ONLINE SUPPLEMENTAL DATA

Materials and Methods (supplementals)

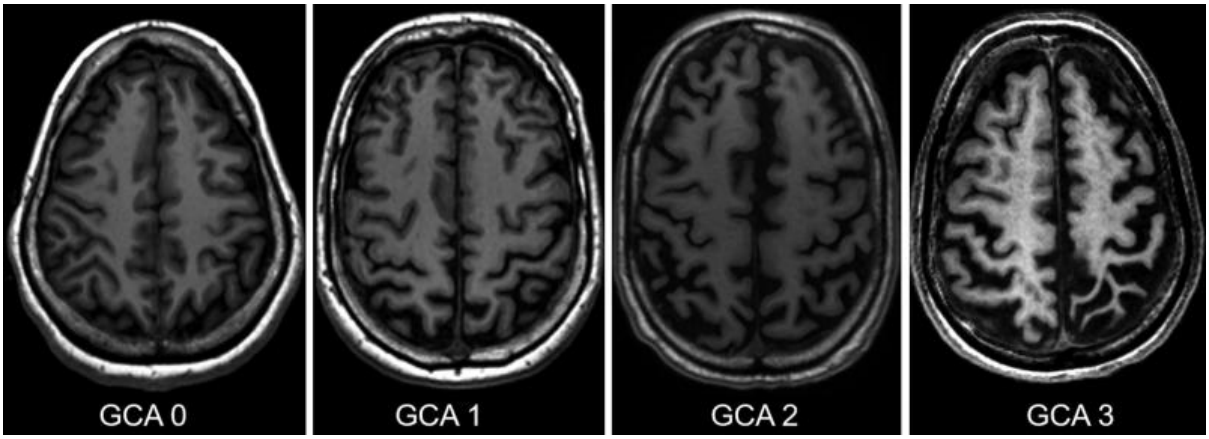
The ESCAPE-NA1 (Safety and Efficacy of Nerinetide [NA-1] in Subjects Undergoing Endovascular Thrombectomy for Stroke) trial is a multicenter, double-blind, randomized controlled trial that investigated the safety and efficacy of IV nerinetide in patients with acute ischemic stroke due to large vessel occlusion who were undergoing endovascular treatment. Informed consent was obtained from all participants or their legally authorized representatives. The ethics board at each participating center and the local regulatory authorities approved the study. Between March 1, 2017, and August 12, 2019, trial participants of ESCAPE-NA1 were enrolled and randomized to receive one 2.6 milligram per kilogram of body weight dose of IV nerinetide or a placebo in addition to best medical therapy, including IV alteplase if indicated. In brief, inclusion criteria were (1) age of 18 years or older, (2) baseline NIHSS >5, (3) functional independence before the index stroke (Barthel index score >90), and (4) time since last known well <12 hours. Imaging eligibility criteria included (1) large-vessel occlusion (intracranial internal carotid artery, M1 occlusion, or functional M1 occlusion [occlusion of both M2 branches]) on baseline CTA, (2) moderate-to-good collaterals (defined as filling ≥50% of the middle cerebral artery territory on multiphase CTA), and (3) an ASPECTS of ≥5 on baseline NCCT. Diagnostic criteria for the current study included: at least one appropriate plane (according to the scale used: axial for the GCA scale, coronal for the MTA and at least sagittal for the Koedam scale) and no important artefacts disturbing interpretation abilities of the reader (e.g., motion or beam hardening).

eTable E1. Imaging core laboratory members.

Name	**Subspecialty**	**Stroke imaging experience, years**	**Role in the core lab**
FaBe	Neuroradiology (diagnostic)	4	Cortical atrophy, subcortical atrophy and WMD burden assessments
FB	Neuroradiology (diagnostic & interventional)	7	Cortical atrophy, subcortical atrophy and WMD burden assessments
JF	Stroke neurology	7	Cortical atrophy, subcortical atrophy and WMD burden assessments
NS	Stroke neurology	7	Cortical atrophy, subcortical atrophy and WMD burden assessments
AG	Stroke neurology	10	Cortical atrophy, subcortical atrophy and WMD burden assessments *

* In case of ≥ 2 grade disagreements.

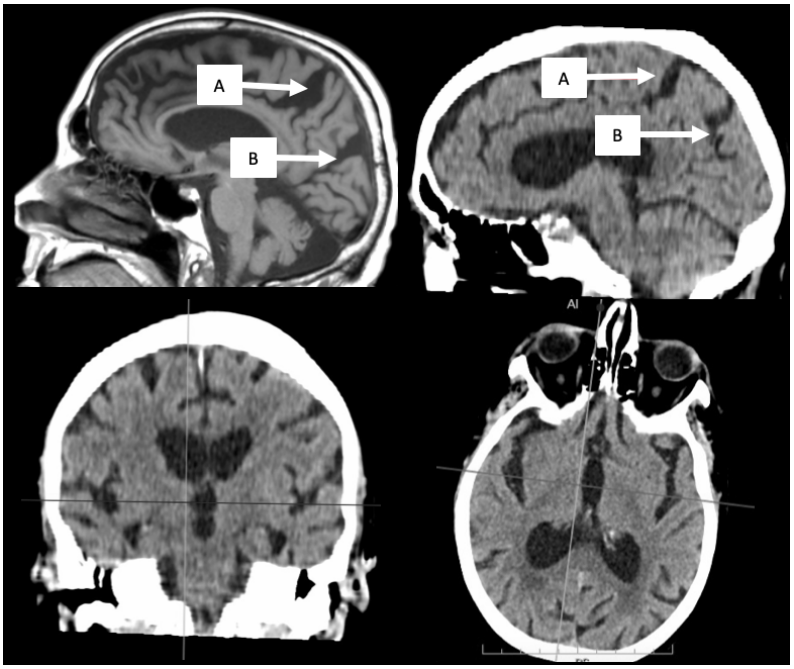
eFigure 1a. Global cortical atrophy (GCA) assessment: the GCA score.



Axial MRI images show each GCA score. The score is based on the width of the sulci and the volume of the gyri. Score 0 (no atrophy): no widening of the sulci, score 1 (mild atrophy): mild widening of the sulci, score 2 (moderate atrophy): widening of the sulci and some volume loss of the gyri, score 3 (severe atrophy): extensive knife-blade volume loss of the gyri.

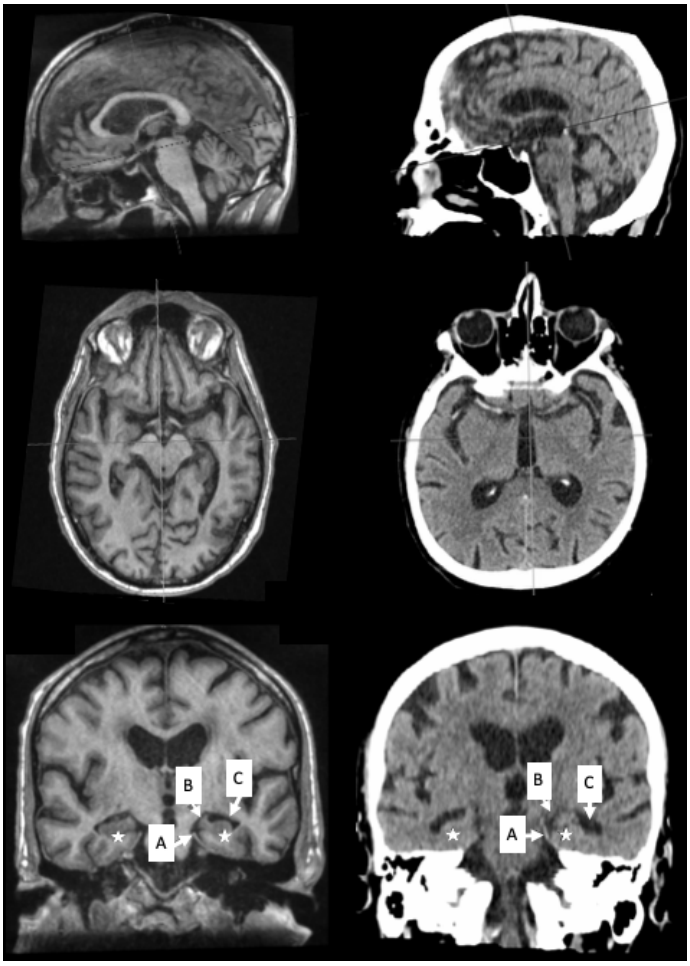
Reference: Vernooij MW, van Buchem MA. Neuroimaging in Dementia. 2020 Feb 15. In: Hodler J, Kubik-Huch RA, von Schulthess GK, editors. Diseases of the Brain, Head and Neck, Spine 2020–2023: Diagnostic Imaging [34]. Cham (CH): Springer; 2020. Fig. 11.3, [Global cortical atrophy scale. Illustration...]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK554327/figure/ch11.Fig3/doi: 10.1007/978-3-030-38490-6_11

eFigure 1b. Assessment of parietal lobe atrophy: the Koedam score.



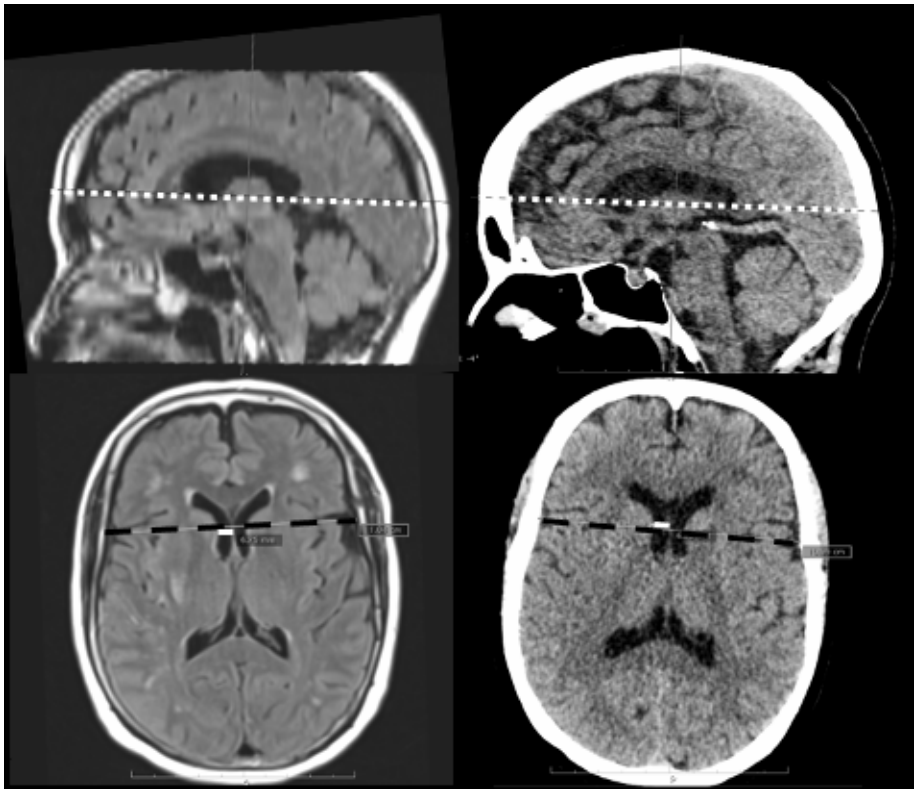
Sagittal (top right), coronal (bottom left), and axial (bottom right) planes of NCCT; and sagittal plane of MRI (bottom right) show the assessment of parietal lobe atrophy. Three dimensional MPR is used to assure the optimal sagittal slice for evaluating parietal lobe atrophy. Note: other orientations (i.e., coronal and axial) can also be used. In case of different scores with different orientations, the maximal score is annotated. This grading system is based on the width of the posterior cingulate (A) and the width of the parieto-occipital sulcus (B).

eFigure 1c. Assessment of hippocampal atrophy: the medial temporal atrophy (MTA) score.



Sagittal plane (top), axial plane (middle) and coronal plane (bottom) of MRI (left column) and NCCT (right column) show the assessment of hippocampal atrophy. Three dimensional multiplanar reconstruction (3D MPR) is used to select a consistent slice at the level of the anterior pons, involving the corpus of the hippocampus. The MTA grading system is based on the width of the choroid fissure (B), the width of the temporal horn (C) and the volume of the hippocampus (star). Further key anatomic landmarks on the coronal plane are the parahippocampal gyrus, along with the ambient cistern (A). In case of severe asymmetry (i.e., ≥ 2 points difference between left and right), the most severe affected side was scored.

eFigure 1d. Measurement of the hemi-intercaudate distance (h-ICD) and inner table width.



MRI (left) and NCCT (right) show the measurement of h-ICD. Measurements are done with multiplanar reconstruction, to assure an accurate anterior-posterior commissural line (white dot line) seen in sagittal views (top). Measurements of the h-ICD are performed on the contralateral side to the AIS to account for any ischemic areas or hemorrhages associated with potential edema. To determine the h-ICD, the distance between the septum pellucidum and the caudate head is measured (white line). The h-ICD is multiplied by 2 to obtain the intercaudate distance. The inner table width is measured on the same axial plane (black dash line). The intercaudate distance to inner table width ratio is calculated by dividing intercaudate distance by inner table width.

eTable E2: Agreements between assessments on NCCT vs MRI for regional cortical atrophy for standard scale and binary scale (no vs. any atrophy), n = 558

	NCCT	**MRI**	**Gwet's AC1**
Frontal*	0 (0-2)	0 (0-3)	0.835
Frontal ≥1, n (%)	128 (22.9)	225 (40.3)	0.536
Temporal*	0 (0-2)	0 (0-3)	0.850
Temporal ≥1, n (%)	99 (17.7)	189 (33.9)	0.611
Occipital*	0 (0-3)	0 (0-3)	0.895
Occipital ≥1, n (%)	84 (15.1)	142 (25.5)	0.714

*Median (min-max), full categorical scale is provided. Linear-weighted Gwet's AC1.

All p-values are <0.001.