Selecting patients for endovascular therapy and recent developments and clinical experience with Medtronic devices

Antonio Dávalos[(1)], René Chapot[(2)], Wolfgang Reith[(3)], Mario Martinez-Galdámez[(4)]

[1] Clinical Director, Department of Neurosciences, Hospital Germans Trias i Pujol, Universitat Autònoma de Barcelona, Spain

[2] Alfried Krupp Krankenhaus Hospital, Department of Neuroradiology and Intracranial Endovascular Therapy, Essen, Germany

[3] University of Saarland, Clinic for Diagnostics and Interventional Neuroradiology, Homburg, Germany

[4] Interventional Neuroradiology, Hospital Universitario Fundación Jiménez-Díaz Grupo Quironsalud, Madrid, Spain

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A B S T R A C T

This article summarizes Medtronic-sponsored symposia presented at the World Federation of Interventional and Therapeutic Neuroradiology (WFITN) 14th Congress held October 16-19, 2017, in Budapest, Hungary. The topics included: the definition and analysis of optimal neuroimaging criteria for selecting patients for endovascular treatment using perfusion and diffusion neuroimaging (iSchema View RAPID). This review was presented by Professor Antonio Dávalos. First-year clinical experience, in Germany, with the next generation Solitaire™ Platinum Revascularization Device, for the restoration of blood flow and retrieval of clots from occluded blood vessels, in acute ischaemic stroke (AIS) patients with large vessel occlusion (LVO), was reviewed and summarized by Professor René Chapot. Recent clinical experience and outcomes achieved with the Barrel™ vascular reconstruction device (VRD) for the treatment of bifurcation aneurysms was reviewed and summarized by Professor Wolfgang Reith. In addition, an overview of the Pipeline™ Flex Embolization Device with Shield Technology™, outlining the benefits of this technology, and the associated available supportive clinical data, were presented by Professor Mario Martinez-Galdámez.

Key words: Endovascular therapy, Pipeline™ Flex Embolization Device, Shield Technology™, Solitaire™ Platinum Device, bifurcation aneurysms, Barrel™ Vascular Reconstruction Device.

Corresponding author: Mario Martinez-Galdámez - mariomgaldamez@hotmail.com

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OPTIMAL CRITERIA FOR SELECTING PATIENTS FOR ENDOVASCULAR THERAPY: PROFESSOR ANTONIO DÁVALOS

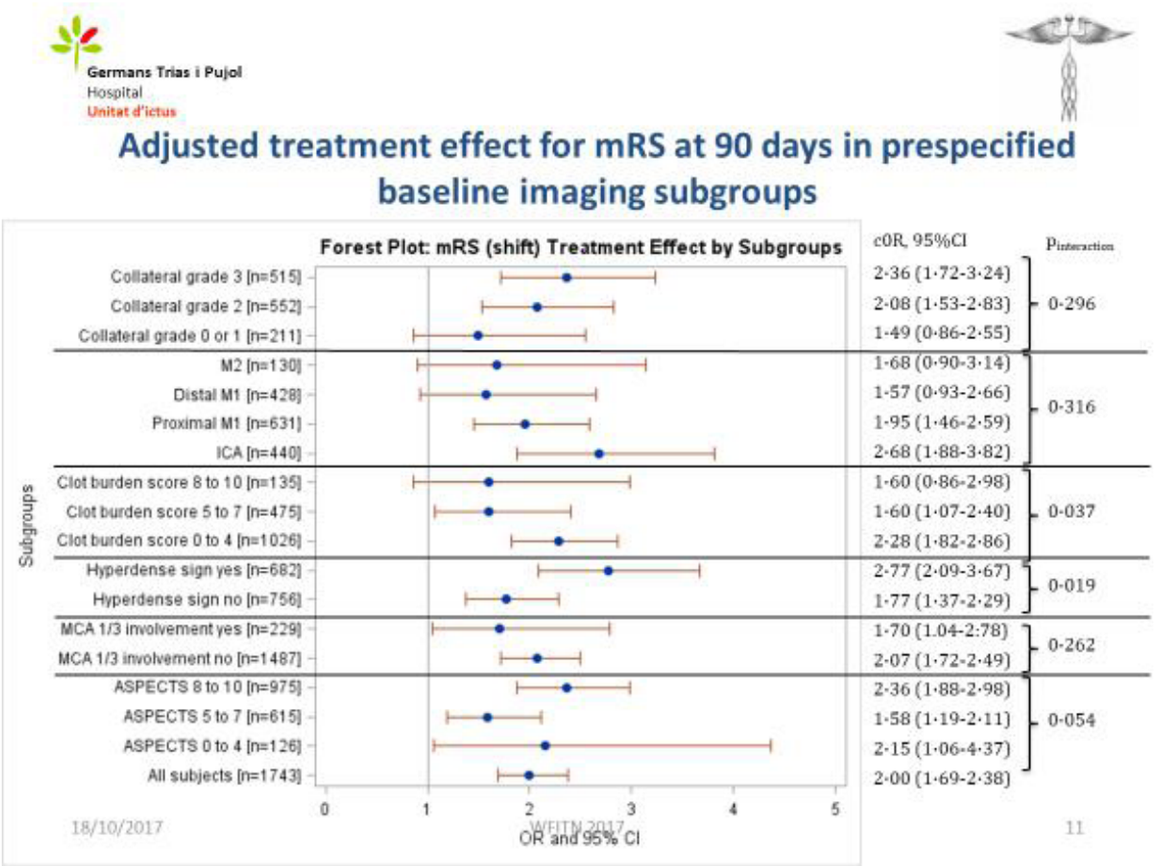
Professor Dávalos reviewed clinical trial data from the HERMES collaboration meta-analysis of randomized controlled trials (RCTs) that investigated endovascular thrombectomy after large vessel ischaemic stroke.[1] The absolute risk difference benefit of thrombectomy, compared with control medical treatment, that emerged from this meta-analysis was almost 20%, representing an adjusted odds ratio of 2.7 for functional recovery, and the number needed to treat (NNT) to achieve functional independence was five.

The effect of thrombectomy treatment was homogenous across patients. Subgroup analysis revealed no interaction between the RCT clinical variables and treatment effects. Hence, treatment effects were independent of age, sex, Alberta Stroke Program Early CT Score (ASPECTS), alteplase use, stroke location, stroke severity, stroke onset to randomisation, and presence of tandem occlusion. Professor Dávalos highlighted the importance of time on the treatment effect. Although endovascular therapy is of benefit for up to seven hours after stroke symptom onset, the treatment effects diminish as time from stroke onset to treatment increases. The meta-analysis conducted by Saver et al (2016) confirmed that

earlier treatment with endovascular thrombectomy plus medical therapy, compared with medical therapy alone, is associated with lower degrees of disability at three months. Notably, benefit became nonsignificant after 7.3 hours.[2]

Professor Dávalos explained that all the neuroimages from seven RCTs (MR CLEAN, EXTEND-IA, ESCAPE, SWIFT PRIME, REVASCAT, THRACE, PISTE) have been prospectively pooled and analysed in the HERMES collaboration central core laboratory, with a view to providing insights for improved selection of patients most likely to benefit from endovascular treatment. For each patient, the ASPECTS score and whether there was ≥ or <1/3 hypodensity of their middle cerebral artery (MCA) territory was documented. Non-contrast computed tomography (NCCT) was utilized to determine hyperdensity of MCA, and the clot burden score (CBS) was utilized to identify patients' relative clot burden (scores 0-4 signifying patients with the greatest burden and large thrombi). Clot location i.e. internal carotid artery (ICA), M1, M2 was recorded. Assessment of patients' collateral status was determined with computed tomography angiograms (CTAs) and categorized on a 4-point (0-3) scale, where 0 = absent collaterals; 1 = >0% and <50% filling of the occluded territory; 2 = >50% and <100% filling of the occluded territory, and 3 = 100% filling of the occluded territory.

According to the pre-specified central analysis of the imaging data, very little heterogeneity was found between the different neuroimaging variables and the treatment effect, as assessed by the modified Rankin Score (mRS) at 90 days. Professor Dávalos noted there was some heterogeneity associated with clot burden as a variable; those patients with a large thrombus experienced the greatest benefit from thrombectomy. A further notable finding was the patients graded in the 0-4 ASPECTS band who benefitted from endovascular treatment compared with control medical treatment. These findings are illustrated in the table below.



Professor Dávalos hypothesised that a sudden perfusion in e.g. those patients with a low ASPECTS score might predispose them to increased risk of sICH. This observed heterogeneity was also reflected in Forest Plot summary data of the adjusted risk effect of sICH in the imaging subgroups. Of note, the odds ratio for sICH in patients with more than MCA 1/3 involvement was 4.17. For patients with an ASPECTS score of 0-4, the odds ratio was 3.94 i.e. the risk of sICH was increased by almost four times. These summary data are presented in the following table.

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Incidence of sICH by treatment allocation and prespecified imaging categories

Subgroup	Endovascular group % (n/N)	Control group % (n/N)
ASPECTS		
8-10	2.1% (10/473)	3.4% (17/498)
5-7	3.8% (12/319)	3.7% (11/297)
0-4	19.2% (10/52)	4.5% (3/66)
MCA 1/3 involvement		
No	2.3% (17/736)	3.6% (27/748)
Yes	13.9% (15/108)	3.5% (4/113)
Hyperdense sign		
No	3.3% (12/360)	3.5% (14/401)
Yes	4.5% (16/353)	5.2% (17/328)
Clot burden score		
8-10	0.0% (0/69)	7.5% (5/67)
5-7	4.7% (11/233)	2.9% (7/240)
0-4	3.4% (17/503)	3.1% (16/513)
Occlusion location		
ICA	3.3% (7/210)	2.6% (6/227)
Proximal M1	3.9% (12/307)	3.5% (11/318)
Distal M1	4.1% (9/218)	2.9% (6/207)
M2	0.0% (0/67)	7.8% (5/64)
Collateral grade		
3	3.1% (8/259)	2.7% (7/259)
2	3.2% (9/281)	2.9% (8/275)
0-1	5.3% (5/94)	10.5% (12/114)

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With respect to mortality at 90 days, Professor Dávalos stressed this was not significantly increased by any of the sub-group imaging variables. However, he noted a concern with respect to the incidence of symptomatic intracranial haemorrhage (sICH). In patients with an ASPECTS score of 0-4, the incidence of sICH in the endovascular treatment group was 19.2% compared with 4.5% in the control group. Also, in patients with a large hyperdensity (MCA involvement 1/3), the incidence of sICH in the endovascular treatment group was 13.9% compared with 3.5% in the control group. The incidence of sICH, by prespecified imaging sub-group categories, is shown in the table below.

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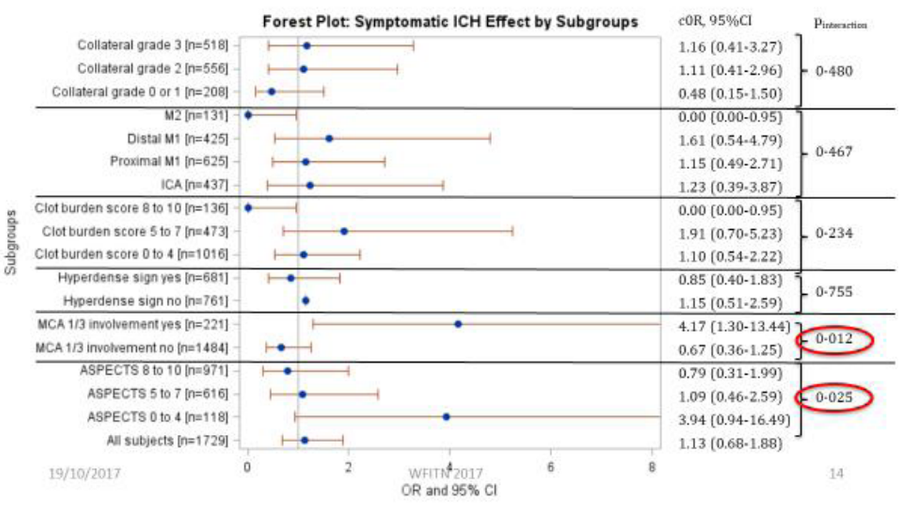
Adjusted risk effect for SICH in prespecified baseline imaging subgroups



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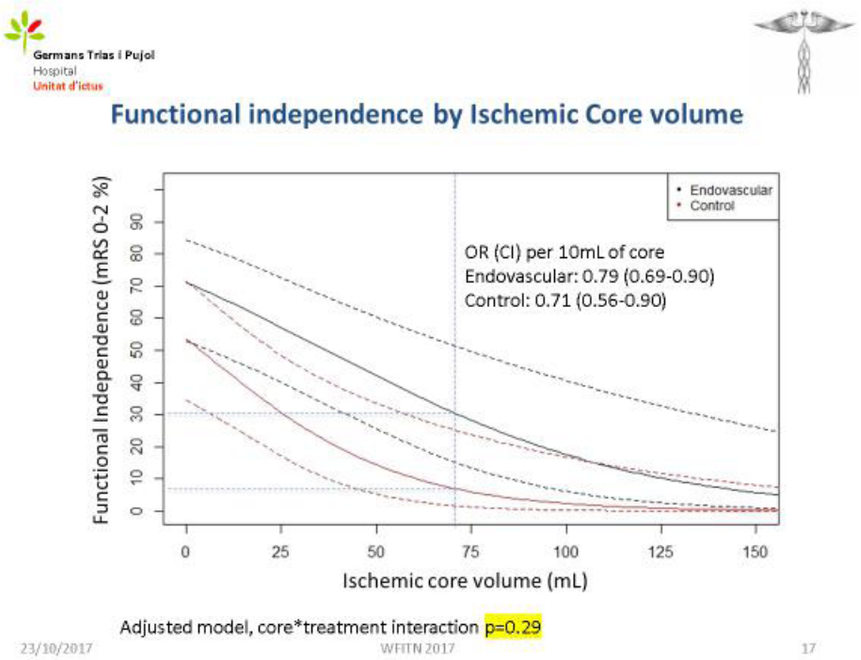
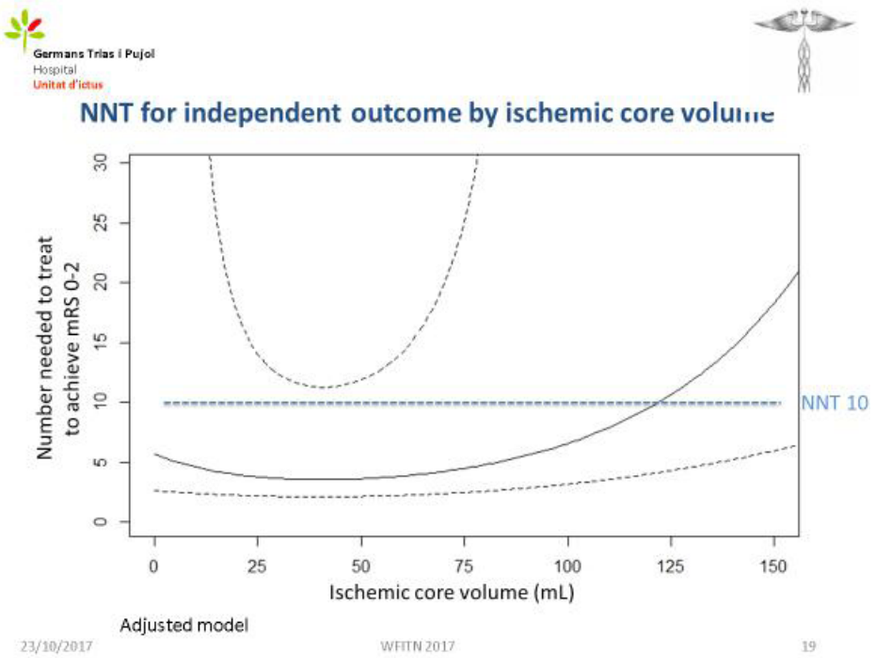
Of 1,764 patients included in the seven HERMES trials, 625 (35%) underwent CT perfusion imaging. Of these, 591 (95%) were processed using RAPID software (iSchema View). RAPID is a fully automated image processing platform that provides accurate and reliable perfusion and diffusion imaging. RAPID includes motion correction, automated arterial input function selection, threshold application, and lesion segmentation. Using the RAPID software, ischemic core (i.e. irreversibly injured brain) was defined using a relative cerebral blood flow threshold of <30% of normal brain.

Based on an analysis of almost 600 patients, using the RAPID software, the observation that emerged was: the larger the infarct core, the lower the probability of the patient achieving functional independence. This is illustrated in the following figure. The rate of functional independence decreased, with increased ischaemic core volume, for both patients allocated to endovascular treatment and those who received control medical treatment. Hence, the ischaemic core volume is closely related to patients' functional outcome in both arms of the studies included in the HERMES meta-analyses. This indicates a lack of an interaction between the treatment effect and the infarct core.



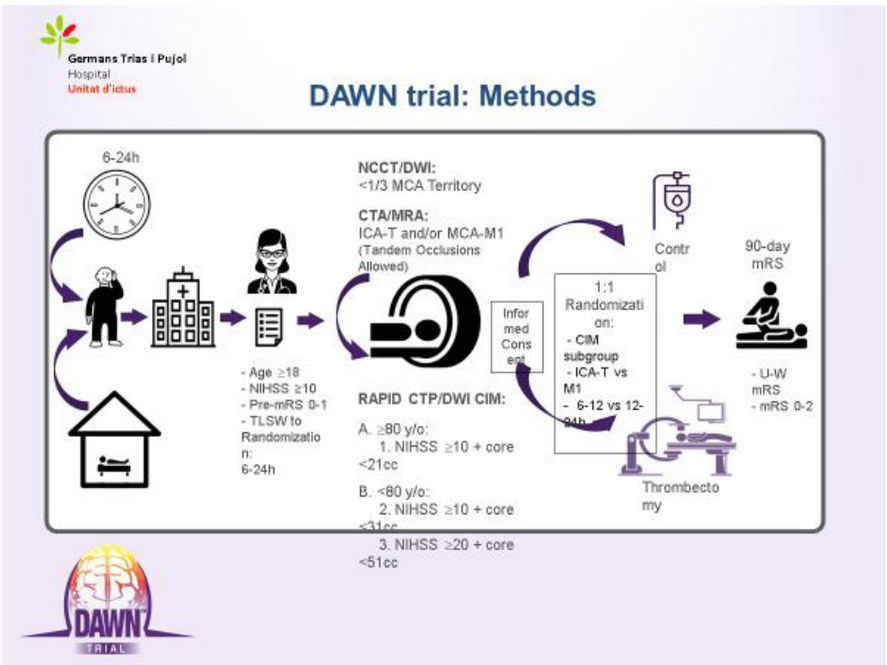
Professor Dávalos noted that with an ischaemic core of approximately 70 mL, the treatment effect, as measured by mRS, in the medical treatment arm was negligible; however, functional independence was achieved in 30% of patients treated with endovascular therapy. In the small group of patients (n = 50) with an ischaemic core of >70 mL, the protective effect of endovascular treatment was minor, compared with those patients with an ischaemic core of <70 mL.

An examination of the number needed to treat (NNT) to obtain a functional independence benefit, even in patients with large ischaemic core volumes at baseline, revealed that the NNT was less than 10. The NNT for independent outcome (mRS 0-2), by ischaemic core volume data, are summarized in the following graph.

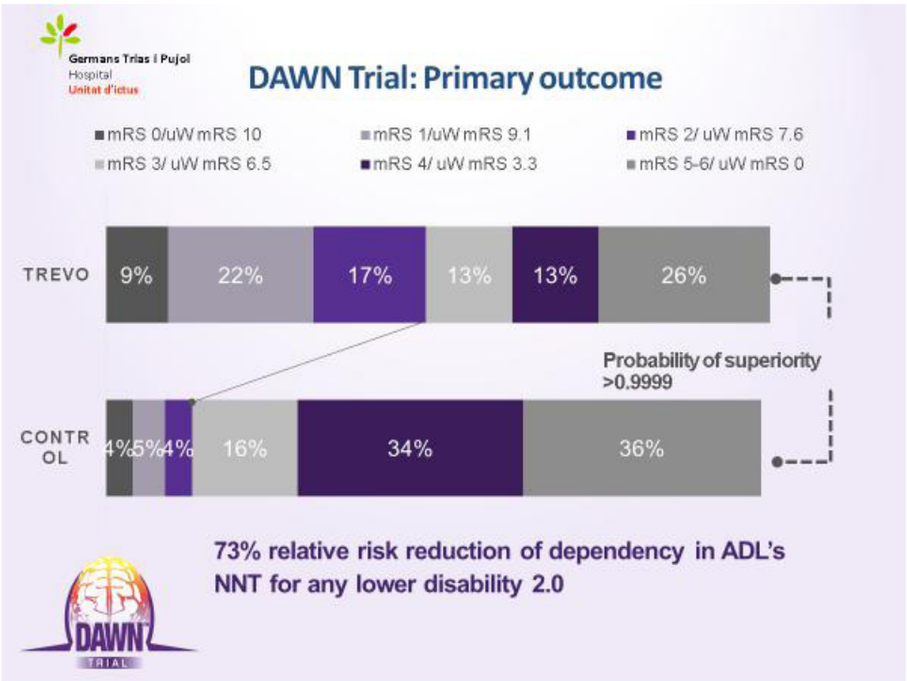


Professor Dávalos stressed that, until very recently, pivotal RCTs involving acute ischaemic stroke patients have investigated outcomes following treatment administered within six hours of symptom onset. This raises the question of how effective treatment is when administered outside this time window.

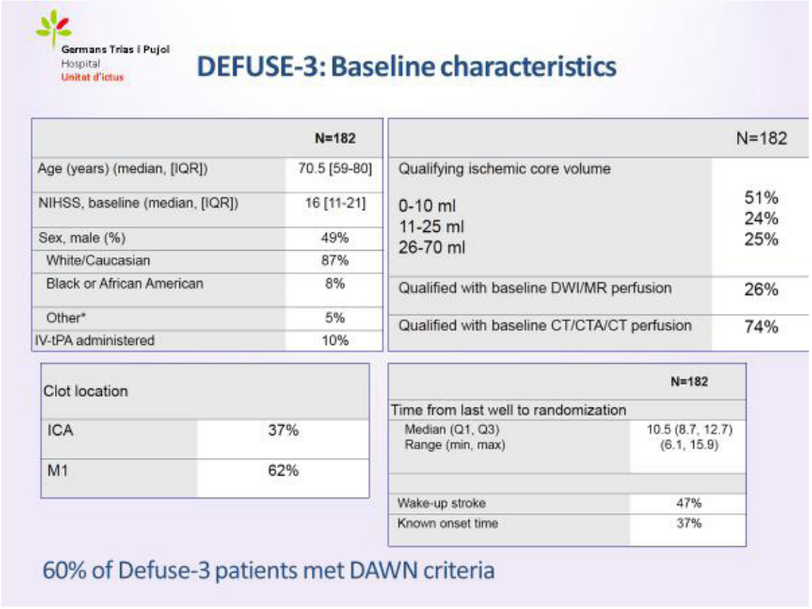
The DAWN trial (Diffusion Weighted Imaging (DWI) or Computerized Tomography Perfusion (CTP) Assessment With Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention) has demonstrated an important beneficial effect of endovascular treatment, in a late-window and wake-up stroke patient population, when initiated within the period of 6-24 hours after symptom onset. In this study, the neuroimaging was based on the calculation of the infarct core using RAPID (iSchema View) software. For eligibility in DAWN, patients >80 years old had to meet inclusion criteria of NIHSS scores of ≥ 10 and an 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. The methodology and design of the DAWN study are illustrated in the following figure.



The DAWN trial demonstrated a 73% reduction in the risk of dependence relating to activities of daily living (ADLs) with endovascular treatment with a stent retriever for mechanical thrombectomy, compared with control medical treatment. Furthermore, only two patients needed to receive endovascular treatment for a benefit to be obtained. These primary outcomes are summarized in the following figure.



DEFUSE-3 is a prospective, randomized, Phase III, multi-centre, controlled trial of patients with acute ischaemic anterior circulation strokes due to large artery occlusion treated between 6-16 hours of stroke onset. Patients who had evidence of an ICA or MCA M1 occlusion and a Target Mismatch Profile were randomized, in a 1:1 ratio, to treatment with one or more DEFUSE-3 approved thrombectomy devices plus standard medical therapy, versus standard medical therapy alone. In contrast to the DAWN trial, this trial utilized more permissive inclusion criteria. Median time from symptom onset to randomization was 10.5 hours, and only 25% of patients had an ischaemic core volume >25 mL. The baseline characteristics of DEFUSE-3 patients are summarized in the following table. This study was based on a novel adaptive design to identify, at interim analyses, the group with the best prospect for showing benefit from endovascular treatment, based on baseline core lesion volumes, and the times since stroke onset.



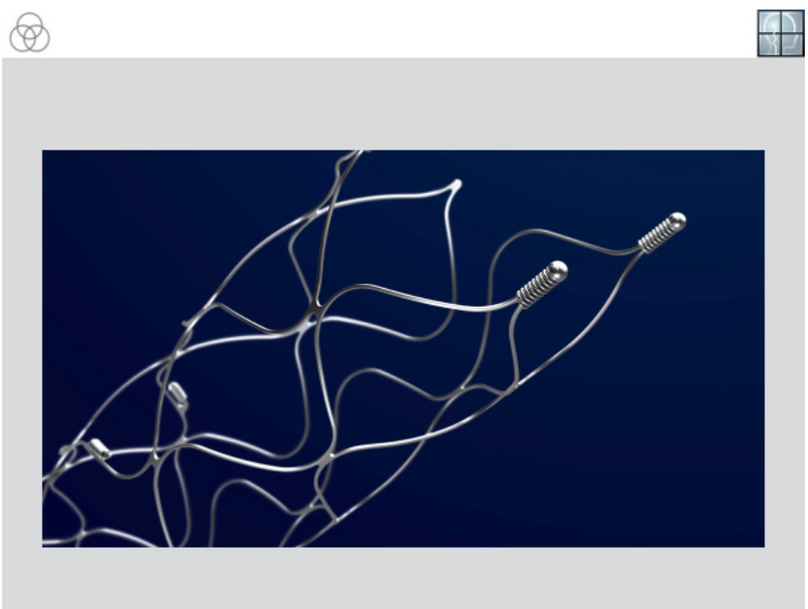
Professor Dávalos explained that the DEFUSE-3 trial was recently interrupted as a result of the DAWN study results, and the emergence of a clear statistical outcome indicating a high likelihood of a beneficial effect of the investigational treatment versus control during a DEFUSE-3 interim analysis based on 182 patients. Hence, two RCTs that both used RAPID software to calculate the size of the core of the infarction, have now demonstrated, in longer windows (6-24 hours), that when the infarct core is small, the patients benefit from endovascular treatment.

In conclusion, Professor Dávalos emphasized that endovascular thrombectomy provides substantial benefit across all ages of acute ischaemic stroke patients, across the strata of stroke severity, and in all predefined clinical and neuroimaging subgroups. These include patients with large baseline infarcts, poor baseline collateral extent, presence of hyperdense MCA sign, and patients with a large thrombus burden. Increasing ischemic core volume is independently associated with poor outcome. The number needed to treat (NNT) to achieve functional independence tends to increase with increasing ischemic core volume, although these data are associated with wide confidence intervals. With respect to thrombectomy performed during windows longer than six hours after symptom onset (DAWN and DEFUSE-3 studies), patients selected by using RAPID software to measure irreversible ischemic core and to identify those with smaller ischaemic core volumes are associated with improvement in clinical outcomes.

SOLITAIRE™ PLATINUM DEVICE – FIRST YEAR EXPERIENCE WITH THE NEWEST GENERATION OF THE SOLITAIRE STENT: PROFESSOR DR. RENÉ CHAPOT

Professor Chapot explained that the number of mechanical thrombectomy interventions at Alfried Krupp Krankenhaus (AKK) hospital in Essen, Germany, has increased progressively over the period from 2008 to 2017. During the period from October 2016 to July 2017, Solitaire™ Platinum was used at AKK as the first device in 255 mechanical thrombectomy procedures. The Solitaire™ Platinum Revascularization Device has enhanced meaningful visibility, providing feedback during placement, deployment, and retrieval of thrombi in the treatment of stroke patients. Currently, the new 6x40mm stent retriever is the longest and widest stent retriever commercially available.

Professor Chapot reviewed the methodology used for performing mechanical thrombectomy at AKK with Solitaire™ Platinum. All patients received general anaesthesia, and all interventions were conducted in association with a balloon guiding catheter. Aspiration catheters are not used. A Rebar-18 microcatheter was passed beyond the thrombus and used in conjunction with a Traxess guidewire. Although available in different sizes, the largest size i.e. Solitaire™ Platinum (6 x 40 mm) has been almost exclusively used at AKK, and always placed in the M2 segment. Professor Chapot stressed the importance of repositioning the balloon guiding catheter as soon as the stent retriever is withdrawn until aspiration becomes efficient, with blood arriving in the aspiration syringe. He added that very often, the clot was found in the aspiration syringe rather than in the Solitaire™ Platinum device. The Solitaire™ Platinum device is illustrated in the following figure. The new marker configuration provides improved visibility during the thrombectomy procedure.



Professor Chapot explained his preference for the largest size Solitaire™ Platinum (6 x 40 mm) device regardless of the diameter of the vessels. In small vessels, the 6 x 40 mm size is not an issue due to the greater degree of overlap. In addition, the larger size prevents loss of the clot in the internal carotid artery (ICA), whereas, a 3 mm Solitaire will be fully opened in the ICA, which is usually >3 mm in diameter, and this increases the risk of losing the clot.

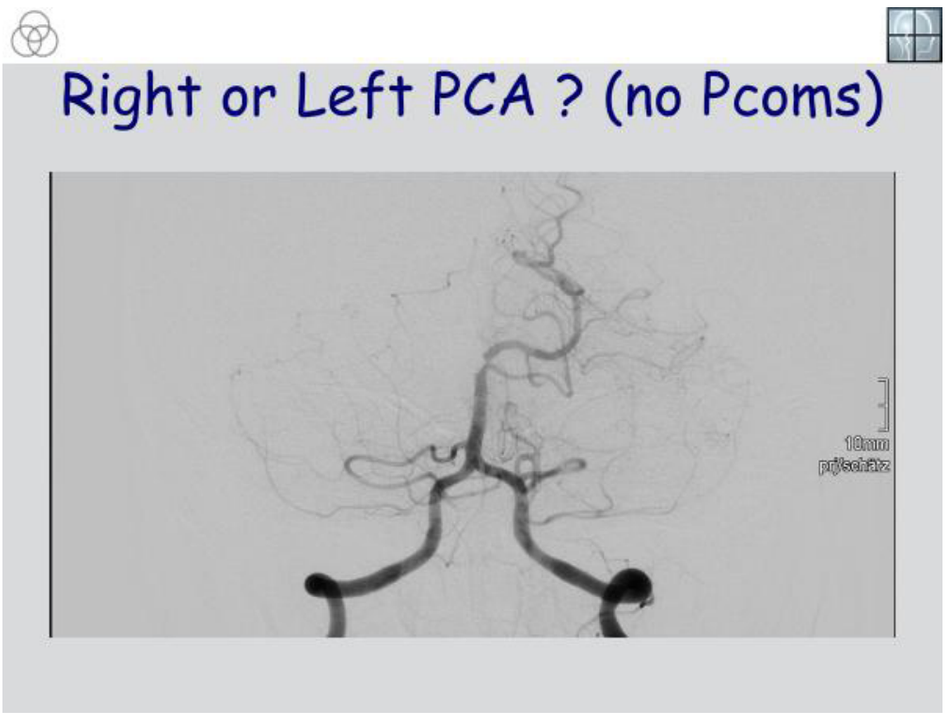
Use of the Solitaire™ Platinum 6 x 40 mm in conjunction with a Rebar-18 microcatheter was associated with a low device placement failure rate (n = 11; 4.3%); in these cases, deployment was hampered by a high degree of friction. No increased risk of haemorrhage was associated with the use of Solitaire™ Platinum 6 x 40 mm. Five patients experienced a haemorrhage (1.9%). An M1 dissection occurred in one patient and was treated by delayed stenting. The single pass recanalization rate with Solitaire™ Platinum 6 x 40 mm was 58%. Of these, recanalization was achieved in 136 patients (53%) with a single Solitaire™ device, and in 13 (5%) with concomitant deployment of two Solitaire™ devices.

Recanalization was achieved successfully after two passes in 52 patients (20.4%). The second pass was either achieved with a single Solitaire™ Platinum device in 44 patients (17.2%), or with two Solitaire™ Platinum devices in eight patients (3.1%). Hence, successful recanalization, as assessed by Thrombolysis in Cerebral Infarction (TICI) 2b and 3 outcomes, following one or two passes with Solitaire™ Platinum 6 x 40 mm, was achieved in 201 (79%) of the 255 thrombectomy procedures performed during the assessment period.

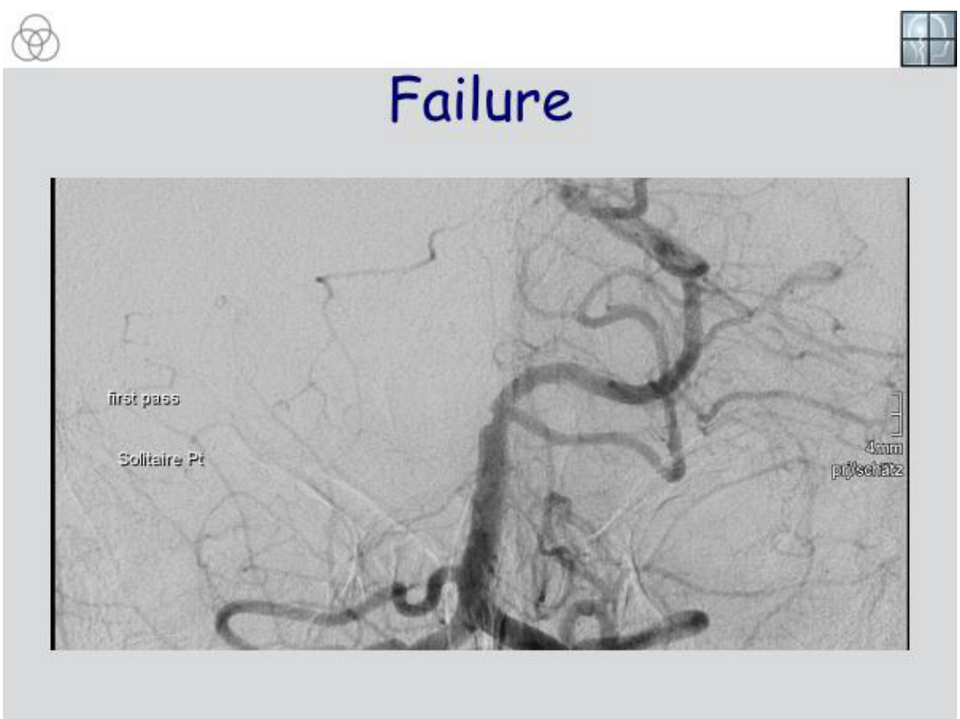
Successful recanalization became progressively more difficult with more than two passes during the thrombectomy procedure. Three passes were associated with a failure rate of 12%, and more than three passes with a failure rate of 50%. Summary data are presented in the following table.

Three passes	n = 19	12% failure
3 single device passes	n =9	
Combinations only with Solitaire	n =4	
Combinations with devices other than Solitaire	n = 6	
More than three passes	n = 55	50% failure
4 passes	n = 14	
5 passes	n = 8	
6 passes	n = 3	
7 passes	n =5	

Professor Chapot stressed that key considerations to achieve success are: the proper choice of vessel, where to position the device, and correct positioning of the stent retriever with regard to the clot. He posed the question where would you place the Solitaire™ Platinum device in the patient who provided the following scan?

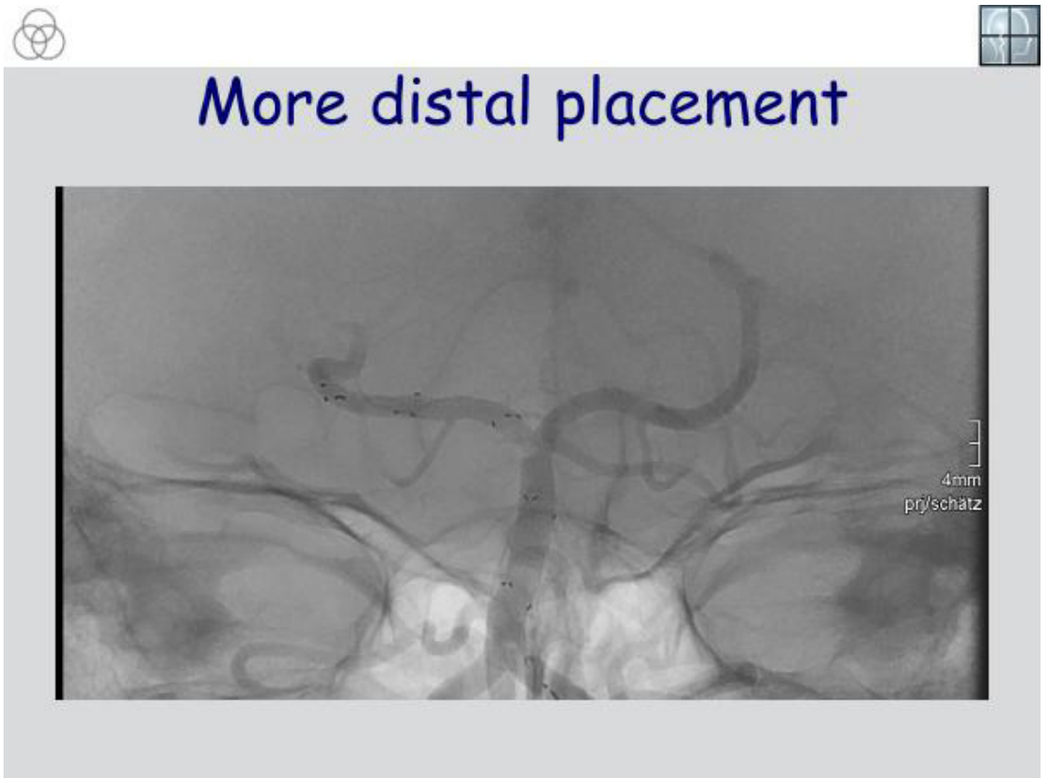


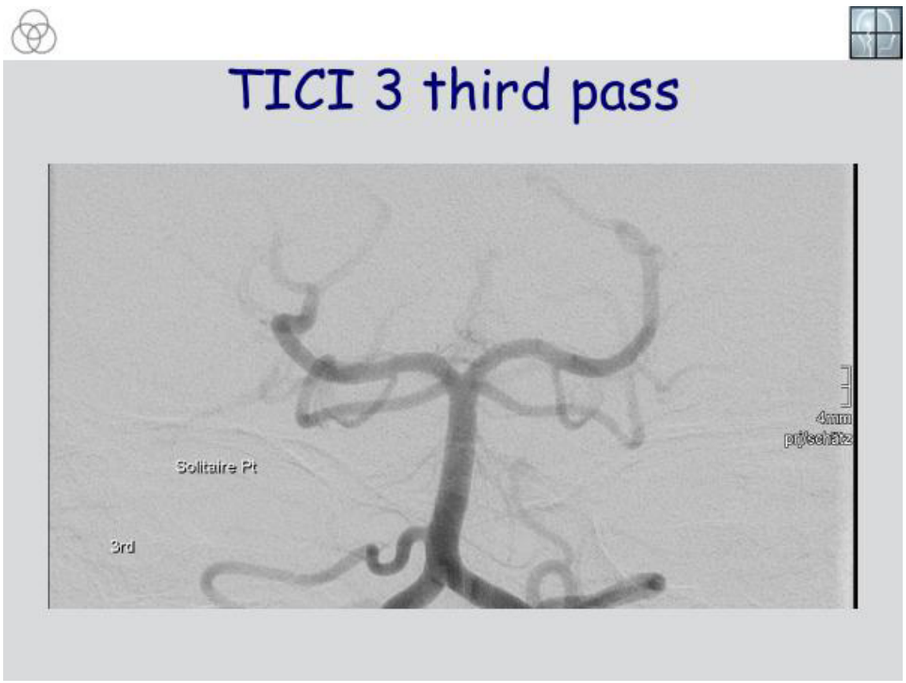
Wrong placement in the left posterior cerebral artery (PCA) resulted in failure.



Second pass involved too proximal placement also leading to failure.

A third pass, with more distal placement, resulted in successful recanalization with a TICI 3 outcome.





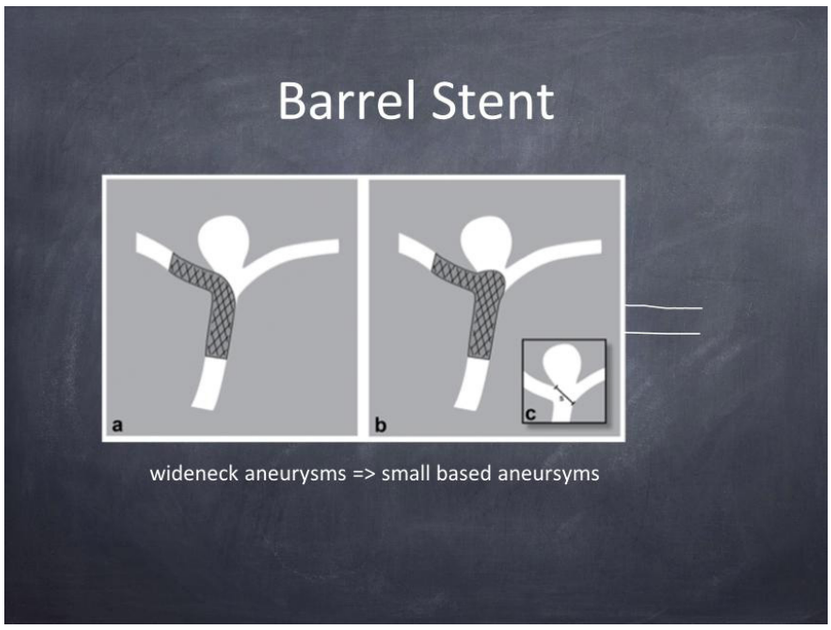
An important but difficult to answer question is at what point should the interventional neurologist stop? Professor Chapot reviewed example cases where persistency with difficult thrombectomy challenges using the Solitaire™ Platinum device in conjunction with other smaller supporting devices (e.g. Echelon 10/Minicatch) have led to favourable TICI outcomes, but at the cost of reduced efficiency with respect to first-pass success rate. For patients requiring device placement distal to the M3 position, whether the patient has received IV lysis treatment, or not, is an important consideration due to the increased haemorrhagic risk associated with IV lysis treatment. However, Professor Chapot noted that an increasing number of patients at AKK are proposed for mechanical thrombectomy without prior IV lysis treatment. Although experience with the Solitaire™ Platinum device has not answered the question of when intervention should stop, Professor Chapot stressed that a better clinical outcome is to be expected in patients with a TICI 3 recanalization.

Reviewing the overall results, Professor Chapot explained that TICI 3 recanalization was achieved in 181 patients (70.9%) with Solitaire™ Platinum as the sole device, and TICI 2b was achieved 36 patients (14.1%). Hence, 217 patients (85%) were recanalized with a TICI 2b or TICI 3 assessment. When Solitaire™ Platinum was deployed in conjunction with other supporting devices to remove additional small clots, TICI 3 recanalization was achieved in 185 patients (72.5%) and TICI 2b was achieved 54 patients (21.1%). Hence, 239 patients (93.7%) were recanalized with a TICI 2b or TICI 3 assessment in these patients. These recanalization rates compare very favourably with those reported in stent retriever thrombectomy RCTs (MR CLEAN, ESCAPE, EXTEND-IA, REVASCAT, SWIFT Prime), and in prospective registries (STRATIS, STAR) and retrospective stroke registries (NASA), where TICI 2b/3 recanalization rates of 58.7% – 87.9% have been reported.

In conclusion, Professor Chapot confirmed that the Solitaire™ Platinum Revascularization Device is now the first choice for mechanical thrombectomy in his hospital department, and has improved the overall efficiency of the department to perform this intervention. The 6 x 40 mm largest size in conjunction with a Rebar-18 microcatheter has been found to be the most valuable, and improved visibility helps optimize placement, deployment, and retrieval of the device. Currently, the modus operandi adopted at AKK is that after two passes, there is a switch in technique, from single to double Solitaire™ Platinum procedure.

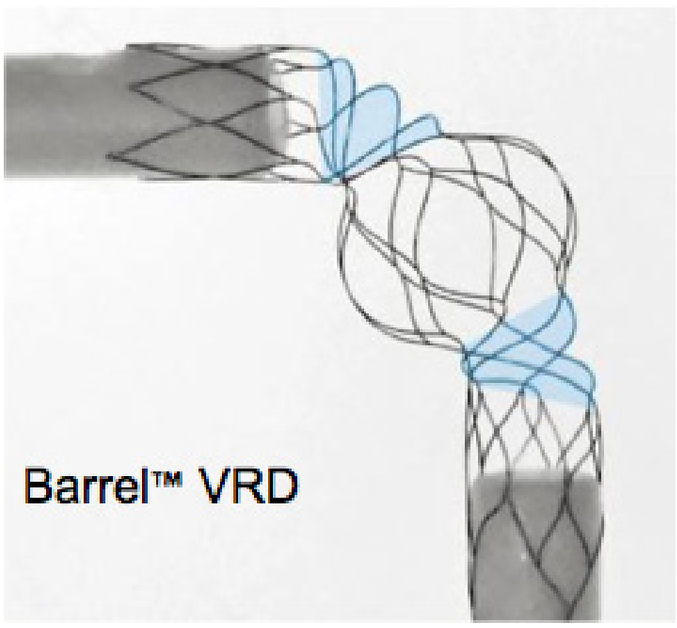
BARREL™ VRD – FOR THE TREATMENT FOR BIFURCATION ANEURYSMS: PROFESSOR WOLFGANG REITH

The BARREL™ vascular reconstruction device (VRD) is a laser cut stent designed for stent-assisted coil embolization of wide-necked bifurcation or branch aneurysms with a single device, and with the purpose of lowering the metal-to-artery ratio and the associated inherent risk of thromboembolic complications with multiple stents. The BARREL™ VRD has inbuilt hinge technology that allows the barrel portion of the stent to be used as a neck reconstruction device in bifurcation aneurysms. The barrel section of the device herniates over the ostium and reduces the aneurysm neck to support coiling. Professor Reith explained that the BARREL™ VRD has widespread application in the treatment of bifurcation aneurysms. The device allows a wide neck aneurysm to be closed to a much smaller neck as illustrated in the following figure.

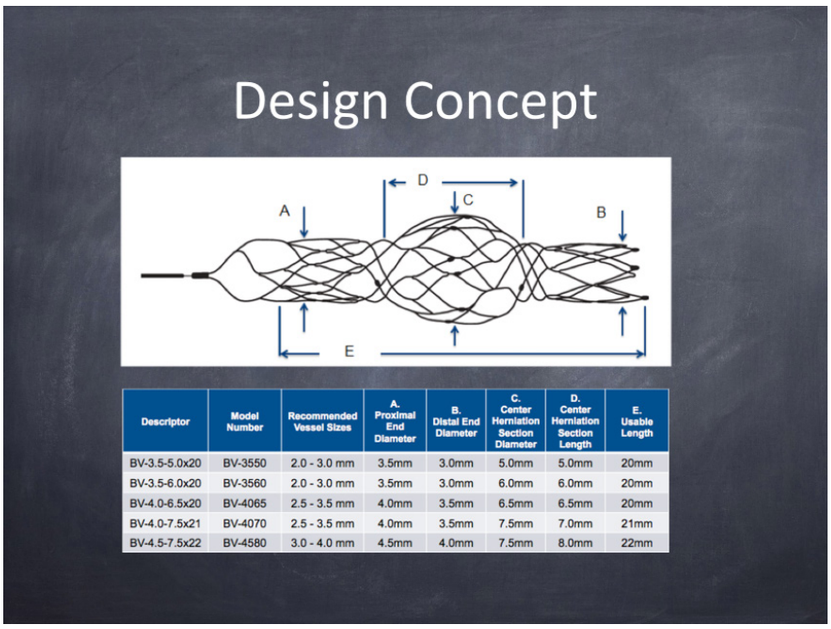


Professor Reith reviewed some of the technical problems that can arise with laser cut stents. Kinking can occur, and this can cause difficulty in placing the stent inside the curved and often convoluted anatomy of neurovascular blood vessels. With Y and V-stenting, problems can occur when there is a necessity to pass one stent through another; this can lead to stenosis. Other reported problems with Y-configuration double stent assisted coiling include: the provided angle of entry through the placed stent may not allow safe intra-aneurysmal or branch access, and the risk of a thromboembolic event increases with use of two stents compared with one. In addition, stent migration during adjunctive coiling procedures, with low-profile braided devices with an associated lower radial force, has been reported.[3] Incomplete opening of low profile devices with reduced apposition of the vessel wall may also occur.[4] Importantly, low profile braided devices are not 100% retrievable and this can cause re-positioning difficulties.

Professor Reith stressed that Balloon-assisted coiling is a proven therapy; it provides stable, long-term beneficial outcomes.[5] Therefore, the BARREL™ VRD design concept was to engineer a device that provides both coil containment and branch vessel patency with one device. Key design considerations were simplicity and ease of use in stent-assisted coiling, to avoid kinking, and the protruding barrel "bulge" of the device gives protection to the side branches in the neck of the aneurysm. The BARREL™ VRD device is shown in the following figure with the flexible zones highlighted in blue.

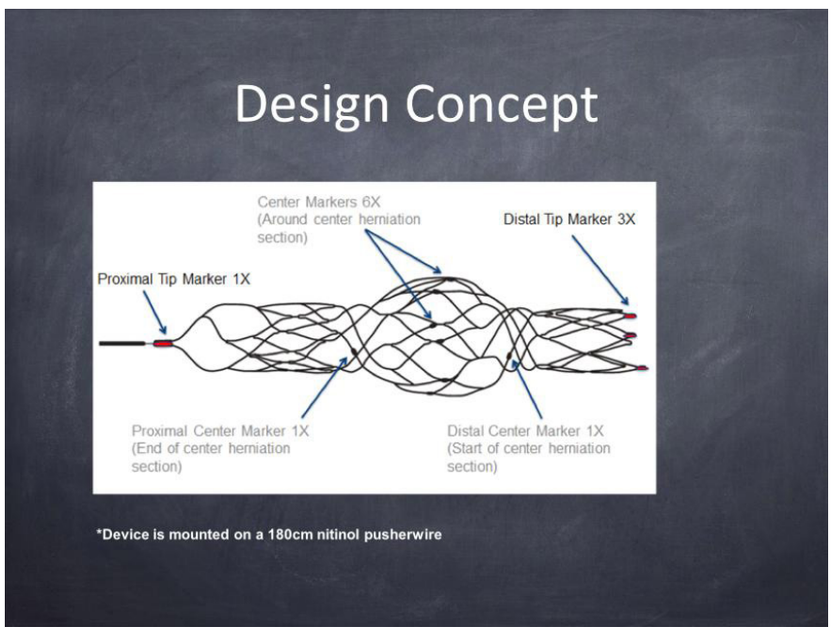


The BARREL™ VRD device is available in five sizes, and the characteristics of these variants and their respective recommended vessel sizes are summarized in the following table. The device is fixed to a nitinol push wire and Professor Reith explained this, together with the device markers, allows for re-sheathing and repositioning. The BARREL™ VRD device is detached from the delivery wire using an electrolytic detachment process. This is similar to electrolytically detachable GDC coils.



Descriptor	Model Number	Recommended Vessel Sizes	A. Proximal End Diameter	B. Distal End Diameter	C. Center Herniation Section Diameter	D. Center Herniation Section Length	E. Usable Length
BV-3.5-5.0x20	BV-3550	2.0 - 3.0 mm	3.5mm	3.0mm	5.0mm	5.0mm	20mm
BV-3.5-6.0x20	BV-3560	2.0 - 3.0 mm	3.5mm	3.0mm	6.0mm	6.0mm	20mm
BV-4.0-6.5x20	BV-4065	2.5 - 3.5 mm	4.0mm	3.5mm	6.5mm	6.5mm	20mm
BV-4.0-7.5x21	BV-4070	2.5 - 3.5 mm	4.0mm	3.5mm	7.5mm	7.0mm	21mm
BV-4.5-7.5x22	BV-4580	3.0 - 4.0 mm	4.5mm	4.0mm	7.5mm	8.0mm	22mm

The marker configuration for the BARREL™ VRD device is illustrated in the following figure. There is a proximal tip marker, three distal tip markers, a proximal and distal center marker in the flexible zones, and a total of six markers in the central herniation section.



The following figure shows the BARREL™ VRD device central markers, once the device has been correctly positioned to give complete expansion and coverage over the neck of the aneurysm. It is important to measure the bifurcation span carefully and accurately to ensure a correct sizing decision.

Professor Reith presented a series of images showing the correct positioning of the BARREL™ VRD device, highlighting ease of visualization of the device markers with fluoroscopy, and case studies showing successful coiling and occlusions of aneurysms treated with the BARREL™ VRD device.

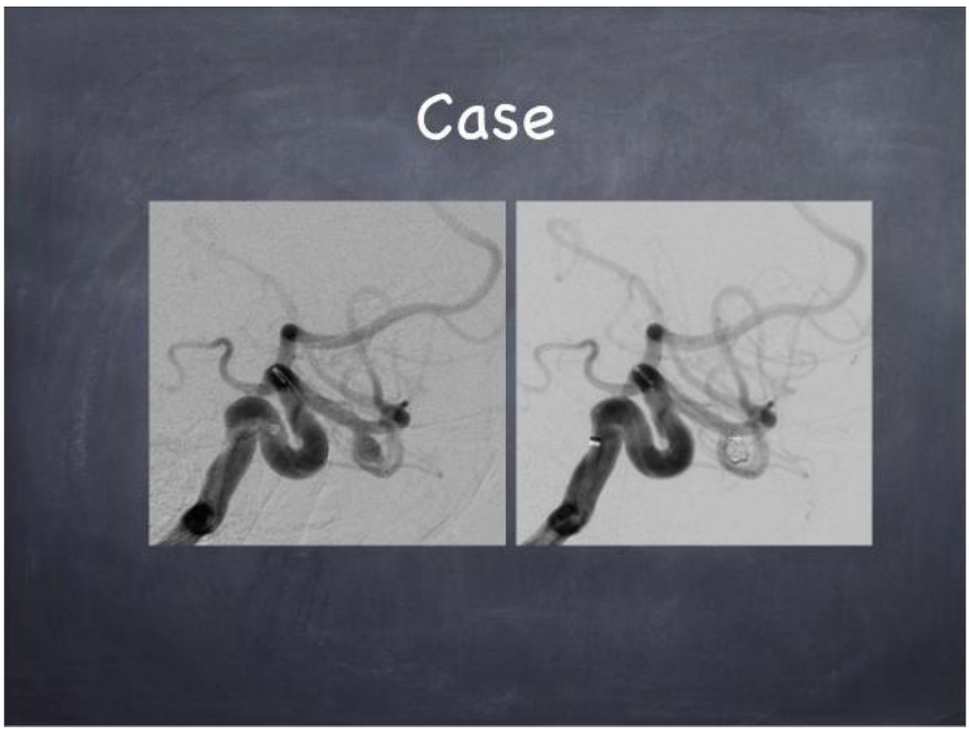
Early clinical experience has been documented in a retrospective single-centre study conducted in 17 consecutive patients (mean age 58 ± 12 years) who underwent stent-assisted coil embolization of wide-necked bifurcation aneurysms with the BARREL™ VRD device.[6] This study analyzed the feasibility of successful deployment and evaluated post-treatment angiographic results. The median dome-to-neck (D/N) ratio of treated aneurysms in the anterior and posterior circulation was 1.3, and 47% of patients had aneurysms with a neck diameter of <4 mm and 53% ≥4 mm. Technical success i.e. adequate occlusion was observed in 16/17 (94.1%) of aneurysms. In one patient, where difficulty in inserting the microcatheter through the stent occurred, the patient experienced a transient ischaemic attack. A total of 13/17 (76.5%) patients underwent short-term follow-up angiography after 3 months, all of which showed adequate occlusion of the aneurysm. The occlusion rates achieved in the study are summarized in the following table.

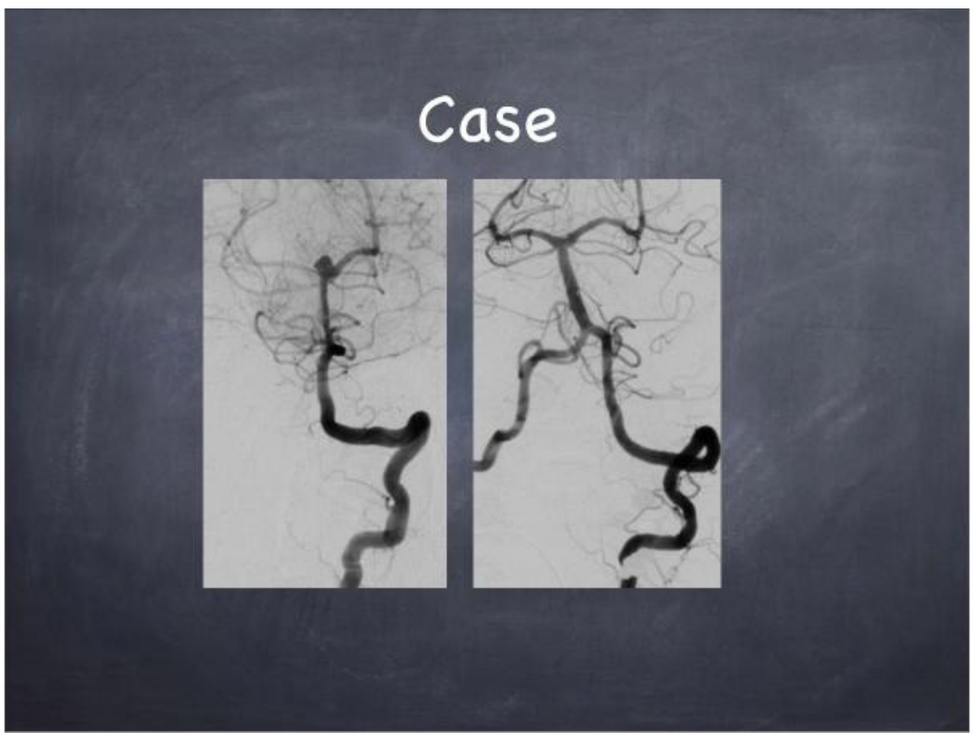
Post-op occlusion rate	64.7% (11/17) RROC 1 29.4% (5/17) RROC2 5.8% (1/17) RROC3
Short-term follow up (3-4 months) in 13/17 (76.5%) of patients	84.6% (11/13) RROC 1 15.3% (2/13) RROC 2
Long-term follow up (>12 months) in 11/17 (64.7%) of patients	81.8% (9/11) RROC 1 18.2% (2/11) RROC 2

RROC = Raymond-Roy Occlusion Classification

Hence, in this small retrospective single-centre analysis, stent-assisted coiling with the BARREL™ VRD device was a safe and effective option for the endovascular treatment of intracranial wide-necked bifurcation aneurysms.

The following two images show aneurysms pre-operatively and the occlusion achieved after intervention with BARREL™ VRD device.

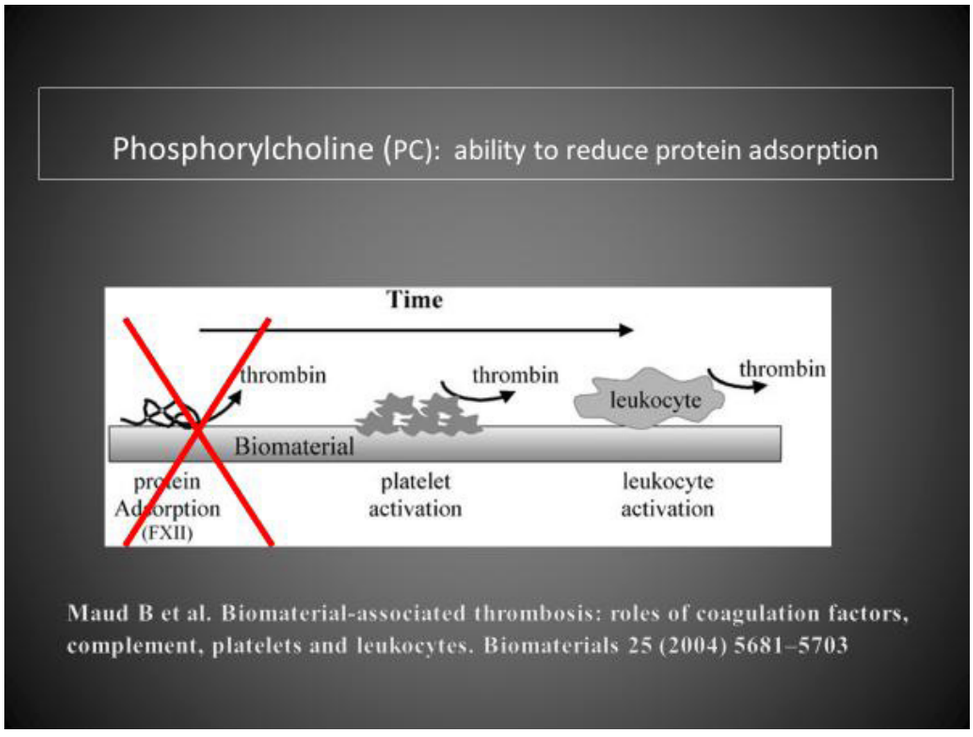




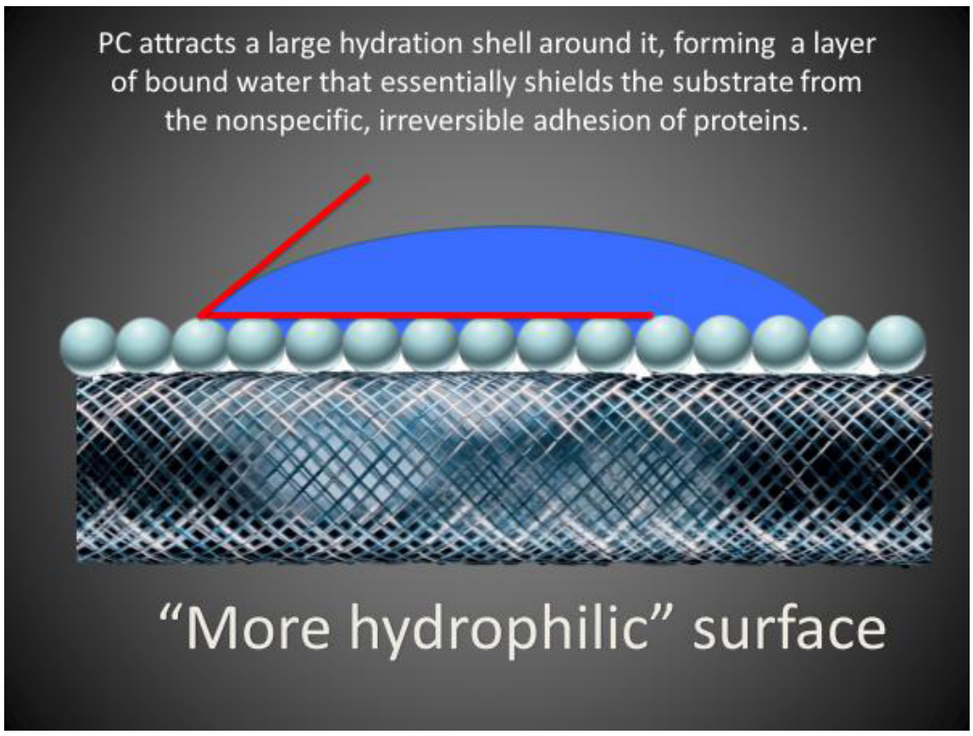
To conclude, Professor Reith summarized his experience of the BARREL™ VRD device: he stated it is a safe and effective alternative to other devices for the endovascular treatment of bifurcation aneurysms. The key advantages of the BARREL™ VRD device are: it is simple to handle; it is easy and safe to position and deploy, with good visualization, and the device is repositionable and can be re-sheathed. In addition, there is less potentially thromboembolic material introduced into the neurovasculature than with Y-stenting, but similar occlusion rates are achieved.

THE PIPELINE™ FLEX DEVICE WITH SHIELD TECHNOLOGY™ – CLINICAL DATA: PROFESSOR MARIO MARTINEZ-GALDÁMEZ

Professor Martinez-Galdámez explained that the latest Medtronic Pipeline™ Flex embolization device differs from its earlier predecessors by the incorporation of a novel surface modification applied to the device components to provide greater haemocompatibility. Thromboembolic events have been a principal cause of procedural complications with earlier Pipeline embolization devices (PEDs). Professor Martinez-Galdámez explained that protein adsorption is the initial stage of a biomaterial thrombosis; however, the inert synthetic polymer, phosphorylcholine (PC), prevents the adsorption of protein as illustrated in the following figure.

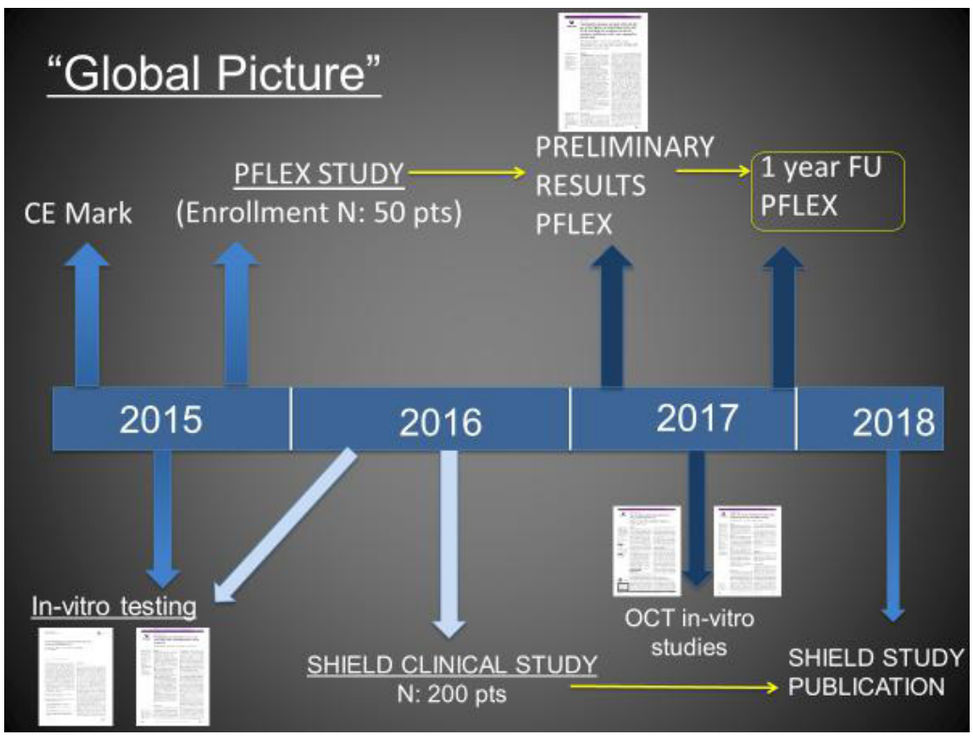


The Pipeline™ Flex Embolization Device with Shield Technology™ utilizes an inert phosphorylcholine (PC) surface treatment covalently bonded to the strands of the implant to make the device more biocompatible. Essentially, the role of PC, when the device is in situ, is to attract a large hydration shell around it. This hydrophilic surface shields the substrate from the nonspecific, irreversible adhesion of proteins.

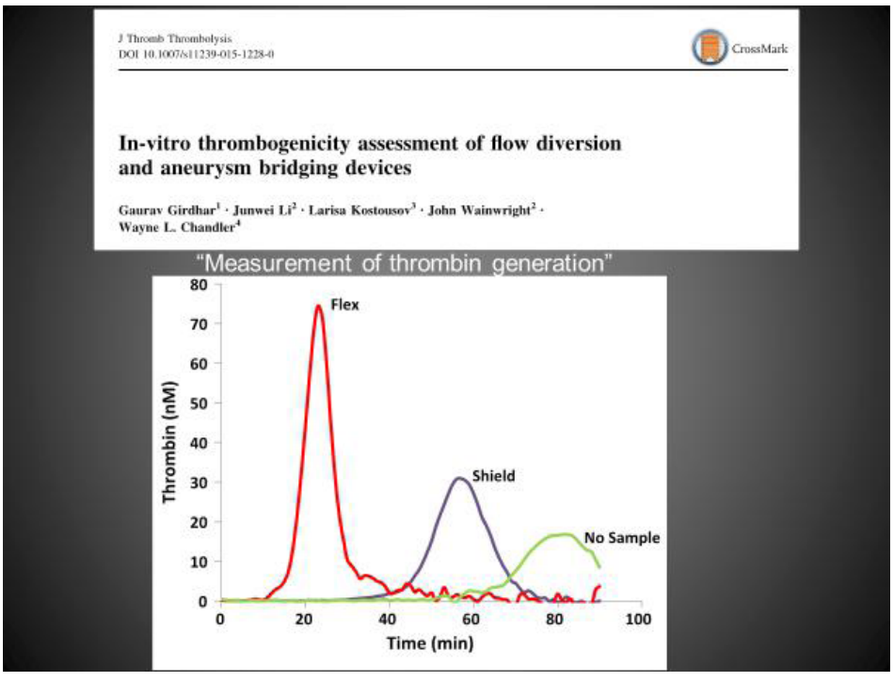


Hence, the Shield™ surface modification technology has been designed to improve biocompatibity and to reduce thrombogenicity.

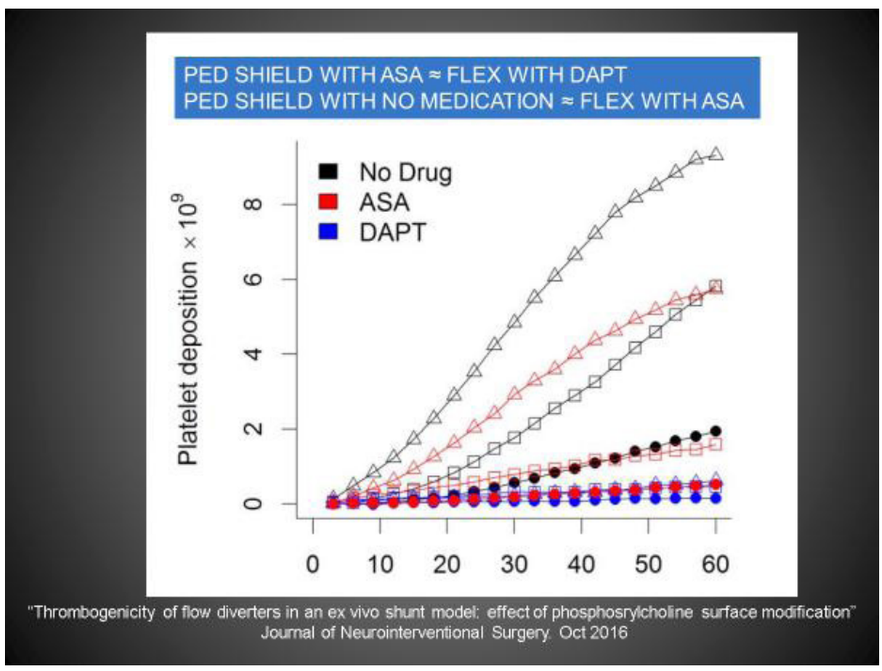
Professor Martinez-Galdámez summarized the *in vitro* and clinical studies that have been conducted or are in progress with the Pipeline™ Flex Embolization Device with Shield Technology™ (PFEDST).



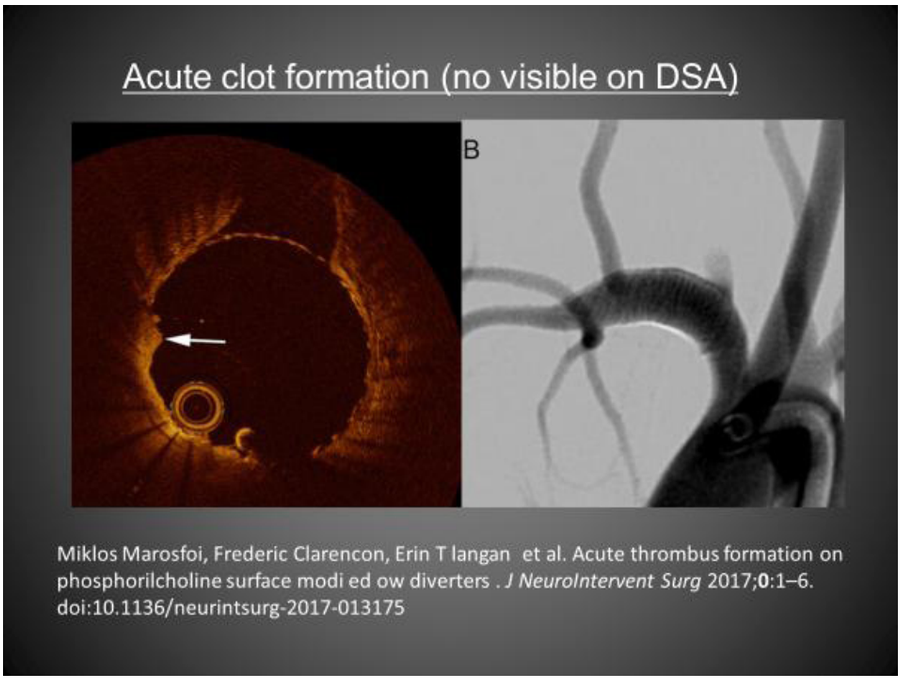
In vitro thrombogenicity assessment, as measured by thrombin generation, has demonstrated significantly less (and later) thrombin generation with PFEDST than the standard Flex device without Shield Technology™ surface modification.[7]



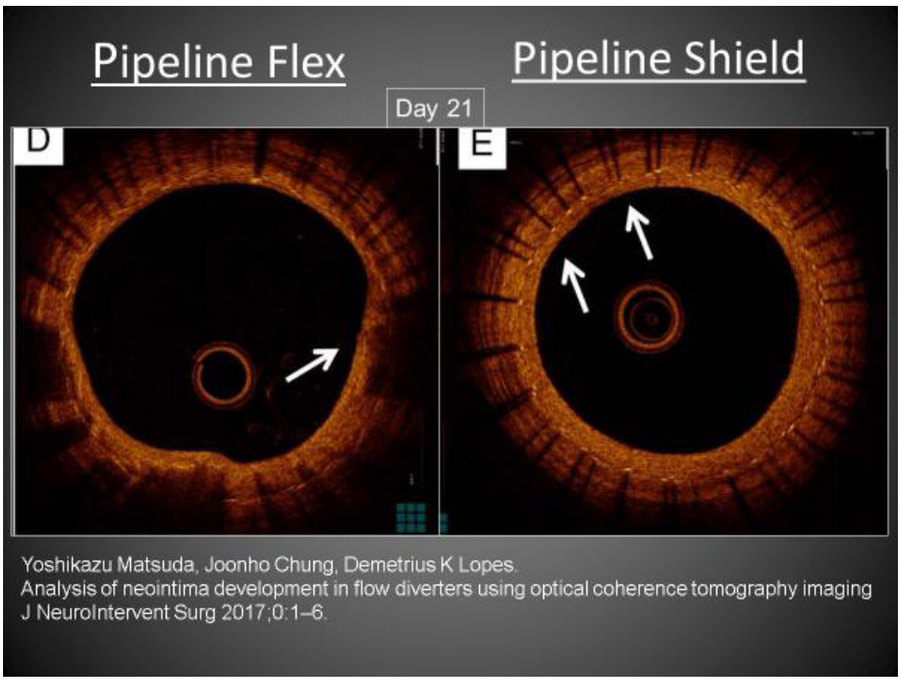
Significantly reduced in vitro thrombogenicity attributable to phosphorylcholine surface modification has been demonstrated in a radiolabelled platelet deposition.[8] The Pipeline Embolization Device (PED) plus Shield™ showed significant reductions in platelet deposition compared with unmodified PED, without antiplatelet therapy, and with dual antiplatelet therapy (DAPT). Notably, the PED plus Shield™ with acetylsalicylic acid (ASA) monotherapy was associated with comparable platelet deposition to that observed with the Flex PED and DAPT. Additionally, the PED plus Shield™ with no medication resulted in comparable platelet deposition with that seen with unmodified PED plus ASA. These observations are summarised in the graph shown below.



Professor Martinez-Galdámez explained that acute thrombus formation is often not seen when using digital subtraction angiography (DSA); however, clots are more clearly seen using optical coherence tomography (OCT) as shown in the following figure. Of note, branching of clots on the surface was more evident with use of the earlier version of the Pipeline device, without Shield Technology™, compared with latest generation device.



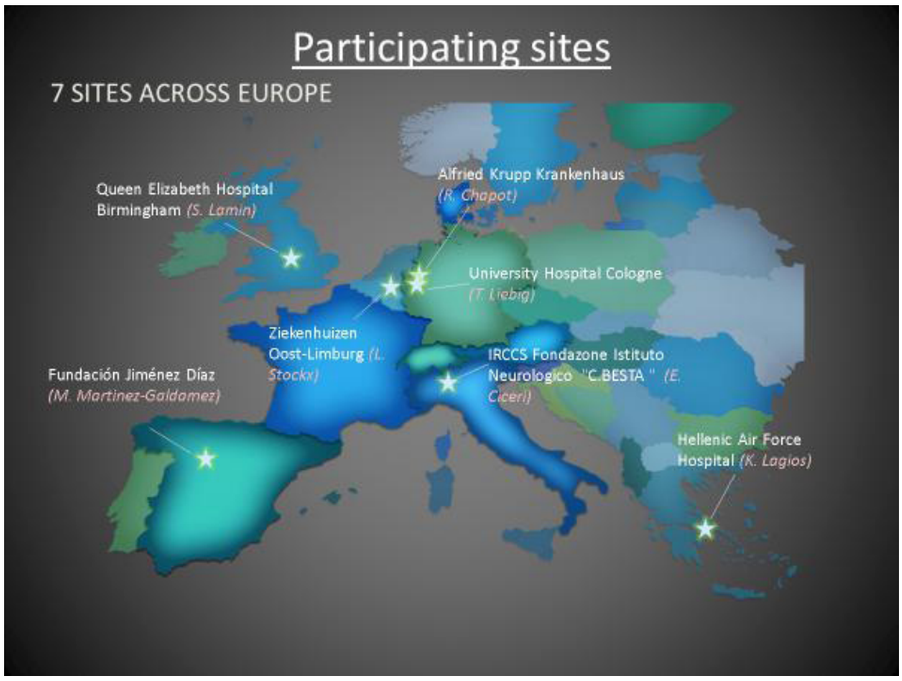
In addition, neointimal patterns associated with latest generation 3.0 PFEDST device appear to be more symmetrical and homogenous compared with the asymmetrical and heterogenous neointima evident with use of the earlier version of the device, as illustrated in the following figure. This may suggest the latest generation PFEDST device is more benign with respect to thrombogenicity than its predecessors.



In summary, key points that have emerged from these preclinical studies are:

- Optical coherence tomography (OCT) is superior compared with digital subtraction angiography (DSA) for detecting the presence of a thrombus;
- OCT is superior than DSA to analyze intimal hyperplasia;
- The neointimal pattern associated with the use of SHIELD Technology™ is more homogeneous and symmetrical, compared with earlier versions of the device, possibly suggesting a more benign influence with respect to thrombogenicity;
- SHIELD Technology™ is associated with less thrombus formation on the surface.

Professor Martinez-Galdámez reviewed the ongoing clinical programme for the Pipeline™ Flex Embolization Device with Shield Technology™ (PFEDST). The PFLEX study[9] is a prospective, single-arm, multi-centre clinical study designed to assess the technical success and safety of the Pipeline™ Flex Embolization Device with Shield Technology™ in up to 50 patients, with follow-up at 30 days, 6 months, and 1 year. The seven participating European countries are illustrated in the following figure.



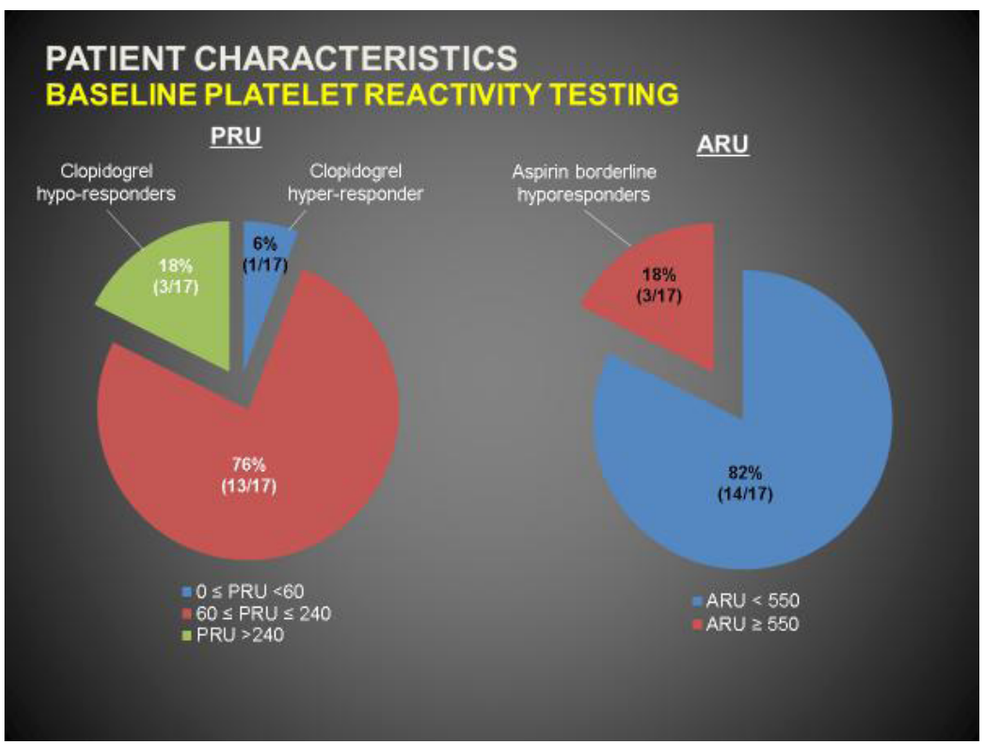
The study inclusion criteria were: patients pre-selected for flow diversion therapy aged 8-80 years with an unruptured target aneurysm; parental vessel diameter 1.5-5.0 mm distal/proximal to the target intracranial artery; target aneurysm located in the internal carotid artery (up to the carotid terminus), or, located in the vertebral artery segment up to and including the posterior inferior cerebellar artery. Patients' written informed consent was required. Exclusion criteria applied were: subarachnoid haemorrhage or major surgery in the past 30 days; anatomy not appropriate for treatment (e.g. severe intracranial vessel tortuosity or stenosis); history of intracranial vasospasm not responsive to medical therapy; known contraindications to the Pipeline™ Shield device, and pregnant or breastfeeding women.

The mean age of the 50 patients enrolled was 53.0 ± 13.01 years; 41 (82%) were women, and the mean baseline NIHSS score was 0.2 ± 0.85. Patients' medical history and smoking status are summarized in the following table.

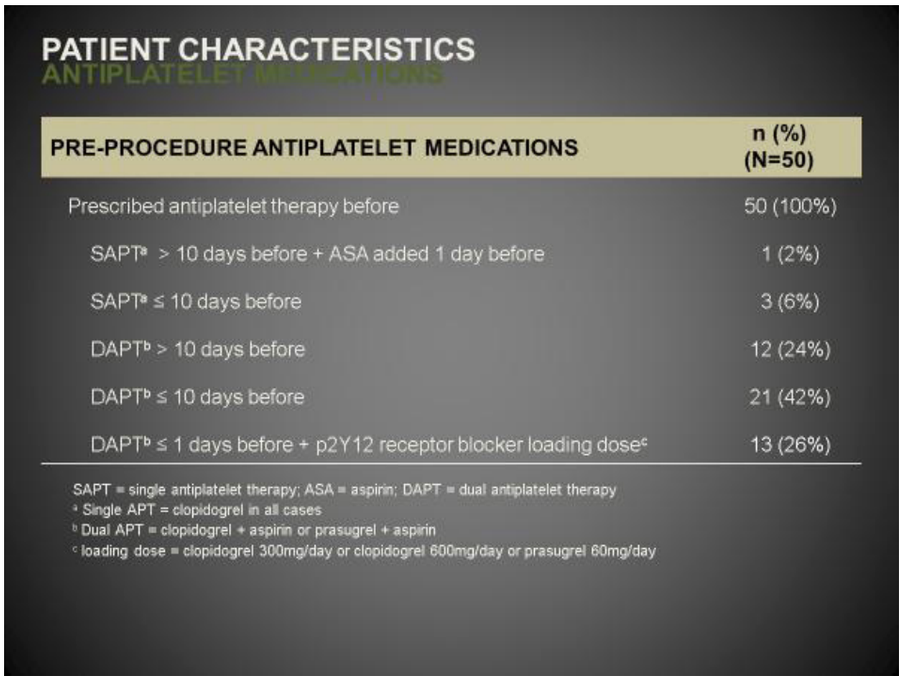
PATIENT CHARACTERISTICS
MEDICAL HISTORY

CHARACTERISTICS	n (%) (N=50)
Medical History	
Hypertension – controlled	12 (24%)
Hyperlipidemia	5 (10%)
Diabetes Type 2	2 (4%)
Subarachnoid hemorrhage	11 (22%)
Smoking History	
Never smoked or has not smoked within the last 10 years	20 (40%)
Not a current smoker, but has smoked within the past 10 years	15 (30%)
Current smoker, less than one pack per day	5 (10%)
Current smoker, greater than or equal to one pack per day	4 (8%)
Unknown	6 (12%)

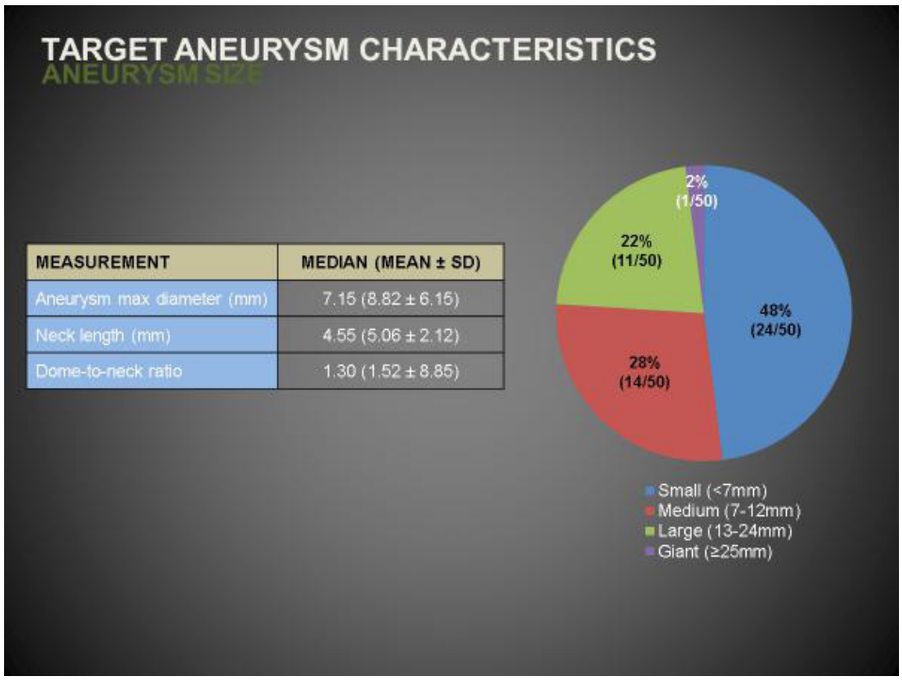
Patients' baseline platelet reactivity testing, reported as aspirin-reaction units (ARU) for aspirin, and P2Y12 reaction units (PRU) for clopidogrel are shown in the following chart.



Patients' pre-procedure antiplatelet medications are listed in the following chart.

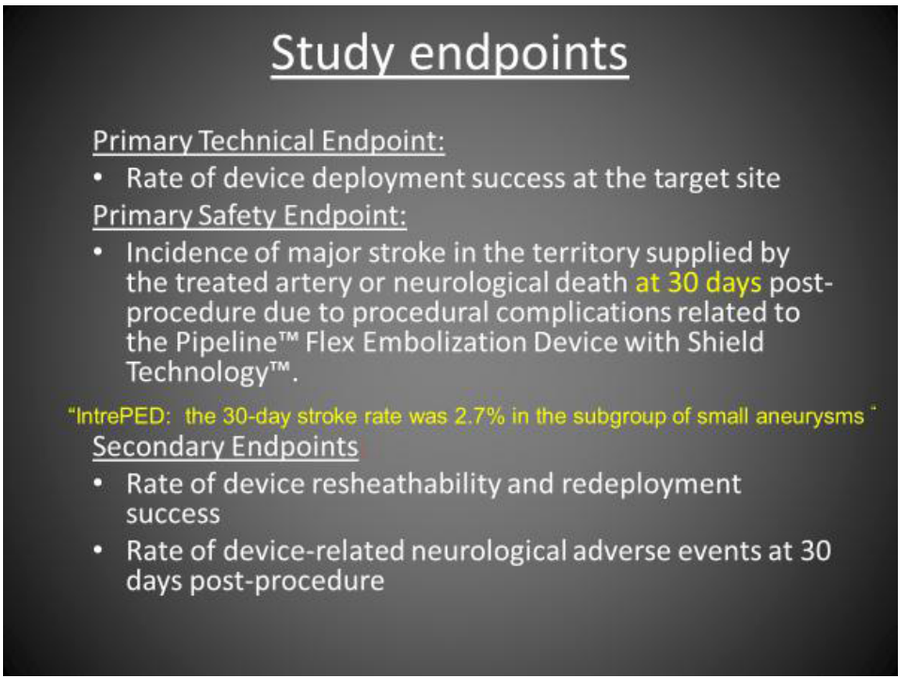


Most of the target aneurysms (76%) were classified as small (<7 mm diameter), or medium (7-12 mm). Median aneurysm diameter, neck length and dome-to-neck ratio measurements are summarized in the following figure.



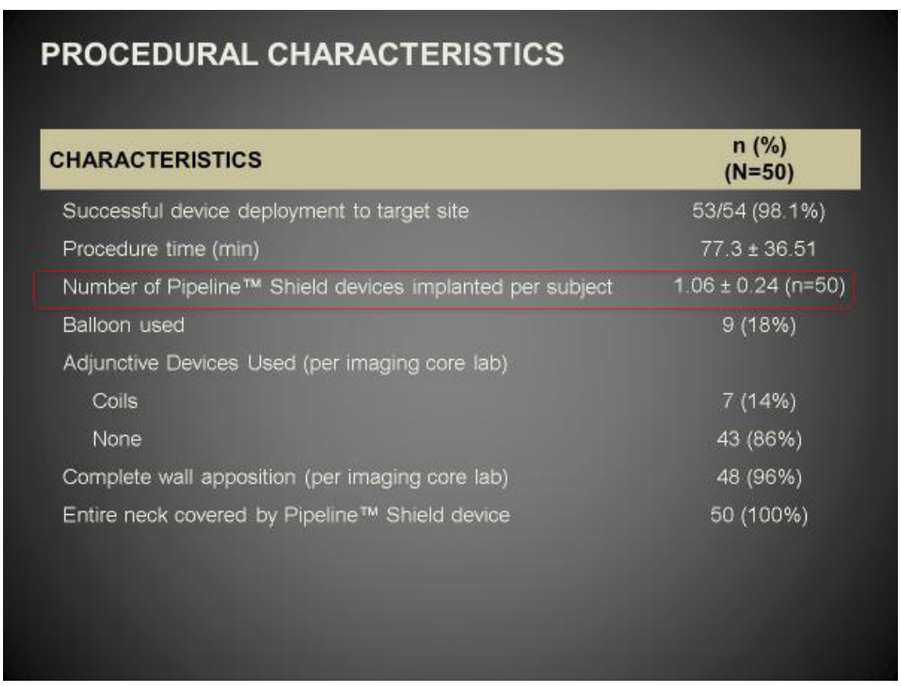
Almost all target aneurysms were saccular (n = 49; 98%) with only one (2%) classified as fusiform. Most target aneurysms were located in the internal carotid artery (n = 47; 94%), with three (6%) located in the vertebral artery.

The primary and secondary study endpoints for the PFLEX study are summarized in the following figure.



Professor Martinez-Galdámez confirmed that the study device deployment procedures involved virtual simulation using Sim&Cure software in conjunction with the Navien-Marksmann triaxial system. Multiple PEDs were used in four cases (8.0%), with an average of 1.1±0.27 devices per aneurysm. Mean procedure time was 77.3 ±36.51 min.

Complete wall apposition was achieved in 48 (96%) of patients, and the entire neck of the aneurysm was covered by the Pipeline™ Shield device in all patients (100%). These procedural outcomes are summarized in the following figure.



Resheathing was attempted in 13/54 patients (24.1%) and was successful in in 12/13 patients (92.3%). Resheathing was conducted for ease of delivery in one case (7.7%), repositioning in five (38.5%), distal braid opening in four (30.8%), and to improve wall apposition in three cases (23.1%). At 30 days post-procedure, no major stroke in the territory supplied by the treated artery, and no neurological death due to procedural complications related to the Pipeline™ Shield device had occurred. Three patients experienced a serious adverse event (SAE); these were reported as: diplopia related to the procedure; retroperitoneal haemorrhage related to the procedure, and a headache related to the procedure. All SAEs resolved without complications.

Professor Martinez-Galdámez reviewed the PFLEX study at 1-year follow-up. The primary safety endpoint was the occurrence of major stroke in the territory supplied by the treated artery, or neurological death at 1-year post-procedure. No major stroke or neurological death (0%) was evident at 1-year post-procedure. A secondary endpoint was the recorded neurologic adverse event rate at 1-year post-procedure. Neurologic adverse events attributable to the Pipeline™ Shield device occurred in seven (14%) patients. In-stent stenosis was reported in six cases; however, all were asymptomatic and non-serious. One device-related serious adverse event (SAE), an asymptomatic ICA thrombosis which resulted in no clinical sequelae, was discovered during endovascular treatment of a contralateral non-target aneurysm 63 days after the Pipeline™ Shield device was implanted. Three procedure-related SAEs were reported (headache, diplopia, and retroperitoneal haemorrhage); all resolved without sequelae.

At 1-year post-procedure, complete aneurysm occlusion was still evident in 27/33 patients (81.8%). Additionally, there was no recurrence (0%) of any target aneurysm and there was no requirement for retreatment of any target aneurysm. No cases of severe stenosis were seen.

Professor Martinez-Galdámez referred to 5-year follow up data in the Pipeline for Uncoilable or Failed Aneurysms trial (PUFS)[10]. In this study, long-term clinical and angiographic outcomes following pipeline embolization device treatment of complex internal carotid artery aneurysms were documented. Complete aneurysm occlusion at 180 days was achieved in 73.6% patients; however, aneurysm occlusion for those patients with angiographic follow-up increased progressively over time to 86.8%, 93.4% and 95.2% at I, 3 and 5 years, respectively. Professor Martinez-Galdámez expected the same progressive increase in occlusion rate will be seen with longer follow-up in the PFLEX study.

To conclude, Professor Martinez-Galdámez stressed that thromboembolic complications are responsible for the main problems with flow diversion procedures. *In vitro* studies have now demonstrated that the Pipeline™ Flex Device with Shield Technology™ is less thrombogenic than earlier versions of this device. Clinical outcomes from the PFLEX study have corroborated the safety and efficacy of the Pipeline™ Flex Device with Shield Technology™ for the treatment of intracranial aneurysms.

CONCLUSIONS

The benefits of endovascular thrombectomy after large vessel ischaemic stroke have been clearly demonstrated in randomized controlled trials. Generally, the accepted time window for this intervention is around 4.5 hours after onset of stroke symptoms. It is evident that the larger the infarct core, the lower the probability of the patient achieving functional independence. Hence, imaging may help select those patients with smaller infarct cores with a higher likelihood of benefit from thrombectomy. The availability of the RAPID automated image analysis platform (iSchema View) allows interventional stroke neurologists to identify patients with salvageable brain tissue (Target Mismatch Profile) and smaller ischaemic core volumes. Use of this software has provided the means to select patients carefully in two late-window randomized controlled trials.

The DAWN study has demonstrated mechanical thrombectomy, performed with 6-24 hours of symptom onset, in patients with an NIHSS score ≥ 10, led to a 73% reduction in the risk of dependence relating to activities of daily living, compared with control medical treatment (Bayesian probability of superiority >0.9999). The DEFUSE-3 trial evaluated the safety and efficacy of endovascular thrombectomy plus standard medical therapy, versus standard medical therapy alone, in patients with an NIHSS score of ≥ 6, during a time window of 6-16 hours. This study has been terminated early. An interim analysis based on 182 patients has shown a high likelihood of benefit in the endovascular intervention group. Assuming the efficacy seen in the DAWN study is confirmed in DEFUSE-3, two positive late-window trials will have a considerable impact on how ischaemic patients, hospitalized within 6-24 hours of symptom onset, are assessed and selected for treatment.

The Solitaire™ Platinum Revascularization Device features Parametric™ technology and a unique overlapping stent retriever-based design. This latest third generation device from Medtronic restores blood flow, and is indicated for the retrieval of clots from occluded blood vessels in patients experiencing acute ischemic stroke due to a large vessel occlusion (LVO). Recent (2016/2017) clinical experience at Essen based on first-line Solitaire™ Platinum use. almost exclusively with the largest 6 x 40 mm size, during 255 mechanical thrombectomy procedures, has been positive. Successful recanalization using Solitaire™ Platinum as the sole device, as assessed by Thrombolysis in Cerebral Infarction (TICI) 2b or TICI 3 outcomes, was achieved in 85% of thrombectomy procedures. When Solitaire™ Platinum was deployed in conjunction with other supporting devices to remove additional small clots,

93.7% of patients were recanalized with TICI 2b or 3 outcomes. Furthermore, a low device placement failure rate (4.3%) and no increased risk of haemorrhage (1.9%) were reported. In the light of these results, Solitaire™ Platinum is now the first-choice device for LVO thrombectomy at the Alfried Krupp Krankenhaus Hospital in Essen.

The Medtronic BARREL™ vascular reconstruction device (VRD) is a laser cut stent designed for stent-assisted coil embolization of wide-necked bifurcation or branch aneurysms with a single device. This VRD lowers the metal-to-artery ratio and the risk of thromboembolic complications compared with multiple stents. Key advantages of the BARREL™ VRD device are its ease of use, it is safe to position and deploy, with good visualization, and the device is repositionable and can be re-sheathed. Early clinical experience in a small retrospective study with 17 consecutive patients who underwent stent-assisted coil embolization of wide-necked bifurcation aneurysms with the BARREL™ VRD device is promising. Adequate occlusion was observed in 16/17 (94.1%) of aneurysms and follow-up at three and 12 months showed satisfactory maintenance of these occlusions.

Thromboembolic complications are a cause for concern with pipeline embolization devices (PEDs). Medtronic's Pipeline™ Flex Embolization Device with Shield Technology™ (PFEDST) utilizes an inert phosphorylcholine (PC) surface treatment modification. *In vitro* studies have confirmed a significantly lower thrombogenic potential with PFEDST than the standard Flex device without Shield Technology™ surface modification. Clinical evaluation of the PFEDST device for the treatment of internal carotid and vertebral artery aneurysms is ongoing in the PFLEX study. In this study, successful device deployment was achieved in 53/54 (98.1%) procedures. Complete aneurysm occlusion at 180 days was 73.6%. At 1-year post-procedure, complete aneurysm occlusion was still evident in 27/33 patients (81.8%). Additionally, there was no recurrence of any target aneurysm and there was no requirement for retreatment of any target aneurysm. No cases of severe stenosis were seen. Longer term angiographic follow-up is in progress and, as seen the PUFS study, a progressive increase in aneurysm occlusion rate is expected over time.

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