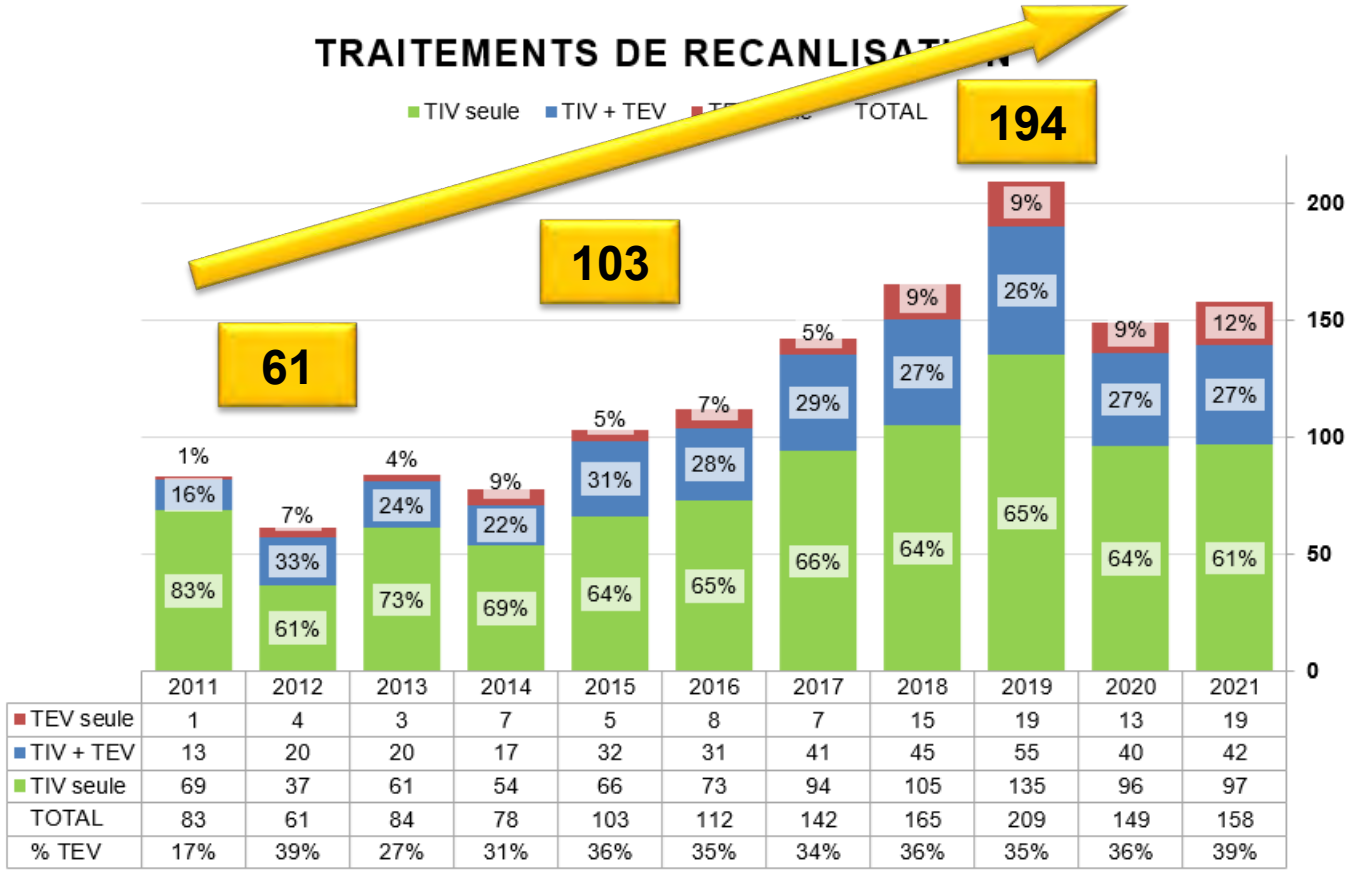
- **La proportion des AVC recanalisés augmente également**



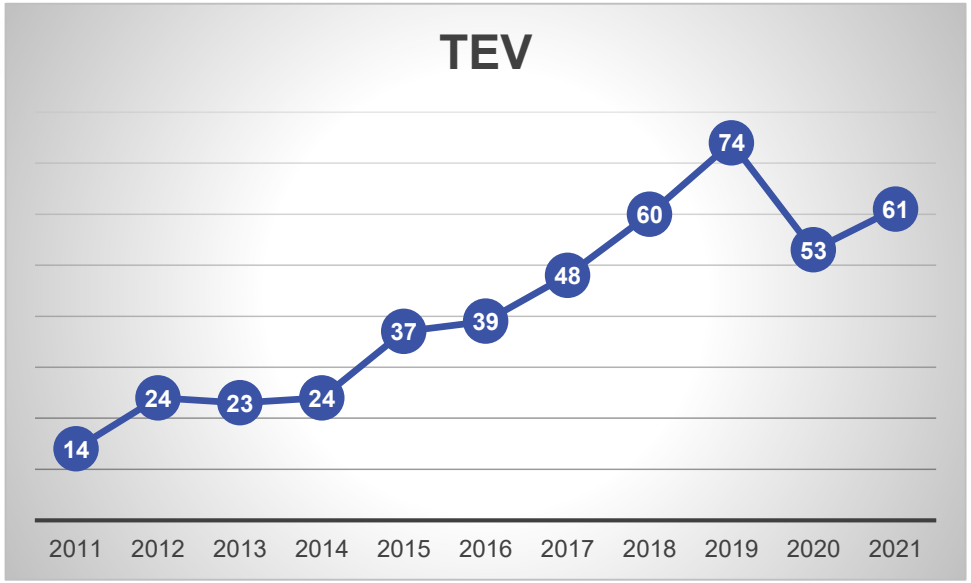
TIV = thrombolyse intraveineuse / TEV = traitement endovasculaire (Réalisé en Stroke Center pour l'instant)

Recanalisations TIV-TEV

Les chiffres actuels dépassent les prévisions



	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
TEV seule	1	4	3	7	5	8	7	15	19	13	19
TIV + TEV	13	20	20	17	32	31	41	45	55	40	42
TIV seule	69	37	61	54	66	73	94	105	135	96	97
TOTAL	83	61	84	78	103	112	142	165	209	149	158
% TEV	17%	39%	27%	31%	36%	35%	34%	36%	35%	36%	39%



La thrombectomie va devenir de plus en plus utilisée en phase aiguë d'AVC

Nouvelles questions pour la prise en charge des AVC

- **TIV : place la TNK**
- **Fibrinolyse vs thrombolyse … nouveaux ttt**
- **Bridging 2.0**
  - TEV directe vs bridging
  - TIV avant, pendant ou après TEV ?
  - TIA après TEV ?
- **TEV distale et nouveaux devices**
- **TEV pour les larges cores**
- **Protection cérébrale … nouveaux ttt**
- **Softwares avec IA pour la détection et sélections des traitements**

- **➔ Augmenter la proportion des cas TEV**
  - Drip & fly
  - Formation de plus de spécialistes endovasculaires
  - Robotique…

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altéplase, ténectéplase

2. Thrombolyse intraveineuse (TIV)

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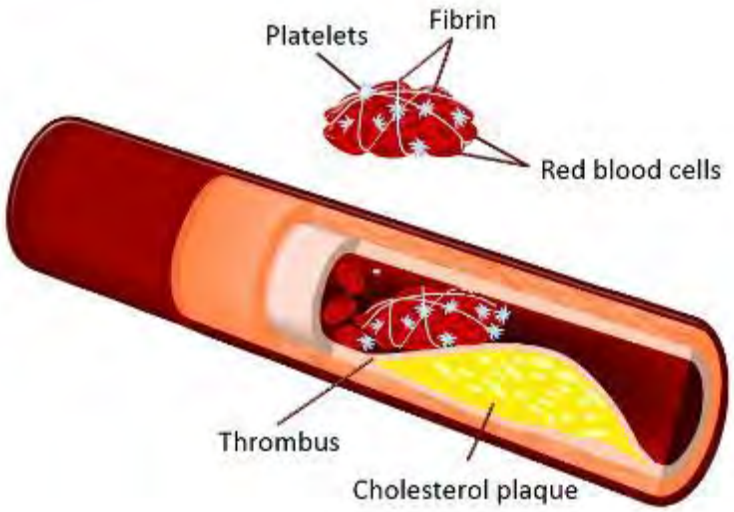
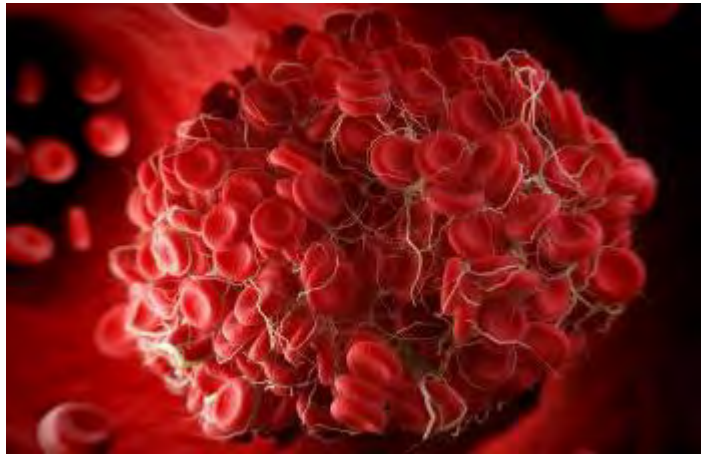
Evolution des traitements :
de grands changements, récents !

- **En constantes évolution depuis 1995 et surtout 2014**
- **Nouveaux délais et nouvelles techniques :**
  - **1995** Début : thrombolyse IV (TIV) jusqu'à 3h (Etude NINDS)
  - **1999** Thrombolyse IA jusqu'à 6h (Etude PROACT II)
  - **2005** Extension de la TIV jusqu'à 4.5h (Etude ECASS 3)
  - **2010** Extension de la TIV pour les patients > 80 ans (Etude SITS)
  - **2010** Premières évidences poolées pour la thrombectomie mécanique
  - **2013** 3 Etude échouent pour le traitement endovasculaire (TEV)
  - **2014** Nouveaux devices (stent retrievers) recananisent mieux >90%
  - **2015** 5 Etudes majeures prouvent l'efficacité supplémentaire de la thrombectomie (TEV) avec ou sans TIV pour les occlusions proximales intracrâniennes (35-33% des cas)
  - **2018** TEV possible dans de rares cas jusqu'à 24h (2-5%)
  - **2018** AVC au réveil : TIV chez certains patients
  - **2018** Tenecteplase meilleure que l'Alteplase ? Oui pour les cas qui vont en TEV
  - **2019** La TEV peut-elle remplacer la TIV dans certains cas ?
  - **2021** En Stroke Center, la combinaison TIV+TEV est meilleure que la TEV directe

Thrombolyse (TIV) : «dissoudre» le caillot, fibrinolyse





- streptokinase
- urokinase
- altéplase
- rétéplase
- ténectéplase

Ténectéplase (TNK) vs Altéplase (tPA)

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Table 1 Comparison of pharmacological properties of TNK and tPA

Property	TNK versus tPA	Comments
Half-life	TNK 20–24 min tPA 5–10 min	TNK administered as a single bolus exhibits a biphasic disposition from the plasma. TNK is cleared from the plasma with an initial half-life of 20 to 24 min and a terminal phase half-life of 90 to 130 min.[30] Arterial venous shunt models of fibrinolysis in rabbits indicate that TNK (by bolus) induces 50% lysis in one-third the time required by tPA (by infusion)[28]
In vivo clearance	TNK 1.9 mL/kg/min tPA 16.1 mL/kg/min	In vivo clearance data from rabbits[28]
Fibrin specificity	TNK 14-fold higher than tPA	Based on the ratio of fibrinolytic activity in the presence compared with the absence of fibrin[28]
Plasma fibrinogen conservation	TNK 10-fold higher than tPA	In vitro data[28]
Resistance to PAI-1	TNK is 80-fold higher resistance to PAI-1 than tPA	This is important locally because PAI-1 is released from a platelet-rich clot[28]
Fibrin binding and plasma clot lysis activity	TNK 87% tPA 82%	TNK has near normal fibrin binding and plasma clot lysis activity compared with tPA indicating that the mutations in TNK do not affect its ability to activate plasminogen
Potency Whole blood clot Platelet-rich clot	TNK 8-fold higher than tPA TNK 13-fold higher than tPA	
Systemic plasmin activation	Reduced with TNK	Infusion of rt-PA occasionally increased plasma thrombin-antithrombin III complexes, prothrombin fragment F1 + 2, kallikrein-like activity and lowers plasma fibrinogen and several other proteins

Table 2 Comparison of TNK and rt-PA for clinical application

Property	TNK	rt-PA (alteplase)
Ease of reconstitution and administration	IV bolus of total dose administered over 5 s	IV bolus of 10% of total dose followed by infusion of remaining 90% over one hour
Potency[17]	22% recanalization of large artery occlusions	10% recanalization of large artery occlusions
Hemorrhagic complications[30]	Less systemic bleeding than rt-PA Same rates of ICH	
Cost (USA $ per vial, average wholesale price)[29]	$7,034.24 (50 mg vial)	$10,560.43 (100 mg vial)
Replacement program for reconstituted but never used vials in the USA[29]	Not currently available	Available

Tenecteplase for Acute Ischemic Stroke Treatment

Alison E. Baird, MBBS, FRACP, PhD, MPH[1] Richard Jackson, MD[1] Weijun Jin, MD[1]

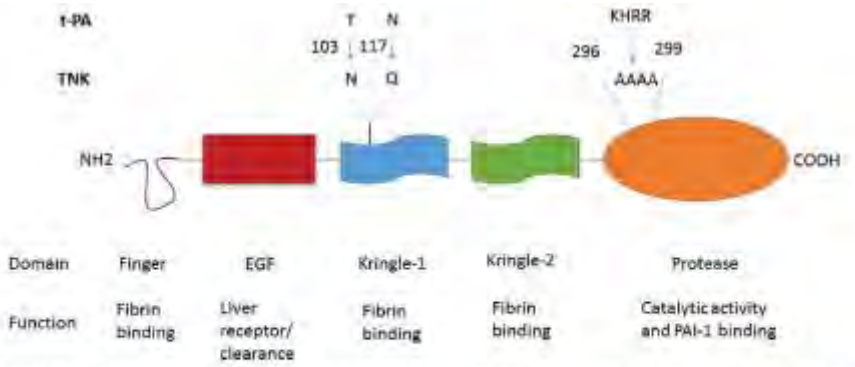

Fig. 1 Structures of tissue plasminogen activator (tPA) and tenecteplase (TNK). The 527 amino acid sequence of native tPA can be subdivided in five domains that are depicted as follows: Finger domain, epidermal growth factor (EGF)-like domain, Kringle 1 domain, Kringle 2 domain, and protease domain. The main roles of the five domains are indicated below each domain. The amino acid substitutions of TNK are shown: a substitution of asparagine (N) 117 with glutamine (Q) to remove a conserved glycosylation site; a substitution of threonine (T) 103 with asparagine (N) to add a new glycosylation site to decrease its binding to fibrin and liver tPA receptors and hence its clearance; and a tetra-alanine (A) substitution at amino acids 296–299 in the protease domain to increase fibrin specificity and resistance to inhibition by plasminogen activator inhibitor-1. K-lysine; H-histidine; R-arginine. COOH, carboxyl group; KHRR, lysine-histidine-arginine-arginine.

Baird AE (2021) https://doi.org/10.1055/s-0040-1722722

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Table 3 Prior clinical studies of TNK for acute ischemic stroke treatment

Study	Comparator groups	Study type	Number of subjects	Primary result	Time window
2005 Haley Jr. et al[38]	Tiered dosing 0.1, 0.2, 0.4, 0.5 mg/kg (planned maximum of 0.6 mg/kg)	Open-label single-arm clinical trial	88	0.5 mg/kg dose abandoned because of ICH, overall mRS at 3 mo similar to historical alteplase controls	Within 3 h
2009 Parsons et al[41]	0.1 mg/kg TNK versus alteplase 0.9 mg/kg	Nonrandomized clinical trial	122	TNK 69% MCA recanalization, 53% alteplase	TNK between 3–6 h; alteplase <3 h
2010 Haley Jr. et al[39]	Tiered TNK dosing 0.1, 0.25, 0.4 mg/kg versus tPA 0.9 mg/kg	Phase 2B clinical trial, terminated before planned phase 3	112	0.4 mg/kg dose abandoned; unable to differentiate between 0.1 mg/kg and 0.25 mg/kg as optimal dose	Within 3 h
2011 Smadja et al[47]	Failed recanalization of M1 MCA occlusion with tPA followed by TNK 0.1 mg/kg	Case series	13	16.8 h post-thrombolysis recanalization 100%. Asymptomatic ICH 31%, no symptomatic ICH	Mean treatment time 290 min
2011 Molina[a]	TNK 0.4 mg/kg versus alteplase 0.9 mg/kg	Nonrandomized consecutive enrollment	122	2.5-fold greater major improvement at 24 h with TNK	Within 4.5 h
2012 Parsons et al[42,48]	TNK 0.1m/kg and 0.25 mg/kg versus alteplase 0.9mg/kg	Phase 2B clinical trial	75	Both TNK groups showed greater improvement. 0.25 dose greater than 0.1 than alteplase	Within 6 h
2012 Georgiadis et al[49]	IA TNK versus IA alteplase or IA reteplase or thrombectomy alone	Retrospective analysis of prospectively enrolled patients	114	No difference in outcomes	Within 6 h
2015 Huang et al[43]	TNK 0.25 mg/kg versus alteplase 0.9 mg/kg	Prospective randomized open label phase 2 trial	104	No difference in penumbral salvage or outcome	Within 4.5 h
2015 Coutts et al[50]	TNK 0.1 mg/kg versus 0.25 mg/kg, patients with minor stroke	Prospective uncontrolled	50	39% compete recanalization in 0.1 mg/kg group, 52% in 0.25 mg/kg group	Within 4.5 h
2017 Logallo et al[37]	TNK 0.4 mg/kg versus alteplase	Phase 3 RCT	1100	No differences in outcomes; TNK not superior to alteplase	Within 4.5 h
2018 Campbell et al[17]	TNK 0.25 mg/kg versus alteplase 0.9 mg/kg	Phase 2 RCT	202	≥50% restoration of blood flow TNK 22% alteplase 10%	Within 4.5 h
2018 Kate et al[51]	TNK 0.25 mg/kg	Case series	16	Feasible	Within 24 h in patients selected by penumbra imaging
2018 Ramakrishnan et al[52]	TNK 0.1 mg/kg, TNK 0.2 mg/kg	Study 1—comparison of 2 TNK doses Study 2—comparison to historical controls	Study 1 20 Study 2 62	TNK at a dose of 0.2 mg/kg was well tolerated and effective	Within 3 h
2018 Owais et al[53]	TNK 0.2 mg/kg	Case series	14	Safe and feasible	Within 3 h
2019 Seners et al[54]	0.25 mg/kg TNK or 0.9 mg/kg alteplase, prior to thrombectomy	Retrospective analysis, propensity—score cohorts	262	Same rates of early recanalization, alteplase 18% versus TNK 21%	Mean treatment time 147 min

NEJM 2012

NOR-TEST

Extend-IA TNK

- **Peu de RCT !**
- **Volume patients faible !**
- **Doses TNK variables !**

Baird AE (2021) https://doi.org/10.1055/s-0040-1722722

Tenecteplase for thrombolysis in stroke patients: Systematic review with meta-analysis

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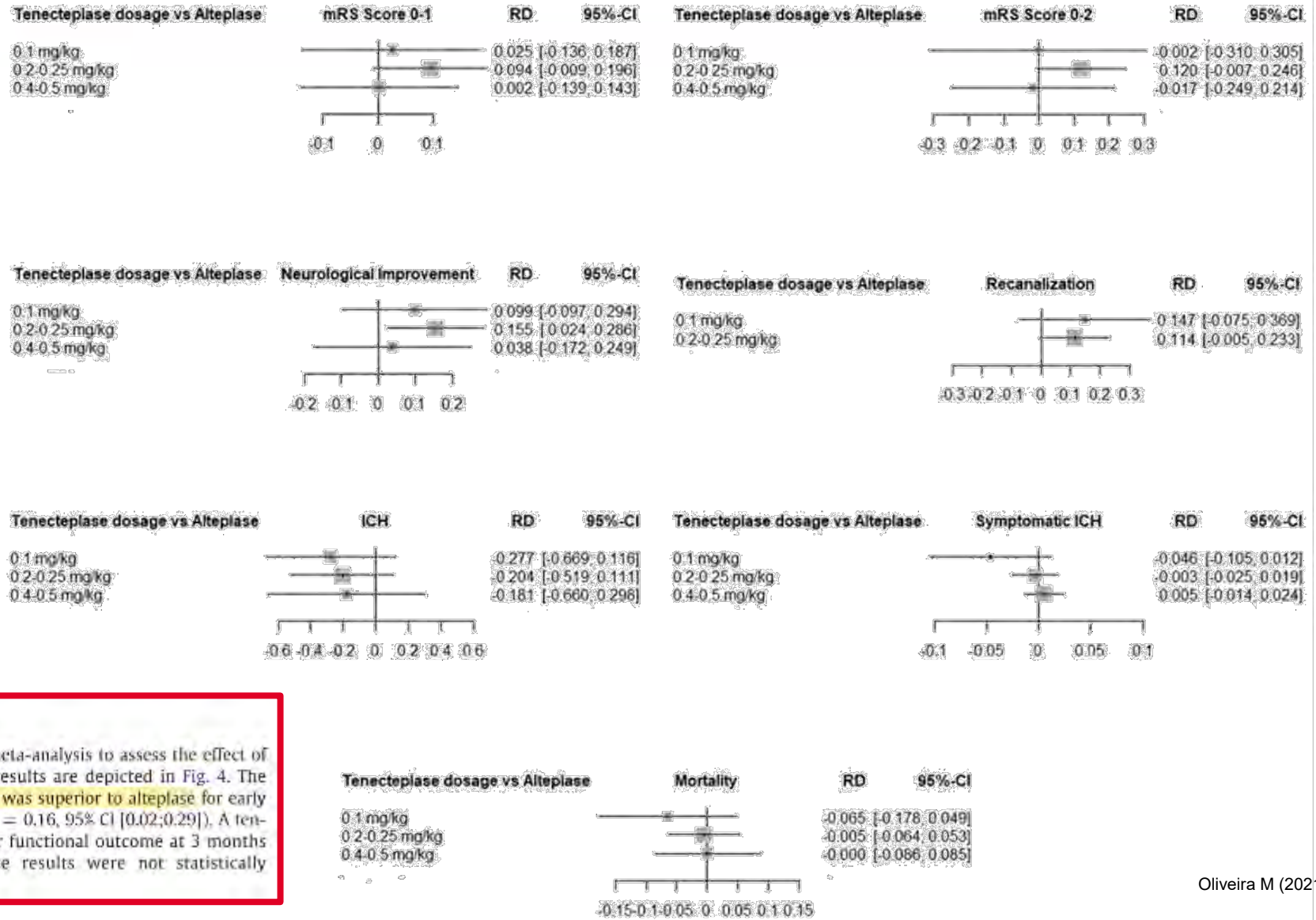

3.3. Tenecteplase dose analysis

The results of the network meta-analysis to assess the effect of tenecteplase dosage on study results are depicted in Fig. 4. The 0.20–0.25 tenecteplase dose tier was superior to alteplase for early neurological improvement (ARD = 0.16, 95% CI [0.02;0.29]). A tendency was also noted for better functional outcome at 3 months with this dose tier, but these results were not statistically significant.

Oliveira M (2021) https://doi.org/10.1016/j.ajem.2020.12.026

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Table 5 Ongoing TNK trials in acute ischemic stroke

Trial name	Intervention	Type of trial	Planned number of patients	Planned time window	Outcome measure
TASTE Australian New Zealand Clinical Trials Registry ID ACTRN12613000243718	TNK 0.25 mg/kg versus alteplase 0.9 mg.kg	Phase 3 RCT	1,024	Within 4.5 h	mRS at 3 mo
ATTEST 2 ClinicalTrials.gov Identifier: NCT02814409	0.25 mg/kg TNK versus 0.9 mg/kg alteplase	Randomized open label phase 3	1,870	Within 4.5 h	mRS at 90 d
AcTQuICR ClinicalTrials.gov Identifier: NCT03889249	Pragmatic Registry based 0.25 mg/kg TNK versus 0.9 mg/kg alteplase	Randomized open label	1,600	Within 4.5 h	mRS 0–1 at 90 d
NOR-TEST 2 ClinicalTrials.gov Identifier: NCT03854500	0.25 mg/kg TNK versus 0.9 mg/kg alteplase	Prospective randomized open label blinded endpoint	1,342	Within 4.5 h onset Within 4.5 h on wakening Within 4.5 h, bridging therapy to thrombectomy	mRS 0–1 at 90 d
EXTEND-IA TNK 2 ClinicalTrials.gov Identifier: NCT03340493	0.4 mg/kg TNK versus 0.25 mg/kg TNK	Phase 2 randomized open label blinded end point	188	Within 4.5 h of symptoms	TICI 2b/3 recanalization
TIMELESS ClinicalTrials.gov Identifier: NCT03785678	0.25 mg/kg TNK versus placebo	Phase 3 double blind randomized controlled	456	4–24 h of symptoms	mRS at 90 d
TWIST ClinicalTrials.gov Identifier: NCT03181360	0.25 mg/kg TNK plus best medical therapy versus best medical therapy	Randomized open label blinded end point phase 3	500	Within 4.5 h of waking	mRS at 90 d
TEMPO-2 ClinicalTrials.gov Identifier: NCT02398656	0.25 mg/kg TNK versus antiplatelet therapy	Prospective randomized open label blinded phase 3	1,274	Within 12 h	mRS at 90 d

Baird AE (2021) https://doi.org/10.1055/s-0040-1722722

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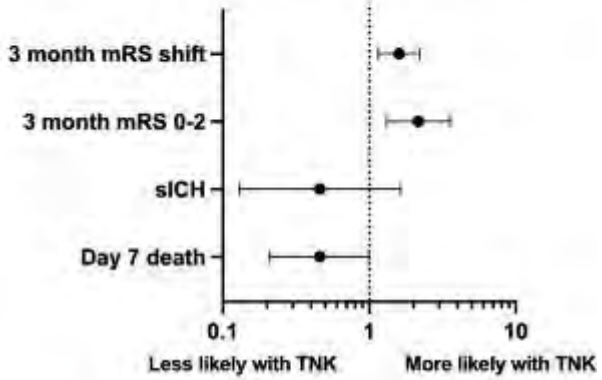
Comparaison vraie vie : switch tPA ➔ TNK

Switching to tenecteplase for stroke thrombolysis: real-world experience and population-based outcomes in a regional stroke network

Door to needle times were shorter with tenecteplase

Patient outcomes showed some improvement and no harm



Pre-implementation, all healthcare providers supported the change and remained satisfied 12 months later

- **2018-2021**
- **555 tPA, 283 TNK**

- **CONCLUSIONS:** Following stakeholder endorsement, a region-wide switch from alteplase to tenecteplase was successfully implemented. We found evidence of benefit and no evidence of harm

Mahawish K (2021) https://doi.org/10.1161/strokeaha.121.035931

Futur ?

Ténectéplase…
c'est pour bientôt en pratique clinique

Thrombolysis for Central Retinal Artery Occlusion in 2020: Time Is Vision!

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- 7 études 1995-2018
- 2 à 30 patients !
- TIV 2-18h post CRAO !

Conclusions: In 2020, nonarteritic CRAO patients should theoretically receive the same thrombolytic therapies, in the same time window, as patients with acute cerebral ische-

Acute monocular painless visual loss, presumed acute nonarteritic CRAO

EYE STROKE CODE activation

History:
- Visual symptoms onset time and tempo
- Last known well
- Systemic symptoms suggestive of giant cell arteritis
- Other neurological symptoms
- Current medications list and allergies
- Recent surgery or recent bleeding, past medical history

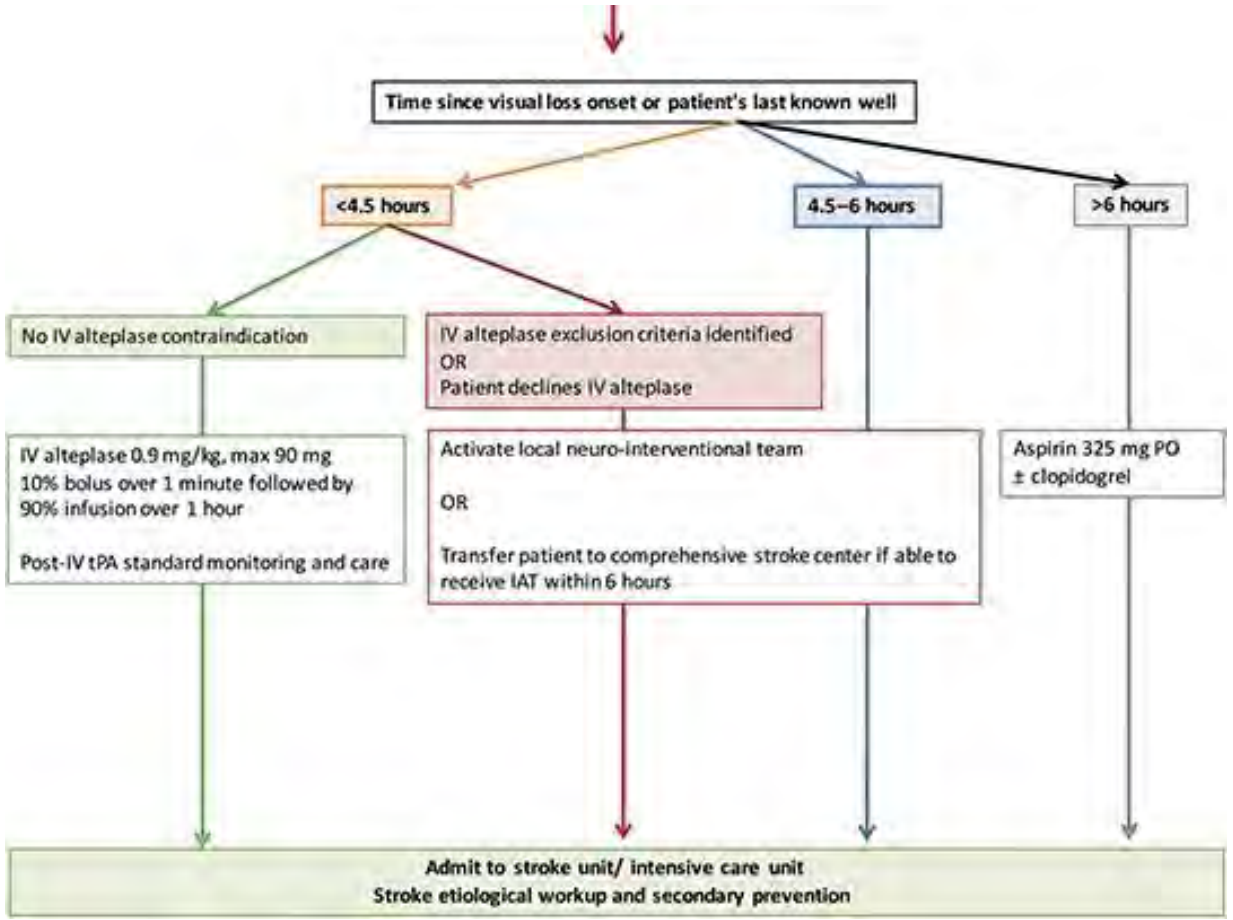
Ophthalmological evaluation:
- Visual acuity, pupillary examination (RAPD?), anterior segment and dilated funduscopic examination
- If possible (patient in eye clinic), fundus photograph and macular OCT before transfer to ED/Stroke Center

Acute nonarteritic CRAO

Neurological examination:
- NIHSS
- Modified Rankin Score

Place two 18 gauge antecubital intravenous lines

Laboratories: BMP, PT, PTT, INR, CBC, ESR, CRP
Electrocardiogram / Cardiac telemetry
Noncontrast head CT (before tPA)
CT angiogram head and neck (after tPA, if applicable; it should not delay tPA)



Dumitrascu OM (2020) https://doi.org/10.1097/WNO.0000000000001027

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TEV directe / bridging ?

TEV distale ?

Traitement des AVC avec large core

3. Traitement endovasculaire (TEV)

TEV directe vs bridging

«drip&ship» vs «mothership»

Is intravenous thrombolysis still necessary in patients who undergo mechanical thrombectomy?

Curr Opin Neurol 2019, 32:3–12
DOI:10.1097/WCO.0000000000000633

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Utilité de la TIV avant TEV ?

Table 1. Potential advantages and disadvantages of pretreatment with intravenous thrombolysis in acute ischemic stroke patients with large vessel occlusions who are eligible for mechanical thrombectomy

Potential advantages	Potential disadvantages
Improvement in collateral circulation (because of dissolution of distal microthrombi)	Increased systemic and intracranial bleeding risk because of pretreatment with rt-PA
Reperfusion of distal occlusions (M3/M4 MCA, A2 ACA) that are inaccessible to catheters	Orolingual angioedema reaction related to rt-PA administration
Thrombus softening leading to faster complete reperfusion with fewer number of passes during mechanical thrombectomy	Contraindication for heparin/antiplatelet use during mechanical thrombectomy that may increase the likelihood of reocclusion or preclude stenting of extracranial lesions
Prompt treatment initiation ('drip and ship') in primary stroke centers	Delay in mechanical thrombectomy initiation, especially in low-volume centers
May reduce the likelihood of infarct in new (previously unaffected) territory complicating mechanical thrombectomy	Proximal clot breakdown and migration causing new infarctions in the affected territory of LVO
May avert mechanical thrombectomy (approximately 10% of LVO) because of rt-PA-induced complete reperfusion	Increased cost because of rt-PA administration

Katsanos AH (2019) https://doi.org/10.1097/WCO.0000000000000633

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Risque de la TIV avant TEV

Potential harm	Effect
IV tPA-related local and systemic bleeding complications	Puncture-site hematoma (1%–2%) and major systemic bleeding (1%)
IV tPA-related coagulopathy and small vessel fragility	More large symptomatic extraischemic parenchymal hemorrhage (1%–2%)
IV tPA-related coagulopathy and sICH in patients at risk	Higher rates of sICH and aICH with poor functional outcome
IV tPA-related blood–brain barrier breakdown, coagulopathy, and potentiated large vessel damage because of stent retrievers	Increased symptomatic parenchymal hemorrhage when infarct. Poorer functional outcome and increased infarct volume
Tandem extracranial and intracranial occlusions may require additional procedures during EVT and potentially immediate antiplatelet therapy	Increased symptomatic intracranial hemorrhage (10%)
Distal thrombus migration	Inability to retrieve thrombus with MT. Neurological deterioration and more severe/ extensive ischemia
Increase thrombus fragility by softening the thrombus	Higher rates of peri-interventional thrombus fragmentation leading to lower rates of complete (TICI 3) reperfusions
IV tPA lysis of left atrial appendage or other proximal thrombus	Early stroke recurrence or multiple systemic emboli
Delay to MT initiation	Later median onset to reperfusion resulting in worse outcomes
IV tPA-associated allergic reactions (1%)	During IV tPA infusion/EVT procedure, which may worsen ischemia or require intubation/prolonged ICU stay
IV tPA-related neurotoxicity in animal models	More neuronal loss
IV tPA cost	Adds to procedural cost

Fischer U (2017) https://doi.org/10.1161/STROKEAHA.117.017208

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Bénéfice de Ténectéplase (TNK) pour les LVO (adressés pour TEV)

BRIEF REPORT

Intravenous Thrombolysis With Tenecteplase in Patients With Large Vessel Occlusions

Systematic Review and Meta-Analysis

4 RCT
433 LVO pts

Outcomes	No. of participants (studies); follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Effect with alteplase	Effect difference with TNK
SR	315 (3 studies); before EVT	⊕⊕⊕◯ Moderate*	OR, 3.05 (1.73–5.40)	227 per 1000	245 more per 1000 (109 more to 385 more)
mRS 0–2	277 (2 studies); 3 mo	⊕⊕⊕◯ Moderate†	OR, 2.06 (1.15–3.69)	500 per 1000	173 more per 1000 (35 more to 287 more)
mRS 0–1	433 (4 studies); 3 mo	⊕⊕⊕◯ Moderate‡	OR, 1.49 (0.95–2.32)	368 per 1000	97 more per 1000 (12 fewer to 207 more)
Functional improvement	315 (3 studies); 3 mo	⊕⊕⊕◯ Moderate*	cOR, 1.84 (1.18–2.87)	…	…
ENI	395 (3 studies); 72 h	⊕◯◯◯ Very low*‡§	OR, 1.09 (0.37–3.16)	510 per 1000	22 more per 1000 (232 fewer to 257 more)
Mortality	395 (3 studies); 3 mo	⊕⊕◯◯ Low*‡	OR, 0.93 (0.31–2.80)	130 per 1000	8 fewer per 1000 (86 fewer to 165 more)
Symptomatic ICH	395 (3 studies); 48 h	⊕⊕◯◯ Low*‡	OR, 0.66 (0.19–2.23)	31 per 1000	10 fewer per 1000 (25 fewer to 36 more)
Any ICH	395 (3 studies); 48 h	⊕⊕◯◯ Low*‡	OR, 0.87 (0.35–2.17)	115 per 1000	13 fewer per 1000 (71 fewer to 105 more)

cOR indicates common odds ratio; ENI, early neurological improvement; EVT, endovascular treatment; GRADE, Grading of Recommendations Assessment, Development and Evaluation; ICH, intracranial hemorrhage; mRS, modified Rankin Scale; OR, odds ratio; SR, successful recanalization; and TNK, tenecteplase.

Katsanos AH (2021) https://doi.org/10.1161/STROKEAHA.120.030220

Données vraie vie TNK vs tPA pour LVO

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Real-world comparative safety and efficacy of tenecteplase *versus* alteplase in acute ischemic stroke patients with large vessel occlusion

Table 3. Univariable and multivariable binary and ordinal logistic regression analyses evaluating the association of thrombolytic agent (tenecteplase *versus* alteplase) with outcomes.

	Crude OR/cOR (95% CI)	*p*-value	Adjusted OR/cOR (95% CI)	*p*-value
Averted thrombectomy	2.11 (0.59, 7.49)	0.248	2.75 (0.70, 10.70)	0.145
Any ICH	3.20 (0.64, 16.10)	0.158	3.60 (0.66, 19.70)	0.139
sICH	3.47 (0.53, 22.80)	0.195	4.25 (0.51, 35.07)	0.179
Major neurological improvement at 24 h	3.60 (0.99, 13.13)	0.052	10.22 (0.73, 142.98)	0.084
Discharge modified Rankin Scale	1.20 (0.32, 2.15)	0.699	1.49 (0.53, 4.17)	0.442
3-month modified Rankin Scale	1.31 (0.51, 3.33)	0.574	1.47 (0.53, 4.00)	0.464
Functional independence	1.45 (0.48, 4.37)	0.512	1.50 (0.48, 4.71)	0.489
Mortality	0.54 (0.10, 2.88)	0.469	0.40 (0.06, 2.46)	0.315

CI, confidence interval; cOR, common odds ratio; ICH, intracranial hemorrhage OR, odds ratio; sICH, symptomatic intracranial hemorrhage.

Psychogios K (2021) https://doi.org/10.1177/1756286420986727

tPA < 4.5h : différencier les cas pour TEV ➔ Tenecteplase

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Recommendation

For patients with acute ischaemic stroke of <4.5 h duration and not eligible for thrombectomy, we suggest intravenous thrombolysis with alteplase over intravenous thrombolysis with tenecteplase. Please see paragraph 5.2 for patients eligible for mechanical thrombectomy.

Quality of evidence: **Low** ⊕⊕

Strength of recommendation: **Weak** ⁉

sICH idem

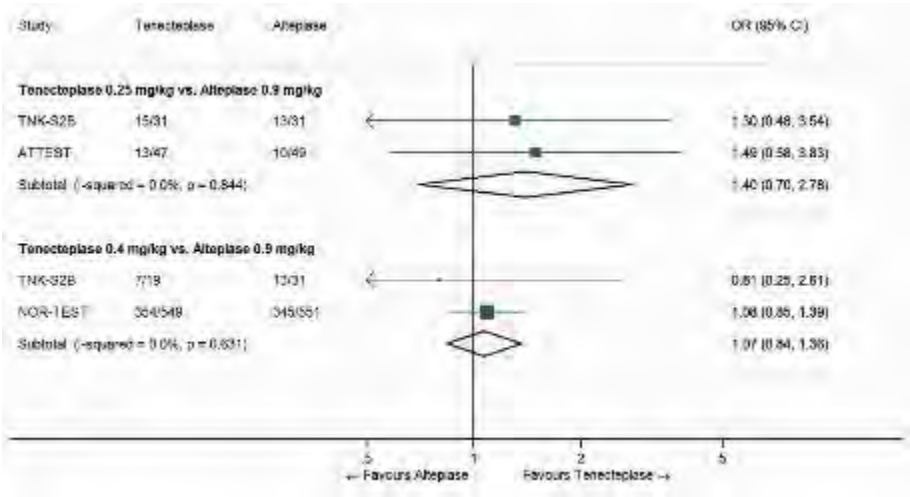

Figure 6. Pooled odds ratio for sICH in 'unselected' patients with ischaemic stroke of<4.5 h duration, treated with tenecteplase (0.25 or 0.4 mg/kg) vs. alteplase (0.9 mg/kg).

Recommendation

For patients with acute ischaemic stroke of < 4.5 h duration and with large vessel occlusion who are candidates for mechanical thrombectomy and for whom intravenous thrombolysis is considered before thrombectomy, we suggest intravenous thrombolysis with tenecteplase 0.25 mg/kg over intravenous thrombolysis with alteplase 0.9 mg/kg.

Quality of evidence: **Low** ⊕⊕

Strength of recommendation: **Weak** ⁉

TEV directe «mothership» vs TIV➔TEV «drip&ship»

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Stroke

EMERGING THERAPY CRITIQUES

Section Editors: Keith Muir, MD, and Gustavo Saposnik, MD, MSc

Large Vessel Occlusion Strokes After the DIRECT-MT and SKIP Trials

Is the Alteplase Syringe Half Empty or Half Full?

Raul G. Nogueira, MD; Georgios Tsivgoulis, MD

Factors Potentially Favoring Primary Thrombectomy:

Lower Chances of Reperfusion or Benefit with IVT:
- Long Clots (≥ 8 mm) [15]
- Low Clot Burden Scores [16]
- More Proximal Occlusions (ICA) [17]
- Tandem Occlusions [18]
- Absence of HDVS [31]
- Longer Times from Stroke Onset [15,20]
- ? Calcific Emboli

Higher Chances of Complications with IVT:
- Large Infarct Sizes/ Low ASPECTS [21,22]
- Antiplatelet or Anticoagulant use [23,24]
- Very Old Patients [23]
- Severe Hyperglycemia [23]
- Microbleeds/ Amyloid Angiopathy [24]
- Severe Leukoaraiosis [25]
- ICA/ Proximal M1 Occlusions worsened Perfusion from Clot Fragmentation [26]
- Full Basal Ganglia Infarcts [27]

? Requirement for Peri-Procedural Anti-Thrombotics: [23,24]
- Intracranial Atherosclerotic Disease
- Tandem Occlusions
- Dissections
- Calcific Emboli (due to potential need for stenting rescue)

Geographic and Center Specific Characteristics:
- High IVT Costs
- Fast Local MT Workflow [28]
- Neuroendovascular Team immediately available

Factors Potentially Favoring Mothership Bridging:

Higher Chances of Reperfusion or Benefit with IVT:
- Very Early Time Window [18,29]
- Short Dense Clots (< 8mm) [15,31]
- More Distal Thrombus Location [17]
- Higher Residual Flow/ Thrombus Permeability [17]
- Good Collaterals [32]

Lower or Uncertain MT versus IVT Benefit:
- Low Stroke Severity (NIHSS <10) [5]
- MCA-M2 Occlusions [5]
- Distal Occlusions (ACA, PCA, M3)
- Multi-territorial infarcts complicating MT

Expected Delays in Endovascular Reperfusion:
- Unfavorable Vascular Anatomy [14]
- Expected Unusual Delays related to the of Sedation or General Anesthesia

Geographic and Center Specific Characteristics:
- Low IVT Costs
- Prolonged Local MT Workflow
- Neuroendovascular team not in-house/ immediately available

Nogueira RG (2020) https://doi.org/10.1161/STROKEAHA.120.030796

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"Direct mechanical thrombectomy versus bridging therapy for acute ischaemic stroke"

A study-level meta-analysis of the DIRECT-MT, MR CLEAN-NO IV, DEVT, SKIP and SWIFT-DIRECT randomized controlled trials

Improving Reperfusion strategies in Ischemic Stroke (IRIS) collaborators

ESOC 2021 - U Fischer https://kenes.cloud.panopto.eu/Panopto/Pages/Viewer.aspx?id=4166894f-fa57-477b-8cc3-ad960108f994

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Characteristics	DIRECT-MT	SKIP	DEVT	MR CLEAN-NO IV	SWIFT DIRECT
Main inclusion criteria	Age ≥18 years, mRS of 0 or 1 before onset ICA, MCA-M1, or M2 occlusion on CTA NIHSS: ≥2 ASPECTS: no limit Onset to IV rt-PA ≤4 hours 30 min	Age ≥18 and <86 years, mRS of 0, 1 or-2 before onset ICA or MCA-M1 occlusion on CTA or MRA NIHSS: ≥6 ASPECTS: DWI ≥5, CT ≥6 Onset to puncture <4 hours	Age ≥18 years, mRS of 0 or 1 before onset ICA or MCA-M1 occlusion on CTA or MRA NIHSS: no limit ASPECTS: no limit Onset to randomization ≤4 hours 15 min	Age ≥18 years, mRS of 0 or 1 before onset ICA or MCA-M1 or proximal M2 occlusion on CTA or MRA NIHSS: ≥2 ASPECTS: no limit	Age ≥18 years, mRS of 0 or 1 before onset ICA or MCA-M1 occlusion or both on CTA or MRA NIHSS of ≥5 and <30 ASPECTS: DWI/CT ≥4 Onset to randomization ≤4 hours 15 min
Treatment	MT (n=327) IVT before MT (n=329)	MT (n=101) IVT before MT (n=103)	MT (n=116) IVT before MT (n=118)	MT (n=273) IVT before MT (n=266)	MT (n=201) IVT before MT (n=207)
Device	Any approved device	Any approved device	Any approved device	Any approved device	Stent retrievers with proximal protection device
tPA	Alteplase, 0.9 mg/kg	Alteplase, 0.6 mg/kg	Alteplase, 0.9 mg/kg	Alteplase, 0.9 mg/kg	Alteplase, 0.9 mg/kg
Country	China	Japan	China	Europe	North America and Europe
Design	Non-inferiority	Non-inferiority	Non-inferiority	Superiority (non-inferiority as secondary outcome)	Non-inferiority
Non-inferiority margins	mRS shift with a non-inferiority margin OR 0.80	mRS 0–2 with a non-inferiority margin OR of 0.74	mRS 0–2 with a non-inferiority margin of 10%	mRS shift with a non-inferiority margin OR 0.80	mRS 0–2 with a non-inferiority margin of 12%

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Results

- DIRECT MT: non-inferiority (NI) shown (NI margin cOR 0.8)
- SKIP: non-inferiority not shown but outcomes nominally similar (NI margin cOR 0.74)
- DEVT: stopped early because non-inferiority criteria were met (NI margin for mRS 0-2 10%)
- MR CLEAN NO IV: neither superiority nor non-inferiority shown but outcomes nominally similar (NI margin cOR 0.8)
- SWIFT DIRECT: non-inferiority not show (NI margin for mRS 0-2 12%)

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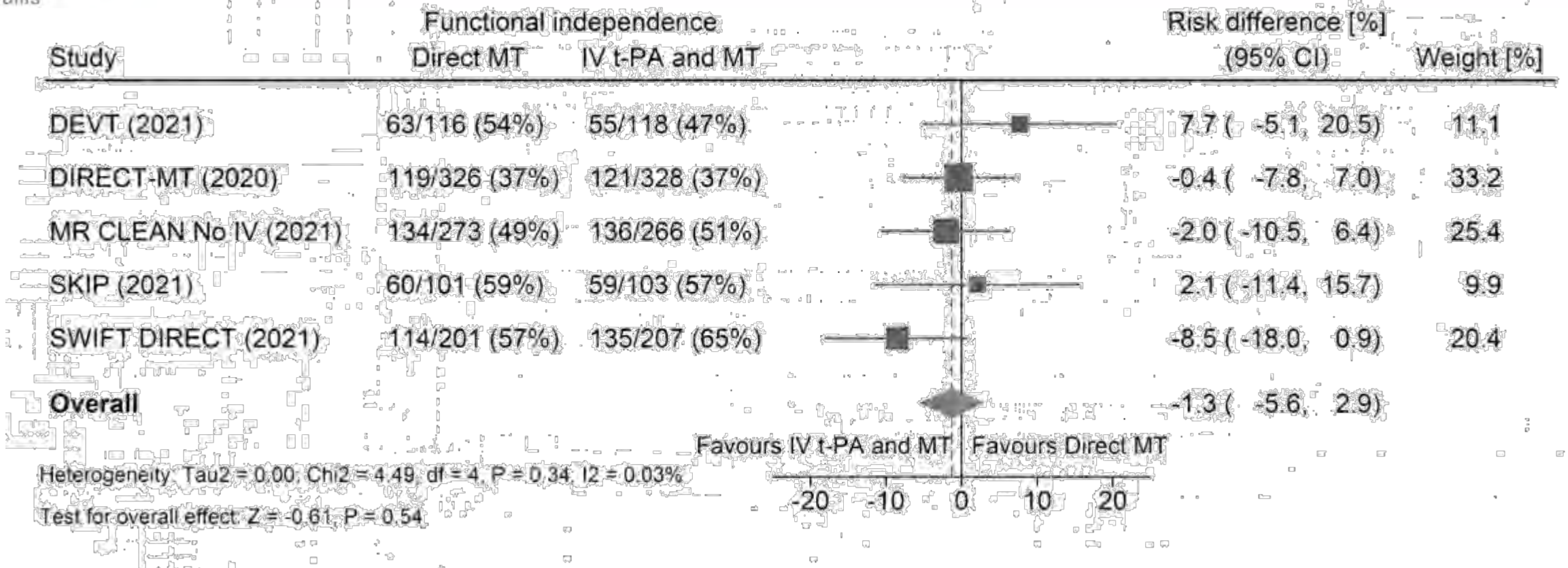
mRS ≤2



Functional independence (mRS ≤2) at 90 days using unadjusted risk differences.

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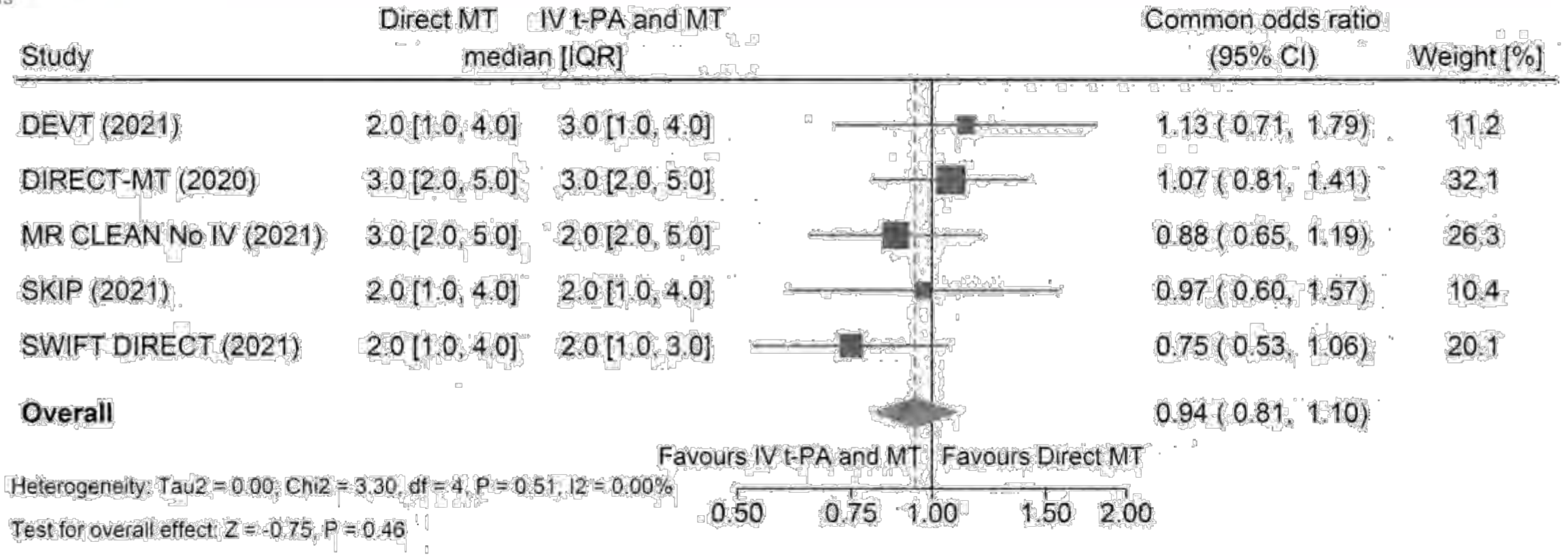
mRS shift analysis



mRS at 90 days using adjusted common odds ratios for a better outcome (lower score)

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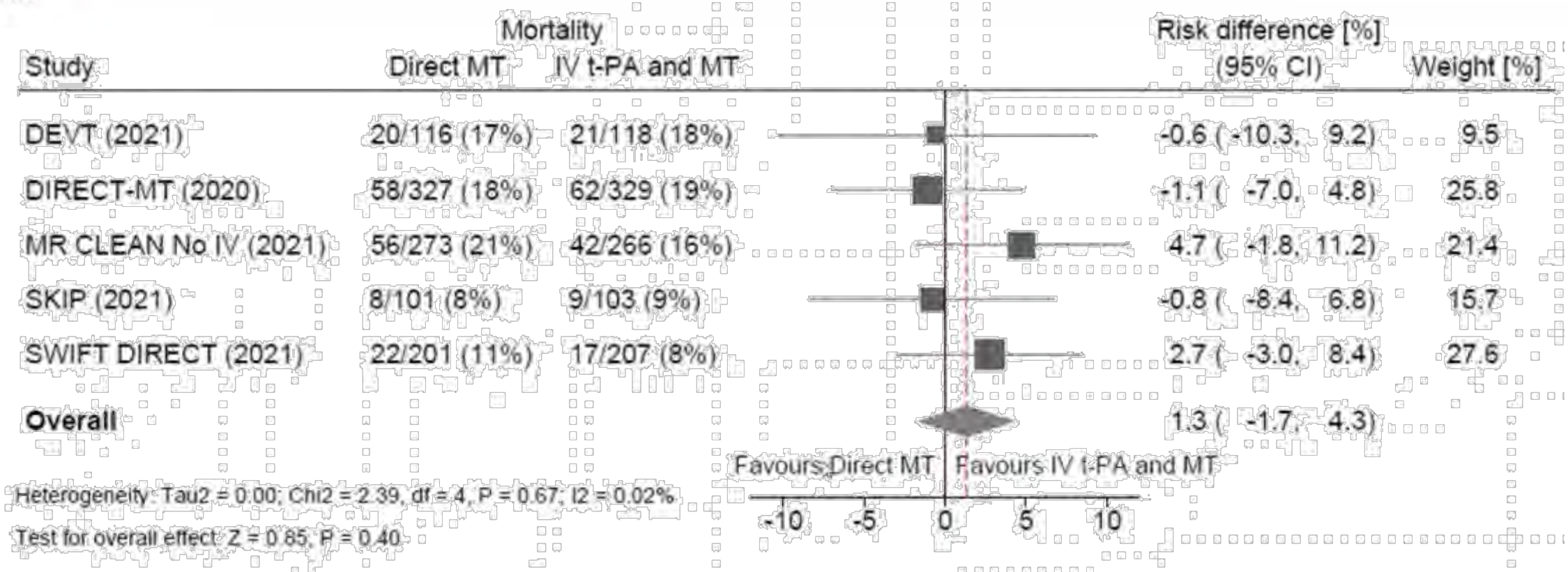
Mortality



Mortality at 90 days using unadjusted risk differences

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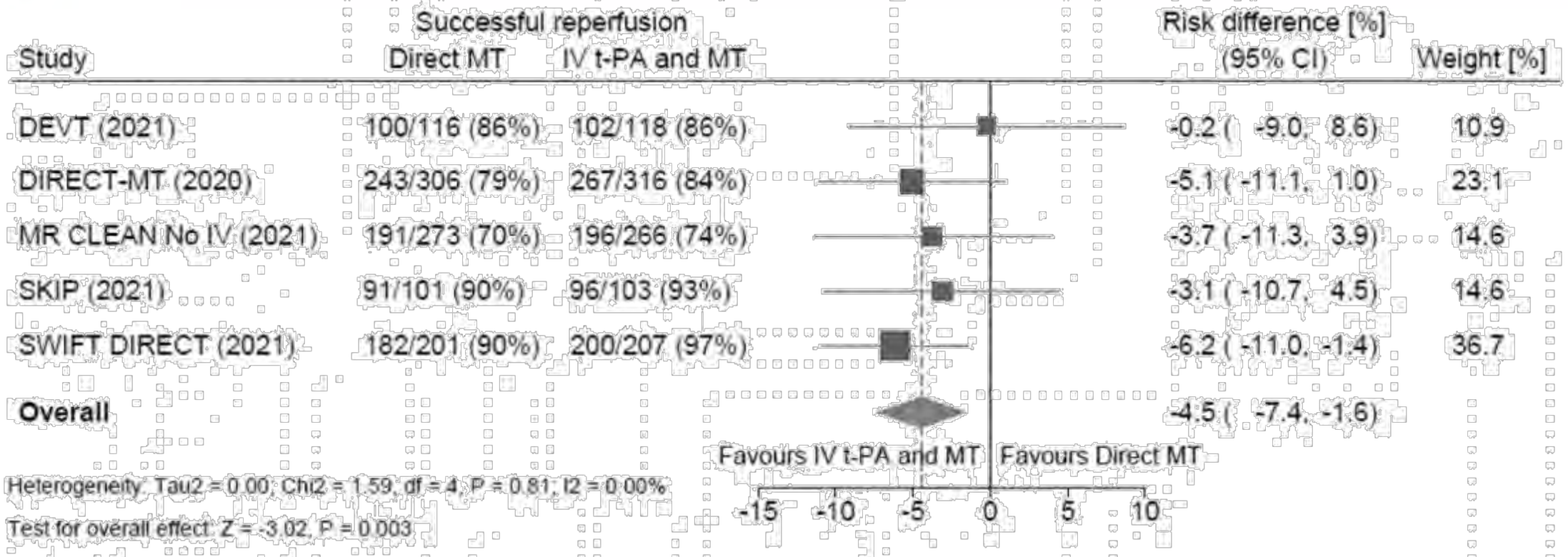
Successful reperfusion



Successful reperfusion (TICI ≤2b) using unadjusted risk differences

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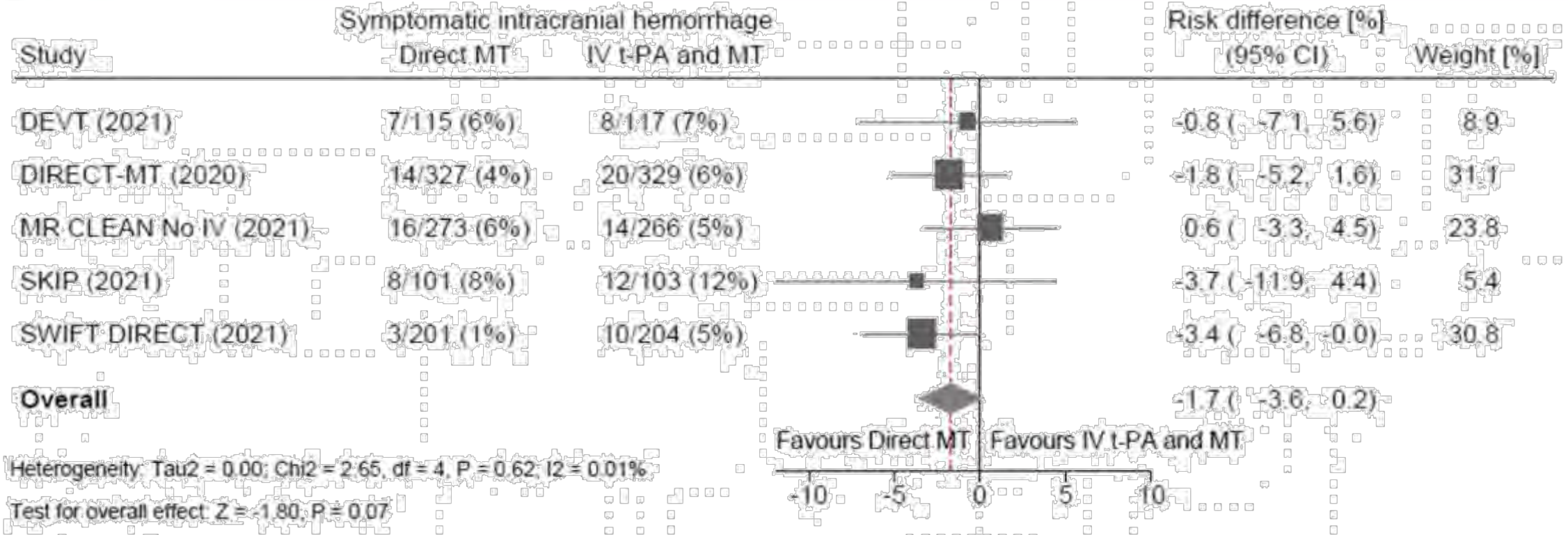
Symptomatic ICH



Symptomatic intracranial hemorrhage using unadjusted risk differences

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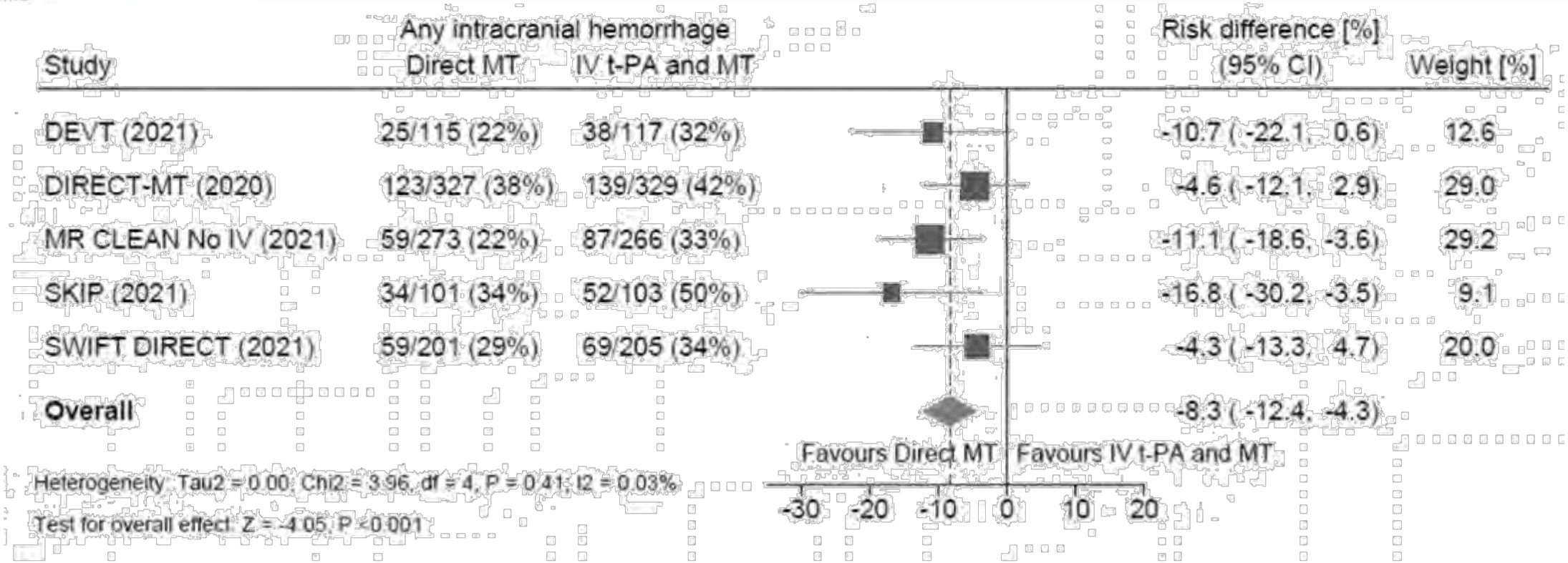
Any ICH



Any intracranial hemorrhage using unadjusted risk difference

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Conclusion I

- This meta-analysis suggests that direct MT is non-inferior to IVT plus MT for the three least severe, but not for more stringent non-inferiority margins.
- There was no evidence of a difference in mortality and mRS shift between both groups.
- Successful reperfusion is better after MT plus IVT than after direct MT.
- Haemorrhage rates are higher in the MT plus IVT group than in the direct MT group.

Conclusion II

- Individual patient data meta-analyses are needed to identify subgroup of patients who respond better to one of the treatment strategies in order to individualize future therapies.
- The "Improving Reperfusion strategies in Ischemic Stroke" (IRIS) working group* will start to collaborate in early 2022.

From U Fischer

Aucune raison de ne pas thrombolyser un patient qui a les critères en vue d'une TEV !

AVC 4.5-9h avec heure de début connue, imagerie perfusion mismatch

Recommendation

For patients with ischaemic stroke of 4.5–9 h duration (known onset time) and with CT or MRI core/perfusion mismatch*, and for whom mechanical thrombectomy is either not indicated or not planned, we recommend intravenous thrombolysis with alteplase.

Quality of evidence: Low ⊕⊕

Strength of recommendation: Strong ↑↑

*In the individual participant data meta-analysis by Campbell et al.,[34] core/perfusion mismatch was assessed with an automated processing software and defined as follows:

- Infarct core** volume < 70 ml
- and Critically hypoperfused† volume/Infarct core** volume > 1.2
- and Mismatch volume > 10 ml

** rCBF < 30% (CT perfusion) or ADC < 620 $\mu m^2/s$ (Diffusion MRI)

†Tmax >6 s (perfusion CT or perfusion MRI)

For patients with no CT or MRI core/perfusion mismatch, please see the expert consensus statement below.

Expert consensus statement

For patients presenting directly to a thrombectomy centre with ischaemic stroke of 4.5–9 h duration (known onset) with CT or MRI core/perfusion mismatch and who are eligible for mechanical thrombectomy, the group members could not reach a consensus regarding whether intravenous thrombolysis should be used before mechanical thrombectomy.

For patients presenting to a non-thrombectomy centre with ischaemic stroke of 4.5–9 h duration (known onset) with CT or MRI core/perfusion mismatch and who are eligible for mechanical thrombectomy, 6 of 9 group members suggest intravenous thrombolysis before mechanical thrombectomy.

TEV distale

Futur ou futilité ?


SPECIAL REPORT

Thrombectomy for Distal, Medium Vessel Occlusions

A Consensus Statement on Present Knowledge and Promising Directions

Stroke. 2020;51:2872–2884. DOI: 10.1161/STROKEAHA.120.028956

Slides de la présentation ESOC 2021, Dr J. Kaesmacher

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Distal Vessel Occlusions

Thrombectomy for Distal, Medium Vessel Occlusions

A Consensus Statement on Present Knowledge and Promising Directions

Jeffrey L. Saver, MD, Rene Chapot, MD, Ronit Agid, MD, Ameer E. Hassan, DO, Ashutosh P. Jadhav, MD, David S. Liebeskind, MD, Kyriakos Lobotesis, MD, Dan Meila, MD, Lukas Meyer, MD, Guy Raphaeli, MD, Rishi Gupta, MD, the Distal Thrombectomy Summit Group*†.

MeVO: the next frontier?

Mayank Goyal [1,2], Johanna Maria Ospel [1,3], Bijoy K Menon,[1,2] Michael D Hill [1,2]

DMVO

1. vessel distance/tortuosity (distal vessel)
2. Vessel size/diameter (medium vessel)

ACA	MCA	PCA	Cerebellar
A1	M2	P1	PICA
A2	M3/4	P2	AICA
A3-5		P3-5	SCA

MeVO

1. Anatomical Segments
2. Clinical deficit

ACA	MCA	PCA	Cerebellar
A2	M2	P2	
A3	M3	P3	

ESOC 2021 - J Kaesmacher https://kenes.cloud.panopto.eu/Panopto/Pages/Viewer.aspx?pid=093e5f70-7bdf-4b87-972e-ad43008169f5&id=aaae6414-153c-408a-9ff6-ad6501211335&advance=true

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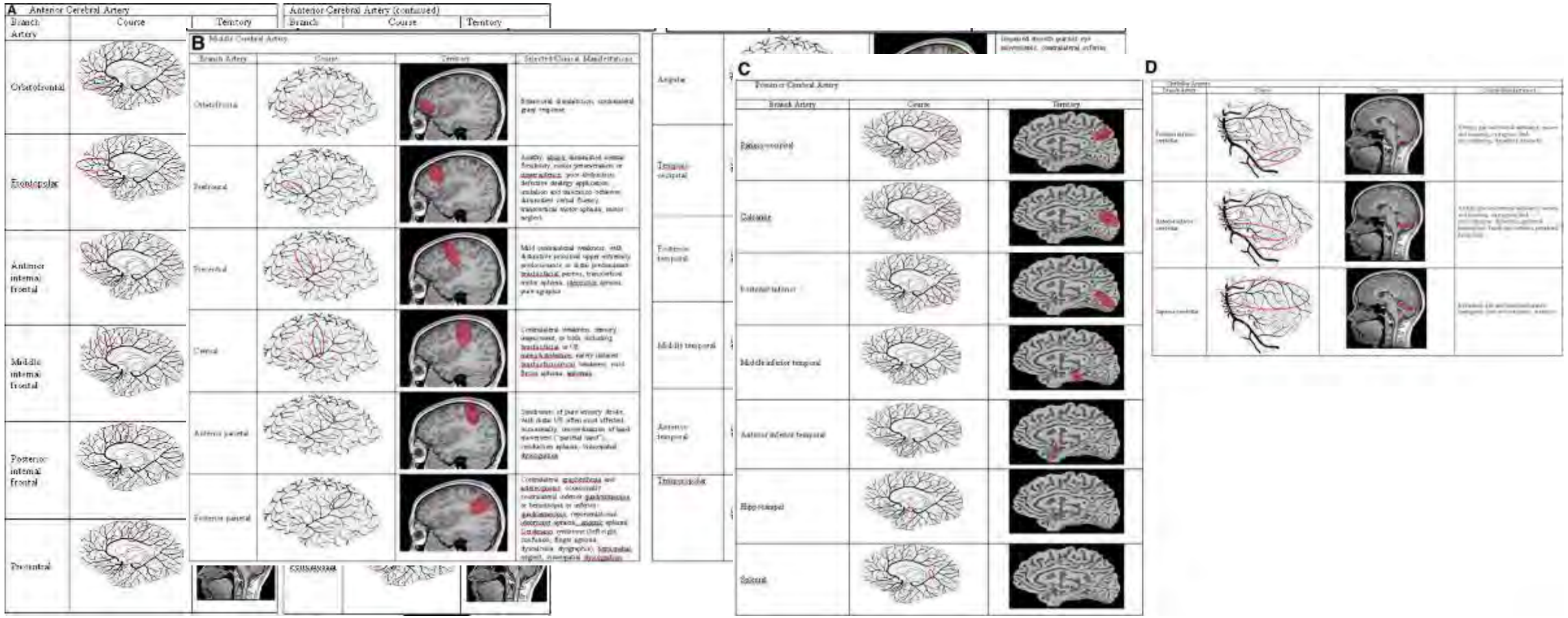
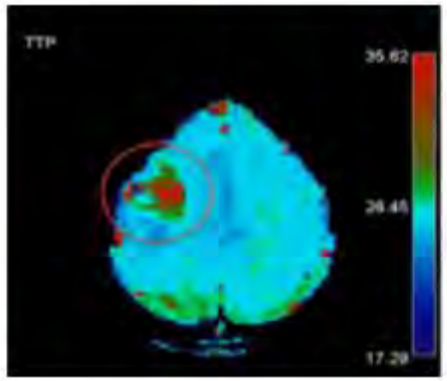
Vaisseaux distaux : plusieurs localisations / symptômes, mais souvent **zones corticales éloquentes**



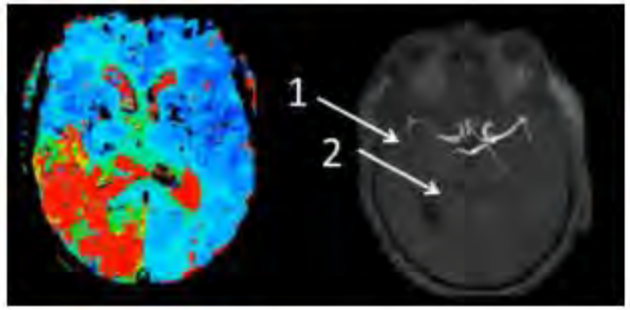
Saver JL (2020) https://doi.org/10.1161/STROKEAHA.120.028956

Distal Vessel Occlusions

Primary DMVO/MeVOs



Beware: 10-15% have multiple vessel occlusions:

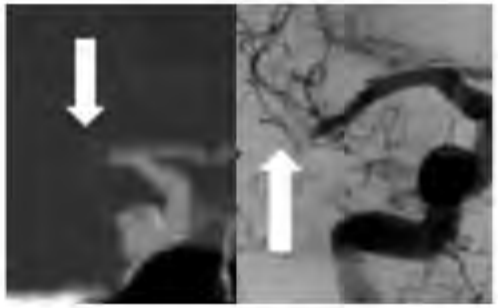


Multiple occlusions
More common in
More distal vessels

Kaesmacher et al. JAHA 2018

Secondary DMVO/MeVOs

Spontaneous / after IVT



Following MT

Kaesmacher et al. JAHA 2018
Goyal et al. STROKE 2021

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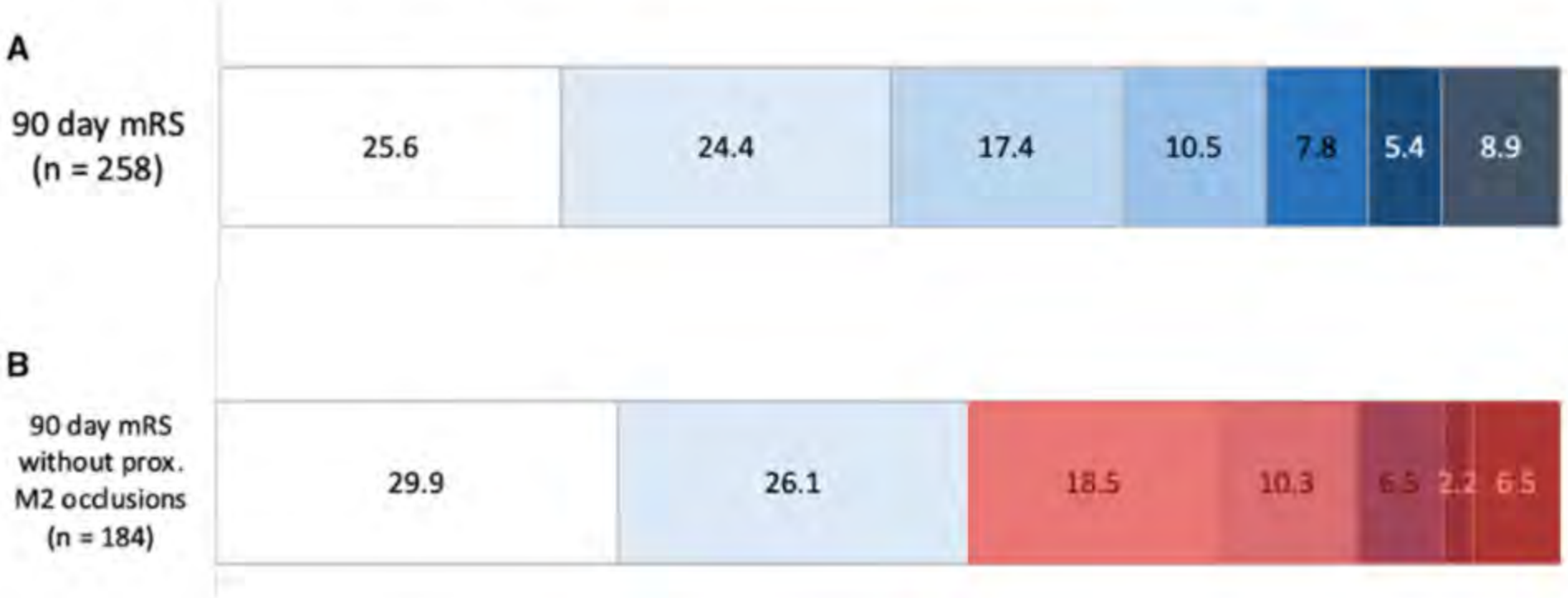
Distal Vessel Occlusions

DMVO/MeVOs - do we need new treatments?



Ospel et al. STROKE 2021

Distal Vessel Occlusions

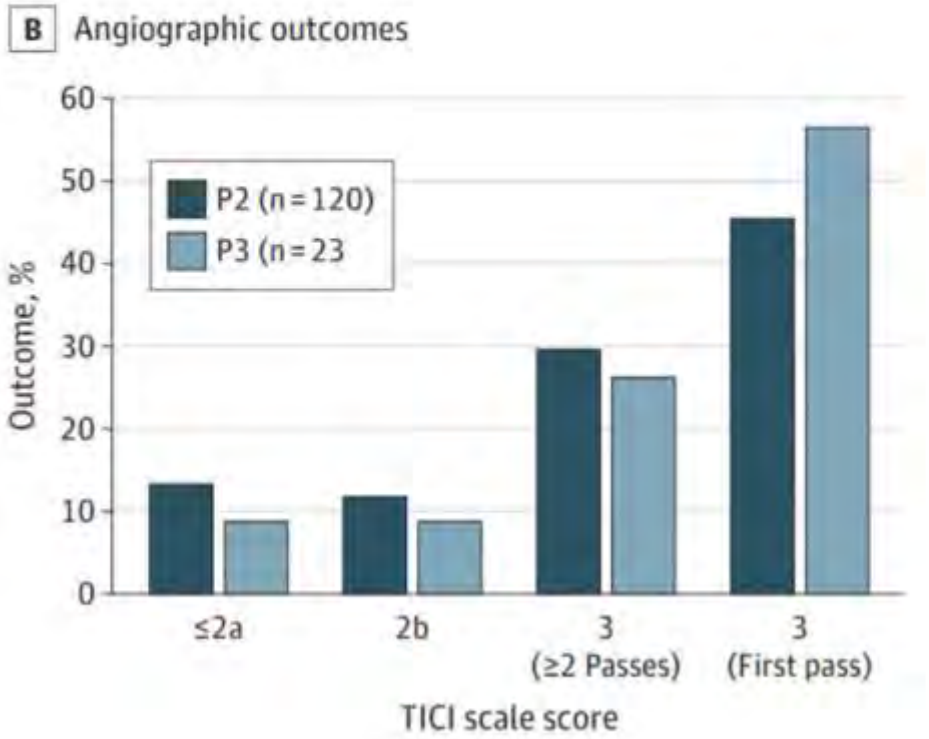
DMVO/MeVOs – does reperfusion help?

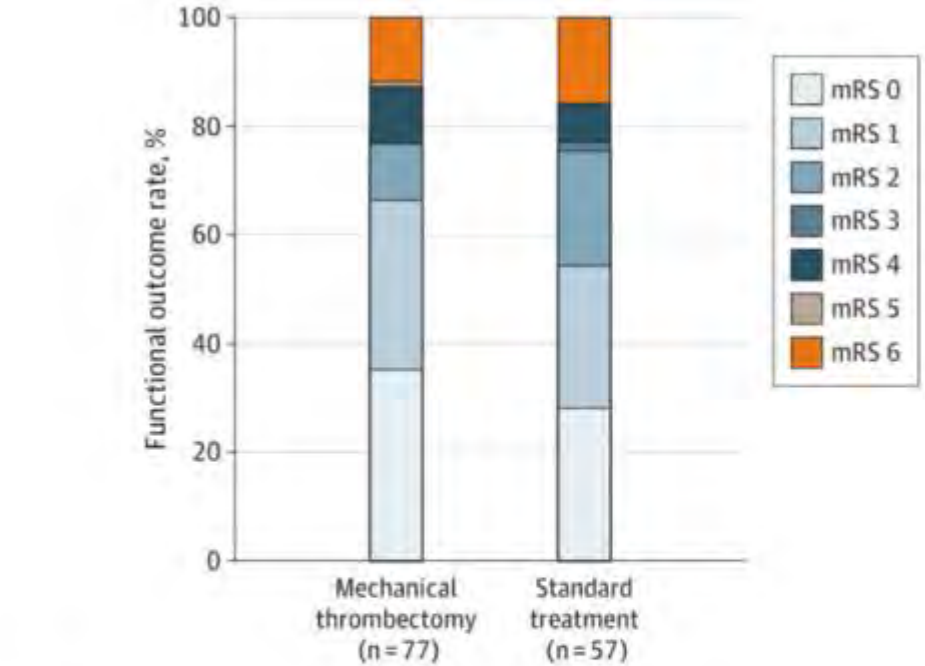
Ospel et al. STROKE 2021

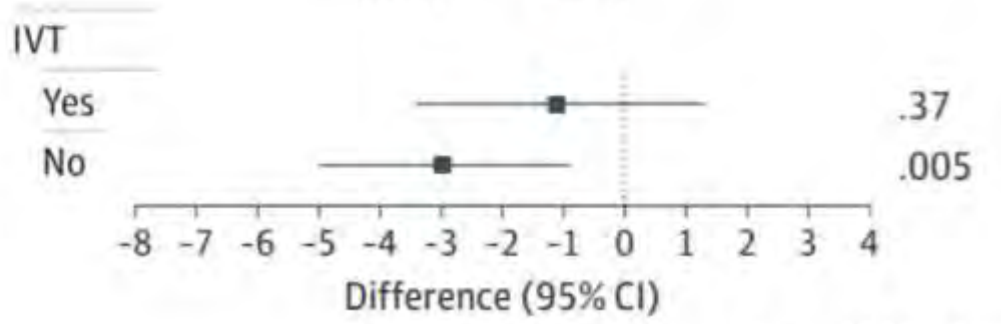
Ospel JM (2020) https://doi.org/10.1161/STROKEAHA.120.030227

Distal Vessel Occlusions

DMVO/MeVOs - does thrombectomy help?







Meyer et al. JAMA NL

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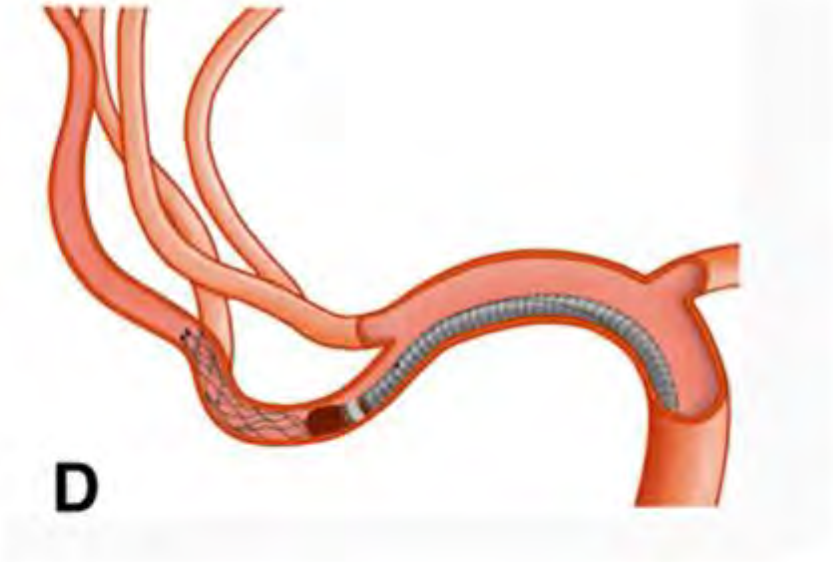
INSELGRUPPE

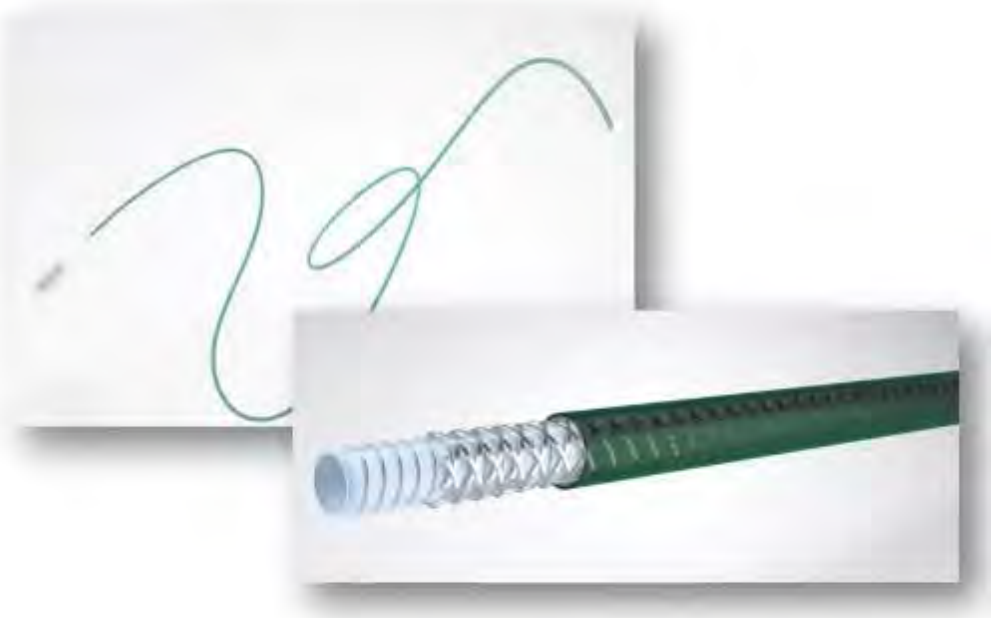
STROKE RESEARCH CENTER BERN (SRCB)

Distal Vessel Occlusions

How to?



Mini-Pinning Technique
Peres-Garcia et al. STROKE 2020



«Micro-ADAPT»
Crockett et al. JNIS 2018

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Distal Vessel Occlusions

The current state

- **serious disease** associated with a considerable amount of patients not achieving excellent functional outcomes
- can be **primary** and **secondary** with different pathophysiology, infarct patterns and eligibility for trial and treatments
- **Reperfusion** is consistently associated with **better outcomes**
- Report, define and grade according to current consensus/recommendations.

Distal vessel occlusion is a more complicated and heterogenous disease than it appears

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Distal Vessel Occlusions

TRIALS

Upcoming RCTs

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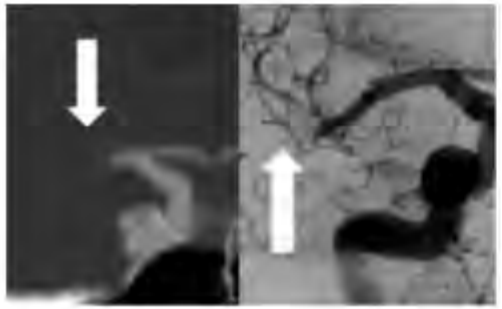
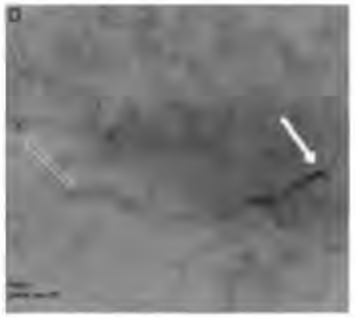
Distal Vessel Occlusions

Secondary DMVO/MeVOs

Spontaneous / after IVT



Following MT



Reperfusion often poor, thrombus no longer accessible

BUT

Outcome is often excellent

«Thrombus Migration Paradox»

Original research

Thrombectomy for secondary c
occlusions of the posterior circ
complete reperfusion

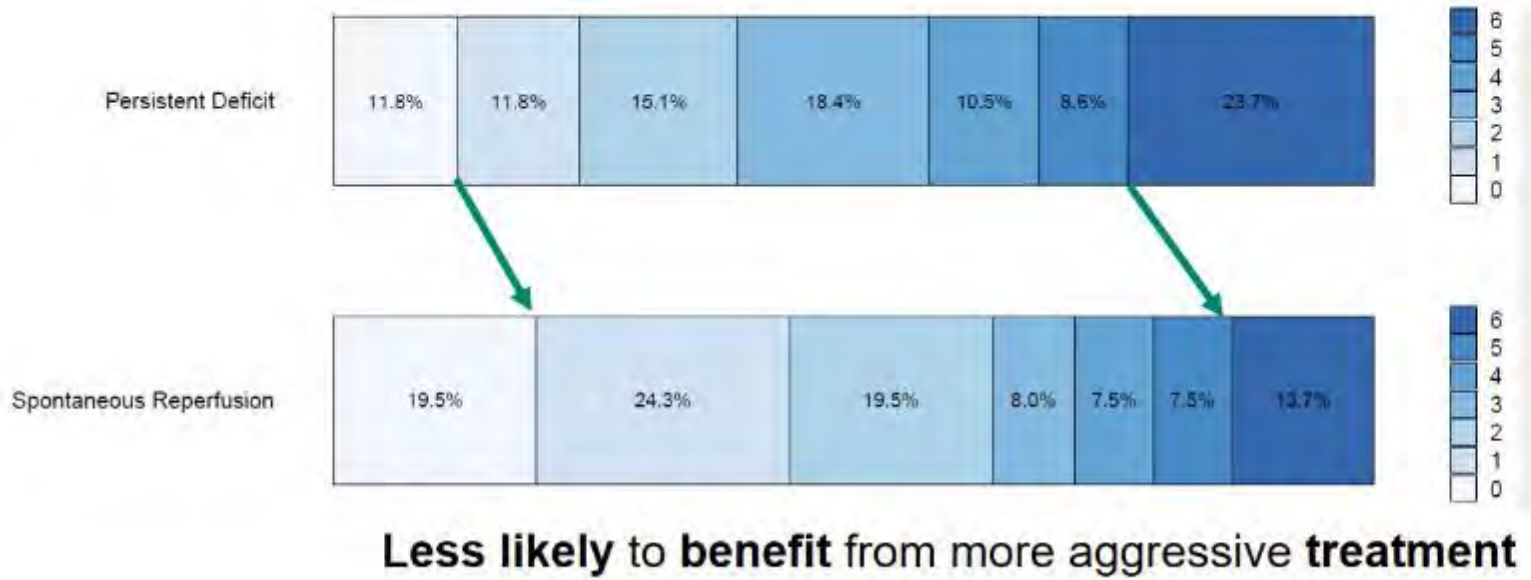
INTERVENTIONAL

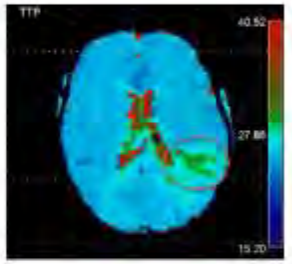
Improving mTICI2b reperfusion to mTICI2c/3 reperfusions: A retrospective observational study assessing technical feasibility, safety and clinical efficacy

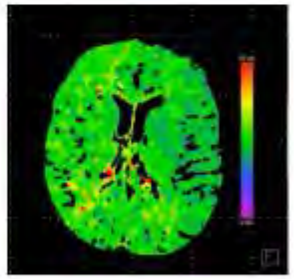
Distal Vessel Occlusions

Secondary DMVO/MeVOs

Probably benefit from more aggressive **treatment**







Less likely to **benefit** from more aggressive **treatment**

UNPUBLISHED DATA – DO NOT COPY OR DISTRIBUTE

Mujanovic et al.

AVC avec large core

Que faire ?

Slides de la présentation ESOC 2021, Dr J. Kaesmacher

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TOPICAL REVIEW

Challenging the Ischemic Core Concept in Acute Ischemic Stroke Imaging

Lésion homogène vs inhomogène / corticale pure…

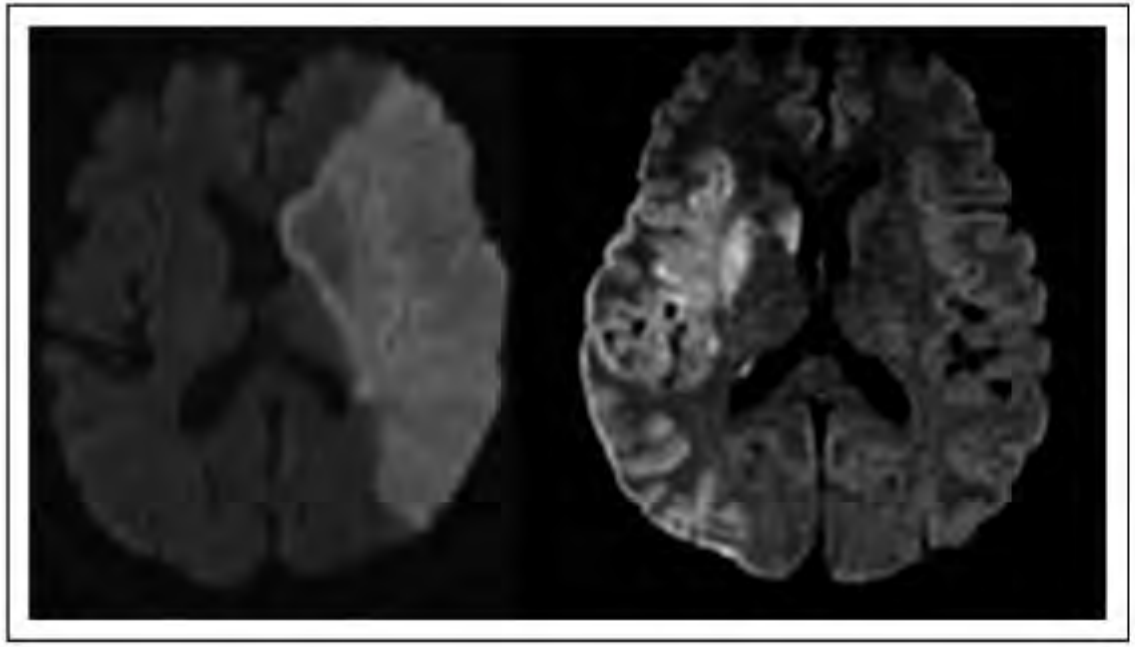

Figure 1. Exemplary diffusion-weighted magnetic resonance imaging (MRI) sequences of 2 acute ischemic stroke patients. Homogeneous infarct pattern (**left**) in which both gray and white matter are completely affected vs patchy cortical/white matter sparing infarct pattern (**right**). In the latter one, the patient's National Institutes of Health Stroke Scale (NIHSS) at the time of the MRI was 3, despite the apparently extensive infarcts.

Goyal M (2020) https://doi.org/10.1161/STROKEAHA.120.030620

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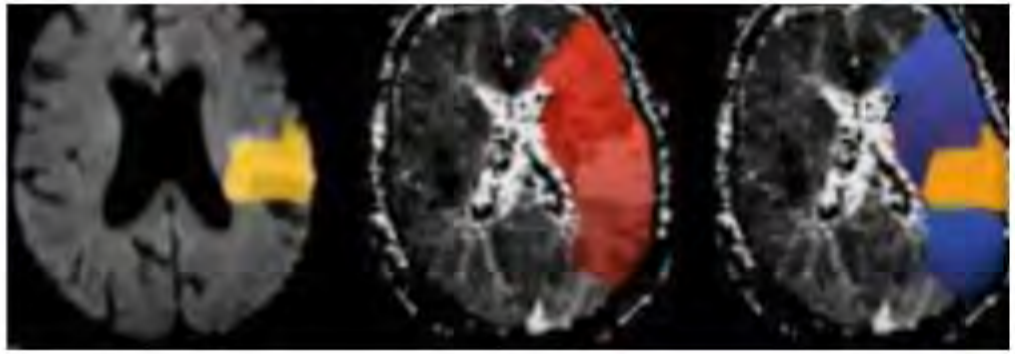
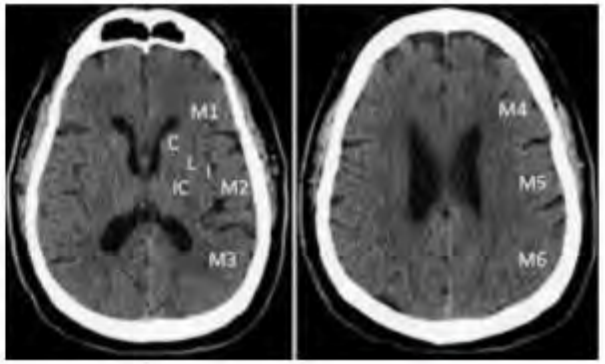
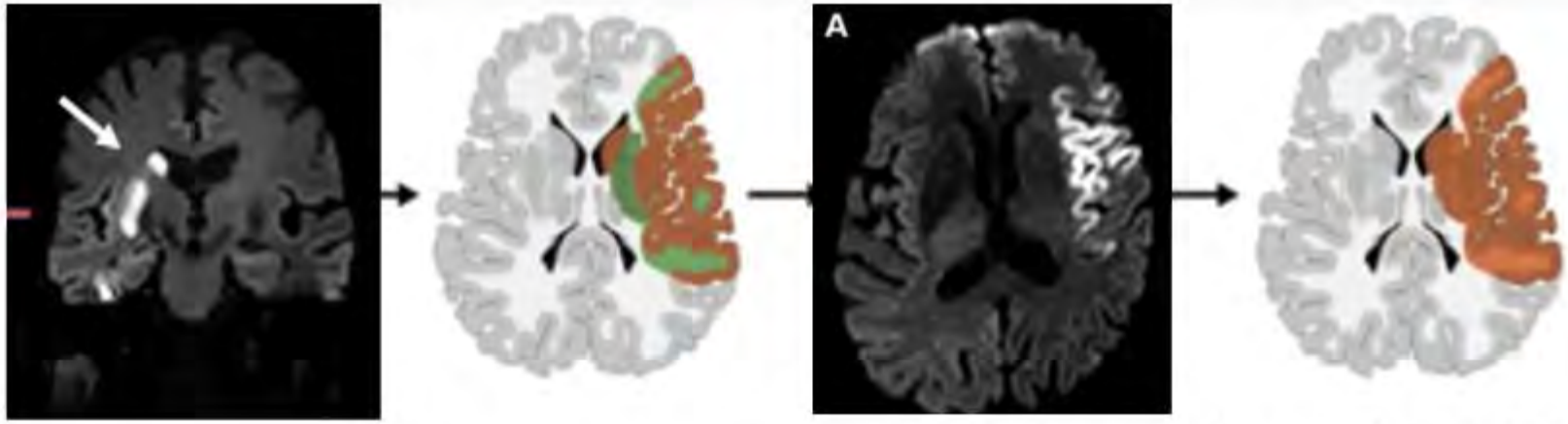
Large Infarct Core

What you see is what you get







Kaesmacher et al. STROKE 2021

AVC : un phénomène *dynamique* dans *le temps* et *l'espace*

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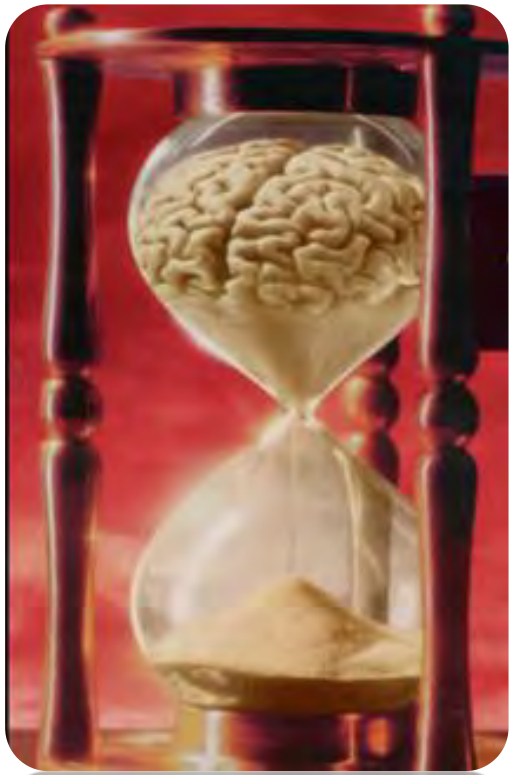
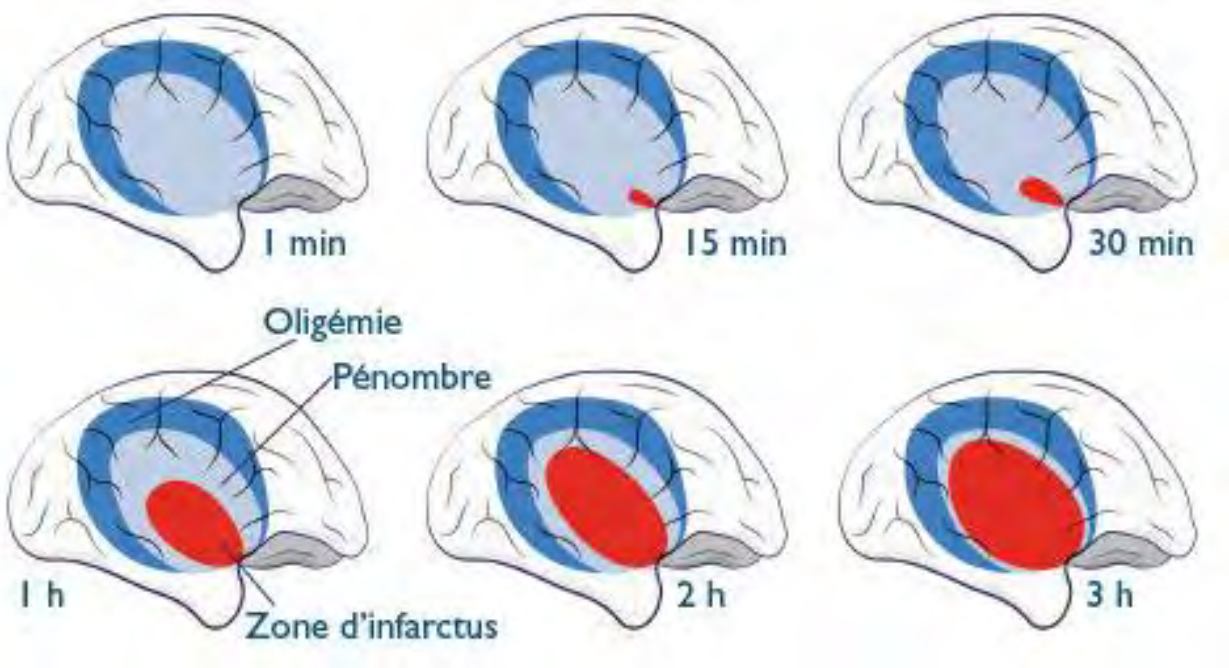


- **Lorsqu'un AVC survient, chaque minute, le cerveau perd environ 2 millions de neurones !**



Rev Med Suisse 2015; volume 11.1476 – Jones, J Neurosurg 1981;54:773 – Baron, Cerebrovasc Dis 1999;9:193

Réversibilité du core (CBV au CT / DWI à l'IRM)

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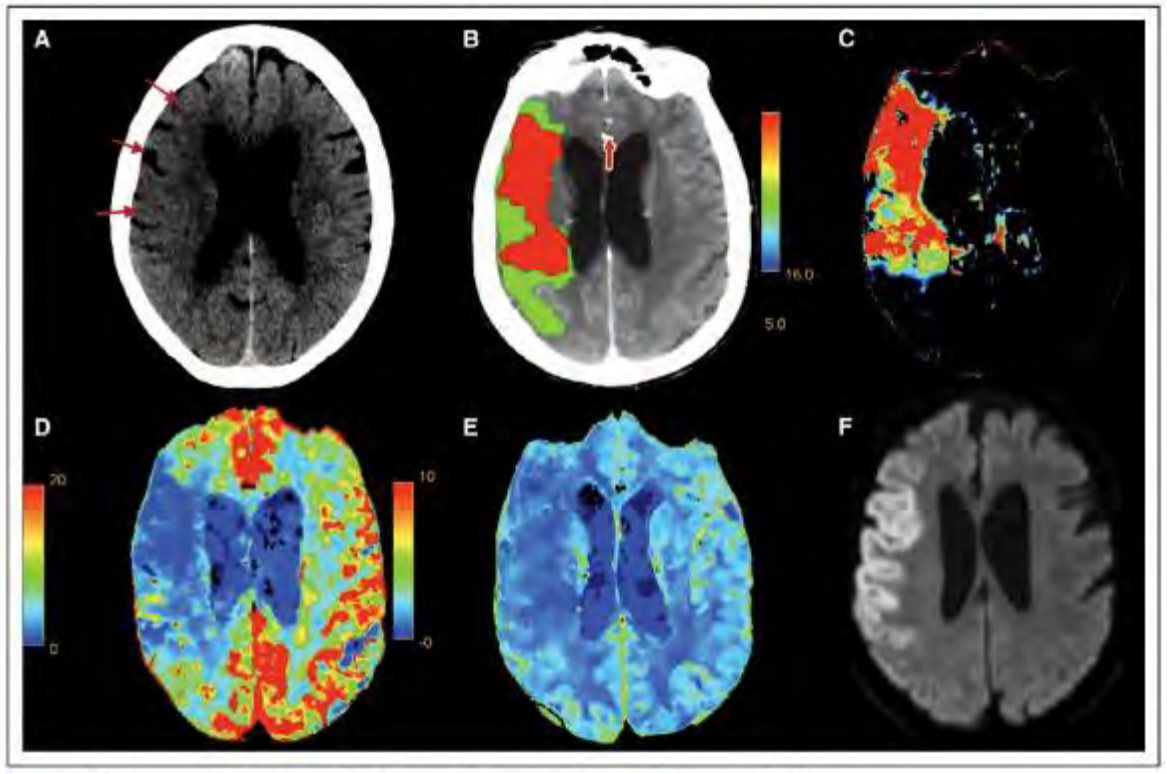
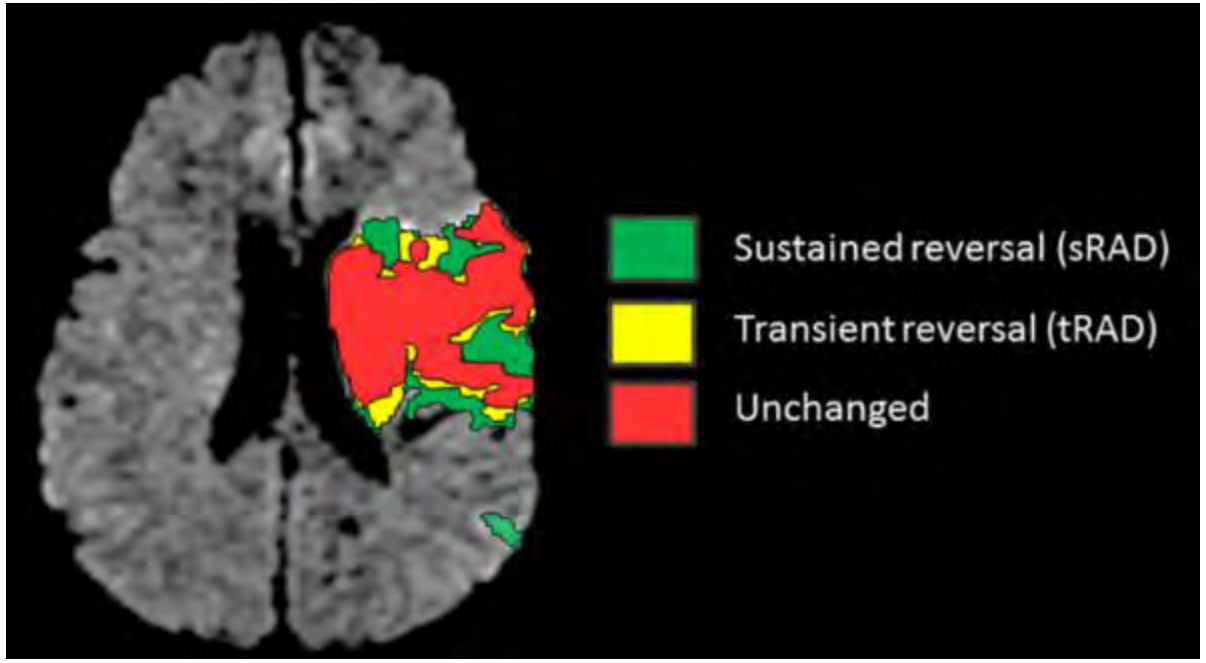


Figure 2. **Core reversibility on computed tomography (CT) perfusion and noncontrast CT.**



Goyal M (2020) https://doi.org/10.1161/STROKEAHA.120.030620 et Soize S (2015) https://doi.org/10.1161/STROKEAHA.114.008322

NCCT… même ASPECT score … mais AVC différents !

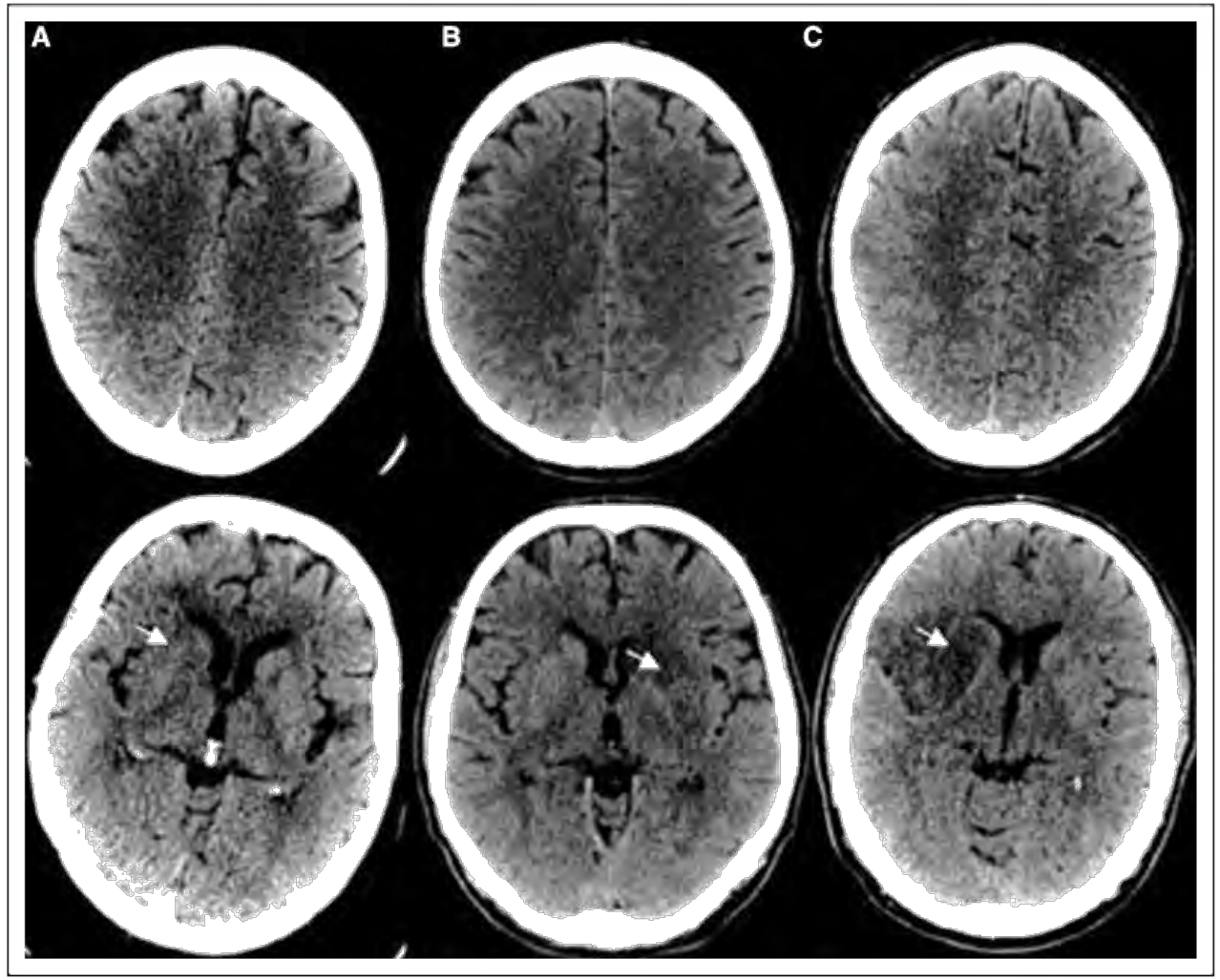


Figure 3. Continuum of hypodensity on noncontrast computed tomography (NCCT).
In **A**, there is only mild hypodensity of the caudate and lentiform nucleus, while in (**B**), the hypodensity is patchy and more conspicuous. In **C**, there is frank hypodensity of the caudate and lentiform nucleus as well as the insula and M1 region. These qualitative density differences are neither reflected in the Alberta Stroke Program Early CT Score (ASPECTS) nor in core volume.

Goyal M (2020) https://doi.org/10.1161/STROKEAHA.120.030620

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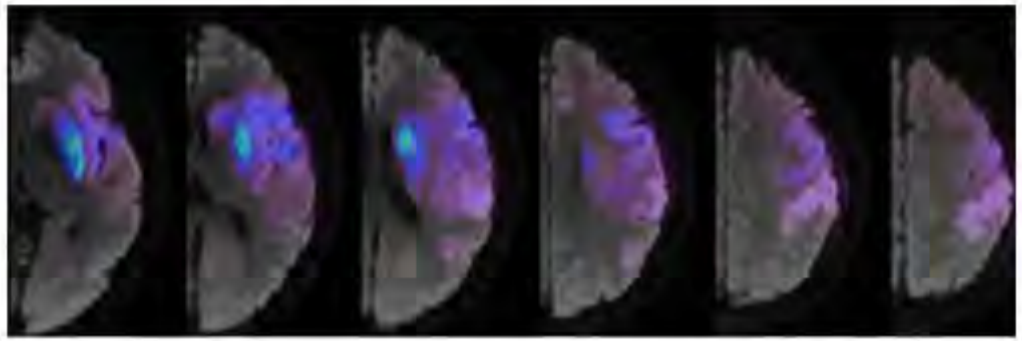
Large Infarct Core

Dichotomization

0 ⟷ 1



Moulton et al. PLOS ONE

Swelling / Viscosity changes

Selective neuronal Loss/apoptosis

Selective layer necrosis

Selective tissue type necrosis

Edema and vascular integrity

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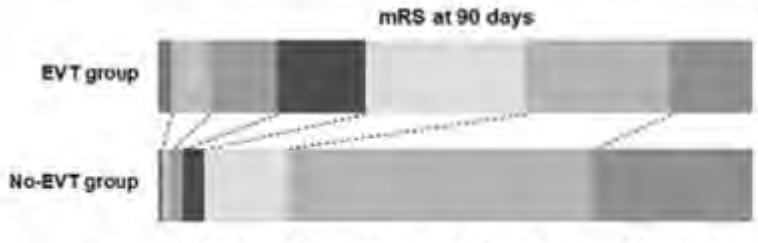
Large Infarct Core

Large Infarct Core – Does Reperfusion help?

Impact of Endovascular Therapy in Patients With Large Ischemic Core

Subanalysis of Recovery by Endovascular Salvage for Cerebral Ultra-Acute Embolism Japan Registry 2

Hiroto Kakita, MD; Shinichi Yoshimura, MD, PhD; Kazutaka Uchida, MD; Nobuyuki Sakai, MD, PhD; Hiroshi Yamagami, MD, PhD; Takeshi Morimoto, MD, PhD, MPH; RESCUE-Japan Registry 2 Investigators*

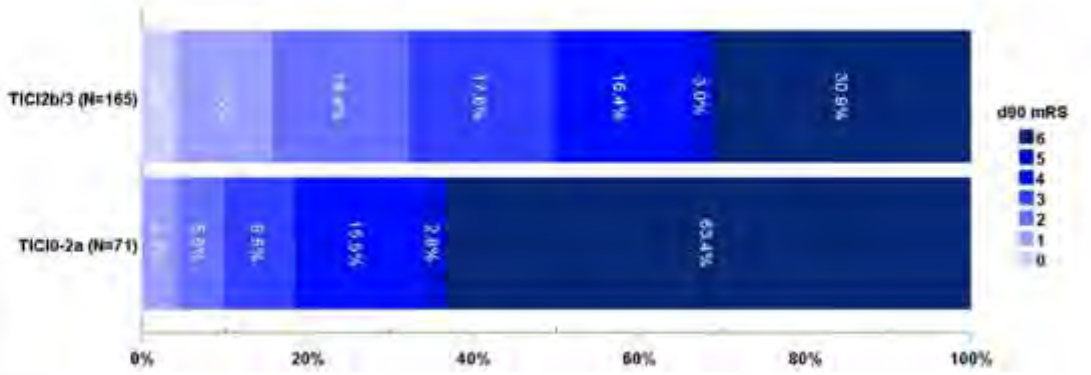


	mRS at 90 days	0	1	2	3	4	5	6	cOR (95% CI)	p value	Adjusted cOR (95% CI)	p value
EVT group (n=172)	n (%)	4 (2.3)	11 (6.4)	19 (11.1)	26 (15.1)	45 (26.2)	43 (25)	24 (14)	4.63 (3.23-6.62)	<0.0001	2.85 (1.87-4.34)	<0.0001
No-EVT group (n=332)	n (%)	2 (0.6)	5 (1.5)	7 (2.1)	11 (3.3)	47 (14.2)	171 (51.5)	89 (26.8)				

OPEN

Mechanical Thrombectomy in Ischemic Stroke Patients With Alberta Stroke Program Early Computed Tomography Score 0–5

Johannes Kaesmacher, MD; Panagiotis Chaloulos-Iakovidis, MD; Leonidas Panos, MD; Pasquale Mordasini, MD; Patrik Michel, MD; Steven D. Hajdu, MD; Marc Ribo, MD; Manuel Requena, MD; Christian Maegerlein, MD; Benjamin Friedrich, MD; Vincent Costalat, MD; Amel Benali, MSc; Laurent Pierot, MD; Matthias Gawlitza, MD; Joanna Schaafsma, MD; Vitor Mendes Pereira, MD; Jan Gralla, MD;* Urs Fischer, MD*



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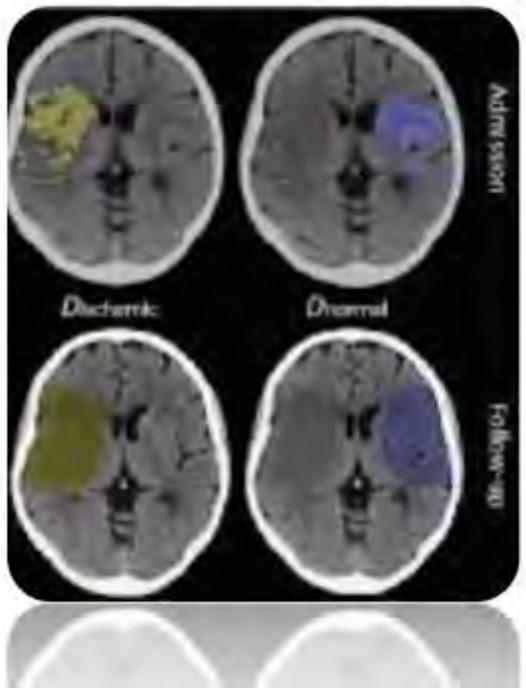
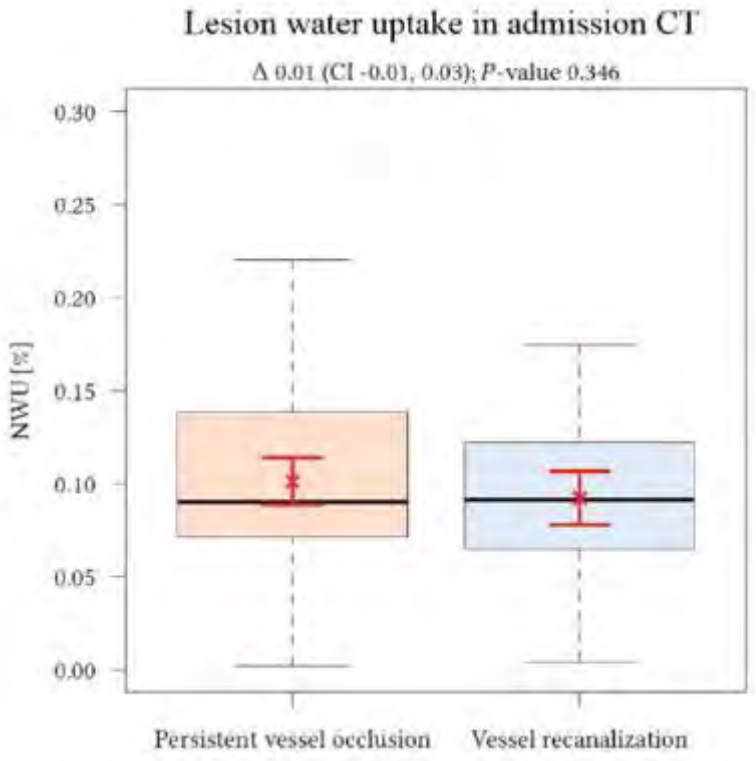
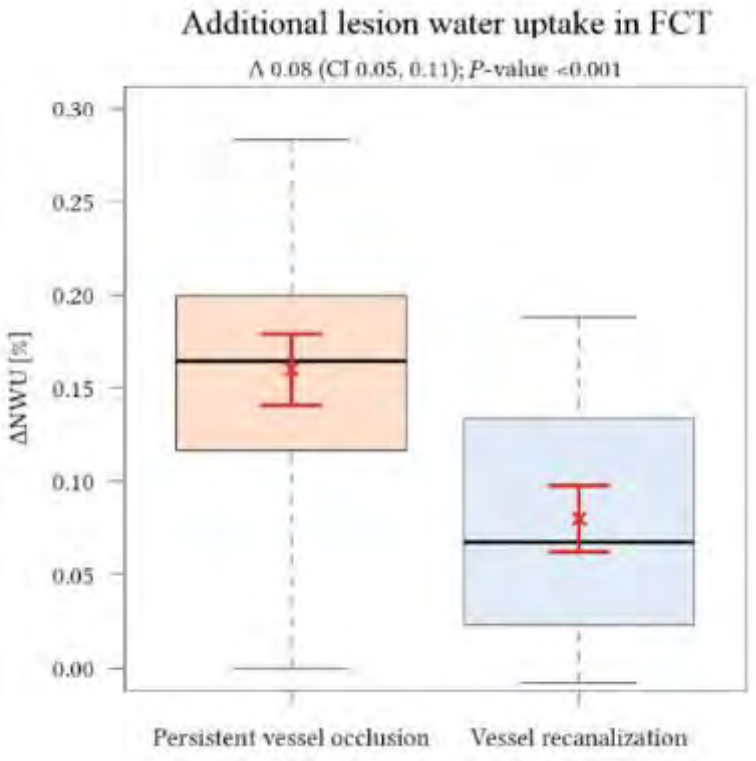
Large Infarct Core

Large Infarct Core – Does Reperfusion help?

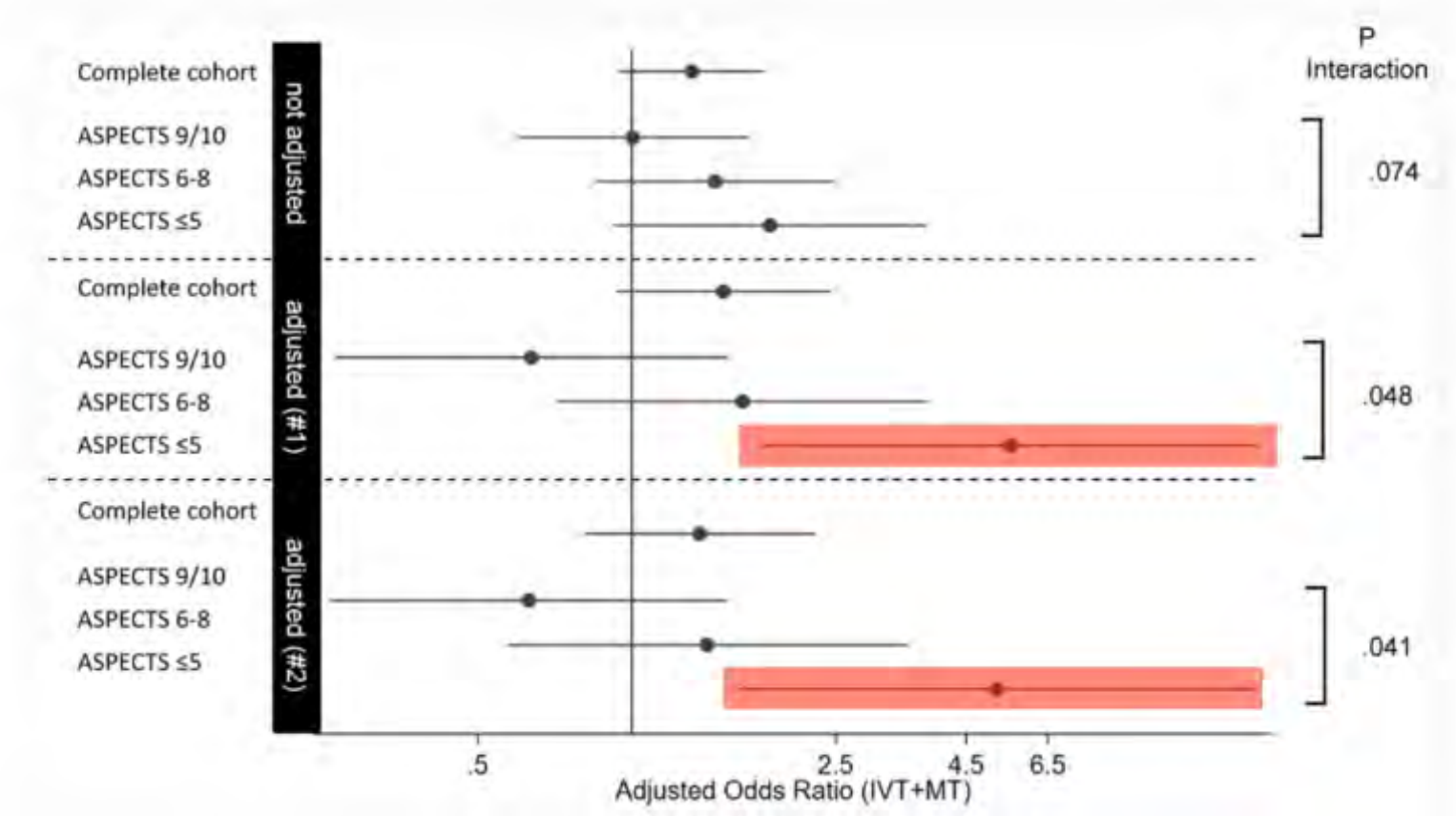






Large Infarct Core

Large Infarct Core – Role of IVT?



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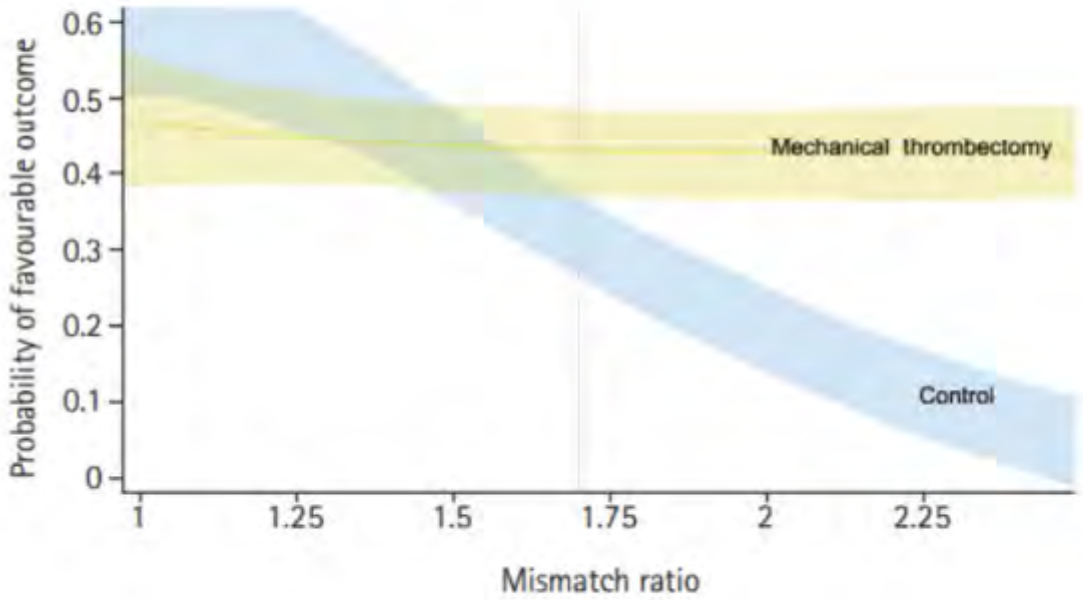
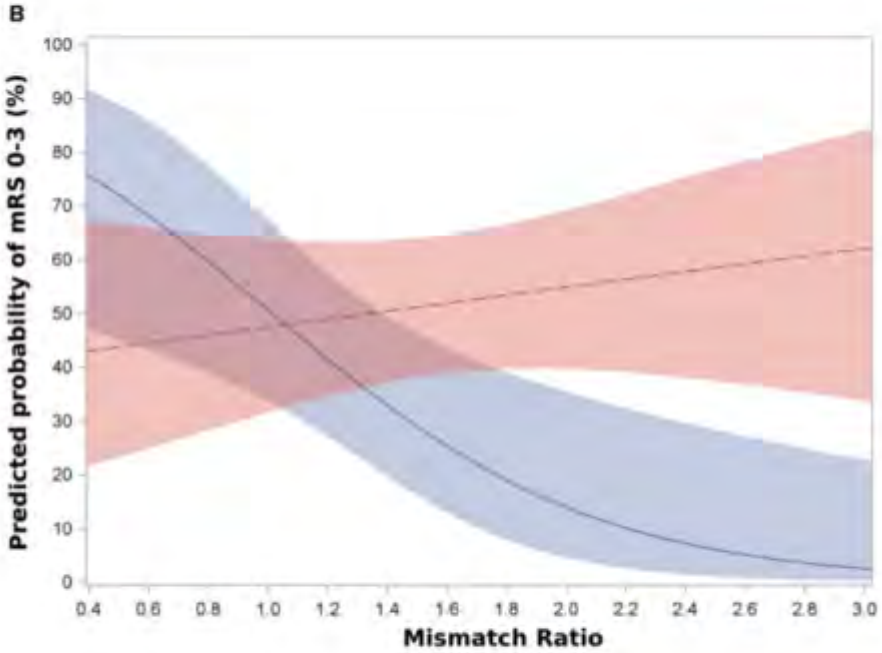
Large Infarct Core

Patient selection?



Kerleroux et al. JoS 2020



Seners et al. Annals of Neurology 2021

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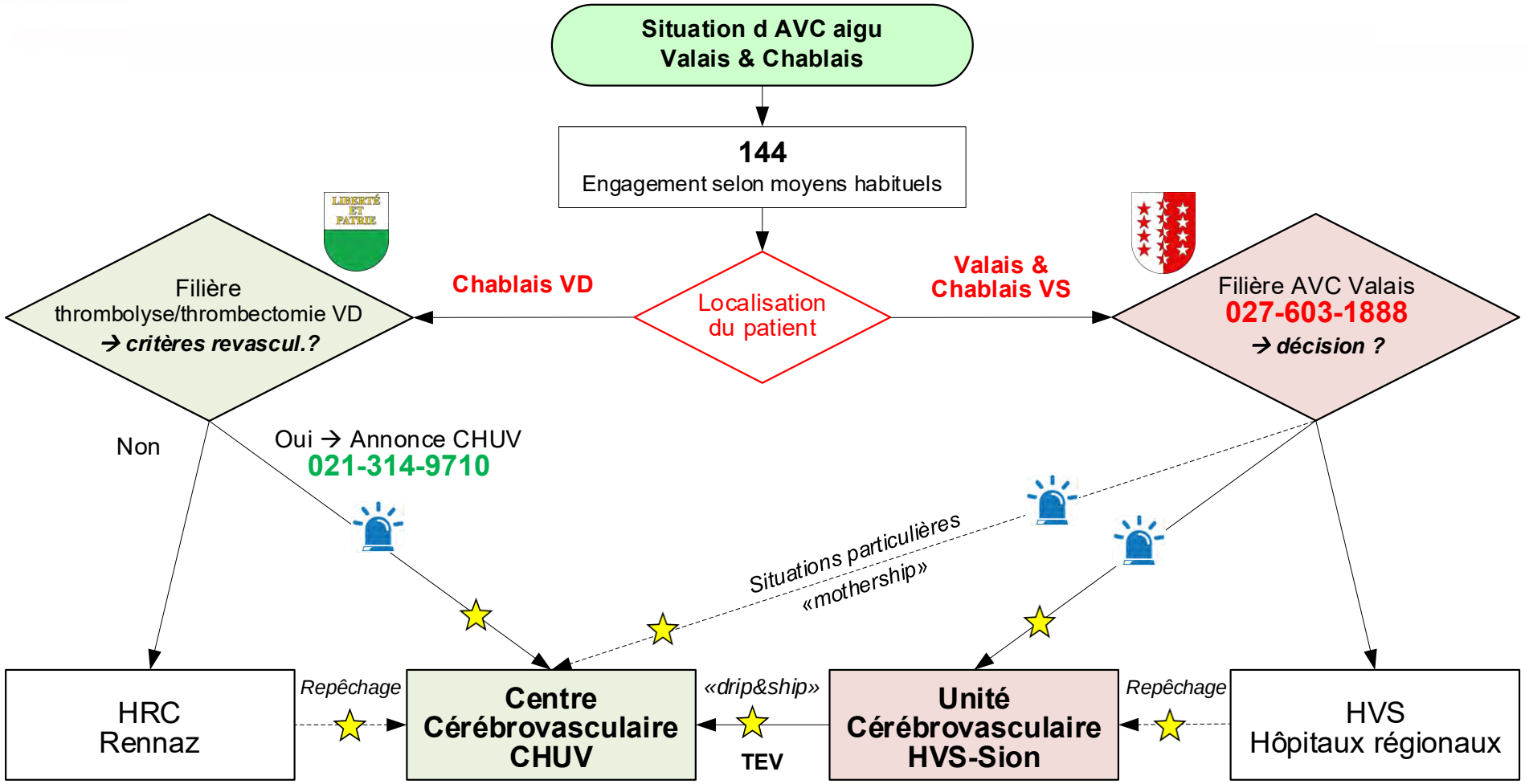
Large core stroke : RCT en cours… pas pour tout de suite !

	TENSION	IN-EXTREMIS (LASTE)	RESCUE LIMIT	TESLA	SELECT II
N	**665**	**450**	200	300	560
Large Core	CT-ASPECTS 3-5	CT/DWI-ASPECTS 0-5 (>80y: 4-5)	CT/DWI-ASPECTS 3-5	CT-ASPECTS 2-5	CT-ASPECTS 3-5 OR perfusion core >50ml
Outcome	mRS shift	mRS shift + mortality	mRS ≤3	Utility-weighted 90-day Modified Rankin Score	mRS shift
Recruiting	Yes, **150** (07/2021)	Yes **158** (07/2021)	Yes	Yes	Yes

4. Protocole AVC Valais

Orientation préhospitalière des AVC Valais – Chablais



★ *Annonce obligatoire par ambul. / hélico. 10 min avant arrivée*

Dr C. Bonvin (HVS) & Prof. P. Michel (CHUV)

Acute LVO Stroke: Where to go?

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Mobile stroke unit

Stroke in Wallis

«drip & ship»

«mothership»

«reverse»

Stroke Unit Sion

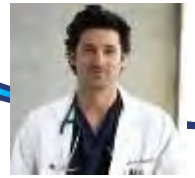
Stroke Center CHUV, Insel, HUG

Remote robotic EVT

1/3 patients thrombolysed

More in the future

«drip & fly»



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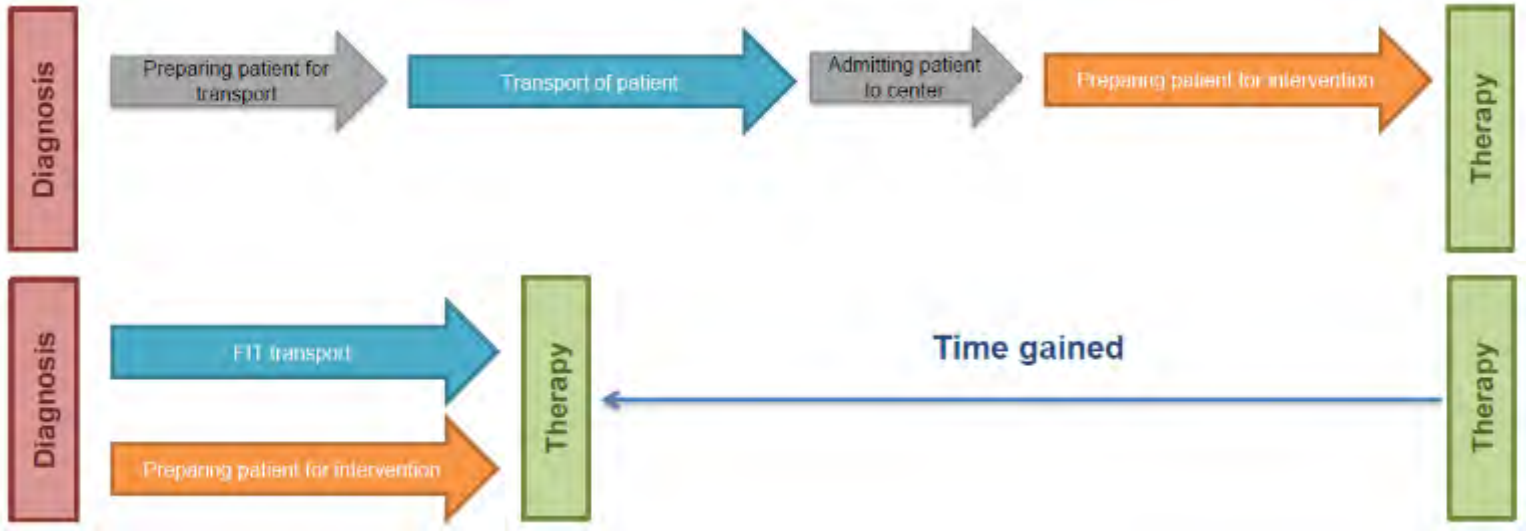
Flying Intervention Team

Association between a Novel System of Care and Functional Outcome of Stroke Patients in Remote Areas

Gordian Hubert & Nikolai Hubert
Telemedical Stroke Network TEMPiS
München Klinik, Munich, Germany

Background

- Effect of endovascular treatment (EVT) is time dependent
- Interventional expertise is scarce in rural areas
- Rural patients experience significant treatment delays and worse outcomes



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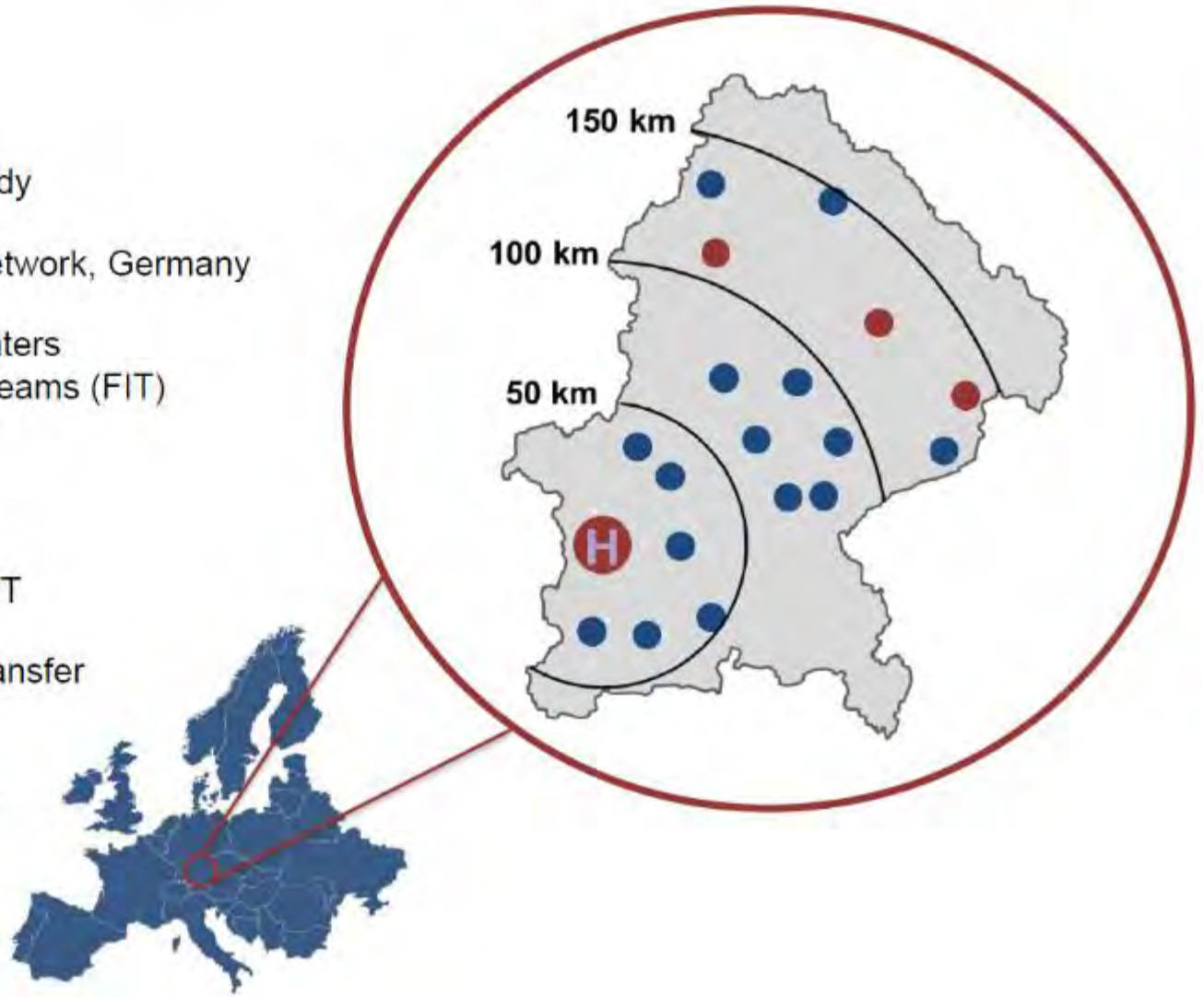
Spital Wallis

TEMPiS

Flying Intervention Team
Southeast Bavaria

Methods

Study type:	Prospective cohort study
Setting:	TEMPiS Telestroke Network, Germany
Participation:	15 Primary Stroke Centers 2 Flying Intervention Teams (FIT) 5 Intervention Centers
Recruiting period:	Feb 2018 – Jan 2021
Inclusion:	Patients eligible for EVT
Group allocation:	FIT vs. Interhospital transfer
Number of patients:	134 FIT patients 210 Transfer patients
Primary endpoint:	mRS at 3 months



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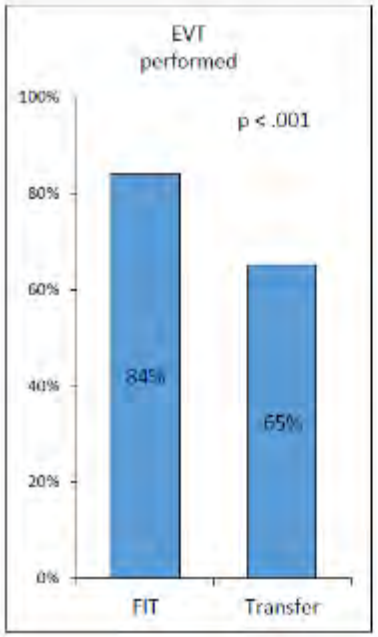
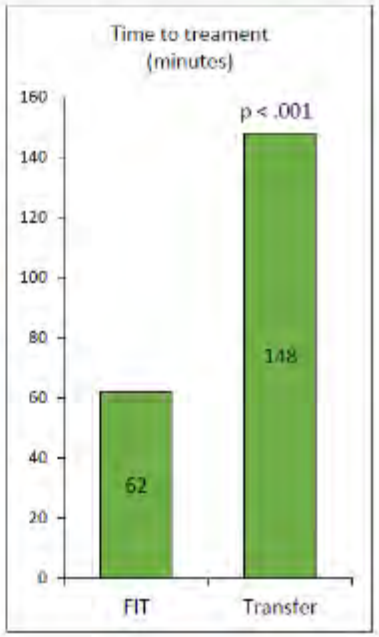
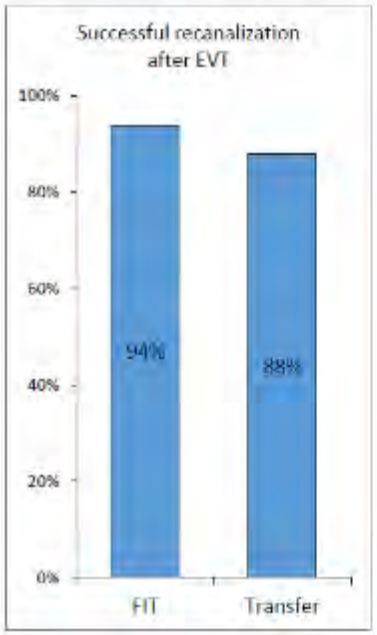
Results







Complications

> similar in both groups

Functional Outcome at 3 months

Primary endpoint: No significant difference. Trend towards better outcome in the FIT group.
(acOR: 1.47; 95%-CI: 0.97-2.23)

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Remote Robotic Endovascular Treatment (RRET)

Conclusions In this proof-of-concept evaluation, the technical feasibility of RRET was demonstrated in an ex vivo model and was collaboratively performed by an offsite neurosurgeon and an onsite interventional cardiologist. This report supports the design of future studies to determine if RRET could be used to increase access to ET for patients with acute ischaemic stroke.

DOI: 10.1002/rcs.2249

ORIGINAL ARTICLE

The International Journal of Medical Robotics and Computer Assisted Surgery
WILEY

Preclinical study testing feasibility and technical requirements for successful telerobotic long distance peripheral vascular intervention

Peter Legeza[1,2] | Kalyna Sconzert[3] | John-Michael Sungur[3] | Thomas M. Loh[1] | Gavin Britz[4] | Alan Lumsden[1]

Singer J (2021) https://doi.org/10.1136/bmjno-2021-000141

Antiagrégant vs anticoagulant, pour qui et quand ?

➔ Ça se complique !!

5. Antithrombotiques

Antithrombotiques après AVC

- **La plupart du temps y.c ESUS ➔ antiagrégants ➔ AVC aigue : charge**
  - Aspirine
  - Clopidogrel (Plavix)
  - DAPT (NEXT SLIDE)

- **Certains AVC spéciaux (d'origine cardiaque, états hypercoagulabes, …) ➔ anticoagulants**
  - AVK
  - **Nouveaux anticoagulants oraux (DOAC)**

Phase aiguë post-AVC

- **Aspirine**
  - Marche si donnée RAPIDMENT
  - Efficace pour **tous les sous-types d'AVC**
  - A la bonne dose (charge IV puis dose d'entretien PO)
  - **NNT=79 pour éviter mort ou dépendance**
  - Mini-augmentation du risque hémorragique cérébral mais beaucoup plus faible que le bénéfice du traitement (AVC & EP)

- **Clopidogrel**
  - **Aucune étude en phase hyperaiguë !**

The majority of the data relating to orally active antiplatelet agents is derived from trials of aspirin. Data regarding the utility of other single oral antiplatelet agents, including clopidogrel, dipyridamole or cilostazol, for the treatment of acute stroke are limited (CAIST 2011; Chairangsarit 2005; Suri 2008). Overall, the data do not provide solid evidence about the utility of these antiplatelet agents in the management of people with acute ischaemic stroke. There

Rothwell PM, Lancet (2016) https://doi.org/10.1016/S0140-6736(16)30468-8 Sandercock PA, Cochrane (2014) https://doi.org/10.1002%2F14651858.CD000029.pub3

AIT à HAUT RISQUE et AVC MINEUR ➔ DAPT : 1 mois

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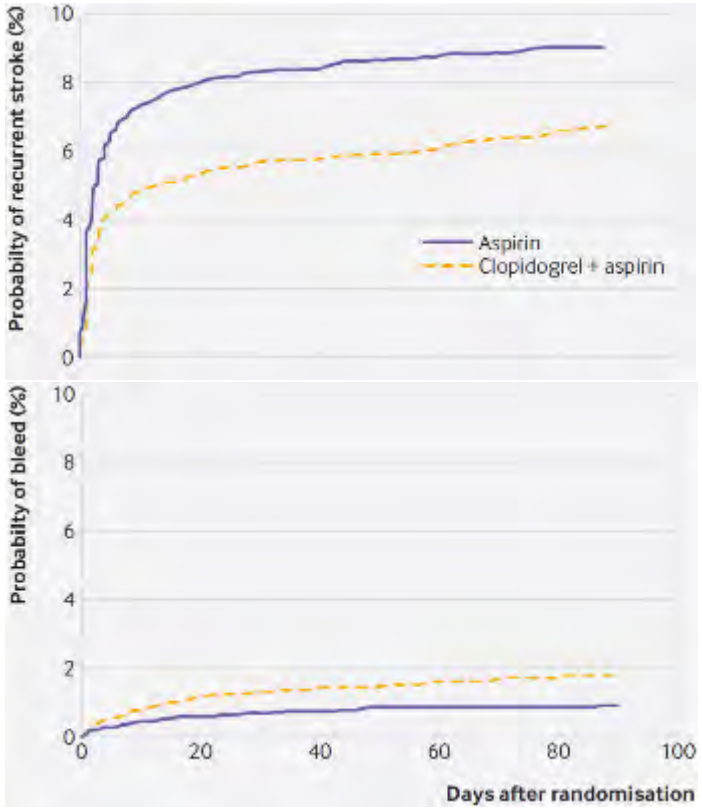
- **Combinaison Aspirine + Clopidogrel**
  - SEULEMENT POUR **AIT à HAUT RISQUE (ABCD2 ≥4)** et **AVC MINEUR (NIHSS 0-3)**



Réduction du risque d'AVC de 2%

Traitement 3-4 semaines

Dose de charge ASA 250mg Clopi 300mg

Study
CHANCE 2013
FASTER 2007
POINT 2018

Hao Q, BMJ (2018) https://doi.org/10.1136/bmj.k5108 Johnston SC, NEJM (2018) https://doi.org/10.1056/NEJMoa1800410 Wang Y, NEJM (2013) https://doi.org/10.1056/NEJMoa1215340
Kennedy J, Lancet Neurol (2007) https://doi.org/10.1016/S1474-4422(07)70250-8 Pan Y, JAMA Neurol (2019) https://doi.org/10.1001/jamaneurol.2019.2531

DAPT avec ticagrelor !

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THALES Study Design

Study population:

Acute ischemic stroke (NIHSS ≤ 5)

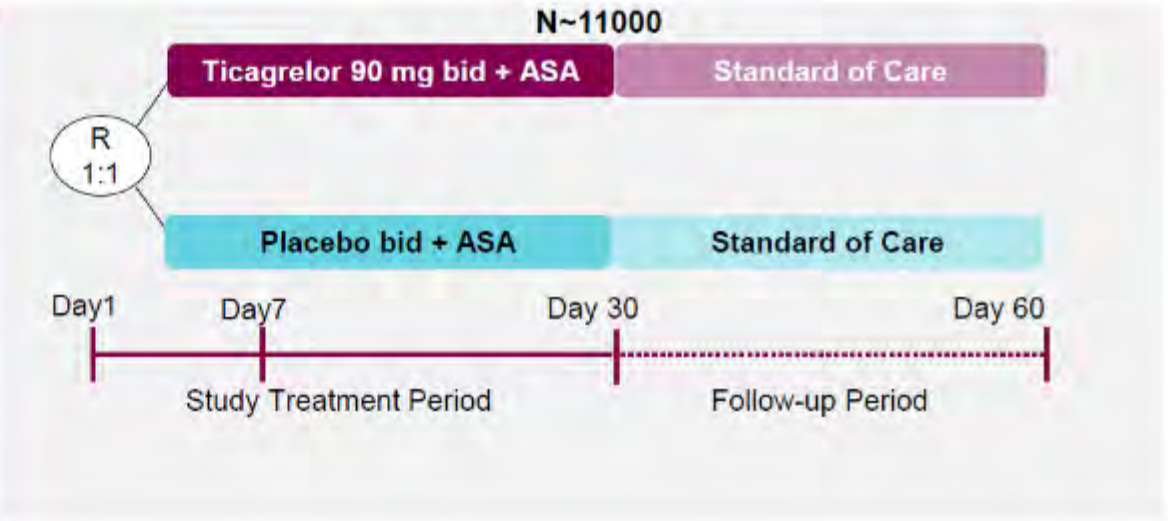
OR

High-risk transient ischemic attack (TIA) (ABCD² ≥ 6 or symptomatic arterial stenosis ≥ 50%)

- Randomised within 24 hours
- Patients ≥ 40 years

Key exclusion criteria:

- Cardioembolic origin
- Thrombolysis or thrombectomy
- Indication for antiplatelet other than ASA (aspirin) or for anticoagulation therapy
- Previous intracranial hemorrhage
- Planned carotid intervention within 3 days



Johnston SC. Int J Stroke 2019. Vol. 14(7) 745–751. Johnston SC. et al. Engl J Med. 2020:383:207-17.

THALES – ESOC 2021

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Conclusions

Benefit risk analysis of the THALES trial including 11,016 patients with acute ischemic stroke or high-risk TIA disentangling the benefit (reduction in major ischemic events) and the risk (increase in major hemorrhage), suggests that the benefit of 30-day treatment with ticagrelor-aspirin instead of aspirin alone outweighs the risk 4:1

Major ischemic event

absolute risk reduction 1.19%
(95% CI, 0.31%–2.07%)

Major hemorrhage

absolute risk increase 0.29%
(95% CI, 0.10%–0.48%)

Limitations

- Secondary analysis of clinical trial data.
  - While not defined a priori, was guided by regulatory questions.
- Major hemorrhage was rare, limiting ability to identify risk factors.

Sténose symptomatique ➔ DAPT : 3 mois

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- **Combinaison Aspirine + Clopidogrel (autres situations)**
  1. **Sténoses intracrâniennes symptomatiques**
     - CLAIR : DAPT = réduction des microemboli (MES)
     - SAMMPRIS : TT agressif mieux que stenting pour récidive d'AVC
     - VISSIT : TT agressif mieux que stent ballonnable pour récidive d'AVC
     - CHANCE sub-study ICAS : DAPT surtout efficaces pour ICAS
  2. **Sténoses carotidiennes symptomatiques**
     - CARESS : DAPT = réduction des microemboli (MES)
     - CHARISMA : DAPT = SAPT pour endpoint composite MACE

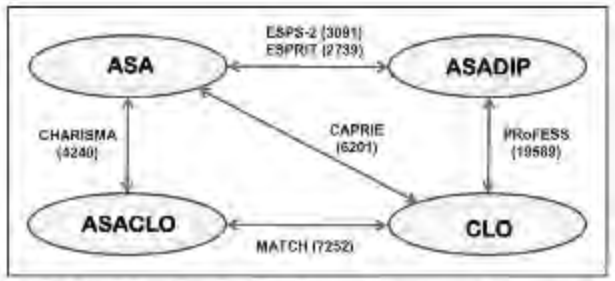

Figure 1. Network of randomized controlled trial evidence. Ellipses represent comparators. Arrows represent comparisons of interventions for which trial data were available. Patient numbers represent the total number of patients enrolled in each trial informing the comparison of interest. ASA indicates aspirin; ASACLO, aspirin/clopidogrel combination; ASADIP, aspirin/dipyridamole combination; and CLO, clopidogrel.


Eur J Vasc Endovasc Surg (2015) 50, 412–419

Dual Antiplatelet Therapy Prior to Expedited Carotid Surgery Reduces Recurrent Events Prior to Surgery without Significantly Increasing Peri-operative Bleeding Complications

A. Batchelder, J. Hunter, V. Cairns, R. Sandford, A. Munshi, A.R. Naylor

Wong KSL, Lancet Neurol (2010) https://doi.org/10.1016/S1474-4422(10)70060-0 Derdeyn CP, Lancet (2014) https://doi.org/10.1016/S0140-6736(13)62038-3
Zaidat OO, JAMA (2015) https://doi.org/10.1001/jama.2015.1693 Markus HS, Circulation (2005) https://doi.org/10.1161/01.CIR.0000163561.90680.1C
Bhatt DL, NEJM (2006) https://doi.org/10.1056/nejmoa060989 Greving JP, Stroke (2019) https://doi.org/10.1161/STROKEAHA.118.024497

Traitement d'une sténose symptomatique …
Beaucoup d'évolution depuis les études princeps !

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EDITORIAL

Treatment of a hot carotid

More fuel is needed to clarify the best treatments

Seemant Chaturvedi, MD

Neurology: Clinical Practice December 2018 vol. 8 no. 6 466-467 doi:10.1212/CPJ.0000000000000561

transcranial Doppler (TCD).[10] The utilization of heparin instead of antiplatelet therapy for patients with an intravascular thrombus is a common practice but high-quality studies are lacking. The 3 neurology experts sometimes use short-term anticoagulation followed by reimaging. If the thrombus is resolving or nonmobile, antithrombotic therapy can be continued. If the thrombus is mobile or not resolving and especially if the patient has further symptoms, then a more aggressive approach is taken.

Table Medical therapy then and now

	1991	2018
Antiplatelet therapy	Aspirin monotherapy	Short-term dual antiplatelet therapy
Lipid-lowering medication	Little use	Widespread use
High-potency statins	Not available	Commonly used
Blood pressure control	Suboptimal	More stringent targets
Lifestyle	No organized approach	Mediterranean diet/increased physical activity recommended

Anticoagulation pour thrombus flottant ?

Chaturvedi S, Neurol Clin Pract (2018) https://doi.org/10.1212/CPJ.0000000000000561

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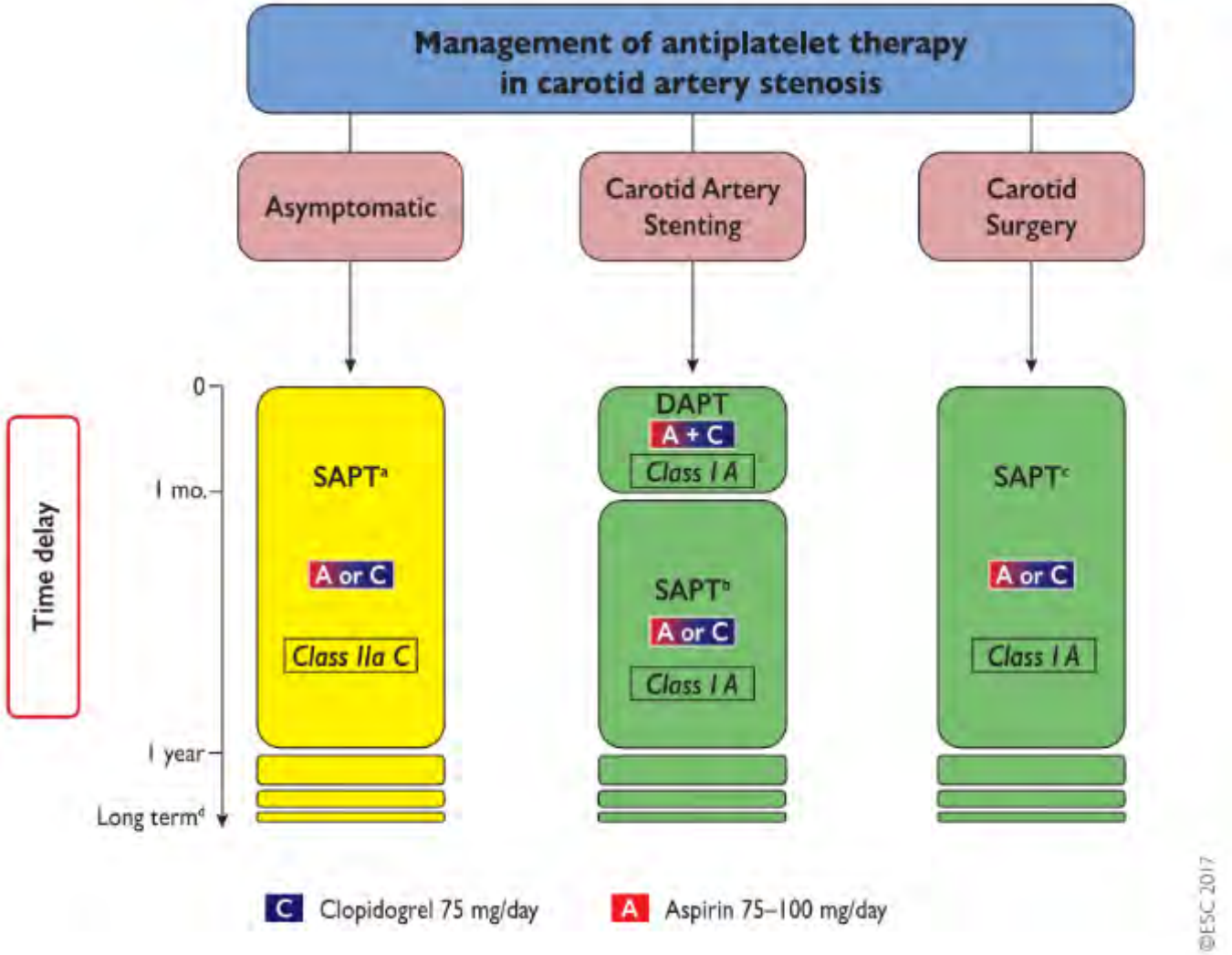
Recommandation ESC et ESVS …



Aboyans V, Eur Heart J (2018) https://doi.org/10.1093/eurheartj/ehx095

Quelle protection optimale chez patient athéromateux ou vasculopathe stable? Traitement sur la durée

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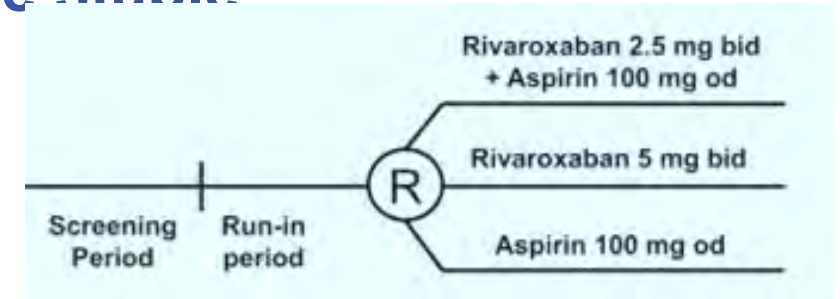
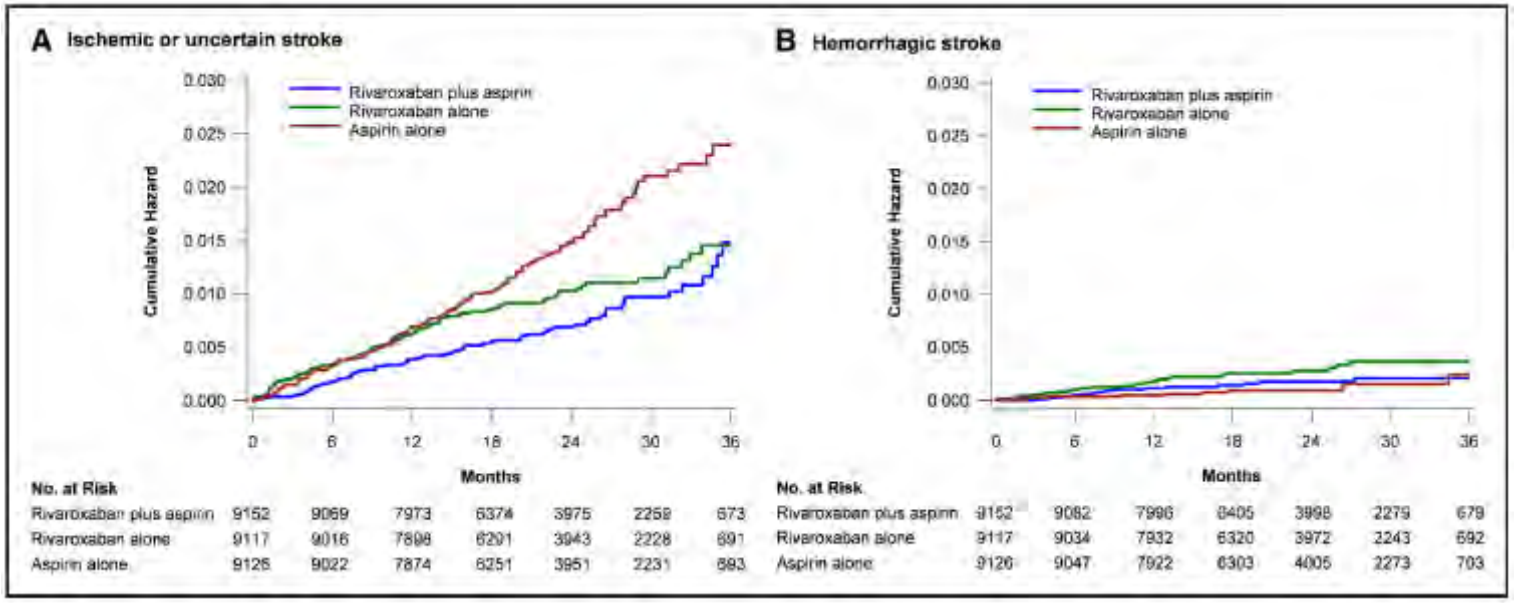
NEW

- **COMPASS trial, 27'000 patients**
- **Pas de FA mais athéromatose vasculaire stable (CAD, PAD, ATS carotidienne)**

Combinaison
ASA 100 + Rivaro 2x2.5 meilleure !!!





Circulation. 2019;139:1134–1145. DOI: 10.1161/CIRCULATIONAHA.118.035864

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Anticoagulation for secondary stroke prevention: another nail in the coffin?

Published in 1997, the Stroke Prevention in Reversible Ischemia Trial (SPIRIT) randomised patients to aspirin (30mg daily) or oral anticoagulation (international normalised ratio [INR] 3·0–4·5).[2] The trial was stopped because of the high haemorrhagic complication rate in the anticoagulation group, showing that an INR of 3·0–4·5 is not safe for cerebrovascular disease patients,

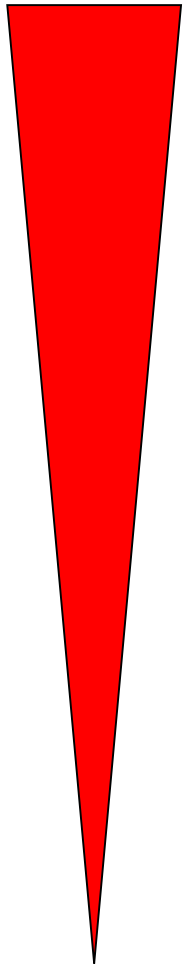
WARSS : favorise ASA

WASID : favorise ASA

Anticoagulation pour AVC non cardioembolique ➔ RARE !! Sauf ?

Indications relatives à une anticoagulation précoce après AVC

- **Embolie pulmonaire et/ou thrombose veineuse profonde**
  - (alternative : filtre veine cave)
- **Valve mécanique**
- **Thrombus intracardiaque**
- **Thrombus intra-artériel flottant**
- **Embolisation *répétitive* d'une plaque sténosante malgré antiaggrégation *efficace***
- **Certains cas de dissection des artères cervicales (subocclusives, récidivante sous antiaggrégation)**



Poids de l'indication

Anticoagulation pour FA

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Treat AF: The ABC pathway

1. Identify low-risk patients CHA_2DS_2-VASc 0(m), 1(f)
2. Offer stroke prevention if $CHA_2DS_2VASc \geq 1(m), 2(f)$

Assess bleeding risk, address modifiable bleeding risk factors

3. Choose OAC (NOAC or VKA with well-managed TTR)

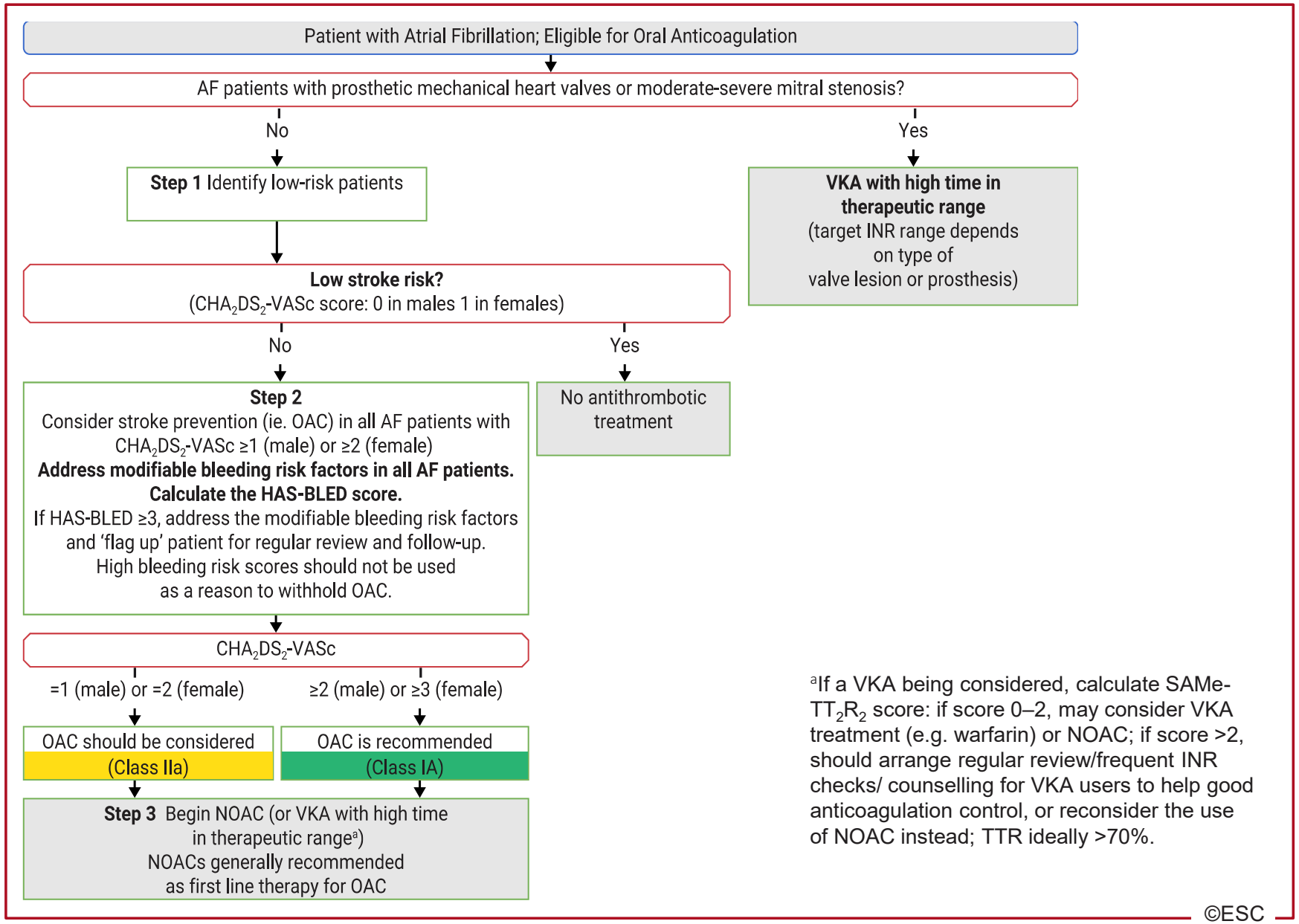
Assess symptoms, QoL and patient's preferences

Optimize rate control

Consider a rhythm control strategy (CV, AADs, ablation)

Comorbidities and cardiovascular risk factors

Lifestyle changes (obesity reduction, regular exercise, reduction of alcohol use, etc.)



www.escardio.org/guidelines

2020 ESC Guidelines for the diagnosis and management of atrial fibrillation (European Heart Journal 2020-doi/10.1093/eurheartj/ehaa612)

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Quel DOAC chez patient avec FA ?

Quel DOAC pour FA ?

PAS DE RCT mais beaucoup de patients dans les registres…

- Vinogradova BMJ 2018
- Hohnloser Thromb Haemost 2018
- Lip Stroke 2018
- Wetmore Stroke 2020
- VanGanse Stroke 2020
- Ray JAMA 2021

Phase IV studies confirm that **apixaban (Eliquis®)** seems safer and/or more effective then other DOACs.

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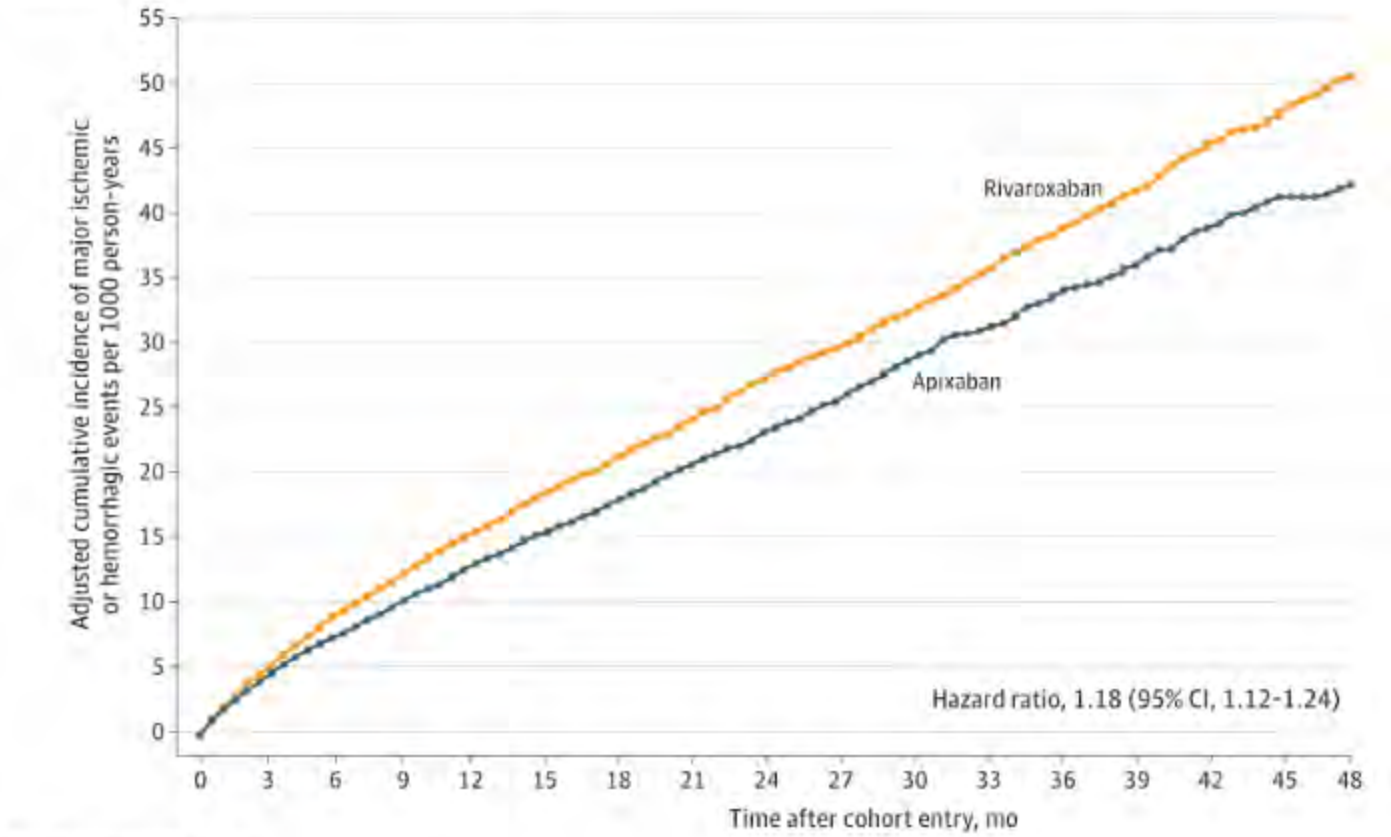
Efficacité et sécurité de Apixaban vs Rivaroxaban :
Très large registre

Figure 2. Primary Outcome in a Study of the Association of Rivaroxaban vs Apixaban With Major Ischemic or Hemorrhagic Events in Atrial Fibrillation



No. of participants at risk

Apixaban	353879	174291	96974	59800	37560	34769	13576	7657	3731
Rivaroxaban	227572	110654	64836	40716	26621	18224	12392	8452	5507

Apixaban (Eliquis®)

- **Plus efficace**
- **Plus sûr**

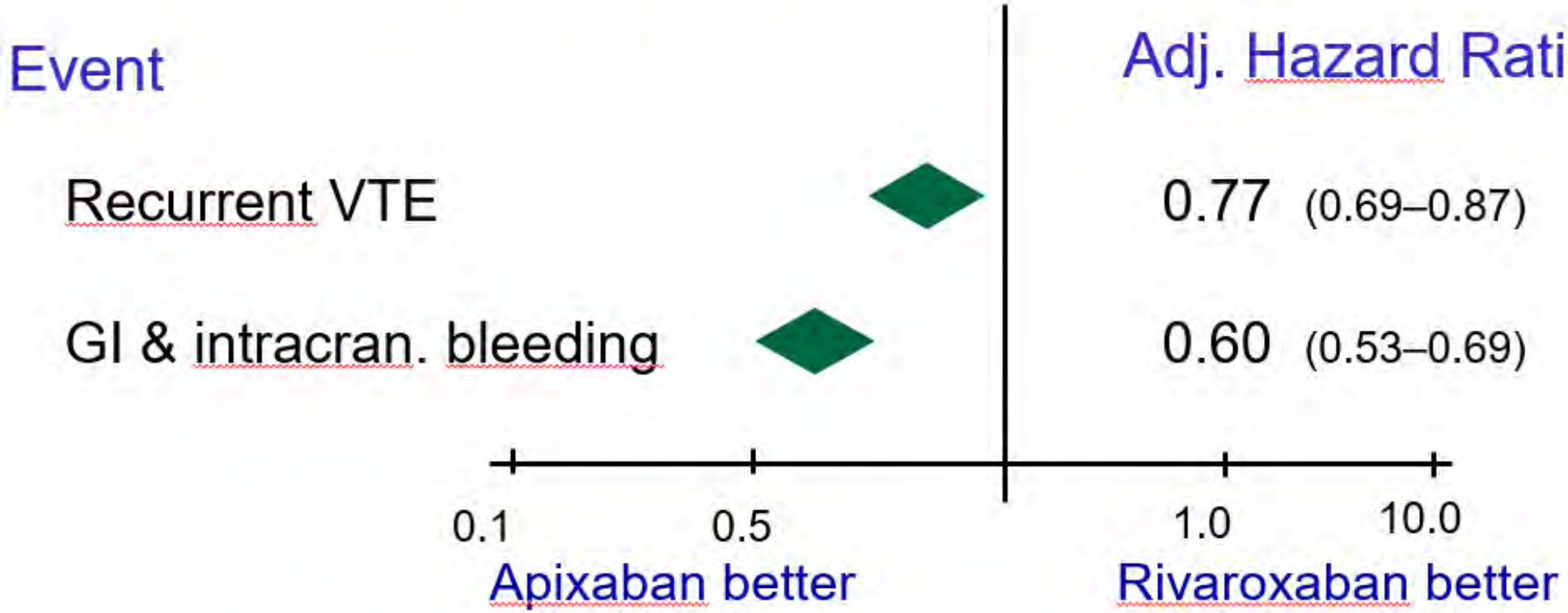
Les courbes divergent dans le temps !

Ray WA (2021) https://doi.org/10.1001/jama.2021.21222

Which DOAC for VTE ?

Phase IV data; N 49'900

Privately insured population in the USA



Retrospective new-user cohort study, with propensity score matching

Dawwas et al, Ann Int Med 2022

Quand débuter l'AC après un AVC ischémique sur FA

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- **Pas d'argument scientifique pour débuter immédiatement si AVC**
  ➔ hémorragie !, l'Aspirine suffit

<u>RECOMMANDATIONS</u> (Diener's law «1, 3, 6, 12»)

- **AIT** **➔ débuter J1 immédiatement**
- **AVC mineur** **➔ attendre J3**
  (< 20 % ACM ou cérébelleux)
- **AVC modéré** **➔ attendre J6**
  (20-40% ACM ou cérébelleux)
- **AVC important** **➔ attendre J12**
  (>40% ACM ou cérébelleux)

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TIMING

Timing of oral anticoagulant therapy in acute ischaemic stroke with atrial fibrillation - a registry-based randomised controlled study

Randomisation (1:1) was performed within 72 h from stroke onset, to early (≤4 days) or delayed (5-10 days) NOAC start, with choice of specific NOAC at the discretion of the investigator

TIMING

Primary outcome 90 days

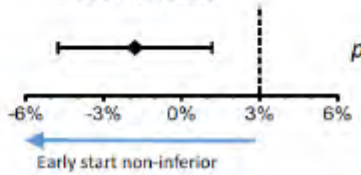
Composite of ischaemic stroke, symptomatic intracerebral haemorrhage or all-cause mortality

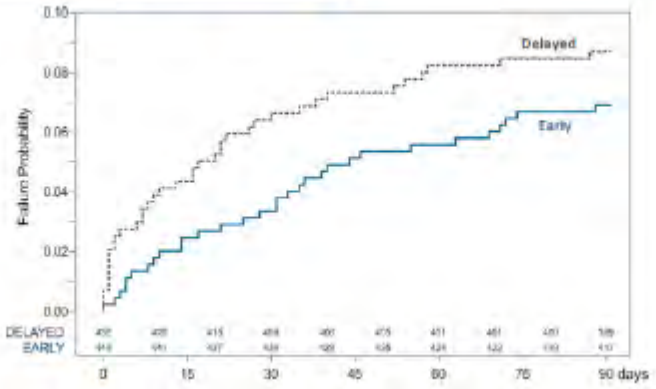
	Primary outcome/n	Risk, %	95% Confidence limits	
Early	31/450	6.89	4.55	9.23
Delayed	38/438	8.68	6.04	11.31

Early start of NOAC therapy was non-inferior to delayed start of NOAC therapy

Non-inferiority test

Risk Difference, % (90% CI)
-1.79 (-4.57; 1.17)





There were numerically lower numbers of ischaemic strokes and deaths in patients starting NOAC early,
and no symptomatic intracerebral haemorrhages in any of the study groups

RIKSSTROKE
The Swedish Stroke Register

UCR
Uppsala Clinical Research Center

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Early vs Late DOAC in stroke with AF: *ongoing RCT*

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Reprise d’antithrombotique après ICH

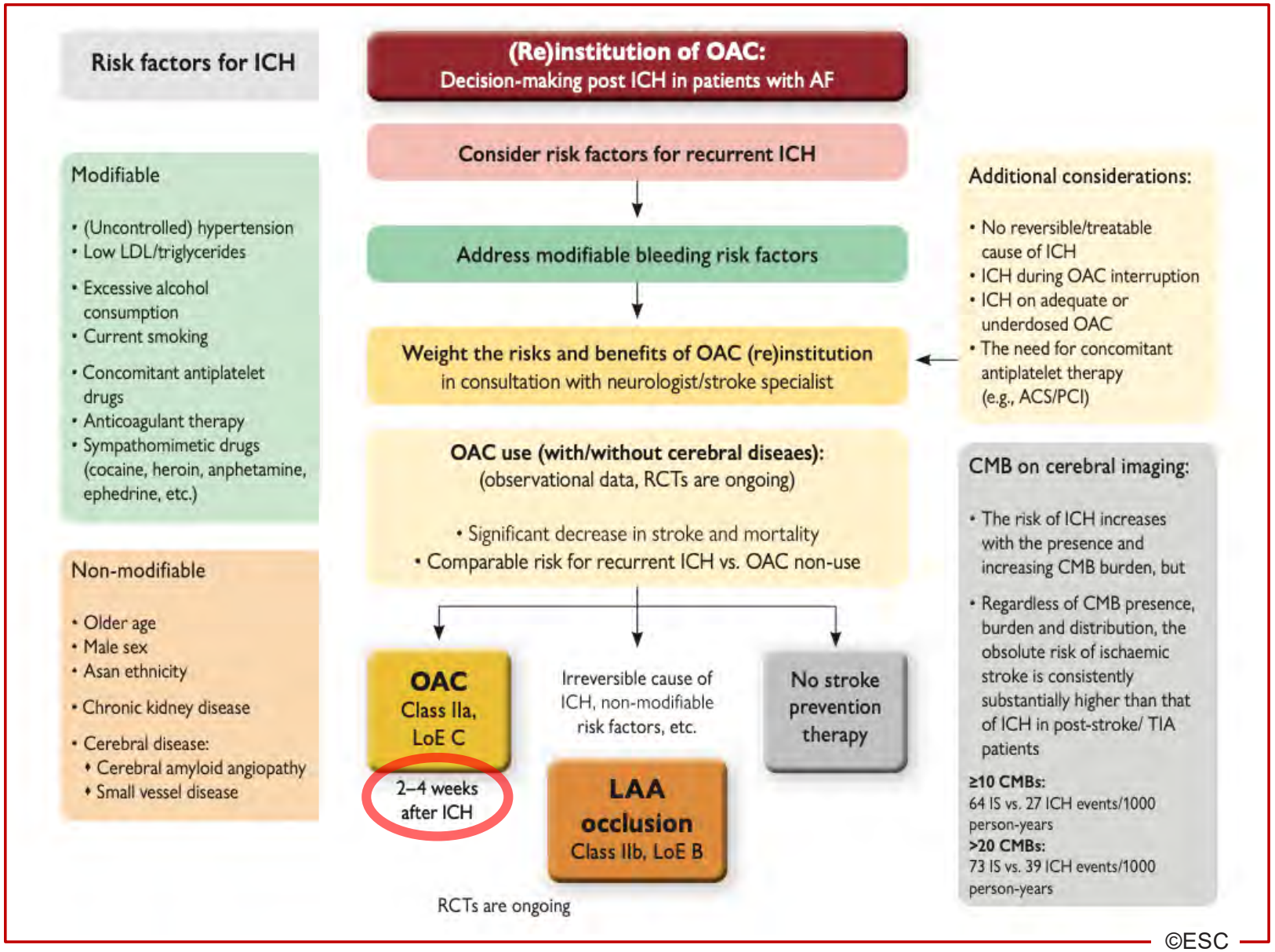

Figure 21
(Re-) initiation of anticoagulation post-intracranial bleeding

A pooled analysis of individual patient data from cohort studies (n=20 322 patients; 38 cohorts; >35 225 patient-years) showed that although cerebral microbleeds can inform regarding the risk for ICH in patients with recent ischaemic stroke/TIA treated with antithrombotic therapy, the absolute risk of ischaemic stroke is substantially higher than that of ICH, regardless of the presence, burden, or location of cerebral microbleeds

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Interprétation des données ???

The optimal timing of anticoagulation after ICH is unknown, but should be delayed beyond the acute phase, probably for at least 4 weeks; in AF patients at very high risk of recurrent ICH, LAA occlusion may be considered. Ongoing RCTs of NOACs and LAA occlusion may inform decision making in the future.

Hindricks G (2021) https://doi.org/10.1093/eurheartj/ehaa612

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APACHE-AF

ESOC 2021

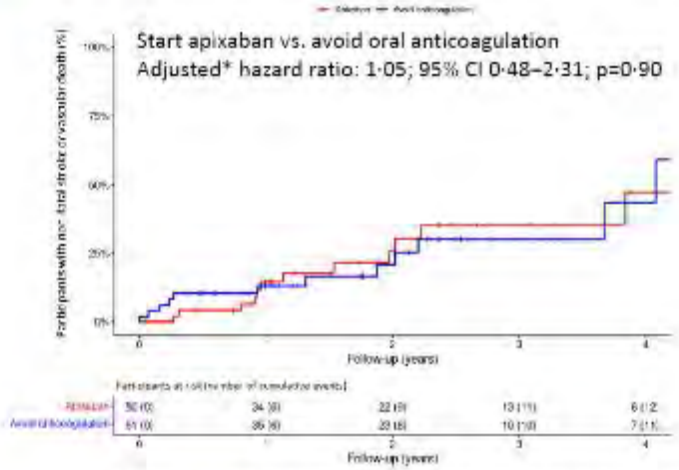
Clinical dilemma: In patients with atrial fibrillation (AF) who survive an anticoagulation-associated intracerebral haemorrhage (ICH), a longstanding and pressing clinical dilemma is whether restarting or avoiding anticoagulation is the best long-term strategy for the prevention of recurrent stroke and systemic thrombo-embolism.

Results

101 participants enrolled (median age 78 years; 55 male; 28 lobar ICH)

Median duration of follow-up 1.9 years (IQR 1.0-3.1); 222 person-years of follow-up

	Primary outcome	Annual event rate
Assigned to apixaban	13/50 participants (4 ICH, 6 ischaemic stroke, 3 vasc death)	12.6 (95% CI 6.7 to 21.5)
Assigned to avoid anticoagulation	12/51 participants (1 ICH, 6 ischaemic stroke, 5 vasc death)	11.9 (95% CI 6.2 to 20.8)



*adjusted for one aggregated risk variable including age as a continuous variable and ICH location (lobar versus non-lobar)

Conclusion: High annual risks of non-fatal stroke or vascular death in patients with AF who had an ICH while on anticoagulation, irrespective of allocation to apixaban or to avoiding anticoagulation

Need for large (and pooled) randomised controlled trials to determine which patients benefit most of either treatment

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THE UNIVERSITY of EDINBURGH

Edinburgh Stroke Trials

Effects of antiplatelet therapy after stroke due to intracerebral haemorrhage (ICH): extended follow-up of the REstart or STop Antithrombotics Randomised Trial (RESTART)

122 hospitals in the UK

537 adults ≥18y, taking antithrombotic (antiplatelet or anticoagulant) therapy for the prevention of occlusive vascular disease at intracerebral haemorrhage (ICH) onset, who discontinued antithrombotic therapy, and survived ≥24h

Brain MRI before randomisation

Randomisation (central)

1:1

268 START antiplatelet therapy*

269 AVOID antiplatelet therapy

Follow-up (central, masked) for vascular events, death, mRS, adherence, BP control

* Aspirin or clopidogrel or dipyridamole (open, no placebo)

ISRCTN71907627

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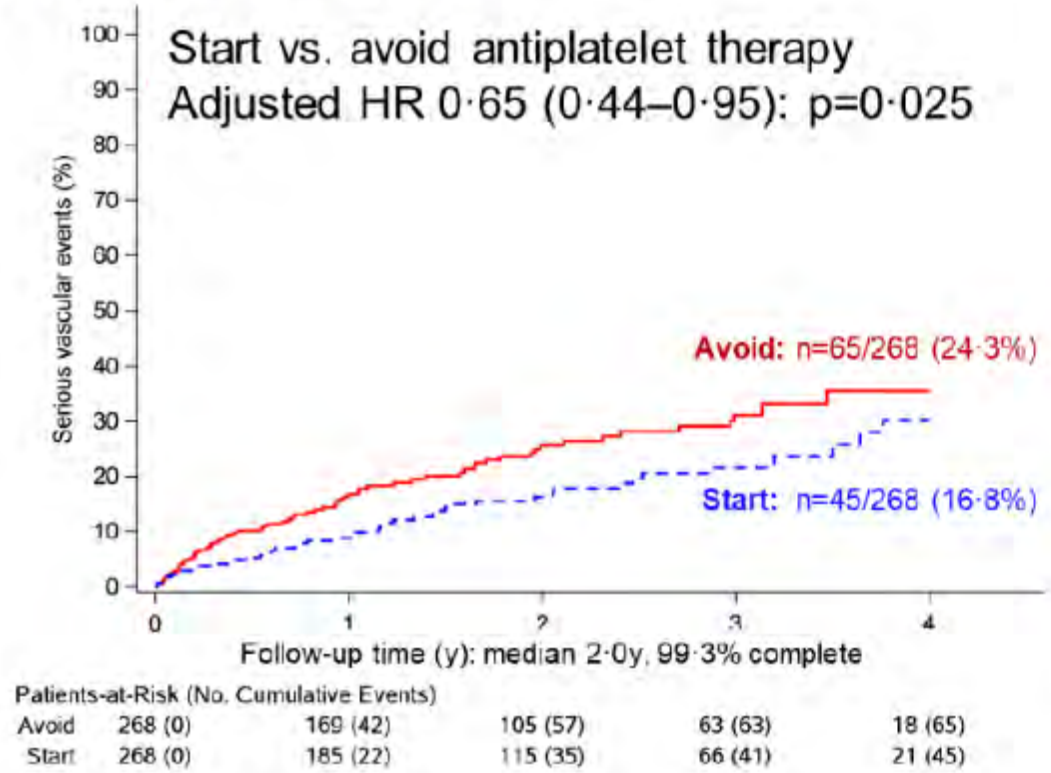
Effects of antiplatelet therapy on major vascular events

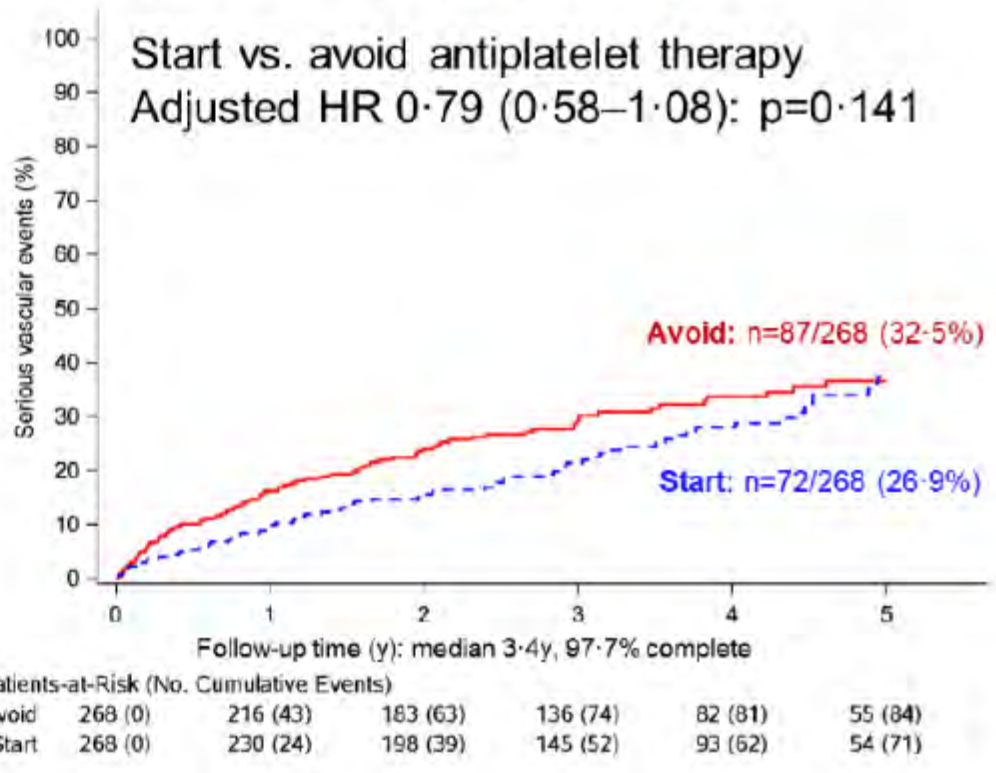
Main results



Patients-at-Risk (No. Cumulative Events)

Avoid	268 (0)	169 (42)	105 (57)	63 (63)	18 (65)
Start	268 (0)	185 (22)	115 (35)	66 (41)	21 (45)

Extended follow-up



Patients-at-Risk (No. Cumulative Events)

Avoid	268 (0)	216 (43)	183 (63)	136 (74)	82 (81)	55 (84)
Start	268 (0)	230 (24)	198 (39)	145 (52)	93 (62)	54 (71)

Questions ?

Merci
pour
votre
attention

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