Stroke Neurologist’s Perspective on the New Endovascular Trials

James C. Grotta, MD; Werner Hacke, MD

Abstract—Before December 2014, the only proven effective treatment for acute ischemic stroke was recombinant tissue-type plasminogen activator (r-tPA). This has now changed with the publication of the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN), Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times (ESCAPE), Extending the Time for Thrombolysis in Emergency Neurological Deficits—Intra-Arterial (EXTEND IA), Solitary With the Intention for Thrombectomy as Primary Endovascular Treatment Trial (SWIFT PRIME), and Randomized Trial of Revascularization With the Solitaire FR Device Versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting Within Eight Hours of Symptom Onset (REVASCAT) studies. We review the main results of these studies and how they inform stroke patient management going forward. The main take home points for neurologists are (1) intra-arterial thrombectomy is a potently effective treatment and should be offered to patients who have documented occlusion in the distal internal carotid or the proximal middle cerebral artery, have a relatively normal noncontrast head computed tomographic scan, severe neurological deficit, and can have intra-arterial thrombectomy within 6 hours of last seen normal; (2) benefits are clear in patients receiving r-tPA before intra-arterial thrombectomy; r-tPA should not be withheld if the patient meets criteria, and benefit in patients who do not receive r-tPA or have r-tPA exclusions requires further study; and (3) these favorable results occur when intra-arterial thrombectomy is performed in an endovascular stroke center by a coordinated multidisciplinary team that extends from the prehospital stage to the endovascular suite, minimizes time to recanalization, uses stent-retriever devices, and avoids general anesthesia. In conclusion, stroke teams, including practicing neurologists caring for patients with stroke should now provide the option for intra-arterial thrombectomy for a subset of patients with acute stroke. (Stroke. 2015;46:1447-1452. DOI: 10.1161/STROKEAHA.115.008384.)

Key Words: cerebral infarction ■ clinical trials, randomized ■ thrombolytic therapy

In 1995, the first effective treatment for acute stroke was demonstrated in a randomized controlled trial leading to the approval of intravenously administered recombinant tissue-type plasminogen activator (r-tPA).1 Although the benefits of r-tPA were eventually confirmed in multiple additional studies and pooled analyses during the next 2 decades,2–5 the wide adoption of this therapy was initially hindered by a lack of consensus about its efficacy among the neurological community.6,7 Furthermore, r-tPA provides incomplete benefit in patients with the worse strokes, for example, those with large artery occlusions who usually are left severely disabled or dead.8 Intra-arterial stroke treatment was introduced early for this population of patients, but it took until 2012 for 3 randomized controlled trials using first generation devices to be published, and their results disappointingly did not show a benefit of intra-arterial thrombectomy (IAT) over standard treatment.9–11 Suddenly, between December 2014 and February 2015, 4 similar trials finally demonstrated the efficacy of IAT for patients with large artery occlusions.12–15 The main results, plus a 5th study published in April,16 are summarized in the Table. This remarkable syzygy of studies provides practicing neurologists with the opportunity to rapidly absorb a substantial amount of information and reach a consensus about how the data should be interpreted. Hopefully, this might help the stroke community avoid some of the confusion that occurred 20 years ago with the launch of r-tPA and integrate IAT into practice in an evidence-based manner, thereby improving the outcome of patients who otherwise have a poor prognosis.

We will briefly review the 5 studies, focusing on their differences and unifying aspects, how they should be interpreted, and finally discuss their implications for the practicing clinical neurologist.

What Were the Important Components of Each of These Studies of Interest to Neurologists?

MR CLEAN

The first and largest study, the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the
Table. Summary of Data From the 5 Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>NIHSS Range</th>
<th>LSN to Groin</th>
<th>mRS 0–2 at 90 d</th>
<th>sICH</th>
<th>Device Complications</th>
<th>Mortality</th>
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<tr>
<td></td>
<td></td>
<td>CTL</td>
<td>IAT+</td>
<td>r-tPA</td>
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<td>CTL IAT+ CTL IAT+</td>
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<tr>
<td>MR CLEAN</td>
<td>500</td>
<td>18 (14–21)</td>
<td>17 (14–22)</td>
<td>90% 59%</td>
<td>260</td>
<td>19% 33%</td>
<td>22% 21%</td>
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<tr>
<td>233/267</td>
<td></td>
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<tr>
<td>ESCAPE</td>
<td>315</td>
<td>17 (12–20)</td>
<td>16 (13–20)</td>
<td>76% 72%</td>
<td>200</td>
<td>29% 53%</td>
<td>19% 10%</td>
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<tr>
<td>EXTEND IA</td>
<td>70</td>
<td>13 (9–19)</td>
<td>17 (13–20)</td>
<td>100%</td>
<td>210</td>
<td>40% 71%</td>
<td>20% 9%</td>
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<tr>
<td>SWIFT PRIME</td>
<td>196</td>
<td>17 (13–19)</td>
<td>17 (13–20)</td>
<td>98% 88%</td>
<td>224</td>
<td>36% 60%</td>
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<tr>
<td>REVASCAT</td>
<td>206</td>
<td>17 (12–19)</td>
<td>17 (14–20)</td>
<td>73% 66%</td>
<td>269</td>
<td>28% 44%</td>
<td>16% 18%</td>
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CTL indicates control group; Embol, distal embolization; IAT+, intra-arterial thrombectomy on top of standard treatment including r-tPA; LSN, time (minutes) from last seen normal to groin puncture in IAT+ group; Mdn, median; mRS 0–2 at 90 d, modified Rankin Scale of 0–2 at 90 days after randomization; NIHSS, baseline National Institutes of Health Stroke Scale; Perfor, vessel perforation; r-tPA, patients in trial treated with recombinant tissue-type plasminogen activator; REVASCAT, Randomized Trial of Revascularization With the Solitaire FR Device Versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting Within Eight Hours of Symptom Onset; SAH, subarachnoid hemorrhage; sICH (SITS), symptomatic intracerebral hemorrhage based on safe implementation of treatments in stroke criteria; and TICI 2b/3, patients in IAT+ group achieving thrombolysis in cerebral infarction grade 2b or 3 reperfusion.

Netherlands (MR CLEAN) differed from the others in several respects. First, it was the only study that completed its planned enrollment. The positive results led the leadership of the other ongoing studies to analyze their data before study completion. MR CLEAN provides us with the largest data set (500 total patients, 233 IAT patients) randomized equally to standard management with or without IAT. It was required that groin puncture could be performed within 6 hours of last seen normal (LSN). A wide range of the National Institutes of Health Stroke Scale Score (NIHSS) was allowed (as low as 2), with no upward age restriction. Another difference was a pragmatic design: patients were only randomized if the team was uncertain if they would benefit. Some patients who met inclusion criteria may have received r-tPA but were not randomized because it was judged that they either did not need IAT or would not respond. Unfortunately, we do not have any information on the number, clinical characteristics, or outcome of those patients. It is unlikely that many patients received IAT outside the study because the procedure was not reimbursed by insurers in the Netherlands outside the study. r-tPA was administered to 87% of IAT patients (average 85 minutes after LSN), but patients were not randomized to IAT until 204 minutes, 2 hours after r-tPA bolus. At that time, the qualifying noncontrast computed tomography (NCCT), read remotely by a central reader, had a median Alberta Stroke Program Early CT Score (ASPECTS) of 9 (range, 7–10), CT angiography (CTA) documented distal internal carotid artery (ICA) or initial segment middle cerebral artery-M1 occlusions in 92%, and median NIHSS was 17 (interquartile range, 14–21). Groin puncture for IAT occurred an hour after that.

Therefore, more than in the other studies, MR CLEAN patients represent r-tPA failures because persisting arterial occlusion and severe neurological deficits were documented >2 hours after r-tPA was started. Yet, their good ASPECTS at this delayed interval indicates that most included patients probably still had a relatively small core infarct. Although only 44% of patients in the study were actually drip and ship patients, the evaluation and treatment time intervals of the average MR CLEAN patient are more typical of management where patients receive r-tPA at stroke hospitals and then transported to hubs for IAT, and less similar to patients initially presenting to endovascular-ready centers. The percentage of patients achieving good outcome was low in both arms of this study (35% reaching modified Rankin Scale (mRS) 0–2 with IAT versus 19% in controls), whereas mortality was similarly high (21 versus 22%, respectively), probably reflecting relatively delayed treatment, lack of imaging selection beyond NCCT, and relatively low rates of recanalization (thrombolysis in cerebral infarction 2b/3=59%). Also, MR CLEAN included 145 patients with extracranial carotid occlusion, a higher proportion than in any of the other trials, and this may also have contributed to the lower rate of complete recanalization and excellent outcome. IAT added no additional risk of bleeding over standard management with r-tPA (7.7%), although there was a 5.6% incidence of new symptomatic embolism, indicating an opportunity for further technical improvement.

ESCAPE
Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times (ESCAPE) was stopped early by its Data Safety Monitoring Board after the MR CLEAN results were published and 315 patients had been enrolled and analyzed. ESCAPE had several unique protocol features. It identified patients with >50% of the middle cerebral artery territory with collateral flow on a delayed CTA image. Although it had a time window ≤12 hours, it required the fastest time from imaging to groin puncture (<1 hour) so that the actual time recanalization was achieved was the fastest of the trials, perhaps indicating an effective strategy
for achieving rapid treatment. Wake-up strokes and patients ineligible for r-tPA were also accepted by the protocol, although 72% of IAT patients received r-tPA (average 110 minutes after LSN). In fact, despite broad inclusion criteria, the investigators were able to obtain excellent results: thrombolysis in cerebral infarction 2b3 flow in 72% and mRS 0 to 2 in 53% of the IAT patients (compared with 29% with standard therapy). There was also a significant reduction in mortality from 19.0% to 10.4%.13

EXTEND IA
The Extending the Time for Thrombolysis in Emergency Neurological Deficits—Intra-Arterial (EXTEND IA) study was the smallest study (70 patients) but the only one to rely completely on penumbral imaging (RAPID software) rather than NCCT to select patients. Primarily terminal ICA and proximal M1 occlusions were included. This study presented better outcomes than expected in both treatment arms, perhaps based on the selection of more responsive patients by imaging. A total of 25% of patients with appropriate arterial occlusion that probably would have been enrolled into the NCCT-based studies were excluded from EXTEND IA based on imaging criteria. All patients in this trial received r-tPA (average 127 minutes after LSN) and stent-retriever technology. Thrombolysis in cerebral infarction 2b3 flow was obtained in 86% and mRS 0 to 2 in 71% with IAT, versus 40% with r-tPA alone.14

SWIFT PRIME
Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment Trial (SWIFT PRIME) was stopped after enrolling 196 patients (an interim analysis had been planned at 200 patients). Patients were selected based on NCCT ASPECTS or RAPID software (selection by RAPID was required in the first 71 patients) and occlusion on CTA (almost exclusively distal ICA and M1 occlusions). Patients were excluded if they had extracranial carotid occlusion. A total of 98% of patients received r-tPA (average 110 minutes after LSN) and 100% were treated by stent-retrievers. SWIFT PRIME achieved high rates of complete recanalization (LSN to groin 224 minutes, first deployment 252 minutes, and thrombolysis in cerebral infarction 2b3 flow in 88%) and also enjoyed a high percentage of good outcome (mRS, 0–2 in 60% for IAT versus 36% for controls).15

Figure. Relationship of percentage of patients achieving thrombolysis in cerebral infarction grade 2b or 3 (TICI2b3) flow and patients achieving modified Rankin Scale (mRS) of 0 to 2 in intervention (intra-arterial thrombectomy [IAT]) and control (CTL) groups (y axis) vs minutes from last seen normal to groin puncture for each of the 5 studies (x axis). The exact time to achieving maximal reperfusion is not available from published data for all studies, but where available is proportionate to time to groin puncture. Note the following: (1) the percentage of patients achieving good outcome is strikingly proportionate to the percentage of patients achieving TICI2b3 flow. (2) There is a consistent difference between the IAT and CTL groups in the percent achieving mRS 0 to 2 across all studies with the difference diminishing with increased time from last seen normal to groin puncture. (3) The percentage of patients achieving good outcome is roughly proportionate to the time from last seen normal to groin puncture (earlier groin puncture=higher proportion good outcome) with the exception being the EXTEND IA study, which was the only study to use advanced imaging for patient selection suggesting its use to identify responsive patients at delayed time intervals. ESCAPE indicates Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times; EXTEND IA, Extending the Time for Thrombolysis in Emergency Neurological Deficits—Intra-Arterial; MR CLEAN, Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands; SWIFT PRIME, Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment Trial; and REVASCAT, Randomized Trial of Revascularization With the Solitaire FR Device Versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting Within Eight Hours of Symptom Onset.
What About the New Studies Is So Convincing That Our Current Treatment Much Be Changed?

Taken in-toto, the 5 studies were alike in design with results that were strikingly consistent and favorable for IAT (Figure). All 5 relied on referral to experienced endovascular centers, required documentation of intracranial occlusion, and aimed at recanalization within 6 hours using stent-retriever technology (82%–100% overall). Patients included were similar; median NIHSS scores were 17 (interquartile range, 13–21), ASPECTS were 9 (range, 6–10), most patients (73%–100%) received r-tPA, patients >80 years were included in all but SWIFT PRIME and also benefited, and most patients (82%–96%) had M1 or distal ICA occlusions documented by CTA. Furthermore, and perhaps most reassuringly, despite differences in the timing and amount of recanalization achieved, there was a consistent difference across all studies in good outcome between the interventional and control arms favoring IAT of 14% to 31% (number needed to treat for one additional good outcome, =4; Figure). Variability in benefit between studies probably reflects differences in the patients selected irrespective of IAT treatment. In all the studies there was no signal of increased bleeding risk compared with r-tPA alone, and an overall trend showing a reduction in mortality with IAT. Also reassuringly, the likelihood of good outcome increased with greater amount of recanalization (Figure). The consistency and logic of the results can make neurologists confident that they should refer similar acute stroke patients as evaluated in these IAT trials.

Why Were These Studies Positive When Previous Studies Did Not Show Benefit?

The main difference was that the 5 new studies required documentation of occlusion, had a time window goal of <6 hours for recanalization (except REVASCAT <8 hours), and for the most part used stent-retrievers that achieved faster and more complete recanalization than previous studies. Interestingly, in a subgroup analysis, Interventional Management of Stroke III patients with documented occlusion and similar NIHSS ranges who achieved recanalization within 6 hours also benefitted. By requiring CTA documentation of occlusion before randomization, the investigators in these trials optimized their ability to detect differences between the 2 groups; first, they assured that the intervention group all had the disease they were intended to intervene on and second that the control group was going to do badly without the intervention.

What Are the Main Take Home Points From These Studies for Practicing Neurologists?

The main take home points for neurologists from the body of evidence contained in the 5 trials are (1) IAT is a potently effective treatment and should be offered to patients who have documented occlusion in the distal ICA or M1 arteries, have a relatively normal NCCT, significant neurological deficit, and can have recanalization within 6 hours of LSN; (2) benefits refer to patients receiving r-tPA before IAT; r-tPA should not be withheld if the patient meets criteria, and benefit in patients who do not receive r-tPA or have r-tPA exclusions requires further study; (3) favorable results occur when IAT is performed at an endovascular stroke center by a coordinated multidisciplinary team that extends from the prehospital stage to the endovascular suite, minimizes time to recanalization, uses stent-retriever devices, and avoids general anesthesia (GA).

Which Questions Are Still Open?

1. What kind of imaging is necessary? Does normal or high ASPECTS really mean small core, or can we be more precise in selecting patients using demonstration of mismatch as suggested by EXTEND IA? However, if we use more precise (specific) imaging, will we lose sensitivity and exclude patients who might benefit? Is demonstration of the occlusion by CTA or MR angiography needed in all cases before deciding about IAT? It certainly was pivotally important for the 5 successful randomized trials and not only helps distinguish the target population but also assists in planning the procedure. In a patient with a high NIHSS score who could be quickly moved into the endovascular suite, is the time and information required for the CTA worth the added information? Although not much time is lost obtaining the CTA at the time of the NCCT, the added time needed for a CTA might be more relevant in patients where the NCCT has already been done at a referring hospital or clinic. CTA at the referring hospital should probably be avoided especially if groin puncture will be longer than 1 hour later.

2. What about patients excluded from these trials? Most patients who did not qualify for r-tPA or who could not have groin puncture by 6 hours were not included. Therefore, further studies of IAT in these groups are needed. Probably, patients in later time windows may require more extensive physiological and anatomic imaging for selection, but even with intravenous r-tPA, there is still no convincing evidence that this hypothesis is valid.

3. Is r-tPA necessary before IAT in all patients? Hemorrhage rates were no higher in IAT compared with control patients, most of whom received r-tPA, suggesting that most of the bleeding in both arms in these studies was because of the r-tPA. However, r-tPA will completely lyse some proximal occlusions before IAT can take place and may facilitate stent-retriever thrombectomy by partially lysing the clot. Therefore, these trials support that r-tPA should be given in all patients meeting current r-tPA guidelines even if IAT is planned. However, it is worth exploring if r-tPA might be omitted in patients who can be quickly moved to the endovascular suite and who have higher bleeding risk from r-tPA (eg, severe strokes, borderline coagulation status, advanced age, and high blood glucose).

4. If practicing at a community hospital without CTA/MR angiography or endovascular capability, how do we select patients for referral on clinical grounds? The majority of patients in these studies had NIHSS >12, so it would be logical to refer patients with NIHSS >12, with or without CTA, and with a NCCT that still looks mostly normal. It is still uncertain if patients with lower NIHSS but persisting occlusion benefit from IAT as their relatively good score may indicate adequate collateral flow. This is another group that would benefit from further study.

5. What about peri- and postinterventional treatment? Should we use GA or conscious sedation? There are centers and
even regions that prefer GA over conscious sedation, based on personal preferences. Others claim that outcome may be worse with GA. We have subgroup data from MR CLEAN presented at the International Stroke Conference in February 2015, indicating that the advantage of IAT may disappear with GA. However, these are nonrandomized subgroups and it is possible that features of the patient’s condition that requires GA also carries a risk for an overall poorer outcome. Randomized controlled trials are needed to give more insight into this complex issue.

6. For which patients do the results not apply? Overall, the results of the current studies plus previous data do not suggest that treatment with recanalization devices other than stent-retrievers, in a time window >6 hours, in patients with large infarct size at treatment, with mild symptoms, with distal occlusions of the M2, and without r-tPA bridging can be recommended. Three more trials were presented in April 2015 and provide more evidence about the effects of other devices and patient populations. Randomized Trial of Resuscitation With The Solitaire FR Device Versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting Within Eight Hours of Symptom Onset (REVASCAT) was an investigator-initiated RCT performed in Spain that was stopped prematurely after an interim analysis performed after the MR CLEAN results were presented. It used Solitaire stent-retriever thrombectomy in Carotid T and M1 occlusions in an 8-hour time window and showed similar results to MR CLEAN. Trial and Cost Effectiveness Evaluation of Intra-Arterial Thrombectomy in Acute Ischemic Stroke (THRACE; ClinicalTrials.gov identifier: NCT01062698) was an investigator-initiated RCT performed in 31 centers in France. It had a narrow time window of 4 hours from onset to presentation, included Carotid T, M1, and basilar artery occlusions and allowed a broad variety of older and newer thrombectomy devices. Device treatment was on top of standard r-tPA treatment. The study was stopped prematurely after an interim analysis. THERAPY (ClinicalTrials.gov Identifier: NCT01429350) was a company-sponsored trial evaluating the Penumbra aspiration system in an 8-hour time window on top of r-tPA against standard treatment. It required evidence of anterior circulation large vessel occlusion by a thrombus with a length of at least 8 mm. This trial was also stopped prematurely and did not reach the estimated enrollment of 692 patients. The results have not been published, but reportedly failed to show significant benefit with IAT.

7. What kind of results can we expect in clinical practice? The response rates differed between the 5 trials. If in clinical practice patients will be treated later, have larger infarct core, and do not have initial CTA, it may be that the results we observe will be closer to those seen in MR CLEAN. The broader the use of IAT the more patients with limited response will be seen.

8. How many patients are candidates for IAT and how many endovascular centers do we need? In EXTEND IA, of 1044 patients treated with r-tPA, only 70 patients were eligible; 25% of exclusions were based on penumbral imaging. Using only NCCT as an imaging screen, the proportion qualifying would be higher, but still probably on average not >10% to 15% of r-tPA-treated patients. In large referral centers, =5% to 10% of all acute ischemic strokes and 20% to 30% of r-tPA eligible patients may be candidates for IAT. Although not supported by data, and probably also not by some stakeholders in the field, we think that IAT centers should meet a threshold number (established by a committee of experts) of appropriately selected cases per year to guarantee quality and justify the high financial and logistic investments. The endovascular procedures in these 5 studies were performed at relatively high-volume referral centers with, in some trials, rigid requirements for the individual interventionalist to participate, which may have contributed substantially to the excellent results, supporting the concept of centralization of IAT resources and expertise. And how many centers do we need? This will differ from health system to health system and from region to region. The Dutch example of 16 centers in a country of 17 million inhabitants suggests a ratio of 1 center per million, which would currently also be close to the situation in some parts of Germany. It may be different in the United States, but too many competing endovascular centers will not be cost-effective, will lack quality, and might encourage widening the time window, accepting large core patients and distal occlusions thereby increasing the number of patients beyond the evidence-based target population.

9. Can we do better? Although IAT provided a powerful effect in these trials, patients ending up with a poor outcome (mRS >3) ranged from 29% to 67%, so there is plenty of room for improvement. In addition to technological advancements, it is possible that speeding treatment even faster, or ancillary therapies such as augmenting thrombolysis by antithrombotic/antiplatelet agents or ultrasound, or adding cytoprotection may help improve outcome further.

How Should Neurologists Change Our Practices Now?
The neurologist treating patients in community hospitals must now be prepared to arrange timely transfer of some patients with stroke for IAT. It is important to appreciate that patients similar to those who benefitted from IAT in these studies represent a relatively small proportion of patients with stroke. Nevertheless, it is a critically important subset because they have a high likelihood of severe disability without treatment, and IAT will have a relatively high impact on improving their outcome to little or moderate disability. Consequently, neurologists practicing in referral hospitals now need to establish a diagnostic and selection algorithm at their hospitals, based on the data from these studies, which quickly identifies patients who should then be immediately referred to endovascular centers. They also need to establish communication/transportation pathways ensuring direct and accurate transmission of data and the patient to the referral center. In centers capable of performing IAT, neurologists should implement expedited pathways to identify potential IAT candidates, move them quickly to CTA, and then to the endovascular suite. Finally, organizations that produce practice guidelines should promptly review the data from these new trials and revise acute stroke recommendations accordingly.
Conclusions

Five published studies have shown consistent and persuasive benefits for IAT using advanced technology in patients with stroke because of intracranial large artery occlusion. Stroke teams, including practicing neurologists caring for patients with stroke, should now provide the option for IAT for the subset of patients with acute ischemic stroke with persistent distal ICA or M1 occlusions who can be treated within 6 hours. Further research to enhance these gains is needed.

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References

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(Stroke. 2015;46:1447-1452.)

Key Words: cerebral infarction ▪ clinical trials, randomized ▪ thrombolytic therapy

2014년 12월 이전에는, 급성 혈관내 치료의 엄격한 시험 과정에서 고효율 치료로 제조한 조직플라스미노겐 환생체(recombinant tissue–type plasminogen activator, r–tPA)가 유일히었다. 이는 MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands), ESCAPE (Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times), EXTEND IA (Extending the Time for Thrombolysis in Emergency Neurological Deficits—Intra–arterial), SWIFT PRIME (Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment Trial) 및 REVASCAT (Randomized Trial of Revascularization With the Solitaire FR Device Versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting Within Eight Hours of Symptom Onset) 연구가 발표되면서 바뀌었다. 연구자들은 이 연구들의 주요 결과를 종합할 것이며, 임상의 임상 시험 결과가 뇌졸중 환자의 치료 패턴을 어떻게 바꾸게 될 것인지 정리할 것이다. 신경과 의사로서 알아야 하는 요전은 다음과 같다. (1) 동맥내 혈전제거술은 훌륭한 효과를 갖는 치료 방법으로 내경동맥 전방부 혹은 중대뇌동맥 근위부 폐색 환자로 비–조영 두부 CT가 비교적 정상적이며 심각한 신경학적 결손이 있으며 마지막으로 정상적이었던 시간부터 6시간 이내의 환자에서 시행되어야만 하는 치료 방법이다. (2) 동맥내 혈전제거술을 받기 전 r–tPA를 투여한 환자에서의 효과는 분명하며, 따라서 기준에 맞는 환자라면 r–tPA를 투여하지 않아야 할 이유는 없다는 점(그리고 r–tPA가 투여되지 않은 환자 및 r–tPA의 금기를 갖고 있는 환자에서 동맥내 혈전 제거술의 이점은 계속 연구되어야 한다); (3) 동맥내 혈전제거술의 환상적인 결과는, 병원 내 여러 부서가 긴밀한 협조와 통제 속에서 운영되며 내원 단계에서 혈관조영술까지 원활한 흐름이 이루어지며, 세계적으로 보완도 시행하지 않게 되며, 혈전 제거 스텝트를 이용하고, 전신마취를 하지 않는 혈관내 치료를 시행하는 뇌졸중 센터에서 기대할 수 있다. 그러므로 뇌졸중 환자를 치료하는 신경과 의사들을 포함한 뇌졸중 팀은 이제 기준에 하향한 급성 뇌졸중 환자의 치료로 동맥내 혈전제거술을 이용해야 한다.

### Table. Summary of Data From the 5 Trials

<table>
<thead>
<tr>
<th>Trial N</th>
<th>NIHSS Range</th>
<th>TICI</th>
<th>LSN to Groin Mdn</th>
<th>r-tPA 0–2 at 90 d</th>
<th>sICH</th>
<th>Complications</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>IAT+/CTL</td>
<td>CT+</td>
<td>IAT+</td>
<td>r-tPA</td>
<td>2B/3</td>
<td>r-tPA</td>
<td>IAT+</td>
<td>IAT+</td>
</tr>
<tr>
<td>MR CLEAN12</td>
<td>18/18</td>
<td>17/17</td>
<td>17/17</td>
<td>90%</td>
<td>59%</td>
<td>260</td>
<td>19%</td>
</tr>
<tr>
<td>233/267</td>
<td>(14–21)</td>
<td>(14–22)</td>
<td>(14–22)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESCAPE13</td>
<td>17/17</td>
<td>16/16</td>
<td>16/16</td>
<td>76%</td>
<td>72%</td>
<td>200</td>
<td>29%</td>
</tr>
<tr>
<td>315</td>
<td>(12–20)</td>
<td>(13–20)</td>
<td>(13–20)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>165/150</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EXTEND IA14</td>
<td>13/13</td>
<td>13/13</td>
<td>13/13</td>
<td>100%</td>
<td>86%</td>
<td>210</td>
<td>40%</td>
</tr>
<tr>
<td>70</td>
<td>(9–19)</td>
<td>(13–20)</td>
<td>(13–20)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>35/35</td>
<td>17/17</td>
<td>17/17</td>
<td>17/17</td>
<td>98%</td>
<td>88%</td>
<td>224</td>
<td>36%</td>
</tr>
<tr>
<td>196</td>
<td>(13–19)</td>
<td>(13–20)</td>
<td>(13–20)</td>
<td></td>
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</tr>
<tr>
<td>98/98</td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>SWIFT PRIME15</td>
<td>17/17</td>
<td>17/17</td>
<td>17/17</td>
<td>73%</td>
<td>66%</td>
<td>269</td>
<td>28%</td>
</tr>
<tr>
<td>206/206</td>
<td>(12–19)</td>
<td>(14–20)</td>
<td>(14–20)</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>103/103</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

CTL indicates control group; Embol, distal embolization; IAT+, intra-arterial thrombectomy on top of standard treatment including r-tPA; LSN, time (minutes) from last seen normal to groin puncture in IAT+ group; Mdn, median; mRS 0–2 at 90 d, modified Rankin Scale of 0–2 at 90 days after randomization; NIHSS, baseline National Institutes of Health Stroke Scale; Perfor, vessel perforation; r-tPA, patients in trial treated with recombinant tissue-type plasminogen activator; REVASCAT, Randomized Trial of Revascularization With the Solitaire FR Device Versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting Within Eight Hours of Symptom Onset; SAH, subarachnoid hemorrhage; sICH (SITS), symptomatic intracerebral hemorrhage based on safe implementation of treatments in stroke criteria; and TICI 2b/3, patients in IAT+ group achieving thrombolysis in cerebral infarction grade 2b or 3 reperrfusion.
왼쪽 심방 비대와 뇌졸중 재발

복부 면하부 뇌졸중 연구

Left Atrial Enlargement and Stroke Recurrence

The Northern Manhattan Stroke Study

Shadi Yaghi, MD; Yeseon P. Moon, MS; Consuelo Mora-McLaughlin, MS; Joshua Z. Wylie, MD, MS; Ken Cheung, PhD; Marco R. Di Tullio, MD; Shunichi Homma, MD; Hooman Kamel, MD; Ralph L. Sacco, MD, MS; Mitchell S.V. Elkind, MD, MS

(Stroke. 2015;46:1488-1493.)

Key Word: embolism

배경과 목적

왼쪽 심방 비대(left atrial enlargement, LAE)가 뇌졸중 발병위

험을 높이는 세기지만 뇌졸중 재발과의 연관성은 불분명하다. 본
 연구의 목적은 LAE와 색전증(원인불명과 심장성색전증)과 모든
 혈관뇌졸중 재발과 연관이 높은 재발성 뇌졸중의 연관을 조사
하는 것이다.

방법

Northern Manhattan Stroke Study에 등록된 655명의 첫
혈관뇌졸중 환자를 5년 이상의 기간 동안 추적 조사하였다. 2D

Figure. Relationship of percentage of patients achieving thrombolysis in cerebral infarction grade 2b or 3 (TICI2b3) flow and patients achieving modified Rankin Scale (mRS) of 0 to 2 in intervention (intra-arterial thrombectomy [IAT]) and control (CTL) groups (y axis) vs minutes from last seen normal to groin puncture for each of the 5 studies (x axis). The exact time to achieving maximal reperfusion is not available from published data for all studies, but where available is proportionate to time to groin puncture. Note the following: (1) the percentage of patients achieving good outcome is strikingly proportionate to the percentage of patients achieving TICI2b3 flow. (2) There is a consistent difference between the IAT and CTL groups in the percent achieving mRS 0 to 2 across all studies with the difference diminishing with increased time from last seen normal to groin puncture. (3) The percentage of patients achieving good outcome is roughly proportionate to the time from last seen normal to groin puncture (earlier groin puncture = higher proportion good outcome) with the exception being the EXTEND IA study, which was the only study to use advanced imaging for patient selection suggesting its use to identify responsive patients at delayed time intervals. ESCAPE indicates Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times; EXTEND IA, Extending the Time for Thrombolysis in Emergency Neurological Deficits—Intra-Arterial; MR CLEAN, Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands; SWIFT PRIME, Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment Trial; and REVASCAT, Randomized Trial of Revascularization With the Solitaire FR Device Versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting Within Eight Hours of Symptom Onset.