LA PLACE DU TENECTEPLASE (TNK) DANS LES ACCIDENTS VASCULAIRES CÉRÉBRAUX

SSVQ de Neurologie Vasculaire Octobre 2022

Célina Ducroux

Neurologue vasculaire

The Ottawa Hospital – Civic Campu

SSVQ Société des sciences vasculaires du Québec
Chef de file en santé vasculaire.

OTTAWA STROKE PROGRAM

CONFLITS D'INTÉRÊT

- Aucun conflit d'intérêt

SOMMAIRE

LES AGENTS THROMBOLITYQUES

LES AGENTS THROMBOLITYQUES

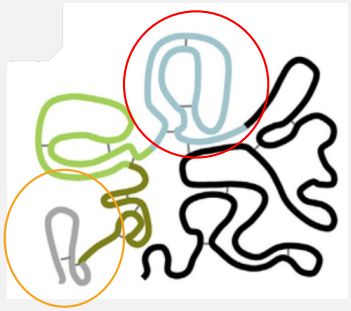
Tissue-type Plasminogen activator (Alteplase): preuve de son efficacité dans plusieurs études randomisées (NINDS / ECASS III)

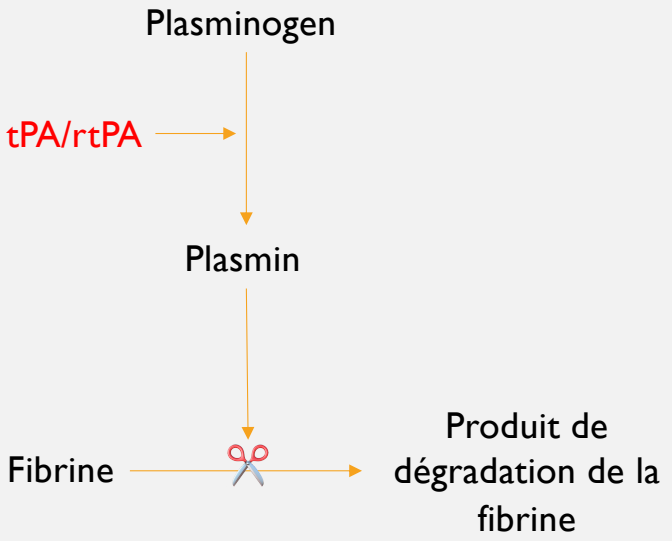
Autres agents: Urokinase-type Plasminogen activator; Streptokinase; Reteplase; Ectaplase; Monteplase; Pamiteplase

Tenecteplase: preuve de son efficacité ?

TISSUE-TYPE PLASMINOGEN ACTIVATOR / ALTEPLASE

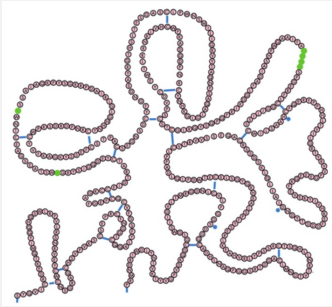
- Molécule de 70 k-DA
- Single-chain glycosylée serine protéase avec 4 domaines:
  - Finger domain: liaison à la fibrine
  - Epidermal growth factor (EGF)
  - 2 domaines kringle (K1 et K2): activation du plasminogen
  - Domaine serine protéase
- Demi-vie 3 à 8 minutes
- Production endogène (cellules endotheliales, neurones, astrocytes, microglie)





TENECTEPLASE

- Mutant du tPA: 3 sites de mutations
  - Augmentation de l'affinité avec la fibrine (14x)
  - Réduction de la clairance (4-8x) et augmentation du temps de demi-vie



Désignation	Substitution d'un amino-acide	Effet
T (threonine)	Substitution de threonine par asparagine	Nouveau site de glycosylation Kringle-1 Diminution de la clairance Diminution de l'affinité avec la fibrine
N (asparagine)	Substitution d'asparagine par glutamine	Diminution de la clairance Augmentation de l'affinité à la fibrine
K (Lysine)	Substitution d'une lysine et une histidine et 2 arginines par 4 alanines	Augmentation de l'affinité à la fibrine Augmentation de la resistance à PAI-1 (80x)

ALTEPLASE VERSUS TENECTEPLASE

	Alteplase	Tenecteplase
Indications	AVC, STEMI, Embolie pulmonaire massive	STEMI (0.5mg/kg)
Dose dans l'AVC	0.9 mg/kg max 90mg (Bolus puis infusion sur 1h)	0.25mg/kg en bolus max 25mg
Demi-vie (clairance complète)	3-8 minutes (1 heure)	20-24 minutes (2 heures)
Métabolisme	Hépatique	Hépatique

INDICATIONS DE THROMBOLYSE INTRAVEINEUSE

ALTEPLASE

	NINDS (1995)	ECASS I (1995)	ATLANTIS (1999)	ECASS II (1998)	ECASS III (2008)	EPITHET (2008)
NBR PATIENTS	**624**	620	613	800	**821**	101
AGE	≥ **18**	18 ≤ Age ≤ 80	18 ≤ Age ≤ 79	18 ≤ Age ≤ 80	**18 ≤ Age ≤ 80**	≥ 18
DELAY	≤ **3 h**	≤ 6h	3 ≤ Hours ≤ 5	≤ 6h	**3 ≤ Hours ≤ 4.5**	3 ≤ Hours ≤ 6
INTERVENTION	**Actilyse (Rt-PA) 0,9mg/Kg vs Placebo**	Actilyse (Rt-PA) 1,1mg/Kg vs Placebo	Actilyse (Rt-PA) 0,9mg/Kg vs Placebo	Actilyse (Rt-PA) 0,9mg/Kg vs Placebo	**Actilyse (Rt-PA) 0,9mg/Kg vs Placebo**	Actilyse (Rt-PA) 0,9mg/Kg vs Placebo
PRIMARY OUTCOME	**Part 1 : Improvement (resolution of neurologic deficit or an improvement NIHSS ≥4) at 24 hours. Part 2 : the proportion of patients who recovered with minimal or non deficit at 3 months. (Barthel Index 95-100%; ≤1 NIHSS and Rankin; 1 Glasgow outcome scale).**	Difference between rt-PA and placebo in activities of daily living = difference of 15 points in the Barthel Index at 90 days after ttt AND difference of one grade in Rankin at 90 days after ttt.	The percentage of patients at 90 days with an excellent neurologic recorvery defined as a score of 0 or 1 on the NIHSS	The proportion of patients who had a favourable outcome (score 0 or 1) on the Rankin at 90 +/- 14 days after treatment	**Disability at day 90, as assessed by means of Rankin, dichotomized as a favorable outcome (0 or 1) or an unfavorable outcome (2 to 6).**	Infarct growth attenuation in mismatch patients between alteplase and placebo
RESULTATS	**Positive for primary outcome of Part 2.**	Negative for primary outcome	Negative for primary outcome	Negative for primary outcome	**Positive for primary outcome**	Negative for primary outcome
IMAGERY MODALITY	**CT-scan**	CT-scan	CT-scan	CT-scan	**CT-scan and MRI**	CT-scan and MRI

ALTEPLASE

- NINDS TRIAL
- ECASS 3 TRIAL
- WAKE-UP STROKE (MISMATCH DWI-FLAIR)

WAKE-UP

- EXTEND-IV (≤ 9 HEURES; CORE<70ML; RATIO 1.2)

The New England
Journal of Medicine

©Copyright, 1995, by the Massachusetts Medical Society

Volume 333 DECEMBER 14, 1995 Number 24

TISSUE PLASMINOGEN ACTIVATOR FOR ACUTE ISCHEMIC STROKE

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 25, 2008 VOL. 359 NO. 13

Thrombolysis with Alteplase 3 to 4.5 Hours after Acute Ischemic Stroke

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 16, 2018 VOL. 379 NO. 7

MRI-Guided Thrombolysis for Stroke with Unknown Time of Onset

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 9, 2019 VOL. 380 NO. 19

Thrombolysis Guided by Perfusion Imaging up to 9 Hours after Onset of Stroke

H. Ma, B.C.V. Campbell, M.W. Parsons, L. Churilov, C.R. Levi, C. Hsu, T.J. Kleinig, T. Wijeratne, S. Curtze, H.M. Dewey, F. Miteff, C.-H. Tsai, J.-T. Lee, T.G. Phan, N. Mahant, M.-C. Sun, M. Krause, J. Sturm, R. Grimley, C.-H. Chen, C.-J. Hu, A.A. Wong, D. Field, Y. Sun, P.A. Barber, A. Sabet, J. Jannes, J.-S. Jeng, B. Clissold, R. Markus, C.-H. Lin, L.-M. Lien, C.F. Bladin, S. Christensen, N. Yassi, G. Sharma, A. Bivard, P.M. Desmond, B. Yan, P.J. Mitchell, V. Thijs, L. Carey, A. Meretoja, S.M. Davis, and G.A. Donnan, for the EXTEND Investigators*

INDICATIONS DE L'ALTEPLASE

- ≤ 4h30 après le début des symptômes ou la dernière fois vue normale
- 0.9mg/kg (dose maximum 90mg), 10% de la dose totale en bolus puis perfusion du reste sur 60 minutes.
- Quand peut-on donner du rtPA dans les patients < 4h30:
  - Accessibilité à l'IRM: Mismatch DWI-FLAIR pour les patients du réveil
  - Accessibilité au CT-perfusion:
    - ≤9h
    - Critères imageries: core ≤ 70mL; ratio région hypoperfusée/core ≥ 1.2

- ≤ 4h30
- 0.9mg/kg (dose max 90mg) - bolus puis perfusion sur 1h
- Wake up stroke (IRM)
- 4h30 – 9h (imagerie avancée)

TENECTEPLASE

	Parson et al (Australia) 2012	NORTEST 2017	EXTEND-IA TNK 2018	EXTEND IA TNK part 2 2020	NORTEST-2 part A 2022	TASTE A 2022	ACT 2022
STUDY DESIGN	Superiority	Superiority	Both	Both	Non inferiority	Superiority	**Non inferiority**
NBR PATIENTS	75 patients	1100 patients	204 patients	300 patients	216 patients	104 patients	**1600 patients**
DELAY	≤ 6 hours	≤ 4.5 hours or wake-up with mismatch criteria	≤ 4.5 hours	≤ 4.5 hours	≤ 4.5 hours	≤ 4.5 hours	≤ **4.5 hours**
THROMBOLYSE Product	TNK 0.1 or 0.25mg/kg vs tPA	TNK 0.4mg/kg vs tPA	TNK 0.25mg/kg vs tPA	TNK 0.4mg/kg vs TNK 0.25mg/kg	TNK 0.4mg/kg vs tPA	TNK 0.25 mg/kg vs tPA	**TNK 0.25 mg/kg vs tPA**
PRIMARY OUTCOME	The percentage of the perfusion lesion that was reperfused 24 hours as w… extent of clinical improvement at 24 hours, as measured by the change on the NIHSS score from before treatment to 24 hours after treatment. (TNK 0.25 > 0.1)	…s) functional outcome at 3 months measured with mRS.	Restoration of blood flow to greater than 50% of the involved territory or an absence of retrievable thrombus in the target vessel at the time of the initial angiographic assessment.	Restoration of blood flow to greater than 50% of the involved territory or an absence of retrievable intracranial thrombus.	Excellent (0–1 points) functional outcome at 3 months measured with mRS. Marge non inferiority 3%	Volume of the perfusion lesion on arrival at hospital, assessed by CT-perfusion imaging.	**Rankin score of 0 or 1 on the mRS at 90 days, up to 120 days after randomisation**
RESULTATS	Positive for primary outcome	Negative for primary outcome	Positive for primary outcome	No difference 0.4mg/kg and 0.25mg/kg	Negative for primary outcome Hight rate of HT, death and sICH with TNK Stopped early for safety reasons	Positive for primary outcome	**Positive for primary outcome Mage non inferiority -2,6%**
COMMENTS		17% stroke mimic				Mobile stroke unit	**Canadian**

Aucune différence
Taux hémorragie similaire

EXTEND-IA TNK

W ENGLAND
JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 26, 2018 VOL. 378

2018

Tenecteplase versus Alteplase before Thrombectomy for Ischemic Stroke

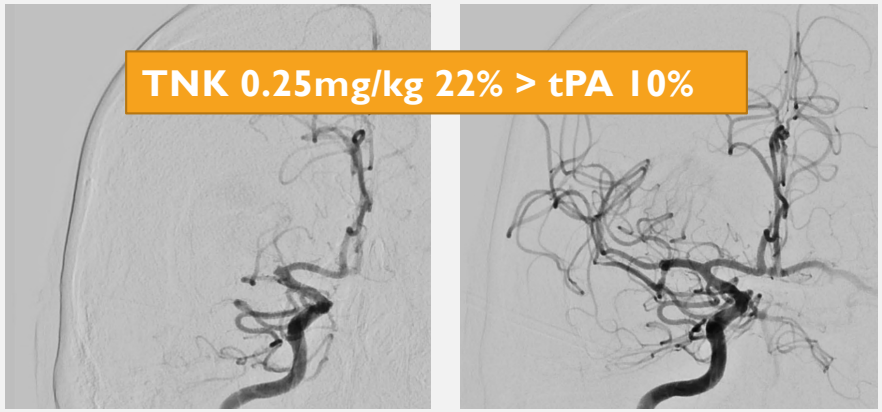
JAMA | Original Investigation

Effect of Intravenous Tenecteplase Dose on Cerebral Reperfusion Before Thrombectomy in Patients With Large Vessel Occlusion Ischemic Stroke
The EXTEND-IA TNK Part 2 Randomized Clinical Trial

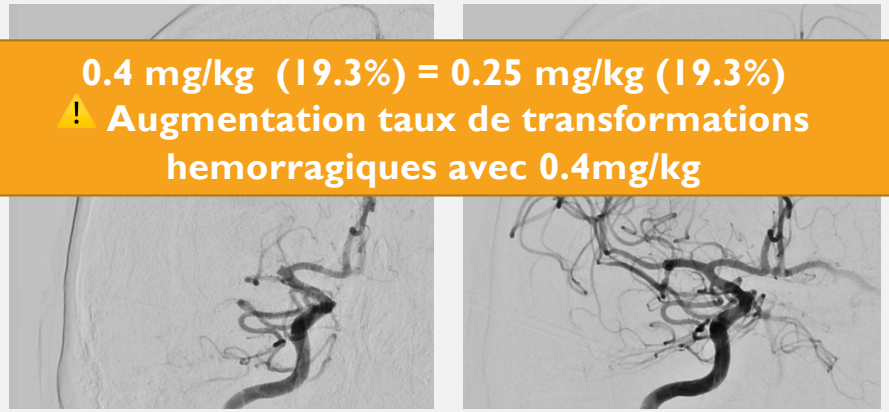
2020

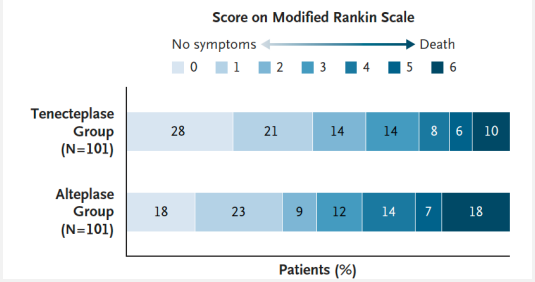
Critère de jugement principal: Restoration of blood flow to greater than 50% of the involved territory or an absence of retrievable thrombus in the target vessel at the time of the initial angiographic assessment.

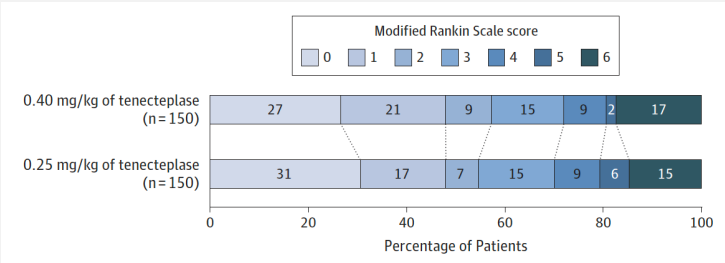
TNK 0.25mg/kg 22% > tPA 10%



0.4 mg/kg (19.3%) = 0.25 mg/kg (19.3%)
⚠ Augmentation taux de transformations hemorragiques avec 0.4mg/kg







TENECTEPLASE

	Parson et al (Australia) 2012	NORTEST 2017	EXTEND-IA TNK 2018	EXTEND IA TNK part 2 2020	NORTEST-2 part A 2022	TASTE A 2022	ACT 2022
STUDY DESIGN	Superiority	Superiority	Both	Both	Non inferiority	Superiority	**Non inferiority**
NBR PATIENTS	75 patients	1100 patients	204 patients	300 patients	216 patients	104 patients	**1600 patients**
DELAY	≤ 6 hours	≤ 4.5 hours or wake-up with mismatch criteria	≤ 4.5 hours	≤ 4.5 hours	≤ 4.5 hours	≤ 4.5 hours	≤ **4.5 hours**
THROMBOLYSE Product	TNK 0.1 or 0.25mg/kg vs tPA	TNK 0.4mg/kg vs tPA	TNK 0.25mg/kg vs tPA	TNK 0.4mg/kg vs TNK 0.25mg/kg	TNK 0.4mg/kg vs tPA	TNK 0.25 mg/kg vs tPA	**TNK 0.25 mg/kg vs tPA**
PRIMARY OUTCOME	The percentage of the perfusion lesion that was reperfused 24 hours after treatment, as assessed on perfusion-weighted MRI, and the extent of clinical improvement at 24 hours, as measured by the change on the NIHSS score from before treatment to 24 hours after treatment. (TNK 0.25 > 0.1)	Excellent (0–1 points) functional outcome at 3 months measured with mRS.	Restoration of blood flow to greater than 50% of the involved territory or an absence of retrievable thrombus in the target vessel at the time of the initial angiographic assessment.	Restoration of blood flow to greater than 50% of the involved territory or an absence of retrievable intracranial thrombus.	Excellent (0–1 points) functional outcome at 3 months measured with mRS. Marge non inferiority 3%	Volume of the perfusion lesion on arrival at hospital, assessed by CT-perfusion imaging.	**Rankin score of 0 or 1 on the mRS at 90 days, up to 120 days after randomisation**
RESULTATS	Positive for primary outcome	Negative for primary outcome	Positive for primary outcome	No difference 0.4mg/kg and 0.25mg/kg	Negative for primary outcome Hight rate of HT, death and sICH with TNK	Positive for primary outcome	**Positive for primary outcome** **Mage non inferiority -2,6%**
COMMENTS		17% stroke mimic			Stopped early for safety reasons	Mobile stroke unit	**Canadian**

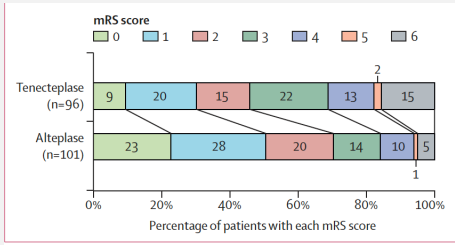
NORTEST 2 PART A

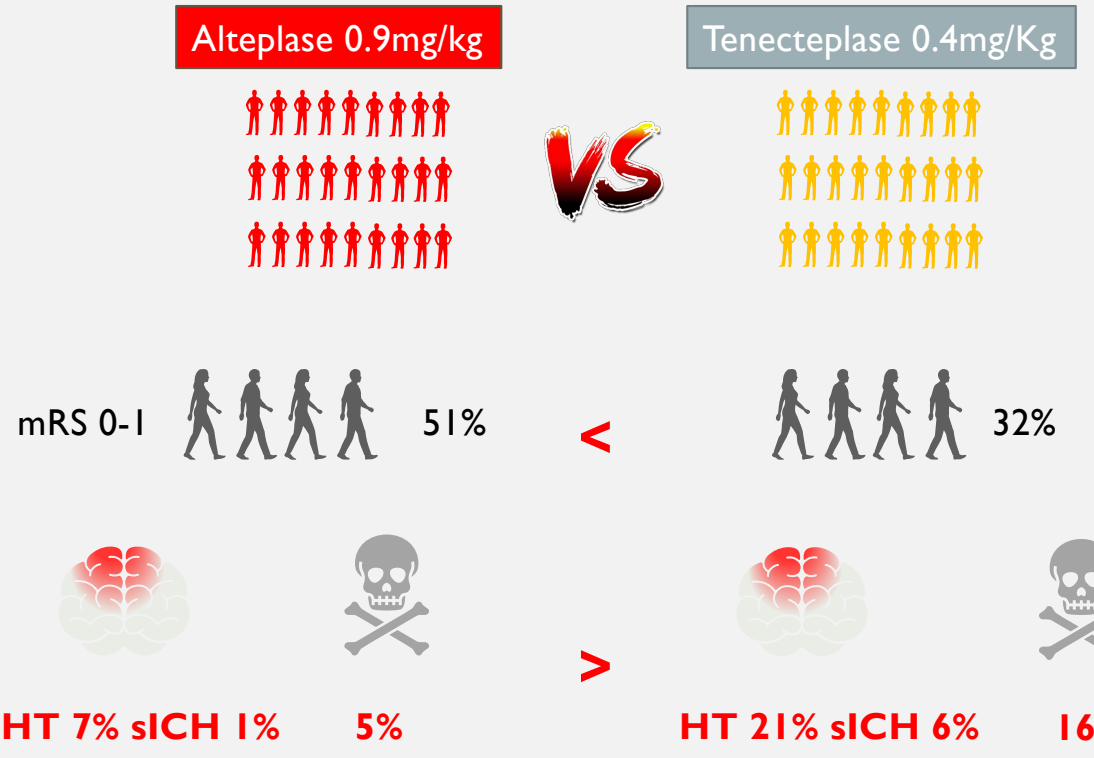
Tenecteplase versus alteplase for the management of acute ischaemic stroke in Norway (NOR-TEST 2, part A): a phase 3, randomised, open-label, blinded endpoint, non-inferiority trial

Christopher Elnan Kvistad, Halvor Næss, Bernt H Helleberg, Titto Idicula, Guri Hagberg, Linn Marie Nordby, Kristian N Jenssen, Håkon Tobro, Dag M Rörholt, Kamaljit Kaur, Agnethe Eltoft, Kristin Evensen, Judit Haasz, Guruparan Singaravel, Annette Fromm, Lars Thomassen

NORTEST 2017
1100 patients
≤ 4.5 hours or wake-up with mismatch criteria
TNK 0.4mg/kg vs tPA
Excellent (0–1 points) functional outcome at 3 months measured with mRS.
Negative for primary outcome
17% stroke mimic

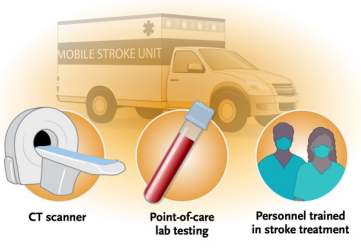
- Etude Norvégienne
- Inclusion de 216 patients
- NIHSS ≥ 6
- Non-infériorité
- mRS 0-1 à 3 mois

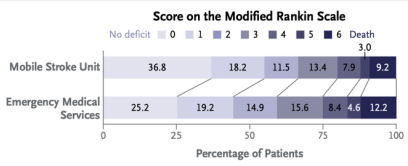




TASTE A

Mobile Stroke Unit (2021)



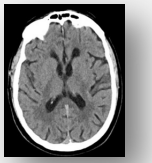


CONCLUSIONS
For patients with acute ischemic stroke deemed eligible for t-PA treatment, MSU care led to less disability at 90 days than standard EMS care.

Comparison of tenecteplase with alteplase for the early treatment of ischaemic stroke in the Melbourne Mobile Stroke Unit (TASTE-A): a phase 2, randomised, open-label trial

*Andrew Bivard, Henry Zhao, Leonid Churilov, Bruce C V Campbell, Skye Coote, Nawaf Yassi, Bernard Yan, Michael Valente, Angelos Sharobeam, Anna H Balabanski, Angela Dos Santos, Jo Lyn Ng, Vignan Yogendrakumar, Felix Ng, Francesca Langenberg, Damien Easton, Alex Warwick, Elizabeth Mackey, Amy MacDonald BN, Gagan Sharma, Michael Stephenson, Karen Smith, David Anderson, Philip Choi, Vincent Thijs, Henry Ma, Geoffrey C Cloud, Tissa Wijeratne, Liudmyla Olenko, Dominic Italiano, Stephen M Davis, Geoffrey A Donnan, Mark W Parsons, on behalf of the TASTE-A collaborators**

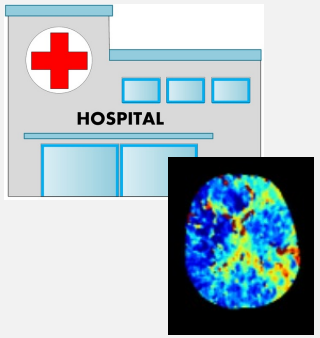
- Inclusion 104 patients
- Phase 2
- Supériorité
- Volume ischémique



Alteplase 0.9mg/kg

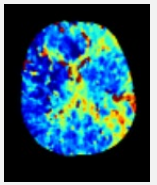
OU

Tenecteplase 0.25mg/Kg



Volume ischémique

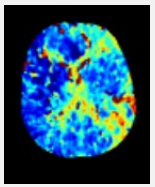
Alteplase



35mL

<

Tenecteplase



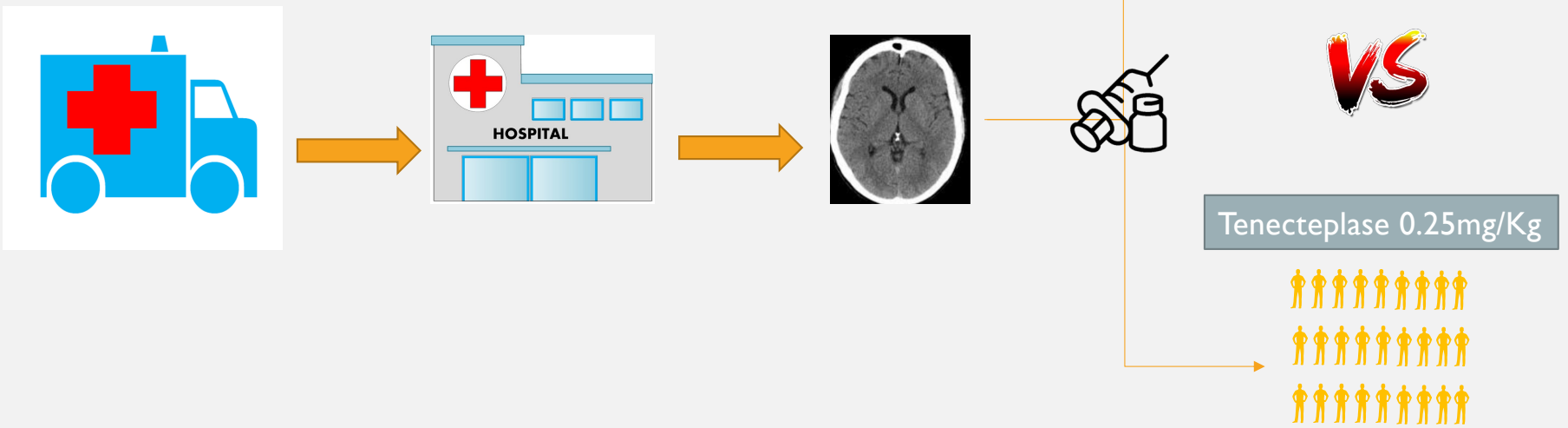
12mL

ACT

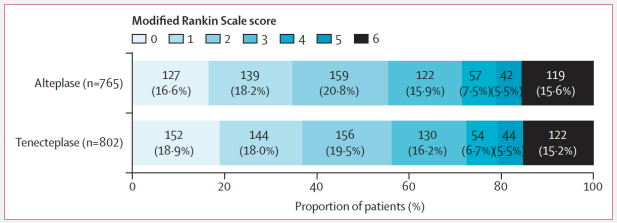
Intravenous tenecteplase compared with alteplase for acute ischaemic stroke in Canada (AcT): a pragmatic, multicentre, open-label, registry-linked, randomised, controlled, non-inferiority trial

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

- Etude Canadienne
- Inclusion de 1600 patients
- Non-infériorité
- Pragmatique


Alteplase 0.9mg/kg
HOSPITAL
VS
Tenecteplase 0.25mg/Kg

Proportion de mRS 0-1 à 90 jours, jusqu'à 120 jours après randomisation



Alteplase

VS

Tenecteplase

mRS 0-1

34.8%

=

36.9%

Hémorragie symtpomatique

3.4%

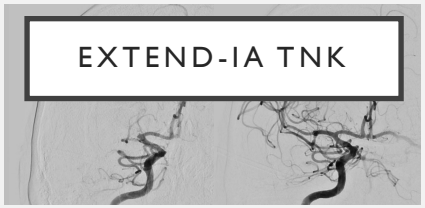
Mortalité

15.3%

=

3.2%

15.4%



2018 et 2020

Tenecteplase 0.25mg/kg vs Alteplase 0.9mg/kg
Amélioration du taux de recanalisation
Pas d'avantage du Tenecteplase 0.4mg/kg

+

NORTEST 2
PART A

2022

Tenecteplase 0.4mg/kg
Pas d'amélioration de l'outcome
Augmentation du risque hémorragique

-

2022

Tenecteplase 0.25mg/kg > Alteplase 0.9mg/kg
Réduction du volume ischémique
≤ 4h30 en pré-hospitalier

+

ACT
QuICR

2022

Tenecteplase 0.25mg/kg = Alteplase 0.9mg/kg

≤ 4h30

+

LA PLACE DU TENECTEPLASE DE NOS JOURS

Recommandations actuelles

RECOMMANDATIONS ACTUELLES

American Heart association 2019: TNK peut être envisagé chez les patients candidat pour un thrombectomie

1. It may be reasonable to choose tene… …0.25-mg/kg, maximum 25 mg) over IV alte… …traindications for IV fibrinolysis who are also… …ical thrombectomy.	IIb	B-R

European Guidelines 2021: TNK peut êt… envisagé chez les patients candidat … thrombectomie

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

Quality of evidence: **Low** ⊕⊕

Strength of recommendation: **Weak** ↑?

Canadian Gui… …18: Pas d'indication pour le tenect… …e dans la thrombolyse

ii. Intravenous alteplase is considered the standard of care and is currently the only approved thrombolytic agent for acute ischemic stroke treatment. There are other drugs being investigated; however, at this time are not approved for use in stroke patients.

AVANT LA PUBLICATION DE ACT et TASTE A


21:19
Général
Mise à jour logicielle
MÀJ automatiques
Oui
Recherche de mise à jour...

L’AVENIR

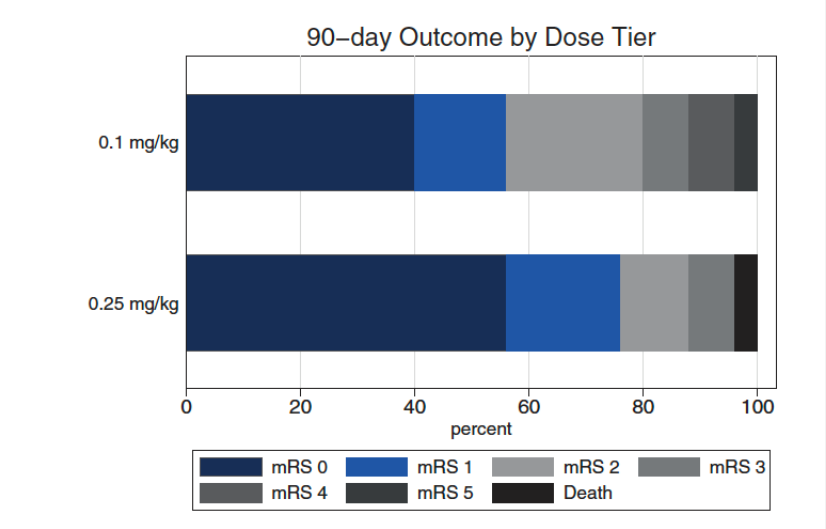
TENECTEPLASE VS ALTEPLASE

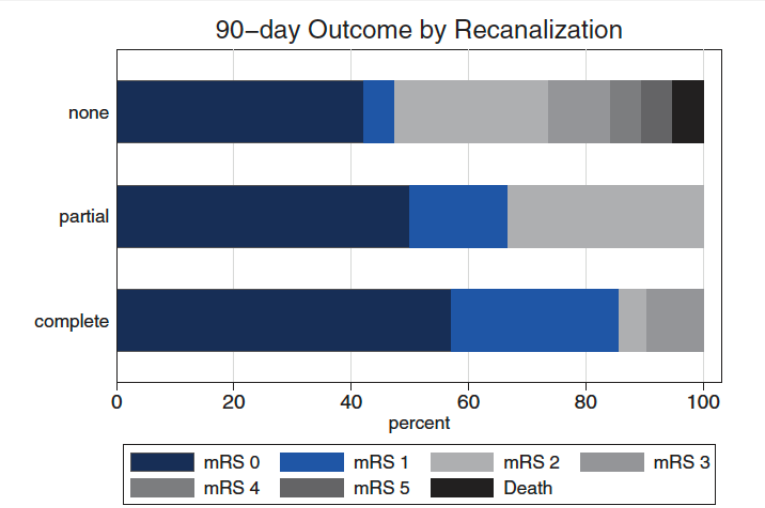
NORTEST 2 PART A	2022	Tenecteplase 0.4mg/kg Pas d'amélioration de l'outcome Augmentation du risque hémorragique	-

- **NORTEST 2 – Part B** :TNK 0.25mg/kg vs Alteplase 0.9mg/kg
  - Critère principale : taux d'indépendance à 3 mois
  - NIHSS ≥ 6
  - Etude de non-infériorité

THROMBOLYSES CHEZ LES AVCS MINEURES

- **TEMPO-1**: étude prospective non-randomisée de TNK pour patients avec AVC mineur (NIHSS ≤ 5 et preuve d'occlusion
  - Taux de récanalisation (52%) et d'indépendance (76%) élevés avec une seule hémorragie intracérébrale





THROMBOLYSES CHEZ LES AVCS MINEURES

- **TEMPO-2**: TNK contre ASA/Plavix pour patients avec AVC mineur et occlusion sur angioscan moins de 12h du début de symptômes
  - Critère de jugement: taux d'indépendance à 3 mois
  - Hypothèse : Taux élevé d'indépendance et risque acceptable d'hémorragie (2% vs. 1%)

UTILISATION DU TNK DANS DES HEURES ÉTENDUES

- **TIMELESS** : TNK contre traitement standard (Placebo) – 4h30 à 24 h début des symptômes avec occlusion sur angioscanner et scanner de perfusion favrable.
  - Critère de jugement: Taux d'indépendance à 3 mois

- **TWIST** : TNK contre traitement standard – wake-up stroke – sélection par scanner et angioscanner
  - Critère de jugement: Taux d'indépendance à 3 mois

CONCLUSION

- Alteplase versus Tenecteplase :
  - Affinité augmentée pour la fibrine
  - Demi-vie plus longue
- Après ACT :
  - Tenecteplase équivalent alteplase
- Avenir :
  - Tenecteplase 0.25mg/kg > Alteplase 0.9mg/kg ?
  - AVCs hors délai
  - AVCs mineures

MERCI DE VOTRE ATTENTION

cducroux@toh.ca

SSVQ Société des sciences vasculaires du Québec
Chef de file en santé vasculaire.

OTTAWA STROKE PROGRAM