Updates from Industry and New Technology Symposia, Friday 9th September, 2022 in Nice, France: 14th Congress of the European Society of Minimally Invasive Neurological Therapy (ESMINT)

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Meeting summary

These presentations were sponsored by Medtronic as part of the 14th Congress of the European Society of Minimally Invasive Neurological Therapy (ESMINT), in Nice, France. At the Industry Symposium on Friday 09 September 2022, Professor Urs Fisher presented the background to the evidence leading to the results of the SWIFT DIRECT trial and Professor Marios-Nikos Psychogios gave an account of his experience using the 3 mm Solitaire™ X device. At the New Technology Symposium, also held on Friday 09 September 2022, Luis Morales Cardona of Medtronic presented a product overview of the Rist™ Radial Access System.

KEYWORDS: ENDOVASCULAR THERAPY, INTRAVENOUS, REPERFUSION, RIST™, SOLITAIRE™ X, SWIFT DIRECT, THROMBECTOMY, THROMBOLYSIS.

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Introduction

The necessity of pretreatment with intravenous thrombolysis (IVT) before mechanical thrombectomy (MT) is an issue which remains highly topical. At the time of publishing the rationale for bridging thrombolysis (IVT + MT) in large vessel occlusions,[1] there was no evidence that the direct MT approach was equally effective. Arguments in favour of the bridging concept are that it offers better pre-interventional reperfusion, better success, and thus, better outcomes. On the other hand, IVT can produce symptomatic intracerebral haemorrhage (ICH). Complete reperfusion is key and here we discuss the noninferiority margins of endovascular stroke treatment alone compared with bridging thrombolysis.

Since the European launch in 2012 of the 1st generation Solitaire™ FR revascularisation device, these devices have continued to improve; the current 3 mm Solitaire™ X has the ability to be used in vessels of 1.5 cm. The device is compatible with 0.017–0.027 inch microcatheters for maximum versatility and the effectiveness of the procedure now goes beyond large vessels to medium and distal vessels. Details of personal experience and of a new trial led by Universitätsspital, Basel, are presented in this report.

Mr Morales Cardona explained how Medtronic is focused on creating a comprehensive portfolio backed up with real-life data, clinical data and outcomes. The aim is to optimise current care with the tools available while creating more access to health management by helping physicians to treat more patients.

The SWIFT DIRECT Trial

Professor Urs Fischer, on behalf of the SWIFT DIRECT trial study group (Co-PI Professor Jan Gralla)

Evidence before SWIFT DIRECT

The first trial to be presented was The SKIP Randomized Clinical Trial,[2] in 2020. This Japanese trial failed to demonstrate noninferiority of the direct MT approach. Patients were randomised in a 1:1 ratio to direct MT (n=101) and IVT + MT (n=103). It is important to note that in Japan only 0.6 mg/kg of recombinant tissue plasminogen activator (rt-PA) is approved by the Japanese authorities, compared with higher approved doses in Europe and North America. Good functional outcome was achieved in approximately 60% of patients and was comparable in both treatment groups.

DIRECT-MT[3] was a large Chinese clinical trial which demonstrated noninferiority of the direct MT approach compared with bridging thrombolysis. Patients were randomised in a 1:1 ratio to endovascular thrombectomy (EVT) alone (n=327), or combination therapy (n=329; EVT preceded by 0.9 mg/kg intravenous alteplase, administered within 4.5 hours after symptom onset). Functional outcome was achieved in approximately 40% of patients.

The DEVT[4] trial, also a Chinese trial, was prematurely stopped since the predefined non-inferiority margin of EVT alone compared to IVT + MT was met. Patients were randomised in a 1:1 ratio to EVT alone (n=116) and combined IVT + EVT (n=118). Functional outcome was achieved in approximately 55% of patients.

The MR CLEAN-NO IV[5] trial was the first European trial to compare direct EVT with intravenous treatment followed by EVT. The primary aim of this trial was to show superiority of the MT approach. They failed to show superiority, but also failed to show noninferiority. There were no major differences observed for the Modified Rankin Scale (mRS) scores between the groups and good functional outcome was achieved in approximately 50% of patients.

A noninferiority meta-analysis of these randomised clinical trials suggested noninferiority of EVT alone compared with bridging thrombolysis if you apply noninferiority margins up to 5%, but not for stringent noninferiority margins of 1.3%.

The SWIFT DIRECT[6] randomised, open-label, blinded-endpoint (PROBE), multicentre clinical trial (N=404), sought to determine the noninferior functional outcome of patients at 90 days when treated with direct MT compared to combined intravenous t-PA + MT. The secondary objectives were mortality, dependency, and quality of life. The intervention arm was MT with Solitaire™ devices. The standard arm was IVT with alteplase (0.9 mg/kg) plus MT with Solitaire™ devices and trial physicians were encouraged to administer the full dose of t-PA. For thrombectomy, it was strongly advised to use balloon-guided or large-bore aspiration catheters. The primary efficacy endpoint was functional independence (mRS 0–2) at 90 days with a noninferiority margin of 12%. Secondary outcomes were mortality at 90 days, mRS shift, successful reperfusion, and rates of symptomatic and asymptomatic ICH.

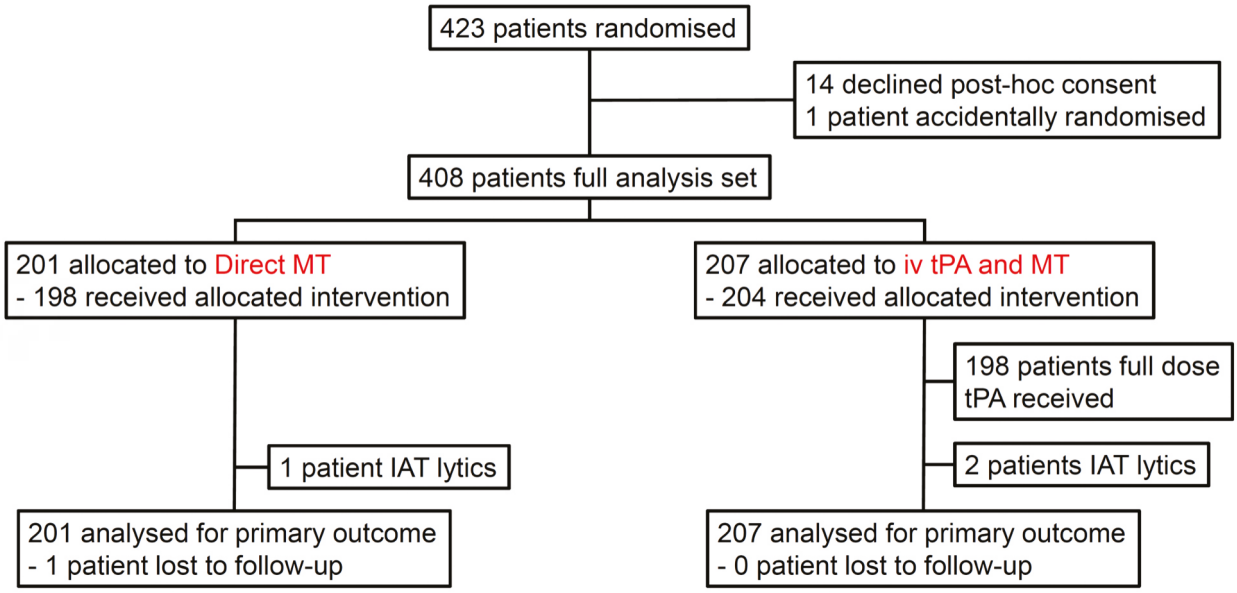

Figure 7. Randomisation of patients to direct mechanical thrombectomy (MT) and bridging thrombolysis (IVT + MT) groups.

This international trial took place across 48 sites in North America with 423 randomised patients (Figure 1.)

Baseline characteristics were comparable between females and males with no major gender imbalance. The median age was 73 years and the median NIHSS was 17. The vast majority of patients had M1 occlusion (66%). A total of 16% of patients had tandem lesions.

Primary outcome

In the direct MT arm, 57% of patients had good functional outcome compared with 65% of patients in the bridging arm. Noninferiority of direct MT compared with the bridging arm was not shown. There was a tendency that the bridging arm had improved functional outcome, although not statistically significant.

Secondary outcomes

It is particularly important to note that the rate of successful postinterventional reperfusion was very high in both treatment arms and significantly higher in the bridging arm (96%) versus 91% in the direct MT arm. There was no significant difference in rates of ICH between the groups.

What does it mean in comparison to other trials?

What is striking is the very high reperfusion rates (core lab adjudicated). In contrast to the other trials, SWIFT DIRECT was a single device trial, and proximal protection devices were strongly encouraged; patients were given the full t-PA dose which may explain the high reperfusion rates in the trial but is yet unproven. The next steps will be to perform an individual patient data meta-analysis of DIRECT-MT, MR CLEAN-NO IV, DEVT, SKIP, SWIFT DIRECT and the recent DIRECT-SAFE[7] trial to investigate whether there are subgroups of patients for whom there may be a potential benefit. The DIRECT-SAFE trial did not show noninferiority of the direct MT approach compared with bridging therapy.

There is an ongoing debate on accepted noninferiority margins in the case of skipping tPA prior to EVT. The strict noninferiority margin of 1.3% is based on a superiority design scenario of a novel and safe neuroprotective agent.[8] Accordingly, a recent survey was distributed to a cross-section of 600 physicians globally, to determine the level of certainty at which they would feel comfortable skipping IVT, based on the results of a hypothetical trial where a similar proportion of patients achieved functional independence at 90 days.[9] The vast majority considered that 5% was acceptable (median=3%). Based on the analyses of the aforementioned trials, The European Stroke Organisation-European Society for Minimally Invasive Neurological Therapy (ESO-ESMINT) guidelines do not recommend skipping t-PA in patients who are eligible for t-PA, if they have large vessel occlusion, and if they are a candidate for thrombectomy.[10] However, for a study

with 80% power and 95% confidence intervals, calculations show that it would require 18,205 patients per group to show a noninferiority margin of 1.3%; something which is not achievable within a clinical trial setting.[11]

Further unanswered questions are whether IVT is needed before, during, or after endovascular therapy and whether all subgroups of patients with LVO (i.e. large ischaemic core, tandem occlusion, etc.) have a similar outcome.[12]

Distal treatment experience with the 3 mm Solitaire™ X

Professor Marios-Nikos Psychogios

The 3 mm Solitaire™ X is a new revascularisation device; an ultra-precise instrument designed for minimal movement or straightening of fragile vessels. One of the unique aspects of this new device is the ability to use it up to 1 mm vessel diameter and is compatible with 0.017–0.027 inch microcatheters for maximum versatility. There are two lengths, 20 mm and 40 mm.

Professor Psychogios discussed his experience using the 3 mm Solitaire™ X device and presented an example of an M3 distal vessel occlusion (DVO) setup where he used a combination of different catheters; long 6F sheath, large-bore 0.70-inch aspiration catheter in M1, small-bore 0.35-inch (and short 153 cm) aspiration catheters in M3, and a long (167 cm) microcatheter. In addition, he used a small stent retriever from M4/distal M3 to M2, a small-bore aspiration catheter in the M3, and a large-bore aspiration catheter in the M1 segment. He explained how the normal procedure is to place the stent retriever and pull from the M1 or from the carotid artery if you have a balloon guide. A problem with this approach is that you can straighten the M2 causing perforator rupture and complications such as subarachnoid haemorrhage (SAH). The solution is to provide the system that you have with multiple stable positions, followed by shortening the lever with which you are pulling, i.e. multiple stable points and short levers are the answer. Also, if you aspirate early enough with a large-bore catheter there will be vessel collapse, dissection and vessel rupture, SAH and ICH.[13] Thus, if you aspirate in the M1 and pull from the M3, this approach will result in even larger problems than a small SAH. Professor Psychogios's recommendation is to take a small-bore aspiration catheter and go all the way to the clot, aspirate there, and then pull the stent retriever, clot, and aspiration catheter inside the M1. In the M1 you have another aspiration catheter and then perform a type of SAVE-to-Solumbra technique in the distal occlusions.[14]

Moving on to discuss the existing evidence from randomised controlled trials for performing such a thrombectomy, he emphasised that although there is evidence for dominant M2s,[15] no RCT data exist for medium or distal vessel occlusions. The EnDovascular Therapy Plus Best Medical Treatment (BMT) Versus BMT Alone for MedIum VeSsel Occlusion sTroke (DISTAL) trial is a pragmatic, parallel group, randomised, open label, superiority trial with blinded endpoint assessment.[16] This interventional study will investigate whether endovascular therapy plus best medical treatment (BMT) reduces the degree of disability and dependency in daily activities after a medium vessel occlusion (MeVO) stroke, compared with BMT alone. The study cohort (N=526) is aged ≥18 years of age and participants were randomised 1:1 to endovascular therapy or no endovascular therapy. Inclusion criteria include isolated MeVO (occlusion of the co-/non-dominant M2, the M3/M4 segment of the MCA, the A1/A2/A3 segment of the ACA or the P1/P2 segment of the PCA), NIHSS ≥4 or symptoms deemed clearly disabling by the treating physician, along with informed consent/agreement of the treating physician to perform the procedure. Currently, there are 52 planned sites, 20 initiated sites, 13 activated sites, and 9 recruiting sites. At the time of this report, 42 patients have been randomised.

Blind Exchange with Mini-Pinning Technique for Distal MeVOs

A retrospective review of 102 patients with MeVOs treated with the Blind Exchange with Mini-Pinning (BEMP) technique (n=56) or mini retriever (n=50), revealed the BEMP technique

Table 1. Blind exchange with mini-pinning technique for distal occlusion thrombectomy

	BEMP cohort (n=25)	Standard* cohort (n=144)	p
First pass mTICI ≥2b	20 (80%)	81 (56%)	0.03
First pass mTICI 3	15 (60%)	58 (40%)	0.07
Final mTICI ≥2b	21 (84%)	114 (79%)	0.58
Final mTICI 3	16 (64%)	78 (54%)	0.36
Parenchymal Haematoma	0	7 (5%)	0.26
SAH	3 (12%)	9 (6%)	0.3

*Standard = stent-retriever or aspiration

Abbreviations: BEMP, blind exchange with mini-pinning; mTICI, modified treatment in cerebral infarction; SAH, subarachnoid haemorrhage.

may result in increased rates of first-pass recanalisation and a decreased incidence of symptomatic ICH compared to mini-stent retrievers alone.[17] A separate retrospective review concluded that the BEMP technique appeared both effective and safe when used for the treatment of distal occlusions, although additional studies are recommended (Table 1.[18])

Professor Psychogios concluded his talk with some tips and tricks for the audience from his experience:

- Placement primarily distally to the clot
- Combination with 5F aspiration catheter for M2
- Combination with 3Max catheter for M3, A2
- 3 mm Solitaire™ X with a Headway Duo microcatheter
- No need for blind mini-pinning with the 153 cm 3Max catheter
- Try to create multiple joints to reduce drag or straightening of the vessels

Rist™ Radial Access System Product Overview

Luis Morales Cardona

One example of how Medtronic has optimised access to health management is through the introduction of the Rist™ Radial Access System. The system has two main guide catheters; the 6F and 7F guide catheters are both approved by the FDA. The 7F catheter is currently approved by the CE mark and submission is underway for the 6F catheter CE mark. In addition, Medtronic also has approval from the FDA for compatibility to use the Rist™ Radial Access System in combination with the Axium™ Detachable Coil System and The Pipeline™ Flex embolization device with Shield Technology™. The principal outcomes favouring radial access are, 1) lower access location complications which also drive hospital costs down, and 2) patient preference due to the recovery period after the procedure being considerably shorter.

Design characteristics of Rist™ Radial Access System

Both 6F and 7F catheters provide improved distal navigability. The distal flexible section of the catheters is 40–50% longer on the 6F, and twice as long on the 7F, compared with other commercially available products for use in the radial space.

The tip of the 6F and 7F catheters is designed using a nitinol coil that provides a more atraumatic tip, combined with various transition zones along the distal section of the catheter to accommodate the tortuosity of the radial access. More importantly, both 6F and 7F catheters are available to be used with the Rist™ Radial Access Select Catheter which is designed with two different tip shapes to help navigate the tight bends in the radial pathway. The tips of both 6F and 7F catheters provide options for different levels of flexibility depending on the procedure.

These catheters are also offered in different lumen sizes. The 7F catheter allows for contrast administration and comes in three different sizes; both 6F and 7F are available in 95 cm, 100 cm and 105 cm for different application use.

Conclusion

Complete reperfusion is key and associated with better outcomes. Accordingly, all efforts have to be made to achieve complete reperfusion. The SWIFT DIRECT trial did not show statistical noninferiority of direct MT over intravenous t-PA plus MT. Good functional outcome was very high in both treatment arms with the point estimate in favour of the bridging arm (65% vs 57%, respectively). Preinterventional reperfusion was very low in both treatment arms but postinterventional reperfusion was significantly higher in the bridging arm. Rates of symptomatic ICH were low in both treatment arms.

More evidence is needed on whether IVT should be given before, during, or after MT, and will be obtained through further trials and individual patient data meta-analyses. Reperfusion results appear to be improved with a combined manoeuvre technique versus a mini stent retriever alone, and also when compared with aspiration only. Evidence shows that medium vessel occlusion-distal vessel occlusion MT is feasible using a combined approach, and eagerly awaited randomised data will be available from the ongoing DISTAL trial.

The Rist™ Radial Access System reduces the rate of location access complications which results in decreased hospital costs. Optimised access to health management for patients and physicians continues to be improved through the technological development of catheter design.

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