TNK pour traiter l'AVC ischémique aigu

(Étude AcT: Ténectéplase comparé à l'altéplase)

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Neurologue vasculaire - CHUM

Janvier 2023

En commençant par la fin
TNK 0,25 mg/kg *vs* rtPA

- Efficacité similaire
  - mRS 0-1 à 3 mois 36,9% *vs* 34,8% - non-inférieur (marge de 5%)
- Taux de complications similaires
  - Mortalité 15,3% *vs* 15,4% ns
  - Hémorragie
    - HICs 3,4% *vs* 3,2% ns
    - Toute HIC 19,3% *vs* 20,6% ns
  - Angioedème 1,1% *vs* 1,2% ns
- Coût identique - 2745,00 $
- Administration plus facile - bolus *vs* perfusion

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Préparation du TNK

Step 1

Remove the shield assembly from the supplied B-D 10 mL syringe with TwinPak™ Dual Cannula Device.

Step 2

Aseptically WITHDRAW 10 mL of Sterile Water for Injection, USP, using the B-D 10 mL syringe with TwinPak™ Dual Cannula Device included in the kit. Do not use Bacteriostatic Water for Injection, USP.

Step 3

INJECT entire contents (10 mL) into the TNKase vial, directing the diluent into the powder. Slight foaming upon reconstitution is not unusual; any large bubbles will dissipate if the product is allowed to stand undisturbed for several minutes.

Step 4

GENTLY SWIRL until contents are completely dissolved. DO NOT SHAKE. Solution should be colorless or pale yellow and transparent. Once the appropriate dose of TNKase is drawn into the syringe, stand the shield vertically and recap the red tab cannula.

Step 5

USE UPON RECONSTITUTION. If not used immediately, refrigerate solution (which does not contain bacterial preservative) at 2–8°C (36–46°F) and use within 8 hours. DO NOT FREEZE. Final concentration of TNKase is 5 mg/mL.

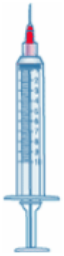
https://www.tnkase.com/dosing-and-administration/dosing-administration-and-reconstitution.html

Administration du TNK

Step 1

Determine the correct dose of TNKase based on patient weight. TNKase is for IV administration only.

Patient Weight (kg)	TNKase (mg)	mL of Reconstituted TNKase
<60	30	6
60 to <70	35	7
70 to <80	40	8
80 to <90	45	9
≥90	50	10



(doses en cardiologie)

Step 2

WITHDRAW the appropriate volume of solution based on patient weight. **The recommended total dose should not exceed *25* mg.** Discard solution remaining in the vial.

Step 3

FLUSH a dextrose-containing line with a saline-containing solution prior to and following administration (precipitation may occur when TNKase is administered in an IV line containing dextrose). ADMINISTER as an IV BOLUS over 5 seconds.

https://www.tnkase.com/dosing-and-administration/dosing-administration-and-reconstitution.html

Doses arrondies utilisées

Tableau des doses de TÉNECTÉPLASE TNKase (0,25mg / kg - max 25 mg)

Poids (kg)	Dose (mg)	Volume (mL)
Moins de 60	15	3
60 à 69,9	17,5	3,5
70 à 79,9	20	4
80 à 89,9	22,5	4,5
90 et plus	25	5

Fiole de 50 mg diluée avec 10 mL d'ESI (5 mg/mL)

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CHUM – Tableau indicatif des dosages d'altéplase (Activase - rt-PA de 100 mg / 100 mL) à administrer selon le poids

Poids (lb)	Poids (kg)	Dose totale (mg)	Bolus IV (mg)	Volume exact à retirer (mL)*	Perfusion en 60 min (mg)
90	40,9	36,8	3,7	50	33,1
92	41,8	37,6	3,8	49	33,8
94	42,7	38,4	3,8	48	34,6
96	43,6	39,2	3,9	47	35,3
98	44,6	40,1	4	46	36,1
100	45,5	41	4,1	46	36,9
102	46,4	41,8	4,2	45	37,6
104	47,3	42,6	4,3	44	38,3
106	48,2	43,4	4,3	43	39,1
108	49,1	44,2	4,4	42	39,8
110	50	45	4,5	42	40,5
112	50,9	45,8	4,6	41	41,2
114	51,8	46,6	4,7	40	41,9
116	52,7	47,4	4,7	39	42,7
118	53,6	48,2	4,8	38	43,4
120	54,6	49,1	4,9	37	44,2
122	55,5	50	5	37	45
124	56,4	50,8	5,1	36	45,7
126	57,3	51,6	5,2	35	46,4
128	58,2	52,4	5,2	34	47,2
130	59,1	53,2	5,3	33	47,9
132	60	54	5,4	33	48,6
134	60,9	54,8	5,5	32	49,3
136	61,8	55,6	5,6	31	50
138	62,7	56,4	5,6	30	50,8
140	63,6	57,2	5,7	29	51,5
142	64,6	58,1	5,8	28	52,3
144	65,5	59	5,9	28	53,1
146	66,4	59,8	6	27	53,8
148	67,3	60,6	6,1	26	54,5
150	68,2	61,4	6,1	25	55,3
152	69,1	62,2	6,2	24	56
154	70	63	6,3	24	56,7
156	70,9	63,8	6,4	23	57,4
158	71,8	64,6	6,5	22	58,1
160	72,7	65,4	6,5	21	58,9
162	73,6	66,2	6,6	20	59,6
164	74,6	67,1	6,7	19	60,4
166	75,5	68	6,8	19	61,2
168	76,4	68,8	6,9	18	61,9
170	77,3	69,6	7	17	62,6
172	78,2	70,4	7	16	63,4
174	79,1	71,2	7,1	15	64,1
176	80	72	7,2	15	64,8
178	80,9	72,8	7,3	14	65,5
180	81,8	73,6	7,4	13	66,2
182	82,7	74,4	7,4	12	67
184	83,6	75,2	7,5	11	67,7
186	84,6	76,1	7,6	10	68,5
188	85,5	77	7,7	10	69,3
190	86,4	77,8	7,8	9	70
192	87,3	78,6	7,9	8	70,7
194	88,2	79,4	7,9	7	71,5
196	89,1	80,2	8	6	72,2
198	90	81	8,1	6	72,9
200	90,9	81,8	8,2	5	73,6
202	91,8	82,6	8,3	4	74,3
204	92,7	83,4	8,3	3	75,1
206	93,6	84,2	8,4	2	75,8
208	94,6	85,1	8,5	1	76,6
210	95,5	86	8,6	1	77,4
212	96,4	86,8	8,7	---	78,1
214	97,3	87,6	8,8	---	78,8
216	98,2	88,4	8,8	---	79,6
218	99,1	89,2	8,9	---	80,3
≥ 220	≥ 100	90	9	---	81

* Inclus la quantité du vide d'air de la tubulure (décimale éliminée). Une fois diluée, la teneur de la solution d'altéplase (Activase - fiole de 100 mg) est de 1 mg = 1 mL

Préparation de la perfusion de rtPA…

Délai moyen entre le bolus et la perfusion: 4 min (données CHUM de AcT, 82 pts avec tPA)

CHUM

Int J Stroke 2014; 9: 939-42

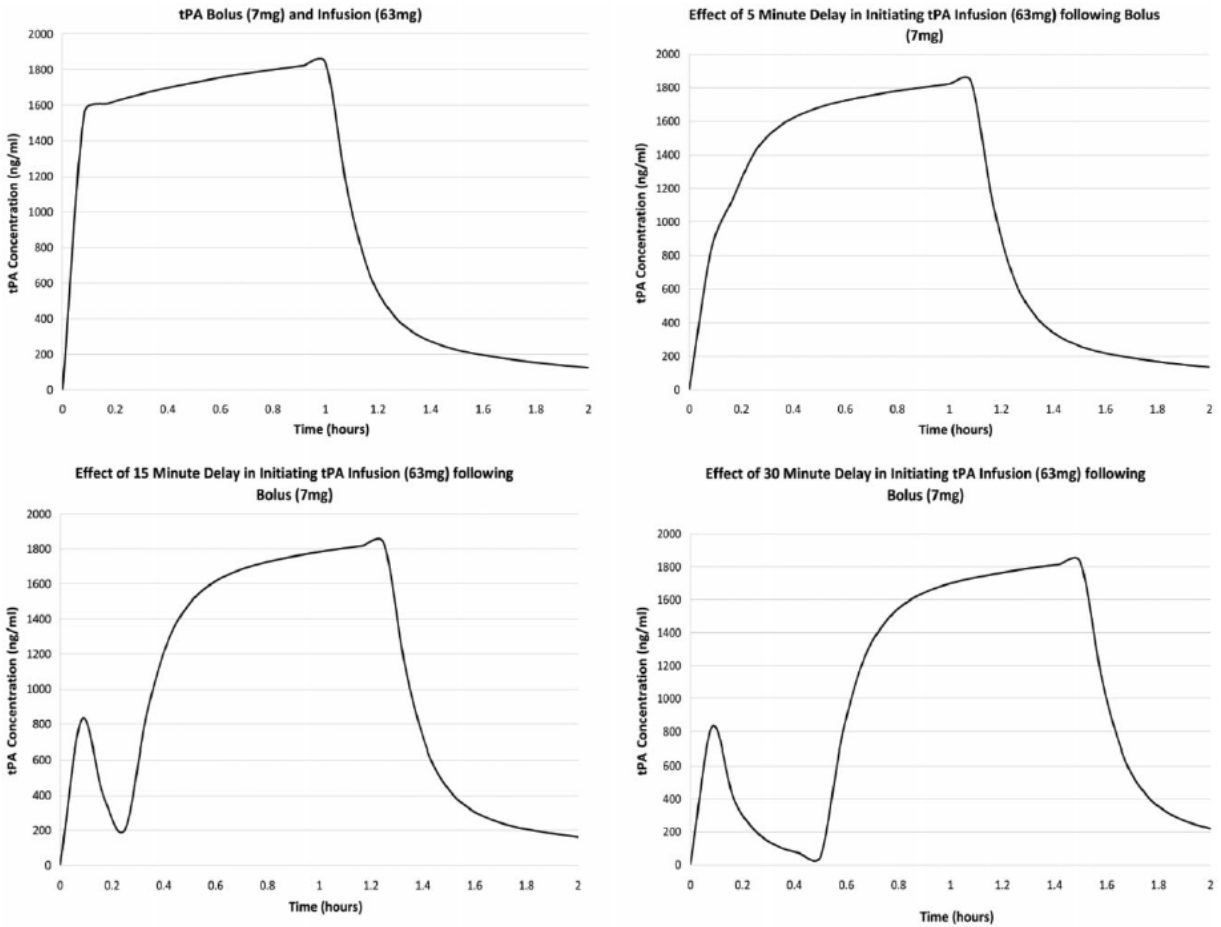


Fig. 1 The influence of bolus to infusion delays on serum TPA concentrations. (a) No delay, (b) five-minute delay, (c) 15 min and (d) 30 min.

https://ici.radio-canada.ca/nouvelle/1862676/infirmiere-rapport-bien-etre-surcharge-soins-ratio-patients-conditions-travail

Présentateur

- Dr Yan Deschaintre
  - Formé à l'Université de Montréal (1995-2005)
  - Fellowship en troubles cognitifs vasculaires avec Pr Pasquier à Lille (2005-2007)
  - Neurologue vasculaire au CHUM (depuis 2007)
- Pas de conflit d'intérêt à déclarer pour les deux dernières années
  - Présentateur pour le CPASS, l'UdeM et l'ANQ
  - 4e auteur pour l'étude AcT

https://ici.radio-canada.ca/nouvelle/1079015/infirmieres-quittent-chum-retour-hopital

CHUM

TNK pour l'AVC

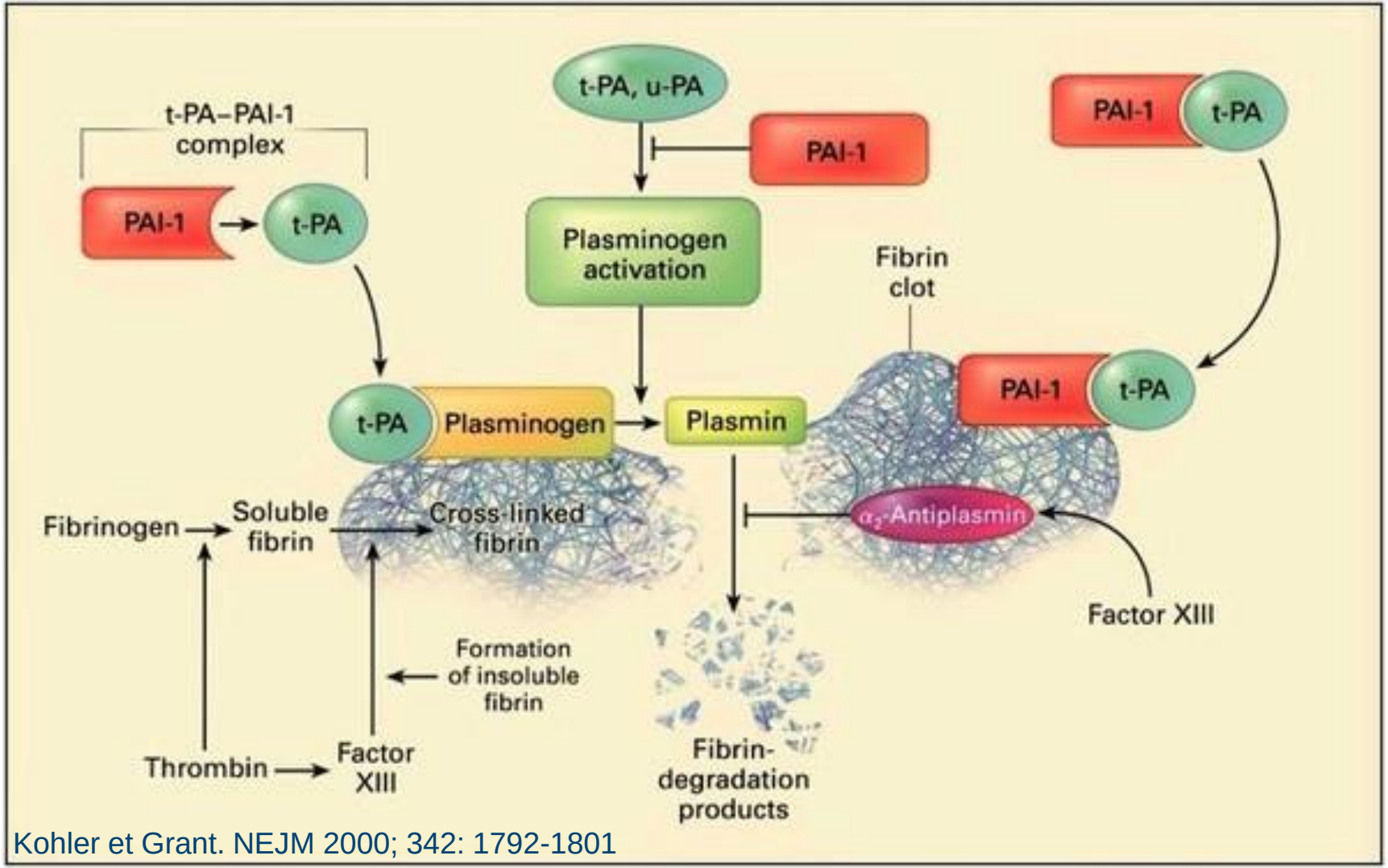
- Origines
- Données antérieures
- Étude AcT
- Autres études
- Conclusion

CHUM

Origines – rtPA

- Altéplase – 1987
  - Identique à l'activateur du plasminogène humain (« tissue plasminogen activator » ou tPA)
  - Synthétisé avec ADN recombinant sur des cellules ovariennes de hamster de Chine
  - Utilisé pour:
    - Infarctus du myocarde
    - Embolie pulmonaire
    - AVC ischémique (NINDS 1995)
    - Cathéters bloqués

https://www.rodipet.de/div/Chinese-md.jpg



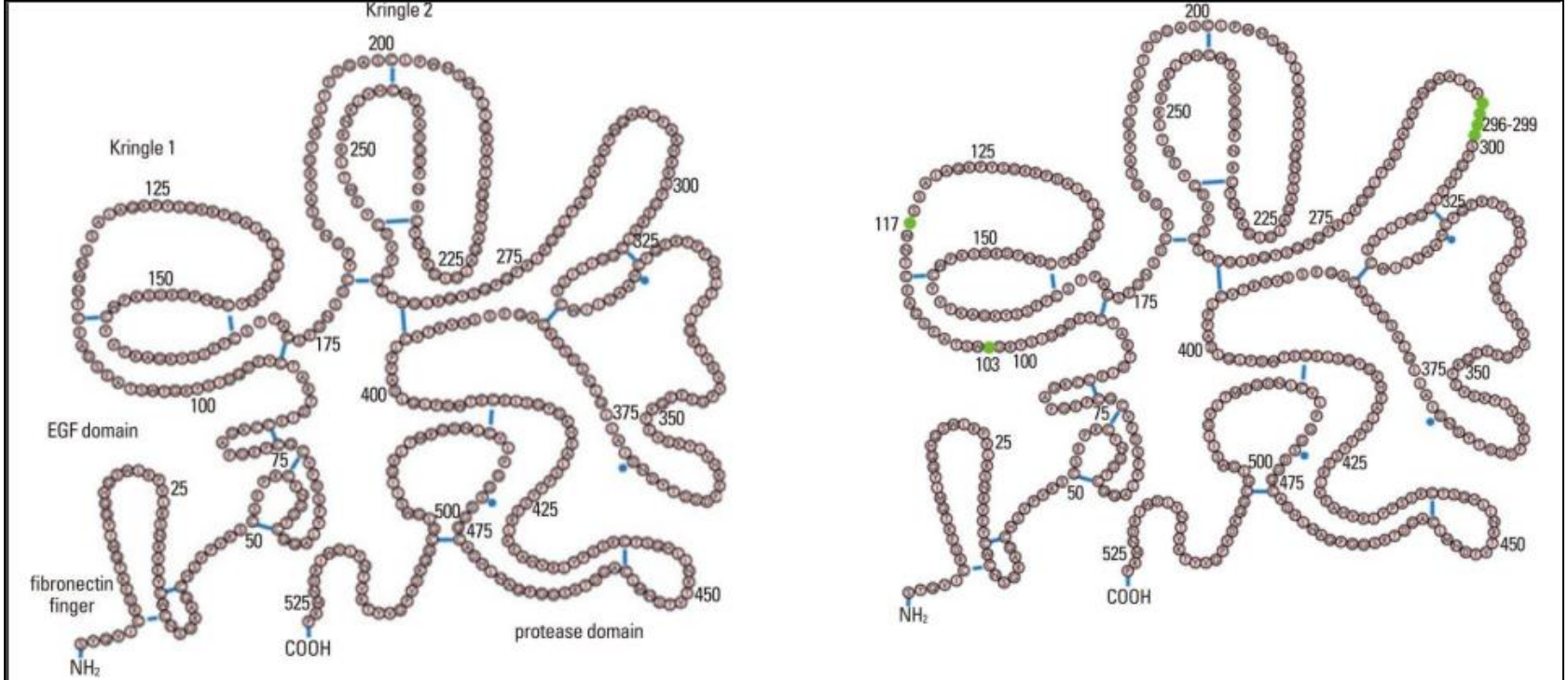
Kohler et Grant. NEJM 2000; 342: 1792-1801

Origines – TNK

- Ténectéplase – (breveté en 1993)
  - Modification du tPA portant sur 6 de ses 527 acides aminés
  - D'abord approuvé seulement pour l'infarctus du myocarde suite à l'étude ASSENT-2, 1999:
    - Résultats similaires au tPA
      (mortalité, hémorragie intra-crânienne)
    - Moins de saignement extra-crânien
    - Plus facile à utiliser (bolus plutôt que perfusion)

Origines du nom

- Altéplase
  - Al(pha?) t(issue) é pl(asminogen) ase(activator)
- Ténectéplase
  - Mutations du tPA sur 3 sites
  - **T**103N **N**117Q **K**HRR(296-299)AAAA
    - Thréonine (T) -> asparagine (N)
    - Asparagine (N) -> glutamine (Q)
    - Lysine (K), histidine (H) et 2 arginine (R) -> 4 alanine (A)



Agent	Fibrin specificity	Thrombolytic potency	PAI-1 resistance	Fibrinogen depletion	PRT activity	Clearance (mL/kg/min)
TPA	++	+	−	++	++	16.1
TNK	+++	+++	++	+	+++	1.9

PAI-1 plasminogen activator inhibitor type 1, *PRT* platelet-rich thrombus

https://cumming.ucalgary.ca/sites/default/files/teams/239/QI_2018%20Acute%20Stroke%20Day/12.-tenecteplase-tnk-tpa-quicr-meeting.pdf

TNK pour l’AVC

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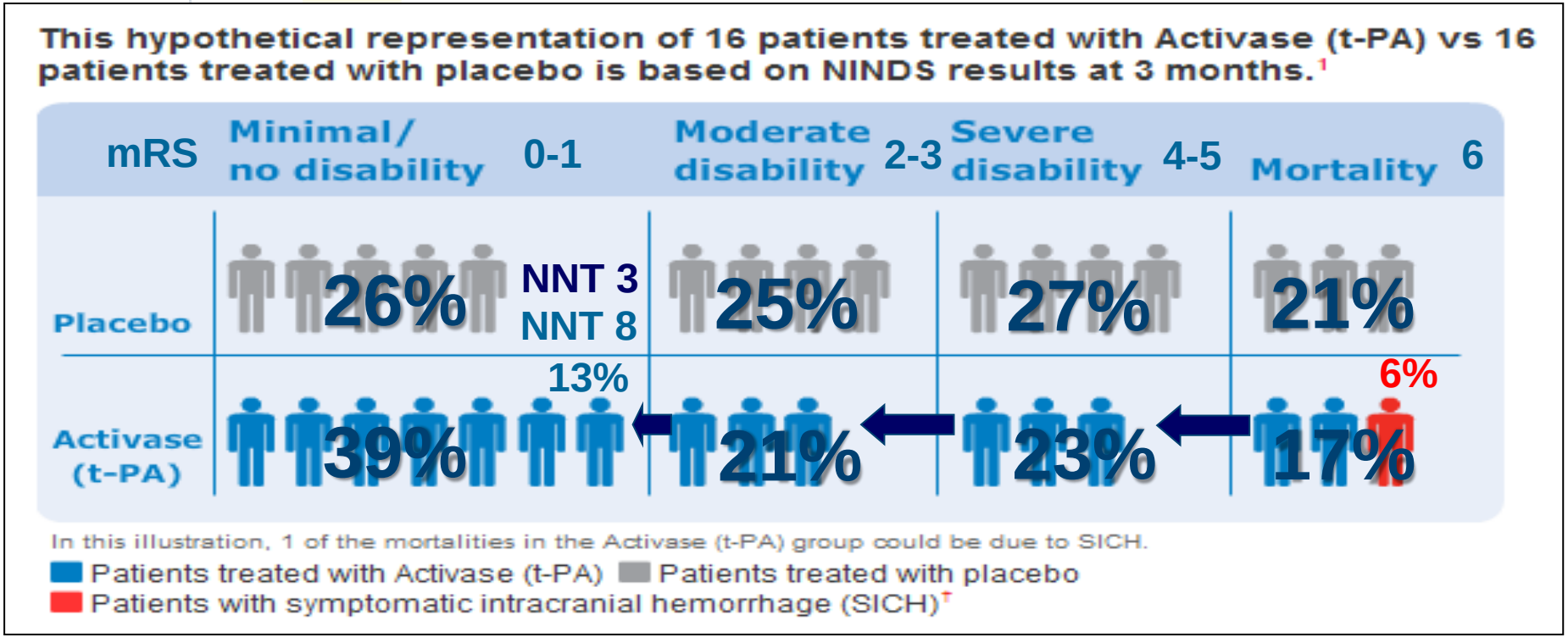
Bénéfice de la thrombolyse IV avec rtPA



NEJM 1995; 333: 1581-7 et Neurology 2003; 60(Suppl 1): A427-428

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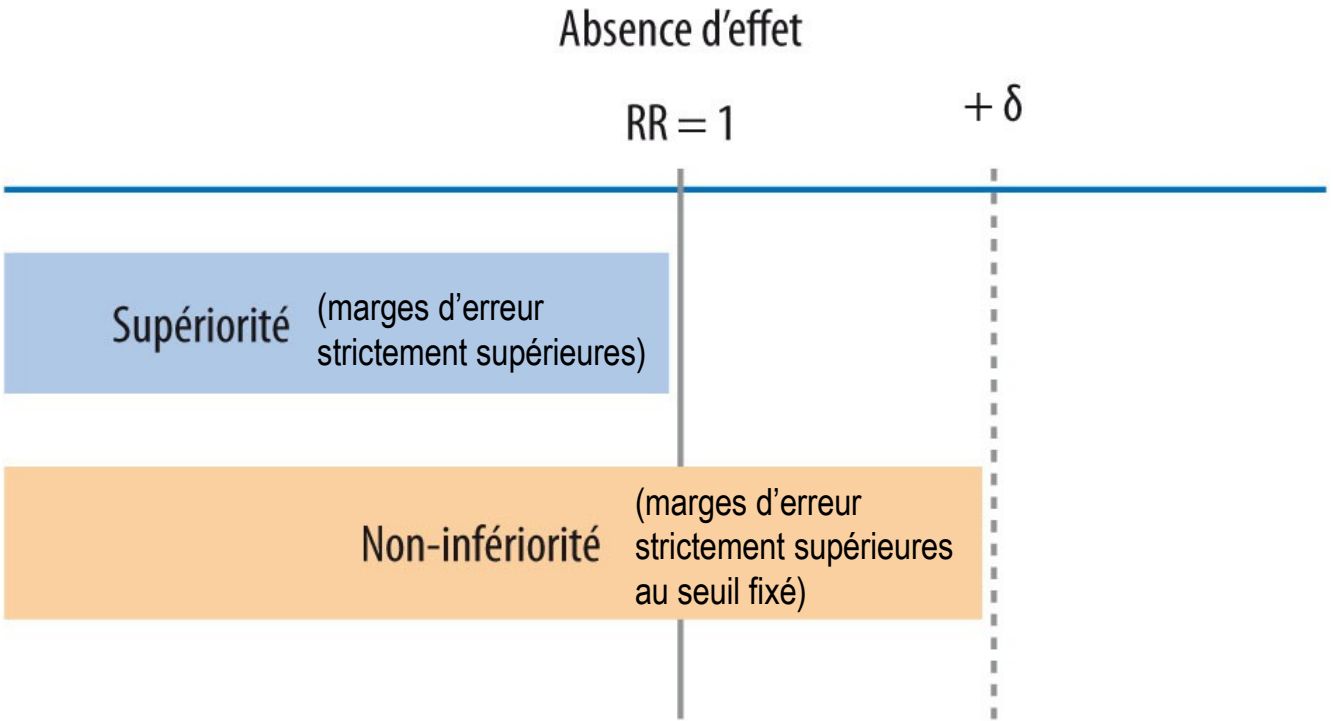
Ce qu'on savait déjà sur le TNK en AVC

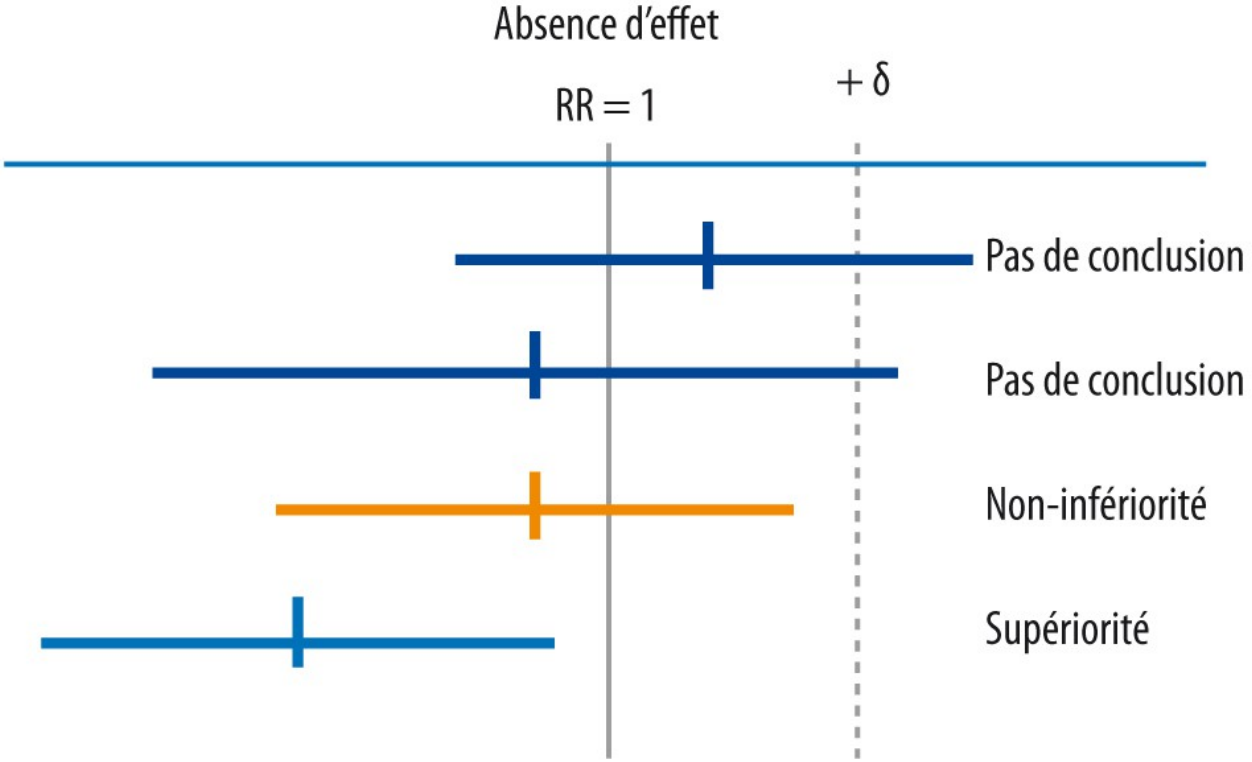
Étude	Journal	Date	Détails	N	Issue primaire	mRS 0-1 à 3 mois	HIC Sx
EXTEND-IA TNK	NEJM	Avril 2018	rtPA IV vs TNK 0,25 mg/kg avant thrombectomie	202	Reperfusion TICI2b-3 TNK 22% vs 10% p=0,03	TNK 49% vs 41% ns? (médiane 2 vs 3 p=0,04)	**Similaire :** **1% les 2**
NOR-TEST	Lancet Neurol	Oct. 2017	rtPA IV vs TNK 0,4 mg/kg (NIHSS médian de 4…)	1107	mRS 0-1 à 3 mois	TNK 64% vs 63% ns (18% de « mimics »)	**Similaire :** **TNK 0,4 3% vs 2%**
Analyse regroupée ATTEST + Australian TNK	Neurol	Juillet 2017	rtPA IV vs TNK (0,1 et 0,25 mg/kg)	146	Recanalisation à 24h TNK 71% vs 43% p<0,001	TNK 49% vs 25% (OR mRS 0-1 : 4.82, p=0.05)	**TNK 0% vs 3%**
TEMPO-1	Stroke	Mars 2015	TNK 0,1 vs 0,25 mg/kg (pas de rtPA IV) NIH < 6, délai < 12h, occl. prox.	50	% effets indésirables sérieux (HIC Sx) : similaires	TNK 0,25 vs 0,1 : 76% vs 56% ns?	**Similaire :** **TNK 0,25 : 4% (1/25)** **TNK 0,1 : 0% (0/25)**
Méta-analyse des 3 études ci-dessous (Huang et al.)	Int J Stroke	Avril 2016	Méta-analyse avec données individuelles des patients	291	mRS à 3 mois, NIHSS à 24h HIC, HIC Sx Mortalité à 3 mois	Tous similaires (TNK 0,25 numériquement prometteur mais ns p=0,093)	**Tous similaires**
ATTEST	Lancet Neurol	Avril 2015	rtPA IV vs TNK 0,25 mg/kg	104	% pénombre sauvée au CTP Similaire : 68% les 2	TNK 28% vs 20%	**Similaire :** **TNK 2% vs 4%**
Australian TNK (Parsons et al)	NEJM	Mars 2012	rtPA IV vs TNK 0,1 et 0,25 mg/kg Délai < 6h	75	% reperfusion (IRM) et NIHSS 24h TNK 79% vs 55% et 8 vs 3	TNK 54% vs 40% (TNK 0,25 mg/kg supérieur à 0,1 mg/kg)	**TNK 4% vs 12%**
Prematurely terminated (Haley et al.)	Stroke	Mars 2010	rtPA IV vs TNK (0,1, 0,25 et 0,4 mg/kg) Délai ≤ 3h	112	mRS à 3 mois TNK 0,4 inférieur similaire pour les autres	TNK 0,25 : 48% vs 42% TNK 0,1 : 45% vs 42% TNK 0,4 : 37% vs 42%	**TNK 0,25 : 6,5% vs 3,2%** **TNK 0,1 : 0% vs 3,2%** **TNK 0,4 : 16% vs 3,2%**

Supériorité *vs* non-infériorité



https://www.edimark.fr/ressources/peut-on-conclure-a-superiorite-a-partir-etude-non-inferiorite-figure-1

Exemple de supériorité *vs* non-infériorité



https://www.edimark.fr/ressources/peut-on-conclure-a-superiorite-a-partir-etude-non-inferiorite-figure-2

Études de non-infériorité

- Légitimes uniquement lorsqu'il y a un autre avantage évident
  - Anticoagulants directs : pas besoin de suivre l'INR
  - TNK : bolus uniquement, pas besoin de perfusion
- Choix du seuil de non-infériorité utilisé à justifier

TNK pour l’AVC

- Origines
- Données antérieures
- Étude AcT
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- Conclusion

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Wednesday, 4 May , 10:30 - 12:30

Official Welcome & Large Clinical Trials

Joanna Wardlaw (United Kingdom)
Bart van der Worp (Netherlands)

Introduction	10:30 – 10:35 5 min
O034 ALTEPLASE COMPARED TO TENECTEPLASE (ACT) RANDOMIZED CONTROLLED TRIAL Bijoy Menon (Canada) Rick Swartz (Canada)	10:35 – 10:45 10 min
Q&A	10:45 – 10:47 2 min
O039 TENECTEPLASE VERSUS ALTEPLASE FOR MANAGEMENT OF ACUTE ISCHEMIC STROKE (NOR-TEST 2 PART A): A PHASE 3, RANDOMISED, OPEN-LABEL, BLINDED ENDPOINT TRIAL Annette Fromm (Norway)	10:47 – 10:57 10 min
Q&A	10:57 – 10:59 2 min

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QUALITÉ | INTÉGRITÉ | INNOVATION | COLLABORATION | PERFORMANCE

STAR WARS DAY
MAY THE 4TH
BE WITH YOU

Intravenous tenecteplase compared with alteplase for acute ischaemic stroke in Canada (AcT): a pragmatic, multicentre, open-label, registry-linked, randomised, controlled, non-inferiority trial

Bijoy K Menon, Brian H Buck, Nishita Singh, Yan Deschaintre, Mohammed A Almekhlafi, Shelagh B Coutts, Sibi Thirunavukkarasu, Houman Khosravani, Ramana Appireddy, Francois Moreau, Gord Gubitz, Aleksander Tkach, Luciana Catanese, Dar Dowlatshahi, George Medvedev, Jennifer Mandzia, Aleksandra Pikula, Jai Shankar, Heather Williams, Thalia S Field, Alejandro Manosalva, Muzaffar Siddiqui, Atif Zafar, Oje Imoukhuede, Gary Hunter, Andrew M Demchuk, Sachin Mishra, Laura C Gioia, Shirin Jalini, Caroline Cayer, Stephen Phillips, Elsadig Elamin, Ashkan Shoamanesh, Suresh Subramaniam, Mahesh Kate, Gregory Jacquin, Marie-Christine Camden, Faysal Benali, Ibrahim Alhabli, Fouzi Bala, MacKenzie Horn, Grant Stotts, Michael D Hill, David J Gladstone, Alexandre Poppe, Arshia Sehgal, Qiao Zhang, Brendan Cord Lethebe, Craig Doram, Ayoola Ademola, Michel Shamy, Carol Kenney, Tolulope T Sajobi, Richard H Swartz, for the AcT Trial Investigators

Summary

Background **Intravenous thrombolysis with alteplase bolus followed by infusion is a global standard of care for patients with acute ischaemic stroke. We aimed to determine whether tenecteplase given as a single bolus might increase reperfusion compared with this standard of care.**

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S0140-6736(22)01054-6

Sites across Canada

Étude AcT

- Étude canadienne, mutlti-centrique (22 centres)
- Ouverte, randomisée, basée sur un registre
- Évaluation centralisée de l'issue primaire (mRS à 3 mois)
- TNK 0,25 mg / kg *vs* rtPA 0,9 mg / kg
- Non-infériorité

CHUM

Doses arrondies utilisées

Tableau des doses de TÉNECTÉPLASE TNKase (0,25mg / kg - max 25 mg)

Poids (kg)	Dose (mg)	Volume (mL)
Moins de 60	15	3
60 à 69,9	17,5	3,5
70 à 79,9	20	4
80 à 89,9	22,5	4,5
90 et plus	25	5

Fiole de 50 mg diluée avec 10 mL d'ESI (5 mg/mL)

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Seuil de non-infériorité

- Fixé à -5%
  - Plus de la moitié de l'effet du rtPA contre placebo (environ 10%)
  - Moins que l'intervalle de confiance inférieure du rtPA contre placebo (environ 6%)
  - Avec un taux de 35% pour le rtPA,

    le seuil de non-infériorité serait de 34,7%

	Tenecteplase group (n=806)	Alteplase group (n=771)
Age, years	74 (63–83)	73 (62–83)
Sex		
Female	382 (47·4%)	373 (48·4%)
Male	424 (52·6%)	398 (51·6%)
Baseline NIHSS score (n=1569)	9 (6–16)	10 (6–17)
Baseline NIHSS score categories		
<8	325/803 (40·5%)	294/766 (38·4%)
8–15	247/803 (30·8%)	256/766 (33·4%)
>15	231/803 (28·8%)	216/766 (28·2%)
Occlusion site on baseline CT angiography (n=1558)*		
Intracranial internal carotid artery	69/801 (8·6%)	66/757 (8·7%)
M1 segment MCA	118/801 (14·7%)	119/757 (15·7%)
M2 segment MCA	174/801 (21·7%)	141/757 (18·6%)
Other distal occlusions†	130/801 (16·2%)	138/757 (18·2%)
Vertebrobasilar arterial system	26/801 (3·2%)	38/757 (5·0%)
Cervical internal carotid artery	17/801 (2·1%)	9/757 (1·2%)
No visible occlusions	267/801 (33·3%)	246/757 (32·5%)
Presence of large vessel occlusion on baseline CT angiography (n=1558)	196/801 (24·5%)	193/757 (25·5%)
Type of enrolling centre		
Primary stroke centre	56/806 (6·9%)	43/771 (5·6%)
Comprehensive stroke centre	750/806 (93·1%)	728/771 (94·4%)
Source registry		
QuiCR	346/806 (42·9%)	342/771 (44·4%)
OPTIMISE	460/806 (57·1%)	429/771 (55·6%)
Workflow times, min		
Stroke symptom onset to hospital arrival (n=1560)	82 (54–140)	83 (55–138)
Stroke symptom onset to randomisation (n=1570)	121 (85–179)	123 (88–179)
Door (hospital arrival) to baseline CT (n=1561)	15 (12–21)	16 (12–22)
Stroke symptom onset to needle (intravenous thrombolysis start; n=1562)	128 (93–186)	131 (95–188)
Door (hospital arrival) to needle (intravenous thrombolysis start; n=1556)	36 (27–49)	37 (29–52)
Baseline CT to arterial puncture (in patients undergoing EVT; n=505)	60 (43–88)	58 (41–85)
Arterial puncture to successful reperfusion (in patients undergoing EVT; n=445)	31 (19–47)	27 (17–45)

Data are n (%), n/N (%) or median (IQR). Large vessel occlusion is defined as large vessel occlusion of the internal carotid artery, M1 segment MCA, or functional M1 segment MCA occlusion—ie, all M2 segments MCA occluded on baseline CT angiography scan. If patients had more than one occlusion site, the most proximal occlusion is listed. EVT=endovascular thrombectomy. MCA=middle cerebral artery. NIHSS=National Institute of Health Stroke Scale. OPTIMISE=Optimizing Patient Treatment in Major Ischemic Stroke with EVT registry. QuiCR=Quality Improvement and Clinical Research registry. *19 patients had baseline non-contrast CT but did not have a baseline CT angiography; these patients' characteristics were not different from those who had a baseline CT angiography. †Middle cerebral artery, anterior cerebral artery, or posterior cerebral artery.

Table 1: **Baseline characteristics, intention-to-treat population**

Groupes similaires

- NIH médian 9-10
- DtoN médian 36-37 min

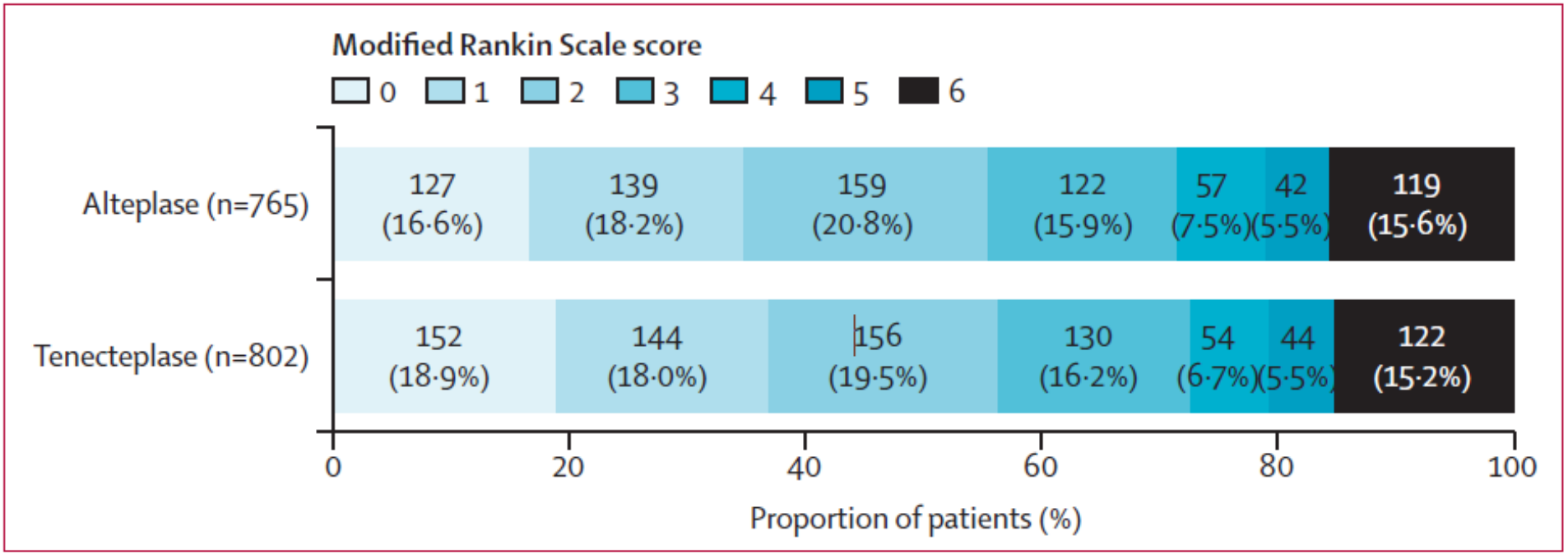

Figure 2: **Distribution of the modified Rankin Scale scores at 90–120 days, intention-to-treat population**
Scores range from 0 to 6, with 0 indicating no symptoms, 1 no clinically significant disability, 2 slight disability, 3 moderate disability, 4 moderately severe disability, 5 severe disability, and 6 death.

mRS 0-1 36,9% *vs* 34,8% ; IC95% -2,6% à 6,9%,
< marge de non-infériorité de -5% (non supérieur avec p = 0,19)

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	Tenecteplase group (n=806)	Alteplase group (n=771)	Unadjusted difference in proportion	Adjusted risk ratio*	Difference in medians	Adjusted common odds ratio*†	Adjusted β coefficient*
Primary outcome							
mRS score 0–1 at 90–120 days (n=1567)	296/802 (36·9%)	266/765 (34·8%)	2·1 (–2·6 to 6·9)	..	..	..	..
Secondary outcomes*							
mRS score 0–1 at 90–120 days (n=1567)	296/802 (36·9%)	266/765 (34·8%)	..	1·1 (1·0 to 1·2)	..	..	..
mRS score 0–2 at 90–120 days (n=1567)	452/802 (56·4%)	425/765 (55·6%)	0·8 (–4·1 to 5·7)	1·0 (1·0 to 1·1)	..	..	..
Actual mRS score at 90–120 days (n=1567)	2 (1 to 4)	2 (1 to 4)	..	..	0	0·9 (0·8 to 1·1)	..
Return to baseline function (n=1454)	219/740 (29·6%)	199/714 (27·9%)	1·7 (–2·9 to 6·4)	1·1 (0·9 to 1·2)	..	..	..
EQ-VAS at 90–120 days (n=1262)	70·5 (21·3)	68·1 (22·6)	2·4 (–0·1 to 4·8)	..	..	..	2·1 (–0·3 to 4·5)
Endovascular thrombectomy use (n=1577)	258/806 (32·0%)	248/771 (32·2%)	–0·2 (–4·8 to 4·5)	1·0 (0·8 to 1·2)	..	..	..
eTICI score of ≥2b on initial angiography of EVT (n=502)‡	26/256 (10·2%)	27/256 (10·5%)	–0·8 (–6·3 to 4·6)	0·9 (0·6 to 1·6)	..	..	..
rAOL score of ≥2b on initial angiography of EVT (n=499; post hoc)§¶	48/253 (19·0%)	40/246 (16·3%)	2·7 (–4·0 to 9·4)	1·1 (0·7 to 1·7)	..	..	..
Length of hospital stay (n=1479; post hoc)	5 (2 to 11)	5 (3 to 11)	..	1·0 (0·9 to 1·1)	0	..	..

Data are n/N (%), median (IQR), mean (SD), or effect estimate with 95% CI in parentheses. EQ-VAS=EuroQol visual analogue scale. eTICI=extended Thrombolysis in Cerebral Infarction. EVT=endovascular thrombectomy. mRS=modified Rankin Scale. rAOL=revised Arterial Occlusive Lesion score. *Adjusted for age, sex, baseline stroke severity, stroke symptom onset-to-needle time, and source registry as fixed-effects variables, and site as a random effects variable. †Common odds ratio is the odds ratio for a unit increase in the modified Rankin scale score for tenecteplase *vs* alteplase. ‡Four patients did not have initial intracranial endovascular thrombectomy images. §Scored as follows: 0, primary occlusive thrombus remains same; 1, debulking of proximal part of the thrombus but without any recanalisation; 2a, partial or complete recanalisation of the primary thrombus with occlusion in major distal vascular branch; 2b, partial or complete recanalisation of the primary thrombus with occlusion in minor distal vascular branch, or partial recanalisation of the primary thrombus with no thrombus in the vascular tree at or beyond the primary occlusive thrombus; and 3, complete recanalisation of the primary occlusive thrombus with no clot in the vascular tree beyond. ¶rAOL was not assessable in six patients because of missing initial intracranial angiography or missing baseline CT angiography images.

Table 2: **Efficacy outcomes in the intention-to-treat population**

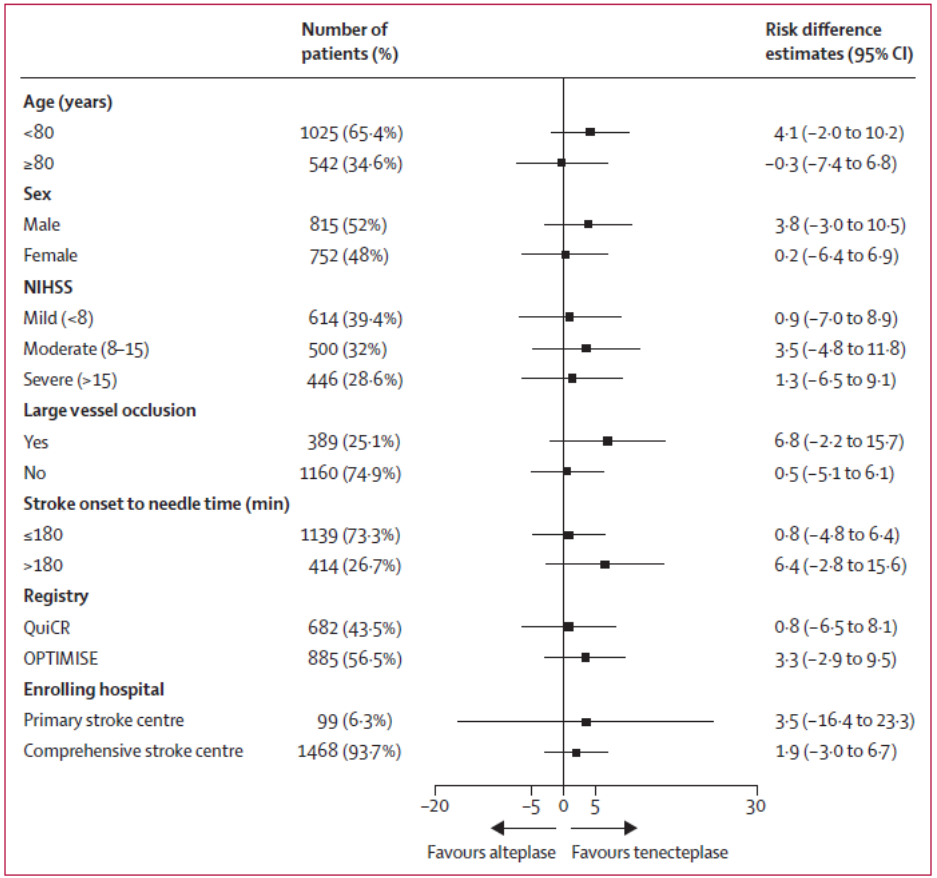

Figure 3: **Forest plot of unadjusted risk difference estimates for the primary outcome (modified Rankin Scale score of 0–1) stratified by prespecified subgroups, intention-to-treat population**
EVT=endovascular thrombectomy. NIHSS=National Institutes of Health Stroke Scale. OPTIMISE=Optimizing Patient Treatment in Major Ischemic Stroke with EVT registry. QuiCR=Quality Improvement and Clinical Research registry.

Résultats homogènes

- Y compris analyses post-hoc non-publiées sur petits poids <60kg…

Tableau des doses de TÉNECTÉPLASE TNKase (0,25mg / kg - max 25 mg)

Poids (kg)	Dose (mg)	Volume (mL)
Moins de 60	15	3
60 à 69,9	17,5	3,5
70 à 79,9	20	4
80 à 89,9	22,5	4,5
90 et plus	25	5

Fiole de 50 mg diluée avec 10 mL d'ESI (5 mg/mL)

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	Tenecteplase group (n=800)	Alteplase group (n=763)	Risk difference (95% CI)
Death within 90 days of randomisation (n=1554)	122/796 (15·3%)	117/758 (15·4%)	−0·1 (−3·7 to 3·5)
24 h symptomatic intracerebral haemorrhage	27/800 (3·4%)	24/763 (3·2%)	0·2 (−1·5 to 2·0)
Extracranial bleeding requiring blood transfusions	6/800 (0·8%)	6/763 (0·8%)	0·0 (−0·9 to 0·8)
Orolingual angio-oedema	9/800 (1·1%)	9/763 (1·2%)	−0·1 (−1·1 to 1·0)
Other serious adverse events	81/800 (10·0%)	69/763 (9·1%)	1·1 (−1·8 to 4·0)
Imaging-identified intracranial haemorrhage	154/800 (19·3%)	157/763 (20·6%)	−1·3 (−5·3 to 2·6)
Subarachnoid haemorrhage	53/800 (6·6%)	52/763 (6·8%)	−0·2 (−2·7 to 2·3)
Subdural haemorrhage	2/800 (0·3%)	5/763 (0·7%)	−0·4 (−1·1 to 0·3)
Intraventricular haemorrhage	24/800 (3·0%)	17/763 (2·2%)	0·8 (−0·8 to 2·3)
Haemorrhagic infarction type 1 (scattered small petechiae)	18/800 (2·3%)	24/763 (3·2%)	−0·9 (−2·5 to 0·7)
Haemorrhagic infarction type 2 (confluent petechiae)	62/800 (7·8%)	67/763 (8·8%)	−1·0 (−3·8 to 1·7)
Parenchymal haematoma type 1 (haematoma occupying <30% of infarct with no substantive mass effect)	28/800 (3·5%)	20/763 (2·6%)	1·1 (−1·0 to 2·6)
Parenchymal haematoma type 2 (haematoma occupying ≥30% of infarct with obvious mass effect)	21/800 (2·6%)	18/763 (2·4%)	0·3 (−1·3 to 1·8)
Remote parenchymal haematoma type 1†	6/800 (0·8%)	9/763 (1·2%)	−0·4 (−1·4 to 0·5)
Remote parenchymal haematoma type 2‡	2/800 (0·3%)	3/763 (0·4%)	−0·1 (−0·7 to 0·4)

Data are n/N (%) or risk difference with 95% CI in parentheses. Imaging-identified intracranial haemorrhages were assessed in a central core laboratory in a blinded manner and classified using the Heidelberg classification.[19] *Within the intention-to-treat population. †Remote parenchymal haematoma type 1 was defined as haematoma outside the infarcted tissue with no substantive mass effect. ‡Remote parenchymal haematoma type 2 was defined as haematoma outside the infarcted tissue, with obvious mass effect.

Table 3: **Safety outcomes in patients who received at least some dose of either thrombolytic agent and reported as treated***

TNK *vs* rtPA

- Efficacité similaire
  - mRS 0-1 à 3 mois 36,9% *vs* 34,8% - non-inférieur (marge de 5%)
- Taux de complications similaires
  - Mortalité 15,3% *vs* 15,4% ns
  - Hémorragie
    - HICs 3,4% *vs* 3,2% ns
    - Toute HIC 19,3% *vs* 20,6% ns
  - Angioedème 1,1% *vs* 1,2% ns
- Coût identique - 2745,00 $
- Administration plus facile - bolus *vs* perfusion

Conclusion (tirée du résumé)

- Le ténectéplase intra-veineux (0,25 mg/kg) est une alternative raisonnable à l'altéplase pour tous les patients présentant un AVC ischémique aigu qui rencontrent les critères standards de thrombolyse.

Interpretation Intravenous tenecteplase (0·25 mg/kg) is a reasonable alternative to alteplase for all patients presenting with acute ischaemic stroke who meet standard criteria for thrombolysis.

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Mise à jour en septembre des recommandations canadiennes

Section 5.2

iv. **(NEW FOR 2022) Tenecteplase** may be considered as an alternative to alteplase within 4.5 hours of acute stroke symptom onset [Strong recommendation; Moderate quality of evidence].

a. **Tenecteplase dose**: If administering Tenecteplase, the dose of 0.25 mg/kg up to a maximum of 25 mg should be administered, given as a single bolus over 5 seconds [Strong recommendation; Moderate quality of evidence].

Caution: The dosing of alteplase and tenecteplase for stroke is NOT the same as the dose protocols for administration of these medications for myocardial infarction or massive pulmonary embolism.

https://www.strokebestpractices.ca/recommendations/acute-stroke-management

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TNK pour l’AVC

- Origines
- Données antérieures
- Étude AcT
- Autres études
- Conclusion

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Amphithéâtre

Wednesday, 4 May , 10:30 - 12:30

Official Welcome & Large Clinical Trials

Joanna Wardlaw (United Kingdom)
Bart van der Worp (Netherlands)

Introduction	10:30 – 10:35 5 min
O034 ALTEPLASE COMPARED TO TENECTEPLASE (ACT) RANDOMIZED CONTROLLED TRIAL Bijoy Menon (Canada) Rick Swartz (Canada)	10:35 – 10:45 10 min
Q&A	10:45 – 10:47 2 min
O039 TENECTEPLASE VERSUS ALTEPLASE FOR MANAGEMENT OF ACUTE ISCHEMIC STROKE (NOR-TEST 2 PART A): A PHASE 3, RANDOMISED, OPEN-LABEL, BLINDED ENDPOINT TRIAL Annette Fromm (Norway)	10:47 – 10:57 10 min
Q&A	10:57 – 10:59 2 min

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QUALITÉ | INTÉGRITÉ | INNOVATION | COLLABORATION | PERFORMANCE

NOR-TEST 2 partie A

- Non-infériorité, dose de 0,4 mg/kg
- Arrêt précoce après 216 / 1036 patients

Issue	TNK	rtPA	OR (IC95%)	p	AcT
mRS 0-1 à 3 mois	32%	51%	0,45 (0,25-0,80)	0,0064	36%
Mortalité à 3 mois	16%	5%	3,56 (1,24-10,21)	0,013	15%
HICs	6%	1%	6,57 (0,78-55,62)	0,061	3,3%
Toute HIC	21%	7%	3,68 (1,49-9,11)	0,0031	20%

TASTE-A

- Tenecteplase versus Alteplase for Stroke Thrombolysis Evaluation in the Ambulance trial
  - 104 pts
  - Taille de l'AVC au scan de perfusion
  - 12 ml avec TNK vs 35 ml avec rtPA
  - Adjusted incidence ratio 0,55, IC95% 0,37-0,81; p=0,0030
  - Impact clinique? (mRS 0-1 similaires 45 et 44%)

Lancet Neurol 2022; 21: 520-527

Primary outcome

- The primary outcome of the CT-perfusion lesion volume, was significantly smaller in patients treated with tenecteplase.
  - Tenecteplase median 12mL, Q1, Q3: 3, 28mL
  - Alteplase median 35mL Q1, Q3: 18, 76mL
  - Adjusted Incidence Rate Ratio 0·55, 95% CI: 0·37, 0·81; **p=0·003**.
  - The results were maintained in the pre-specified robustness analysis.

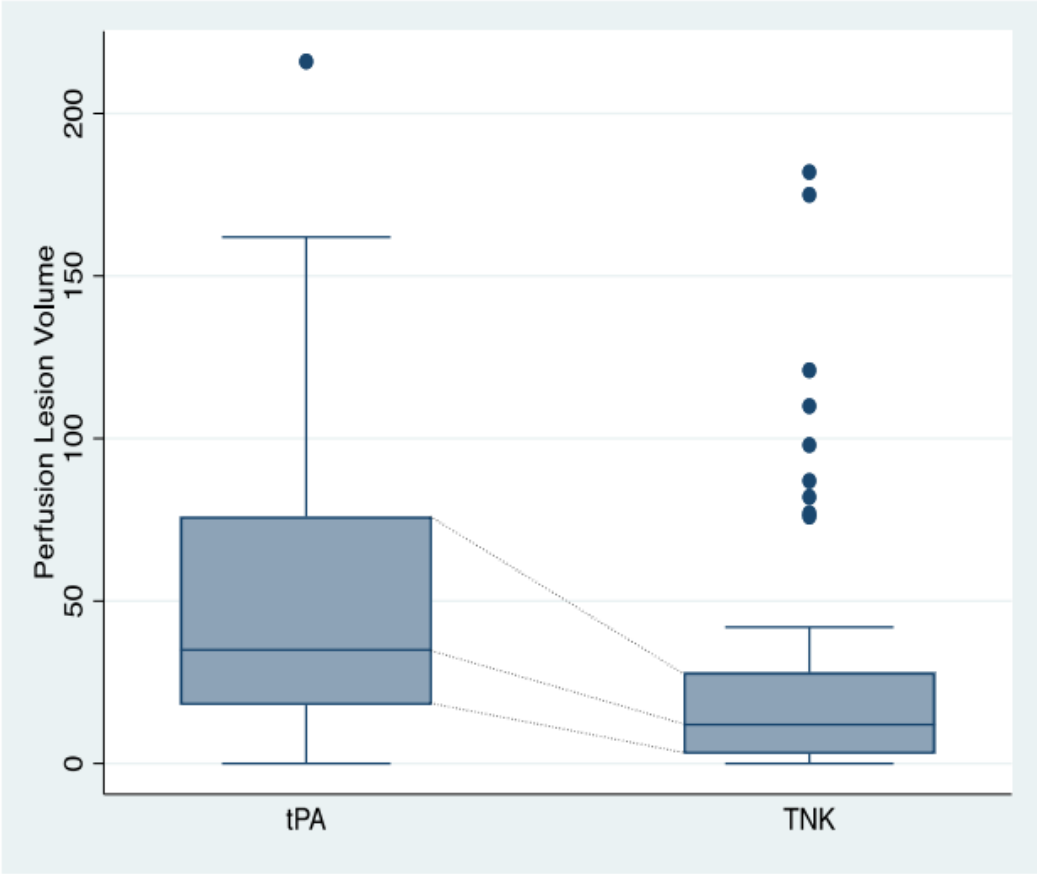

Figure 1. Perfusion lesion volume on Computed Tomography Perfusion imaging performed on arrival at the receiving hospital by treatment group

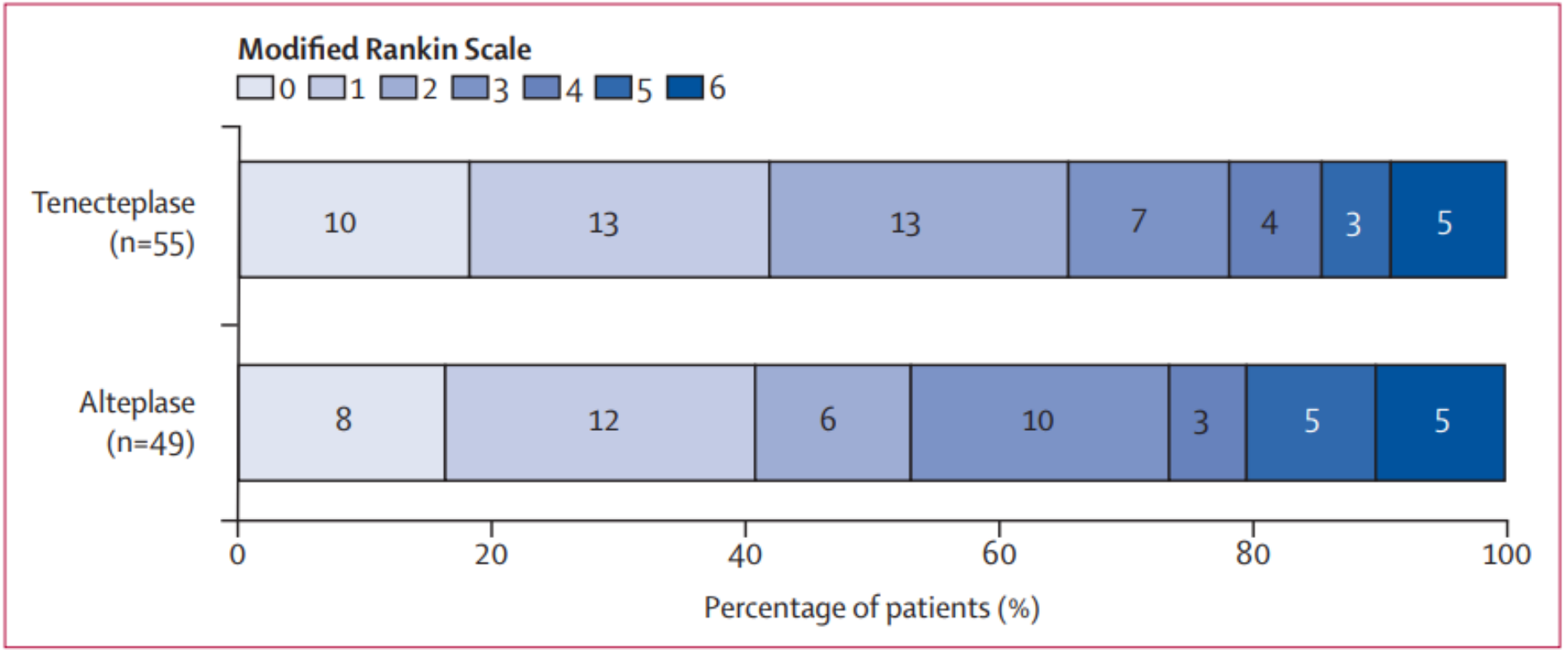

***Figure 3*: Proportion of patients with each mRS score by treatment group**

The numbers within each shaded box represent the absolute number of patients for each mRS score at 90 days after trial enrolment. mRS=modified Rankin Scale.

Études en cours (1) – TNK 0,25 mg/kg

- (1) Devis similaire à AcT
- NOR-TEST 2 partie B
  - Norwegian Tenecteplase Stroke Trial 2
- ATTEST 2
  - Alteplase-Tenecteplase Trial Evaluation for Stroke Thrombolysis 2
- TRACE II
  - Tenecteplase Reperfusion therapy in Acute ischaemic Cerebrovascular Events-II

Fenêtre étendue: TWIST

- TNK in Wake-up Ischemic Stroke Trial
  - TNK *vs* rien
  - 578 pts
  - AVC au réveil (LSTN médian 10h52, FTSS médian 1h51)
  - Scan C$^-$: >1/3 MCA exclu (ASPECTS <7? >70% ASPECTS 10)
    - Première étude de fenêtre étendue sans imagerie supplémentaire…
  - Issues similaires
    - mRS 0-1 45% *vs* 38% p=0,27
    - HICs (IST-3) 4% *vs* 3% ns
    - Mortalité 10% *vs* 8% ns

Lancet Neurol déc. 2022; https://doi.org/10.1016/ S1474-4422(22)00484-7

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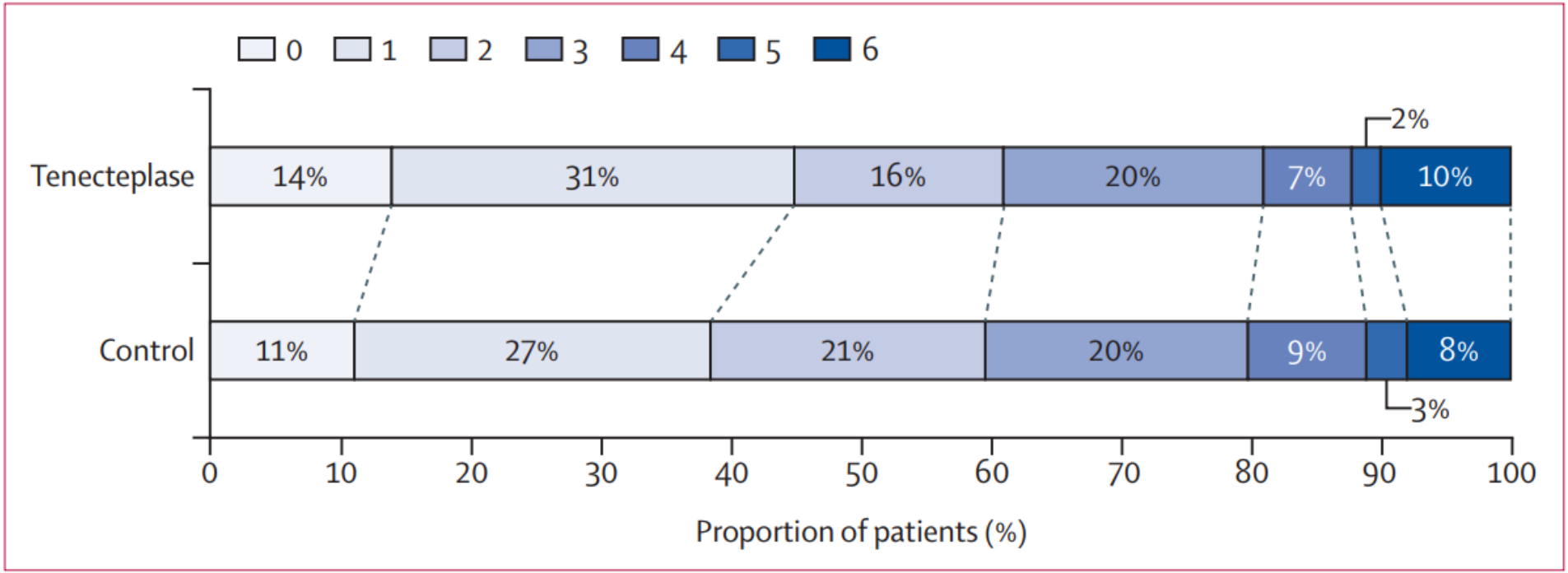

Figure 2: **Distribution of modified Rankin Scale scores in each treatment group at 90 days follow-up (intention-to-treat analysis)**

Étude	n	Délai (médiane)	Critères d'inclusion (et dans les faits)	Issue primaire	Hémorragie (sICH)	Décès	Âge
EPITETH Stroke 2010	95 /99	LTSN 3-6 (5h04)	(NIH 12) (**DWI 20, PWI 167**) Mismatch ≥10 (42) Ratio >1,2 (8,4)	Croissance 0,58 (1,02 *vs* 1,77, p=0,046) mRS 0-1 36 *vs* 21% p=0,159	8% avec rtPA (*vs* ?)	?	(75)
MR WITNESS Ann Neurol Mai 2018	80	LTSN 4,5-24 (11h12) FTSS <4,5 (3h29)	(NIH 7) **DWI + / FLAIR –** ou SIR <1,15 (1,08)	mRS 0-1 39% (tous avec rtPA)	1,3%	8,8%	≤85 (67,5)
WAKE-UP NEJM Août 2018	503 /800	LTSN >4,5 (10h21) FTSS <4,5 (3h09)	NIH ≤25 (6) **DWI + / FLAIR –** Pas de thrombectomie	mRS 0-1 53,3 *vs* 41,8% p=0,02	2,0 *vs* 0,4% p=0,15	4,1 *vs* 1,2% p=0,07	≤80 (65)
THAWS Stroke Avril 2019	131 /300	LTSN >4,5 (9h48) FTSS <4,5 (2h48)	(NIH 7) **DWI + / FLAIR –** MR ASPECTS >4 (9) ou ≤50% du territoire Pas de thrombectomie	mRS 0-1 47,1 *vs* 48,3% p=0,892 Dose japonaise 0,6 mg/kg	1 *vs* 0 p>0,999	2 *vs* 2 p>0,999	(74)
ECASS-4 Int J stroke Avril 2019	119 /264	LTSN 4,5-9 (7h42)	**MRI perfusion** (comme EXTEND)	mRS 0-1 25,0 *vs* 29,0% OR 1,20, 95%CI 0,63-2,27 p=0,58	1 *vs* 0	11,5 *vs* 6,8% p=0,53	
EXTEND			mRS 0-1, NIH 4-26 (11) **« Core ≤1/3 ACM**	mRS 0-1			

Études en cours (2) – TNK 0,25 mg/kg

- (2) Fenêtre étendue
- TIMELESS (mars 2023?)
  - 456 pts, mRS 0-2
  - **4,5 à 24h**, **occlusion proximale** ICA, M1 ou M2 avec **décalage** (core <70, pénombre ≥15, ratio ≥1,8)
- RESILIENT (EXTEND-IV) (mai 2024?)
  - 642 pts, **4,5h à 12h**, **sans TEV**, **décalage** (core >10 mais <50, ratio >1,4)
- TEMPO-2 (déc. 2024?)
  - 1274 pts, **0 à 12h**, **occlusion proximale**, ASPECTS >7, **NIHSS <6**
- ETERNAL-LVO (déc. 2025?)
  - 740 pts, <24h, **occlusion proximale**, **décalage** à la perfusion

Études en cours (3) – TNK 0,25 mg/kg

- (3) Avec TEV
- RESILIENT DIRECT TNK (mai 2024?)
  - 530 pts, mRS 0-1, NIHSS ≥6, <4,5h
  - TNK et TEV *vs* TEV seule
- BRIDGE-TNK (mars 2026?)
  - 586 pts, mRS 0-2, <4,5h
  - TNK et TEV *vs* TEV seule

Études en cours (4) – TNK IA

Table 3. Ongoing Studies of Tenecteplase for Acute Ischemic Stroke

Study name	Study design	ClinicalTrials.gov identifier	Experimental group	Comparator group	Timing	Number of planned patients
INSIST-TNK	Prospective non randomized	NCT04201964	Intraarterial tenecteplase (0.2-0.4 mg/min for 30-40 min) after insufficient endovascular perfusion (mTICI 1/2a)	None	<24h	30
BRETIS-TNK	Prospective non randomized	NCT04202458	Intraarterial tenecteplase (4 mg+0.4 mg/min for 30 min) after the first attempt of thrombectomy device pass	None	<24 h	30
ALLY	Prospective non randomized	NCT05172934	Intraarterial tenecteplase after successful but incomplete endovascular perfusion (mTICI 2b/2c)	None	<24 h	20
TECNO	RCT	Not available	Intraarterial tenecteplase (3 mg) after incomplete endovascular perfusion (mTICI 2a/2b)	Standard of care mechanical thrombectomy	<24 h	120

Imad Derraz review, Stroke 4 mai 2022; 53(8): 2683-94
https://www.ahajournals.org/doi/epdf/10.1161/STROKEAHA.122.039287

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TNK pour l’AVC

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    - HICs 3,4% *vs* 3,2% ns
    - Toute HIC 19,3% *vs* 20,6% ns
  - Angioedème 1,1% *vs* 1,2% ns
- Coût identique - 2745,00 $
- Administration plus facile - bolus *vs* perfusion