Original Investigation | CLINICAL TRIAL

Time to Reperfusion and Treatment Effect for Acute Ischemic Stroke
A Randomized Clinical Trial

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IMPORTANCE Intra-arterial treatment (IAT) for acute ischemic stroke caused by intracranial arterial occlusion leads to improved functional outcome in patients treated within 6 hours after onset. The influence of treatment delay on treatment effect is not yet known.

OBJECTIVE To evaluate the influence of time from stroke onset to the start of treatment and from stroke onset to reperfusion on the effect of IAT.

DESIGN, SETTING, AND PARTICIPANTS The Multicenter Randomized Clinical Trial of Endovascular Treatment of Acute Ischemic Stroke in the Netherlands (MR CLEAN) was a multicenter, randomized clinical open-label trial of IAT vs no IAT in 500 patients. The time to the start of treatment was defined as the time from onset of symptoms to groin puncture (TOG). The time from onset of treatment to reperfusion (TOR) was defined as the time to reopening the vessel occlusion or the end of the procedure in cases for which reperfusion was not achieved. Data were collected from December 3, 2010, to June 3, 2014, and analyzed (intention to treat) from July 1, 2014, to September 19, 2015.

MAIN OUTCOMES AND MEASURES Main outcome was the modified Rankin Scale (mRS) score for functional outcome (range, 0 [no symptoms] to 6 [death]). Multiple ordinal logistic regression analysis estimated the effect of treatment and tested for the interaction of time to randomization, TOG, and TOR with treatment. The effect of treatment as a risk difference on reaching independence (mRS score, 0-2) was computed as a function of TOG and TOR. Calculations were adjusted for age, National Institutes of Health Stroke Scale score, previous stroke, atrial fibrillation, diabetes mellitus, and intracranial arterial terminus occlusion.

RESULTS Among 500 patients (58% male; median age, 67 years), the median TOG was 260 (interquartile range [IQR], 210-311) minutes; median TOR, 340 (IQR, 274-395) minutes. An interaction between TOR and treatment (P = .04) existed, but not between TOG and treatment (P = .26). The adjusted risk difference (95% CI) was 25.9% (8.3%-44.4%) when reperfusion was reached at 3 hours, 18.8% (6.6%-32.6%) at 4 hours, and 6.7% (0.4%-14.5%) at 6 hours.

CONCLUSION AND RELEVANCE For every hour of reperfusion delay, the initially large benefit of IAT decreases; the absolute risk difference for a good outcome is reduced by 6% per hour of delay. Patients with acute ischemic stroke require immediate diagnostic workup and IAT in case of intracranial arterial vessel occlusion.

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For decades, intra-arterial treatment (IAT) was considered a potentially valuable expansion of the therapeutic options for acute ischemic stroke. However, until the end of 2014, IAT with mechanical devices had not been proven effective in randomized clinical trials.[1-3] The Multicenter Randomized Clinical Trial of Endovascular Treatment of Acute Ischemic Stroke in the Netherlands (MR CLEAN) trial was a randomized clinical trial of IAT for acute ischemic stroke in patients with a confirmed intracranial occlusion in the anterior cerebral circulation who could be treated within 6 hours of onset. The intervention contrast was IAT vs no IAT against a background of best medical care, including intravenous alteplase if indicated. The trial demonstrated a shift in the distribution of functional outcomes on the modified Rankin Scale (mRS) in favor of the intervention, and this finding was consistent in almost all subgroup analyses.[4] With IAT, the rate of patients achieving independence (mRS score, 0-2) increased from 19% to 33%. Four published trials[5-8] and 2 unpublished trials[9,10] confirmed the effect of IAT.

Time is an important predictor of the clinical outcome and treatment effect in cerebral ischemia. Intravenous treatment (IVT) with alteplase within 4.5 hours after stroke onset is effective, although the size of the treatment effect diminishes over time. In a large meta-analysis of individual patient data from randomized clinical trials,[11] the odds ratio (OR) for a good outcome was 1.75 for treatment within 3 hours of stroke onset and 1.26 for treatment between 3 and 4.5 hours; the absolute benefit decreased from 9.8% to 4.2% in these time windows. In the setting of IAT, delay to reperfusion has been shown to have a negative effect on the likelihood of a good outcome.[12] However, no evidence supports the notion that delay also influences the size of the treatment effect.

Time from onset of stroke to groin puncture (TOG) is considered a practical and useful clinical marker in the delivery of IAT. However, TOG might not be the best indicator because duration of the intervention may vary widely. Therefore, the time from onset of stroke to reperfusion (TOR) is thought to be a more relevant marker.[12-14] We evaluated the effect of time from the onset of stroke to randomization (TORnd), TOG, and TOR on the effectiveness of treatment and outcomes in the MR CLEAN study. We also wanted to investigate whether the treatment effect pertained to the full 6-hour time window in our study and whether and by how much the treatment effect decreased as a function of TOG and TOR.

Methods

The detailed methods of the MR CLEAN trial have been described earlier.[4,15] The trial was conducted in 16 hospitals in the Netherlands. In short, MR CLEAN is a multicenter clinical trial for IAT of acute ischemic stroke caused by a proximal intracranial arterial occlusion in the anterior circulation. A proximal occlusion had to be confirmed on vessel imaging before randomization. Intra-arterial treatment consisted of arterial catheterization with a microcatheter to the level of occlusion and delivery of a thrombolytic agent, mechanical thrombectomy, or both. The method of IAT was left to the discretion of the local interventionist, but almost all patients were treated with retrievable stents. Only devices approved by US Food and Drug Administration or Conformité Européenne mark certification and by the steering committee could be used in the trial. Treatment needed to be initiated within 6 hours after stroke onset. In total, 500 patients were included in the trial, with 233 assigned to the intervention arm and 267 assigned to the control arm. All patients received usual treatment, including IVT if indicated. The full study protocol can be found in the Supplement. Approval was obtained from all ethical boards of the participating centers (listed with the trial investigators at the end of the article), and all participants (or their legal representatives) provided written informed consent.

Clinical Definitions

We defined *TOG* as the time from stroke onset to the placement of a catheter in the groin. We defined *TOR* as the time from stroke onset to reperfusion or the end of procedure. *Stroke onset* was defined as the moment of witnessed symptom onset or the moment last confirmed as healthy in cases in which symptom onset was not observed by the patient or by a second person. *Reperfusion* was defined as a modified Thrombolysis in Cerebral Infarction (mTICI) score of 2b or 3. The mTICI scores range from grade 0 (no reperfusion) to grade 3 (complete reperfusion).[16] An independent reader who was masked for clinical outcome (A.J.Y.) blindly assessed all digital subtraction angiographies and checked timing.

Outcome Measures

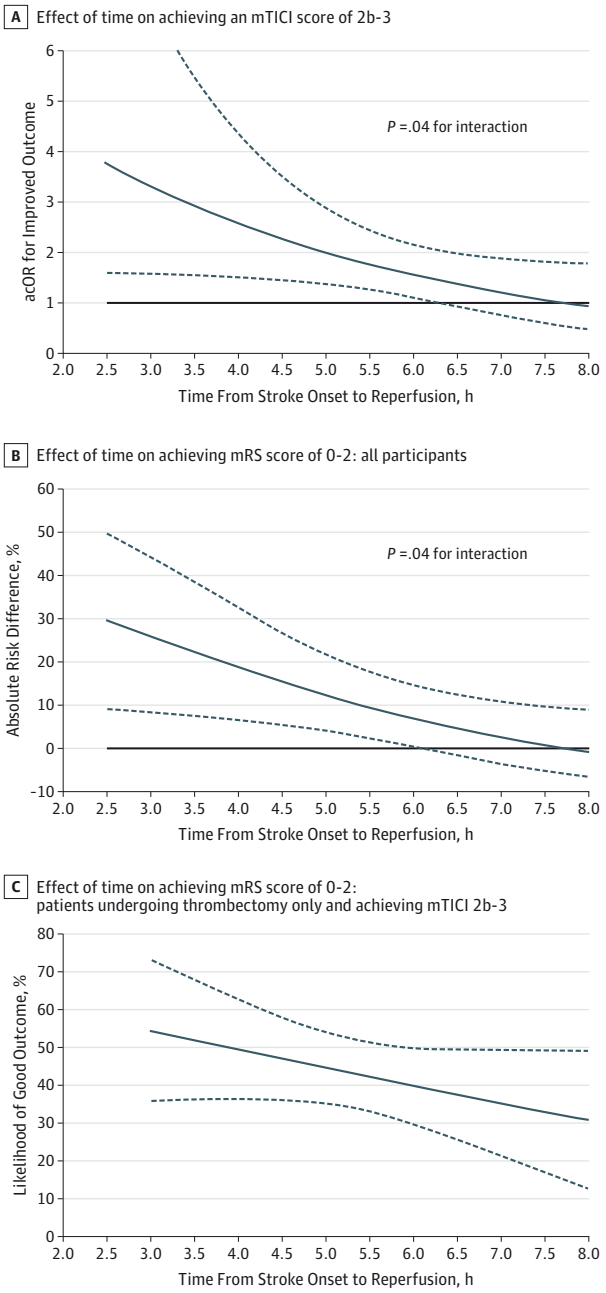
For the present analysis, the primary outcome was the mRS score at 90 days. The mRS is a 7-point scale ranging from 0 (no symptoms) to 6 (death). A score of 2 points or less indicates functional independence.[17]

Statistical Analysis

Data were collected from December 3, 2010, to June 3, 2014, and analyzed from July 1, 2014, to September 19, 2015. All analyses were based on the intention-to-treat principle. Baseline characteristics of our study population were presented in tertiles of TOG. The primary effect variable was the adjusted common OR (acOR), which was analyzed with ordinal logistic regression models. The secondary effect variable was the absolute risk difference (ARD) for chances of a good outcome (mRS score, 0-2). Furthermore, we compared treatment duration in patients undergoing successful reperfusion (mTICI score, 2b-3) and those with unsuccessful treatment (mTICI score, 0-2a) using the 2-tailed unpaired *t* test.

We tested for the interaction of TORnd, TOG, and TOR with treatment by including interaction terms in the ordinal logistic regression model. We computed unadjusted estimates first. Thereafter, all estimates were adjusted for the following prespecified clinical variables according to the original statistical analysis of the MR CLEAN study: age, National Institutes of Health Stroke Scale score, history of stroke, atrial fibrillation, diabetes mellitus, and intracranial arterial terminus occlusion. We tested the shape of the relationship between the treatment effect and TOG or TOR with a linear interaction term

Figure. Effect of Time From Onset of Reperfusion (TOR) and Intra-arterial Treatment on Stroke Outcomes



A, The effect of time from the onset of stroke to reperfusion (TOR) on a good outcome (modified Thrombolysis in Cerebral Infarction [mTICI] score, 2b-3; range, 0 [no reperfusion] to 3 [complete reperfusion]) or the end of the procedure on the effect of intra-arterial therapy expressed as adjusted common odds ratio (acOR). B, The effect of TOR on a good outcome (modifed Rankin Scale [mRS] score, 0-2; range, 0 [no symptoms] to 6 [death]) expressed as the absolute risk difference. C, The association of TOR with the chances of a good outcome (mRS scale, 0-2) is plotted in the subset of patients who underwent thrombectomy only and achieved an mTICI score of 2b to 3.

and with restricted cubic splines with 3 knots.[18] Selection of the final model was based on a χ^2 test finding.

We plotted the acOR of treatment and its 95% CI over time on the basis of parameters (β values and SEs) estimated in the models with the adjusted interaction terms. In the primary analysis, we imputed TOG and TOR with the study mean in all patients in the control and intervention groups who did not receive an angiogram or IAT. In a secondary analysis, the absolute probability of reaching an mRS score of 0 to 2 over time was calculated from the ordinal model separately for the intervention and control arms and with all other covariates at the mean (dichotomous covariates) or median (continuous covariates). To do this, we imputed TOG and TOR for untreated patients with linear regression. We plotted the ARDs and corresponding 95% CIs. In addition, we estimated the treatment effect stratified for tertiles of TOG and TOR. For a better understanding of our results and comparison with other trials, we performed a tertiary analysis in which we looked at the chances of a good outcome in thrombectomy only for patients who achieved good reperfusion (mTICI score, 2b-3). All statistical analyses were performed with STATA/SE software (version 13.1; StataCorp). The **Figure** was composed using R statistical software (https://www.r-project.org/).

Results

Patient Characteristics

Clinical baseline characteristics of the 500 study participants are given per tertile of TOG (**Table**), but all analyses were performed with the continuous variables. Median TOG was 256 (interquartile range, 210-314) minutes; median TOR, 333 (interquartile range, 279-394) minutes. In total, 17 of 233 patients in the intervention arm (7.3%) did not reach the intervention room.[4] In 25 of 233 patients (10.7%), treatment started within 3 hours after stroke onset; in 96 of 233 patients (41.2%), between 3 and 4.5 hours after stroke onset; and in 95 of 233 patients (40.8%), more than 4.5 hours after stroke onset, including 19 patients (8.2%) for whom treatment started more than 6 hours after stroke onset (range, 360-455 minutes). All patients were included in the analysis. We found no major imbalances in risk factors for poor outcome, clinical risk factors for stroke, and prerandomization treatment details among the early, middle, and late tertiles of TOG.

Primary Analysis

In the MR CLEAN study, a shift in the distribution of the primary outcome in favor of the intervention (acOR, 1.67; 95% CI, 1.21-2.30) was observed.[4] The interaction of TOG with treatment was not significant (unadjusted P = .10 and adjusted P = .26 for interaction); also, the interaction of TORnd with treatment was not significant (unadjusted P = .17 and adjusted P = .36 for interaction). Interaction of TOR with treatment was stronger and statistically significant (unadjusted P = .01 and adjusted P = .04 for interaction). A nonlinear interaction term did not significantly improve the fit for TOG modeling (TOG model with linear term, χ^2 = 150.75; TOG model with restricted cubic line with 3 knots, χ^2 = 155.22; P = .11) and TOR modeling (TOR model with linear term, χ^2 = 160.20; TOR model with restricted cubic line with 3 knots, χ^2 = 166.07; P = .051) significantly. Thus, modeling of both interaction terms remained linear.

Table. Baseline Characteristics per Tertile of TOG

Clinical Characteristic	TOG Tertile		
	Early (n = 167)	Middle (n = 168)	Late (n = 165)
All patients			
Demographic data			
Age, median (IQR), y	67 (57-77)	66 (53-75)	64 (55-75)
Male sex, No. (%)	94/167 (56.3)	99/168 (58.9)	99/165 (60.0)
NIHSS score, median (IQR)	17 (13-22)	17 (14-22)	18 (15-22)
History of ischemic stroke, No. (%)	19/167 (11.4)	17/168 (10.1)	18/165 (10.9)
Atrial fibrillation, No. (%)	42/167 (25.1)	42/168 (25.0)	51/165 (30.9)
Diabetes mellitus, No. (%)	26/167 (15.6)	17/168 (10.1)	25/165 (15.2)
Intracranial carotid terminus occlusion, No. (%)	45/167 (26.9)	52/168 (31.0)	37/165 (22.4)
TOG, median (IQR) min	198 (180-210)	256 (242-273)	331 (314-360)
Time from onset to IVT, median (IQR), min	72 (58-90)	86.5 (70-110)	110 (76-155)
Patients undergoing reperfusion[a]			
TORnd, median (IQR), min	137 (117-153)	205 (184-225)	284 (262-313)
TOR, median (IQR), min	260 (240-280)	332 (314-353)	411 (391-450)

Abbreviations: IQR, interquartile range; IVT, intravenous treatment; NIHSS, National Institutes of Health Stroke Scale; TOG, time from onset of stroke to groin puncture; TOR, time from onset of stroke to reperfusion; TORnd, time from stroke onset to randomization.

[a] Fifty-five patients did not achieve reperfusion, including 20 in the early tertile, 20 in the middle tertile, and 15 in the late tertile.

The largest treatment effect was observed if reperfusion was achieved early after the onset of symptoms. For TOR, the acOR (95% CI) decreased from 2.28 (1.28-4.06) in the early tertile to 1.13 (0.64-2.01) in the late tertile. The ARD in reaching functional independence was 16.5% in favor of the intervention in the early tertile and only 2.8% in the late tertile.

We plotted the treatment effect against TOR (Figure, A). Treatment effect was significant until 6 hours 18 minutes (acOR 1.42; 95% CI, 1.00-2.03); at 7 hours 43 minutes, the point estimate crossed the line that indicated unity.

Secondary Analyses

To obtain an indication of the change in the absolute risk for a good outcome (mRS score, 0-2) as a function of TOR, we calculated chances for a good outcome in the intervention and control groups and subsequently computed and plotted the ARD against TOR. When reperfusion was reached at 3 hours after stroke onset, the ARD (95% CI) was 25.9% (8.3%-44.4%); at 4 hours, 18.8% (6.6%-32.6%); and at 6 hours, 6.7% (0.4%-14.5%) (Figure, B). These ARDs indicate a mean reduction in the effect of treatment (risk difference for the chance of a good outcome) of 6.4% per hour of reperfusion delay.

Mean treatment duration was 88 minutes in patients with poor reperfusion (mTICI score, 0-2a) and 67 minutes in patients with good reperfusion (mTICI score, 2b-3), with a mean difference in treatment duration of 21 (95% CI, 10-32) minutes. The dispersion of imputed values for TOR in the control group (mean: 339; median, 327; interquartile range, 281-394 minutes) and actual values for TOR in the intervention group (mean, 338; median, 338; interquarile range, 275-393) was very similar.

Tertiary Analysis

We plotted the chances of a good outcome for patients undergoing thrombectomy who achieved an mTICI score of 2b to 3 against TOR (Figure, C). In the group of patients who reached mTICI 2b to 3 at 3 hours, the likelihood of reaching mRS 0 to 2 was 55% (95% CI, 36% to 73%), but after 8 hours this diminished to 31% (95% CI, 13% to 49%).

Sensitivity Analysis

In a sensitivity analysis, we assessed the effect of different assumptions concerning TOR in patients with failed recanalization (mTICI score, 0-2a). We calculated the interaction of TOR with treatment effect by subtracting 21 minutes of TOR in patients who did not achieve reperfusion because TOR was a mean of 21 minutes longer for patients who did not achieve reperfusion. The unadjusted value for interaction was $P = .02$, and the adjusted value for interaction was $P = .08$.

Discussion

Summary

Our findings reveal a strong inverse relationship between TOR and the effect of IAT in patients with acute ischemic stroke caused by a proximal vessel occlusion of the anterior circulation. With regard to TOG, we found a similar association that did not reach statistical significance. Although the treatment effect is highest among patients treated early, our results do not provide arguments for withholding treatment from patients within the 6-hour time window.

Explaining the Intervention Effect Results (Internal Validity)

This study demonstrates that eligible patients benefit from IAT when treatment is started within 6 hours of stroke onset. We did not observe a significant interaction of TOG with treatment effect, although this interaction was biologically plausible beforehand. The fact that a significant interaction was found between TOR and treatment effect but not between TOG and treatment effect can be explained by the variable duration of the intervention itself found in the MR CLEAN study (median [interquartile range], 66 [46-94] minutes). Therefore, TOR might be a better indicator than TOG of the mecha-

nism of treatment effect modification. We adjusted all analyses for predefined clinical prognostic factors, and all estimates in the interaction models were based on the adjusted interaction terms, which decreased the precision of our estimates but increased their reliability and generalizability.

External Validity

In the MR CLEAN study, the study population represented typical patients who are likely to undergo IAT in clinical practice. No or minimal restrictions were placed on the upper age limit, severity of the neurologic deficit, presence of ipsilateral cervical carotid occlusion or stenosis on computed tomographic angiography, and extent of early infarct signs on pretreatment imaging. The median age of participants in the study was 67 years, and the median National Institutes of Health Stroke Scale score was 17, which are consistent with the data from previous studies. The intervention was almost exclusively performed with a retrievable stent, which is the most commonly used device for this indication at present.

The mean time from the start of IVT to randomization was 109 minutes longer in the late-TOG tertile compared with the early-TOG tertile. Therefore, we believe that later TOR is more related to patient transportation instead of procedure difficulty or later presentation to medical attention.

Other Studies

Several IAT trials have examined the clinical impact of the timing of intervention. The IMS III (Interventional Management of Stroke phase 3) trial investigators[12,19] performed 2 such studies. They analyzed the time to angiographic reperfusion in 240 of 654 patients who underwent IAT, had a complete occlusion at baseline, and finished angiography within 7 hours. The time to reperfusion was inversely associated with the likelihood of a good clinical outcome. Subsequently, the investigators developed a decision-analytic model based on their trial data and comprehensive literature review. With sensitivity analysis, they demonstrated the superiority of IAT to IVT unless TOR exceeded 347 minutes (close to 6 hours).[19] These data should be interpreted with care because the controls were not included in the analysis. In this setting, interpretation of a time by treatment interaction is difficult and may lead to overestimation of the effect size. This uncontrolled approach may be valid for IVT because abundant data from controlled studies suggest that at approximately 6 hours, the point estimate of the treatment effect approaches unity.[20] The tertiary analysis of the effect of time from onset to good reperfusion in patients undergoing thrombectomy only suggests that the likelihood of a good outcome diminishes by 5% per hour to 40% at 8 hours. This analysis emphasizes the effect of time delay on a good outcome but is not very helpful as a decision support tool because, at the end of the scale (8 hours), a considerable chance of a good outcome remains. Whether this possible good outcome is a result of the intervention and, more important, whether the treatment is still effective beyond 6 or 8 hours cannot be inferred from our analysis.

The ESCAPE (Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke)[5] and SWIFT PRIME (Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment)[7] trials placed a strong emphasis on reducing delay to treatment and consequently had relatively short TOG and first TOR intervals. To minimize time to treatment, the study design allowed verbal informed consent before randomization, in contrast to the MR CLEAN trial, which required written informed consent. Median TOR in the ESCAPE trial was 241 minutes; in the MR CLEAN study, 331 minutes. The overall treatment effect in the ESCAPE trial was larger than in the MR CLEAN study, which might be partly explained by the shorter TOR.

Limitations

Our study allows conclusions only with respect to the 6-hour time window because it was a requirement for inclusion in the MR CLEAN study that treatment could be started within 6 hours. Nevertheless, the 19 of 233 patients (8.2%) who received treatment outside the 6-hour time window were included in the analyses.

As expected, the numbers of patients who were treated at the beginning and end of the time window were small, so the 95% CIs in our interaction models are wide, and effect estimates from these areas should be interpreted with caution. Future analyses of pooled data from several randomized clinical trials will be needed to increase the precision of these estimates.

The definition of TOR was based on the point when an mTICI score of 2b to 3 was reached or the end of the procedure when reperfusion was not achieved. This definition could lead to an overestimation of the interaction of time and treatment when intervention was prolonged in failed treatment. We found that the treatment duration was 21 minutes longer in patients who did not achieve reperfusion compared with those with successful reperfusion. In a sensitivity analysis in which we adjusted the longer TOR in patients who failed to achieve reperfusion, the interaction term lost its significance (adjusted P = .08 for interaction), although the unadjusted estimate was still significant and the direction and size of the interaction effect remained the same. We therefore conclude that this potential bias did not have a major effect on our results.

Conclusions

This study highlights the critical importance of reducing delays in time to IAT for patients with acute ischemic stroke. The absolute treatment effect and its decrease over time are larger than those reported for intravenous treatment. For every hour of reperfusion delay, the ARD for chances of a good outcome is reduced by 6%. Most important, our findings imply that patients with acute ischemic stroke should undergo an immediate diagnostic workup and IAT in case of intracranial arterial vessel occlusion.

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