

Original research

Thrombus imaging characteristics within acute ischemic stroke: similarities and interdependence

Nerea Arrarte Terreros , , , , Agnetha AE Bruggeman , , Manon Kappelhof , , , , Manon L Tolhuisen , , , , Josje Brouwer , , Jan W Hoving , , , , Praneeta R Konduri, , Katinka R van Kranendonk, Bruna G Dutra, , , Heitor CBR Alves , , , , Diederik WJ Dippel , , Wim H van Zwam , , , Ludo FM Beenen, Lonneke SF Yo, Ed van Bavel, Charles BLM Majoie, , Henk A Marquering, , MR CLEAN Registry Investigators

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For numbered affiliations see end of article.

Correspondence to

Nerea Arrarte Terreros, Department of Biomedical Engineering and Physics, Amsterdam UMC, location University of Amsterdam, Amsterdam, The Netherlands; n. arrarteterreros@amsterdamumc.nl

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ABSTRACT

Background The effects of thrombus imaging characteristics on procedural and clinical outcomes after ischemic stroke are increasingly being studied. These thrombus characteristics — for eg, size, location, and density — are commonly analyzed as separate entities. However, it is known that some of these thrombus characteristics are strongly related. Multicollinearity can lead to unreliable prediction models. We aimed to determine the distribution, correlation and clustering of thrombus imaging characteristics based on a large dataset of anterior-circulation acute ischemic stroke patients.

Methods We measured thrombus imaging characteristics in the MR CLEAN Registry dataset, which included occlusion location, distance from the intracranial carotid artery to the thrombus (DT), thrombus length, density, perviousness, and clot burden score (CBS). We assessed intercorrelations with Spearman's coefficient (ρ) and grouped thrombi based on 1) occlusion location and 2) thrombus length, density and perviousness using unsupervised clustering.

Results We included 934 patients, of which 22% had an internal carotid artery (ICA) occlusion, 61% M1, 16% M2, and 1% another occlusion location. All thrombus characteristics were significantly correlated. Higher CBS was strongly correlated with longer DT (ρ =0.67, p<0.01), and moderately correlated with shorter thrombus length (ρ =-0.41, p<0.01). In more proximal occlusion locations, thrombi were significantly longer, denser, and less pervious. Unsupervised clustering analysis resulted in four thrombus groups; however, the cohesion within and distinction between the groups were weak.

Conclusions Thrombus imaging characteristics are significantly intercorrelated – strong correlations should be considered in future predictive modeling studies. Clustering analysis showed there are no distinct thrombus archetypes – novel treatments should consider this thrombus variability.

INTRODUCTION

Multiple thrombus characteristics are increasingly being studied for their effects on procedural and clinical outcomes after ischemic stroke.¹⁻³

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Collinearity of thrombus imaging characteristics in predictive models of acute ischemic stroke is commonly disregarded.

WHAT THIS STUDY ADDS

⇒ We presented distributions, intercorrelations and clustering analysis of thrombus imaging characteristics measured in 937 acute ischemic stroke patients. Thrombus imaging characteristics are significantly intercorrelated, but there are no distinct thrombus archetypes.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Strong correlations between thrombus characteristics should be considered in future predictive models in acute ischemic stroke. The continuous spectrum and specific variability of thrombus characteristics need to be addressed when developing novel treatment approaches.

Currently, the most straightforward way to assess the thrombus is via radiological imaging, mostly computed tomography (CT), since it is part of the standard-of-care diagnostic workup for stroke.⁴ Thrombus imaging characteristics can provide information on the size and (micro)structure of the thrombus, which may be useful to improve and optimize treatment.

After administration of intravenous thrombolysis with alteplase (IVT), the lysis process of the clot can be influenced by the permeability⁵ and size of the thrombus. Thrombus density, which has been associated with thrombus histology and etiology, can also affect the chance of recanalization success after IVT. In addition, thrombus density may suggest the use of specific endovascular treatment (EVT) strategies. The optimal size and positioning of the EVT stent-retriever is dependent on thrombus length, and EVT success can be affected by thrombus volume.

As such, there is a whole spectrum of thrombus imaging characteristics influencing treatment, and these characteristics are not independent from



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each another. Including multicollinearity in prediction models reduces their statistical significance and should therefore be accounted for. Moreover, in case of strong correlations, there is no added value in measuring all parameters and a reduced number of thrombus measures may be sufficient.

Thrombi are commonly classified by occlusion location, etiology, and/or histopathology.3 Currently, occlusion location is the only thrombus characteristic that is used for treatment selection. However, the occlusion location does not account for the biomechanical characteristics of the clot, which actually may have a larger effect on treatment response and chance of successful revascularization. Alternatively, thrombi are also classified based on stroke etiology as eg, cardioembolic, atherosclerotic or cryptogenic, according to the TOAST criteria. 15 With different thrombus origins, it could be expected that thrombi show distinct (imaging) features as part of typical thrombus archetypes. Clustering techniques allow for grouping of thrombus characteristics, and therefore, may determine interrelated imaging characteristics that distinguish typical groups of thrombi. Certain sets of thrombus characteristics may be associated with a better response to specific (combinations of) treatments, such as IVT with alteplase or tenecteplase, or specific EVT techniques/devices. For example, thrombolysis was shown to be successful in small, distal, pervious thrombi, whereas its beneficial effect is being debated for large, proximal, impermeable thrombi.

In this study, we present a detailed analysis of interrelations of thrombus imaging characteristics on a large data set of EVT-treated acute ischemic stroke patients. Specifically, we aim to provide information on the distribution and correlation of thrombus imaging characteristics and to study whether thrombi can be grouped based on their imaging characteristics.

METHODS

Patient selection

We included patients from the MR CLEAN Registry, a multicenter prospective observational registry of all patients undergoing EVT for acute ischemic stroke in the Netherlands. ¹⁶ This registry was approved by the central medical ethics committee of the Erasmus Medical Center Rotterdam, which served as the review board of all participating centers and granted permission to carry out the study as a registry (MEC-2014–235). All patients or legal representatives were provided with oral and written information on the registry and had the opportunity to withdraw consent to use their data.

We included acute ischemic stroke patients aged 18 or older, with an anterior circulation occlusion who underwent EVT (defined as groin puncture with the intent of thrombectomy) less than 390 minutes after stroke onset between March 2014 and November 2017. Patients without contraindications received 0.9 mg/kg of intravenous alteplase before EVT. The EVT approach and choice of material was left to the individual interventionalist. All patients underwent a standardized stroke imaging protocol at baseline, consisting of baseline non-contrast computed tomography (NCCT) followed by single arterialphase computed tomography angiography (CTA). Other imaging modalities, such as CT perfusion, were acquired at the discretion of the treating physician. Patients with thick-slice (>2.5 mm) CT imaging, and with NCCT and CTA images not acquired within 30 minutes from each other were excluded. Source data for this study are not available as we did not obtain patient approval for sharing individual, coded patient data. All analytic methods,

codes, and results are available from the corresponding author on reasonable request.

Data collection

The thin-slice NCCT and CTA images were acquired in GE Medical Systems, Philips, Siemens, or Toshiba scanners with a median tube peak voltage of 100 (100-120) kV for CTA, and 120 (100-120) kV for NCCT. The median exposure was 156 (73-221) mA·s for CTA and 301 (240-394) mA·s for NCCT. All details on the image acquisition parameters and protocols can be found in online supplemental table S1.

The MR CLEAN Registry imaging core laboratory consisting of 31 interventional neuroradiologists (with at least 5 years of experience assessing CTA scans in routine clinical practice) assessed the occlusion location and the clot burden score (CBS) based on the contrast-filling defects found on baseline CTA. The CBS is a 10-point scale assessing the extension of the occlusion: the 10 points are divided between vessel segments in the anterior circulation, and for each occluded segment the corresponding points are deducted from 10. ¹⁶ Therefore, more occlusive thrombi have lower CBS. Core-lab members were blinded to all clinical information (demographic, treatment and outcome data) except symptom side. ¹⁶ Each rater assessed a subset of the total number of cases following the provided training and guidelines.

We additionally measured the following radiological thrombus characteristics: distance from the internal carotid artery (ICA) terminus to the thrombus (DT), thrombus length, thrombus density, and thrombus perviousness. Thrombus measurements of patients included between March 2014 and June 2016 were already available. For patients included between June 2016 and November 2017, additional measurements were performed similar to Bruna et al. These measurements were performed by trained observers (AAEB, JB, JWH, KRK, MK, MLT, NA, NAT, NB, and PRK) who were blinded to all clinical information except symptom side. Each observer was assigned a unique subset of the total number of cases. To ensure consistency and homogeneity across the measurements, the observers received training and guidelines to place the markers, including definitions of each vessel segment and a scheme similar to the one shown in figure 1A,B. Difficult cases (such as bifurcated or very long thrombi and cases without distal collateral filling) were marked and discussed among the group of observers. If the marker-placement remained unclear, the case was reviewed by a senior radiologist.

For these measurements, the thin-slice NCCT and CTA images were corregistered using Elastix' rigid-registration. ¹⁷ Scans with uncorrectable registration errors, imaging artifacts (eg, beam hardening, metal artifacts), excessive noise, poor CTA contrast opacification, or an incomplete field of view were excluded. Partial occlusions (thrombi occluding 50% of the vessel diameter), bilateral thrombi, too short thrombi (<2 mm), thrombi very close to bone (affected by partial volume/blooming artifact of bone), and/or calcified emboli were also excluded. ¹

For each occlusion, we placed up to nine markers along the occluded artery: one marker defining the ICA-terminus, up to three markers along the vessel segment between the ICA-terminus and the proximal thrombus border, two markers defining the thrombus' proximal and distal borders, and three markers in the proximal, middle, and distal parts of the thrombus (figure 1). These markers were simultaneously placed on the corregistered NCCT and CTA scans using ITK-snap software. We used three views (axial, sagittal, and coronal) for the marker placement. The occlusion extension was determined based on the contrast-filling

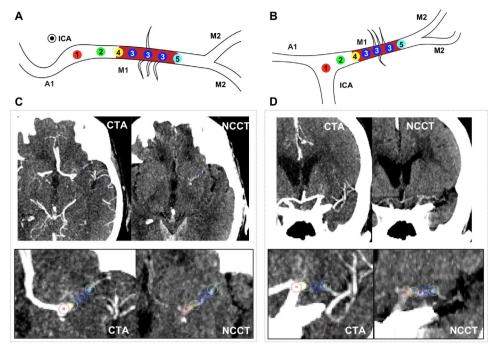


Figure 1 Thrombus markers. A) Schematic overview of thrombus marker placement, axial view. (B) Schematic overview of thrombus marker placement, coronal view. (C) Axial view of CTA and NCCT scans showing a left-MCA occlusion and placed markers. To visualize the markers, a zoomin of the occlusion is displayed and the markers are circled in their corresponding color in the image in the lower row. These circles do not represent the 1 mm radius spherical regions of interest used to compute density and perviousness. (D) Coronal view of the CTA and NCCT scans displayed in C showing a left-MCA occlusion and placed markers. A closer view of the occlusion is displayed in the image in the lower row, with the markers circled in their corresponding color. A1, anterior cerebral artery A1 segment; CTA, computed tomography angiography; ICA, internal carotid artery; M1, middle cerebral artery M1 segment; M2, middle cerebral artery; M2, middle cerebral artery; NCCT, non-contrast computed tomography.

defects found on CTA, and aided by the NCCT hyperdense artery sign if present. Because of NCCT was performed before CTA, hyperdensities are expected to come from the thrombus rather than residual contrast.

DT was computed as the total path length between the ICA-terminus and the proximal thrombus border marker. DT is thereby a measure of thrombus distality with respect to the ICA-terminus. If the proximal part of the thrombus was located proximal to the ICA-terminus, DT was set to zero. Thrombus length was computed as the total path length between the proximal and distal thrombus border markers. The three in-thrombus markers were used to define 1 mm radius spherical regions of interest, which were used to compute the average thrombus density and perviousness values, as described previously. \(^1\)

Statistical analyses

Our analysis includes three main sections: summary statistics which describes the methods to present characteristic distributions, correlation analyses to assess the collinearity of these characteristics, and clustering of thrombus imaging characteristics to determine whether typical thrombus archetypes with distinct imaging features can be found. We used Python's statistics library for the statistical analysis, Seaborn library for data visualizations and scikit-learn library for clustering analysis. We set the significance level for all analyses at p<0.05.

Summary statistics

For numerical variables, we presented summary statistics as median and interquartile range (IQR). For categorical variables, we presented summary statistics as frequencies and percentages. Baseline characteristics were compared between the currently included patient sample and the overall MR CLEAN Registry

population. For between-group comparisons, the Kruskal-Wallis and/or Mann-Whitney-U tests were used to compare medians, and χ^2 tests to compare frequencies. Post-hoc analyses were adjusted with Bonferroni corrections for multiple testing.

Correlation analyses

We included the following variables in our correlation analysis: DT, thrombus length, thrombus density, thrombus perviousness, and CBS. We generated bivariate scatterplots and computed the correlation using the pairwise Spearman's correlation coefficient, ρ , for all occlusion locations. We evaluated the correlation strength as follows: $0.10 \le |\rho| < 0.40$, weak correlation; $0.40 \le |\rho| < 0.60$, moderate correlation; $|\rho| \ge 0.60$, strong correlation. In addition, we built pairwise linear regressions to further assess the association and variability between the variables. Although a smooth polynomial relationship like LOESS would be more appropriate to further assess the association and trend of the correlated variables, linear regressions provide simple models to explore the spectrum of thrombus characteristics. These analyses were performed for all thrombi combined and also per occlusion location (ICA, M1, and M2).

Clustering analysis

We used a classical, widely-used, unsupervised learning algorithm to perform the clustering: Hartigan-Wong k-means unsupervised clustering. For n number of features and k cluster centroids, this method aims to minimize the Euclidean distance between each point in the n-dimensional space and its closest cluster centroid k_p , that is, to minimize the sum of the squared error (SSE). The following thrombus characteristics were used as features: thrombus length, density, and perviousness. All variables were standardized (transformed to a mean of 0 and a standard

deviation of 1), such that their weights evenly contribute. We selected the optimal number of clusters based on three complementary techniques: the elbow method, the calculation of the silhouette coefficient, and the calculation of the Davies-Bouldin coefficient.²⁰ For the elbow method, we computed the SSE for each cluster to find the optimal k value. By definition, the SSE decreases with an increasing number of clusters. The elbowpoint indicates the optimal trade-off between the SSE and the number of clusters, and is found where the decrease in the SSE becomes linear. The silhouette coefficient is a measure of cohesion within a cluster and separation between the clusters, and ranges between -1 and 1. The higher the silhouette coefficient, the better the cohesion within the clusters and better separation from the other groups. The Davies-Bouldin coefficient is also a measure of intra-cluster similarity and inter-cluster difference. It is computed as the average ratio between within-cluster and between-cluster distances, and therefore, smaller Davies-Bouldin values indicate better clusters. For each k, we ran the algorithm for 1000 iterations with 100 different initial configurations of the cluster centroids.

Online supplemental table 2 includes definitions of association, correlation, collinearity and unsupervised clustering for additional information.

RESULTS

Our study population consisted of 934 out of3637 patients from the MR CLEAN Registry (online supplemental figure S1). Included patients had a median age of 72 (IQR 62–80) years. Median National Institutes of Health Stroke Scale (NIHSS) score at baseline was 15 (IQR 11–20). Baseline characteristics of our study cohort and the full MR CLEAN Registry cohort can be found in online supplemental table S3. Patients in our study were more often presented directly to an EVT-capable center (ie, no interhospital transfer), and correspondingly their median onset to groin puncture time was slightly shorter (188 [IQR 139–246] min vs 195 [IQR 150–260] min, p<0.01). NIHSS scores at 24–48 hours were lower in our study population (9 [IQR 3–16] vs 10 [IQR 4–17], p=0.02) compared with the full MR CLEAN Registry cohort.

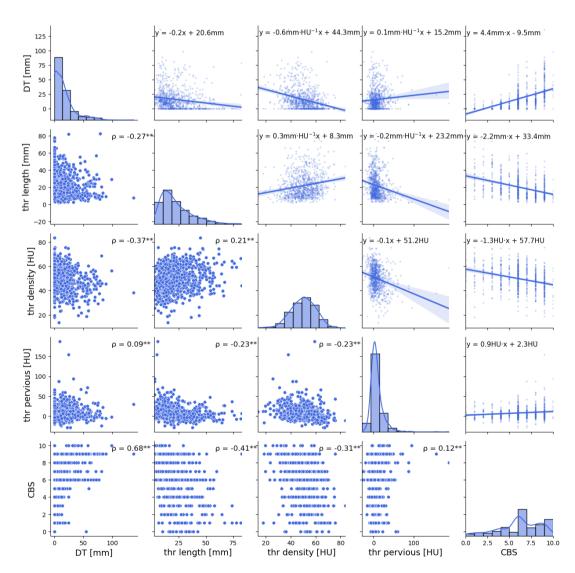


Figure 2 Thrombus imaging characteristics. The diagonal shows the histograms of DT, thrombus length, density, perviousness and CBS. The graphs below the diagonal show bivariate scatter plots, Spearman's correlation coefficient (ρ) and significance level of the correlation, where ** means p<0.01. The plots above the diagonal show bivariate scatter plots with a linear fit. CBS, clot burden score; DT, distance from the internal carotid artery terminus to the thrombus; HU, Hounsfield units; mm, millimeters; thr, thrombus.

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Table 1 Thrombus imaging characteristics per occlusion location (ICA, M1, and M2).

Thrombus imaging characteristics, median (IQR)	ICA, n=202	M1, n=566	M2, n=148	p-value
DT (mm)	0 (0–0)	12 (6–18)	30 (22–55)	<0.01
Thrombus length $^{\alpha}$ (mm)	26 (17–43)	18 (12–27)	12 (9–22)	<0.01
Thrombus density (HU)	55 (49–61)	50 (44–57)	44 (38–50)	<0.01
Thrombus perviousness (HU)	3 (-3–12)	5 (-2–12)	6 (-1–18)	0.02
CBS ^β	3 (1–4)	6 (6–7)	9 (9–9)	<0.01

Missing values: $^{\alpha}1,^{\beta}191$.

CBS, clot burden score; DT, distance from ICA-terminus to the thrombus; HU, Hounsfield units; ICA, internal carotid artery; IQR, interquartile range; M1, middle cerebral artery M1 segment; M2, middle cerebral artery M2 segment; mm, millimeters

Summary statistics of the thrombus imaging characteristics can be found in online supplemental table S4. The most common occlusion location was the M1 segment (61%), followed by the ICA (22%), and the M2 (16%). The distributions and correlations of thrombus imaging characteristics are visualized in figure 2 and online supplemental table S5. We found that higher CBS was strongly correlated with longer DT (ρ =0.68, ρ <0.01), and moderately correlated with shorter thrombus length (ρ =-0.41, ρ <0.01). These correlations are individually visualized in online supplemental figure S2. The other correlations, although statistically significant, were weak ($|\rho|$ <0.40).

Subgroup analysis: occlusion location

A between-group comparison of the thrombus characteristics per occlusion location can be found in table 1. Thrombus characteristics significantly differed per occlusion location. Thrombi located in the ICA were longer, denser, and less pervious compared with M1 and M2 thrombi. Similarly, M1 thrombi were longer, denser, and less pervious compared with M2 thrombi. More details on the significance level of pairwise comparisons can be found in online supplemental table S6.

Similar to figure 2, the distribution and correlations of these characteristics, color-coded by occlusion location, can be found in online supplemental figure S3 and online supplemental table S7. All found correlations were weak ($|\rho|$ < 0.40).

Clustering analysis

Both the elbow method and silhouette coefficients indicated that the optimal number of clusters lay around 4 and 6 (figure 3A,B). The low silhouette coefficients, with values all under 0.30, indicate that the clusters cannot be clearly discerned. Davies-Bouldin coefficients indicated that the optimal number of clusters was in the range of 4–10, with two local minima at k=6 and k=9 (figure 3C). Based on the three methods, we chose to continue our analysis with four clusters. A 3D visualization of the thrombus features of the four clusters is displayed in figure 3D, next to a similar visualization clustered by occlusion location (figure 3E). The cluster centroids can be found in online supplemental table S8. The distribution characteristics for each cluster are also summarized in online supplemental table S8. Cluster 2 consists of longer, denser, and less pervious thrombi, while cluster four includes shorter and less dense thrombi, with higher

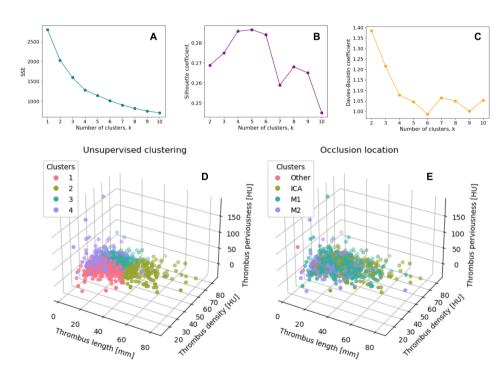


Figure 3 Finding the optimal number of clusters. (A)SSE as a function of the number of clusters. The elbow point is found around 4–6, after which the decrease in SSE becomes linear. (B) Silhouette coefficients as a function of the number of clusters. The highest (and therefore, preferred) silhouette coefficients are found around 4–6. (C) Davies-Bouldin coefficients as a function of the number of clusters. Lower coefficients indicate better clustering. From k=4 onwards, Davies-Bouldin coefficients showed similar values, with two local minima at k=6 and k=9. (D) 3D visualization of thrombus imaging features clustered by 4-means unsupervised clustering. (E) 3D visualization of thrombus imaging features clustered by occlusion location. SSE, sum of the squared error.

perviousness values. Cluster 1 and 3 reflect a mixture of both: shorter thrombi, less pervious, with lower and higher densities, respectively.

DISCUSSION

In our analysis of thrombus imaging characteristics in EVT-treated acute ischemic stroke patients, we found that all assessed thrombus imaging characteristics were significantly intercorrelated. Higher CBS was strongly correlated with longer DT and was moderately correlated with shorter thrombus length. These correlations became weak when stratifying per occlusion location. Longer, denser, and less pervious thrombi were mostly found in more proximal occlusion locations. Our clustering analysis suggests that thrombus imaging characteristics form a continuum, and that no typical thrombus types can be identified similar to the TOAST classification.

To our knowledge, this is the largest dataset of thrombus imaging characteristics of acute ischemic stroke patients. Previous studies have focused on the association of thrombus imaging characteristics with treatment and patient outcome, and have partially assessed associations between thrombus characteristics.²¹ Other studies have related thrombus imaging characteristics to their histopathology, ²² etiology, ²³ and biomechanical characteristics. 24 The statistical models used to study these associations between thrombus characteristics and outcomes do not commonly account for the collinearity between these characteristics. This collinearity can lead to unreliable or unrepresentative model results, or a reduction in statistical significance. In a multivariable regression, collinearity hinders the relationship of the independent variable with the dependent one, since the independent variables change simultaneously. This implies that, although the overall predictions are unaffected, the regression coefficients, corresponding standard errors and significance can be 'wrongly' estimated.²⁵ Moreover, in case of collinearity, the predictive value can be assigned to one of the parameters whereas the relation with outcome could also be affected by another collinear parameter.

Although the results of our study do not imply a direct change in current clinical practice, they illustrate the importance of studying collinearity when building predictive models – which are used to draw conclusions of treatment effects and outcomes consequence of current clinical practice.

In our study, we found that the correlations between most thrombus characteristics are significant but weak. This means there is still a large variety of other thrombus characteristics that are given a single thrombus variable. This was also reflected in our clustering analysis. When clustering by occlusion location, we found that even if the distributions of length, density, and perviousness significantly differed between the groups, some overlap still existed. With unsupervised clustering, thrombi were classified based on their length, density and perviousness. However, we did not observe clearly distinct thrombus archetypes, but rather found that thrombus imaging characteristics form a continuum which hinders their clustering.

In current clinical practice, occlusion location (among other baseline characteristics) determines EVT eligibility. Stroke guidelines indicate that patients with proximal occlusions are eligible for EVT,⁴ whereas the eligibility of (more distal) medium vessel occlusion stroke is currently being researched. The definition of, eg, M1, M2, and M3 segments can be challenging and highly dependent on the observer.²⁶ DT better defines the distality of the occlusion.²⁷ However, DT does not take anatomical landmarks such as bifurcations into account (which are used to determine occlusion location) and can be critical for the chance of

EVT success. In our results, we saw that for the same DT, the patient could either have an M1 or M2 occlusion. Unfortunately, the number of M3 occlusions in our database was insufficient to further study this relation.

We found that thrombus imaging characteristics significantly differ per occlusion location and that some of these characteristics are moderately and strongly correlated with CBS. Currently, the manual assessment of thrombus characteristics is time-consuming and requires thin-slice CT imaging. On the other hand, assessment of occlusion location and CBS is commonly done in clinical practice/studies, is less time-consuming than manual thrombus measurements, and does not require thin-slice images. Correlations between occlusion-location/CBS and DT/length/density/perviousness offer the possibility of uncomplicated characterization of the thrombus, which could ultimately lead to a reduction of time-consuming assessments. With the enhanced development of automated measurements and thrombus segmentations, quantitative characterization of the thrombus might be optimized.

Finally, in-silico models that simulate stroke onset, treatment, and outcome require, among others, an accurate and quantitative representation of the thrombus.²⁹ Combining thrombus imaging, histological and biomechanical properties can help to capture the whole spectrum of thrombus characteristics needed for such in-silico modeling. Once the correlations between these characteristics are well-established, typical thrombi can be sampled from such distributions and can be used to study treatment success in different scenarios. Our study contributes to the quantification of such correlations.

Limitations

Our study had some limitations. We only included patients with available thin-slice imaging, which led to a high exclusion rate, and therefore, to selection bias (less intra-hospital transfers, shorter onset-to-groin times, and lower NIHSS scores at 24–48 hours compared with the whole MR CLEAN Registry population).

Occlusion location and thrombus measurements were not assessed by the same group of observers (MR CLEAN Registry core lab for occlusion location and CBS vs trained observers for DT, thrombus length, density, and perviousness) nor in the same CT modality (CTA only by MR CLEAN Registry core lab vs NCCT and CTA by trained observers). This might create some incongruencies between occlusion location and DT, especially close to the ICA-terminus. For example: on CTA, lack of contrast in distal ICA-terminus can be scored as an M1 occlusion (expected $DT \neq 0$), while when looking at both NCCT and CTA simultaneously, it is scored as an ICA-T occlusion (expected DT=0). In addition, because occlusion location was defined as the most proximal occluded (intracranial) vessel segment on CTA, patients with multiple occlusions might have been classified as one occlusion location, while the thrombus characteristics were measured in a more distal occluded segment where the NCCT hyperdense artery sign was visible.

The measured thrombus length was based on the absence of contrast as seen in single-phase CTA, supported by the NCCT hyperdense artery sign, if present. Measurements on multiphase CTA might more accurately capture the true thrombus length.³⁰

CONCLUSION

Thrombus imaging characteristics are significantly intercorrelated and some of them show moderate and strong correlations. The collinearity of these thrombus characteristics should be considered when multiple thrombus characteristics are

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included in future predictive modeling studies. The observed weak correlations reflect that there is still a large variety of characteristics for a given single thrombus variable: thrombus imaging characteristics form a continuum, which does not allow for grouping of typical thrombus archetypes based on these features. The continuous spectrum and specific variability of thrombus imaging characteristics should be considered when developing novel treatment approaches.

Author affiliations

¹Department of Biomedical Engineering and Physics, Amsterdam UMC, location University of Amsterdam, Amsterdam, The Netherlands

²Department of Radiology and Nuclear Medicine, Amsterdam UMC, location University of Amsterdam, Amsterdam, The Netherlands

³Department of Neurology, Amsterdam UMC, location University of Amsterdam, Amsterdam. The Netherlands

⁴Department of Neurology, Erasmus MC, Rotterdam, The Netherlands

⁵Department of Radiology and Nuclear Medicine, Maastricht UMC, Maastricht, The Netherlands

⁶Department of Radiology, Catharina Hospital Eindhoven, Eindhoven, The Netherlands

Collaborators MR CLEAN Registry investigators – Group authors: Executive committee: Diederik W.J. Dippel (Department of Neurology, Erasmus MC University Medical Center); Aad van der Lugt (Radiology, Erasmus MC University Medical Center); Charles B.L.M. Majoie (Department of Radiology and Nuclear Medicine, Amsterdam UMC, University of Amsterdam, Amsterdam); Yvo B.W.E.M. Roos (Neurology, Amsterdam UMC, University of Amsterdam, Amsterdam); Robert J. van Oostenbrugge (Department of Neurology, Maastricht University Medical Center and Cardiovascular Research Institute Maastricht (CARIM)); Wim H. van Zwam (Radiology, Maastricht University Medical Center and Cardiovascular Research Institute Maastricht (CARIM)); Jelis Boiten (Neurology, Haaglanden MC, the Hague); Jan Albert Vos (Radiology, Sint Antonius Hospital, Nieuwegein). Study coordinators: Ivo G.H. Jansen (Department of Radiology and Nuclear Medicine, Amsterdam UMC, University of Amsterdam, Amsterdam); Maxim J.H.L. Mulder (Department of Neurology, Radiology, Erasmus MC University Medical Center); Robert- Jan B. Goldhoorn (Department of Neurology, Radiology, Maastricht University Medical Center and Cardiovascular Research Institute Maastricht (CARIM)); Kars C.J. Compagne (Radiology, Erasmus MC University Medical Center); Manon Kappelhof (Department of Radiology and Nuclear Medicine, Amsterdam UMC, University of Amsterdam, Amsterdam); Josje Brouwer (Neurology, Amsterdam UMC, University of Amsterdam, Amsterdam); Sanne J. den Hartog (Department of Neurology, Radiology, Public Health, Erasmus MC University Medical Center); Wouter H. Hinsenveld (Department of Neurology, Radiology, Maastricht University Medical Center and Cardiovascular Research Institute Maastricht (CARIM)). Local principal investigators: Diederik W.J. Dippel (Department of Neurology, Erasmus MC University Medical Center); Bob Roozenbeek (Department of Neurology, Erasmus MC University Medical Center); Aad van der Lugt (Radiology, Erasmus MC University Medical Center); Adriaan C.G.M. van Es (Radiology, Erasmus MC University Medical Center); Charles B.L.M. Majoie (Department of Radiology and Nuclear Medicine, Amsterdam UMC, University of Amsterdam, Amsterdam); Yvo B.W.E.M. Roos (Neurology, Amsterdam UMC, University of Amsterdam, Amsterdam); Bart J. Emmer (Department of Radiology and Nuclear Medicine, Amsterdam UMC, University of Amsterdam, Amsterdam); Jonathan M. Coutinho (Neurology, Amsterdam UMC, University of Amsterdam, Amsterdam); Wouter J. Schonewille (Department of Neurology, Sint Antonius Hospital, Nieuwegein); Jan Albert Vos (Radiology, Sint Antonius Hospital, Nieuwegein); Marieke J.H. Wermer (Department of Neurology, Leiden University Medical Center); Marianne A.A. van Walderveen (Radiology, Leiden University Medical Center); Julie Staals (Department of Neurology, Maastricht University Medical Center and Cardiovascular Research Institute Maastricht (CARIM)); Robert J. van Oostenbrugge (Department of Neurology, Maastricht University Medical Center and Cardiovascular Research Institute Maastricht (CARIM)); Wim H. van Zwam (Radiology, Maastricht University Medical Center and Cardiovascular Research Institute Maastricht (CARIM)); Jeannette Hofmeijer (Department of Neurology, Rijnstate Hospital, Arnhem); Jasper M. Martens (Radiology, Rijnstate Hospital, Arnhem); Geert J. Lycklama à Nijeholt (Department of Radiology, Haaglanden MC, the Hague); Jelis Boiten (Neurology, Haaglanden MC, the Hague); Sebastiaan F. de Bruijn (Department of Neurology, HAGA Hospital, the Hague); Lukas C. van Dijk (Radiology, HAGA Hospital, the Hague); H. Bart van der Worp (Department of Neurology, University Medical Center Utrecht); Rob H. Lo (Radiology, University

Medical Center Utrecht); Ewoud J. van Dijk (Department of Neurology, Radboud University Medical Center, Niimegen): Hieronymus D. Boogaarts (Neurosurgery, Radboud University Medical Center, Nijmegen); J. de Vries (Department of Neurology, Isala Klinieken, Zwolle); Paul L.M. de Kort (Department of Neurology, Elisabeth-TweeSteden ziekenhuis, Tilburg); Julia van Tuijl (Department of Neurology, Elisabeth-TweeSteden ziekenhuis, Tilburg); Jo P. Peluso (Radiology, Elisabeth-TweeSteden ziekenhuis, Tilburg): Puck Fransen (Department of Neurology, Isala Klinieken, Zwolle); Jan S.P. van den Berg (Department of Neurology, Isala Klinieken, Zwolle); Boudewijn A.A.M. van Hasselt (Radiology, Isala Klinieken, Zwolle); Leo A.M. Aerden (Department of Neurology, Reinier de Graaf Gasthuis, Delft); René J. Dallinga (Radiology, Reinier de Graaf Gasthuis, Delft); Maarten Uyttenboogaart (Department of Neurology, University Medical Center Groningen); Omid Eschai (Radiology, University Medical Center Groningen); Reinoud P.H. Bokkers (Radiology, University Medical Center Groningen); Tobien H.C.M.L. Schreuder (Department of Neurology, Atrium Medical Center, Heerlen); Roel J.J. Heijboer (Radiology, Atrium Medical Center, Heerlen); Koos Keizer (Department of Neurology, Catharina Hospital, Eindhoven); Lonneke S.F. Yo (Radiology, Catharina Hospital, Eindhoven); Heleen M. den Hertog (Department of Neurology, Isala Klinieken, Zwolle); Tomas Bulut (Radiology, Medisch Spectrum Twente, Enschede); Paul J.A.M. Brouwers (Department of Neurology, Medisch Spectrum Twente, Enschede). Imaging assessment committee: Charles B.L.M. Majoie (Department of Radiology and Nuclear Medicine, Amsterdam UMC, University of Amsterdam, Amsterdam) (chair); Wim H. van Zwam (Radiology, Maastricht University Medical Center and Cardiovascular Research Institute Maastricht (CARIM)); Aad van der Lugt (Radiology, Erasmus MC University Medical Center); Geert J. Lycklama à Nijeholt (Department of Radiology, Haaglanden MC, the Hague); Marianne A.A. van Walderveen (Radiology, Leiden University Medical Center): Marieke E.S. Sprengers (Department of Radiology and Nuclear Medicine. Amsterdam UMC, University of Amsterdam, Amsterdam); Sjoerd F.M. Jenniskens (Radiology, Radboud University Medical Center, Nijmegen); René van den Berg (Department of Radiology and Nuclear Medicine, Amsterdam UMC, University of Amsterdam, Amsterdam); Albert J. Yoo (Department of Radiology, Texas Stroke Institute, Texas, United States of America): Ludo F.M. Beenen (Department of Radiology and Nuclear Medicine, Amsterdam UMC, University of Amsterdam, Amsterdam); Alida A. Postma (Radiology, Maastricht University Medical Center and Cardiovascular Research Institute Maastricht (CARIM)); Stefan D. Roosendaal (Department of Radiology and Nuclear Medicine, Amsterdam UMC, University of Amsterdam, Amsterdam): Bas F.W. van der Kallen (Department of Radiology, Haaglanden MC, the Hague); Ido R. van den Wijngaard (Department of Radiology, Haaglanden MC, the Hague); Adriaan C.G.M. van Es (Radiology, Erasmus MC University Medical Center); Bart J. Emmer, (Department of Radiology and Nuclear Medicine, Amsterdam UMC, University of Amsterdam, Amsterdam); Jasper M. Martens (Radiology, Rijnstate Hospital, Arnhem); Lonneke S.F. Yo (Radiology, Catharina Hospital, Eindhoven); Jan Albert Vos (Radiology, Sint Antonius Hospital, Nieuwegein); Joost Bot (Department of Radiology, Amsterdam UMC, Vrije Universiteit van Amsterdam, Amsterdam); Pieter-Jan van Doormaal (Radiology, Erasmus MC University Medical Center); Anton Meijer (Radiology, Radboud University Medical Center, Nijmegen); Elyas Gharig (Department of Radiology, Haaglanden MC, the Hague); Reinoud P.H. Bokkers (Radiology, University Medical Center Groningen); Marc P. van Proosdij (Department of Radiology, Noordwest Ziekenhuisgroep, Alkmaar); G. Menno Krietemeijer (Radiology, Catharina Hospital, Eindhoven); Jo P. Peluso (Radiology, Elisabeth-TweeSteden ziekenhuis, Tilburg); Hieronymus D. Boogaarts (Neurosurgery, Radboud University Medical Center, Nijmegen); Rob Lo (Radiology, University Medical Center Utrecht); Wouter Dinkelaar (Radiology, Erasmus MC University Medical Center); Auke P.A. Appelman (Radiology, University Medical Center Groningen); Bas Hammer (Radiology, HAGA Hospital, the Hague); Sjoert Pegge (Radiology, Radboud University Medical Center, Nijmegen); Anouk van der Hoorn (Radiology, University Medical Center Groningen); Saman Vinke (Neurosurgery, Radboud University Medical Center, Nijmegen). Writing committee: Diederik W.J. Dippel (Department of Neurology, Erasmus MC University Medical Center) (chair); Aad van der Lugt (Radiology, Erasmus MC University Medical Center); Charles B.L.M. Majoie (Department of Radiology and Nuclear Medicine, Amsterdam UMC, University of Amsterdam, Amsterdam); Yvo B.W.E.M. Roos (Neurology, Amsterdam UMC, University of Amsterdam, Amsterdam); Robert J. van Oostenbrugge (Department of Neurology, Maastricht University Medical Center and Cardiovascular Research Institute Maastricht (CARIM)); Wim H. van Zwam (Radiology, Maastricht University Medical Center and Cardiovascular Research Institute Maastricht (CARIM)); Geert J. Lycklama à Nijeholt (Department of Radiology, Haaglanden MC, the Hague); Jelis Boiten (Neurology, Haaglanden MC, the Hague); Jan Albert Vos (Radiology, Sint Antonius Hospital, Nieuwegein); Wouter J. Schonewille (Department of Neurology, Sint Antonius Hospital, Nieuwegein); Jeannette Hofmeijer

(Department of Neurology, Rijnstate Hospital, Arnhem); Jasper M. Martens (Radiology, Riinstate Hospital, Arnhem); H. Bart van der Worp (Department of Neurology, University Medical Center Utrecht); Rob H. Lo (Radiology, University Medical Center Utrecht). Adverse event committee: Robert J. van Oostenbrugge (Department of Neurology, Maastricht University Medical Center and Cardiovascular Research Institute Maastricht (CARIM)) (chair); Jeannette Hofmeijer (Department of Neurology, Riinstate Hospital, Arnhem): H. Zwenneke Flach (Radiology, Isala Klinieken, Zwolle). Trial methodologist: Hester F. Lingsma (Public Health, Erasmus MC University Medical Center). Research nurses / local trial coordinators: Naziha el Ghannouti (Department of Neurology, Erasmus MC University Medical Center); Martin Sterrenberg (Department of Neurology, Erasmus MC University Medical Center): Wilma Pellikaan (Department of Neurology, Sint Antonius Hospital, Nieuwegein); Rita Sprengers (Neurology, Amsterdam UMC, University of Amsterdam, Amsterdam); Marjan Elfrink (Department of Neurology, Rijnstate Hospital, Arnhem); Michelle Simons (Department of Neurology, Rijnstate Hospital, Arnhem); Marjolein Vossers (Radiology, Rijnstate Hospital, Arnhem); Joke de Meris (Neurology, Haaglanden MC, the Hague): Tamara Vermeulen (Neurology, Haaglanden MC, the Hague); Annet Geerlings (Department of Neurology, Radboud University Medical Center, Nijmegen); Gina van Vemde (Department of Neurology, Isala Klinieken, Zwolle); Tiny Simons (Department of Neurology, Atrium Medical Center, Heerlen); Gert Messchendorp (Department of Neurology, University Medical Center Groningen); Nynke Nicolaij (Department of Neurology, University Medical Center Groningen); Hester Bongenaar (Department of Neurology, Catharina Hospital, Eindhoven); Karin Bodde (Department of Neurology, Reinier de Graaf Gasthuis, Delft); Sandra Kleijn (Department of Neurology, Medisch Spectrum Twente, Enschede); Jasmijn Lodico (Department of Neurology, Medisch Spectrum Twente, Enschede): Hanneke Droste (Department of Neurology, Medisch Spectrum Twente, Enschede); Maureen Wollaert (Department of Neurology, Maastricht University Medical Center and Cardiovascular Research Institute Maastricht (CARIM)); Sabrina Verheesen (Department of Neurology, Maastricht University Medical Center and Cardiovascular Research Institute Maastricht (CARIM)); D. Jeurrissen (Department of Neurology, Maastricht University Medical Center and Cardiovascular Research Institute Maastricht (CARIM)); Erna Bos (Department of Neurology); Yvonne Drabbe (Department of Neurology, HAGA Hospital, the Hague); Michelle Sandiman (Department of Neurology, HAGA Hospital, the Hague); Nicoline Aaldering (Department of Neurology, Rijnstate Hospital, Arnhem); Berber Zweedijk (Department of Neurology, University Medical Center Utrecht); Jocova Veryoort (Department of Neurology, Elisabeth-TweeSteden ziekenhuis, Tilburg); Eva Ponjee (Department of Neurology, Isala Klinieken, Zwolle); Sharon Romviel (Department of Neurology, Radboud University Medical Center, Nijmegen); Karin Kanselaar (Department of Neurology, Radboud University Medical Center, Nijmegen); Denn Barning (Radiology, Leiden University Medical Center). PhD / Medical students: Esmee Venema (Public Health, Erasmus MC University Medical Center); Vicky Chalos (Department of Neurology, Public Health, Erasmus MC University Medical Center); Ralph R. Geuskens (Department of Radiology and Nuclear Medicine, Amsterdam UMC, University of Amsterdam, Amsterdam); Tim van Straaten (Department of Neurology, Radboud University Medical Center, Nijmegen); Saliha Ergezen (Department of Neurology, Erasmus MC University Medical Center); Roger R.M. Harmsma (Department of Neurology, Erasmus MC University Medical Center); Daan Muijres (Department of Neurology, Erasmus MC University Medical Center); Anouk de Jong (Department of Neurology, Erasmus MC University Medical Center); Olvert A. Berkhemer (Department of Neurology, Erasmus MC University Medical Center; Department of Radiology and Nuclear Medicine, Amsterdam UMC, University of Amsterdam, Amsterdam; Radiology, Maastricht University Medical Center and Cardiovascular Research Institute Maastricht (CARIM)); Anna M.M. Boers (Department of Radiology and Nuclear Medicine, Biomedical Engineering & Physics, Amsterdam UMC, University of Amsterdam, Amsterdam); J. Huguet (Department of Radiology and Nuclear Medicine, Amsterdam UMC, University of Amsterdam, Amsterdam); P.F.C. Groot (Department of Radiology and Nuclear Medicine, Amsterdam UMC, University of Amsterdam, Amsterdam); Marieke A. Mens (Department of Radiology and Nuclear Medicine, Amsterdam UMC, University of Amsterdam, Amsterdam); Katinka R. van Kranendonk (Department of Radiology and Nuclear Medicine, Amsterdam UMC, University of Amsterdam, Amsterdam); Kilian M. Treurniet (Department of Radiology and Nuclear Medicine, Amsterdam UMC, University of Amsterdam, Amsterdam); Manon L. Tolhuisen (Department of Radiology and Nuclear Medicine, Biomedical Engineering & Physics, Amsterdam UMC, University of Amsterdam, Amsterdam); Heitor Alves (Department of Radiology and Nuclear Medicine, Amsterdam UMC, University of Amsterdam, Amsterdam); Annick J. Weterings (Department of Radiology and Nuclear Medicine, Amsterdam UMC, University of Amsterdam, Amsterdam), Eleonora L.F. Kirkels (Department of Radiology and Nuclear Medicine, Amsterdam

UMC, University of Amsterdam, Amsterdam), Eva J.H.F. Voogd (Department of Neurology, Rijnstate Hospital, Arnhem); Lieve M. Schupp (Department of Radiology and Nuclear Medicine, Amsterdam UMC, University of Amsterdam, Amsterdam); Sabine L. Collette (Department of Neurology, Radiology, University Medical Center Groningen); Adrien E.D. Groot (Neurology, Amsterdam UMC, University of Amsterdam, Amsterdam); Natalie E. LeCouffe (Neurology, Amsterdam UMC, University of Amsterdam, Amsterdam); Praneeta R. Konduri (Biomedical Engineering & Physics, Amsterdam UMC, University of Amsterdam, Amsterdam); Haryadi Prasetya Biomedical Engineering & Physics, Amsterdam, Amsterdam; Nerea Arrarte Terreros Biomedical Engineering & Physics, Amsterdam UMC, University of Amsterdam, Amsterdam UMC, University of Amsterdam, Amsterdam, Amsterdam, Amsterdam, Amsterdam, Amsterdam, Amsterdam.

Contributors NAT developed the study, performed the data analysis, wrote the manuscript, and is the guarantor of the study. AAEB, MK, MLT, JB, JWH, PRK, KRvK, BGD, and HCBRA contributed to the data analysis and interpretation. DWJD, WHvZ, LFMB, and LSFY contributed to the clinical assessment of the data. EvB, CBLMM, and HAM contributed to the research development and project supervision. All authors contributed to the final version of the manuscript by critical revisions.

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Patient consent for publication Not applicable.

Ethics approval These patients are part of the MR CLEAN Registry, a multicenter prospective observational registry of all patients undergoing EVT for acute ischemic stroke in the Netherlands. This registry was approved by the central medical ethics committee of the Erasmus Medical Center Rotterdam, which served as the review board of all participating centers (MEC-2014-235). The requirement for written informed consent was waived, but all patients or legal representatives were provided with oral and written information on the registry, and had the opportunity to withdraw consent to use their data via an opt-out form, conforming to the European Union General Data Protection Regulation.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. All data relevant to the study are included in the article or uploaded as supplementary information. All data relevant to the study are included in the article or uploaded as Supplemental Material. Source data for this study are not available due to privacy regulations, but analysis methods, codes, and results are available from the corresponding author upon reasonable request.

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ORCID iDs

Nerea Arrarte Terreros http://orcid.org/0000-0002-9912-7508
Agnetha AE Bruggeman http://orcid.org/0000-0002-6873-2545
Manon Kappelhof http://orcid.org/0000-0001-5250-8955
Manon L Tolhuisen http://orcid.org/0000-0002-2695-1117
Josje Brouwer http://orcid.org/0000-0003-0310-2616
Jan W Hoving http://orcid.org/0000-0003-3310-3973
Heitor CBR Alves http://orcid.org/0000-0002-4693-8278
Diederik WJ Dippel http://orcid.org/0000-0002-9234-3515
Wim H van Zwam http://orcid.org/0000-0003-1631-7056

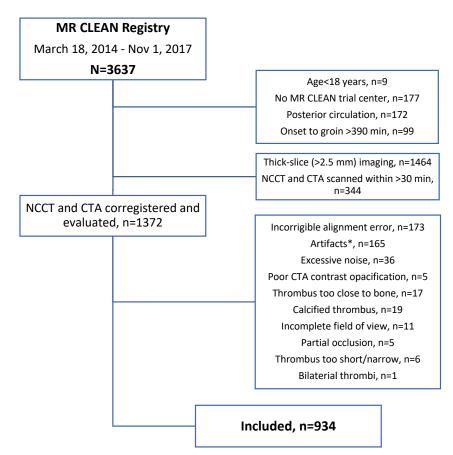
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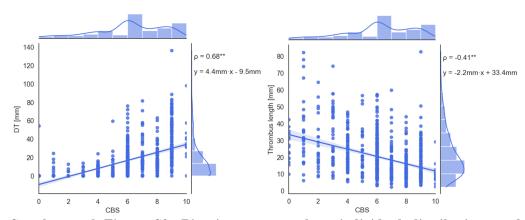
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SUPPLEMENTAL MATERIAL

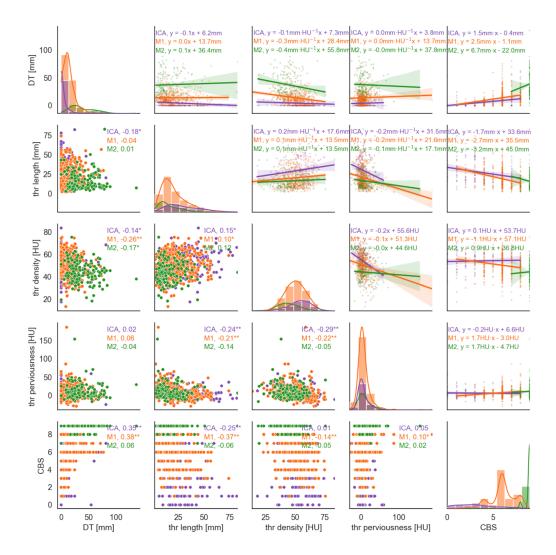
FIGURES



Supplemental Figure S1. Patient inclusion flowchart. *movement, metal and beam hardening artefacts. CTA, computed tomography angiography; MR CLEAN, Multicenter Randomized CLinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands; NCCT, non-contrast computed tomography.



Supplemental Figure S2. Bivariate scatter plots, individual distributions and Spearman's correlation coefficient of thrombus characteristics with a moderate $(0.40 \le |\rho| < 0.60)$ or strong $(|\rho| \ge 0.60)$ correlation. A) DT [mm] against CBS displaying a strong correlation ρ =0.68 with p<0.01. B) Thrombus length [mm] against CBS displaying a moderate correlation ρ =-0.41 with p<0.01. Each graph also includes a linear fit to illustrate the relationship between the variables. CBS, clot burden score; DT, distance from the internal carotid artery terminus to the thrombus; mm, millimeters; thr, thrombus.



Supplemental Figure S3. Thrombus imaging characteristics for ICA, M1 and M2 occlusions. The diagonal shows the histograms of DT, thrombus length, density, perviousness and CBS. The graphs below the diagonal show the bivariate scatter plots, Spearman's correlation coefficient (ρ) and significance level of the correlation, where * indicates p<0.05 and ** indicates p<0.01. The graphs above the diagonal show bivariate scatter plots with a linear fit. All graphs are color-coded by occlusion location: ICA occlusions in purple, M1 occlusions in orange, and M2 occlusions in green. CBS, clot burden score; DT, distance from the internal carotid artery terminus to the thrombus; HU, Hounsfield units; mm, millimeters; thr, thrombus.

TABLES

Supplemental Table S1. Image acquisition parameters.

Scanner manufacturer	Scar	nner model	no./total (%)			
	BrightS	peed	3/935 (0)			
	Discovery CT		17/935 (2)			
GE MEDICAL	LightSp		1/935 (0)			
SYSTEMS		eed VCT	12/935 (1			
	Optima		15/935 (2)		
	Revolut: Brilliand		2/935 (0)			
	Brilliand		2/935 (0) 8/935 (1)			
	Brilliand		18/935 (2)		
PHILIPS	iCT 256		204/935 (2			
THILHS	Ingenuit		20/935 (2			
		Spectral CT	2/935 (0)	<u>) </u>		
		IDT 16	1/935 (0)			
	Sensatio	on 16	1/935 (0)			
	Sensation 64		83/935 (9)		
	SOMATOM Def. AS		45/935 (5)			
SIEMENS	SOMATOM Def. AS+		20/935 (2)			
	SOMATOM Def. Edge		80/935 (9)			
	SOMATOM Def. Flash		182/935 (20)			
		OM Force	62/935 (7)			
TOGYNDA	Aquilion		31/935 (3)			
TOSHIBA	Aquilion		112/935 (12)			
	Aquilloi	n PRIME	14/935 (1)			
Imaging protocol		NCCT	CTA			
	EC	Hr38s	A	FC03	IMR1	
	FC21	Hr40s	В	FC05	J30f	
	FC26	Hr59h	B20f	FC08	J40f	
	FC30	IMR1	B26f	FC12	J45s	
	FC41	J30f	B30f	FC41	Q30f	
Convolution kernel	FC64	J30s	B31f	FC43	Q33f	
	H20f	J40f	B40f	H20f	Q40f	
	H30f	J40s	B46f	H30f	Qr40d	
	H30s	J45s	Bv36d	H41f	SOFT	
	H31f	J70h	Bv40d	H70h	STANDARD	
	H31s	SE	Bv44d	Hf38d	UA	

	H41s	SOFT	С	I26f	UB
	H60f	STANDARD	D	I30f	UC
	H60s	UA	D24f	I31f	
	H70h	UB	D45f	I40f	
	Hf38s	UC	DETAIL	I46f	
Imaging parameters – median (IQR)	1	NCCT		CTA	1
Peak Voltage [kV]	120 (100-120)		100 (100-120)		
Tour voltage [RV]	120 (100	-120)	100 (100	1=0)	
Tube3 current [mA]	240 (175		314 (188-		
	`	-320) α	`	446) ^β	

Missing values: $^{\alpha}9$, $^{\beta}3$, $^{\gamma}9$, $^{\delta}5$, $^{\epsilon}18$, and $^{\zeta}11$.

CTA, computed tomography angiography; Def, definition; IQR, interquartile range; kV, kilovoltage; mA, milliamperes; NCCT, non-contrast computed tomography; s, seconds.

Supplemental Table S2: Glossary.

Word	Definition
Association	(between two variables) defines the relationship or dependency between two variables. The associations can be linear, logarithmic, exponential, etc. Association does not imply causation.
Correlation	(between two variables) is a specific type of association which implies that the relation between two variables follows a monotonically decreasing or increasing function. If two variables are correlated, they are associated, but the opposite is not true: two associated variables do not have to be correlated.
Collinearity	(between two variables) the two variables are linearly correlated, i.e.: the monotonically decreasing/increasing function is a linear function.
Unsupervised clustering	machine learning algorithm used to group (i.e., cluster) items based on specific item's features without any prior information/rules.

Supplemental Table S3. Baseline characteristics of the MR CLEAN Registry population (N=3637) and our study population (n=934).

population (N=3637) and our study p	MR CLEAN	Current study	
Baseline characteristics	Registry,	population,	p-value
Dasenne characteristics	N=3279	n=934	p-value
Age [years] – median (IQR)	72 (61-80)	72 (62-80)	0.89
Sex, female – no./total (%)	1696/3279 (52)	489/934 (52)	0.73
Medical history – no./total (%)	1070/32/7 (32)	109/931 (32)	0.75
Previous stroke	546/3252 (17)	158/925 (17)	0.84
Diabetes mellitus	532/3255 (16)	153/925 (17)	0.89
Hypertension	1688/3213 (53)	447/913 (49)	0.06
Atrial fibrillation	772/3236 (24)	236/920 (26)	0.26
Pre-stroke mRS – no./total (%)	772/3230 (21)	230/720 (20)	0.86
0	2170/3207 (68)	619/913 (68)	0.00
1	424/3207 (13)	112/913 (12)	
2	241/3207 (7)	72/913 (8)	
≥3	372/3207 (12)	110/913 (12)	
	312/3207 (12)	110/913 (12)	
Systolic blood pressure ^α [mmHg] – median (IQR)	150 (131-165)	149 (132-165)	0.50
Diastolic blood pressure ^β [mmHg] – median (IQR)	80 (71-91)	80 (71-90)	0.84
$NIHSS_{BL}^{\gamma}$ – median (IQR)	16 (11-20)	15 (11-20)	0.87
$ASPECTS_{BL}^{\delta}$ – median (IQR)	9 (7-10)	9 (8-10)	0.38
CS – no./total (%)	,		0.09
0	187/3072 (6)	61/914 (7)	
1	1100/3072 (36)	341/914 (37)	
2	1190/3072 (39)	369/914 (40)	
3	595/3072 (19)	143/914 (16)	
Treatment and workflow			
IVT – no./total (%)	2450/3275 (75)	680/933 (73)	0.14
Transferred patients – no./total (%)	1783/3278 (54)	343/933 (37)	<0.01
Stroke onset* to first hospital presentation ⁶ [min] – median (IQR)	57 (39-105)	60 (40-108)	0.23
Hospital presentation to IVT $^{\zeta}$ [min] – median (IQR)	24 (18-33)	23 (17-31)	0.13
Stroke onset* to groin puncture ⁿ [min] – median (IQR)	195 (150-260)	188 (139-246)	<0.01
Procedure time ^{θ} – median (IQR)	59 (38-84)	55 (37-81)	0.13
Retrieval attempts – median (IQR)			0.18
1	954/3279 ()	305/934 ()	
2	575/3279 ()	168/934 ()	
3	398/3279 ()	96/934 ()	
≥4	495/3279 ()	130/934 ()	

eTICI 2B-3 – no./total (%)	1965/3191 (62)	588/912 (65)	0.11
Outcome			
NIHSS FU ¹ – median (IQR)	10 (4-17)	9 (3-16)	0.02
mRS ^κ − median (IQR)	3 (2-6)	3 (2-6)	0.18
siCH – no./total (%)	193/3279 (6)	51/934 (6)	0.62

Missing values: $\alpha 110, \beta 120, \gamma 71, \delta 112, \varepsilon 770, \zeta 1746, \eta 21, \theta 394, \zeta 405$ and $\kappa 278$.

ΔNIHSS, change in NIHSS score at 24-48h compared to baseline; ASPECTS, Alberta Stroke Programme Early CT Score; BL, baseline; CBS, clot burden score; CS, collateral score; CT, computed tomography; ENT, embolization to new (previously unaffected) vascular territory; eTICI, expanded thrombolysis in cerebral infarction; EVT, endovascular treatment; IQR, interquartile range; IVT, intravenous treatment with alteplase; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; sICH, symptomatic intracranial hemorrhage.

^{*}Time of stroke onset was defined as the time of witnessed symptom onset or, if unknown, as the time the patient was last seen well.

Supplemental Table S4. Thrombus imaging characteristics.

Thrombus imaging characteristics	Study population, n=934
Occlusion location – no./total (%)	
ICA	202/925(22)
M1	566/925 (61)
M2	148/925 (16)
Other (M3, anterior)	9/925 (1)
DT [mm] – median (IQR)	11 (2-22)
Thrombus length ^α [mm] – median (IQR)	18 (11-29)
Thrombus density [HU]– median (IQR)	50 (44-57)
Thrombus perviousness [HU] – median (IQR)	5 (-2-13)
CBS^{β} – median (IQR)	6 (5-8)

Missing values: α1, β194,

CBS, clot burden score; DT, distance from ICA-T to the thrombus; HU, Hounsfield units; ICA-T, internal carotid artery T-junction; IQR, interquartile range; mm, millimeters.

Supplemental Table S5. Correlation and regression analyses. Below the diagonal: Spearman's correlation coefficient (ρ) and significance level of the correlation. Above the diagonal: linear regression coefficients

Thrombus imaging chars.		DT [mm]	Thrombus length ^a [mm]	Thrombus density [HU]	Thrombus perviousne ss [HU]	CBSβ
		Regression models of the form: y= ax + b, where (a, b) =				
DT [mm]			(-0.2, 20.6)	(-0.6, 44.3)	(0.1, 15.2)	(4.4, -9.5)
Thrombus length ^α [mm]		-0.27**		(0.3, 8.3)	(-0.2, 23.2)	(-2.2, 33.4)
Thrombus density [HU]	ρ=	-0.37**	0.21**		(-0.1, 51.2)	(-1.3, 57.7)
Thrombus perviousnes s [HU]		0.09**	-0.23**	-0.23**		(0.9, 2.3)
CBSβ		0.68**	-0.41**	-0.32**	0.12**	

^{**}significance level of Spearman's correlation coefficient is p<0.01.

Missing values: $\alpha 1$, $\beta 194$.

CBS, clot burden score; DT, distance from ICA-T to the thrombus; HU, Hounsfield units; ICA-T, internal carotid artery T-junction; IQR, interquartile range; mm, millimeters.

Supplemental Table S6. Thrombus imaging characteristics per occlusion location (ICA, M1, and M2): distance from ICA-terminus to the thrombus, thrombus length, thrombus density, thrombus perviousness and clot burden score. The diagonal shows the median with IQR. The lower diagonal shows the p-value of the corresponding pairwise Mann-Whitney-U test with Bonferroni corrections for multiple tests.

DT [mm] – median (IQR)							
Occlusion location	ICA, n=202 M1, n=566		M2, n=148				
ICA, n=202	0 (0-0)						
M1, n=566	p<0.01	12 (6-18)					
M2, n=148	p<0.01	p<0.01	30 (22-55)				
TI	hrombus lengthα [mm]	– median (IQR)					
Occlusion location	ICA, n=202	M1, n=566	M2, n=148				
ICA, n=202	26 (17-43)						
M1, n=566	p<0.01	18 (12-27)					
M2, n=148	p<0.01	p<0.01	12 (9-22)				
Thrombus density [HU] – median (IQR)							
Occlusion location	ICA, n=202	M1, n=566	M2, n=148				
ICA, n=202	55 (49-61)						
M1, n=566	p<0.01	50 (44-57)					
M2, n=148	p<0.01	p<0.01	43.5 (38-50)				
Thro	ombus perviousness [H	[U] – median (IQR)					
Occlusion location	ICA, n=202	M1, n=566	M2, n=148				
ICA, n=202	3 (-3-12)						
M1, n=566	p=0.40	5 (-2-12)					
M2, n=148	p=0.02	p=0.18	6 (-1-18)				
CBS ^β – median (IQR)							
Occlusion location	ICA, n=202	M1, n=566	M2, n=148				
ICA, n=202	3 (1-4)						
		1	· —				
M1, n=566	p<0.01	6 (6-7)					

Missing values: $^{\alpha}1$, $^{\beta}191$,

CBS, clot burden score; DT, distance from ICA-T to the thrombus; HU, Hounsfield units; IQR, interquartile range.

Supplemental Table S7. Correlation and regression analyses. Below the diagonal: Spearman's correlation coefficient (ρ) and significance level of the correlation. Above the diagonal: linear regression coefficients.

Thr. ima. chars.		DT [mm]	Thr. length ^a [mm]	Thr. density [HU]	Thr. pervious. [HU]	CBS^{β}	Occl.
			Regression	models of the where (a, b	•	- b,	100.
			(-0.1, 6.2)	(-0.1, 7.3)	(0.0, 3.8)	(1.5, -0.4)	ICA
DT [mm]			(0.0, 13.7)	(-0.3, 28.4)	(0.0, 13.7)	(2.5, -1.1)	M1
[]			(0.1, 36.4)	(-0.4, 55.8)	(0.0, 37.8)	(6.8, -22.0)	M2
Thr.		-0.18*		(0.2, 17.6)	(-0.2, 31.5)	(-1.7, 33.6)	ICA
length ^a		-0.04		(0.1, 13.5)	(-0.2, 21.6)	(-2.7, 35.5)	M1
[mm]		0.01		(0.1, 13.5)	(-0.1, 17.1)	(-3.2, 45.0)	M2
				T		T	
Thr.		-0.14*	0.15*		(-0.2, 55.6)	(0.1, 53.7)	ICA
density		-0.26**	0.10*		(-0.1, 51.3)	(-1.1, 57.1)	M1
[HU]		-0.17*	0.12		(-0.0, 44.6)	(0.9, 36.8)	M2
	ρ						
Thr.		0.02	-0.24**	-0.29**		(-0.2, 6.6)	ICA
pervio us.		0.06	-0.21**	-0.22**		(1.7, -3.0)	M1
[HU]		-0.04	-0.14	-0.05		(1.7, -4.7)	M2
		0.35**	-0.25**	0.01	0.05		ICA
CBS^{β}		0.38**	-0.37**	-0.14**	0.10*		M1
		0.06	-0.06	-0.05	0.02		M2

Significance level of Spearman's correlation coefficient, *p<0.05, **p<0.01 Missing values: $^{\alpha}1,^{\beta}194.$

CBS, clot burden score; DT, distance from ICA-T to the thrombus; HU, Hounsfield units; ICA-T, internal carotid artery T-junction; mm, millimeters; thr, thrombus.

Supplemental Table S8. Cluster centroids and summary statistics for each cluster.

Cluster centroids	Cluster 1, n=313	Cluster 2, n=185	Cluster 3, n=347	Cluster 4, n=88
Thrombus length [mm]	15	44	18	14
Thrombus density [HU]	42	53	58	43
Thrombus perviousness [HU]	6	2	3	42
M. P. (IOD)	Cluster 1,	Cluster 2,	Cluster 3,	Cluster 4,

Median (IQR)	Cluster 1, n=313	Cluster 2, n=185	Cluster 3, n=347	Cluster 4, n=88
Thrombus length [mm]	14 (9-20)	42 (36-49)	18 (12-23)	12 (8-18)
Thrombus density [HU]	43 (39-47)	52 (47-59)	57 (54-61)	44 (37-50)
Thrombus perviousness [HU]	5 (0-13)	2 (-5-7)	3 (-2-9)	36 (28-46)
THE HE OF 11 IS TOR I	- ()	****	- (-)	()

 $HU,\,Hounsfield\,\,units;\,IQR,\,interquartile\,\,range;\,mm,\,\,millimeters.$

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	pending		
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	Monitoring Board or		
10	Advisory Board Leadership or	None	
10	fiduciary role in other board,	NOITE	
	outer bourd,		

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	fiduciary role in other board,		
	,		

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8	Patents planned, issued or pending	None	
9	Participation on a Data Safety Monitoring Board or Advisory Board	None None	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	None	

			e all entities with whom you have this ionship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
11	Stock or stock options		None	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services		None	
13	Other financial or non-financial interests		None	
	Please place an "X" next to the following statement to indicate your agreement:			
\boxtimes	I certify that I have answered every question and have not altered the wording of any of the questions on this form.			

Date:	5/2/2022
Your Name:	Henk A. Marquering
Manuscript Title:	Thrombus imaging characteristics: similarities and interdependence within acute ischemic stroke
Manuscript Number (if known):	Click or tap here to enter text.

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i	any entity (if not indicated in item #1 above).		
3	Royalties or licenses	None	

		Name all entities with whom you have this relationship or indicate none (add rows as needed) Specifications/Comments (e.g., if payments v made to you or to your institution)	vere
4	Consulting fees	None None	
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	None	
6	Payment for expert testimony	None	
7	Support for attending meetings and/or travel	None	
8	Patents planned, issued or pending	None	
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11	Stock or stock options	None			
		I.A. Marquering reports co-founder and hareholder of Nicolab, a company that focuses n the use of artificial intelligence for medical mage analysis.			
12	Receipt of equipment, materials, drugs, medical writing,	☑ None			
	gifts or other services				
13	Other financial or non-financial interests	None			
	interests				
Plea	Please place an "X" next to the following statement to indicate your agreement:				
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Date:	5/2/2022
Your Name:	Heitor CBR Alves
Manuscript Title:	Thrombus imaging characteristics: similarities and interdependence within acute ischemic stroke
Manuscript Number (if known):	Click or tap here to enter text.

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Date:	5/2/2022
Your Name:	Josje Brouwer
Manuscript Title:	Thrombus imaging characteristics: similarities and interdependence within acute ischemic stroke
Manuscript Number (if known):	Click or tap here to enter text.

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Date:	5/2/2022
Your Name:	Jan W. Hoving
Manuscript Title:	Thrombus imaging characteristics: similarities and interdependence within acute ischemic stroke
Manuscript Number (if known):	Click or tap here to enter text.

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Date:	5/2/2022
Your Name:	Katinka R. Kranendonk
Manuscript Title:	Thrombus imaging characteristics: similarities and interdependence within acute ischemic stroke
Manuscript Number (if known):	Click or tap here to enter text.

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Date:	5/2/2022	
Your Name:	Ludo FM Beenen	
Manuscript Title:	Thrombus imaging characteristics: similarities and interdependence within acute ischemic stroke	
Manuscript Number (if known):	Click or tap here to enter text.	

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Date:	5/2/2022
Your Name:	Lonneke S.F. Yoo
Manuscript Title:	Thrombus imaging characteristics: similarities and interdependence within acute ischemic stroke
Manuscript Number (if known):	Click or tap here to enter text.

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Date:	5/2/2022
Your Name:	Manon Kappelhof
Manuscript Title:	Thrombus imaging characteristics: similarities and interdependence within acute ischemic stroke
Manuscript Number (if known):	Click or tap here to enter text.

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Date:	5/2/2022
Your Name:	Manon L Tolhuisen
Manuscript Title:	Thrombus imaging characteristics: similarities and interdependence within acute ischemic stroke
Manuscript Number (if known):	Click or tap here to enter text.

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Date:	5/2/2022	
Your Name:	Nerea Arrarte Terreros	
Manuscript Title:	Thrombus imaging characteristics: similarities and interdependence within acute ischemic stroke	
Manuscript Number (if known):	Click or tap here to enter text.	

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Date:	5/2/2022
Your Name:	Praneeta R Konduri
Manuscript Title:	Thrombus imaging characteristics: similarities and interdependence within acute ischemic stroke
Manuscript Number (if known):	Click or tap here to enter text.

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13	Other financial or non-financial interests		None	
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