State of the art on acute ischemic stroke: late breaking clinical trials

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A B S T R A C T

This article summarizes a Medtronic-sponsored webinar held on the 29th of January 2018 in Bern, Switzerland. This webinar was moderated by Professor Jens Fiehler, and the two speakers, Professor Jan Gralla and Professor Urs Fischer, presented key data emerging from recent landmark studies evaluating endovascular treatment interventions in patients with acute anterior circulation ischemic strokes resulting from large vessel occlusion (LVO). Both speakers provided expert interpretive commentary on the significance of the latest published data. This event was streamed live, via the Oruen Ltd website, to a wide audience of interventional neuroradiologists and physicians involved in the treatment of acute ischemic stroke. The viewing audience were able to participate in a Questions and Answers session after the speakers' presentations.

Results from the late-window DAWN and DEFUSE 3 studies were reviewed, and the implications of the outcomes achieved with thrombectomy procedures, versus standard medical therapy, in these studies, were discussed. These studies show that stroke is an ongoing continuum, and that carefully selected patients with low ischemic cores and significant mis-match can be successfully treated beyond the accepted time window of six hours since their onset of symptoms. Interventional neurologists currently face a number of unanswered questions regarding patient selection, and how and when mechanical thrombectomy procedures should be used to best effect. Interrogation of newly emergent data from recent randomized controlled trials provides insights and guidance for improving outcomes and reducing morbidity, with endovascular thrombectomy, in patients with acute ischemic stroke due to LVO.

Key words: stroke, DAWN, DEFUSE 3, endovascular thrombectomy, i.v. thrombolysis

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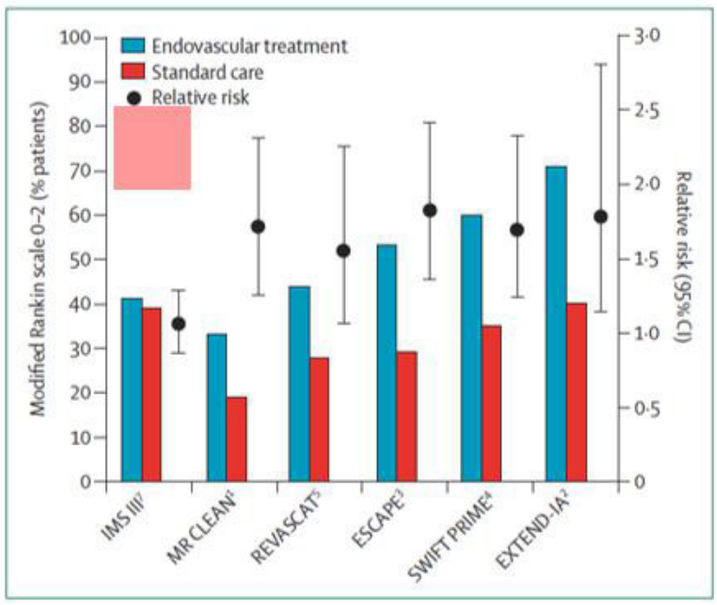
STATE OF THE ART: ACUTE ISCHEMIC STROKE – WHERE ARE WE NOW? PROFESSOR JAN GRALLA.

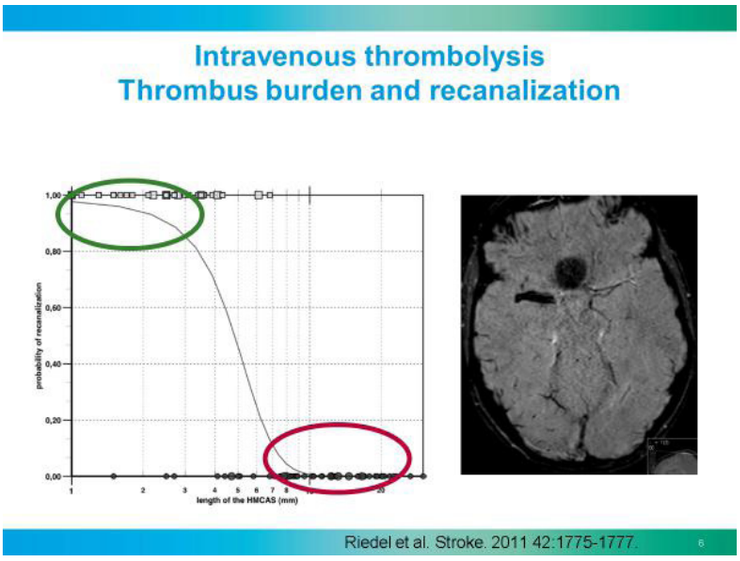
Endovascular thrombectomy: the new standard of care for large vessel ischemic stroke

Initial investigations, notably the IMS III study[1], failed to show a clear benefit of endovascular thrombectomy in addition to i.v. tissue plasminogen activator (tPA) treatment, versus i.v. tPA alone, in acute stroke. However, since 2014, a growing body of positive evidence from published randomized controlled trials (RCTs) confirms the efficacy of endovascular thrombectomy for the treatment of acute stroke resulting from large vessel occlusion (LVO). Professor Gralla summarized the outcomes from five RCTs i.e. MR CLEAN[2], REVASCAT[3], ESCAPE[4], SWIFT PRIME[5], and EXTEND-IA[6]; these studies reported improved functional outcome following endovascular thrombectomy compared with standard stroke care treatment in acute stroke patients. These outcomes are illustrated in the following figure.



Professor Gralla explained that the positive outcomes achieved in these five RCTS was, in part, due to different study designs, but the main factor was the availability of new and improved stent-retriever revascularization devices for treating anterior circulation stroke. Referring to summary data from the SWIFT PRIME study[5], when endovascular thrombectomy was performed as an additional intervention to i.v. thrombolysis, this resulted in a 60% of patients who recovered with a good functional outcome, as assessed by a modified Rankin Score (mRS) of 0-2, compared with 36% in those patients who received i.v. thrombolysis only. The number needed to treat (NNT) to achieve a functionally independent outcome with endovascular thrombectomy in addition to i.v. thrombolysis, in this study, was 2-3. These data provided proof of principle for endovascular thrombectomy on top of i.v. thrombolysis as the new standard of care for acute ischemic stroke due to LVO in the anterior circulation.

Professor Gralla presented pooled data from controlled studies[7] to illustrate that i.v. thrombolysis is most effective in acute stroke patients with low National Institutes of Health Stroke Scale (NIHSS) scores. An explanation for this may be that the characteristics of the occlusion i.e. its size and location are the important determinants, rather than the NIHSS assessment. This explanation is supported by a study conducted by Riedel and co-workers[8] who demonstrated that probability of recanalization with i.v. thrombolysis decreases markedly with increasing thrombus burden. Notably, this study showed that in acute middle cerebral artery stroke, i.v. thrombolysis has nearly no potential to recanalize occluded vessels if the thrombus length exceeds 8 mm.



Consequently, although i.v. thrombolysis is effective for achieving recanalization when thrombi are ≤ 7 mm, larger thrombi are more effectively targeted with endovascular thrombectomy. The two treatments can therefore be viewed as complementary rather than competing interventions.

The RCTs that have demonstrated the efficacy of endovascular thrombectomy adhered to strict patient inclusion and exclusion criteria, and the recruited study populations were relatively small. Accordingly, patients who underwent this intervention in RCTs may not be typical of acute stroke patients presenting in routine acute stroke hospital practice. Pooled analyses from several studies are therefore important; they give a more inclusive and representative overall picture, from a larger population, and allow analyses of sub-sets of patients. Meta-analysis of the Hermes data[9], from 1,283 individual patients in five RCTS: MR CLEAN, REVASCAT, ESCAPE, SWIFT PRIME and EXTEND-IA has revealed that the NNT with endovascular thrombectomy, to reduce disability by at least one level on mRS, for one patient, was 2·6. Reviewing the individual Hermes patient sub-group analyses, Professor Gralla emphasized endovascular thrombectomy, in addition to i.v. thrombolysis, is of benefit to most patients with acute ischaemic stroke caused by occlusion of the proximal anterior circulation, irrespective of patient characteristics or occlusion site.

The Hermes meta-analyses showed that endovascular thrombectomy, in addition to i.v. thrombolysis, was beneficial to patients of all ages, including those patients >80 years old. Similarly, most patients with differing Alberta Stroke Programme Early CT Scores (ASPECTS), and differing NIHSS scores, all showed some degree of benefit with endovascular thrombectomy. For patients with occlusions in the internal carotid artery (ICA), and in the M1 section of the middle cerebral artery (MCA), endovascular thrombectomy is clearly beneficial; however, the benefit for patients with occlusion in the M2 section of the MCA is less clear-cut. Further investigation of endovascular thrombectomy in the M2 section is therefore warranted. Professor Gralla also noted that the Hermes data illustrate endovascular treatment is effective in patients treated >300 minutes after randomization to endovascular treatment and in cases of tandem occlusion.

NEW PERSPECTIVES: THE DAWN AND DEFUSE 3 STUDIES

Shifting the boundaries of endovascular intervention – the DAWN study: Professor Gralla highlighted the importance of the DAWN trial (**D**iffusion Weighted Imaging [DWI] or Computerized Tomography Perfusion [CTP] **A**ssessment with Clinical Mismatch in the Triage of **W**ake Up and Late Presenting Strokes Undergoing **N**eurointervention). In DAWN, thrombectomy was conducted in late window patients, 6-24 hours after they were last seen well, and beyond the specified time window for i.v. thrombolysis treatment. Furthermore, the patient selection procedures and rationale used in DAWN are expected to aid interventional neurologists in decisions on which patients with acute stroke will benefit most from endovascular treatment. Professor Gralla presented a brief review of the DAWN study based on data presented by Jovin and Nogueira at ESOC 2017, and the subsequent publication by Nogueira et al.[10] The DAWN study objective and design are summarized in the following figure.

MT + MM versus MM alone

Study Objective

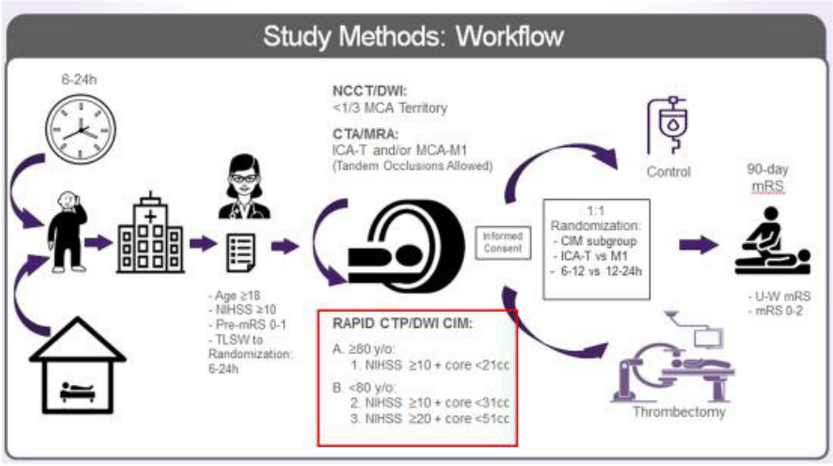
To demonstrate superior functional outcomes at 90 days with Trevo plus medical management compared to medical management alone in appropriately selected patients treated six to 24 hours after last seen well

Study Design

Study design	Global, multi-center, adaptive, population enrichment, prospective, randomized, open, blinded endpoint (PROBE), controlled **FDA** IDE trial
Patient population	• Acute ischemic stroke (AIS) with large vessel occlusion • Able to be randomized between six to 24 hours after time last known well • Clinical imaging mismatch (CIM) defined by age, core, and NIHSS
Target vessel	Intracranial ICA, M1 segment of the MCA
Randomization	1:1 Trevo + medical management vs. medical management alone
Sites	Up to 50 sites worldwide (30 US and 20 international)
Sample size	500 maximum subjects: 250 in the treatment arm and 250 in the control arm. Minimum sample size is 150 subjects.
Follow-up	24 hours (-6/+24), day 5-7/discharge, day 30 (± 14), and day 90 (± 14)

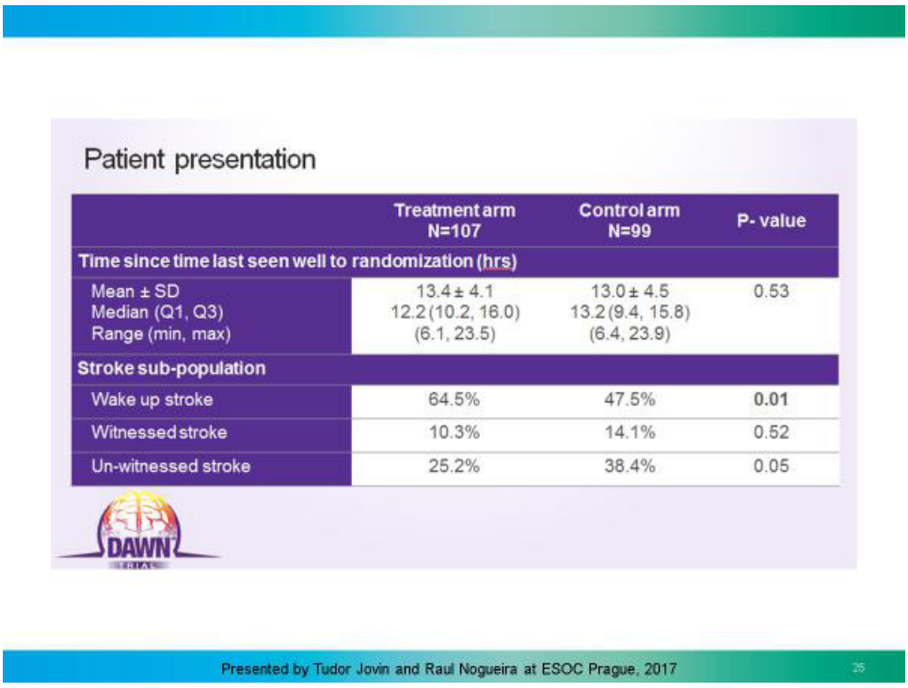
Presented by Tudor Jovin and Raul Nogueira at ESOC Prague, 2017 19

The primary efficacy endpoint in DAWN was patient disability assessed at 90 days using the Utility-Weighted mRS, and the primary safety endpoint was stroke-related mortality at 90 days. For eligibility in DAWN, patients >80 years old had to meet inclusion criteria of NIHSS scores of ≥ 10 and a low ischaemic core volume of <21 mL, and for patients <80 years old, NIHSS scores of ≥ 10 (≥ 20 for severe stroke) and an ischaemic core volume of <31 mL (≥ 51cc for severe stroke) were required. Automated perfusion software (RAPID) was used to select these patients. The study work-flow is illustrated in the following figure.

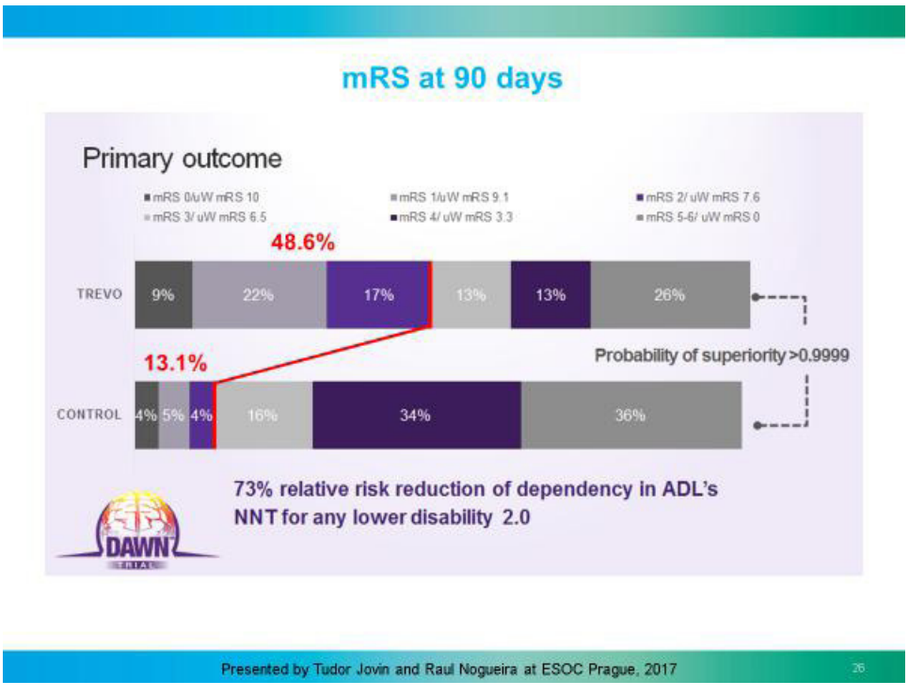


Presented by Tudor Jovin and Raul Nogueira at ESOC Prague, 2017 21

In total, 206 patients were randomized on a 1:1 basis to either endovascular treatment (Trevo device) plus medical management (n = 107), or best medical management (control treatment) alone (n = 99). Patients were stratified by clinical core mismatch, time, and occlusion location. Patients were well matched in the two treatment groups for age, baseline NIHSS, gender, race, and baseline clot location (ICA, M1 and M2). There was a higher proportion of patients with wake-up stroke in the treatment group compared with the control group. Details of these patients are illustrated in the following figure.

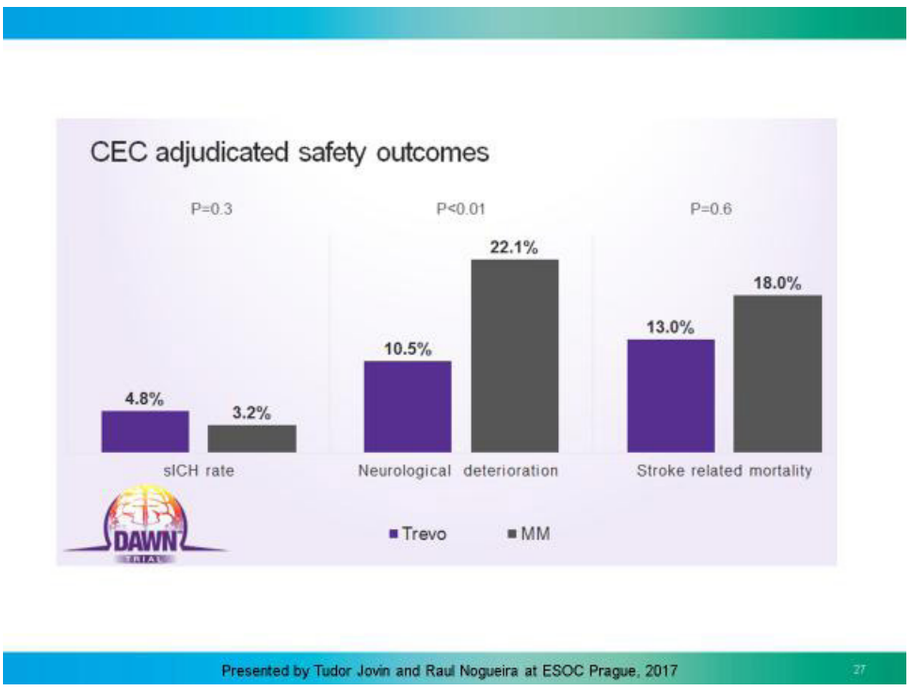


The DAWN study was terminated early due the positive and highly significant outcomes achieved in favour of endovascular thrombectomy plus medical management over medical management alone. Primary outcome results are summarized in the following figure.



A total of 48.6% of patients, who received a thrombectomy plus medical management treatment, were able to perform normal daily activities independently 90 days after this treatment (i.e. utility-weighted mRS 0-2 assessments). This compares with 13.1% of patients who achieved a comparable level of recovery after receiving best medical management therapy alone. Thrombectomy resulted in a 73% relative risk reduction for dependency, and the NNT to achieve any lower disability is 2.0.

The incidence of symptomatic intracranial haemorrhage (sICH) was higher in patients who received a thrombectomy (4.8% vs. 3.2%), but the difference between the two groups was not significant. Stroke-related mortality was lower in patients who received a thrombectomy (13.0% vs. 18.0%), and neurological deterioration was significantly lower in patients who received a thrombectomy (10.5% vs. 22.1%). These safety outcomes are presented in the figure below.



The DAWN study has shown that thrombectomy with a stent-retriever device (Trevo), in DAWN-eligible patients (i.e. with a disproportionately severe clinical deficit in comparison with the size of the stroke on imaging) is associated with improved clinical outcomes across the entire range of utility-weighted mRS, and with higher rates of functional independence (i.e. mRS 0-2) compared with standard medical therapy alone. The probability of superiority is >0.999 and the NNT is 2.0. These results indicate that for every 100 patients treated with endovascular therapy, 49 will have a less disabled outcome as a result, including 36 patients who will be functionally independent. Of note, the thrombectomy treatment effect persisted throughout the 24-hour period from time last seen well (TLSW); however, patients treated earlier benefited the most from treatment. Thrombectomy in patients presenting after six hours from TLSW had a comparable safety profile to those patients who received their thrombectomy within six hours.

The DAWN study shows an evident benefit of mechanical thrombectomy in stroke patients beyond the previously recognised time frame of six hours, providing they are carefully selected flior egibility with advanced imaging and clinical-core mis-match. Whether the allied mismatch criteria are relevant for patients' section is a subject for further investigations in the future. Accordingly, the DAWN study may pave the way for more patients to receive effective endovascular treatment when, previously, they may have been denied it.

DEFUSE 3: thrombectomy in an extended time window

This US study evaluated thrombectomy plus standard medical therapy versus standard medical therapy alone in stroke patients 6-16 hours after they were last known to be well. These patients had proximal middle-cerebral-artery or internal-carotid-artery occlusion, an initial infarct size of <70 ml, and a ratio of the volume of ischemic tissue on perfusion imaging to infarct volume of 1.8 or more. The study was terminated early since the efficacy of thrombectomy treatment was clearly evident after 182 patients had been randomized and treated. Professor Gralla presented the key summary results from a recent DEFUSE 3 New England Journal of Medicine publication.[11] The results indicated there was a significantly higher percentage of patients who were functionally independent

in the endovascular therapy group, compared with patients receiving standard medical therapy alone (47% vs. 17%, respectively; p< 0.001). These results are illustrated in the following figure.

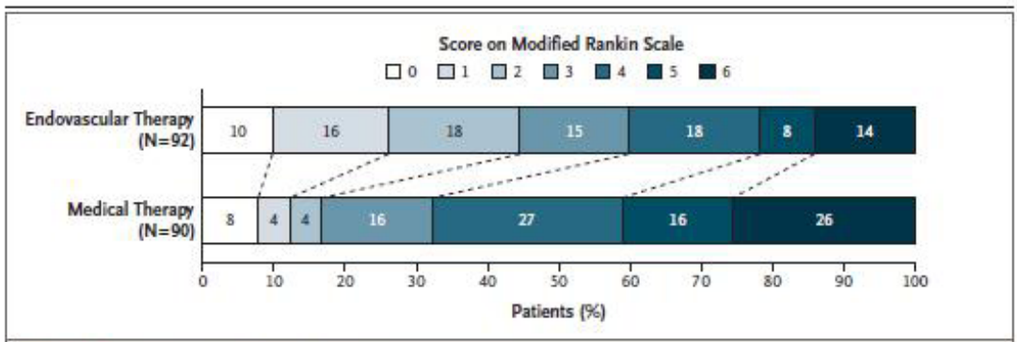
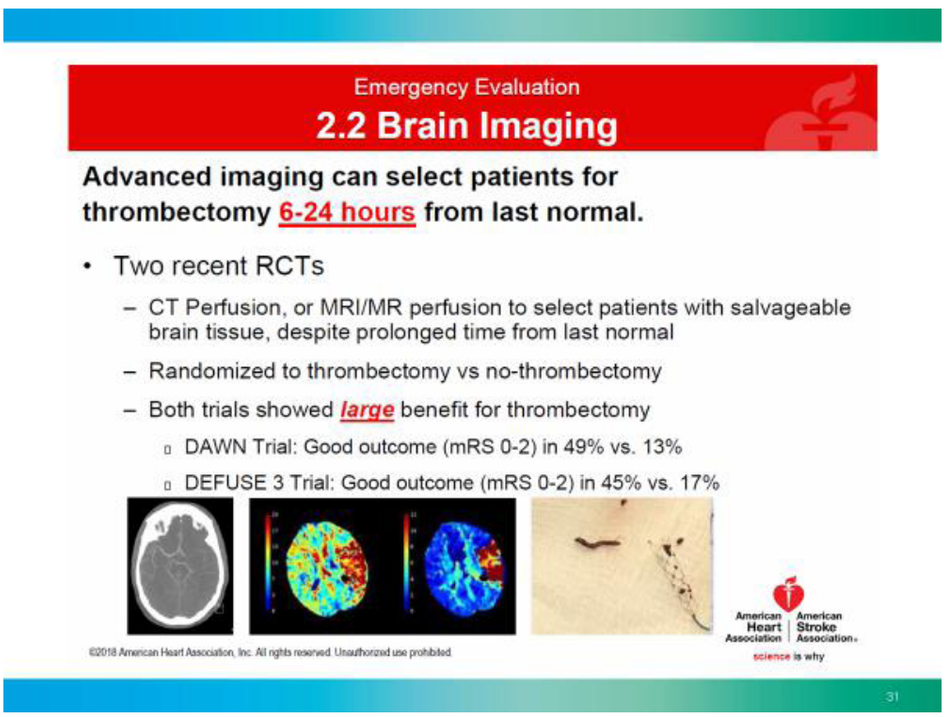


Figure 2. Scores on the Modified Rankin Scale at 90 Days.

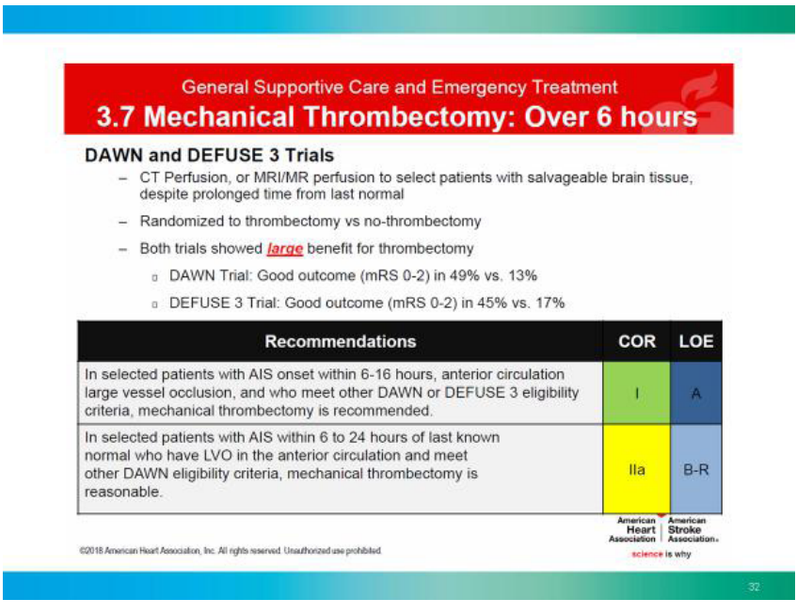
Patients in the endovascular-therapy group received endovascular therapy plus standard medical therapy. Patients in the medical-therapy group received standard medical therapy alone. Scores on the modified Rankin scale range from 0 to 6, with 0 indicating no symptoms, 1 no clinically significant disability, 2 slight disability, 3 moderate disability, 4 moderately severe disability, 5 severe disability, and 6 death. There was a significant difference favoring the endovascular-therapy group over the medical-therapy group in the overall distribution of scores (unadjusted common odds ratio, 2.77; 95% CI, 1.63 to 4.70; P<0.001).

Source: Albers GW et al. N Eng J Med, 2018.

Professor Gralla confirmed the results from both the DEFUSE 3 and DAWN studies have been acknowledged and quickly incorporated into the 2018 AHA/ASA guidelines for the early management of patients with acute ischemic stroke.[12] The updated guidelines note advanced imaging can be used to select stroke patients for thrombectomy 6-24 hours from time last seen normal, as summarized in the figure below.



The 2018 AHA/ASA guidelines now include recommendations for thrombectomy in acute ischemic stroke patients, beyond six hours, who meet DAWN or DEFUSE 3 eligibility criteria. These recommendations are summarized in the following figure.



To summarize the state of the art journey for the treatment of acute ischemic stroke, Professor Gralla felt that interventional neurologists have progressed from a historical position where i.v. thrombolyis was the gold standard for any type of occlusion, to the addition of endovascular thrombectomy to i.v. thrombolysis for proximal LVO in the anterior circulation, which is now the accepted new gold standard. He added that it is currently not clear whether M2 and M3 occlusions are appropriate targets for endovascular thrombectomy; further investigation and clarification is required here. Now there is good evidence to support the effectiveness of endovascular thrombectomy, as a sole procedure, in late-window stroke patients who meet the DAWN and DEFUSE 3 eligibility criteria. This brings the prospect of providing effective endovascular treatment to selected patients presenting beyond the 6-hour time window, and who, previously, may have been considered ineligible for this treatment.

ENDOVASCULAR INTERVENTION: THE UNANSWERED QUESTIONS. PROFESSOR URS FISCHER

Professor Fischer explained that despite an increasing volume of evidence available supporting the efficacy of endovascular thrombectomy for the treatment of acute stroke, there are still unanswered questions surrounding how and when to use this treatment to best effect. RCTs are in progress to provide answers to the most pressing of these important unanswered questions.

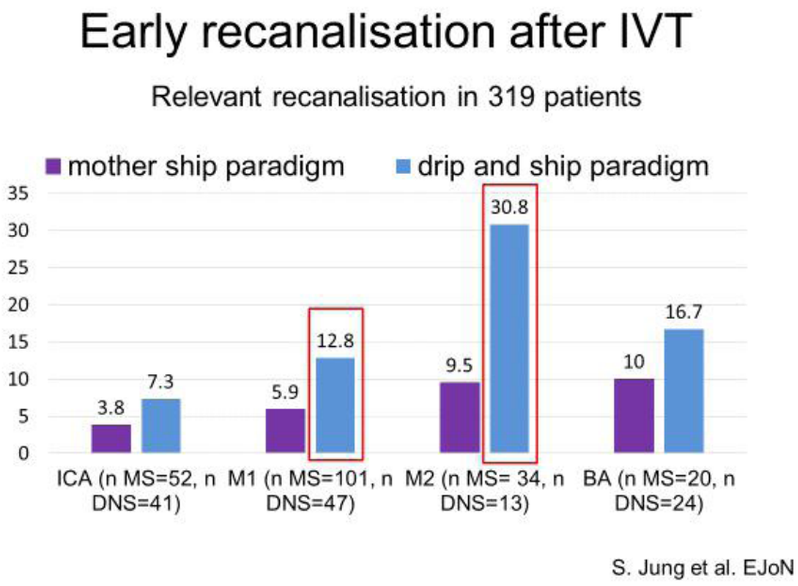
Drip and ship or mothership?

The dilemma here is: should the acute stroke patient receive i.v. thrombolysis at the nearest hospital and then be subsequently transferred to a comprehensive stroke center with endovascular treatment capabilities, or should the patient be sent directly to the comprehensive endovascular-capable stroke center? Professor Fischer reviewed the advantages of the 'drip and ship' and 'mothership' paradigms, and these are summarised in the table below.

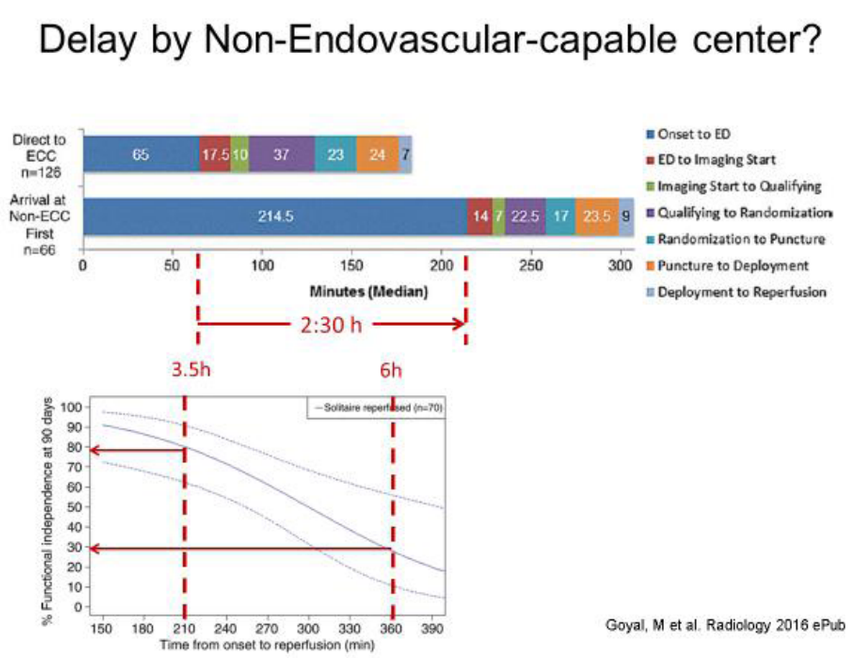
Arguments

Drip and ship	Mothership
Advantages	Advantages
• Earlier initiation of IVT	• Earlier initiation of EVT
• Improved patient selection	• Shorter time to reperfusion
• Higher proportion of IVT	• Higher proportion of EVT
• Preinterventional recanalisation	
Disadvantages	Disadvantages
• Delayed time to reperfusion	• Delay (or even deny) of IVT
• Resources	• Transfer of ineligible EVT patients (futile transports)
	• Resources

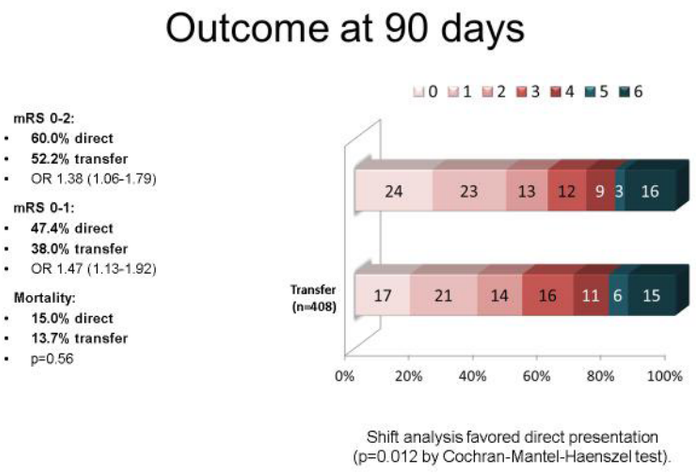
Consequently, stroke physicians are faced with the question: should they prioritize i.v. thrombolysis or prioritize endovascular thrombectomy? Professor Fischer presented data on early recanalization with i.v. thrombolysis in a cohort of his own patients. This examined the site of vessel occlusion, whether the patient received thrombolysis in a peripheral hospital or in the Bern 'mothership' setting. For patients who receive i.v. thrombolysis in a peripheral hospital, with an M1 or M2 occlusion, the chances of recanalization are relatively high; however, in the mothership setting, the chances of recanalization in ICA and M1 occlusions are very low.[13] These findings are illustrated in the histogram below.



Professor Fischer examined the delays incurred in sending patients for initial i.v. thrombolyis to a non-endovascular capable center followed by transfer to an endovascular-capable center (EVC) versus direct transfer to an EVC. Referring to SWIFT PRIME data[14], patients sent directly to an EVC have a much shorter time from symptom onset to reperfusion. The median delay incurred in sending the patient to a non-EVC first, rather than direct transfer, based on SWIFT PRIME data, was 2 hours and 30 minutes. By sending the patient directly to an EVC and avoiding this delay, the probability of achieving functional independence was shifted from around 30% to 80%. This significant benefit is illustrated in the following figure.

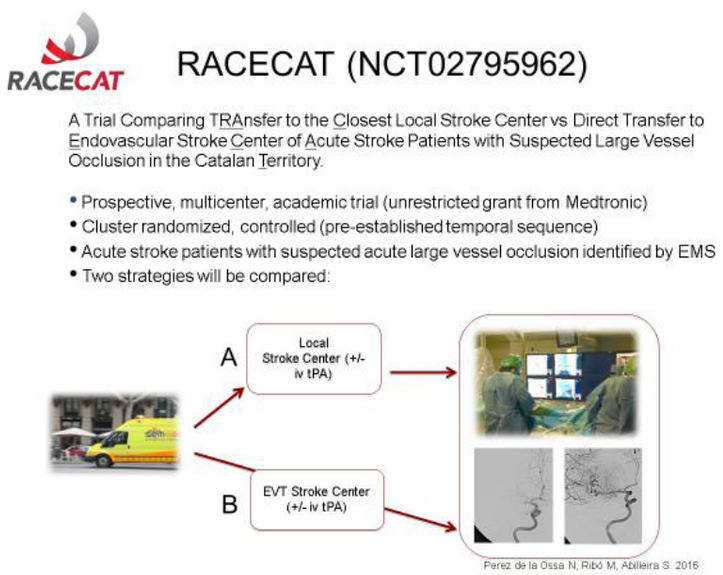


The STRATIS (**S**ystemic evaluation of patients **TR**eated with neurothrombectomy devices for **A**cu**T**e **I**schemic **S**troke) study, conducted in the USA, also reported a significant delay due to inter-hospital transfer. Patients transferred directly had shorter times from initial onset of symptoms to revascularization (169 vs. 268 minutes; p<0.0001) and, unsurprisingly, achieved better mRS 0-2 functional outcomes at 90 days, with no significant difference in mortality, compared with patients who had an inter-hospital transfer. These outcomes are illustrated in the following figure.



Professor Fischer summarized the conclusions that can be drawn from this non-randomized study: inter-hospital transfer was associated with significant delays to treatment. These delays significantly lowered the chance of a good functional outcome in the affected patients. Additionally, strategies to facilitate more rapid identification of LVO and direct routing to endovascular capable centers for some severe stroke patients may help improve outcomes.

Professor Fischer explained there are currently no published RCTs that have evaluated the drip and ship versus mothership question. However, Professor Fischer and colleagues have performed a recent systematic meta-analysis of non-randomized evidence; this has been submitted for publication. In summary, this meta-analysis has shown no significant difference in mortality, functional outcome, or successful reperfusion between drip and ship and mothership acute stroke patients. The randomized, controlled RACECAT (TRAnsfer to the Closest local stroke center vs. direct transfer to Endovascular stroke Center of Acute stroke patients with suspected large vessel occlusion in the Catalan Territory) study has been designed to provide randomized data that will help decide which transportation option provides the best outcomes for acute stroke patients.[15] The methodology for the RACECAT study, which is currently being performed in Catalonia, is illustrated in the following figure.



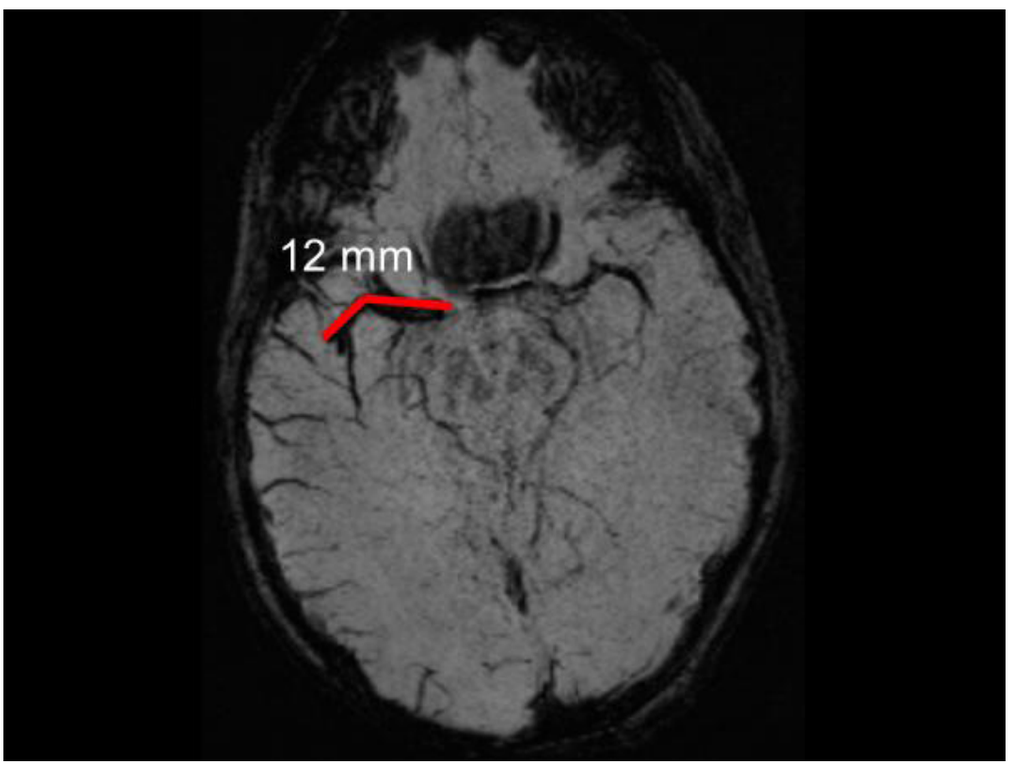
Professor Fischer explained there are several scoring systems for identifying LVO. The G-FAST scoring system, for example, scores one point each for gaze deviation, face weakness, arm weakness and speech/language problems. These scoring scales can be problematic in that the higher their sensitivity, the lower their specificity, and vice-versa. Furthermore, most assessment scores, with the exception of RACE (**R**apid **A**rterial o**C**clusion **E**valuation), have not been tested and validated in the pre-hospital setting with paramedics. A further complication is that stroke is not a stable condition and so score assessments will change with time.

Professor Fischer reviewed the profile of those patients who are ideal candidates for direct transport to an endovascular-competent comprehensive stroke center. Such patients are those with a high clinical suspicion of LVO, patients with a time of symptom onset greater than four hours, but less than 24 hours, and those patients where i.v. thrombolysis is contraindicated. In summary, the drip and ship or mothership question remains unanswered because there is no definitive randomized evidence to support which prehospital transfer model should be preferentially adopted. Despite this lack of clarification, the mantra 'time is brain' remains the guiding imperative.

Every effort to shorten time to reperfusion in acute strokes is required; acute stroke patients should be transferred as fast as possible, including patients last seen well beyond the 4.5 hours' time window for i.v. thrombolysis. Score assessments can help identify patients with LVO, although expertise in scoring for LVO needs to be transferred from the hospital setting to responding emergency services. This will improve the prenotification status report on the patient prior to hospital arrival. However, the current greatest unmet need is for definitive evidence that can be used to make informed treatment decisions.

To bridge or not to bridge?

The question here is: should the acute stroke patient receive bridging i.v. thrombolysis, or undergo thrombectomy directly? To address this question, Professor Fischer presented an example case study of a 37-year old patient with an NIHSS score of 16 who was transferred to the University hospital Bern. The patient had a very large clot (12 mm) in the right MCA. This is illustrated in the following image.



Referring to the pooled analysis of ECASS, ATLANTIS, NINDS, EPITHET and IST-3 trials[7] Professor Fischer noted that for patients with NIHSS scores in the range 11-21, the difference in outcomes achieved with i.v. alteplase versus control was very small. Moreover, the data presented by Professor Gralla earlier in the webinar illustrated i.v. thrombolysis has little effect on larger thrombi i.e. >7 mm[8]. Thrombolysis also has contraindications including anticoagulation therapy, wake-up and siesta strokes and limitations, notably, poor recanalization rates in proximal vessel occlusions. Accordingly, the risks and benefits of i.v. thrombolysis have to be carefully balanced when making treatment decisions. The advantages and disadvantages of bridging i.v. thrombolysis have been reviewed and summarized by Professor Fischer and colleagues[16]. These are summarized in the following table.

Pro-bridging arguments	Arguments against bridging
• rtPA: Can be started earlier than EVT • rtPA: May facilitate recanalization • rtPA: May improve reperfusion of small vessels.	• rtPA: Poor recanalization rates in large vessel occlusion • rtPA: Narrow time window with decreasing efficacy • rtPA: contraindications • rtPA: increases risk of hemorrhage • rtPA: May produce thrombus dislocation • rtPA: contraindicated for antiplatelets/heparin during interventions • rtPA: Major impact on health care costs (>$3,000) • rtPA: May delay EVT in some patients.

rtPA = recombinant tissue plasminogen activator.

Referring to the HERMES data[9], Professor Fischer explained this meta-analysis indicated that patients who were eligible and non-eligible for alteplase showed a similar sized treatment effect: endovascular therapy works in both groups of patients. A subsequent meta-analysis of 13 studies[17] concluded that: "MT + IVT patients had better functional outcomes, lower mortality, higher rate of successful recanalization, requiring lower number of device passes, and equal odds of symptomatic hemorrhage compared with MT-IVT patients." However, Professor Fischer pointed out that comparisons made in these analyses included patients contraindicated for i.v. thrombolysis, and patients eligible for i.v. thrombolysis i.e. two groups rather than a single comparative group. When the same comparison was made in a pooled analysis of two stroke registries that included only patients who were eligible for i.v. thrombolysis bridging therapy[18], the authors concluded: "there was no difference in outcome in patients with large vessel occlusion anterior circulation stroke treated with MT direct, compared with those treated with bridging thrombolysis, however, mortality in patents with internal carotid artery occlusion treated with direct MT was significantly lower than after bridging thrombolysis. Randomized trials comparing direct MT with bridging therapy are needed." A summary of the key findings from this pooled analysis is presented in the following table.

Bridging vs direct mechanical thrombectomy
(IV t-PA eligible patients)

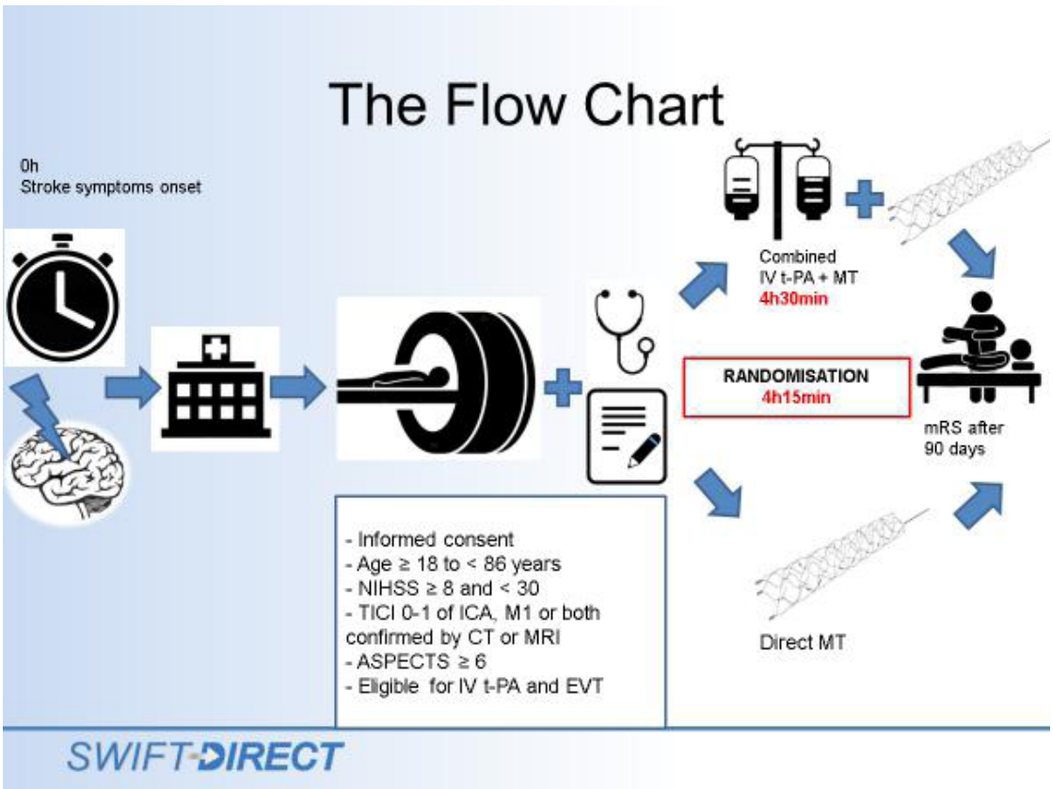
	Bridging n=103	MT n=103	p
Bleeding Complications			
sICH, n (%)	7 (6.9)	2 (2.0)	0.18
aICH, n (%)	20 (19.8%)	11 (10.8%)	0.17
Outcome at 3 months			
mRS 0-2, n (%)	41 (39.8)	47 (45.6)	0.44
mRS 0-1, n (%)	24 (23.3)	30 (29.1)	0.39
Mortality, n (%)	33 (32)	27 (26.2)	0.41

Bellwald S, et al. Stroke

The SWIFT DIRECT trial

This ongoing European/Canadian study aims to determine whether subjects experiencing an acute ischemic stroke (AIS) due to LVO in the anterior circulation, who are referred to a stroke center with endovascular facilities and who are candidates for IV t-PA, will have a non-inferior functional outcome at 90 days when treated with direct MT compared with subjects treated with combined IV t-PA and MT. Secondary objectives are to study causes of mortality, dependency, and quality of life. This is a multi-center, prospective, randomized (1:1), open-label study with blinded endpoint. The planned sample size is 404 patients. The study started in October 2017 and is due to complete in October 2020. Participating countries include: Austria, Canada, Finland, Germany, Spain, Switzerland and Portugal.

The patient inclusion criteria for SWIFT DIRECT are: informed consent; age ≥ 18 to < 86 years; NIHSS ≥ 8 and <30; patients must be eligible for IV t-PA and endovascular thrombectomy; randomization must occur no later than 4 hours and 15 minutes after onset of stroke symptoms; the target occlusions are intracranial ICA, M1 segment of the MCA, or both; ASPECTS ≥ 6 based on baseline CT or MRI. The patient's progress through the SWIFT DIRECT study is shown in the flow chart below.



Professor Fischer stressed that not all intracranial stenoses are equal; consequently, patient care must be individualized. Factors that predispose patients to a lower probability of response to i.v. thrombolysis must be taken into consideration i.e. longer time windows to treatment, very severe strokes, more proximal occlusion, large clots >7 mm, and tandem occlusions. Similarly, factors that can predispose patients to an increased risk of intracranial haemorrhage e.g. a complete basal ganglia infarct must also be taken into consideration in treatment decisions. Accordingly, the SWIFT DIRECT inclusion and exclusion criteria takes these predisposing risk factors into account.

In his closing remarks, Professor Fischer acknowledged that the Drip and ship versus Mothership question, and the MT + i.v. thrombolysis versus direct MT ongoing debate are not the only unanswered questions faced by interventional neurologists. Other important questions remain unanswered. These include: selection procedures - should we treat patients with low NIHSS and patients with low ASPECTS scores? How can we select patients for treatment success with imaging? How should we treat basilar artery, distal, extracranial and tandem occlusions? These and other questions will be the focus at future ESOC and ESMINT congresses.

QUESTIONS AND ANSWERS

Jens Fiehler: *Do you think SWIFT DIRECT will provide a conclusion for the "drip and ship "model as well?*

Urs Fischer: No, the study will not provide any conclusion about this question. The only thing we are testing is whether patients receiving bridging thrombolysis will have a similar outcome to patients receiving direct mechanical thrombectomy in a comprehensive stroke center. The drip and ship scenario will be addressed by the RACECAT trial.

Jens Fiehler: *What is your protocol for M2 and M3 patients, and who are the patients in your hospital at Bern who are left untreated – without thrombectomy?*

Jan Gralla: Patients with M2 and M3 occlusions are very individualized decisions. However, if a patient arrives within the time window of 4.5 hours with an M2 or M3 we would definitely start thrombolysis. Then, if the target is proximal M2 with lots of mis-match, we would probably proceed to thrombectomy. For M3 patients we very often end up performing intra-arterial thrombolysis; however, if it's a left hemispheric occlusion and there is sufficient mis-match we may consider mechanical thrombectomy.

Jens Fiehler: *If you have a tandem occlusion do you start your procedure extracranially or intracranially?*

Jan Gralla: I don't think there is a common agreement to this question. You either recanalize the bifurcation first, and stent it, or perform a percutaneous transluminal angioplasty (PTA) and then proceed intracranially, or vice-versa. Our argument is that you start with the intracranial lesion first. The intracranial lesion is the stroke- the target – the ICA occlusion or stenosis is the obstacle. Usually, most patients will not suffer from the ICA occlusion but from the intracranial thrombus. We don't want to dislodge thrombi elsewhere, so we use the stenosis or occlusion - being artheriosclerotic – to wedge our catheter and by having an 8F guide catheter through the stenosis, without treating it, we don't have antegrade flow and even have the possibility of reversing it. We have the impression that recanalization results intracranially are better and the chance of having a secondary embolus to the previously unaffected territory is lower. So usually we proceed with the intracranial occlusion first, achieve recanalization then put a FilterWire distally to the tip of your guide catheter, cleaning the ICA. Then you have the chance to do a proper angiogram on your ICA stenosis and decide whether it's a PTA, more thrombus aspiration, or a stent that is required.

Jens Fiehler: *Are you a "balloonista" – do you use balloon guide catheters or not?*

Jan Gralla: Our standard procedure at Bern is to use a balloon guide catheter and a stent-retriever device for mechanical thrombectomy. Available data suggest the chances of successful recanalization are higher and the chances of complications are lower. Consequently, we use and 8 or 9 French balloon guide catheter, with aspiration during the time of retrieval; however, there are anatomical settings when it doesn't make sense to use a balloon guide catheter e.g. with elongated vessels. Here the combination of a large (8 or 9 F) guide catheter and a distal aspiration catheter on top of a stent-retriever is more suitable. This is because you will not convert the aspiration force to the intracranial vessels anyway. For most of our patients, first-line treatment is with a balloon guide catheter, and our second-line treatment, especially for elongated anatomy or dissections, is based on local aspiration plus a stent-retriever.

Jens Fiehler: *At what point will you stop the procedure – how many retrieval manoeuvres will you perform? Is there a defined point at which you will stop?*

Jan Gralla: There is no definitive answer here. You have to give up at some point; a 100% recanalization rate is not possible. If you have not recanalized with your standard approach, you might switch to a second stent-retriever, aspiration, or intra-arterial thrombolysis. If you have done five attempts, you have to have a very strong justification to keep going. With any kind of new intervention there is always a risk/benefit ratio to consider: the more you invest, the more risks you are going to take. If, for example, you are dealing with 89-year old patient with lots of infarct, after a first attempt, you may not want to continue with a prolonged series of further attempts.

Jens Fiehler: *In the context of the new studies: DAWN and DEFUSE 3 – do you think we still need perfusion imaging within six hours, or only beyond six hours?*

Urs Fischer: At Bern we have a long tradition of treating patients beyond the guidelines and have published our results regularly. The concept that has been used in the DAWN and DEFUSE 3 studies is one we have already used. We are performing advanced imaging and we base our decision on imaging selection. If we receive a patient with a huge infarction and no mis-match at all, there are cases, like this, where we decided not to proceed even within the time window of the first six hours. Whereas, we have had other cases where patients have come in more than eight hours after symptom onset, with a huge mis-match, and in these cases perfusion imaging is very helpful. Based on the current evidence, we still perform advanced imaging within the time window between 0-6 hours; however, we are fully aware this a current area of debate.

Jens Fiehler: *Do you have an explanation as to why the control groups in the DAWN and DEFUSE 3 studies had such poor outcomes?*

Urs Fischer: If you look at these patients coming in with large vessel occlusion and if they still have a penumbra, we see that after 10-12 hours, usually, the penumbra of these patients is crashing; we see a secondary deterioration in these patients and their outcome is very poor. Why the sub-groups presented in these trials did so poorly compared

with other studies is a matter of debate; however, other trials had more strict criteria than DAWN and DEFUSE 3. They were not looking for patients with LVO and a huge mis-match, and this could be an important explanation.

Jan Gralla: The idea that stroke is ongoing up to a certain time window, and that if you recanalize after that time window, all is lost and nothing beneficial will happen, is wrong. The crucial point is that stroke is ongoing beyond the time window of six hours, and right now we don't know exactly where the cut-off boundary is.

Urs Fischer: We also made the observation that the number of patients having a malignant MCA infarction decreased over time because we recanalized more patients, and even those who have a huge infarction, if you recanalize them, the chance of the patient needing an urgent decompressive craniectomy is decreased.

Jens Fiehler: *What is the number needed to screen to identify the patient in the 6-24 hour time window? How many patients do you treat in the 6-24 hour time window and do you expect these patients to increase after the results of the DAWN and DEFUSE 3 studies?*

Urs Fischer: We have a lot of patients who have had wake-up strokes or in whom we don't know when their onset of symptoms started. For this cohort we expect numbers who are treated to increase. We have a lot of patients who are treated within the time window of 6-10 hours, but don't have many patients presenting beyond 10 hours; however, we were already treating these patients prior to the availability of DAWN and DEFUSE 3 data. We now feel re-assured given the overwhelming evidence available from these studies.

Jens Fiehler: *Do you think there will now be a big wave of stroke patients transferred to your hospital, and that you will only be able to treat a small minority of them – the revenge of DAWN?*

Jan Gralla: I don't think so. DAWN had specific selection criteria. They used core selection criteria based on CT perfusion imaging and subsequently found the NNT was 2. This doesn't mean you have to apply these criteria to justify a patient's treatment. The DAWN study has proven the principle of ischemic core selection with a very good NNT, but there must always be room for the treatment of other patients as well. Sometimes we cannot stick to the inclusion criteria of landmark studies and guidelines completely and without question.

Jens Fiehler: *How do you apply intracranial stenting as a rescue technique? What could be done with permanent stenting and what is your opinion on this?*

Jan Gralla: Before we had stent-retrievers, we did a study on that. In fact, there have been two studies which show that permanent stenting can be a viable treatment for stroke. However, the recanalization rate with stent-retrievers is now beyond 80%, so we are more reluctant to stent in the anterior circulation and tend to use stenting only when we suspect an intracranial stenosis underlying the anterior circulation. In the posterior circulation things are completely different. In the proximal mid-third of the basilar artery we often find an intracranial stenosis, and we are very open to using a stent, immediately after recanalization, in these circumstances. In summary, we are reluctant to use permanent stents in the anterior circulation as results are better with stent-retrievers and there is a risk of re-occlusion after permanent stenting. However, in the posterior circulation there are fewer concerns with permanent stenting.

Jens Fiehler*: How do you organize anti-aggregation in patients who need a carotid stent and who have received i.v. tPA – how do you deal with these patients?*

Jan Gralla: In our setting we would administer 250 mg aspirin i.v. immediately. We do stenting if we really have to stent, then we observe the stent for 10 minutes. If there is nothing going on, the patient goes to the ward. The next day the patient has a scan at 24 hours post-intervention. If there is no major infarct or hemorrhagic transformation we start the patient with Plavix (clopidogrel) 75 mg. All these technical questions that have been raised i.e. i.v. tPA, balloon guide catheters, stenting etc. leads us to a general problem we have regarding interventions in neuroradiology: there are very few guidelines on the procedures. I think we need to be a little more rigid here and come up with proposals for performing specific procedures.

Jens Fiehler*: Do you think there is still a role for intra-arterial tPA or intra-arterial urokinase? Do you use these treatments occasionally?*

Jan Gralla: Yes we do, especially if we have distal emboli – residual distal emboli from M2, M3, M4 occlusions after mechanical thrombectomy in the MCA. If it's an eloquent area, and there is no previous infarct and there is a lot to rescue, and if the patient is ineligible, we would use intra-arterial thrombolysis. We use these treatments much less than before but still relatively frequently, possibly 10% of our patients receive some form of IA. With pericallosal artery occlusions, sometimes dislodged from other sites, if mechanical thrombectomy is not effective, then IA treatment is definitely worth trying.

Urs Fischer: From a neurologist's point of view I don't think intra-arterial thrombolysis is dead. I'm convinced that intra-arterial pharmacological treatment is something that we will hear a lot more about in the near future. I am confident there will be studies addressing these questions coming soon.

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