Stroke

FOCUSED UPDATES

Path From Clinical Research to Implementation

Endovascular Treatment of Ischemic Stroke in the Netherlands

Eveline J.A. Wiegers, BSc; Kars C.J. Compagne, BSc; Paula M. Janssen, MD; Esmee Venema, MD; Jaap W. Deckers, MD, PhD; Wouter J. Schonewille, MD, PhD; Jan Albert Vos, MD, PhD; Geert J. Lycklama à Nijeholt, MD, PhD; Bob Roozenbeek, MD, PhD; Jasper M. Martens, MD; Jeannette Hofmeijer, MD, PhD; Robert-Jan van Oostenbrugge, MD, PhD; Wim H. van Zwam, MD, PhD; Charles B.L.M. Majoie, MD, PhD; Aad van der Lugt, MD, PhD; H.F. Lingsma, PhD; Yvo B.W.E.M. Roos, MD, PhD; Diederik W.J. Dippel, MD, PhD; on behalf of the MR CLEAN Registry Collaborators

ABSTRACT: Before 2015, endovascular treatment (EVT) for acute ischemic stroke was considered a promising treatment option. Based on limited evidence, it was performed in several dedicated stroke centers worldwide on selected patients. Since 2015, EVT for patients with intracranial large vessel occlusion has quickly been implemented as standard treatment in many countries worldwide, supported by the revised international guidelines based on solid evidence from multiple clinical trials. We describe the development in use of EVT in the Netherlands before, during, and after the pivotal EVT trials. We used data from all patients who were treated with EVT in the Netherlands from January 2002 until December 2018. We undertook a time-series analysis to examine trends in the use of EVT using Poisson regression analysis. Incidence rate ratios per year with 95% CIs were obtained to demonstrate the impact and implementation after the publication of the EVT trial results. We made regional observation plots, adjusted for stroke incidence, to assess the availability and use of the treatment in the country. In the buildup to the MR CLEAN (Multicenter Clinical Trial of Endovascular Treatment of Acute Ischemic Stroke in the Netherlands), a slow increase of EVT patients was observed, with 0.2% of all ischemic stroke patients receiving EVT. Before the trial results were formally announced, a statistically significant increase in EVT-treated patients per year was observed (incidence rate ratio, 1.72 [95% CI, 1.46–2.04]), and after the trial publication, an immediate steep increase was seen, followed by a more gradual increase (incidence rate ratio, 2.14 [95% CI, 1.77–2.59]). In 2018, the percentage of ischemic stroke patients receiving EVT increased to 5.8%. A well-developed infrastructure, a pragmatic approach toward the use of EVT in clinical practice, in combination with a strict adherence by the regulatory authorities to national evidence-based guidelines has led to successful implementation of EVT in the Netherlands. Ongoing efforts are directed at further increasing the proportion of stroke patients with EVT in all regions of the country.

Key Words: brain ischemia ■ ischemia ■ implementation science ■ stroke ■ thrombectomy

Endovascular treatment (EVT) in patients with acute ischemic stroke has been proven highly effective in randomized controlled trials.[1–7] The MR CLEAN (Multicenter Clinical Trial of Endovascular Treatment of Acute Ischemic Stroke in the Netherlands) was the first to publish positive results in January 2015, immediately followed by several other trials.[1]

See related articles, p 1928, p 1932, p 1951, p 1961, p 1969 and p 1978

Before the start of the MR CLEAN trial in December 2010, several studies had provided data suggesting that EVT might be beneficial, although convincing evidence was lacking.[8,9] The Dutch stroke guidelines of 2008 mentioned EVT as a rescue treatment, preferably provided within the context of randomized trials. In the Netherlands, EVT for acute ischemic stroke was not reimbursed until 2013, when reimbursement to centers was made conditional on participation in the MR CLEAN trial. This reimbursement policy is still in place and reinforced by

Correspondence to: Diederik W.J. Dippel, MD, PhD, Department of Neurology, Erasmus MC University Medical Center, Doctor Molewaterplein 40, 3015 GD Rotterdam, the Netherlands. Email d.dippel@erasmusmc.nl

The Data Supplement is available with this article at https://www.ahajournals.org/doi/suppl/10.1161/STROKEAHA.119.026731.

For Sources of Funding and Disclosures, see page 1947.

Stroke is available at www.ahajournals.org/journal/str

guidelines and quality criteria provided by the professional societies and endorsed by regulating authorities.

In the early 2000s, 2 stroke centers started providing EVT as an experimental treatment in selected patients, inspired by the results of early trials and by local clinical experience.[10] After 2005, other centers gradually followed. Still, before initiation of the MR CLEAN trial in 2010, there were 2 centers in the Netherlands that had treated >50 patients with IAT. Currently, 17 comprehensive stroke centers provide EVT in the Netherlands for a population of 17 182 000 inhabitants.

The European Stroke Organisation recently stated that in 2030, 95% of eligible patients across Europe should have access to reperfusion therapy and EVT rates should be over 5% in all European countries.[11] Although considerable efforts have been made, a recent study showed large differences between countries in terms of access to appropriate acute stroke treatment.[12] Gaining understanding in the trends of EVT over time might not only provide insight into the accessibility but also about the implementation of new treatments in daily clinical practice.

In this article, we describe the trends in number of patients with acute ischemic stroke who were treated with EVT and the accessibility of EVT in the Netherlands in 3 time periods: before, during, and after the completion of the MR CLEAN trial.

METHODS

The data of the MR CLEAN TRIAL have been made publicly available at the Virtual International Stroke Trials Archive and can be accessed at http://www.virtualtrialsarchives.org/vista/. Individual patient data of the MR CLEAN pretrial registry and the MR CLEAN Registry cannot be made available under the Dutch law, as we did not obtain patient approval for sharing individual patient data, even in coded form. However, all syntax files and output of statistical analyses will be made available upon reasonable request.

Study Population

We analyzed data from the MR CLEAN pretrial period, the MR CLEAN trial, and MR CLEAN Registry.

In the pretrial period, we retrospectively and prospectively collected data of all patients with acute ischemic stroke who received EVT in the Netherlands from October 2002 until a center started participation in the MR CLEAN trial, which included its first patient in December 2010.[13]

Patient selection criteria and methods of the MR CLEAN trial have been reported previously.[14] In short, the MR CLEAN trial was a clinical trial in which patients with a proximal intracranial arterial occlusion in the anterior circulation were randomized to either EVT with usual care or usual care alone. Treatment should be started within 6 hours after onset of stroke symptoms. All patients or their legal representatives provided written informed consent before randomization in the MR CLEAN trial. The study protocol of the MR CLEAN trial was approved by a central medical ethics committee and the research board of each participating center.[14]

Directly after inclusion of the last patient in the trial by March 2014 and before the presentation of the MR CLEAN trial results at the World Stroke Conference in October 2014, all EVT-treated patients were enrolled in the MR CLEAN Registry, which is as a prospective, multicenter, observational study. For our current analysis, we used data from all patients registered until December 31, 2018.[15] The MR CLEAN Registry was approved by the Medical Ethics Committee of the Erasmus MC, Rotterdam, the Netherlands (MEC-2014-235).

We assume that no patients were treated outside the MR CLEAN trial during the study period and that all patients treated before and after the trial are registered in either one of the registries.

Statistical Analysis

We analyzed differences between 3 time periods (pretrial period, MR CLEAN trial, and MR CLEAN Registry). Patients in the MR CLEAN trial who were randomized to usual care were also included, since EVT was considered in these patients.

We used Poisson regression or negative binomial regression to determine whether the incidence ratio of EVT changed during the pretrial period and MR CLEAN Registry with the denominator being the count of EVT in each year. We then computed incidence rate ratios with 95% CIs, using the first year of the time period as reference point. Data were checked for potential overdispersion (variance greater than the mean) to ensure that the assumptions of a Poisson distribution were met. All analyses were adjusted for the number of stroke patients per year.[16–28]

We calculated the use of EVT as a proportion of all patients in the Netherlands who were hospitalized with acute ischemic stroke (including cerebral hemorrhages) between 2002 and 2018, which was based on reports of the Dutch Heart Association.[22–26] Linear regression was used to estimate the number of ischemic stroke patients for years in which another definition of stroke was used or years in which only the number of patients hospitalized with acute stroke was reported.

Maps of the Netherlands at province level were created using R package tmap.[29] Geographic and demographic information was obtained from Statistics Netherlands and Kadaster.[30,31] The number of EVT-treated patients by province was based on the location of first hospital admission. The density of EVT-treated patients was averaged by dividing the total number of patients by, respectively, the years of patient enrollment and number of stroke patients per province. The latter was based on anonymized data obtained from central hospital registration systems.

All statistical analyses were performed in R statistical software 3.4.2 (R Foundation for Statistical Computation, Vienna).

RESULTS

In this 16 years' time period, 6394 patients were treated with EVT. In the pretrial period (2002–2010), 514 patients were treated with EVT. During the MR CLEAN trial (2010–2014), 500 patients were included of whom 233 patients were randomized to intervention. In the ongoing

 Stroke. 2020;51:1941–1950. DOI: 10.1161/STROKEAHA.119.026731

MR CLEAN Registry started directly after inclusion of the last patient in the MR CLEAN trial in March 2014, 5335 patients were registered until December 2018.

Of all treated patients, 2299 (53%) patients were men; 59% in the pretrial period, 58% in MR CLEAN trial, and 52% in the MR CLEAN Registry. The median age was 70 years (interquartile range [IQR], 58–79); 62 in pretrial patients (IQR, 51–71), 66 (IQR, 55–76) during the MR CLEAN trial, and 71 (IQR, 61–80) in the MR CLEAN Registry. The time from onset to groin puncture was 205 minutes (IQR, 155–270). A median onset-to-groin-puncture time of 237 minutes (IQR, 190–315) was observed in the pretrial population, which had increased to 260 (IQR, 210–311) in the MR CLEAN trial and decreased to 195 (IQR, 150–260) in the MR CLEAN Registry. All baseline characteristics significantly differed between study periods (Table 1).

Trend Analyses

From 2006 onward, a gradual increase in thrombectomies was observed (Figure 1). In the buildup to the MR CLEAN trial, more centers provided EVT, and a sharper increase was observed, which continued during the MR CLEAN trial. After the last inclusion in the MR CLEAN trial, the same level of increase was observed until the results of the EVT trials were presented in October 2014. After the presentation of the MR CLEAN trial results at the World Stroke Conference in October 2014, the number of patients treated with EVT increased steeply (Figure 1). During the pretrial period and following the steep increase that occurred immediately after the trial, in the MR CLEAN Registry period, a statistically significant gradual increase in EVT-treated patients per year was observed (pretrial: incidence rate ratio: 1.72 [95% CI, 1.46–2.04], $P<0.001$; MR CLEAN Registry: incidence rate ratio: 2.14 [95% CI, 1.77–2.59], $P<0.001$).

Regional Differences

During the pretrial period, patients were predominantly treated in Utrecht—a province in the center of the Netherlands. During the trial phase, a similar pattern was observed, although the number of patients treated in other regions increased. After announcement of the trial results, the distribution of EVT-treated patients spread more evenly across the Netherlands (Figure 2).

Proportion of Acute Ischemic Stroke Patients Receiving EVT

In 2010, 23 771 patients were hospitalized with acute ischemic stroke in the Netherlands, of whom 170 (0.5%) received EVT. In 2014, 217 (0.8%) acute ischemic stroke patients received EVT. After the MR CLEAN trial, the percentage of acute ischemic stroke patients treated with EVT increased to 3.1% in 2015. In 2018, 29 244 patients were admitted with acute ischemic stroke of whom 1712 (5.8%) received EVT (Figure 3; Table I in the Data Supplement).

DISCUSSION

We described the trends in use of EVT before, during, and after the MR CLEAN trial expressed as the coverage of EVT in the Netherlands across different regions and the proportion of stroke patients who received EVT.

Our time-trend analysis showed increasing rates of treated patients in 3 consecutive time periods. In the pretrial period, the number of treated patients before the MR CLEAN trial in the Netherlands was low. This was probably due to conservative recommendations in the national guidelines that recognized the low level of evidence for this treatment and to the fact that EVT was not reimbursed in that time period. During the pretrial period, a strict policy regarding non–evidence-based treatments was maintained by insurance companies, government, and professional societies.

A strict national policy of evidence-based guidelines is meant to provide the best evidence-based care to the majority of patients. However, it has to be acknowledged that the pioneering centers, which provided EVT as an experimental treatment when guidelines were not yet

Table 1. Baseline Characteristics

	In Total: October 2004 to June 2016 (n=4308)	Pretrial: October 2004 to December 2010 (n=514)	MR CLEAN Trial: December 2010 to March 2014 (n=500)	MR CLEAN Registry: April 2014 to October 2017 (n=3294)	*P* Value
Age, y; median (IQR)	70 (58–79)	62 (51–71)	66 (55–76)	71 (61–80)	<0.001
Men, n (%)	2299 (53)	305 (59)	292 (58)	1702 (52)	<0.001
NIHSS, median (IQR)	16 (11–20)	16 (12–21)	16 (12–21)	16 (11–20)	<0.001
SBP, mm Hg; mean (SD)	149 (28)	148 (24)	145 (25)	150 (28)	0.01
Intravenous alteplase treatment, n (%)	3217 (75)	323 (64)	445 (89)	2449 (75)	<0.001
Onset-to-groin-puncture time, min; median (IQR)	205 (155–270)	237 (190–315)	260 (210–311)	195 (150–260)	<0.001

mRS was missing in 373 patients; NIHSS was missing in 189 patients; SBP was missing in 189 patients. MR CLEAN Registry contains information on baseline characteristics up to October 2017. IQR indicates interquartile range; MR CLEAN, Multicenter Clinical Trial of Endovascular Treatment of Acute Ischemic Stroke in the Netherlands; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; and SBP, systolic blood pressure.

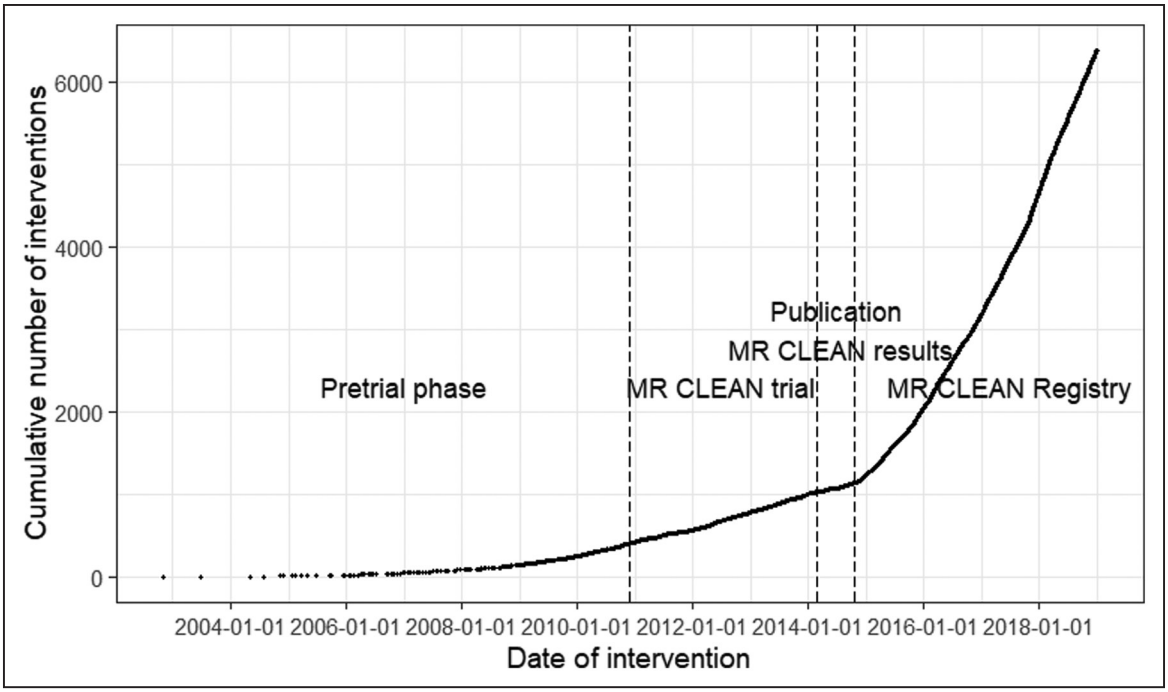

Figure 1. Trends over time regarding the use of endovascular treatment (EVT) in patients with acute ischemic stroke, presenting the observed number of EVT procedures.
MR CLEAN indicates Multicenter Clinical Trial of Endovascular Treatment of Acute Ischemic Stroke in the Netherlands.

accommodating this intervention, played an important role in the pretrial development of acute stroke networks and treatment experience necessary to successfully perform a randomized clinical trial.

The adherence to guideline-based treatment strategies continued until the steep increase of EVT-treated patients just after the results of MR CLEAN were formally announced at the World Stroke Conference in October 2014.[32] From the last inclusion in the trial until the presentation of these results, the use of EVT increased with the same level as during the MR CLEAN trial. The sharp acceleration of EVT use after October 2014 indicates that centers and physicians quickly adopted EVT and rapidly reorganized their acute stroke care to be able to provide this new treatment to more patients, even ahead of incorporation of EVT in the national guidelines in 2017.

The Netherlands belong to the countries with one of the highest annual proportion of patients with ischemic stroke receiving EVT.[12] In 2017, 5.1% of the acute ischemic stroke patients received EVT.[12] In the United States

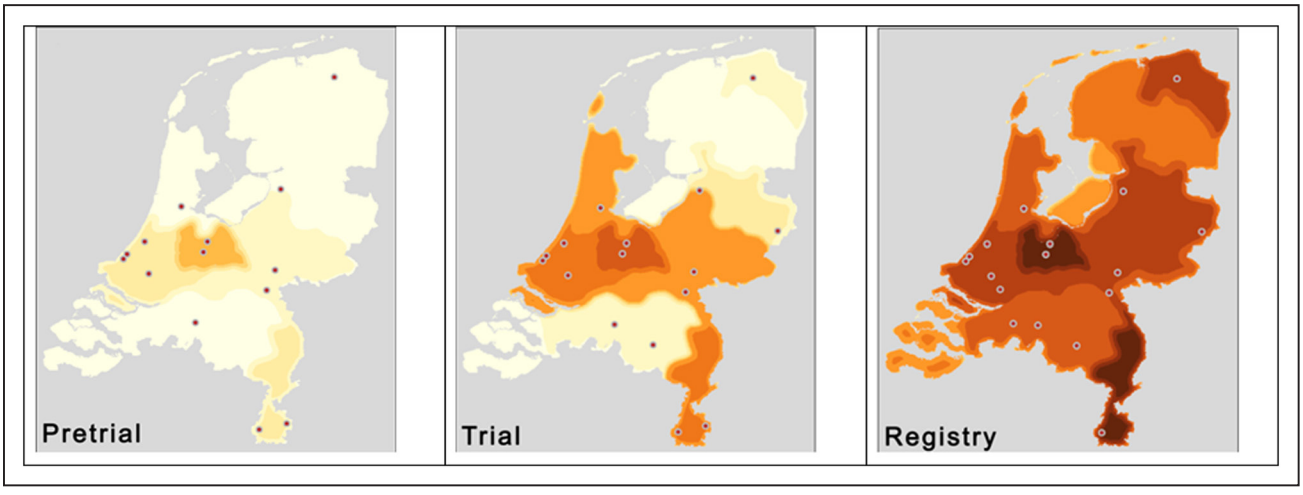

Figure 2. Maps of the coverage of endovascular treatment (EVT) in the Netherlands per province in 3 different time periods (Pretrial, MR CLEAN trial [Multicenter Clinical Trial of Endovascular Treatment of Acute Ischemic Stroke in the Netherlands], MR CLEAN Registry).
Number of EVT-treated patients for each province are indicated per province. The density of EVTs was averaged by dividing the total number of treated patients by the average incidence during the observation period in that province. The red dots indicate intervention centers.

 Stroke. 2020;51:1941–1950. DOI: 10.1161/STROKEAHA.119.026731

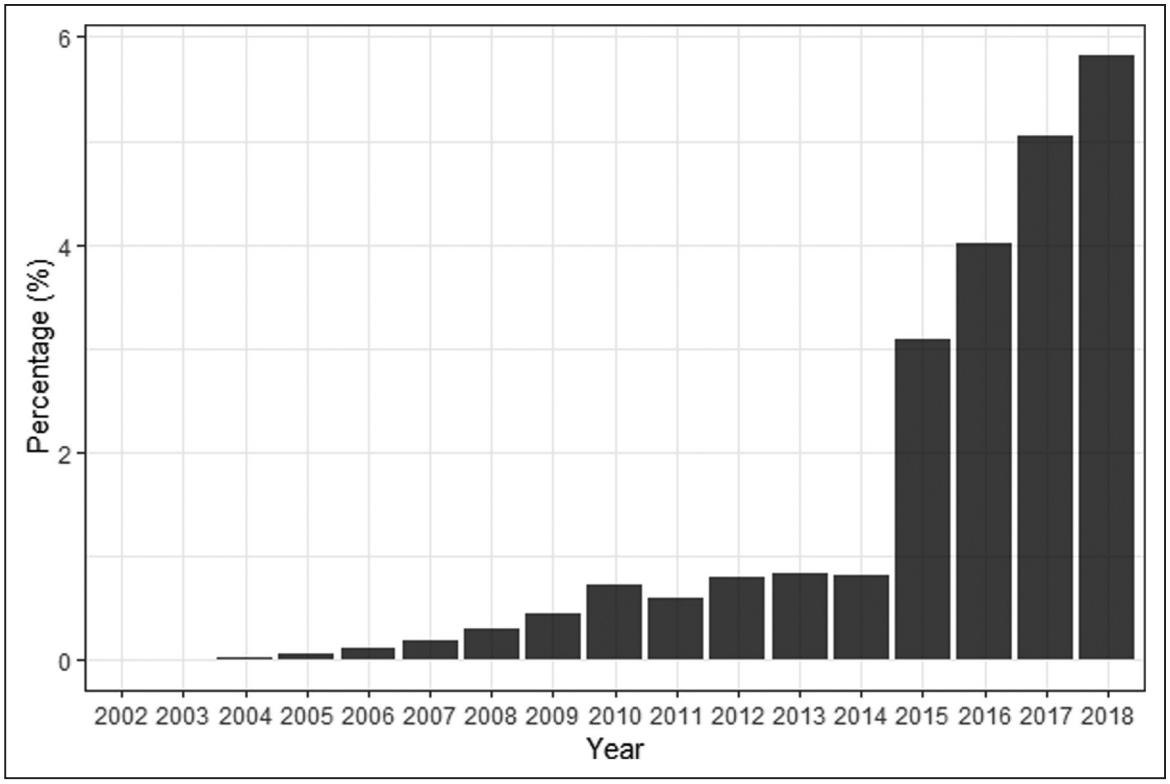

Figure 3. Proportion of ischemic stroke patients receiving endovascular treatment in the Netherlands per year.

during the same time period, 3.3% of ischemic stroke patients were treated with EVT in selected centers.[33]

It has been estimated that about 10% of the patients with ischemic stroke are eligible for EVT.[34,35] Therefore, it could be roughly estimated that almost 50% of the number of ischemic stroke patients eligible for EVT actually received this treatment in 2018. This implies that many patients who are eligible still do not receive the treatment. This can be partially explained by the fact that a lot of patients arrived >6 hours after symptom onset, and treatment of patient in this late treatment window was not yet included in national and European guidelines.[36,37] Another explanation might be that not yet all patients who might benefit from EVT are being recognized in time prehospital and in hospital, even though CTA has been advised as standard diagnostic procedure for all patients with acute ischemic stroke.[38] Also, in current clinical practice, most suspected stroke patients are first transported to the nearest hospital for immediate treatment with IVT, which can lead to delay of the start of EVT and worse outcomes because of additional time needed for transfer to an endovascular capable center.[39]

Acute stroke care in the Netherlands is organized as follows. A national network for acute medical care has been established, with expert committees for subsections for acute stroke care, trauma, obstetrics, acute psychiatry, and acute myocardial infarction. The acute stroke care expert committee consists of vascular neurologists representing all stroke centers in the region, a GP, ambulance service coordinators, and a secretary. Every region has a regional network protocol for acute stroke care, based on the national stroke guideline and the requirements proposed by the national societies of neurology and radiology. The regional protocol prescribes the pathway from onset to ER of primary stroke center and intervention center. Triage systems are being evaluated for implementation in prehospital settings, but meanwhile, all patients are being transferred to the most nearby hospital with IVT available[40] (Figure I in the Data Supplement).

Our density plots show that some regions implemented EVT earlier and with a faster rate than other regions. These between-region differences indicate that access to EVT in the Netherlands can still be improved. Increasing the availability of EVT might contribute to equally divided stroke care in the Netherlands, although the number of stroke units per ischemic stroke patients is already at a high level.[12] Considering that patients treated with EVT at higher volume centers have better outcomes than those treated at lower volume centers and that time is brain, especially in EVT-eligible stroke patients,[41–43] a careful trade-off between centralization and accessibility of acute stroke care should be made.[43]

Experience from related medical areas, for instance from cardiology, could provide valuable lessons and some guidance. In the eighties and nineties, patients with large myocardial infarction were being treated with thrombolytics. But when the superiority of the more effective and

safer percutaneous coronary intervention (PCI) had been established, the country-wide introduction of this therapy was hampered and delayed by almost a decade by the specific requirements that the hospitals offering this form of treatment had to meet. Not infrequent and serious complications associated with the PCI procedure mandated the presence of on-site cardiac surgery in the early years following the introduction of PCI and limited the number of sites that could offer optimal treatment. Both technical and organizational developments subsequently made the requirements of on-site cardiac surgery less of an issue and gradually enabled the development of PCI programs in hospitals without on-site cardiac surgery from the year 2002 onward. Since then, the number of sites offering primary PCI for large myocardial infarctions increased from 16 to 30, more than sufficient to treat all patients with large myocardial infarctions within a reasonable time frame.[44]

Inspired by this example, professional societies, governmental agencies, and insurance companies concluded that one stroke intervention center per million inhabitants should be sufficient. Hospitals are supported in providing EVT, given the relatively small effect on hospital costs but substantial cost savings in the social service sector.[45,46] To facilitate the development of EVT centers in the Netherlands and to ensure sufficient quality, requirements have been kept at an essential minimum of 50 EVT procedures per center per year and include 24/7 availability, sufficient facilities, and trained personnel (Table 2). These requirements were proposed by the Dutch Society for Neurology and the Dutch Society for Radiology and adopted by insurance companies and regulatory bodies. However, the requirements for EVT centers are being updated because of the extension of the time window for reperfusion treatment based on advanced perfusion imaging.[47–51] The national guidelines require acquisition of NCCT and CTA (or magnetic resonance imaging/MRA) in all patients with acute ischemic stroke and are being updated with perfusion imaging for late-window ischemic stroke patients.

Table 2. Quality Criteria for Primary Stroke Centers Providing Intravenous Alteplase Treatment and for Stroke Intervention Centers Providing Endovascular Treatment for Ischemic Stroke, Established by the Professional Societies for Radiology and Neurology in 2017

Primary stroke centers should
admit and treat at least 100 acute stroke patients annually (mean of last 3 y)
have a median door-to-needle time of <45 min
have CT and CTA, of cervical and intracranial vessels 24/7 available, with direct assessment provided by or supervised by a radiologist
have treatment with intravenous alteplase 24/7 available, with the treatment performed by or under supervision of a neurologist, who has direct access to neuroimaging
have a stroke team 24/7 available, with a stroke nurse under supervision of a neurologist
have stroke unit with 24/7 care and 24/7 admission through ER
have neurosurgery available 24/7 or collaboration with a nearby neurosurgical center
have a registry of acute stroke patients, which includes the percentage of patients treated with intravenous alteplase and the number of patients admitted within 4.5 h after onset of stroke
participate in a regional stroke service and have a regional coordinator
have arrangements with an intervention center for endovascular treatment and with the regional ambulance service for rapid transfer of patients eligible for endovascular treatment
Stroke intervention centers should
fulfill the criteria for primary stroke centers
have a multidisciplinary team at least consisting of a neurologist, radiologist, interventionalist, and anesthesiologist
provide EVT on a 24/7 basis with the multidisciplinary team
have arrangements with at least one other center in the same region to provide EVT when because of unusual circumstances EVT is not available in their own center
have at least 2 angio suites, of which one is readily available with sufficient and appropriate personnel
be equipped with an intensive care unit and a stroke unit
have a local protocol, which includes description of logistics, responsibilities of all involved professionals, patients' safety, and benchmarks for door-to-needle and door-to-groin-puncture time
have neurologists with vascular expertise available 24/7
have at least 3 interventionalists
perform at least 50 EVT procedures per year
have at least 20 EVT procedures per interventionalist per year (procedures done by 2 interventionalists count for both)
have median door-to-groin-puncture times of <60 min
have a local registry of quality-of-care parameters concerning logistics, complications, and technical as well as clinical outcomes (at least door-to-groin-puncture time and onset-to-groin-puncture time, eTICI, and mRS at 3 mo)

CT indicates computed tomography; CTA, computed tomography angiography; ER, emergency room; eTICI, expanded Thrombolysis in Cerebral Infarction; EVT, endovascular treatment; and mRS, modified Rankin Scale.

More than a decade ago, criteria were established by the national professional societies that require a 2-year training in neurointervention with certification that is open to all medical specialties but in practice to neurologists, radiologists, and neurosurgeons.[52] Almost all interventionists in the Netherlands are radiologists. For general interventional radiologists who want to qualify for EVT of ischemic stroke, a short additional training is required that amounts to doing at least 25 thrombectomies, 50 digital subtraction angiographies, 200 other endovascular procedures, and assessment of 200 NCCT and ≥50 head/neck CTA or MRAs under supervision.

Interestingly, during the trial, onset-to-groin times had increased by about 1 hour, and after the trial, a gradual decrease was noted. The increase may be attributed to the consent and randomization procedure in the trial, whereas improved awareness, logistics, and increasing experience has led to the gradual decrease after the trial. Median age of EVT treated patients increased, likely because trial results and guidelines point out that high age by itself should not be considered as a contraindication for EVT[53] (Figure II through VI in the Data Supplement).

Our study has some limitations. No information about the residence of the EVT-treated patients was available for all time periods. Therefore, we estimated the coverage of EVT in the Netherlands based on the first hospital admission. Since not all patients are at home at the moment of their stroke onset and the first hospital is often close to the place of stroke onset, this should reflect daily clinical care.

Our study only describes EVT in the Netherlands, and it does only touch upon factors that have facilitated its rapid implementation. Comparisons with other countries may help in this regard. Still, several factors may have played an important role in the implementation of EVT in the Netherlands, including the dense population (17 million people living on an area of 33 671 km^2, for an average population density of 510/km^2), the dense highway network, the large number of primary stroke centers (85, 5 per million inhabitants) and EVT centers (17, 1 per million inhabitants),[12] and last, an ambulance network that has to comply with the requirement that every patient should be picked up within 15 minutes after calling 112 and should be delivered at the ER of the most nearby primary stroke center within 30 minutes.

CONCLUSIONS

A well-developed infrastructure, a pragmatic approach toward the use of EVT in clinical practice, in combination with a strict adherence by the regulatory authorities to national evidence-based guidelines has led to successful implementation of EVT in the Netherlands. Ongoing efforts are directed at further increasing the proportion of stroke patients with EVT in all regions of the country.

ARTICLE INFORMATION

Affiliations

Department of Public Health (E.J.A.W., E.V., H.F.L.), Department of Radiology and Nuclear Medicine (K.C.J.C., A.v.d.L.), and Department of Neurology (K.C.J.C., P.M.J., E.V., B.R., D.W.J.D.), Erasmus MC University Medical Center, Rotterdam, the Netherlands. Department of Cardiology, Thoraxcenter, Erasmus MC, Rotterdam, the Netherlands (J.W.D.). Department of Neurology (W.J.S.) and Department of Radiology (J.A.V.), St. Antonius Hospital, Nieuwegein, the Netherlands. Department of Radiology, Haaglanden MC, the Hague, the Netherlands (G.J.L.à.N.). Department of Radiology, Rijnstate Hospital, Arnhem, the Netherlands (J.M.M.). Department of Clinical Neurophysiology, Clinical Neurophysiology, University of Twente, Enschede, the Netherlands (J.H.). Cardiovascular Research Institute Maastricht, Maastricht University, the Netherlands (R.-J.v.O., W.H.v.Z.). Department of Neurology (R.-J.v.O.) and Department of Radiology (W.H.v.Z.), Maastricht University Medical Center, the Netherlands. Department of Radiology (C.B.L.M.M.) and Department of Neurology (Y.B.W.E.M.R.), Amsterdam UMC, the Netherlands.

Sources of Funding

The MR CLEAN trial (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands) was partly funded by the Dutch Heart Foundation and by unrestricted grants from AngioCare BV, Medtronic/Covidien/EV3, MEDAC GmbH/LAMEPRO, Penumbra, Inc, Stryker, and Top Medical/Concentric. The MR CLEAN is registered under number NTR1804 in the Dutch trial register and under ISRCTN10888758 in the ISRCTN register. The Multicenter Randomized Clinical trial of EVT for AIS in the Netherlands (MR CLEAN) Registry was partly funded by the Applied Scientific Institute for Neuromodulation (Toegepast Wetenschappelijk Instituut voor Neuromodulatie), the Erasmus University Medical Center, the Academic Medical Center Amsterdam, and the Maastricht University Medical Centre.

Disclosures

Dr Majoie reports grants from Netherlands Cardiovascular Research Initiative (CVON)/Dutch Heart Foundation, during the conduct of the study (paid to institution); grants from TWIN Foundation; grants from European Commission; grants from Stryker, outside the submitted work (paid to institution); and is the shareholder of Nico.lab—a company that focuses on the use of artificial intelligence for medical image analysis. Dr Dippel reports grants from the Dutch Heart Foundation, Brain Foundation Netherlands, Netherlands Organisation for Health Research and Development, Health Holland Top Sector Life Sciences and Health, AngioCare BV, Medtronic/Covidien/EV3, MEDAC Gmbh/LAMEPRO, Penumbra, Inc, Top Medical/Concentric, Stryker, and Thrombolytic Science during the conduct of the study; other from Stryker, Medtronic, Bracco Imaging, and Servier, outside the submitted work. Dr van der Lugt reports grants from Ceronovus, Dutch Heart Foundation, AngioCare BV, Medtronic/Covidien/EV3, MEDAC Gmbh/LAMEPRO, Penumbra, Inc, Stryker, and Top Medical/Concentric, during the conduct of the study; grants from Stryker; other from Stryker, outside the submitted work. Dr van Zwam reports personal fees from Cerenovus and Stryker outside the submitted work. The other authors report no conflicts. The MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands) Registry was approved by the ethics committee of the Erasmus University MC, Rotterdam, the Netherlands (MEC-2014-235). With this approval, it was approved by the research board of each participating center. At UMC Utrecht, approval to participate in the study has been obtained from their own research board and ethics committee.

APPENDIX

MR CLEAN (Multicenter Clinical Trial of Endovascular Treatment of Acute Ischemic Stroke in the Netherlands) Registry Investigators: Executive Committee: Diederik W.J. Dippel (Department of Neurology, Erasmus MC University Medical Center), Aad van der Lugt (Department of 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 (Department of Neurology, Amsterdam UMC, University of Amsterdam, Amsterdam), Robert J. van Oostenbrugge (Department of Neurology, Maastricht University Medical Center and Cardiovascular Research Institute Maastricht), Wim H. van Zwam (Department of Radiology, Maastricht University Medical Center and

Cardiovascular Research Institute Maastricht), Jelis Boiten (Department of Neurology, Haaglanden MC, the Hague), Jan Albert Vos (Department of Radiology, St. Antonius Hospital, Nieuwegein); study coordinators: Josje Brouwer (Department of Neurology, Amsterdam UMC, University of Amsterdam, Amsterdam), Sanne J. den Hartog (Department of Neurology, Erasmus MC University Medical Center; Department of Radiology, Erasmus MC University Medical Center; Department of Public Health, Erasmus MC University Medical Center), Wouter H. Hinsenveld (Department of Neurology, Maastricht University Medical Center and Cardiovascular Research Institute Maastricht; Department of Radiology, Maastricht University Medical Center and Cardiovascular Research Institute Maastricht), Manon Kappelhof (Department of Radiology and Nuclear Medicine, Amsterdam UMC, University of Amsterdam, Amsterdam), Kars C.J. Compagne (Department of Radiology, Erasmus MC University Medical Center), Robert-Jan B. Goldhoorn (Department of Neurology, Maastricht University Medical Center and Cardiovascular Research Institute Maastricht; Department of Radiology, Maastricht University Medical Center and Cardiovascular Research Institute Maastricht), Maxim J.H.L. Mulder (Department of Neurology, Erasmus MC University Medical Center; Department of Radiology, Erasmus MC University Medical Center), Ivo G.H. Jansen (Department of Radiology and Nuclear Medicine, Amsterdam UMC, University of Amsterdam, Amsterdam); 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 (Department of Radiology, Erasmus MC University Medical Center), Adriaan C.G.M. van Es (Department of 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 (Department of 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 (Department of Neurology, Amsterdam UMC, University of Amsterdam, Amsterdam), Wouter J. Schonewille (Department of Neurology, St. Antonius Hospital, Nieuwegein), Jan Albert Vos (Department of Radiology, St. Antonius Hospital, Nieuwegein), Marieke J.H. Wermer (Department of Neurology, Leiden University Medical Center), Marianne A.A. van Walderveen (Department of Radiology, Leiden University Medical Center), Julie Staals (Department of Neurology, Maastricht University Medical Center and Cardiovascular Research Institute Maastricht), Robert J. van Oostenbrugge (Department of Neurology, Maastricht University Medical Center and Cardiovascular Research Institute Maastricht), Wim H. van Zwam (Department of Radiology, Maastricht University Medical Center and Cardiovascular Research Institute Maastricht), Jeannette Hofmeijer (Department of Neurology, Rijnstate Hospital, Arnhem), Jasper M. Martens (Department of Radiology, Rijnstate Hospital, Arnhem), Geert J. Lycklama à Nijeholt (Department of Radiology, Haaglanden MC, the Hague), Jelis Boiten (Department of Neurology, Haaglanden MC, the Hague), Sebastiaan F. de Bruijn (Department of Neurology, HAGA Hospital, the Hague), Lukas C. van Dijk (Department of Radiology, HAGA Hospital, the Hague), H. Bart van der Worp (Department of Neurology, University Medical Center Utrecht), Rob H. Lo (Department of Radiology, University Medical Center Utrecht), Ewoud J. van Dijk (Department of Neurology, Radboud University Medical Center, Nijmegen), Hieronymus D. Boogaarts (Department of Neurosurgery, Radboud University Medical Center, Nijmegen), J. de Vries (Department of Neurology, Isala Klinieken, Zwolle), Paul L.M. de Kort (Department of Neurology, St. Elisabeth Hospital, Tilburg), Julia van Tuijl (Department of Neurology, St. Elisabeth Hospital, Tilburg), Jo Jo P. Peluso (Department of Radiology, St. Elisabeth Hospital, 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 (Department of Radiology, Isala Klinieken, Zwolle), Leo A.M. Aerden (Department of Neurology, Reinier de Graaf Gasthuis, Delft), René J. Dallinga (Department of Radiology, Reinier de Graaf Gasthuis, Delft), Maarten Uyttenboogaart (Department of Neurology, University Medical Center Groningen), Omid Eschgi (Department of Radiology, University Medical Center Groningen), Reinoud P.H. Bokkers (Department of Radiology, University Medical Center Groningen), Tobien H.C.M.L. Schreuder (Department of Neurology, Atrium Medical Center, Heerlen), Roel J.J. Heijboer (Department of Radiology, Atrium Medical Center, Heerlen), Koos Keizer (Department of Neurology, Catharina Hospital, Eindhoven), Lonneke S.F. Yo (Department of Radiology, Catharina Hospital, Eindhoven), Heleen M. den Hertog (Department of Neurology, Isala Klinieken, Zwolle), Emiel J.C. Sturm (Department of Radiology, Medical Spectrum Twente, Enschede), Paul Brouwers; Imaging Assessment Committee: Charles B.L.M. Majoie (chair; Department of Radiology and Nuclear Medicine, Amsterdam UMC, University of Amsterdam, Amsterdam), Wim H. van Zwam (Department of Radiology, Maastricht University Medical Center and Cardiovascular Research Institute Maastricht), Aad van der Lugt (Department of Radiology, Erasmus MC University Medical Center), Geert J. Lycklama à Nijeholt (Department of Radiology, Haaglanden MC, the Hague), Marianne A.A. van Walderveen (Department of 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 (Department of 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, TX), Ludo F.M. Beenen (Department of Radiology and Nuclear Medicine, Amsterdam UMC, University of Amsterdam, Amsterdam), Alida A. Postma (Department of Radiology, Maastricht University Medical Center and Cardiovascular Research Institute Maastricht), 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 (Department of Radiology, Erasmus MC University Medical Center), Bart J. Emmer (Department of Radiology and Nuclear Medicine, Amsterdam UMC, University of Amsterdam, Amsterdam), Jasper M. Martens (Department of Radiology, Rijnstate Hospital, Arnhem), Lonneke S.F. Yo (Department of Radiology, Catharina Hospital, Eindhoven), Jan Albert Vos (Department of Radiology, St. Antonius Hospital, Nieuwegein), Joost Bot (Department of Radiology, Amsterdam UMC, Vrije Universiteit van Amsterdam, Amsterdam), Pieter-Jan van Doormaal (Department of Radiology, Erasmus MC University Medical Center), Anton Meijer (Department of Radiology, Radboud University Medical Center, Nijmegen), Elyas Ghariq (Department of Radiology, Haaglanden MC, the Hague), Reinoud P.H. Bokkers (Department of Radiology, University Medical Center Groningen), Marc P. van Proosdij (Department of Radiology, Noordwest Ziekenhuisgroep, Alkmaar), G. Menno Krietemeijer (Department of Radiology, Catharina Hospital, Eindhoven), Jo P. Peluso (Department of Radiology, St. Elisabeth Hospital, Tilburg), Hieronymus D. Boogaarts (Department of Neurosurgery, Radboud University Medical Center, Nijmegen), Rob Lo (Department of Radiology, University Medical Center Utrecht), Dick Gerrits (Department of Radiology, Medical Spectrum Twente, Enschede), Wouter Dinkelaar (Department of Radiology, Erasmus MC University Medical Center), Auke P.A. Appelman (Department of Radiology, University Medical Center Groningen), Bas Hammer (Department of Radiology, HAGA Hospital, the Hague), Sjoert Pegge (Department of Radiology, Radboud University Medical Center, Nijmegen), Anouk van der Hoorn (Department of Radiology, University Medical Center Groningen), Saman Vinke (Department of Neurosurgery, Radboud University Medical Center, Nijmegen); Writing Committee: Diederik W.J. Dippel (chair; Department of Neurology, Erasmus MC University Medical Center), Aad van der Lugt (Department of 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 (Department of Neurology, Amsterdam UMC, University of Amsterdam, Amsterdam), Robert J. van Oostenbrugge (Department of Neurology, Maastricht University Medical Center and Cardiovascular Research Institute Maastricht), Wim H. van Zwam (Department of Radiology, Maastricht University Medical Center and Cardiovascular Research Institute Maastricht), Geert J. Lycklama à Nijeholt (Department of Radiology, Haaglanden MC, the Hague), Jelis Boiten (Department of Neurology, Haaglanden MC, the Hague), Jan Albert Vos (Department of Radiology, St. Antonius Hospital, Nieuwegein), Wouter J. Schonewille (Department of Neurology, St. Antonius Hospital, Nieuwegein), Jeannette Hofmeijer (Department of Neurology, Rijnstate Hospital, Arnhem), Jasper M. Martens (Department of Radiology, Rijnstate Hospital, Arnhem), H. Bart van der Worp (Department of Neurology, University Medical Center Utrecht), Rob H. Lo (Department of Radiology, University Medical Center Utrecht); Adverse Event Committee: Robert J. van Oostenbrugge (chair; Department of Neurology, Maastricht University Medical Center and Cardiovascular Research Institute Maastricht), Jeannette Hofmeijer (Department of Neurology, Rijnstate Hospital, Arnhem), H. Zwenneke Flach (Department of Radiology, Isala Klinieken, Zwolle); trial methodologist: Hester F. Lingsma (Department of 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), Corina Puppels (Department of Neurology, St. Antonius Hospital, Nieuwegein), Wilma Pellikaan (Department of Neurology, St. Antonius Hospital, Nieuwegein), Rita Sprengers (Department of 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 (Department of Radiology, Rijnstate Hospital, Arnhem), Joke de Meris (Department of Neurology, Haaglanden MC, the Hague), Tamara Vermeulen (Department of 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), Cathelijn van Rijswijk (Department of Neurology, St. Elisabeth Hospital, Tilburg), Gert Messchendorp (Department of Neurology, University Medical Center Gron-

 Stroke. 2020;51:1941–1950. DOI: 10.1161/STROKEAHA.119.026731

ingen), 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, Medical Spectrum Twente, Enschede), Jasmijn Lodico (Department of Neurology, Medical Spectrum Twente, Enschede), Hanneke Droste (Department of Neurology, Medical Spectrum Twente, Enschede), Maureen Wollaert (Department of Neurology, Maastricht University Medical Center and Cardiovascular Research Institute Maastricht), Sabrina Verheesen (Department of Neurology, Maastricht University Medical Center and Cardiovascular Research Institute Maastricht), D. Jeurrissen (Department of Neurology, Maastricht University Medical Center and Cardiovascular Research Institute Maastricht), Erna Bos (Department of Neurology, Leiden University Medical Center), Yvonne Drabbe (Department of Neurology, HAGA Hospital, the Hague), Michelle Sandiman (Department of Neurology, HAGA Hospital, the Hague), Marjan Elfrink (Department of Neurology, Rijnstate Hospital, Arnhem), Nicoline Aaldering (Department of Neurology, Rijnstate Hospital, Arnhem), Berber Zweedijk (Department of Neurology, University Medical Center Utrecht), Mostafa Khalilzada (Department of Neurology, HAGA Hospital, the Hague), Jocova Vervoort (Department of Neurology, St. Elisabeth Hospital, Tilburg), Hanneke Droste (Department of Neurology, Medical Spectrum Twente, Enschede), Nynke Nicolaij (Department of Radiology, Erasmus MC University Medical Center), Michelle Simons (Department of Neurology, Rijnstate Hospital, Arnhem), 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), Erna Bos (Department of Neurology, Leiden University Medical Center), Denn Barning (Department of Radiology, Leiden University Medical Center); PhD/medical students: Esmee Venema (Department of Public Health, Erasmus MC University Medical Center), Vicky Chalos (Department of Neurology, Erasmus MC University Medical Center; Department of 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; Department of Radiology, Maastricht University Medical Center and Cardiovascular Research Institute Maastricht), Anna M.M. Boers (Department of Radiology and Nuclear Medicine, Amsterdam UMC, University of Amsterdam, Amsterdam; Department of Biomedical Engineering and 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), Ivo G.H. Jansen (Department of Radiology and Nuclear Medicine, Amsterdam UMC, University of Amsterdam, Amsterdam), Manon L. Tolhuisen (Department of Radiology and Nuclear Medicine, Amsterdam UMC, University of Amsterdam, Amsterdam; Department of Biomedical Engineering and 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 Collette (Department of Neurology, University Medical Center Groningen; Department of Radiology, University Medical Center Groningen), Adrien E.D. Groot (Department of Neurology, Amsterdam UMC, University of Amsterdam, Amsterdam), Natalie E. LeCouffe (Department of Neurology, Amsterdam UMC, University of Amsterdam, Amsterdam), Praneeta R. Konduri (Department of Biomedical Engineering and Physics, Amsterdam UMC, University of Amsterdam, Amsterdam), Haryadi Prasetya (Department of Biomedical Engineering and Physics, Amsterdam UMC, University of Amsterdam, Amsterdam), Nerea Arrarte-Terreros (Department of Biomedical Engineering and Physics, Amsterdam UMC, University of Amsterdam, Amsterdam), Lucas A. Ramos (Department of Biomedical Engineering and Physics, Amsterdam UMC, University of Amsterdam, Amsterdam).

REFERENCES

1. Berkhemer OA, Fransen PS, Beumer D, van den Berg LA, Lingsma HF, Yoo AJ, Schonewille WJ, Vos JA, Nederkoorn PJ, Wermer MJH, et al; MR CLEAN Investigators. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med*. 2015;372:11–20. doi: 10.1056/NEJMoa1411587
2. Bracard S, Ducrocq X, Mas JL, Soudant M, Oppenheim C, Moulin T, Guillemin F. THRACE investigators. Mechanical thrombectomy after intravenous alteplase versus alteplase alone after stroke (THRACE): a randomised controlled trial. *Lancet Neurol*. 2016;15:1138–1147. doi: 10.1016/S1474-4422(16)30177-6
3. Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, Thornton J, Roy D, Jovin TG, Willinsky RA, Sapkota BL, et al; ESCAPE Trial Investigators. Randomized assessment of rapid endovascular treatment of ischemic stroke. *N Engl J Med*. 2015;372:1019–1030. doi: 10.1056/NEJMoa1414905
4. Jovin TG, Chamorro A, Cobo E, de Miquel MA, Molina CA, Rovira A. REVASCAT Trial Investigators. Thrombectomy within 8 hours after symptom onset in ischemic stroke. *N Engl J Med*. 2015;372:2296–2306. doi: 10.1056/NEJMoa1503780
5. Muir KW, Ford GA, Messow CM, Ford I, Murray A, Clifton A, Brown MM, Madigan J, Lenthall R, Robertson F, et al; PISTE Investigators. Endovascular therapy for acute ischaemic stroke: the Pragmatic Ischaemic Stroke Thrombectomy Evaluation (PISTE) randomised, controlled trial. *J Neurol Neurosurg Psychiatry*. 2017;88:38–44. doi: 10.1136/jnnp-2016-314117
6. Saver JL, Goyal M, Bonafe A, Diener HC, Levy EI, Pereira VM, Albers GW, Cognard C, Cohen DJ, Hacke W, et al; SWIFT PRIME Investigators. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. *N Engl J Med*. 2015;372:2285–2295. doi: 10.1056/NEJMoa1415061
7. Campbell BC, Mitchell PJ, Kleinig TJ, Dewey HM, Churilov L, Yassi N. EXTEND-IA Investigators. Endovascular therapy for ischemic stroke with perfusion-imaging selection. *N Engl J Med*. 2015;372:1009–1018. doi: 10.1056/NEJMoa1414792
8. Broderick JP, Palesch YY, Demchuk AM, Yeatts SD, Khatri P, Hill MD, Jauch EC, Jovin TG, Yan B, Silver FL, et al; Interventional Management of Stroke (IMS) III Investigators. Endovascular therapy after intravenous t-PA versus t-PA alone for stroke. *N Engl J Med*. 2013;368:893–903. doi: 10.1056/NEJMoa1214300
9. Kidwell CS, Jahan R, Gornbein J, Alger JR, Nenov V, Ajani Z, Feng L, Meyer BC, Olson S, Schwamm LH, et al; MR RESCUE Investigators. A trial of imaging selection and endovascular treatment for ischemic stroke. *N Engl J Med*. 2013;368:914–923. doi: 10.1056/NEJMoa1212793
10. Schonewille WJvD, E J, Vos JA, Boiten J, Dippel DW, Reekers JA, Kappelle LJ. Behandeling van het acute herseninfarct via de veneuze en arteriële route. *Ned Tijdschr Geneeskd*. 2010:154:A1665.
11. Norrving B, Barrick J, Davalos A, Dichgans M, Cordonnier C, Guekht A, Kutluk K, Mikulik R, Wardlaw J, Richard E, et al. Action plan for stroke in Europe 2018-2030. *Eur Stroke J*. 2018;3:309–336. doi: 10.1177/2396987318808719
12. de Sousa DA, Martial RV, Abilleira S, Gattringer T, Kobayashi A, Gallofré M, Fazekas F, Szikora I, Feigin V, Caso V, et al. Access to and delivery of acute ischaemic stroke treatments: a survey of national scientific societies and stroke experts in 44 european countries. *Eur Stroke J*. 2018;0:1–16. doi: 10.1177/2396987318786023
13. Rozeman AD, Wermer MJ, Vos JA, Lycklama à Nijeholt GJ, Beumer D, Berkhemer OA, Dippel DWJ, Algra A, Boiten J, Schonewille WJ. MR CLEAN Pretrial Study Group. Evolution of Intra-arterial Therapy for Acute Ischemic Stroke in The Netherlands: MR CLEAN Pretrial Experience. *J Stroke Cerebrovasc Dis*. 2016;25:115–121. doi: 10.1016/j.jstrokecerebrovasdis.2015.09.002
14. Fransen PS, Beumer D, Berkhemer OA, van den Berg LA, Lingsma H, van der Lugt A, van Zwam WH, van Oostenbrugge RJ, Roos YBWEM, Majoie CB, et al; MR CLEAN Investigators. MR CLEAN, a multicenter randomized clinical trial of endovascular treatment for acute ischemic stroke in the Netherlands: study protocol for a randomized controlled trial. *Trials*. 2014;15:343. doi: 10.1186/1745-6215-15-343
15. Jansen IGH, Mulder MJHL, Goldhoorn RB; MR CLEAN Registry Investigators. Endovascular treatment for acute ischaemic stroke in routine clinical practice: prospective, observational cohort study (MR CLEAN Registry). *BMJ*. 2018;360:k949. doi: 10.1136/bmj.k949

16. Van Leest L, Koek H, Van Trijp M, Van Dis S, Peters R, Bots M. *Ea hart-en vaatziekten in nederland 2005*. Den Haag: Nederlandse Hartstichting. 2005.
17. Jager-Geurts M, Peterse R, Van Dis S, Bots M. *Hart-en vaatziekten in nederland, 2006. Cijfers over leefstijl en risicofactoren, ziekte en sterfte*. Den Haag: Nederlandse Hartstichting. 2006.
18. Vaartjes I, van Dis S, Peters R, Visseren F, Bots M. *Hart-en vaatziekten in nederland naar geslacht. Hart-en vaatziekten in Nederland*. 2008:9–22.
19. Vaartjes I, Van Dis I, Visseren F, Bots M. *Hart-en vaatziekten in nederland. Hart-en vaatziekten in Nederland 2009*. Den Haag: Nederlandse Hartstichting. 2009.
20. Vaartjes I, van Dis I, Visseren F, Bots M. *Hart-en vaatziekten in nederland 2010: Cijfers over leefstijl-en risicofactoren, ziekte en sterfte*. Den Haag: Nederlandse Hartstichting. 2010.
21. Vaartjes I, van Dis I, Visseren F, Bots M. *Hart-en vaatziekten in nederland 2011. Cijfers over leefstijl-en risicofactoren, ziekte en sterfte*. Den Haag: Nederlandse Hartstichting. 2011.
22. Koopman C, Van Dis I, Visseren F, Vaartjes I, Bots M. *Hart-en vaatziekten in Nederland 2012, cijfers over risicofactoren, ziekte en sterfte*. Den Haag: Hartstichting. 2012;2014
23. Vaartjes I, Van Dis I, Visseren F, Bots M. *Hart-en vaatziekten in nederland 2013, cijfers over leefstijl, risicofactoren, ziekte en sterfte*. Den Haag: Hartstichting. 2013:2941–2947.
24. Koopman C, Van Dis I, Vaartjes I, Visseren F, Bots M. *Hart-en vaatziekten in Nederland 2014, cijfers over kwaliteit van leven, ziekte en sterfte*. Den Haag: Hartstichting. 2014.
25. Bots ML, Buddeke J, van Dis I, Vaartjes C, Visseren F. *Hart-en vaatziekten in nederland in 2015: Cijfers over heden, verleden en toekomst*. Den Haag: Nederlandse Hartstichting. 2015.
26. Buddeke J, Visseren F, Vaartjes I. *Hart-en vaatziekten in nederland, cijfers over prevalentie, ziekte en sterfte*. Den Haag: Hartstichting. 2016.
27. Buddeke J, Van Dis I, Visseren F, Vaartjes I, Bots M. *Hart-en vaatziekten in nederland 2017, cijfers over leefstijl, risicofactoren, ziekte en sterfte*. Den Haag: Hartstichting. 2017:7–44.
28. De Boer A.R. VDI, Visseren FLJ, Vaarjtes I, Bots ML. *Hart- en vaatziekten in nederland 2018, cijfers over risicofactoren, hartinterventies, ziekte en sterfte*. Den Haag: Nederlandse Hartstichting. 2018.
29. Tennekes M. Tmap: Thematic maps in r. *2018. J Statistical Software*. 2018;84:39.
30. Statistics Netherlands (2014) The Hague, Netherlands. http://www.cbs.nl. Accessed March 4, 2019.
31. Kadaster The Netherlands' Cadastre, Land Registry, and Mapping Agency (2014), Apeldoorn, Netherlands. http://www.kadaster.nl. Accessed March 4, 2019.
32. Dippel DW. A Randomized Trial of Intraarterial Treatment for Acute Ischemic Stroke. Paper presented at: 9th World Stroke Congress; October I; Turkey. *International J Stroke*. https://onlinelibrary.wiley.com/doi/10.1111/ijs.12366.
33. Smith EE, Saver JL, Cox M, Liang L, Matsouaka R, Xian Y, Bhatt DL, Fonarow GC, Schwamm LH. Increase in endovascular therapy in get with the guidelines-stroke after the publication of pivotal trials. *Circulation*. 2017;136:2303–2310. doi: 10.1161/CIRCULATIONAHA.117.031097
34. McMeekin P, White P, James MA, Price CI, Flynn D, Ford GA. Estimating the number of UK stroke patients eligible for endovascular thrombectomy. *Eur Stroke J*. 2017;2:319–326. doi: 10.1177/2396987317733343
35. Chia NH, Leyden JM, Newbury J, Jannes J, Kleinig TJ. Determining the number of ischemic strokes potentially eligible for endovascular thrombectomy: a Population-Based Study. *Stroke*. 2016;47:1377–1380. doi: 10.1161/STROKEAHA.116.013165
36. Addo J, Ayis S, Leon J, Rudd AG, McKevitt C, Wolfe CD. Delay in presentation after an acute stroke in a multiethnic population in South london: the South london stroke register. *J Am Heart Assoc*. 2012;1:e001685. doi: 10.1161/JAHA.112.001685
37. Wahlgren N, Moreira T, Michel P, Steiner T, Jansen O, Cognard C, Mattle HP, van Zwam W, Holmin S, Tatlisumak T, et al; ESO-KSU, ESO, ESMINT, ESNR and EAN. Mechanical thrombectomy in acute ischemic stroke: consensus statement by ESO-Karolinska Stroke Update 2014/2015, supported by ESO, ESMINT, ESNR and EAN. *Int J Stroke*. 2016;11:134–147. doi: 10.1177/1747493015609778
38. Venema E, Boodt N, Berkhemer OA, Rood PPM, van Zwam WH, van Oostenbrugge RJ, van der Lugt A, Roos YBWEM, Majoie CBLM, Lingsma HF, et al; MR CLEAN Investigators. Workflow and factors associated with delay in the delivery of intra-arterial treatment for acute ischemic stroke in the MR CLEAN trial. *J Neurointerv Surg*. 2018;10:424–428. doi: 10.1136/neurintsurg-2017-013198
39. Venema E, Groot AE, Lingsma HF, Hinsenveld W, Treurniet KM, Chalos V. Effect of interhospital transfer on endovascular treatment for acute ischemic stroke. *Stroke*. 2019;50:923–930. doi: 10.1161/STROKEAHA.118.024091
40. Venema E, Duvekot MHC, Lingsma HF, Rozeman AD, Moudrous W, Vermeij FH, Biekart M, van der Lugt A, Kerkhoff H, Dippel DWJ, et al; PRESTO Investigators. Prehospital triage of patients with suspected stroke symptoms (PRESTO): protocol of a prospective observational study. *BMJ Open*. 2019;9:e028810. doi: 10.1136/bmjopen-2018-028810
41. Rinaldo L, Brinjikji W, Rabinstein AA. Transfer to high-volume centers associated with reduced mortality after endovascular treatment of acute stroke. *Stroke*. 2017;48:1316–1321. doi: 10.1161/STROKEAHA.116.016360
42. Gupta R, Horev A, Nguyen T, Gandhi D, Wisco D, Glenn BA, Tayal AH, Ludwig B, Terry JB, Gershon RY, et al. Higher volume endovascular stroke centers have faster times to treatment, higher reperfusion rates and higher rates of good clinical outcomes. *J Neurointerv Surg*. 2013;5:294–297. doi: 10.1136/neurintsurg-2011-010245
43. Saber H, Navi BB, Grotta JC, Kamel H, Bambhroliya A, Vahidy FS, Chen PR, Blackburn S, Savitz SI, McCullough L, et al. Real-world treatment trends in endovascular stroke therapy. *Stroke*. 2019;50:683–689. doi: 10.1161/STROKEAHA.118.023967
44. Lemkes JS, Peels JO, Huybregts R, de Swart H, Hautvast R, Umans VA. Emergency cardiac surgery after a failed percutaneous coronary intervention in an interventional centre without on-site cardiac surgery. *Neth Heart J*. 2007;15:173–177. doi: 10.1007/BF03085976
45. Aronsson M, Persson J, Blomstrand C, Wester P, Levin LÅ. Cost-effectiveness of endovascular thrombectomy in patients with acute ischemic stroke. *Neurology*. 2016;86:1053–1059. doi: 10.1212/WNL.0000000000002439
46. Steen Carlsson K, Andsberg G, Petersson J, Norrving B. Long-term cost-effectiveness of thrombectomy for acute ischaemic stroke in real life: an analysis based on data from the Swedish Stroke Register (Riksstroke). *Int J Stroke*. 2017;12:802–814. doi: 10.1177/1747493017701154
47. Albers GW, Marks MP, Kemp S, Christensen S, Tsai JP, Ortega-Gutierrez S, McTaggart RA, Torbey MT, Kim-Tenser M, Leslie-Mazwi T, et al; DEFUSE 3 Investigators. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. *N Engl J Med*. 2018;378:708–718. doi: 10.1056/NEJMoa1713973
48. Nogueira RG, Jadhav AP, Haussen DC, Bonafe A, Budzik RF, Bhuva P. DAWN Trial Investigators. Thrombectomy 6 to 24 Hours after Stroke with a mismatch between deficit and infarct. *N Engl J Med*. 2018;378:11–21. doi: 10.1056/NEJMoa1706442
49. Thomalla G, Simonsen CZ, Boutitie F, Andersen G, Berthezene Y, Cheng B, Cheripelli B, Cho TH, Fazekas F, Fiehler J, et al; WAKE-UP Investigators. MRI-Guided thrombolysis for stroke with unknown time of onset. *N Engl J Med*. 2018;379:611–622. doi: 10.1056/NEJMoa1804355
50. Ma H, Campbell BCV, Parsons MW, Churilov L, Levi CR, Hsu C, Kleinig TJ, Wijeratne T, Curtze S, Dewey HM, et al; EXTEND Investigators. Thrombolysis guided by perfusion imaging up to 9 hours after onset of stroke. *N Engl J Med*. 2019;380:1795–1803. doi: 10.1056/NEJMoa1813046
51. Campbell BCV, Ma H, Ringleb PA, Parsons MW, Churilov L, Bendszus M, Levi CR, Hsu C, Kleinig TJ, Fatar M, et al; EXTEND, ECASS-4, and EPITHET Investigators. Extending thrombolysis to 4·5-9 h and wake-up stroke using perfusion imaging: a systematic review and meta-analysis of individual patient data. *Lancet*. 2019;394:139–147. doi: 10.1016/S0140-6736(19)31053-0
52. Flodmark O, Grisold W, Richling B, Mudra H, Demuth R, Pierot L. Training of future interventional neuroradiologists: the European approach. *Stroke*. 2012;43:2810–2813. doi: 10.1161/STROKEAHA.112.657882
53. Goyal M, Menon BK, van Zwam WH, Dippel DW, Mitchell PJ, Demchuk AM, Dávalos A, Majoie CBLM, van der Lugt A, de Miquel MA. et al; HERMES Collaborators. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet*. 2016;387:1723–1731. doi: 10.1016/S0140-6736(16)00163-X