Clot Burden Score on Baseline Computerized Tomographic Angiography and Intra-Arterial Treatment Effect in Acute Ischemic Stroke

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Background and Purpose—A high clot burden score (CBS) is associated with favorable outcome after intravenous treatment for acute ischemic stroke. The added benefit of intra-arterial treatment might be less in these patients. The aim of this exploratory post hoc analysis was to assess the relation of CBS with neurological improvement and endovascular treatment effect.

Methods—For 499 of 500 patients in the MR CLEAN study (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands), the CBS was determined. Ordinal logistic regression models with and without main baseline prognostic variables were used to assess the association between CBS (continuous or dichotomized at CBS of 6) and a shift toward better outcome on the modified Rankin Scale. The model without main baseline prognostic variables only included treatment allocation and CBS. Models with and without a multiplicative interaction term of CBS and treatment were compared using the χ² test to assess treatment effect modification by CBS.

Results—Higher CBS was associated with a shift toward better outcome on the modified Rankin Scale; adjusted common odds ratio per point CBS was 1.12 (95% confidence interval, 1.04–1.20]. Dichotomized CBS had an adjusted common odds ratio of 1.67 (95% confidence interval, 1.12–2.51). Both effect estimates were slightly attenuated by adding baseline prognostic variables. The addition of the interaction terms did not significantly improve the fit of the models. There was a small and insignificant increase of intra-arterial treatment efficacy in the high CBS group.

Conclusions—A higher CBS is associated with improved outcome and may be used as a prognostic marker. We found no evidence that CBS modifies the effect of intra-arterial treatment.


Key Words: intracranial embolism ■ neuroimaging ■ stroke ■ thrombectomy ■ thrombolytic therapy

Recanalization of the occluded vessel is the major focus of modern treatment for acute ischemic stroke. With the accumulating evidence of the additional benefit of intra-arterial treatment (IAT) in patients with anterior circulation acute ischemic stroke, a new era has started in stroke management. However, even after IAT, up to 67% of patients with acute
ischemic stroke do not regain functional independence. With the use of stent-retrievers, successful revascularization was not achieved in 12% to 42% of treated patients. Thrombus location and the length of the occlusion are known to be associated with recanalization rates in patients treated with intravenous treatment (IVT). Both parameters are included in the clot burden score (CBS) in which a lower score reflects more extensive thrombus. Patients with a lower CBS have lower odds of reperfusion and larger final infarct volumes at follow-up in patients treated with IVT. For patients treated with IAT, the association of CBS with treatment efficacy is still sparsely studied. A post hoc analysis of the IMS-III trial (Interventional Management of Stroke III) data showed that recanalization rates were consistent across occlusion locations in patients treated with IAT. In comparison, recanalization rates dropped in the internal carotid artery (ICA)-T subgroup for patients with IVT. As the carotid-T (ICA-T) occlusions are commonly associated with a low CBS, this finding would imply that the treatment effect of IAT relative to IVT is dependent on CBS and decreases for higher values of CBS.

We hypothesized that the added benefit of IAT relative to IVT decreases with lower clot burden (ie, higher values of CBS). The aim of this exploratory post hoc analysis was to assess the relation of CBS with neurological improvement and endovascular treatment effect.

Methods

Patients and Procedures

MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands) was a prospective, multicenter randomized trial comparing usual care for an anterior circulation ischemic stroke caused by a proximal large-vessel occlusion to endovascular therapy in addition to usual care. Patients who presented within 6 hours of symptom onset were randomly assigned to either group. Additional inclusion and exclusion criteria and procedures in the trial were reported previously. Before randomization, written informed consent was obtained from all patients or their legal representatives. The MR CLEAN study protocol was approved by a central medical ethics committee and by the research board of each participating center.

All patients underwent baseline computerized tomographic angiographic (CTA) imaging to confirm the presence of a proximal large-vessel occlusion. Two experienced observers from the core imaging committee assigned the appropriate CBS according to the methods of Puetz et al. A score of 10 on the CBS indicates that no occlusion is present. Two points are deducted for lack of opacification in M2 branch, the A1 segment, or the infraclinoid ICA. In case of discrepancies between the 2 observers, a third observer performed a consensus reading.

Outcome Measures

The primary outcome measure in MR CLEAN was functional outcome at 90 days, measured on the modified Rankin Scale (mRS). On this scale, a value of 0 to 2 constitutes functional independence. Secondary outcome measures were (among others) the recanalization status on CTA or magnetic resonance angiography at 24 hours and the final infarct volume (FIV) on noncontrast CT (at 24 hours or 5–7 days) determined with an automated algorithm. 

Statistical Analyses

All analyses were performed according to the intention-to-treat principle. For this post hoc analysis, the primary effect variable was the adjusted common odds ratio (cOR) for a shift in the direction of better outcome on the mRS at 90 days. The association between full-scale or dichotomized CBS (0–6 versus 7–10) and shift in the direction of better outcome on the mRS was assessed using ordinal logistic regression. A binary logistic regression model and a linear regression model were generated to assess the association of CBS with recanalization status and FIV as secondary outcome measures, respectively. For the linear regression model, the underlying assumptions were checked and data were transformed using the ln((x+1)) transformation accordingly. For all outcome parameters, 2 models were generated. Model A contains the CBS variable (continuous or dichotomized) and treatment. In model B, the main prognostic baseline variables as defined in the MR CLEAN protocol were added: age, stroke severity (National Institute of Health Stroke Scale) at baseline, time from onset to randomization, status with respect to previous stroke, atrial fibrillation, and diabetes mellitus. As the CBS incorporates thrombus location in its determination, the model was not corrected for the presence of carotid terminus occlusions. An interaction term of treatment allocation with CBS was added to the both unadjusted and adjusted models to assess whether CBS was a treatment effect modifier. The models with and without added interaction term (nested models) were compared using the $\chi^2$ test.

Patient characteristics are reported for groups with a low (0–6) and high (7–10) CBS. The groups were compared using the $\chi^2$ test for categorical data, the unpaired t test for normally distributed continuous data and the Mann–Whitney U test for non-normally distributed continuous data. All statistics were performed using R (R foundation for Statistical Computing, Vienna, Austria; used packages: Stats, Ordinal, Foreign, Tableone, ggplot2).

Role of the Funding Source

The sponsors of this study were not involved the design of this study, writing of the protocol, study conduct or preparation or review of the article. These tasks were performed solely by members of the executive committee and by local investigators of the participating centers.

Results

Patient Characteristics

In total, 502 patients were randomized in the MR CLEAN trial. Of these, 2 withdrew their consent and were excluded from the data set. One more patient was excluded from the data set because no baseline CTA was available. Overall, the median
CBS was 5 (interquartile range, 3–6), and the median did not differ between the intervention (median [interquartile range], 5 [3–6]) and control group (median [interquartile range], 5 [4–6]). Three patients had an A2 occlusion, resulting in a CBS of 10. After dichotomizing the CBS, 396 patients had a CBS of 0 to 6 and 103 of 7 to 10. Patients in the lower CBS group had a significantly higher baseline National Institute of Health Stroke Scale, lower ASPECTS, and a smaller proportion of patients with diabetes mellitus. Further patient characteristics are summarized in Table 1.

### Primary Outcome
The results for the models with the mRS as outcome are presented in Table 2. The mRS distributions for the treatment arms according to the dichotomized CBS are shown in Figure 2. A higher CBS was associated with increased odds of improving on the mRS for both models A and B (cOR, 1.11 [95% confidence interval [CI], 1.04–1.18] and cOR, 1.12 [95% CI, 1.04–1.20], respectively). For the dichotomous CBS, similar results were found (cOR, 1.73 [95% CI, 1.17–2.55] and cOR, 1.04–1.20], respectively). For the dichotomized CBS, the models yielded similar results. Comparison of the nested model A with and without the interaction of treatment and CBS yielded P values of 0.60 and 0.18 for continuous and dichotomized CBS, respectively, indicating no added value of the interaction term to the fit of the model. These results remained consistent for model B. We did observe a small but insignificant increase in the odds of improvement within the higher dichotomized CBS group (adjusted cORs, 1.61 [95% CI, 1.13–2.31] and 2.68 [95% CI, 1.27–5.77] for CBS 0–6 and 7–10, respectively). However, the absolute risk difference for good functional outcome (mRS, 0–2) between treatment arms did not differ between CBS groups (14.0% [95% CI, 0.06–22.2] and 14.2% [95% CI, 0.05–33.0] for the low and high groups, respectively).

### Secondary Outcomes
The results about the analyses with recanalization and FIV as outcome parameters are listed in Tables I and II in the online-only Data Supplement, respectively. For 105 patients (IAT, 46; usual care, 59) and 64 patients (IAT, 31; usual care, 33), recanalization status and FIV could not be determined for reasons previously reported. A higher CBS was associated with increasing odds of recanalization at 24 hours for both models (model A: OR, 1.25 [95% CI, 1.13–1.38] and model B, 1.27 [95% CI, 1.14–1.41]). For the dichotomized CBS, the models yielded similar results. Comparison of the nested models with and without the added interaction between treatment allocation and CBS showed no added value of the interaction term for either model (Figure 3).

Patients in the higher CBS group after dichotomization had significantly lower FIV (mL; median [interquartile range], 19.1 [16.5–71.4] compared with 75.1 [29.9–155]; P<0.001). To meet the assumptions for linear regression, the FIV was transformed using the ln(x+1) transformation as it had a right-skewed distribution. A higher CBS was associated with a lower FIV (model A, −0.15 [95% CI, −0.20 to −0.10] and model B, −0.13 [95% CI, −0.17 to −0.08]). This association was also present in both models including the dichotomized CBS. Again, no significant interaction was found between treatment allocation and CBS.

### Discussion
In this study, we found that a higher CBS was associated with a higher likelihood of recanalization, smaller FIV’s, and improved neurological outcome at 90 days. Pathophysiologically this translates to a lower likelihood of recanalization for larger and more proximally located thrombi, resulting in consistently worse clinical and tissue outcomes across the panel of trial end points. Interestingly, we found no statistically significant interaction between treatment and CBS for any of the outcome variables.

Our findings confirm the prognostic value of CBS for patients treated with IVT found in earlier studies and further extends this finding to patients treated with IAT. Studies reporting the influence of thrombus length (measured on susceptibility weight imaging on magnetic resonance imaging) on recanalization rates after thrombectomy are conflicting. Two studies found significantly shorter thrombi in the group with successful recanalization, whereas another found no difference in thrombus length between these groups. It
should be noted that these findings are from retrospective studies without adjustment for potential baseline differences between groups.

The nonsignificant interaction between treatment allocation and CBS contrasts to findings from other studies. According to a personal communication by Dr Demchuk published by Puetz et al,14 an increase in benefit from IAT for lower CBS (0–4) was found in the ESCAPE trial (Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times) when compared with higher values of the CBS (5–10). Furthermore, in a post hoc analysis of the IMS-III trial, a significant difference in recanalization rates was found between the IAT and IVT groups for ICA-L or ICA-T occlusions and tandem occlusions in favor of IAT. For M1 and M2 occlusions, no such difference was found.13 As ICA-L and ICA-T occlusions generally correspond to a lower CBS, this would imply a higher efficacy of IAT relative to IVT for lower CBS. No analyses were performed with the CBS in that post hoc analysis. As our study is the first to investigate the potential role of CBS as a treatment effect modifier in a population randomized for usual care or IAT using interaction analysis, the results cannot be compared directly.

The strength of our study is that no patients were excluded based on any advanced imaging in the MR CLEAN trial. This resulted in the inclusion of patients with unfavorable clinical and imaging profiles, in turn, resulting in widely generalizable findings. The used intention-to-treat analysis and relative lack of patient selection also allow for a less biased assessment of the efficacy of baseline imaging parameters to select patients for IAT. However, this analysis also harbors a potential weakness. In the MR CLEAN trial, several patients who were allocated to the intervention arm did not receive IAT. When evaluating whether an imaging parameter is suited to select patients for a treatment, it could add to the sensitivity of the analysis to only include the patients who actually received the studied treatment.

A further limitation is our assumption of continuity of the CBS. Although CBS is a semicontinuous score with 11 levels (0–10), it is still possible that information is lost when

<table>
<thead>
<tr>
<th>Variables</th>
<th>Common Odds Ratios for a Shift in the Direction of Better Outcome on the mRS at 90 d (n=499)</th>
<th>Full Scale CBS</th>
<th>CBS Dichotomized at 6</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Model A</td>
<td>Model B</td>
<td>Model A</td>
</tr>
<tr>
<td>CBS</td>
<td>1.11</td>
<td>(1.05–1.19)*</td>
<td>1.10</td>
</tr>
<tr>
<td>Treatment allocation</td>
<td>1.70</td>
<td>(1.24–2.33)*</td>
<td>1.45</td>
</tr>
<tr>
<td>Interaction term</td>
<td>NA</td>
<td>1.03</td>
<td>(0.91–1.18)</td>
</tr>
<tr>
<td>Comparison of nested models ($\chi^2$ test)</td>
<td>$P=0.60$</td>
<td>$P=0.76$</td>
<td>$P=0.18$</td>
</tr>
</tbody>
</table>

The odds ratios presented express the increase in odds of improving on the mRS for each unit increase of the variable. The values between the parentheses represent the 95% confidence intervals. CBS denotes clot burden score; and mRS, modified Rankin Scale.

*Statistically significant ($P\leq0.05$).
we assess this variable as being continuous. In addition, CTA can overestimate the extent of thrombus involvement if the collateral circulation is weak or if not enough time has elapsed between contrast injection and brain imaging, such that contrast does not reach the distal end of the thrombus.\textsuperscript{25–27} However, this lack of collateral filling on conventional CTA might add to the prognostic strength of the CBS as poor collaterals result in lower CBS.\textsuperscript{27} Furthermore, similar correlations between CBS and mRS at 3 months were found for 4D-CTA and conventional CTA.\textsuperscript{26} The imaging protocols utilized at the enrolling centers in MR CLEAN reflect the real-world variability in the current clinical practice. Future studies should examine the impact of collateral strength and imaging acquisition timing on the CBS variability and the association of CBS with neurological outcome.

Finally, this study is an exploratory, post hoc subgroup analysis. As the MR CLEAN trial was not powered for these analyses, significant results could constitute false-positive findings. Therefore, an absent treatment effect in a subgroup observed in post hoc analyses would have to be confirmed in subsequent prospective trials before guidelines or clinical practice are modified.

The observed decline in successful recanalization after IAT for lower values of CBS can be explained by several factors. As stent-retrievers are of a fixed length, there might be mismatch between stent- and thrombus-length resulting in suboptimal stent placement. Currently, longer stents are being manufactured, which might improve the efficacy of IAT for larger occlusions. Also, comorbidities or other patient characteristics could influence efficacy. When we compare the present cohort with the study population from the ESCAPE study, in which a higher efficacy of IAT was found relative to usual care for lower CBS,\textsuperscript{14} we find several important differences. For instance, a higher proportion of patients with a concomitant ipsilateral extracranial carotid artery occlusion were found in the intervention arm of the MR CLEAN trial (32.2% versus 12.7%).\textsuperscript{1,2} However, a recent multicenter case series of patients with tandem occlusions reported recanalization rates similar to those of trials that excluded patients with tandem occlusions.\textsuperscript{28} Further differences between populations include longer times from symptom onset to groin puncture in the MR CLEAN study and differences in the proportions of patients with diabetes mellitus or atrial fibrillation.\textsuperscript{1,2} These factors might impact thrombus composition and in turn influence the efficacy of IAT. However, our results remained consistent after adjusting for all the latter variables. To elucidate other factors influencing IAT efficacy, further research is warranted. Our study shows that although CBS is associated with poor outcome, it is not a treatment effect modifier.

**Conclusions**

A higher CBS is associated with improved neurological outcome and may be used as a prognostic marker. We found no evidence that CBS modifies the effect of IAT.

**Appendix**

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![Figure 3. Association of the clot burden score (CBS) on the odds of recanalization at 24 h in both treatment arms for model A. The bands express the 95% confidence interval. The difference on the y-axis between both lines represents the treatment effect. A, The plot for model A with added interaction term between CBS and treatment allocation. The difference in slopes between both lines represents the (insignificant) interaction. B, Model A without the interaction term. Both lines run parallel from each other and can therefore never identify a point for which the treatment efficacy of both groups is equal.](http://stroke.ahajournals.org/Download)
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References


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SUPPLEMENTAL MATERIAL
Supplemental tables

Supplemental table I. Odds ratios expressing the association between Clot Burden Score and recanalization at 24 hours*

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<th>Variables</th>
<th>Full Scale CBS</th>
<th>CBS dichotomized at 6</th>
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<td>1.27 (1.14-1.41)†</td>
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<td>11.28 (4.05-33.28)†</td>
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<td>Interaction Term</td>
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<td>0.92 (0.75-1.11)†</td>
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Comparison of the nested models (χ²-test)

|                      | p= 0.38 | p = 0.95 | p= 0.37 | p = 0.82 |

*The presented odds ratios express the increase of the odds of recanalization at 24 hours for each unit increase. No data regarding the recanalization at 24 hours was available for 105 patients. CBS denotes clot burden score and NIHSS the National Institute of Health Stroke Scale. The values between the parentheses represent the 95% confidence intervals. Values presented with a † are statistically significant (p<0.05)
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<th>Variables</th>
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<th>CBS dichotomized at 6</th>
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<tr>
<td></td>
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<td>Clot Burden Score (CBS)</td>
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<tr>
<td></td>
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<td>(-0.20-</td>
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<tr>
<td></td>
<td>-0.10)†</td>
<td>-0.07)†</td>
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<td></td>
<td>-0.11)†</td>
<td>0.34)</td>
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<td>Interaction term</td>
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<td></td>
<td>(-0.13-</td>
<td>(-0.11-</td>
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<tr>
<td></td>
<td>0.06)</td>
<td>0.08</td>
</tr>
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</table>

Comparison of the nested models ($\chi^2$-test)

- p = 0.73
- p = 0.47
- p = 0.73
- p = 0.84

* To meet the assumptions to perform linear regression, final infarct volume underwent an ln(x+1) transformation. The presented values represent the increase of the transformed final infarct volume for each unit increase of the variable. No data concerning their final infarct volume was available for 64 patients. CBS denotes clot burden score and NIHSS the National Institute of Health Stroke Scale. The values between the parentheses represent the 95% confidence intervals. Values presented with a † are statistically significant (p<0.05).