MR CLEAN: TOR Affects Treatment Efficacy in Patients With Acute Ischemic Stroke

Written by Alla Zarifyan

Puck Fransen, MD, Erasmus MC University Medical Center, Rotterdam, The Netherlands, reported results of the analyses that examined the interaction between time from stroke onset to treatment (TOT) and time from stroke onset to reperfusion (TOR) and the effect of treatment on clinical outcome in the MR CLEAN trial, demonstrating that TOR significantly affected treatment outcome.

MR CLEAN was the first study to demonstrate efficacy of intra-arterial treatment received within 6 hours of stroke onset in patients with acute ischemic stroke due to intracranial anterior circulation occlusion [Berkhemer OA et al. *N Engl J Med*. 2015]. According to Dr Fransen, time is an important predictor of clinical outcome in all ischemic diseases, and this analysis was assigned to assess the interaction between TOT and TOR with treatment on clinical outcome and whether treatment was effective in the entire 6-hour time frame used in the trial.

The multicenter MR CLEAN was a randomized, prospective, open-label, phase 3 trial with blinded outcome assessment conducted in The Netherlands. The primary outcome measure in this analysis was the score on the modified Rankin Scale (mRS) at 90 days, with adjusted common odds ratio for shift on the mRS as the primary effect parameter.

The study enrolled a total of 500 patients (167 in early, 168 in medium, and 165 in late TOT groups). The main clinical characteristics—such as patient age, sex, and the National Institute of Health Stroke Scale score at baseline—were similar among the groups.

The median TOT (treatment defined as microcatheter in the groin) was 256 minutes, with 11.5% of patients receiving treatment in <3 hours, 45% between 3 and 4.5 hours, 44% between 4.5 and 6 hours, and 8.8% in >6 hours. The median TOR (reperfusion defined as achieving thrombolysis in cerebral infarction grade 2b/3—which has been regarded as a successful angiographic outcome—or end of the procedure if reperfusion was not reached) was 332 minutes, with 1.5% achieving reperfusion in <3 hours, 22% between 3 and 4.5 hours, 40% between 4.5 and 6 hours, and 37% in >6 hours.

An analysis of the relationship between treatment effect and TOT suggested that the absolute risk difference (ARD) in chances of good outcome (mRS, 0-2) between treated and untreated patients was 19% at TOT equal to 2 hours and 3% at TOT equal to 6 hours. This implied a 4% decrease in ARD per hour, which was not statistically

Figure 1. TOR Affects Chances of Good Outcome
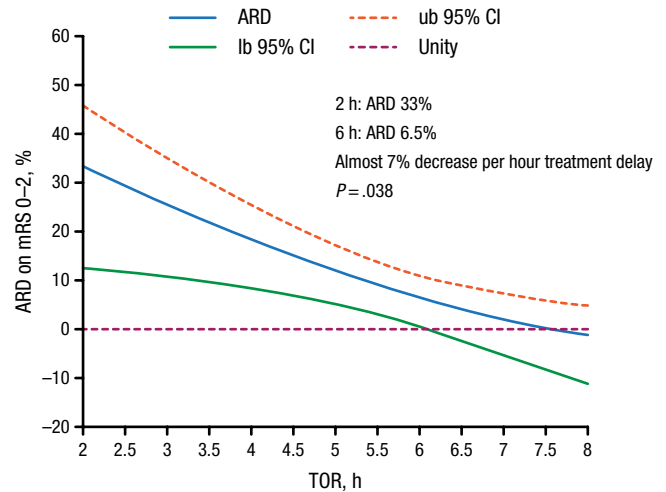
ARD, absolute risk difference; lb, lower bound; mRS, modified Rankin Scale; TOR, time from stroke onset to reperfusion; ub, upper bound.

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significant ($P=.26$). However, the decrease in ARD per hour of TOR was calculated to be almost 7% and statistically significant ($P=.038$), with ARD of 33% at 2 hours and 6.5% at 6 hours (Figure 1). The treatment effect was not statistically significant beyond TOR of 6 hours and 19 minutes.

Dr Fransen concluded that there was a significant interaction between TOR and treatment effect, while the interaction between TOT and treatment effect was not statistically significant but is still considered to be biologically possible. The study demonstrated that the probability of a positive outcome decreases rapidly with every hour of reperfusion delay, and patients with acute ischemic stroke should receive appropriate treatment as soon as possible.

Aspirin Not Effective for Primary Prevention of Stroke in Older Japanese

Written by Wayne Kuznar

Daily aspirin does not significantly reduce the risk of a first fatal or nonfatal stroke in older patients with vascular risk factors. Shinichiro Uchiyama, MD, PhD, International University of Health and Welfare, Sanno Hospital and Sanno Medical Center, Tokyo, Japan, presented an analysis of the effect of aspirin for primary prevention of stroke in the Japanese Primary Prevention Project (JPPP) [Ikeda Y et al. *JAMA*. 2014].

Table 1. Patient Characteristics and Risk Factors at Baseline in JPPP

Factor	Aspirin, %	No Aspirin, %
Men	42.3	42.4
Hypertension	84.9	84.8
Dyslipidemia	72.0	71.8
Diabetes	33.9	33.9
BMI≥25 kg/m^2	36.6	35.9
Currently smoking	13.3	12.9
Family history of premature CV disease	27.4	27.4

CV, cardiovascular; BMI, body mass index; JPPP, Japanese Primary Prevention Project.
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The effect of aspirin on the primary prevention of stroke varies among clinical trials conducted in Western countries, and no data have been available on the effect of aspirin in an Asian population, which is at higher risk of intracranial hemorrhage than a white population.

JPPP included 14 464 Japanese patients aged 60 to 85 years (mean age, 70 years) who presented with hypertension, dyslipidemia, or diabetes [Ikeda Y et al. *JAMA*. 2014]. Patients were randomized 1 to 1 to receive aspirin 100 mg once daily or no aspirin, in addition to ongoing medications. Follow-up was a median of 5.02 years, with a maximum follow-up of 6.5 years.

The primary end point was a composite of death from cardiovascular causes (myocardial infarction, stroke, and other cardiovascular causes), nonfatal stroke (ischemic or hemorrhagic, including undefined cerebrovascular events), and nonfatal myocardial infarction.

The main results of JPPP showed no significant effect of aspirin on the primary composite end point (HR, 0.94; 95% CI, 0.77 to 1.15; P = .54). The prevalence of risk factors in the aspirin and no aspirin groups at baseline are shown in Table 1.

In the analysis, the number of fatal and nonfatal strokes was 128 in each group. In analyzing the data further however, the type of stroke that occurred did vary, depending on the use or non-use of aspirin. Ischemic stroke was less frequent in the aspirin vs no aspirin group (85 vs 102), but hemorrhagic stroke was more common in the aspirin group (38 vs 23). Additionally, the number of transient ischemic attacks (TIAs) was nearly half that in the aspirin vs no aspirin group (19 vs 34).

The cumulative rate of any stroke or TIA at 5 years was not different between the groups (adjusted HR, 0.927; 95% CI, 0.741 to 1.60; P = .509). The cumulative rate of

Table 2. Significant Risk Factors for Cerebrovascular Events by Cox Regression Analysis

Factor	HR (95% CI)	P Value
Age≥70 y	2.207 (1.718 to 2.836)	P < .001
Smoking	1.513 (1.111 to 2.061)	P = .009
Diabetes	1.555 (1.237 to 1.954)	P < .001

any stroke at 5 years was also not significantly different (adjusted HR, 1.011:95% CI, 0.791 to 1.291; P = .932).

The rate of ischemic stroke was lower in the aspirin vs no aspirin group, although this difference failed to achieve significance (adjusted HR, 0.842; 95% CI, 0.631 to 1.123; P = .240).

Cerebral hemorrhage was almost twice as common in the aspirin vs no aspirin group (28 vs 15, respectively), while the rates of subarachnoid hemorrhage, subdural hematoma, and other hemorrhage were comparable. The cumulative rate of intracranial hemorrhage was not significantly different between the groups (adjusted HR, 1.463; 95% CI, 0.956 to 2.237; P = .078). Significant risk factors for cerebrovascular events are listed in Table 2.

The rate of any stroke or TIA was not significantly different between patients randomized to aspirin or no aspirin in the low-risk or the high-risk groups based on a stroke risk score.

Treatment Benefit of Endovascular Therapy in MR CLEAN Quantified

Written by Wayne Kuznar

Endovascular therapy of large vessel acute ischemic stroke allows 1 additional patient to have fully restored neurologic function for every 7 patients treated and 1 additional patient to have improved neurologic function for every 3 to 5 patients treated.

May Nour, MD, PhD, University of California, Los Angeles, Los Angeles, California, USA, presented an analysis of the number needed to treat to benefit (NNTB) and the number needed to treat to harm (NNTH) from the MR CLEAN study [Berkhemer OA et al. *N Engl J Med.* 2015].

MR CLEAN was the first trial of thrombectomy using second-generation devices to demonstrate improved outcomes of intra-arterial treatment plus standard medical treatment compared with medical therapy alone, which included the use of intravenous tissue plasminogen activator. This prospective randomized design enrolled 500 patients in an open-label fashion with blinded end point evaluation.