

On behalf of the MR CLEAN-LATE executive committee: Robert-Jan Goldhoorn, Wouter Hinsenvelde, Anne-France Pirson, Wim van Zwam and Robert van Oostenbrugge, Maastricht
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Introduction:

The recently published DAWN and DEFUSE 3 trials show that endovascular treatment (EVT) of acute ischemic stroke is safe and effective between 6 - 24 hours, and 6 – 16 hours after start of symptoms (or last seen well).^{1,2} However, due to the strict selection criteria these results cannot be easily extrapolated and have limited and difficult applicability to general care. In this letter we will summarize and interpret the DAWN and DEFUSE 3 results.

DAWN:

DAWN randomized between EVT and no EVT in the 6 – 24 hour timewindow.¹ In the EVT group, 49% of patients reached functional independence at 3 months compared to 13% of the control group. However, time of symptom onset was known in only a limited subset of patients (12%) with the median time of observation of symptoms to randomization being 4.8 hours. It can reasonably be assumed that a large proportion of patients in DAWN were not ‘true’ late presentations. After selection using CT perfusion or MR diffusion using the RAPID software, 75% of patients had very small infarct cores of less than 18ml while still having a large neurological deficit (NIHSS 10 or higher). This is a rare occurrence in daily practice, which is supported by the slow inclusion rate of DAWN: on average 2 patients per week with 26 participating centers in the USA, Canada, Europe and Australia.

DEFUSE 3:

Similar results were found in DEFUSE 3 as in DAWN. Similarly strict selection criteria were used with both clinical deficit (NIHSS 6 or higher) and imaging deficit based on CT perfusion

or MR diffusion, again using the RAPID software. 75% of patients in DEFUSE 3 had infarct cores smaller than 26ml and 75% had a penumbra larger than 80ml.²

Imaging selection:

Previous studies show that patient selection based on advanced imaging characteristics increases the chances of good outcome.³⁻⁷ DAWN and DEFUSE 3 used CT perfusion or MR diffusion and calculated infarct cores using the RAPID software which was then used for patient selection. Yet, only a minority of Dutch hospitals have access to RAPID and the prohibitively high costs can act as a barrier for implementation. Several intervention centers do use CT perfusion or MR diffusion but use different software packages to calculate infarct core and penumbra. There are considerable discrepancies between the different software packages which makes it challenging to select patients based on DAWN and DEFUSE 3.^{8,9} A further challenge is the limited availability of CT perfusion or MR diffusion in non-intervention centers where more than 50% of all Dutch stroke patients who ultimately receive EVT first present.

Based on the inclusion criteria of DAWN and DEFUSE 3, only 0.5% (12/2297) patients will be eligible for EVT as was recently shown by American researchers. In daily practice this number will likely be lower because the final selection of candidates for DAWN and DEFUSE 3 was stricter than the inclusion criteria.

MR CLEAN did not use selection based on advanced imaging other than a proven arterial occlusion on CT angiography.¹¹ Patients that did receive CT perfusion showed an association between findings on CT perfusion (analyzed using Philips Brilliance 7.0 software) and outcome, but no association with the treatment effect.¹² Collateral status on CT angiography did show an interaction with treatment effect, with higher collateral grades showing larger

treatment effects.¹³ Due to the combination of these findings and because of practical applicability, MR CLEAN-LATE uses selection based on collateral status.

Conclusion:

In daily practice the advice of the executive committee of MR CLEAN-LATE and of the CONTRAST CONSORTIUM is that:

1. The majority of patients presenting in the 'late' window do not satisfy the patient profile of DAWN and DEFUSE 3.
2. MR CLEAN-LATE questions whether patients with moderate to good collateral scores without signs of advanced demarcation benefit from EVT.

Advice for referral centers (primary stroke centers):

1. Perform CT angiography in patients with ischemic stroke and time since onset of 6 – 24 hours
2. Refer patients with an arterial occlusion and limited infarction and demarcation (<1/3 of the MCA area on non-contrast CT) to an intervention center. The adage 'Time is Brain' also holds true for these patients!

Advice for intervention centers:

1. Select patients for EVT and presentation between 6 and 24 hours after symptom onset based on the following criteria:
 - NIHSS score ≥ 10
 - Ischemic core (RAPID software) ≤ 25 ml
 - Penumbra \geq ischemic core
2. Include all other patients in MR CLEAN-LATE if they conform to the inclusion criteria, among others these are:

- Treatment possible within 24 hours after stroke onset or last seen well
- Proven intracranial occlusion of the anterior circulation
- Poor, moderate or excellent collaterals
- Signs of infarction on NCCT of no more than 1/3 of the affected (MCA) area

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